

**BILATERAL DEEP BRAIN STIMULATION (DBS) OF THE SUBTHALAMIC
NUCLEUS (STN) OR THE GLOBUS PALLIDUS INTERNA (GPi) FOR TREATMENT
OF ADVANCED PARKINSON'S DISEASE**

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EXECUTIVE SUMMARY

Parkinson's disease is a chronic, progressive neurodegenerative disease characterized by resting tremor, rigidity, bradykinesia, and postural instability. No known treatment halts the progression of Parkinson's disease and there is no cure.

Although pharmacologic treatment with levodopa and adjunctive drugs can usually restore smooth motor function for up to 5–10 years after onset, effectiveness gradually diminishes with time. Eventually, most patients experience drug-related complications, such as motor fluctuations and dyskinesias. The most severe motor complications of levodopa tend to occur among patients with early onset (i.e., before age 40) Parkinson's disease.

Because the degenerative nature of Parkinson's disease is not restricted solely to the dopaminergic systems, the brain is affected more globally as the disease advances. Thus, symptoms that are unresponsive to dopamine-active medications ultimately develop. Such symptoms are dementia, dysautonomia, and motor symptoms that affect speech, swallowing, and gait, as well as sleep disturbances, fatigue, and depression.

Deep brain stimulation (DBS), a new surgical treatment for Parkinson's disease, employs high-frequency stimulation to stimulate a targeted region of the brain. Introduced in the late 1980s by Benabid and colleagues in France, DBS is a surgical procedure consisting of the placement of an electrode or electrodes into one of several possible targets in the brain. The electrode is then connected to a computerized pulse generator that is implanted subcutaneously, in a manner similar to that used for a pacemaker. Stimulation parameters are adjusted to maximize therapeutic effects.

Currently, three possible sites may be selected as targets for DBS treatment of Parkinson's disease: the ventralis intermediate nucleus of the thalamus (Vim), the globus pallidus pars interna (GPi), and the subthalamic nucleus (STN). Of these, only the device for unilateral chronic DBS of the ventralis intermediate nucleus (Vim) of the thalamus has received premarket application (PMA) approval from the U.S. Food and Drug Administration (FDA) for treatment of patients with tremor-dominant Parkinson's disease or other tremor disorders. Because it is associated with a higher incidence of speech, swallowing, and cognitive dysfunction, bilateral DBS of the Vim is seldom performed.

In December 1997, the Blue Cross and Blue Shield Association (BCBSA) Medical Advisory Panel (MAP) found that unilateral DBS of the thalamus for patients with disabling, medically unresponsive tremor due to essential tremor or Parkinson's disease met the Technology Evaluation Center (TEC) criteria.

More recent evidence suggests that bilateral DBS of the GPi or the STN may alleviate the entire constellation of parkinsonian symptoms (tremor, rigidity, and bradykinesia). Thus, attention has

shifted to studies of these targets as more appropriate sites than the thalamus for DBS in advanced Parkinson's disease. Unless contraindicated, DBS of either the STN or GPi requires a bilateral procedure.

To date, only a small number of studies have examined chronic bilateral DBS of the GPi. While benefits including reduction of motor fluctuations, reduction of dyskinesias, and significant improvement in the Unified Parkinson's Disease Rating Scale (UPDRS) motor and activities of daily living (ADL) scores in the "off" state were reported, no studies demonstrated any reduction of daily levodopa dose. DBS of the GPi has been, in some cases, associated with the induction of dyskinesia with the foremost electrode and block of the levodopa response with the ventral electrode. These complications, together with preliminary evidence that suggests that the STN may be the more optimal target, have led many centers to focus research efforts upon bilateral DBS of the STN.

However, preliminary studies of DBS of the GPi reveal the existence of a functional somatotopy, meaning that each cardinal symptom of Parkinson's disease appears to have a unique topography and pathophysiology within the GPi. Thus, depending upon the topography of the DBS electrode, stimulation of the GPi target may be more effective for those patients in whom a specific symptom, such as dyskinesia, is a dominant complaint.

This Assessment reviews the available evidence on bilateral deep brain stimulation to address two specific Assessment questions. For patients with medically refractory Parkinson's disease (characterized by "on-off" fluctuations, severe immobility, and/or levodopa-induced dyskinesias uncontrolled with available pharmacologic agents),

1. does chronic bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) improve health outcomes?
2. does chronic bilateral deep brain stimulation (DBS) of the globus pallidus interna (GPi) improve health outcomes?

Based on the available evidence, the Blue Cross and Blue Shield Medical Advisory Panel made the following judgments about whether bilateral DBS of the STN or the GPi for the treatment of advanced Parkinson's disease meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

In August 1997, the U.S. Food and Drug Administration (FDA) approved the premarket application (PMA) for the Aactiva® Tremor Control System (Medtronic, Inc., Minneapolis, MN) for use in patients with essential tremor or tremor caused by Parkinson's disease. In March 2000, the FDA's Neurological Devices Panel Advisory Committee unanimously recommended for final FDA approval the bilateral use of the Medtronic device via supplemental PMA for the treatment of advanced Parkinson's disease (U.S. Food and Drug Administration 2000). The supplemental PMA for the Aactiva® Parkinson's Control Therapy system received final FDA

approval on January 14, 2002. As a condition of approval, the company has agreed to conduct a 3-year, post-approval study of the system to assess its long-term clinical results.

Bilateral DBS of the STN or GPi for the treatment of symptoms of advanced Parkinson's disease, therefore, meets the first criterion.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

There are no large prospective randomized studies with long-term follow-up of bilateral DBS for treatment of advanced Parkinson's disease. In no published studies are patients randomized to treatment arms to compare bilateral DBS with best medical management. Only one small pilot study compares the STN and GPi targets for bilateral DBS using prospective randomization.

Nevertheless, the published scientific evidence is compelling because of the numbers of consecutively treated patients described, the consistency of the findings across studies, and the magnitude of clinical improvements observed on standardized rating scales of neurologic function.

Fourteen published trials present motor outcomes following bilateral STN DBS among 186 patients, with follow-up for at least 6 months for 151 patients and for at least 12 months for 116 patients. Nine published trials present motor outcomes following bilateral GPi DBS among at least 53 patients, with follow-up for at least 3 months (n=53) and for as long as 30 months (n=6).

In addition, 10 trials examine neuropsychological function following bilateral DBS of either nucleus among at least 139 patients.

3. The technology must improve the net health outcome.

Parkinson's disease is a chronic, progressive neurodegenerative disease. Pharmacologic therapy generally relieves symptoms early in the course of the disease, but does not halt disease progression. Most patients, after a time, experience a progressive loss of benefit from levodopa. After 5–10 years of pharmacologic therapy, 50–90% of patients experience motor fluctuations. Motor fluctuations are sudden shifts from the “on” state (during which the effect of levodopa facilitates motor control) to the “off” state (during which medication is not working). In the “off” state, the patient may suddenly become rigid, unable to walk, or even akinetic or “frozen.” Patients with advanced disease may also experience dyskinesias, involuntary movements of the head, neck, torso, or limbs, which are often painful. Thus, advanced disease is characterized by ever-longer “off” periods, and disruption of “on” periods by medication-induced dyskinesia. None of these symptoms can be expected to resolve spontaneously with continued pharmacologic treatment.

In the studies examined in this Assessment, improvement in motor function with bilateral DBS of either the STN or the GPi is consistently demonstrated in each study.

The published studies demonstrate statistically significant improvement in treated patients, as measured by standardized rating scales of neurologic function. The most frequently observed improvements consist of: increased waking hours spent in a state of mobility without dyskinesia; improved motor function during “off” periods; reduction in frequency and severity of levodopa-induced dyskinesia during “on” periods; and improvement in cardinal symptoms of Parkinson’s disease during “off” periods. With bilateral DBS of the STN, reduction in the required daily dosage of levodopa and/or its equivalents is observed.

The magnitude of these changes is both statistically significant and clinically meaningful. In the most recent multicenter trial, “on” time without dyskinesia increased from 27% of waking hours at baseline to 74% of waking hours 6 months after bilateral implantation of electrodes in the STN and to 64% of waking hours with bilateral implantation in the GPi. Similarly, motor scores in the “off” medication state improved by 51% in the STN group and by 35% in the GPi group. In the same trial, a global assessment by both patients and physicians indicated a reduction of severe disability from approximately 75% at baseline to 15% (physician assessment) and 23% (patient assessment) 6 months after surgery. The reduction in disability was due largely to less-frequent and less-severe “off” periods and increased “on” time free of dyskinesia. Other smaller trials report similar outcomes. Among smaller studies, mean “off” period motor scores improved by 34% to 74% in the STN groups. In studies that included patients undergoing bilateral GPi DBS, mean “off” period motor scores improved by 26% to 65% in the GPi groups, with the exception of one small German study, which showed no significant change in motor scores.

The beneficial treatment effect lasts at least for the 6–12 months observed in most trials. The available data with longer term follow-up are generally positive. For example, among 110 patients followed for 1–83 months in a French study, persisting significant motor improvement was observed in 16 patients at 3 years and in 4 patients up to 5 years after bilateral implantation of DBS electrodes.

Adverse effects and morbidity associated with bilateral DBS of the STN or GPi are similar to those known to occur with thalamic stimulation. They include complications related to the procedure, to the device itself, and to the effects of stimulation. In the multicenter DBS Study Group trial, 2.8% of patients had persistent neurologic deficits due to intracranial hemorrhage. Other common adverse effects include infection (n=4 of 143), lead migration (n=5 of 143), and dyskinesia requiring adjustment of stimulation parameters (n=5 of 143). Case reports have shown that inadvertent turning off of the device may bring on a sudden return of severe symptoms and the medical emergency condition of parkinsonian crisis.

Ten studies address the possibility neuropsychological sequelae of bilateral DBS. Altogether, these studies present evidence gathered from 139 patients. Common to nearly all studies is some degree of compromise in the realm of verbal learning and/or language fluency after bilateral implantation of DBS electrodes. For example, in a carefully designed trial examining memory, visuo-spatial and frontal function in 15 patients before and 3 months after implantation, bilateral STN DBS produced both beneficial and detrimental changes. Beneficial changes were moderate improvement in prefrontal task performance and obsessive-compulsive traits, but moderate deterioration of verbal memory was also observed.

In general, all surgical procedures for Parkinson's disease involving the left or both hemispheres appear to negatively affect verbal memory. Therefore, some change in learning ability after these surgical procedures is to be expected, as the involved nuclei are related to memory processes.

4. The technology must be as beneficial as any established alternatives.

Unilateral pallidotomy is an established surgical alternative for treatment of advanced Parkinson's disease. The improvements in "off" period motor function following bilateral DBS of the GPi or STN appear to be as great as, or perhaps greater than, those seen after unilateral pallidotomy. The DBS Study Group reports motor improvements of 34% and 51% for bilateral DBS of the GPi and STN respectively among 127 patients. Studies of pallidotomy offer an indirect comparison: "off" period motor improvements ranged from 14–30% among a total of 115 patients in 5 studies, and a sixth study of 18 patients found 71% improvement.

DBS has other advantages. Unlike pallidotomy, which is no longer recommended as a bilateral procedure because of high risk of serious postoperative neuro-cognitive dysfunction, DBS can be performed as a bilateral procedure. Furthermore, DBS is not an ablative procedure. Unlike an ablative procedure, which cannot be undone, DBS electrodes can be removed. Finally, there appears to be less operative morbidity associated with DBS than with pallidotomy, possibly because the final step of the pallidotomy surgery, thermocoagulation, is unnecessary.

The currently available data suggest that bilateral DBS of the STN may provide a more consistent and more positive improvement than bilateral DBS of the GPi. Using the DBS Study Group data as the most representative evidence, bilateral DBS of the STN resulted in a mean 51% improvement in "off" period motor scores, a 44% improvement in "off" period ADL scores, a 25.8% improvement in "on" period motor scores, and a 57% reduction in "on" period dyskinesia. All of these changes were significant (each with $p < 0.001$).

For bilateral GPi DBS, the magnitude of change is less marked and, for certain measures, reaches a lesser degree of statistical significance. During GPi DBS, mean "off" period motor scores improved by a 32%, "off" period ADL scores by 38%, "on" period motor scores by 26.8%, and "on" period dyskinesia was reduced by a mean of 66%. The changes following GPi DBS reached a statistical significance of $p < 0.001$ only for the "off" period motor and ADL scores.

Reduction in daily levodopa dosage was possible only with bilateral DBS of the STN. The mean levodopa dosage reduction from about 1,200 mg per day preoperatively to about 760 mg per day at 6 months with bilateral DBS of the STN was highly significant ($p < 0.001$). In no studies has the dosage of levodopa been reduced following bilateral DBS of the GPi.

Despite these apparent differences, there are important issues that warrant further examination of GPi DBS. First, the DBS Study Group data indicate that cardinal symptoms of Parkinson's disease (i.e., tremor, rigidity, bradykinesia, gait disturbance) are ameliorated by stimulation of either target, with statistical significance $p < 0.001$ for each symptom.

While a reduction in daily levodopa dosage may be a beneficial health outcome in most cases, it may not always be so. During bilateral DBS of the STN, a reduction in levodopa is often

necessary to reduce the dyskinesia that may accompany the procedure. Observations from a study of bilateral DBS of the STN in 8 patients with early onset Parkinson's disease indicate levodopa reduction may have some negative aspects. Despite the fact that stimulation provided off-period motor function similar to their best on-drug periods, some of these patients complained of a lack of energy and initiative during off-drug periods and other off-drug symptoms such as anxiety following major decreases in levodopa dosage.

Patients who have undergone unilateral pallidotomy represent another subset in whom DBS of the STN may be contraindicated because postoperative levodopa dose reduction that may be required to prevent dyskinesia on the stimulated side may make any further levodopa treatment of parkinsonian symptoms of the ablated side impossible.

Finally, preliminary studies of bilateral DBS of the GPi reveal that each cardinal symptom of Parkinson's disease appears to have a unique topography and pathophysiology within the GPi. Thus, depending upon the topography of the DBS electrode, further study may demonstrate stimulation of the GPi target to be more effective for those patients in whom a specific symptom, such as dyskinesia, is a dominant complaint.

In summary, bilateral DBS of either the STN or GPi have consistently resulted in significant therapeutic response in 14 (n=186) and 9 trials (n=153), respectively. It is unknown whether some of the apparent differences in effectiveness are due to differences in study design (randomization versus consecutive cases), patient selection (age, disease severity, and duration), clinical and technical methodology (location of DBS electrodes, setting of stimulation parameters), or other factors. Judgment about the superiority of one target over the other in the absence of a well-designed, prospective, randomized clinical trial is premature at this time.

At present, only one small trial compares the two targets in a prospective, randomized, blinded study design. Definitive determination of which stimulation target, the STN or GPi, provides most effective therapy may be provided by a recently approved trial. The Veterans Administration/National Institutes of Health Cooperative Trial, involving 6 Parkinson's disease centers and their university affiliates, will enroll 300 patients beginning in the first quarter of 2002.

5. The improvement must be attainable outside the investigational settings.

The results for bilateral DBS for advanced Parkinson's disease that are reported in the literature have been achieved at experienced centers. Bilateral DBS meets this criterion when performed at centers that can demonstrate comparably low procedure-related morbidity and mortality.

Based upon the above, bilateral deep brain stimulation of the subthalamic nucleus or the globus pallidus interna for patients with advanced Parkinson's disease meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

BILATERAL DEEP BRAIN STIMULATION (DBS) OF THE SUBTHALAMIC NUCLEUS (STN) OR THE GLOBUS PALLIDUS INTERNA (GPi) FOR TREATMENT OF ADVANCED PARKINSON'S DISEASE

ASSESSMENT OBJECTIVE

Parkinson's disease is a chronic, progressive neurodegenerative disease characterized by resting tremor, rigidity, bradykinesia, and postural instability. No known treatment halts the progression of Parkinson's disease and there is no cure.

Although pharmacologic treatment with levodopa and adjunctive drugs can usually restore smooth motor function for up to 5–10 years after onset, effectiveness gradually diminishes with time. Eventually, most patients experience drug-related complications, such as motor fluctuations and dyskinesias. The most severe motor complications of levodopa tend to occur among patients with early onset (i.e., before age 40) Parkinson's disease.

Because the degenerative nature of Parkinson's disease is not restricted solely to the dopaminergic systems, the brain is affected more globally as the disease advances. Thus, symptoms that are unresponsive to dopamine-active medications ultimately develop. Such symptoms are dementia, dysautonomia, and motor symptoms that affect speech, swallowing, and gait, as well as sleep disturbances, fatigue, and depression.

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BACKGROUND

Parkinson's Disease

The average annual incidence of Parkinson's disease is approximately 20 cases per 100,000. It currently affects approximately one million people in the U.S. The incidence of Parkinson's disease increases with advancing age, until it reaches a peak at about 75 years of age (Olney 1995; Tanner 1992).

Parkinson's disease is characterized by resting tremor, rigidity, bradykinesia, and postural instability (Tabbal et al. 1998). The condition usually appears after age 40 and progresses slowly over many years. In the advanced stages, there can be a loss of postural and righting reflexes, severe rigidity, and akinesia leading to confinement to a wheelchair and/or bed.

Diagnosis

Diagnosis of early Parkinson's disease may be difficult. Traditionally, the presence of two of the three classic features of Parkinson's disease (resting tremor, rigidity, or bradykinesia) provided the basis for diagnosis. However, clinical diagnoses based upon these criteria alone were found to be incorrect in 25% of cases in the London Britain Bank Study (Hughes et al. 1992a).

Magnetic resonance imaging (MRI) studies support this misdiagnosis rate: Olanow and Koller (1998) report that MRI examination shows 25% of patients with parkinsonian symptoms have an atypical disorder, such as multiple system atrophy (MSA) or progressive supranuclear palsy (PSP), rather than idiopathic Parkinson's disease. The features that best predict pathologic changes of idiopathic Parkinson's disease, according to retrospective analysis based upon postmortem diagnosis are:

- resting tremor;
- asymmetric presentation, with one side affected more than the other;
- good response to levodopa (Hughes et al. 1992b; Olanow and Koller 1998; Jankovic 2000)

Specialists in movement disorders distinguish at least two major subtypes of idiopathic Parkinson's disease: a tremor-dominant subtype and a rigid/akinetic subtype. It is generally accepted that patients with the unilateral, tremor-dominant subtype of disease seem to progress less rapidly, have less cognitive dysfunction, and respond differently to antiparkinsonian medication than patients with the rigid/akinetic subtype. Patients with predominantly rigid/akinetic disease have symptoms that are more symmetrical and experience more dystonia, axial involvement, and early dopamine-induced dyskinesias (Van Horn et al. 2001; Jankovic et al. 1990).

Secondary parkinsonism caused by tumors, hydrocephalus, AIDS, or infarcts is not usually confused with idiopathic Parkinson's disease. Finally, certain neuroleptic agents, such as metoclopramide (Reglan®) and valproate (Depakote®) have been found to induce parkinsonism.

Pathophysiology of Parkinson's Disease

Parkinson's disease is a state of profound dopamine deficiency in the corpus striatum. The corpus striatum, a part of the basal ganglia, is made up of two cellular masses, the putamen and the caudate nucleus. These two masses, arising as a single body early in development, separate partially as the brain develops. They remain continuous ventrally and are also connected dorsally by a number of slender gray bridges across the internal capsule (Truex and Carpenter 1969).

Parkinson's disease is caused by the degeneration of monoaminergic neurons, especially of the dopaminergic neurons of the substantia nigra (Ehringer and Hornykiewicz 1960). Dopaminergic neuron cell bodies located in the substantia nigra project neuritic processes to the striatum. These neurons modulate activities of the extrapyramidal motor system through two critical functions: the production of dopamine and the regulation of its release from nerve terminals in the striatum. Symptoms of Parkinson's disease occur when this modulation of neuronal activity is lost as dopaminergic cells gradually die.

Drug treatment with levodopa can usually restore smooth motor function for at least 5–10 years after onset of Parkinson's disease by permitting surviving dopaminergic cells to bypass a rate-

limiting enzyme, tyrosine hydroxylase, and thus, produce enough dopamine to maintain adequate motor function.

Advanced disease is often characterized by lengthening of predictable “off” periods and by sudden unpredictable shifts in motor control, referred to as motor fluctuations (See Table A, Appendix, for definitions of terms commonly used in studies of Parkinson’s disease). Evidence suggests that use of short-acting forms of levodopa exacerbates these symptoms by exposing dopaminergic receptors to alternating high and low levels of stimulation (Juncos et al. 1989; Engber et al. 1989). Predictable “off” periods, that is, periods of relative immobility and loss of dexterity that occur gradually as a dose of levodopa wears off, occurred in about 20% of patients during the first 5 years of disease and in nearly 60% of patients after 15 years of disease among 811 levodopa-responsive patients stratified by duration of Parkinson’s disease after diagnosis at University of Kansas (Miyawaki et al. 1997).

Motor fluctuations, or “on-off” phenomena, are characterized by abrupt unpredictable “off” periods of relative immobility that may last from 1 minute to an hour, and which are followed by an equally abrupt return of medication effectiveness, or “on” periods. Such “on-off” motor fluctuations may occur frequently throughout the day, or even during an hour, and are not temporally related to levodopa intake (American Hospital Formulary Service 1994).

Studies of long-term levodopa therapy show that:

- 50–90% of patients develop motor fluctuations after 5–10 years of levodopa therapy;
- after 10 years of levodopa treatment, motor fluctuations and dyskinesia are seen in almost 100% of patients with onset of Parkinson’s disease before the age of 50 years;
- these complications, though initially mild, progress over time;
- motor fluctuations are often the major cause of disability for patients with Parkinson’s disease (Obeso et al. 2000a; Fahn 2000; Marsden and Parkes 1977; Poewe et al. 1986; Riley and Lang 1993; Olanow and Koller 1998; Jankovic 2000).

Chronic treatment with levodopa is also complicated by the occurrence of dyskinesias. Levodopa-induced dyskinesias are motor complications consisting of choreiform movements, most often involving the head, neck, torso, limbs, and respiratory muscles, and occurring more often in younger patients with Parkinson’s disease. In addition, other dyskinesias, such as dystonia, myoclonus, and tics, may occur with chronic levodopa use.

Whether dyskinesias and motor fluctuations are causally related to duration of levodopa treatment or to progression of the underlying disease process or to both is not known. Evidence suggests the wearing off phenomenon responsible for these symptoms is due to a shortening of the half-life of levodopa in the striatum without measurable change in its half-life in the peripheral tissues. One theory, the storage hypothesis, attributes the wearing off phenomenon primarily to loss of striatal dopaminergic terminals, and consequent loss of the brain’s ability to store and buffer shifts in striatal levodopa concentration (Jankovic 2000). Orally administered levodopa, in the absence of adequate numbers of dopaminergic nerve terminals to store and release dopamine, “floods” the extrapyramidal motor system, resulting in sudden shifts in motor state rather than the previously attained smooth motor control. Thus, as Parkinson’s disease advances, the therapeutic window becomes, for some patients, quite narrow. For such patients,

the dose of levodopa required to elicit an “on” response is now complicated by dyskinesia and sudden episodes of freezing and akinesia, while the reduction in levodopa dosage needed to avoid these adverse effects of the medication also fails to elicit an adequate “on” response (Obeso et al. 2000a).

Other bodies of evidence suggest that the tolerance to levodopa that develops over time may cause a progressive shortening of response. Yet other studies suggest that dysfunctional postsynaptic striatal mechanisms and basal ganglia output pathways play a significant role in the development of motor fluctuations and dyskinesias (Jankovic 2000).

Since dystonia may also occur as a manifestation of Parkinson’s disease, it is important to determine whether dystonia occurs during an “off” period (indicating it is due to Parkinson’s disease) or during an “on” period (indicating it is due to medication) (Olanow and Koller 1998).

Long-term use of levodopa may be associated with neuropsychiatric complications. Finally, certain late symptoms of Parkinson’s disease, such as freezing episodes, autonomic dysfunction, falling, and dementia, do not respond to levodopa therapy (Olanow and Koller 1998).

Pharmacologic Therapy

Pharmacologic therapy is currently the primary treatment for Parkinson's disease. Since each patient with Parkinson’s disease may have symptoms that not only vary in number and severity from day to day, and from hour to hour, but also progress at different rates over the course of many years, successful pharmacologic treatment is essentially an art: the art of meticulous drug titration based upon close observation by a physician who knows both the individual patient history and the subtlety of available pharmacologic therapy.

Levodopa. The most effective drug for treatment of Parkinson’s disease is levodopa, the immediate metabolic precursor to dopamine. This compound is converted to dopamine in the brain, leading to amelioration of parkinsonian symptoms. Although early levodopa treatment is associated with a lower mortality rate in patients with Parkinson's disease, there is still some controversy over when to begin levodopa therapy because it causes significant adverse effects including gastrointestinal disturbances and cardiovascular reactions. Carbidopa, which is often given in conjunction with levodopa, is a dopa-carboxylase inhibitor that prevents the metabolism of levodopa to dopamine in the peripheral tissues. This reduces the potential for excessive peripheral levels of dopamine that can cause some adverse effects. However, long-term use of levodopa, as mentioned previously, is associated with other problems such as loss of response over time, involuntary movements, “freezing,” and symptom fluctuations (Jankovic 2000; Olanow and Koller 1998; Hoehn 1992; Juncos 1992).

Dopaminergic agonists. Dopaminergic agonists, a class of drugs with diverse characteristics, have in common the capacity to directly stimulate dopamine receptors, presumably because each possesses a dopamine-like structure within its molecular configuration. Dopamine agonists, because they act directly upon striatal receptors, require no metabolic conversion to an active form, and thus are independent of degenerating dopaminergic neurons. Unlike levodopa, dopaminergic agonists do not compete with circulating amino acids for transport into the brain,

most have a longer duration of response than intermediate-release form of levodopa, and they do not generate free radicals or cause oxidative stress. In general, they also have limited antiparkinsonian efficacy (Olanow and Koller 1998).

Four such agents are currently available in the U.S.: bromocriptine (Parlodel®), pergolide (Permax®), and more recently, pramipexole (Mirapex®) and ropinirole (Requip®).

Dopaminergic agonists, when used together with levodopa, have been shown to improve the efficacy of levodopa, decrease “off” time, and provide a levodopa-sparing effect (Olanow and Koller 1998; Olanow et al. 1994; McDonald and Horowski 1983).

Acute adverse effects of the dopaminergic agonists are similar to those of levodopa and include nausea, vomiting, postural hypotension, and psychiatric manifestations. The older ergot-derived dopaminergic agonists are only rarely associated with classic ergot-induced conditions (pulmonary or retroperitoneal fibrosis and Raynaud’s phenomena). Psychiatric adverse effects occur more often in the elderly or in patients who are already cognitively impaired.

Other Agents. Drugs with anticholinergic action (cholinergic receptor blockers and antihistamine-anticholinergics, e.g., benztropine, trihexyphenidyl) are used in younger patients with Parkinson’s disease in whom tremor is a dominant symptom. Their effect is based upon the idea that the normal balance between dopamine and acetylcholine neurotransmission in the basal ganglia is distorted in Parkinson’s disease. Since dopamine depletion leads to a state of relative cholinergic excess, cholinergic drugs exacerbate parkinsonian symptoms while anticholinergic drugs relieve them. These drugs are not used as often or as successfully as levodopa and are sometimes given as adjuvants to levodopa. They are most often used in younger patients in whom tremor is the dominant symptom and in whom there is no cognitive deficit (Goetz and Diederich 1992; Koller et al. 1994; Olanow and Koller 1998).

Adverse effects limit the use of anticholinergic agents. The most significant adverse effects, memory impairment, acute confusion, and hallucinations, occur more often in elderly patients, but even younger patients can experience significant cognitive impairment during treatment with anticholinergic agents. Other complications are sedation, dysphoria, dyskinesias, and peripheral antimuscarinic effects (dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating, and tachycardia). Anticholinergics must be withdrawn gradually to avoid acute withdrawal effects, which include acute exacerbation of parkinsonism (Olanow and Koller 1998).

The antiviral agent amantadine was discovered by chance to possess antiparkinsonian activity (Schwab et al. 1969). It acts at several steps in the dopamine metabolic pathway, stimulating dopamine release, blocking reuptake, and stimulating dopamine receptors. When used as monotherapy in uncontrolled studies, two-thirds of patients experience less akinesia, rigidity and tremor. Important adverse effects are confusion, hallucinations, insomnia, and nightmares. Less commonly, peripheral edema and livedo reticularis may occur. Dry mouth and blurred vision occur when amantadine is combined with anticholinergic agents (Olanow and Koller 1998).

COMT inhibitors. COMT inhibitors block the enzyme catechol-*O*-methyltransferase (COMT), which metabolizes levodopa and dopamine both peripherally and in the central nervous system.

COMT inhibitors, by stabilizing plasma levodopa levels, provide enhanced and smoother levodopa availability in the brain and prevent the peak levodopa concentrations associated with the development of motor fluctuations. The major adverse effects associated with their use are a worsening of dyskinesia in some patients, which can often be controlled by reducing the dose of levodopa; and diarrhea, which may require drug withdrawal (Olanow and Koller 1998; Kielbartz and Hubble 2000).

Surgical Treatments

A number of surgical treatment modalities for advanced Parkinson's disease have been proposed. These modalities may be divided into three groups: ablative therapy (pallidotomy, thalamotomy), restorative therapy (human fetal cell transplantation, porcine fetal cell transplantation, intracerebral injection of growth factors), and deep brain stimulation of various targets (thalamus, pallidum, subthalamic nucleus).

A special report by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology (Hallett and Litvan 1999) described only three of these procedures as "safe and effective":

- unilateral thalamotomy for symptoms consisting primarily of tremor;
- unilateral pallidotomy for symptoms consisting of bradykinesia, tremor, or dyskinesia;
- unilateral DBS of the thalamus for symptoms consisting primarily of tremor.

It should be noted that the strength of the AAN positive recommendation for these three procedures is described as "Type C" (i.e., "positive recommendation, based on strong consensus or Class III evidence"). Class III evidence is evidence provided by "expert opinion, non-randomized historical controls, or case reports of one or more patients." It is contrasted by Class II evidence ("evidence provided by one or more well-designed clinical studies such as prospective open, case-controlled studies, etc.") and Class I evidence ("evidence provided by one or more well-designed randomized controlled clinical trials").

Anatomic rationale for the subthalamic nucleus and globus pallidus interna as targets for DBS.

Several lines of research suggest that Parkinson's disease is characterized by a loss of regulatory inhibition of the GPi and STN. First, increased electrical and metabolic activity in the GPi and STN has been demonstrated in MPTP-treated monkeys (an experimental Parkinson's model) (Obeso et al. 2000c; Filion et al. 1985; Crossman et al. 1985; Bergman et al. 1994). Other studies have demonstrated increased glucose utilization in the GPi of untreated patients with Parkinson's disease (Eidelberg et al. 1994). Finally, it was observed that lesions of the STN are associated with decreased firing in the GPi and result in amelioration of contralateral parkinsonian features in MPTP-treated monkeys (Olanow et al. 2000; Filion et al. 1985; Crossman et al. 1985).

The globus pallidus interna is the main output region of the basal ganglia. When excited, it inhibits thalamo-cortical and brainstem neurons. GPi output to thalamo-cortical and brainstem neurons is controlled by the striatum through two pathways, a direct inhibitory GABAergic

pathway and an indirect excitatory glutaminergic pathway. Dopamine is crucial in modulating striatal control of these two pathways.

When nigrostriatal dopaminergic neurons degenerate, both of these strategic striatal pathways to the GPi become dysfunctional:

- the direct inhibitory striatal neurons fire less often and
- the indirect excitatory striatal neurons fire more often.

This dysfunctional pattern of striatal output, a simultaneous loss of inhibitory effect and increase in excitative effect, leads to an increase in the GPi and STN excitation. The uncontrolled excitation of the GPi and STN causes an excessive inhibition of thalamo-cortical and brainstem neurons, resulting in the motor symptoms of Parkinson's disease (Olanow et al. 2000).

The mechanism of action of DBS is not known. However, it is generally believed that high frequency stimulation has an inhibitory effect similar to that caused by ablative lesions of the same structures (Benazzouz and Hallett 2000). How DBS may cause neuronal inhibition chronically so as to imitate the effects of a permanent lesion has not been not clearly defined. High-frequency stimulation may initiate neuronal inhibition

- by causing a depolarization block,
- by disrupting a neural network with the additional nerve impulses generated by the stimulation (i.e., neural jamming),
- by producing a net inhibition in the network either by preferential activation of inhibitory neurons, or
- by properties of the network itself when driven at high rates (Benazzouz and Hallett 2000).

Deep Brain Stimulation Technology

The device currently used for DBS is the Activa® system developed by Medtronic, Inc. (Minneapolis, MN). The system consists of several components as listed, including a quadripolar electrode (four contact sites arranged along the distal edge), which is stereotactically implanted into the targeted nucleus (STN or GPi) in a bilateral procedure that is identical to the corresponding ablative procedure, except that the creation of a radiofrequency-induced lesion is replaced with implantation of this permanent quadripolar electrode. Stimulation parameters, including electrode contact site selection, stimulation pulse amplitude, frequency, and width are then adjusted to optimize symptom relief.

Components of the implantable Medtronic Activa® brain stimulation system include:

Implantable components:

- Neurostimulator (a small, sealed device implanted beneath the skin in the chest);
- DBS™ Lead (a thin, insulated wire with 4 electrodes at the tip, implanted in the brain);
- Lead extension (a thin, insulated wire implanted under the skin of the head and neck, connecting the lead to the neurostimulator)

Components for system “start-up”/programming stimulation parameters:

- Neurological test stimulator (used to test the effectiveness of the system prior to implantation)
- Physician Programmer with MemoryMod software cartridge (to allow the system to be noninvasively adjusted)

Patient components:

- Handheld control magnet (for turning the system on and off)

When implanted bilaterally, two separate systems must be used (U.S. Food and Drug Administration 2002). More information on the system, including common questions and answers and safety information, can be found online at <http://www.medtronic.com/neuro/parkinsons/product.html>.

FDA Status. In August 1997, the U.S. Food and Drug Administration (FDA) approved the premarket application (PMA) for the Aactiva® Tremor Control System (Medtronic, Inc., Minneapolis, MN) for use in patients with essential tremor or tremor caused by Parkinson's disease. In March 2000, the FDA's Neurological Devices Panel Advisory Committee unanimously recommended for final FDA approval the bilateral use of the Medtronic device via supplemental PMA for the treatment of advanced Parkinson's disease (U.S. Food and Drug Administration 2000). The supplemental PMA for the Aactiva® Parkinson's Control Therapy system received final FDA approval on January 14, 2002 (U.S. Food and Drug Administration 2002). As a condition of approval, the company has agreed to conduct a 3-year, post-approval study of the system to assess its long-term clinical results.

Surgical Implantation Procedure

The overall DBS procedure consists of the following four basic segments:

- a period of stereotactic image acquisition and coordinate calculation, using computed tomography (CT) or magnetic resonance imaging (MRI),
- a stereotactic neurosurgical procedure consisting of the creation of a burr hole and the passage of a probe through brain tissue to the target, under local anesthetic, followed by implantation of the DBS electrode, with interoperative stimulation to ensure the absence of significant adverse effects,
- a general surgical procedure under general anesthesia for implantation of pulse generator, and finally,
- the setting and programming of best stimulation parameters (Guridi et al. 2000; Benabid et al. 2000a, 2000b; Houeto et al. 2000).

As mentioned, a variety of methods are used to confirm the location of the optimal target site, including imaging with MRI and ventriculography as well as the use of macroelectrode stimulation, which allows definition of the boundaries of the targeted nucleus and surrounding structures, or micro-stimulation and micro-recording, which permits definition of the somatotopic organization of the targeted nucleus (Guridi et al. 2000; Benabid et al. 2000a, 200b).

Once the target site is confirmed via micro- or macro-electrode probe, the DBS electrode is inserted, stabilized, and attached to a transcutaneous cable for short-term stimulation. There are

currently two electrode models used for DBS. They vary in length (7.5 mm and 10.5 mm) and in distance between active sites (0.5 mm and 1.5 mm respectively). Both are tetrapolar and both have a diameter of 1.27 mm. Once correct placement is confirmed by control imaging studies, the electrode is fixed to the skull and connected to its percutaneous extension. Patients are hospitalized for a week after electrode implantation. During this time, follow-up MRI studies, adjustment and evaluation of stimulation parameters, and surgical implantation of programmable stimulators and subcutaneous connection of stimulator and electrode extension are completed.

Battery life may be shortened by the high frequency (130–185 Hz) at which neurostimulators are used. Benabid and colleagues report battery replacement in 18 of 20 patients treated for tremor with thalamic stimulation with the Itrel I model stimulator after 38.7 +/- 23.5 months (range 17–109 months). The lifetime of the Itrel II models, which have not yet been changed in their series of STN DBS patients, averages 87 months. Ghika and colleagues (1998) report loss of battery power after one year in one patient.

Acute stimulator failure has been experienced by some patients after passing through security magnets in department stores (Ghika et al. 1998), after exposure to high-speed drill and ultrasound machines during dental procedures, and after use of a portable dictaphone placed in a pocket close to the neurostimulator (Hariz and Johansson 2001). In two of these cases, sudden inadvertent failure of otherwise successful DBS resulted in rapid reappearance of akinetic symptoms and a state close to parkinsonian crisis (Hariz and Johansson 2001).

Target Selection and Identification.

The two targets currently under study for DBS are relatively small structures. The STN is a small ovoid nucleus with a volume of 150–200 cubic mm in humans. It lies 2–3 mm superior and slightly lateral to the substantia nigra, 1–2 mm anterior to the red nucleus, posterior to the mamillary bodies, and is bounded externally by the internal capsule (Benabid et al. 2000a). The GPi is a banana-shaped structure with a volume of about 500 cubic mm, bounded dorsolaterally by the globus pallidus externa, by the internal capsule caudally, and by the optic tract ventrally. Anatomically complex, both structures contain sensorimotor regions with somatotopic organization.

Consideration of the STN as a therapeutic target was prompted by animal studies demonstrating the key role of the STN in organization of the basal ganglia. Beginning in 1993, Benabid and colleagues initiated study of stimulation of the STN. Results of their early studies of GPi DBS and STN DBS among young-onset patients allowed the Grenoble group to suspect that the STN target was superior to the GPi target for both akinetic-rigid and tremor-dominant Parkinson's disease. In general, symptom control can be achieved with less current with the STN target than the GPi target. Thus, since STN DBS has been chosen as the preferred procedure at the Grenoble center, the literature evaluating this target is somewhat larger than that for the GPi target (Benabid et al. 2000a, 2000b).

Use of the GPi as a bilateral DBS target evolved from observations of clinical improvement during pallidotomy surgery. Some investigators note that GPi DBS has certain advantages. Potential hemorrhagic complications are less likely to be life threatening than in STN DBS

(Ghika et al. 1998). Medication can be increased during bilateral pallidal stimulation with no further increase in dyskinesia. This observation is understood differently by Benabid and colleagues, who note that, in the medication-on state, GPi stimulation appears to create a loss of sensitivity to levodopa, which then must be increased (Benabid et al. 2000a).

Methods of target identification vary. In general, there is debate about whether a target may be defined by mainly anatomic (imaging) means or by a combination of anatomic and physiologic (microrecording and microstimulation) means. Targeting by imaging technology alone has been shown to carry an error rate as high as 75%. However, there are no data that define exactly how precise electrode location must be to achieve the best results. It may be argued that since the stimulation electrode generates an electromagnetic field that spreads over a relatively large volume of brain tissue in a current-dependent manner, simply getting into the targeted nucleus suffices to obtain clinical benefit. Others suggest that identifying the sensorimotor region by microrecording reduces or eliminates the often tedious and difficult task of intraoperative clinical evaluation and greatly simplifies programming of the active leads during the postoperative period. The pros and cons of various techniques have been reviewed (Guridi et al. 2000). Data to support or negate the superiority of one method over another are not available.

Given the current level of technical variation, it would seem that, until appropriate clinical trials have been completed, choice of target and method of target localization will depend on the center in which it is performed.

Histopathologic Effects of DBS

Whether DBS causes permanent tissue damage is an important issue. Lesion size in thermocoagulative procedures ranges from 40–200 cubic mm for thalamotomy (Blond and Siegfried 1991) and 28 to 150 cubic mm for pallidotomy (Hariz 1990, 1991).

Two postmortem studies examine the effects of long-term DBS upon brain tissue. Compared to lesion size associated with ablative procedures, lesions associated with DBS are very small. Caparros-LeFebvre and colleagues (1994) report histopathologic findings from the brain of a patient who died 43 months after placement of an electrode for intrathalamic stimulation. Stimulation for treatment of tremor was not continuous during the treatment period. They found the lesion caused by the DBS electrode was small, consisting of small areas of gliosis and small accumulations of lymphoid cells in the 1-mm perimeter of the electrode track.

Haberler and colleagues (2000) report histopathologic findings from brains of 8 patients with Parkinson's disease after stimulation periods of 3–70 months. Stimulation to target sites (the thalamus in 6 cases and the STN in 2 cases) was continuous. In all cases, brains showed well-preserved neural parenchyma with a narrow rim (less than 500 micrometers) of mild gliosis around the lead track, consistent with reactive changes caused by surgical placement of the electrode. The authors concluded that chronic DBS causes no damage to adjacent brain tissue.

It is possible, however, for chronic DBS to cause more significant histologic damage. In a post-mortem analysis case report, Henderson and colleagues (2001) describe a lesion with a volume of approximately 18 cubic millimeters – essentially the size of a small thalamotomy – located in

the thalamic centromedian-parafascicular complex at the tip of a DBS electrode that had been implanted for treatment of tremor.

Clinical Outcome Measures

Measures of clinical outcomes for treatment of Parkinson's disease consist of a set of standardized tests, including the Unified Parkinson's Disease Rating Scale (UPDRS), the Schwab and England scale, scales developed for the Core Assessment Program for Intracerebral Transplantations (CAPIT), tests that quantify tremor and dyskinesia, various timed tests, and questionnaires for patient and caretaker approval evaluation. Use of these methods have been reviewed (Langston et al. 1992; Fahn et al. 1987; Schwab and England 1969).

The UPDRS (see Appendix) is perhaps the most widely used measure for evaluation of treatments of Parkinson's disease. It consists of a comprehensive inventory of symptoms and signs of Parkinson's disease, which are divided into sections pertaining to mood and mentation, activities of daily living and motor function, and muscle rigidity, speech, and gait. Scores for the total inventory range from 0 (normal) to 176 (worst possible). A patient's state is defined as the "off medication" state when testing is conducted before the patient has taken a first morning dose of levodopa and at least 12 hours after taking the last dose of levodopa on the previous day. This convention is intended to replicate the severity of symptoms patients experience in their daily lives as levodopa becomes less effective and motor fluctuations become more frequent and severe. The "on medication" state is defined, by convention, as the best test scores recorded during the day while the patient is taking levodopa. In some studies, "on" scores are measured during a "best 'on' state" created with a suprathreshold dose of levodopa (Fahn et al. 1987; Freed et al. 2001; Benabid et al. 2000a).

The Schwab and England scale is a measure designed exclusively to evaluate performance of activities of daily living. Scoring direction is the reverse of the UPDRS: a score of 100 indicates normal and a score of 0 indicates complete disability. Like the UPDRS, the Schwab and England scale is usually measured in the "off" and "on" states (Schwab and England 1969).

Evaluation of neuropsychological sequelae of DBS requires a special battery of assessment instruments selected for their minimal dependence on motor function. Evaluation must be conducted in a manner that minimizes such variables as fatigue and motor symptoms, at a standard time of day when patients are in their best state. Understanding of these evaluations may be further improved by application of statistical techniques for analyzing longitudinal, repeated measures.

Green and colleagues advise use of a generalized estimating equations (GEE) approach instead of the more standard analysis of variance or multivariate analysis of variance applied in neuropsychological studies of Parkinson's disease (Green and Barnhart 2000; Diggle et al. 1994). More recently, Morrison and colleagues (2000) have proposed a protocol called the Program for Neuropsychological Investigation of Deep Brain Stimulation (PNIDBS), consisting of a relatively brief core battery with multiple versions that can be supplemented to meet individual investigator needs. Their feasibility study demonstrates that patients with severe motor disabilities are able to complete the PNIDBS.

METHODS

Search Methods

The MEDLINE database was searched for the period of 1985 through December 2001. The search terms were the MeSH terms “electric stimulation therapy/de,” and “Parkinson disease” plus the textwords “bilateral,” “globus pallidus,” “subthalamic,” and “deep brain stimulation.” The search was restricted to publications in English about human subjects. The reference lists of retrieved publications were also reviewed for relevant publications. *Current Contents* was also searched. The search was restricted to publications in English about human subjects. Reference lists of retrieved publications were reviewed for relevant publications. In addition, slide presentation of Medtronic data presented at FDA hearings was reviewed.

Study Selection

The evidence used in this Assessment is restricted to those studies that:

- present original data published in full-length articles in peer-reviewed journals;
- represent the most recent publication from a particular medical center, in cases of serial publications of case series;
- include more than one subject;
- examine a range of health outcomes using generally accepted standardized evaluation methods for Parkinson’s disease;
- analyze bilateral and unilateral procedures separately, AND analyze DBS STN and DBS GPi separately, OR present a systematic description of neuropsychological outcomes after bilateral DBS procedures, regardless of target site.

This Assessment addresses bilateral DBS. Therefore, those studies in which outcomes from unilateral procedures are analyzed together with those of bilateral procedures have been excluded. Some studies examine single outcomes, such as the effect of DBS upon axial control, gait, or voice production. These studies often apply special evaluation methodology, such as jaw-opening velocity, jaw opening amplitude, stride length, and phonatory parameters of sustained vowels. Inclusion of studies that focus upon a single outcome and/or require use of highly specialized outcome measures is beyond the scope of this Assessment.

Of the studies meeting these criteria, 14 examine outcomes after bilateral DBS of the STN and 9 examine outcomes after bilateral DBS of the GPi.

Because more recent publications often include subjects whose outcomes were reported in preliminary reports, only the most recent study from each study center will be analyzed in the evidence section. However, to provide observations presented only in a center’s earlier or in an overlapping study, two studies (Fraix et al. 2000; Volkmann et al. 1998) are described in evidence tables; however, only results from the most complete (Benabid et al. 2000a) or most recent (Volkmann et al. 2001) publication is included in the analysis of outcomes.

There is particular concern over potential adverse effects of bilateral surgical procedures involving the STN and GPi upon neuropsychological function. In order to provide as much information as possible, the Assessment provides a special section in which all available trials reporting any neuropsychological outcomes are presented. Most of the studies in this final section are devoted exclusively to this issue use a variety of tests to attempt to measure change in language, memory, visuospatial perception, and behavior. It should be noted that, while the study of the effect of a surgical procedure upon neuropsychological function would be complex in any set of patients, it is particularly so for patients with Parkinson's disease, in whom the changes from progressive disease and from advancing age must also be considered.

At this time, there is no widely accepted standardized methodology, like the UPDRS, for the evaluation of neuropsychological outcomes following bilateral DBS. For this reason, the Assessment provides only a descriptive presentation of these studies.

Because it is the bilaterality of the procedure (rather than the choice of target) that is the primary concern in most these studies, outcomes of DBS STN and DBS GPi are considered together. In all of the included reports, all patients underwent bilateral procedures.

On-going Trials

A Veterans' Administration/National Institutes of Health (VA/NIH) Cooperative trial, involving 6 Parkinson's disease centers and their university affiliates, will enroll 300 patients beginning in February-March 2002. Patients will be randomized to one of two groups, Group 1: immediate DBS surgery; or Group 2: delayed DBS surgery after a 6-month trial of best medical management.

Each surgical group will be further randomized to either STN or GPi target. All patients will be followed for 2 years. Results of the trial will be available in approximately 5 years (personal communication, Matt Stern, M.D., University of Pennsylvania, November 6, 2001).

Medical Advisory Panel Review

This TEC Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on December 6, 2001. In order to maintain the timeliness of the scientific information in this Assessment, literature searches were performed subsequent to the Panel's review. If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate. There were no studies that would change the conclusions of this Assessment.

Previous Assessment. In September 1997, the MAP reviewed evidence on both bilateral and unilateral DBS and concluded that unilateral DBS of the thalamus for patients with disabling, medically unresponsive essential tremor or disabling, medically unresponsive tremor due to Parkinson's disease met the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria. Bilateral DBS of the thalamus did not meet the TEC criteria as only 66 cases had been reported at the time and outcomes were not separated by unilateral or bilateral procedures.

FORMULATION OF THE ASSESSMENT

Patient Indications

Bilateral DBS of either target (STN or GPi) may be indicated in patients with idiopathic Parkinson's disease,

- in whom parkinsonian symptoms are responsive to levodopa, and
- whose disease is complicated by motor complications that cannot be controlled with medications (complications such as “on-off” fluctuations with periods of severe immobility, presence of “off” period dystonic posture, or levodopa-induced dyskinesias uncontrolled with available pharmacologic agents).

Contraindications include:

- significant cognitive dysfunction,
- active psychiatric symptoms,
- other neurologic or unstable medical disorders.

Technologies to be Compared

Bilateral STN DBS and bilateral GPi DBS will be compared with continued pharmacologic management and with unilateral pallidotomy.

Health Outcomes

Key beneficial health outcomes include:

- reduction in severity of motor fluctuations and in the amount of time spent in the “off” state each day;
- amelioration of parkinsonian motor disability in the “off” condition as measured by UPDRS motor and ADL scores;
- amelioration of motor disability during “on” periods and reduction in severity of levodopa-induced dyskinesia,
- reduction in the required daily dose of levodopa or its equivalents.

Other possible beneficial health outcomes include improvement in specific cardinal symptoms of Parkinson's disease (tremor, rigidity, bradykinesia, gait disturbance), in sleep quality, appetite, cognitive function and mood.

Adverse outcomes are those:

- conditions related to the surgical procedure (hemorrhage, ischemic lesions, seizures, adverse cognitive effects, complications of general anesthesia);
- conditions associated with the device (displacement or migration of the electrode, skin erosion or infection, mechanical problems with the electrical system such as battery failure and fracture of implanted materials);
- conditions associated with stimulation (effects such as paresthesia, muscle contraction, pain, abnormal eye movement, adverse cognitive effects).

Specific Assessment Questions

For patients with medically refractory Parkinson's disease (characterized by "on-off" fluctuations, severe immobility, and/or levodopa-induced dyskinesias uncontrolled with available pharmacologic agents):

- does chronic bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) improve health outcomes?
- does chronic bilateral deep brain stimulation (DBS) of the globus pallidus interna (GPI) improve health outcomes?

Neuropsychological outcomes of DBS are reviewed in a separate section that includes evidence from studies of either target (STN or GPI).

REVIEW OF THE EVIDENCE

Deep Brain Stimulation of the Subthalamic Nucleus (STN)

Fourteen published studies examining bilateral DBS of the STN met the criteria for inclusion in this Assessment (Table 1). Studies excluded from Assessment analysis are listed in Table 2. Among included studies is one large multicenter trial (Deep Brain Stimulation for Parkinson's Disease Study Group 2001) and one large case series (Benabid et al. 2000a). The remaining 12 reports consist of smaller single-center studies of fewer than 25 patients.

Number of patients. This body of literature is complicated by the possibility that outcomes from some patients may have been published in more than one of the included reports.

For example, Kumar and colleagues (1998a) state in their report that their patients were also participants of the larger multicenter trial. It should be noted that authors of the Grenoble case series (Benabid et al. 2000a) and of four smaller studies (Rodriguez-Oroz et al. 2000; Moro et al. 1999; Volkmann et al. 2001; Krause et al. 2001) are also listed among investigators in the DBS Study Group. Furthermore, it will be assumed that the 24 patients described by Fraix et al. (2000) have been included among the 51 patients in the Benabid et al. (2000a) report.

If no patients (other than those in the Kumar et al. and Fraix et al. studies) described in any single-center study are included in the recently published multicenter trial, there are then outcomes for 287 patients with advanced Parkinson's disease who have been treated with bilateral DBS of the STN. If, on the other hand, the DBS Study Group investigators (2001) have published outcomes from all or some of the same patients in both the multicenter trial report and in their single-center case series, then the studies listed in Table 1 describe outcomes for as few as 186 patients. For the purposes of this Assessment, it will be assumed that all DBS Study Group investigators have published outcomes from the same patients in both single-center

Table 1. Study descriptions: Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) for Parkinson’s disease

Author Center Year	Study design	Comparison	N Patient characteristics	Subject age Length of follow-up (F/U)	Outcomes examined	Authors’ Conclusions
DBS for PD Study Group 2001 18 centers between July 1995 and July 1999	Prospective multicenter trial: 1) double-blind randomized crossover evaluation of stimulation on versus stimulator off at 3 mos; 2) unblinded evaluation in four possible conditions at 6 mos; 3) home diaries	1) with stimulator and medications discontinued overnight, stimulator on versus stimulator off; 2) 4 conditions: off meds with no stimulation; off meds with stimulation; on meds with no stimulation; on meds with stimulation.	102 enrolled in bilateral STN group 96 received bilateral STN implants (6 experienced complications during first surgical procedure) 91 participated in double blind crossover evaluation and 6 month follow-up, (3 withdrew consent, 2 experienced infected leads) criteria for inclusion: presence of at least 2 cardinal features of PD; a good response to levodopa; score no lower than 30 points on UPDRS when without medication for 12 hours (scores on UPDRS range from 0 to 108, with higher values indicating more severe symptoms); motor complications not controlled by pharmacologic therapy	age: 30 to 75 years F/U: 3 months and 6 months	UPDRS assessment of motor function activities of daily living dyskinesia Home diary: documenting of status at 30 minute intervals during the 2 days before each visit (1 weeks before and 1, 3, 6 months after implantation) in terms of poor mobility (“off”), good mobility without dyskinesia (“on” without dyskinesia), and good mobility with dyskinesia (“on” with dyskinesia). Patient and investigator assessment of global effect of therapy after conclusion of study. Levodopa dose equivalents, mean dosage before and after surgery	double-blind crossover evaluation 3 months after implantation: a significant treatment effect associated with stimulation (p<0.001) and no significant carry-over effects (p=0.38); a mean improvement of 43% and a median improvement of 49% in the UPDRS score (off medication) (p<0.001); unblinded evaluation 6 months after implantation: significant improvement in the UPDRS motor score in the off-medication state at each visit; smaller but significant benefits with stimulation in the on-medication state; significant improvement in tremor, bradykinesia, gait postural stability, and activities of daily living with stimulation in the off-medication state; home diary accounts: an increase in percentage of time with good mobility without dyskinesia during the waking day from 27% to 74% between baseline and 6 months post-implantation (p<0.001) a decrease in time with poor mobility (“off” time) from 49% of waking day to 19% of waking day; mean dyskinesia scores: improved from 1.9 +/- 1.1 at baseline to 0.8 +/- 0.8 at 6 months (p<0.001) daily levodopa dose equivalents: reduced (mean 1218.8 +/- 575 mg at baseline to 764.0 +/- 507 mg at 6 months (p<0.001) global assessment: severe disability, noted at baseline in 74% by physicians and in 77% by patients, was described by 15% of patients and 23 % of physicians 6 months after implantation

Table 1. Study descriptions: Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) for Parkinson's disease (cont'd)

Author	Study design	Comparison	N Patient characteristics	Subject age, Follow-up (F/U)	Outcomes examined	Authors' Conclusions
Lopiano et al 2001 Turin, Italy	Clinical series	Presurgical baseline medical management off meds and on meds compared to off meds with stimulation; and on meds with stimulation	20 patients Advanced PD with motor fluctuations and drug-related dyskinesia, normal MRI of the brain, normal neuropsychological assessment, and an adequate motor response to supramaximal dose of levodopa (defined as a 40–50% improvement in UPDRS motor score after levodopa challenge)	Mean age: 61.2 years F/U; 3 months (n=20) and 12 months (n=8)	At 3 months, (n=20) UPDRS motor scores (part III) Levodopa daily dose equivalents, mean daily dosage reduction after surgery Neuropsychological assessment	UPDRS motor scores: compared to preoperative off-med state, significant improvement in the medication off state with stimulator on (mean preoperative score 58, mean postsurgical score 25.7 at 3 months, 25.1 at 1 year, p<0.05) Reduction in mean daily levodopa dosage from 954 mg daily preoperatively to 160 mg daily at 3 months and 228.1 mg at 12 months. No significant differences in pre- and postoperative neuropsychological assessment.
Broggi et al. 2001 Milan, Italy	Clinical series	Presurgical medical management	17 patients consecutive patients with advanced PD complicated by motor fluctuations and dyskinesias pre-op MRI showed cerebral atrophy in 5, white matter vascular disease in 3, and small frontal meningioma in 1.	Mean age: 59 +/-6 years, range 48-68) F/U: 6-18 months (Mean 8.2 months)	UPDRS motor and ADL scores Percentage of daily time spend in “off” and dyskinetic states Change in daily levodopa dosage	At last examination mean UPDRS ADL and motor scores had improved by 30% in the off-medication state with stimulation. There was a mean 50% reduction in daily “off” time Peak dyskinesias and early morning dystonia improved relative to medication reduction. Hypophonia worsened in 3 patients, persistent postoperative supranuclear oculomotor palsy occurred in 1, and temporary nocturnal confusion occurred in 3.

Table 1. Study descriptions: Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) for Parkinson’s disease (cont’d)

Author	Study design	Comparison	N Patient characteristics	Subject age, Follow-up (F/U)	Outcomes examined	Authors’ Conclusions
Volkman et al. 2001 Cologne, Germany	Clinical series	Presurgical medical management	16 patients 16 consecutive patients in a series of 57 patients treated with DBS GPi or STN between 1996 and 2000; advanced idiopathic PD with motor fluctuations and restricted “off” state mobility	Mean age: 56.6 +/- 9.4 years F/U: 12 months	UPDRS motor UPDRS ADL UPDRS subscores for bradykinesia, rigidity, tremor, posture and gait, speech and swallowing, dyskinesia Levodopa equivalent daily dose Neuropsychiatric evaluation Electrical power of stimulation	STN stimulation improved “off” period motor symptoms, dyskinesias, and fluctuations. STN stimulation reduced medication requirements by 65%. STN stimulation required significantly less electrical power, but required more intensive postoperative monitoring for complications of levodopa withdrawal (transient abulia, anhedonia, depression) and emergence of certain PD symptoms alleviated less by stimulation than by drug therapy (hypophonia, hypersalivation).
Krause et al. 2001 Heidelberg, Germany	Clinical series	Presurgical medical management	12 patients 12 consecutive patients in a series of 33 patients treated with DBS of the GPi or STN since 1995.	Mean age: 58.7 years (range 45-69) F/U: 3, 6, and 12 months	UPDRS mentation (item 1-4) UPDRS motor (18-31) UPDRS ADL (item 5-17) UPDRS complications (items 40-42) Schwab and England Hoehn and Yahr Obeso dyskinesia intensity scale Levodopa equivalent dosage changes	Stimulation improved the UPDRS motor scores significantly in the medication off state Stimulation of the STN suppressed tremor in both the “on” and “off” states, but reached statistical significance only in the “off” state. Stimulation of the STN seemed to reduce UPDRS dyskinesia scores secondarily by reducing drug intake. Levodopa intake remained stable (about 400 mg per day), but dopamine agonists were significantly reduced (from 542 mg to 360 mg levodopa equivalent) as were COMT inhibitors (from 100 mg to 30 mg)
Scotto di Luzio et al. 2001 Florence, Italy	Clinical series	Presurgical medical management med-off and med-on state compared to postop med-off with stimulation and med-on with stimulation	9 patients (STN group= 9/14 patients) Advanced idiopathic PD, complicated by medication-refractory motor fluctuations and levodopa-induced dyskinesias, Hoehn and Yahr stage 3 when off medications, normal brain MRI and MMSE 24, age less than 70 years	Mean age: 54.9 years Mean follow-up 19.6 months, all followed for at least 12 months	UPDRS motor scores (part III) Schwab and England scale Hoehn and Yahr score Mini mental state examination Dyskinesia scale (abnormal involuntary movement scale and items 32,33,34 of UPDRS.) Change in daily levodopa dose	UPDRS motor score in the off-medication state improved from preoperative off-medication baseline by 56.6% at 12 months, p<0.0001. Schwab and England scale and Hoehn and Yahr score improved progressively by 156% and 33.3% respectively at 12 months. On-medication with stimulator-on condition showed significant decrease in levodopa-induced dyskinesia (73.9% improvement at 12 months), and motor score improvement of 38.5% Levodopa dosage was decreased by 37.2% at 12 months

Table 1. Study descriptions: Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) for Parkinson’s disease (cont’d)

Author	Study design	Comparison	N Patient characteristics	Subject age, Follow-up (F/U)	Outcomes examined	Authors’ Conclusions
Benabid et al 2000a Grenoble, France	Clinical series (bilateral =105, unilateral =5)	Presurgical medical management	51 patients (followed for 12 months or more) Idiopathic PD with motor fluctuations and dyskinesias and no tendency to fall spontaneously at time of best “on”-motor period. UPDRS “off”-period motor score of at least 30/108 (range 40–80/108) in whom a supra-threshold morning dose of levodopa decreases the score by at least 50% Good general health	55 +/- 8 years (first 57 patients) F/U: 12 months (n=51) 110 patients followed for 1-83.6 months, mean 29.1 months +/- 18.9 months	At 12 months: Motor effects as measured by: 1) UPDRS III total score (max score 108), subscores for limb akinesia (items 23-25, max score 32) Rigidity (item 22, max score 20), Tremor (item 20, 21, max score 28), Speech (item 18, max score 4), Gait (item 30, max score 4) Axial subscore (Part III, item 29, 30, +Part II items 13-15, max score 20) 2) ADL UPDRS II total score (max score 52), Schwab and England score (max 100%) 3) Motor complications: UPDRS IV total score (max score 23); and subscores for duration of dyskinesia (item 32, max score of 4); dyskinesia disability (item 33, max score 4); Presence of morning dystonia (item 35, max score of 1); and duration of off-periods (item 39, max score 4)	This study confirms in more than 50 patients followed for at least one year that bilateral STN stimulation dramatically improved the severity and reduced the duration of off-period symptoms in patients with PD. Mean motor scores remained improved by more than 60% at 1 year (n=51) and 3 years (n=16); And by more than 50% for up to 5 years (n=4) Tremor almost disappeared. Activities of daily living also clearly improved and patients became independent for most activities Speech was less improved than other motor symptoms “Off”-period dystonia was almost totally suppressed. Drugs were decreased to at least half of the initial dosage and this reduction persisted up to 5 years. In the off-drug, stimulator off condition, there was a slight but non-significant improvement in motor scores that persisted for up to 5 years
Fraix et al. 2000 Grenoble, France	Clinical series	Presurgical medical management	24 patients consecutive patients with severe PD and motor complications some aspects of outcomes may have been included in Benabid et al. 2000a	Mean age 55.7 F/U: 3 months and 12 months	UPDRS motor scores During levodopa challenge before surgery and after surgery: Dyskinesia duration Dyskinesia disability “Off” period dystonia Onset-of-dose dyskinesia Peak-dose dyskinesia Levodopa daily dose change	<u>In the off-drug condition:</u> UPDRS motor scores improved from the preoperative 54.4 (+/- 13) to 49.3 (+/- 19) with stimulator off, 18.2 (+/-8) with stimulator on. <u>In the on-drug condition:</u> UPDRS motor scores changed from 13.3 (+/-6) before surgery to 17.5 (+/-9) in the off stimulation condition, 11.2 (+/- 7.7) in the on stimulation condition 75% (18 of 24) of patients no longer had dyskinesia at the 12 month follow-up. During levodopa challenge, onset-of-dose and peak-dose dyskinesia significantly improved. “Off period” dystonia scores decreased with stimulation at 3- and 12-months, but returned immediately when stimulators were switched off. Levodopa mean daily dosage decreased (952 +/- 509 mg preoperatively to 184 +/- 190 mg at 12 months

Table 1. Study descriptions: Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) for Parkinson’s disease (cont’d)

Author	Study design	Comparison	N Patient characteristics	Subject age, Follow-up (F/U)	Outcomes examined	Authors’ Conclusions
Houeto et al. 2000 Paris, France	Clinical series	Presurgical medical management	23 patients Consecutively treated surgical patients with disabling PD, good response to levodopa but severe motor fluctuations	Age: 53 +/- 2 years	At 6 months: 1. motor disability, 2. levodopa-induced motor fluctuations, 3. dyskinesias, 4. daily dose of levodopa.	All 4 outcomes measures showed significant improvement (67%, 78%, 77%, 61%): “The beneficial effects of subthalamic stimulation depend on 1. The criteria used for patient selection, 2. The precision with which the subthalamic nucleus is targeted (dependent on the 3-dimensional magnetic resonance imaging and the intraoperative electrophysiologic and clinical assessments) and 3. The long-term postoperative adjustment of stimulation variables.”
Rodriguez-Oroz et al. 2000 Pamplona, Spain	Clinical series, randomized to double-blind assessment at the 3-month follow-up	Presurgical medical management	15 patients Diagnosis of PD (UK Brain Bank criteria) with: motor fluctuations, dyskinesias or gait disorders inadequately controlled with available medications	Age: 42-69 years F/U: 12 months	At 12 months (in 15 patients) 30-36 months (in 9 patients) Motor disability (UPDRS motor section part III) Activities of daily living (UPDRS part II) Schwab and England scale CAPIT dyskinesia scale Subjective assessment of global effect of therapy	“The severity of ‘off’ episodes, as assessed by the UPDRS, was drastically reduced by 74% at 12 months and dyskinesia scores (DRS) decreased. The levodopa daily dose was reduced by 55% at 12 months.” “Nine patients have been followed for 3 years with maintained efficacy in the UPDRS ‘off’ score and the dyskinesia score.” “The existence of a learning curve for this procedure should be taken into account when initial results are evaluated.”
Molinuevo et al. 2000 Barcelona, Spain	Clinical series	Presurgical medical management	15 patients Consecutively treated patients with PD and: disabling motor fluctuations and/or LID refractory to medical management; good response to supra-threshold dose of levodopa, age less than 75	Age: 60.9 +/- 6.8 years (range 52-74) F/U: 6 months	At 6 months: UPDRS motor off medication, axial symptoms, bradykinesia, rigidity, tremor, dyskinesia severity; levodopa dose.	“Bilateral STN stimulation safely improves all parkinsonian symptoms, decreases or eliminates the need for levodopa, and ameliorates motor fluctuations and dyskinesias” Patients with cognitive impairment, major depression, marked cerebral atrophy on neuro-imaging studies were excluded from this study.
Moro et al. 1999 Rome, Italy	Clinical series	Presurgical medical management	7 patients Idiopathic PD Disabling motor fluctuations (prolonged and unpredictable “off” periods), on state dyskinesia, Hoehn and Yahr stage >III in the practically defined “off” condition.	Mean age 57.4 +/- 5.5 years F/U: 16.3 +/- 7.6 months	At 16.3 +/- 7.6 months Motor disability in “off” (UPDRS III) Activities of daily living (UPDRS II) Schwab and England scale Dyskinesia in “on” state Weight, appetite change, night sleep; levodopa equivalent daily dose Neuro-psychological evaluation: Mini-Mental State Examination, test of verbal memory, fluency, intelligence	Parkinsonian features improved in all patients – the greatest change seen in rigidity, then tremor, followed by bradykinesia. Night sleep improved in all, insomnia resolved in 5. Mean weight gain at last follow-up was 19%. No neuro-psychological changes <u>Exclusions:</u> heart pacemaker; mild parkinsonian features; unstable drug regimen; severe cognitive impairment; ongoing psychiatric problems, prior brain surgery, inability to comply with protocol.

Table 1. Study descriptions: Bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) for Parkinson’s disease (cont’d)

Author	Study design	Comparison	N Patient characteristics	Subject age, Follow-up (F/U)	Outcomes examined	Authors’ Conclusions
Burchiel et al. 1999 Portland, OR USA	Prospective randomized blinded comparison (STN=6 GPi=4)		6 patients	Age: 62.8 +/- 12 years	At 12 months: UPDRS, dyskinesia scale, Schwab and England ADL Neuropsychological test battery <ul style="list-style-type: none"> visuomotor processing (Symbol Digits Modalities Test) memory (Controlled Oral Work Association Test, Hopkins Verbal Learning Test, Memory Assessment Scale: Names and Faces) attentional capacity (Digit Span), cognitive impairment (Cognitive Difficulties Scale) auditory span (Sentence Repetition) mood (Beck Depression Inventory) 	In the “off” condition, both DBS GPi and DBS STN groups demonstrated similar response, with approximately 40% improvement in the UPDRS motor scores Rigidity, tremor, and bradykinesia improved in both groups. In the “on” condition, UPDRS motor scores were more improved by GPi stimulation than by STN stimulation. LID was reduced by DBS at either site, but medication requirement was reduced only in the STN group. Memory, attention, and visuomotor processing remained unchanged. Scores on Cognitive Difficulty Scale improved compared to on medication baseline. Beck Depression Inventory score improved 49% among all patients (from 14.3+/- 6.2 to 7.3 +/- 3.2, P=0.02, Wilcoxon signed rank test).
Kumar et al. 1998a Toronto, Canada	Clinical series	Presurgical medical management	7*** (7 of 9 consecutively operated patients***)	Age: 67 years (range: 55-75 years) F/U: 6 months	At 6 months: UPDRS motor scores Tremor Bradykinesia (timed tapping test) Ability to walk UPDRS ADL scores	This cohort of late-stage, disabled patients with PD “obtained approximately a 65% reduction in “off” period parkinsonism, a 40% improvement in on period parkinsonism, and an 85% reduction in levodopa-induced dyskinesia.”

***Kumar et al. 1998a: 2 of the 9 patients operated during the study time period were excluded from evaluation due to pre-existing mild cognitive dysfunction and development of intraoperative paranoia causing a halt of the surgical procedure before electrode implantation (1) and perioperative hardware infection from hematogenous spread from an infected intravenous catheter, necessitating removal of the DBS systems.

UK BB- United Kingdom Brain Bank criteria; LID: levodopa-induced dyskinesia; NS: not statistically significant; NA: not applicable; stat: statistically; w/d : withdrawn

Table 2 Trials of DBS of the STN or GPi excluded from main analysis

Robertson et al. 2001 Assessments of axial motor control during deep brain stimulation in parkinsonian patients	addresses two outcomes with specialty evaluation methodology
Katayama et al. 2001 Double-blinded evaluation of effects of pallidal and subthalamic nucleus stimulation of daytime activity in advanced Parkinson's disease	outcomes of bilateral and unilateral procedures not analyzed separately
Faist et al. 2001 Effect of bilateral subthalamic nucleus stimulation on gait in Parkinson's disease	addresses single outcome
Dromey et al. 2000 An investigation of the effects of subthalamic nucleus stimulation on acoustic measures of voice	addresses single outcome with specialty evaluation methodology
Vingerhoets et al. 1999 Cognitive outcome after unilateral pallidal stimulation in Parkinson's disease	examines unilateral procedures only
Kumar et al. 1998b Pallidotomy and deep brain stimulation of the pallidum and subthalamic nucleus in advanced Parkinson's disease	outcomes of bilateral and unilateral procedures not analyzed separately
Krack et al. 1998a Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease	STN data included a more recent report (Benabid et al. 2000a) from the same study center. Thus, only the GPi data from this trial are included in the Assessment
Krack et al. 1998b Opposite motor effects of pallidal stimulation in Parkinson's disease	outcomes of bilateral and unilateral procedures not analyzed separately
Gross et al. 1997 High-frequency stimulation of the globus pallidus internalis in Parkinson's disease; a study of seven cases	examines outcomes after unilateral procedures only
Siegfried and Lippitz 1994 Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach for alleviating all parkinsonian symptoms	uses non-standard evaluation methodology rather than UPDRS or CAPIT system

reports and in the DBS Study Group multicenter trial. This assumption that the actual number of patients treated with bilateral DBS of the STN is the more conservative figure (186 patients) will be reflected in the summary discussion.

Study design. There are no large prospective, randomized studies with long-term follow-up of bilateral DBS of the STN for treatment of advanced Parkinson's disease.

Only one small pilot study applies a prospective, randomized, double-blind trial design (Burchiel et al. 1999). In this small study, 10 patients were prospectively randomized to bilateral DBS of either the STN or the GPi and evaluated with both patient and examining neurologist blinded to the stimulation site. Patients were followed for 12 months.

The remaining 13 studies, including the multicenter trial, consist of retrospective case series. They describe, for the most part, thorough but brief follow-up periods of 3 to 12 months. Most compare postoperative clinical outcomes with presurgical baseline states. The multicenter trial examines, in double-blind randomized fashion, a crossover evaluation of motor function in the off-medication state with stimulation on versus stimulation off.

Subject blinding is problematic in studies of DBS because the adverse effects of and clinically obvious response to stimulation usually reveal the study condition. Benabid and colleagues (2000b) state that "subjects were blinded to the stimulation condition," but whether blinding was effective is not known. In one small double-blinded evaluation of DBS, Kumar and colleagues (1998a) found all patients were able to guess which assessments were performed with the stimulator on. In another trial (Rodriguez-Oroz et al. 2000), results of motor subscores with the "stimulator on" versus those with the "stimulator off" were compared in a double-blind assessment of 9 patients at 3 months after surgery, but a description of blinding techniques as well as other details (e.g., how the 9 patients were selected for double-blind assessment, their medication state during evaluation, etc.) is lacking.

In the DBS Study Group multicenter trial (2001), investigators and patients were unaware of whether stimulation was on or off during the crossover evaluation of motor function after overnight withdrawal of both medication and stimulation. Protocol measures to preserve integrity of the blinding included, in addition to blinding of physician and patient as to stimulation status, use of a randomization coordinator who was independent from the evaluation and who adjusted the stimulators with a console programmer rather than a magnet (personal communication, B. Handke, RN, Medtronic Corp, October 24, 2001). Whether patients might have correctly guessed stimulation status is not known.

Patient selection criteria. All 14 studies uniformly require that study patients have a diagnosis of advanced Parkinson's disease with medication-induced complications, such as motor fluctuations and/or dyskinesia. A requirement of certain additional conditions, such as a normal MRI of the brain, and normal neuropsychological assessment, is mentioned only in some studies.

While it cannot be known whether patients at various study centers had truly similar disease severity, it is notable that all studies used quite similar selection criteria, requiring a diagnosis of idiopathic Parkinson's disease, a response to levodopa, and disabling motor fluctuations and/or

dyskinesia despite all drug therapy. The mean age of patients in the study cohorts at the time of implantation ranged from 53 years (Paris) to 67 years (Toronto). Patients as young as 41 and as old as 75 years underwent the procedure.

In one report, investigators note that a significant number of patients with abnormal MRI findings present on preoperative examination were admitted to the study (Broggi et al. 2001). While the study patients experienced improvement after DBS electrode implantation, results were suboptimal in 3 patients with preoperative MRI evidence of cerebral vasculopathy. The authors advise that bilateral DBS should not be undertaken in patients who have abnormal MRI of the brain.

Criteria for exclusion in the DBS Study Group multicenter trial (2001) were major psychiatric illness, cognitive impairment, other substantial medical problems or laboratory abnormalities, presence of a cardiac pacemaker and previous intracranial surgery. Preoperative MRI of the brain was not included in the study protocol.

Duration of follow-up. Follow-up duration in the majority of reports is from 6 months (n=151) to 12 months (n=116) and ranges from 3 to 60 months.

Benabid and colleagues (2000a) record the longest follow-up, with 4 patients followed-up for 5 years after implantation of DBS electrodes. They state that a levodopa dosage reduction of at least 50%, accompanied by improvements of 50-70% in motor function and gait, persisted for 4 years before deteriorating after 5 years, in these 4 patients.

Rodriguez-Oroz and colleagues (2000) have followed-up 9 patients for 36 months after bilateral STN DBS. Their comparison with assessments done at 12 months show no deterioration in treatment benefit of DBS.

Outcomes Examined. In most studies, treatment outcome is assessed by performance on a battery of assessments (UPDRS, CAPIT, Schwab and England scale, timed tests and walking tasks, and dyskinesia scales) with the “stimulator on” in the medication “on” or “off” state (See Table A, Appendix, for definitions of “off” and “on,” and the Background section for descriptions of outcome assessment tools). The preoperative baseline evaluation in the “on” and “off” medication states is used for comparison. Few studies examine postoperative “stimulator off” in the medication “on” or “off” states to detect the possible micro-ablative effects of electrode insertion.

Of these outcome measures, reference is made most often to the Unified Parkinson’s Disease Rating Scale or UPDRS, which provides a comprehensive inventory of symptoms and signs of Parkinson’s disease(see Appendix).

Outcomes are measured in the “off” and “on” medication state. A patient’s state is defined as the “off” medication state if testing is conducted before the patient has taken a first morning dose of levodopa and at least 12 hours after taking the last dose of levodopa on the previous day. This convention is intended to replicate the severity of symptoms patients experience in their daily lives as levodopa becomes less effective and motor fluctuations become more frequent and

severe. The “on medication” state is, by convention, defined as the best test scores recorded during the day while the patient is taking levodopa. In some studies, “on” scores are measured during a “best ‘on’ state” created with a suprathreshold dose of levodopa (Freed et al. 2001; Benabid et al. 2000a).

Authors’ comments. Some studies provide comment about special aspects of DBS. For example, Volkmann and colleagues (2001) observed that STN stimulation required less electrical power than GPi stimulation, an advantage, presumably, in that battery replacement might be less frequent. They also noted that STN stimulation required more intensive postoperative outpatient monitoring for certain complications of levodopa withdrawal (such as depression) and the emergence of some parkinsonian symptoms (such as hypophonia and hypersalivation), that are alleviated less by stimulation than by medical therapy. Similarly, Broggi and colleagues (2001) found that hypophonia appeared to worsened with bilateral DBS of the STN in 3 of their 17 patients. Benabid and colleagues (2000a) also noted that speech was less improved than other motor symptoms and that approximately 20% (11/51) of patients undergoing DBS of the STN experienced postsurgical onset or worsening of eyelid apraxia.

Key outcomes for this subset of Parkinson’s patients with advanced disease focus primarily upon disabling motor symptoms associated with either complications of medical therapy (motor fluctuations or dyskinesia) or loss of the effect of levodopa (increasing “off” period duration and severity).

Table 3 lists results from the 14 studies for each of the following four broad key outcomes with stimulation of the STN:

- A. Reduction in fluctuations in motor function
- B. Improvement in “off” condition UPDRS scores (motor and ADL)
- C. Improvement in “on” condition UPDRS scores (motor and levodopa-induced dyskinesia)
- D. Reduction in daily levodopa dosage requirement.

Other single-symptom outcomes, such as effect of DBS upon tremor, are less frequently examined. These outcomes are presented in the fifth column.

In most studies, treatment outcome is assessed by performance on a battery of assessments (UPDRS, CAPIT, Schwab and England scale, timed tests and walking tasks, and dyskinesia scales) with the stimulator on in the medication “on” or “off” state. The preoperative baseline evaluation in the “on” or “off” medication states is used for comparison. Few studies examine postoperative stimulator off in the medication “on” or “off” states to detect the possible microablative effects of electrode insertion.

The data presented in Table 3 consistently demonstrate that bilateral DBS of the STN relieves certain symptoms of Parkinson’s disease, particularly motor fluctuations, “off” state immobility, and “on” state dyskinesias. DBS of the STN also permits (or even requires) reduction in, and in some cases elimination of, the need for, levodopa or equivalent medication dosage.

Table 3. Key outcomes, studies of bilateral STN stimulation

Author, Center, Year, N	A Reduction in fluctuations in motor function, length of time in “off” state, “off” period dystonia, with stimulation?	B Improvement in “off” period UPDRS scores with stimulation? % improvement in UPDRS score with stimulation during periods when levodopa is not effective (“off” periods)		C Improvement in on-medication dyskinesia and motor UPDRS scores? % improvement with stimulation	D Levodopa dosage reduced? Yes/No	Other Improvement in “off”-period cardinal symptoms, (UPDRS scores for rigidity, tremor, gait, S/E, H/Y scales) with stimulation?	
	Reduced motor fluctuations	“off” Motor (UPDRS III)	“off” ADL (UPDRS II)	“on” Motor (UPDRS III)	Levodopa-induced Dyskinesia (UPDRS IV)	Levodopa dose reduced?	“off” Cardinal symptoms
DBS Study Group 2001 European and North American centers n=102	YES Percentage of time with good mobility and without dyskinesia during the waking day increased from pre-op 27% to 74% (p<0.001) Percentage of time with poor mobility decreased from 49% to 19% (p<0.001) (home diary evaluation at 6 months compared with baseline)	YES 43% (mean) (n=51, comparison with stimulator off, blinded evaluation at 3 mos.) p<0.001 51% (mean) (n=91, comparison to baseline, unblinded evaluation at 6 months) p<0.001	YES 44% (n=91, comparison with baseline, unblinded evaluation at 6 months, Mean score decreased from 28.4 to 16.0) p<0.001	YES 25.8% (n=91, comparison with baseline, unblinded evaluation at 6 months) p<0.001	YES Dyskinesia score reduced by 57 % (mean score decreased from 1.9 +/- 1.1 to 0.8 +/- 0.8 at 6 months) p<0.001 Percentage of time during waking hours with good mobility but with dyskinesia (“on” with dyskinesia) decreased from 23% to 7% (home diary evaluation at 6 months compared with baseline)	YES Daily levodopa dose equivalents reduced from mean of 1218.8 +/- 575 mg at baseline to 764.0 +/- 507 mg at 6 months p<0.001	YES Significant improvement (i.e., decreases) in UPDRS cardinal symptom mean scores: Tremor: 7.3 +/- 6.5 to 1.5 +/- 2.2, p<0.001 Rigidity: 10.6 +/- 3.9 to 4.4 +/- 3.3, p<0.001 Bradykinesia: 18.6 +/- 6.0 to 10.7 +/- 6.9, p<0.001 Gait: 2.7 +/- 1.1 to 1.2 +/- 1.0, p<0.001 (All comparisons with baseline, unblinded evaluation at 6 months)
Lopiano et al. Turin, Italy 2001 n=20	“improved” (not quantified)	YES 57% (mean score decreased 58 to 25.7) (p<0.05)	Not reported	(decreased mean score 19.8 to 14.3)	Yes (not quantified)	YES Reduced by 74% at 3 months	Not reported

Table 3. Key outcomes, studies of bilateral STN stimulation (cont'd)

Author, Center, Year, N	A Reduction in fluctuations in motor function, length of time in “off” state, “off” period dystonia, with stimulation?	B Improvement in “off”-period UPDRS scores with stimulation ? % improvement in UPDRS score with stimulation during periods when levodopa is not effective (“off” periods)		C Improvement in on-medication dyskinesia and motor UPDRS scores? % improvement with stimulation	D Levodopa Dosage reduced? Yes/No	Other Improvement in “off”-period cardinal symptoms, (UPDRS scores for rigidity, tremor, gait, S/E, H/Y scales) with stimulation?	
Europe	Reduced motor fluctuations	“off” Motor (UPDRS III)	“off” ADL (UPDRS II)	“on” Motor (UPDRS III)	Levodopa-induced Dyskinesia (UPDRS IV)	Levodopa dose reduced?	“off” Cardinal symptoms
Broggi et al. Milan, Italy 2001 n=17	YES Percentage of time with poor mobility decreased from 52% of the day to 15% (p=0.0015) Percentage of time in dyskinetic state decreased from 48% to 25% (p=0.009)	YES 34% Mean score decreased from 52 (range 24–79) to 33 (range 15–55) p=0.027	YES 32%	YES 18% (mean score decreased from 15 (range 3–72) to 10 (range 0–34) p=0.009	YES, permitting a 50% improvement in UPDRS ADL scores during on medication state	YES Reduced from mean 1018 mg/day among 16 patients to 681 mg/day among the 14 who continued levodopa	Not reported
Volkman et al. Cologne, Germany 2001 n=16	Not reported	YES 60% Mean baseline motor score decreased from 56.4 to 22.4 at 12 months, p<0.005	YES Mean baseline ADL score decreased from 28.8 to 12.6 at 12 months, p<0.001	NS Mean baseline “on” motor score decreased from 15.1 to 16.4 at 12 months, mean baseline “on” ADL score 13.7→11.0 at 12 months)	YES Mean baseline “on” dyskinesia score decreased from 2.4 to 0.4 at 12 months, p< 0.001	YES Levodopa-equivalent daily dose reduced from baseline 913 +/- 479 mg/day to 335 +/- 221 mg/day at 12 months P<0.001	YES Cardinal symptoms during off med state improved significantly Preoperative baseline off med UPDRS scores versus off med with stimulator on at 12 months: Tremor: 0.9→0.1 Rigidity 2.4→0.6 Bradykinesia 2.5→ 1.3 Gait, posture 2.7→1.1, P<0.001 for each
Krause et al. Heidelberg, Germany 2001 n=12	YES 64% (UPDRS items 36-39: mean score decreased from 4.2 to 1.5, no p value given)	YES 50% (mean score decreased from 58 to 29, no p value given)	YES 26% (Mean score decreased from 23.7 to 17.5, no p value given)	Yes 25% (Mean score decreased from 25 to 20, no p value given)	YES 58% (UPDRS items 32-35: mean score decreased from 7.3 to 3.1) however, using Obeso dyskinesia score, there was no difference in dyskinesia intensity in the on med state between stim off and stim on.	Daily mean levodopa intake remained the same (~400 mg/day), but dopamine agonist intake was reduced 33% and COMT inhibitor intake was reduced ~60%.	YES Tremor during the “off” state improved significantly with the stimulator on (UPDRS items 20, 21: mean score decreased from 8 to ~1.6, no p value given)

Table 3. Key outcomes, studies of bilateral STN stimulation (cont'd)

Author, Center, Year, N	A	B		C		D	Other
	Reduction in fluctuations in motor function, length of time in “off” state, “off” period dystonia, with stimulation?	Improvement in “off”-period UPDRS scores with stimulation ? % improvement in UPDRS score with stimulation during periods when levodopa is not effective (“off” periods)		Improvement in on-medication dyskinesia and motor UPDRS scores? % improvement with stimulation		Levodopa Dosage reduced? Yes/No	Improvement in “off”-period cardinal symptoms, (UPDRS scores for rigidity, tremor, gait, S/E, H/Y scales) with stimulation?
	Reduced motor fluctuations	“off” Motor (UPDRS III)	“off” ADL (UPDRS II)	“on” Motor (UPDRS III)	Levodopa-induced Dyskinesia (UPDRS IV)	Levodopa dose reduced?	“off” Cardinal symptoms
Scotto di Luzio et al. Florence, Italy 2001 n=9	Yes (not quantified)	YES 44.7% at 3 months, 53% at 6 months, 56 % at 12 months (p<0.0001 for baseline versus 12 months)	Not reported	YES 38.5%	YES Decreased by 84% at 3 months, 84% at 6 months, 74% at 12 months	YES Reduced by 37% at 12 months	Not reported
Benabid et al. Grenoble, France 2000a n=51	YES	YES 61% after 1-3 years (n=51) (p<0.0001)	YES 58–64% at 1 year (p<0.0001)	NS compared to presurgical on medication score	YES Dyskinesia duration, disability, morning dystonia scores improved: range 50-100%	YES At 24 months, reduced >60% of pre-op dosage	YES Tremor: range 63–100% Rigidity: range 50–76% Akinesia : range 43–69% Gait: range 52–70%
Fraix et al. Grenoble, France 2000 n=24	“Off period” dystonia scores decreased significantly with stimulation at 3- and 12-month follow-up, but returned immediately when stimulators were switched off.	In the off drug condition: UPDRS motor scores improved from the preoperative 54.4 (+/- 13) to 49.3 (+/- 19) with stimulator off, and to 18.2 (+/-8) with stimulator on.	Not reported	In the “on” drug condition: UPDRS motor scores changed from 13.3 (+/-6) preoperative to 17.5 (+/-9) off stimulation and to 11.2 (+/- 7.7) with stimulation	During levodopa challenge, onset-of-dose and peak-dose dyskinesia significantly improved. 75% (18 of 24) of patients no longer had dyskinesia at the 12 month follow-up.	Levodopa mean daily dosage significantly decrease from 952 +/- 509 mg pre-operatively to 223 mg at 3 months and 184 +/- 190 mg at 12 months	Not reported
Houeto et al. Paris 2000 n=23	YES Motor fluctuations decreased by 78% in severity	YES 67%	YES 66% (mean score decreased from 30 to 10, p<0.001)	YES 10% ADL- YES 55% (decreased from 11 to 5, p<0.01)	Dyskinesia decreased by 77%	YES Reduced by 61%	NA

Table 3. Key outcomes, studies of bilateral STN stimulation (cont'd)

Author, Center, Year, N	A	B		C		D	Other
	Reduction in fluctuations in motor function, length of time in "off" state, "off" period dystonia, with stimulation?	Improvement in "off"-period UPDRS scores with stimulation? % improvement in UPDRS score with stimulation during periods when levodopa is not effective ("off" periods)		Improvement in on-medication dyskinesia and motor UPDRS scores? % improvement with stimulation		Levodopa Dosage reduced? Yes/No	Improvement in "off"-period cardinal symptoms, (UPDRS scores for rigidity, tremor, gait, S/E, H/Y scales) with stimulation?
	Reduced motor fluctuations	"off" Motor (UPDRS III)	"off" ADL (UPDRS II)	"on" Motor (UPDRS III)	Levodopa-induced Dyskinesia (UPDRS IV)	Levodopa dose reduced?	"off" Cardinal symptoms
Rodriguez-Oroz et al. Pamplona Spain 2000 n=15	Time spent in "off" state reduced from 40% of the day preimplant to 6% of the day at 12 months	Motor YES 74% (p<0.01)	ADL YES 70% (p<0.01)	Motor-YES, but NS at 12 mos ADL-YES, but NS at 12 mos	"On" dyskinesia in "on" med/"off" stim state significantly reduced compared to pre-implant (p<0.05),	YES Reduced by 55%	YES Tremor: 80.6% Rigidity: 70% Bradykinesia: 56% Axial symptoms: 52%
Molinuevo et al. Barcelona Spain 2000 n=15	"off" time reduced by 89.7%; Severity of dyskinesias decreased 80.6% after surgery (p<0.001) in whole group and by 63.7% (p<0.001) in patients still experiencing dyskinesias	Motor YES 65.9% (p<0.001)	ADL YES 71.8% (p<0.001)	Not reported	Reduced 80.6% after surgery (p<0.001)	YES Medication withdrawn entirely in 8/15 patients; Dose reduced by mean of 80.4%	YES Tremor: 81.1% Rigidity: 66.1% Bradykinesia: 60.4% Axial symptoms: 65.8%
Moro et al.* Rome, Italy 1999 n=7	Motor fluctuations improved in all patients, maximal average differential on/off fluctuation (% variation of UPDRS best on and worst off) reduced from 56% preop to 18.6% after implantation.	YES 41.9% (p<0.0002)	YES 52.2% (p<0.0002)	Motor-YES 4.9% ADL-YES 6.5%		YES Reduced by 65%	YES Tremor: 85% Rigidity: 62.5% Gait: 42.9% Postural stability: 35%

*Moro: results given for last visit: 12 months for 5 patients, 6 months for 1 patient, 3 months for 1 patient

Table 3. Key outcomes, studies of bilateral STN stimulation (cont'd)

Author, Center, Year, N	A	B		C		D	Other
	Reduction in fluctuations in motor function, length of time in “off” state, “off” period dystonia, with stimulation?	Improvement in “off”-period UPDRS scores with stimulation? % improvement in UPDRS score with stimulation during periods when levodopa is not effective (“off” periods)		Improvement in on-medication dyskinesia and motor UPDRS scores? % improvement with stimulation		Levodopa dosage reduced? Yes/No	Improvement in “off”-period cardinal symptoms, (UPDRS scores for rigidity, tremor, gait, S/E, H/Y scales) with stimulation?
	Reduced motor fluctuations	“off” Motor (UPDRS III)	“off” ADL (UPDRS II)	“on” Motor (UPDRS III)	Levodopa-induced Dyskinesia (UPDRS IV)	Levodopa dose reduced?	“off” Cardinal symptoms
Burchiel et al. Oregon, USA 1999 n=6	Improvement in motor scores off medication and with stimulation were similar with DBS at either site. on-medication axial symptoms were clinically improved only in the GPi group	Motor YES 44%	NA	Motor YES 15%	Reduced in both groups	YES Reduced only in the STN group	YES Bradykinesia: 47% Tremor: 74%
Kumar et al. Toronto, Canada 1998a n=7		Motor YES 58% (p<0.002)	ADL YES 29.7% (p<0.05)	Motor YES 49.1% (p<0.01) ADL- NO 18.7% worse than on med alone state	Reduced by 83% (p<0.001)	YES Reduced by 40% (p=0.05)	YES Tremor: 82.3% Rigidity: 52.1% Bradykinesia: 56%

NS: not statistically significant; NA: not applicable; stat: statistically; w/d : withdrawn

A. Motor fluctuations, duration of “off” periods. DBS of the STN was consistently associated with a reduction in fluctuations of motor function and reduction in percentage of waking hours spent in the “off” condition and the duration of “off” periods.

In the DBS Study Group multicenter trial (2001), home diaries indicated that the percentage of time spent with poor mobility decreased from 49% of waking hours prior to stimulator implantation to 19% of waking hours with stimulation 6 months after surgery. Similarly, waking time spent in an immobile “off” state decreased by as much as 50–90% in the other studies.

B. Changes in UPDRS motor function and activities of daily living in the “off” medication condition. Severity of motor dysfunction during “off” periods was reduced by DBS STN. In all 14 studies, off-medication motor performance (i.e., usually performance of motor tasks 12 hours or more after the last dose of levodopa) improved during DBS stimulation.

The DBS Study Group (2001) reports a mean UPDRS III score improvement of 43% ($p < 0.001$) among 51 patients evaluated 3 months postoperatively in the blinded crossover comparison of stimulator-on versus stimulator-off in the “off” medication condition. In the same trial, unblinded evaluation of 91 patients at 6 months showed continued statistically significant improvement, with mean UPDRS III scores improved 51% compared to preoperative baseline ($p < 0.001$).

Smaller studies demonstrate similar findings, with improvements measured by UPDRS motor subscales ranging from a low of 34% (Broggi et al. 2001) to 74% ($n=20$, Rodriguez-Oroz et al. 2000). This effect appears to be durable: mean UPDRS motor subscore improvement of 61% was observed among 51 patients followed-up for 1 to 3 years in Grenoble (Benabid et al. 2000a). Rodriguez-Oroz et al. (2000) also report durable off-medication motor improvement among 9 patients followed-up for 36 months after bilateral DBS of the STN.

Similarly, activities of daily living in the off-medication condition, as measured by UPDRS subscores as well as by Schwab and England scales and Hoehn and Yahr scores, showed statistically significant improvement during stimulation in the nine studies examining an ADL outcome. Among 91 DBS Study Group patients, the mean UPDRS ADL score improved 44% compared to preoperative baseline, in unblinded evaluation at 6 months. Benabid and co-workers’ 51 patients (2000a) recorded UPDRS ADL score improvement of 58 to 64% at one year. Among smaller studies, ADL improvements ranged from 30% among the 7 elderly patients in the Canadian study (Kumar et al. 1998a) to 71% among 15 patients in the study by Molinuevo et al. (2000).

C. Changes in motor function and dyskinesia in the “on” medication condition. Smaller, but often significant, motor benefits were reported in the on-medication state in some, but not all studies. The DBS Study Group found that motor scores improved more than 26% with stimulation during on medication periods. Compared to baseline motor scores, this improvement was significant ($p < 0.001$).

Similarly, patients in the Houeto et al. (2000) study experienced a 55% improvement in medication “on” ADL scores during stimulation. The authors suggest this improvement is

probably related to a similarly dramatic relief from levodopa-induced dyskinesia. Kumar and colleagues (1998a) in Canada observed a paradoxical 50% improvement in the medication “on,” stimulation “on” UPDRS motor scores accompanied by a nearly 20% worsening of UPDRS ADL scores among the 7 elderly patients in their case series.

In most other small trials, stimulation generally added little to the enhancement of motor performance brought about by a levodopa response. Authors of small trials often report insignificant or small changes (5-10%) in medication “on” motor scores.

Nevertheless, bilateral DBS of the STN has a dramatic effect during “on” periods, providing clinically significant relief particularly from levodopa-induced dyskinesia, the complication that often prevents patients from taking a therapeutic dose of levodopa and destroys the quality of those hours during which levodopa relieves patients of parkinsonian motor symptoms.

Among 91 patients in the DBS Study Group, STN stimulation improved dyskinesia scores from a mean of 1.9 at baseline to 0.8 at 6 months ($p < 0.001$).

Benabid and colleagues (2000a) report 50–100% reductions in dyskinesia duration, dyskinesia disability, and morning dyskinesia dystonia scores. Other studies report similar results: levodopa-induced dyskinesias were reduced by 80.6% ($n=15$, Molinuevo et al. 2000), 83% ($n=7$, Kumar et al. 1998a), and 77% ($n=23$, Houeto et al. 2000).

There is debate about whether the effect of bilateral DBS of the STN upon dyskinesia should be attributed to a direct effect of stimulation or is due to lowered levodopa doses. Kumar and colleagues (1998a) found no direct antidyskinetic effect of STN DBS, i.e., there was no reduction in dyskinesias when the stimulators were turned on, and, in fact, ipsilateral and contralateral stimulation-induced dyskinesias were observed in 5 of 7 patients during programming search for optimal stimulation settings. Benabid et al. (2000a) attributes the dyskinesia reduction observed among his patients to “strong improvement in akinesia and rigidity, allowing us to decrease by about 55% the amount of drugs in those patients.” He also observed that setting the stimulation parameters higher than is needed to control Parkinson’s disease can induce dyskinesias with ballismus or choreoballismus. However, he also notes a direct effect of stimulation upon a special dyskinesia, “off-dystonia.” In 16 of 20 patients with “off-dystonia,” “when the stimulator is turned on, dystonia disappears within seconds, and, when the stimulator is turned off again, reappears as quickly as well as of course the akinesia and the rigidity” (Benabid et al. 2000a).

D. Levodopa dosage reduction. In all studies in which postoperative change in levodopa dosage was reported, bilateral DBS of the STN permitted significant, and sometimes dramatic, reductions in daily levodopa dosage. Mean dosage reductions range from 40 to 80%.

In the DBS Study Group (2001), mean daily levodopa dosage decreased from approximately 1200 mg per day to approximately 760 mg per day at 6 months ($p < 0.001$). In another larger trial, Benabid and colleagues (2000a), describe postsurgical levodopa dosage reductions of 60% or more among 30 patients at two years follow-up. About 10% of patients in the Grenoble study no longer take any levodopa.

E. Cardinal symptoms. Severity of cardinal symptoms during “off” periods was reduced by DBS STN. When specific cardinal symptoms (such as tremor, rigidity, bradykinesia) were examined in the off-medication state, stimulation of the STN had the greatest effect upon tremor, reducing it by 80% or more in most studies (reported range: 63–100%). Improvements of lesser magnitude were observed during stimulation in the off-medication state in rigidity (reported range: 50–75%), akinesia/bradykinesia (reported range: 43–69%), and axial symptoms (reported range: 35–66%).

In the DBS Study Group trial, reductions in off-medication UPDRS scores for tremor, rigidity, bradykinesia, and gait disturbance were significant, with $p < 0.001$, for each symptoms in the unblinded evaluation of 91 patients 6 months after implantation of electrodes.

Adverse effects of chronic stimulation of the STN are described in Table 4. There were no intraoperative deaths among the 186 patients undergoing surgery for DBS of the STN ($n=186$ based upon assumption that DBS Study Group patients have been described in multiple publications, as noted previously). However, as with any stereotactic neurosurgical procedure, surgery for placement of electrodes for DBS carries a risk of intracerebral hemorrhage.

Adverse effects listed by the DBS Study Group (2001) and data presented by Medtronic Corporation to the FDA in March 2000 indicate 3 cases of intracranial hemorrhage with secondary hemiparesis among 102 patients undergoing DBS electrode implantation. Among 197 patients (some of whom are also DBS Study Group subjects), Benabid and colleagues (2000a) report 3 symptomatic intracerebral hemorrhages, 3 asymptomatic microhematomas, 3 subdural hematomas, and 3 asymptomatic intraventricular hemorrhages revealed on postoperative MRI.

The DBS Study Group reports an infection frequency of 6% associated with electrode implantation, as well as transient stimulation-related symptoms such as dyskinesia, dysarthria, and paresthesia. Approximately 30% of patients in the Grenoble series (Benabid et al. 2000a) experienced transient stimulation-induced dyskinesia or paresthesia, which was reversible with modification of stimulation parameters (Benabid et al. 2000a). Transient complaints of dysarthria, paresthesia, facial dystonia, and confusion have been reported in several studies. A unique adverse effect of stimulation of the STN is eyelid apraxia, which may begin or worsen during stimulation. In about 20% of patients (11/51) followed for one year during STN stimulation, Benabid et al. (2000a) observed eyelid apraxia, which in some patients was severe enough to require treatment with botulinum toxin injections.

Other medical complications (infection, equipment malfunction) occur, but it is not possible to quantify these adverse effects from the available studies.

Table 4. Adverse effects of DBS STN, published literature

Author Year	Number of patients	Mortality	Significant morbidity Adverse effects
DBS Study Group 2001	102	1 (esophageal carcinoma)	<p>Procedure related: 3 intracranial hemorrhage 3 hemiparesis secondary to hemorrhage 3 seizures 4 infection 2 improper lead placement 1 brachial plexus injury 1 confusion 1 non-hemorrhagic paralysis 1 pulmonary embolus</p> <p>Device related: 3 migration 3 infection 1 lead break 1 seroma 1 erosion 1 abnormal healing 1 intermittent infection</p> <p>Related to stimulation: 2 dyskinesia 2 diplopia 1 accidental injury 1 dysarthria 1 headache 1 paresthesia (some patients had more than one adverse effect)</p>
Lopiano et al. 2001	20	0	2 transitory episodes of mental confusion 1 pulse generator inflammatory swelling, treated with antibiotics and temporary removal of the system
Broggi et al. 2001	17	0	1 persistent postoperative supranuclear oculomotor palsy and postural instability 3 worsened off-medication hypophonia 3 temporary nocturnal confusion 1 postoperative “silent” intracerebral hematoma seen on MRI 1 re-operation to correct faulty placement of electrode 3 intra-operative major dyskinesias after high frequency stimulation of the medial subthalamus

Table 4. Adverse effects of DBS STN, published literature (cont'd)

Author Year	Number of patients	Mortality	Significant morbidity Adverse effects
Volkman et al. 2001	16	0	<p>Procedure related: 4 transient confusion 4 infections (2 transient, 2 serious) 2 lead dislodgment (1 transient, 1 serious)</p> <p>System related: 2 lead fracture (1 transient, 1 serious)</p> <p>Therapy related: 9 depression (6 transient, 1 ongoing, 2 serious) 1 abulia, apathy (transient) 18 worsening of hypophonia, dysarthria (9 transient, 9 ongoing) 6 worsening of hypersalivation (3 transient, 3 ongoing) 3 restless legs syndrome (transient) 6 increased daytime sleepiness (3 transient, 3 ongoing) 2 more frequent falls (transient) 4 disabling stimulation-induced dyskinesia (4 transient) 4 apraxia of eyelid opening (2 transient, 2 ongoing) 12 weight gain (> 10 kg) (6 transient, 6 ongoing)</p> <p>“Mild hypophonia or hypersalivation had to be accepted as a permanent side effect in 9 of 16 STN patients” “Four of 16 STN patients with low preoperative LEDD and severe hyperkinesias had disabling choreoballistic dyskinesia for more than 1 month after surgery because of an extremely narrow therapeutic window between ‘off’ and ‘on with dyskinesias’. The adjustment period of increasing stimulation in small steps after complete withdrawal of levodopa lasted more than 3 months in two patients and required almost weekly outpatient visits.”</p>
Krause et al. 2001	12	0	<p>1 intra-operative ventricular hemorrhage, leading to acute mild hemiparesis, resolved in 2 months 1 strong increase in libido requiring inpatient psychiatric care “many”: transient dysaesthesia when turning on stimulator 2 stimulation-related dysarthria, “moderate”</p>
Scotto di Luzio et al. 2001	9	0	<p>4 transient adverse effects, including confusion (4), 3 depression (3), 1 postural instability and dystonia of left foot, relieved by switching off the right stimulator</p>
Benabid et al. Grenoble, France 2000a	Summary of 197 patients operated on 316 sides	None (operative) 1 patient: died on the 11 th postop day, due to pulmonary embolism)	<p>7 deaths from non-neurologic disease at 3, 6, 7, 10, 11, 23, 116 months. 3 symptomatic microhematomas: 1 supraventricular, one thalamic 3 asymptomatic microhematomas along electrode tracks 3 subdural hematomas 3 postoperative MRI showing asymptomatic intraventricular bleed 7 postoperative or late infections, 4 ruptures of external extension requiring replacement 3 thrombophlebitis with 2 pulmonary embolisms with good resolution 3 repositioning of stimulators because of patient’s discomfort No permanent hemiballism, but one case of acute and transient (24 hour) hemiballism. 5 peripheral limb akinesia/involuntary movements, considered symptoms of STN penetration 3 cases of lesioning DC current leak from a defective test generator causing transient hemiballism 7 confusion, disorientation last few days to 3 months ~20 % of cases: eyelid apraxia (11/51 STN patients)</p>

Table 4. Adverse effects of DBS STN, published literature (cont'd)

Author Year	Number of patients	Mortality	Significant morbidity Adverse effects
Houeto et al. Paris, France 2000	23	none	No hemorrhage, infarction or infections. 3 confusional state lasting one day 4 depression during 2 months after surgery, severe in 2 (1 suicide attempt), moderate in 2 transient adverse effects directly related to stimulation observed in all patients: <ul style="list-style-type: none"> transient reversible adverse effects produced by stimulation through contacts that did not improve parkinsonian disability (paresthesia, dysarthria, dystonic contractions, diplopia) abnormal involuntary movements (chorea, ballismus, dystonia) during stimulation through electrode contacts that improved parkinsonian disability appearing at voltage thresholds higher than those needed for symptom improvement.
Rodriguez-Oroz et al. Pamplona, Spain 2000	15 (17 operated)		2 severe intracranial hemorrhage intra-operatively before implantation of stimulator, both remained seriously disabled and were excluded from the study 1 scalp infection requiring explanation after 4 months 1 seroma at battery site 3 severe depression (each had a prior history of mild depression), required pharmacologic treatment, two of whom also developed drug-induced psychotic symptoms at the beginning of depression
Molinuevo et al. Barcelona, Spain 2000	15	none	2 dysarthria and hypophonia (1 intense, 1 mild) 1 mild postoperative depression, persisted at 6 months postsurgery transient confusion, disorientation, abulia during first 2 weeks after surgery (n=?)
Moro et al. Rome, Italy 1999	7	none	2 ballistic or choreic dyskinesia of neck or limbs elicited by contralateral STN stimulation above a given threshold, which varied with the individual 4 slight transient paresthesias when switching on the IPG 1 unilateral anisocoria resolved spontaneously in 3 months 1 speech impairment, resolved completely after about 1 year 1 depression and abulia, resolved completely after 1 month
Burchiel et al. Oregon, USA 1999	10	none	1 severe dyskinesia during intraoperative stimulation 1 infraclavicular hematoma after generator placement, resolved spontaneously adverse events during stimulation parameter adjustment (transient paresthesia, balance impairment, dysarthria, dysphagia, hypomimia) occurred in both GPi and STN groups facial dystonia and limb dyskinesia occurred in STN patients, subsided immediately with stimulation parameter adjustment; unintentional switching off of stimulators by external electromagnetic fields (theft detectors, high-power transmitters) occurred on multiple occasions, leading to spontaneous cessation of stimulation
Kumar et al. Toronto, Canada 1998a	7	none	Transient adverse effects in almost all patients as optimal stimulation settings were sought (paresthesias, dysarthria, tonic contraction contralateral to the side of stimulation, all of which were eliminated with adjustment of stimulation) Operative complications: Cortical venous thrombosis with infarction at site of electrode implantation resulting in marked postoperative dysarthria, resolving by 3 months to subtle worsening of pre-operative hypophonia (1 patient). Thalamic lesion along electrode tract, associated with reduction in verbal memory confirmed with pre-op and serial neuropsychological testing. (1 patient) Pronounced postoperative confusion in both patients with electrode-induced infarcts, lasting 1-2 weeks Mild personality change with intermittent disinhibited or childlike behavior (1 patient) Abrupt postoperative cognitive decline despite motor improvement (1 patient, age 74) Mild transient (<48 hours) hemi-chorea during macroelectrode insertion (2 patients)

Table 4. Adverse effects of DBS STN, published literature (cont'd)

Comparison with complications reported with ablative surgery for Parkinson's disease					
Author Year		Mortality	Significant morbidity Adverse effects		
(1) Samuel et al. 1998		0-8% (1,3)	Confusion	4-10%	(1,2)
(2) Lang et al. 1997			Intracranial hemorrhage	1.5-12%	(1,3,4)
(3) Tasker 1998			Infection	0.5-2.7%	(3)
(4) Vitek et al. 1998			Dysarthria	0.6-27%	(1-4)
			Cognitive difficulty	0.8-12.5%	(2,3)
			Seizures	0.5-8.0%	(1,3,4)

Summary of bilateral DBS of the STN Trials

Patients with medically refractory Parkinson's disease are usually most disabled by

- parkinsonian motor dysfunction, such as loss of mobility and dexterity, rigidity, bradykinesia, and tremor, when the effect of the last dose of levodopa has worn off,
- progressively longer and more severe "off" periods,
- disabling dyskinesia during periods when levodopa is working, and
- an increasingly inconsistent effect of levodopa, which causes rapidly alternating "on" and "off" periods (motor fluctuations).

The data demonstrate clinically meaningful improvement in each of these categories compared with the alternative of continued medical management as represented in presurgical baseline evaluations.

The percentage of time spent in an "off" condition was significantly reduced (DBS Study Group 2001; Broggi et al. 2001; Houeto et al. 2000; Molinuevo et al. 2000). Motor fluctuations decreased in severity (Houeto et al. 2000; Moro et al. 2000).

In all studies, UPDRS scores for motor performance during the "off" state improved consistently. In the DBS Study Group multicenter trial (2001), which is probably most representative, the mean motor UPDRS score was 51% at 6 months among 91 patients.

During those periods when levodopa is working, that is, in the "on" state, patients have fewer or milder parkinsonian symptoms. Thus, most studies of bilateral DBS of the STN found a smaller improvement in motor and ADL measures when patients were examined in the medication "on" state with the stimulator on. In smaller studies, this change often did not reach statistical significance, but in the DBS Study Group trial, improvement in "on" period motor function during stimulation was significant, with $p < 0.001$.

However, for those patients whose "on" periods are marked by levodopa-induced dyskinesia, bilateral DBS of the STN consistently resulted in highly significant reduction of dyskinesia, between 70% and 85% in most studies. Levodopa-induced dyskinesia severity was significantly reduced by a mean of 57% as measured by the UPDRS IV at 6 months among 91 patients in the DBS Study Group (2001) multicenter trial. Similarly, the percentage of time during waking hours with good mobility but disabling dyskinesia decreased from a mean of 23% to 7% among the same patients at 6 months.

Levodopa dosage or its equivalents was decreased by 40 to 74% in all studies. Dosage reduction among 91 patients in the DBS Study Group trial was significant, with $p < 0.001$. Among four patients followed for more than 5 years, the lessened requirement for levodopa continued (Benabid et al. 2000a).

Cardinal symptoms, tremor, in particular, were reduced by approximately 60–100%, prompting some investigators to suggest that the STN may be preferable to the currently accepted thalamus for treatment of parkinsonian tremor. Other cardinal symptoms were less positively affected: rigidity scores were reduced by 50–70%, and bradykinesia scores by 50%.

Duration of DBS treatment effect. The effect of STN DBS appears to be durable for at least 1 to 3 years. Among 82 patients followed-up for a year or more, reported improvements in “off”-period motor scores were clinically significant and stable throughout at least a 12-month period. In the Benabid et al. (2000a) study, 51 patients followed-up for 1 to 3 years maintained a mean “off” UPDRS motor score improvement of 60%. Among 9 patients followed-up for 4 years or longer, mean “off” UPDRS motor score improvements of 50% or greater (compared to presurgical baseline) were maintained in the long term (Benabid et al. 2000a). Four patients in this group have been followed-up for 5 years. After 5 years of stimulation, progressive deterioration of postural stability was noted. Gait remains improved in 2 patients but has become impossible for the other 2 patients in the off-medication condition (Benabid et al. 2000a). Nine patients treated with bilateral DBS of the STN in Spain and followed for 3 years have experienced no loss of DBS therapeutic benefit in motor function (Rodriguez-Oroz et al. 2000).

Adverse hemorrhagic risks associated with DBS appear to be slightly less than those observed after ablative procedures. However, the permanent indwelling device carries increased infection risks and risks associated with mechanical failure. Other complications, such as stimulation-induced dyskinesia and paresthesia, appear to resolve with adjustment of stimulation parameters. Benabid and colleagues report onset or worsening of eyelid apraxia in about 20% of cases (11/51 patients undergoing bilateral DBS of the STN). In another publication, Krack and colleagues describe outcomes after bilateral DBS of the STN among a subset of 8 patients with early-onset of Parkinson’s disease drawn from this cohort. Among these patients, severe immediate postoperative dyskinesias required a decrease in levodopa dosage and progressive increase in DBS voltage. Despite the fact that stimulation provided off-period motor function similar to their best on-drug periods, some of these patients complained of a lack of energy and initiative during off-drug periods and other off-drug symptoms such as anxiety following major decreases in levodopa dosage.

A surgical alternative for patients with medically refractory Parkinson’s disease is pallidotomy. There are no studies directly comparing chronic bilateral DBS of the STN with pallidotomy. Table 5 summarizes the pallidotomy literature. Five studies published between 1995 and 1998 demonstrated only modest motor improvements (14–30%) in most patients (n=115 of 133) after pallidotomy, with more positive motor improvements recorded only in the study published by Dogali and colleagues (1995; 71% motor improvement among 18 of 133 contralateral dyskinesia reduction of 70–92%). However, pallidotomy is limited to a unilateral procedure because of unacceptably high risk of adverse neuropsychological outcomes if performed bilaterally.

No studies directly compare chronic bilateral DBS of the STN with unilateral pallidotomy. However, the degree of improvement in “off” state motor function and “on” state dyskinesia reduction observed in studies of DBS of the STN appears similar to or slightly better than that achieved among 115 patients treated with pallidotomy (Table 5). Five studies published between 1995 and 1998 demonstrated modest motor improvements (14 to 30%) in most patients (115/133) after pallidotomy, with more dramatic motor improvements reported in only one study (71% motor improvement among 18/133).

Table 5. Summary of outcomes after pallidotomy for Parkinson's disease (adapted from text of Clatterbuck et al. 2000)

Author, Center, Year	N	Observer blinded?	Mean % improvement: "off" state UPDRS motor subscales	Other findings	Mortality, Complications, Adverse effects
Dogali et al. NYC, NY 1995	18	yes	At one year: 71%	Total UPDRS improved 65% Walk scores improved 45% Medication requirement unchanged but reduced dyskinesia permitted larger doses as needed.	No significant complications related to pallidotomy
Lozano et al. Toronto, Canada 1995	40	yes	At 6 months: 30%	Akinesia improved 33% "Off" state gait improved 15% Contralateral dyskinesia improved 92% UPDRS ADL improved 33%	No visual or corticospinal complications Transient mild facial weakness for 2 weeks (3/40) Euphoria for several weeks (4/40)
Baron et al. Atlanta GA 1996	15	no	At 3 months: 25%	Mean ADL "off" subscale score improved by 34% at 3 months Mean ADL "on" score improved by 28% at 3 months, but returned to baseline at 6 and 12 months.	Subclinical frontal hemorrhage (2/15, 13%) Transient dysarthria (1/15, 7%) worsening of baseline dysarthria (1/15, 7%) Persistent superior quadrantoanopsia (1/15, 7%) Confusion, transient facial weakness
Ondo et al. 1998	34	yes	At 3 months: 14%	Total tremor improved 59% Gait improved 22% Bradykinesia improved 17%	Transient adverse effects (5/34, 15%) which included aphasia (3%), altered mental status (12%)
Shannon et al. Chicago, IL 1998	26	no	At 6 months: 18%	Contralateral "off" period combined tremor, rigidity and bradykinesia improved 26% Dyskinesia severity scores improved by 73%	Serious adverse effects in 8 patients: fatal hemorrhage (1, 4%) non-fatal hemorrhage (3, 12%) cognitive changes (2, 8%) aphasia (1, 4%) persistent frontal lobe dysfunction (3, 12%) mild persistent hemiparesis (1, 4%) persistent increase in dysarthria (1, 4%)
Lang et al. Toronto, Canada 1997	11*		At 2 years: Overall motor scores still improved by 26%	Effect on contralateral bradykinesia, dyskinesia and rigidity were maintained, ipsilateral effects were lost.	NA
Summary	Total: 133		Range of improvement UPDRS motor scores: 14% to 71% NOTE: Among 115 patients, mean "off" motor improvement 14-30% . Only among the 18 patients in the Dogali study was mean "off" motor improvement 71%	Range of improvement in dyskinesia scores: 73% to 92%	

*11 of 40 described in Lozano et al. 1995

Pallidotomy was associated with contralateral dyskinesia reduction of 70–92%. Unlike the pallidal ablative procedure, stimulation of the STN has advantages of being reversible and adjustable. Furthermore, the fact that stimulation of the STN, unlike pallidotomy, can be offered bilaterally is advantageous, since symptoms of Parkinson’s disease most often affect both sides of the body.

In summary, evidence from uncontrolled trials demonstrates that for patients with medically refractory Parkinson’s disease bilateral chronic stimulation of the STN brings about a clinically important improvement over the alternative treatment, continued medical management represented by presurgical baseline evaluations. “Off” period cardinal symptoms and motor function improved, “on” period dyskinesias were greatly reduced, and “on-off” fluctuations became less severe during bilateral STN stimulation.

Deep Brain Stimulation of the Globus Pallidus Interna (GPi)

The literature examining chronic stimulation of the globus pallidus interna (GPi) and meeting criteria for inclusion in this Assessment consists of 9 full-length articles published between 1994 and 2001. All use standardized outcome measures to evaluate clinical outcomes in patients with advanced Parkinson’s disease following bilateral stimulation of the GPi. They are presented in Table 6.

Five other studies were excluded from analysis. An early study involving 3 patients does not report outcomes in terms of the currently standard UPDRS scores (Siegfried et al. 1994). Two studies involving a total of 26 patients examine only unilateral GPi DBS (Gross et al. 1997; Vingerhoets et al. 1999). Two studies fail to present evidence that would permit separate analysis of outcomes of unilateral and bilateral GPi DBS (Krack et al. 1998a; Katayama et al. 2001).

Among included studies are two multicenter trials (DBS Study Group, 2001; Kumar et al. 2000). There is overlap among the study center participating in these two trials. Three of the 5 centers (Toronto, Canada; Grenoble, France; San Sebastian, Spain) reporting in the Kumar study (2000) are also among the Deep Brain Study Group participants (2001). The remaining 7 studies are small trials, each with fewer than 12 patients.

Table 6. GPI: Study descriptions: Bilateral deep brain stimulation (DBS) of the globus pallidus (GPI) for Parkinson’s disease

Author Center Year	Study design	Comparison	N Patient characteristics	Subject age, Follow-up (F/U)	Outcomes examined	Authors’ Conclusions
DBS for PD Study Group 2001 18 centers between July 1995 and July 1999	Prospective multicenter trial: 1) double blind randomized crossover evaluation of stimulation on versus stimulator off at 3 mos; 2) unblinded evaluation in four possible conditions at 6 mos; 3) home diaries	1) with stimulator and medications discontinued overnight, stimulator on versus stimulator off; 2) 4 conditions: off meds with no stimulation; off meds with stimulation; on meds with no stimulation; on meds with stimulation.	41 patients enrolled in the bilateral GPI stimulation group 38 patients received bilateral GPI implants 35 patients completed the double-blind evaluation, 36 patients completed 6 months’ follow-up criteria for inclusion: presence of at least two cardinal features of PD; a good response to levodopa; score no lower than 30 points on UPDRS when without medication for 12 hours (scores on UPDRS range from 0 to 108, with higher values indicating more severe symptoms); motor complications not controlled by pharmacologic therapy	55.7 +/- 9.8 years F/U: 3 months and 6 months (3/41 did not receive bilateral implants because of complications during surgery, 3 did not participate in the double-blind evaluation, and 2 did not complete the 6-month follow-up)	UPDRS assessment of Motor function Activities of daily living Dyskinesia Home diary: documenting of status at 30-minute intervals during the 2 days before each visit (2 weeks before and 1, 3, 6 months after implantation) in terms of “poor mobility (“off”), good mobility without dyskinesia (“on” without dyskinesia), and good mobility with dyskinesia (“on” with dyskinesia). Patient and investigator assessment of global effect of therapy after conclusion of study. Levodopa dose equivalents, mean dosage before and after surgery	double blind crossover evaluation 3 months after implantation: a significant treatment effect in favor of stimulation (p<0.001) and no significant carry-over effects (p=0.40); a mean improvement of 32% and a median improvement of 37% in the UPDRS score (off medication) (p<0.001); unblinded evaluation 6 months after implantation: significant improvement in the UPDRS motor score in the off-medication state at each visit (p<0.001); smaller but significant benefits with stimulation in the on-medication state p<0.003); significant improvement in tremor, bradykinesia, gait, postural stability, and activities of daily living with stimulation in the off-medication state (p<0.001);benefits of stimulation upon cardinal symptoms in the on-medication state reached significance only for ADL, tremor, and postural stability. home diary accounts: an increase in percentage of time with good mobility without dyskinesia during the waking day from 28% to 64% between baseline and 6 months post-implantation (p<0.001) a decrease in time with poor mobility (“off” time) from 37% to 24% of waking day p<0.01); mean dyskinesia scores: improved from 2.1 +/- 1.5 at baseline to 0.7 +/- 0.8 (p<0.01) daily levodopa dose equivalents: unchanged between baseline (1090.9 +/- 543 mg) and 6 months (1120 +/- 537 mg). global assessment: severe disability, noted at baseline in 76% by physicians and in 82% by patients, was described by 11% of patients and 14% of physicians 6 months after implantation

Table 6. GPi: Study descriptions: Bilateral deep brain stimulation (DBS) of the globus pallidus (GPi) for Parkinson’s disease (cont’d)

Author Center Year	Study design	Comparison	N Patient characteristics	Subject age, Follow-up (F/U)	Outcomes examined	Authors’ Conclusions
Volkman et al. 2001 Cologne, Germany	Clinical series	Presurgical medical management	11 patients advanced idiopathic PD with on/off fluctuations and restricted off mobility	Age: 56.6 +/- 9.4 years F/U: 12 months	UPDRS motor UPDRS ADL UPDRS subscores for bradykinesia, rigidity, tremor, posture and gait speech and swallowing, dyskinesia Levodopa equivalent daily dose (LEDD) Neuropsychiatric evaluation Electrical power of stimulation	GPi stimulation improved “off” period motor symptoms, and activities of daily living at 6 months, but at 12 months, only improvement in “off” period motor scores remained statistically significant. GPi stimulation was associated with significant improvement in dyskinesia There was no significant change in LEDD at any time after placement of electrodes. There was a trend toward reduced Hamilton depression scores, and no change in other neuro-psychiatric parameters (MMSE, Cambridge EMDE, cognitive Subscale, State and trait Anxiety Scale, and MMPI) Electrical stimulation power was on average more than 3 times higher for GPi stimulation than for STN stimulation of patients in the same clinical series.
Krause et al. 2001 Heidelberg, Germany	Clinical series	Presurgical medical management	6 patients advanced PD with “off” state Hoehn and Yahr >2.5; first 6 consecutive patients in a series of 33 patients treated with DBS of the GPi or STN since 1995.	Age: 58.5 years (range 46-65) F/U: 3, 6, 12 months	changes UPDRS mentation (item 1-4) UPDRS motor (18-31) UPDRS ADL (item 5-17) UPDRS complications (items 40-42) Schwab and England Hoehn and Yahr Obeso dyskinesia intensity scale Levodopa equivalent dosage changes	Stimulation of the GPi did not significantly improve UPDRS motor, ADL, or tremor scores in the medication off or on state, but did reduce dyskinesia scores significantly. Levodopa intake increased significantly after stimulator implantation in the GPi group, from an average of 277 mg to 772 mg per day. Dopamine agonist intake remained stable, while COMT inhibitors increased an average of 75 mg/day.

Table 6. GPI: Study descriptions: Bilateral deep brain stimulation (DBS) of the globus pallidus (GPi) for Parkinson's disease (cont'd)

Author Center Year	Study design	Comparison	N Patient characteristics	Subject age, Follow-up (F/U)	Outcomes examined	Authors' Conclusions
Scotto di Luzio et al. 2001 Florence, Italy	Clinical series	Presurgical medical management	5 patients advanced idiopathic PD, medication refractory motor fluctuations, age less than 70 years, levodopa-induced dyskinesia, normal brain MRI	Age: 55.4 +/- 5.4 years F/U: 1, 3, 6, 12 months	At 12 months: UPDRS motor scores (part III) Schwab and England scale Hoehn and Yahr score Mini mental state examination Dyskinesia scale (abnormal involuntary movement scale and items 32, 33, & 34 of UPDRS.) Change in daily levodopa dose	
Krack et al. 1998a Grenoble, France	Clinical series comparison	Presurgical medical management Postsurgical state of similar patients treated with DBS of the STN	5 patients Early onset PD (age<40 years), disabling motor fluctuations and levodopa-induced dyskinesia	Age: 51 +/- 10 years (onset of PD before age 40) F/U: 6 months	At 6 months: UPDRS motor and ADL subscales, "off" state; Reduction of levodopa-induced dyskinesia	Motor scores in the "off" phase improved by 71% with STN stimulation and by 39% with GPi stimulation (p<0.005). Rigidity and tremor improved equally in both groups. Akinesia score improvement was greater in the STN group. Improvement in all motor symptoms was very close or equal, but not greater than to the best levodopa response in the STN group. As measured by the dyskinesia score during an acute levodopa test, "on" phase levodopa-induced dyskinesia were markedly improved in the GPi group, and only slightly improved in STN group. However, in the long term, the reduction of levodopa dosage in the STN groups led to an indirect reduction of levodopa-induced dyskinesia similar to that in the GPi group.
Ghika et al. 1998 Lausanne Switzerland	Clinical series	Presurgical medical management	6 patients idiopathic PD with levodopa-responsive symptoms, severe motor fluctuations	Age: 55 years (range 42-67 years) F/U: 30 months	At 3 month intervals for 24-30 months: UPDRS scoring Hoehn and Yahr stage 24 hour self assessment neuropsychological examination	Bilateral pallidal DBS led to major improvements in motor scores, ADL scores, and off time which persisted for more than 2 years, but with signs of decreased efficacy beginning 12 months after surgery.

Table 6. GPI: Study descriptions: Bilateral deep brain stimulation (DBS) of the globus pallidus (GPi) for Parkinson's disease (cont'd)

Author Center Year	Study design	Comparison	N Patient characteristics	Subject age, Follow-up (F/U)	Outcomes examined	Authors' Conclusions
Volkman et al. 1998 Cologne, Germany	Clinical series	Presurgical medical management	See Volkman et al. 2001 idiopathic PD with on/off fluctuations and restricted off-mobility	Age: 56.4 years (range 38-69) F/U: 3 months, 12 months	At 3 months after surgery (n=9), 12 months (n=4): UPDRS, Dyskinesia scale, Hoehn and Yahr scale, Schwab and England scale	Off state total UPDRS scores improved by 44.2% at 3 months. Amount and severity of on/off fluctuations were reduced No permanent morbidity associated with procedure, but a subtle reduction of verbal fluency, which was not evident to the patients, was the only cognitive adverse effect of the procedure in neuropsychological testing.
Kumar et al. 2000 Toronto, San Sebastian, Grenoble, Ghent	Multicenter clinical series, consecutive DBS GPi 5 unilateral all at Ghent; 17 bilateral	Presurgical medical management	22 patients (17/22 bilateral) diagnosis of idiopathic PD with good response to levodopa, severe motor fluctuations, "off" period immobility, disabling LID	Age: 52.7 +/- 8.5 years F/U: 6 months	At mean 6-month follow-up: (unilateral and bilateral cohort reported separately) UPDRS, ADL, dyskinesia, timed tapping, timed walking.	Results show positive antiparkinsonian effect of pallidal DBS, with no specific complications observed with bilateral procedures. Electrode insertion alone resulted in measurable clinical effects in the absence of stimulation: A 44% reduction in the dyskinesia score in the "on" medication state GPi DBS contralateral to a previous pallidotomy may be a useful alternative for patients with persistent disability ipsilateral to the initial lesion
Burchiel et al. 1999 Oregon, USA	Randomized trial comparing DBS STN with DBS GPi	Presurgical medical management and DBS of STN	4 patients	Age: 46.5 +/- 11 years F/U: 12 months	At 12 months: UPDRS, dyskinesia scale, Schwab and England ADL Neuropsychological test battery: Visuo-motor processing (Symbol Digits Modalities Test) memory (Controlled Oral Work Association Test, Hopkins Verbal Learning Test, Memory Assessment Scale: Names and Faces) attentional capacity (Digit Span), cognitive impairment (Cognitive Difficulties Scale) auditory span (Sentence Repetition) mood (Beck Depression Inventory)	Both pallidal stimulation and STN stimulation appear to be safe and efficacious for management of advanced PD. A larger study is needed to investigate further the differences in symptom response and the interaction of levodopa with stimulation at either site.

Table 6. GPi: Study descriptions: Bilateral deep brain stimulation (DBS) of the globus pallidus (GPi) for Parkinson’s disease (cont’d)

Author Center Year	Study design	Comparison	N Patient characteristics	Subject age, Follow-up (F/U)	Outcomes examined	Authors’ Conclusions
Pahwa et al. 1997 Kansas, USA	Clinical series DBS: 3 bilateral, 2 unilateral	Presurgical medical management	5 patients (3/5 bilateral) advanced idiopathic PD, with a stable levodopa regimen and disabling levodopa related motor fluctuations and dyskinesias	Age: 55.8 (range 48-65) F/U: 3 months	At 3 months after surgery: UPDRS I (mentation), II (ADL), III (motor), off meds baseline, and at 3 months with stimulator on, and meds either off or on. Schwab and England ADL At baseline and at 3 months: Walking time, tapping total, UPDRS III scores, with med off and stimulator off, and with meds on and stimulator either on or off.	There was significant improvement in all subscales of the UPDRS. Chronic DBS of the GPi is a safe and effective procedure in PD patients with motor fluctuations and dyskinesias.

If none of these studies describe the same patients in more than one publication, this body of literature offers outcomes data for 100 patients with advanced Parkinson's disease following DBS of the GPi. If, however, some investigators have published outcomes for the same patients in one or both multicenter trials and in their own single-center case series, it is possible that the outcomes described in the tables have been derived from as few as 53 patients. Since it is not known the degree to which data presented in these trials may overlap, it will be assumed for the purposes of this Assessment that all multicenter trial investigators have published outcomes from the single center and in both multicenter trials. While each of the trials will be described, the Assessment analysis and summary will follow the same procedure as was followed for bilateral DBS of the STN and will assume that the true number of patients treated with GPi DBS is the more conservative figure, that is, a total of 53 patients.

Study design. All 9 published trials of DBS of the GPi, including the 2 larger multicenter trials, follow a clinical series design, with the exception of the small study by Burchiel and colleagues (1999), which employs a prospective, randomized trial design to compare DBS of the STN with DBS of the GPi among 10 patients.

All studies require that study patients have diagnosis of advanced idiopathic Parkinson's disease, a continued response to levodopa, and with medication-induced complications, such as motor fluctuations and dyskinesia. The 53 treated patients ranged in age from 38 to 69 years. In all trials, comparison was made with the baseline condition of presurgical medical management.

In 6 of the 8 studies (DBS Study Group 2001; Volkman et al. 2001; Krause et al. 2001; Scotto di Luzio et al. 2001; Krack et al. 1998; Burchiel et al. 1999), outcomes following stimulation of either the STN or the GPi were discussed in a comparative manner. However, only the Burchiel trial design, with randomization of patients to either target, provides data to support comparison of outcomes, and this study, with only 10 patients, is too small to provide meaningful comparative data.

Criteria for exclusion in the DBS Study Group multicenter trial (2001) were major psychiatric illness, cognitive impairment, other substantial medical problems or laboratory abnormalities, presence of a cardiac pacemaker, and previous intracranial surgery. Preoperative MRI of the brain was not included in the study protocol.

Duration of follow-up. Duration of follow-up was as brief as 3 months (n=3, Pahwa et al. 1997) to as long as 24 months (n=6, Ghika et al. 1998).

Outcomes examined. In most studies, treatment outcome is assessed by performance on a battery of assessments (UPDRS, CAPIT, Schwab and England scale, timed tests and walking tasks, and dyskinesia scales) with the stimulator on in the medication "on" or "off" state (See Table A, Appendix, for definitions of "off" and "on"). The preoperative baseline evaluation in the off and on medication states is used for comparison. Few studies examine postoperative stimulator off in the medication on and off states to detect the possible microablative effects of electrode insertion.

Key outcomes for this subset of Parkinson's patients with advanced disease focus primarily upon disabling motor symptoms associated with either complications of medical therapy (motor fluctuations or dyskinesia) or loss of the effect of levodopa (increasing "off" period duration and severity).

Table 7 lists results from 9 studies for each of the following four key outcomes with stimulation of the GPi:

- A. Reduction in fluctuations in motor function
- B. Improvement in "off" condition UPDRS scores (motor and ADL)
- C. Improvement in "on" condition UPDRS scores (motor and levodopa-induced dyskinesia)
- D. Reduction in daily levodopa dosage requirement.

The data presented in Table 7 show a beneficial effect of bilateral stimulation of the GPi in most, but not all, key outcomes, in most, but not all studies.

A. Motor fluctuations, duration of "off" periods. Five studies report mixed results about the effect of GPi DBS upon motor fluctuations and duration of "off" periods. (The remaining 3 studies present either no data about this outcome or do not separate bilateral and unilateral DBS GPi data.) Two small trials (Ghika et al. [n=6], Scotto di Luzio et al. [n=5]) report decreases in daily time spent in the "off" state, while two other small trials (Krack et al. [n=5]; Krause et al. [n=6]) report either no change or a net loss of "on" time. If sample size is important, then the positive findings reported by the DBS Study Group may be considered more reliable. Among 36 patients treated with bilateral DBS of the GPi, they report that the percentage of time with good mobility without dyskinesia increased from 28% of the waking day before surgery to 64% after surgery, a result that was highly significant ($p < 0.001$).

B. Changes in motor function and activities of daily living in the "off" medication condition. With the exception of the report by Krause and colleagues (2001), all studies report improvement in motor function in the "off" state with GPi stimulation. Off-medication mean UPDRS motor scores improved by 31% (n=22, Kumar et al. 2000) in one multicenter trial and by 32% ($p > 0.001$) in the other multicenter trial (n=36, DBS Study Group 2001). The reported mean motor score improvement reported in smaller studies ranges from 41% (Scotto di Luzio et al. 2001) to 68% (Volkmann et al. 2001).

Activities of daily living improved less consistently after DBS GPi. As measured by UPDRS ADL scores, activities of daily living improved 32-38% in the two multicenter trials, but were not significantly changed in five other studies reporting this outcome.

C. Changes in motor function and dyskinesia in the "on" medication condition. The effect upon quality of "on" time and reduction of dyskinesia is the most consistent and most positive outcome reported among patients whose DBS target was the GPi. All investigators concluded that GPi DBS was therapeutically effective for treatment of dyskinesia.

While changes in "on" medication motor UPDRS scores were mixed, improving in some studies while remaining unchanged in others, all studies report improvement in duration of "on" time that is also free of dyskinesia. In the largest trial (DBS Study Group 2001), bilateral stimulation

Table 7. Key outcomes, studies of bilateral GPi stimulation

Author, Year, N	A Reduction in fluctuations in motor function, length of time in “off” state, “off” period dystonia with stimulation?	B off-medication UPDRS scores improved with stimulation? % improvement in UPDRS score with stimulation during periods when levodopa is not effective (i.e., periods of poor mobility, “off” periods) Motor (III) ADL(II)		C on-medication UPDRS scores improved with stimulation? % improvement in UPDRS scores with stimulation during periods when levodopa is effective, (i.e., periods of good mobility, “on” periods) Motor III Dyskinesia		D Levodopa dosage reduced?	Other Improvement in “off”- medication cardinal symptoms (UPDRS scores for rigidity, tremor, gait; S/E, H/Y scales) with stimulation?
	Reduced motor fluctuations	“off” Motor (UPDRS III)	“off” ADL (UPDRS II)	“on” Motor (UPDRS III)	Levodopa-induced Dyskinesia (UPDRS IV)	Levodopa reduced?	“off” Cardinal symptoms (UPDRS)
DBS Study Group 2001 n=36	YES Percentage of time with good mobility and without dyskinesia during the waking day increased from 28% to 64% (p<0.001) Percentage of time with poor mobility decreased from 37% to 24% (p<0.01)	YES 32% (mean) (n= 35, comparison with stimulator off, blinded evaluation at 3 months) p<0.001 34% (mean) (n= 36, comparison with baseline, unblinded at 6 months) p<0.001	YES 38% (mean) (n=36, comparisons with baseline, unblinded evaluation at 6 months, mean score decreased from 28.9 to 17.9) p<0.001	YES , 26.8% but benefit was smaller with stimulation in the on-medication state (mean score decreased from 24.1 to 16.5 at 6 months) p<0.003	YES 66% Dyskinesia score reduced by 66% (decrease in mean score from 2.1 +/- 1.5 to 0.7 +/- 0.8 at 6 months, unblinded evaluation) p<0.01	NO Mean daily dose of levodopa was unchanged (decreased from 1090 mg/day to 1120 mg/day at 6 months)	YES Significant improvement in UPDRS cardinal symptom mean scores: Tremor 6.9 to 2.8 , p<0.001 Rigidity 10.2 to 7.1 , p<0.001 Bradykinesia 18.0 to 13.3 , p<0.001 Gait 2.6 to 1.7 , p<0.001 (unblinded evaluation at 6 months) Median improvement greater than 25% was seen in 9 of 10 centers
Volkman et al. 2001 n=11	Not reported	YES 68% Mean motor score decreased from 52.5 to 16.7 at 12 months, p<0.005	NOT SIGNIFICANT Mean ADL score decreased from 21.0 to 16.7, p=NS	NOT SIGNIFICANT Mean motor score: decreased from 30.2 to 16.7	YES Mean dyskinesia score: decreased from 2.0 to 0.4, p<0.001	NO Levodopa equivalents decreased from 836 +/- 391mg/day to 605 +/- 189 m/day at 12 months (NS)	NO Tremor 0.8 to 0.2 Rigidity 2.2 to 1.1 Bradykinesia 2.5 to 1.3 Gait 2.2 to 0.8

Table 7. Key outcomes, studies of bilateral GPi stimulation (cont'd)

Author, Year, N	A Reduction in fluctuations in motor function, length of time in “off” state, “off” period dystonia with stimulation?	B off-medication UPDRS scores improved with stimulation? % improvement in UPDRS score with stimulation during periods when levodopa is not effective (i.e., periods of poor mobility, “off” periods) Motor (III) ADL(II)		C “on”-medication UPDRS scores improved with stimulation? % improvement in UPDRS scores with stimulation during periods when levodopa is effective, (i.e., periods of good mobility, “on” periods) Motor III Dyskinesia		D Levodopa dosage reduced?	Other Improvement in off-medication cardinal symptoms (UPDRS scores for rigidity, tremor, gait; S/E, H/Y scales) with stimulation?
	Reduced motor fluctuations	“off” Motor (UPDRS III)	“off” ADL (UPDRS II)	“on” Motor (UPDRS III)	Levodopa-induced Dyskinesia (UPDRS IV)	Levodopa reduced?	“off” Cardinal symptoms (UPDRS)
Krause et al. 2001 n=6	NO No change in mean scores of UPDRS items 36-39	NO Mean UPDRS motor score ~43→~38	NO Mean UPDRS ADL score 17.4 +/- 1.5→16.6 +/- 2.4	NO Mean motor score ~21→~21	YES Mean UPDRS dyskinesia score: 6.2→2.6 at 12 months Mean Obeso dyskinesia score: 1.6→0.6 at 12 months, p<0.05	NO Mean daily dose of levodopa increased from 277mg/day preoperatively to 772 mg/day at 12 months, dopamine agonists remained stable (average 201 mg/day) COMT inhibitors increased by average 75 mg/day.	NO Tremor 2.6→1.9
Scotto di Luzio et al. 2001 n=5	YES (all patients improved, degree of improvement not quantified)	YES 41.7%, p<0.006 at 12 months	Not reported	Not significant 10.6%	YES, but benefit deteriorated from 93.3% improvement at 1 month to 55% at 12 months (p< 0.0004)	NO 5.6% increase in mean daily dose of levodopa	Not reported
Krack et al 1998 n=5	NO Reduction of time spent in “on” phase, loss of sleep benefit, and worsening of on-drug dyskinesia (1 patient).	YES 39% (decreased from 53.6 to 32.5)	No significant change	Mild aggravation of dyskinesia	YES 46% (27.8→15.4)	NO (Mean dose increased 29%)	Akinesia improved 30% Worsening of hypophonia and freezing on exam (3 patients) New mild unilateral hand tremor (1 patient). Stimulation-induced dystonic hand posture (1 patient). Stimulation-induced apraxia of lid opening (1 patient).
Ghika et al. 1998 n=6	Daily time spent in “off” state decreased from 40% to 10%	YES Mean motor score decreased from 66 to 30 at 12 months, to 33 at 24 months; improved >50%	YES Mean ADL score decreased from 31 to 6 at 12 months to 10 at 24 months improved ~60%	No significant change Mean motor score decreased from 38 to 17 at 12 months to 28 at 24 months	YES Dyskinesia scores improved by 66% at 12 mo., by 33% at 24 mo.	NO levodopa dosage unchanged	Sub-items of motor scores for bradykinesia, rigidity, gait, and tremor all improved Relatively drug resistant symptoms such as akinesia, especially gait ignition failure, remained unresponsive to stimulation.

Table 7. Key outcomes, studies of bilateral GPi stimulation (cont'd)

Author, Year, N	A Reduction in fluctuations in motor function, length of time in “off” state, “off” period dystonia with stimulation?	B off-medication UPDRS scores improved with stimulation? % improvement in UPDRS score with stimulation during periods when levodopa is not effective (i.e., periods of poor mobility, “off” periods) Motor (III) ADL(II)		C on-medication UPDRS scores improved with stimulation? % improvement in UPDRS scores with stimulation during periods when levodopa is effective, (i.e., periods of good mobility, “on” periods) Motor III Dyskinesia		D Levodopa dosage reduced?	Other Improvement in off-medication cardinal symptoms (UPDRS scores for rigidity, tremor, gait; S/E, H/Y scales) with stimulation?
	Reduced motor fluctuations	“off” Motor (UPDRS III)	“off” ADL (UPDRS II)	“on” Motor (UPDRS III)	Levodopa-induced Dyskinesia (UPDRS IV)	Levodopa reduced?	“off” Cardinal symptoms (UPDRS)
Kumar et al. 2000 n=22	No data	YES Motor: 31%	YES ADL: 32%	Timed walking worsened in the on medication state by 15%	YES Dyskinesia reduced 66%	NO No change in levodopa equivalent dosage	Timed walking: 39%; Timed tapping: 61%
Burchiel et al. 1999 n=4	No data	YES Motor: 39%	NO ADL: 10% (NS)	on-medication axial symptoms were clinically improved only in the GPi group	YES Dyskinesia 47% LID was reduced in both groups	No change	YES Tremor 73% Rigidity 37% Bradykinesia 24%
Pahwa et al. 1997 (5) n=3 bilateral	No separate data for bilateral GPi, but time in “on” state increased from 21% at baseline to 61% at 3 months for 5 patients (3 bilateral, 2 unilateral)	YES Mean score decreased from 56.7 to 42.26% among 3 bilaterally treated patients	No separate data for bilateral GPi	YES Mean score decreased from 48 to 15.368% among 3 bilaterally treated patients	No separate data for bilateral GPi	No separate data for bilateral GPi	No separate data for bilateral GPi

of the GPi was associated with an increase in percentage of time with good mobility and without dyskinesia. “On” time with good mobility and no dyskinesia increased from mean of 28% of daily waking hours prior to surgery to 64% of daily waking hours with stimulation ($p < 0.001$).

Eight trials report a reduction of levodopa-induced dyskinesia (improvement in mean UPDRS IV score), ranging from 33 to 80%. (The ninth study, which does not permit separation of unilateral and bilateral procedure data for this outcome, is not included.)

The therapeutic benefit of bilateral DBS of the GPi upon dyskinesia is more immediately apparent than with bilateral DBS of the STN. The Grenoble group describe an immediate marked improvement in on-drug dyskinesia scores among 5 patients treated with DBS GPi compared to 8 similar patients treated with bilateral DBS of the STN (Krack et al. 1998). They note, however, that long-term reduction of levodopa dosage in the STN group eventually led to a reduction of dyskinesia similar to that achieved with stimulation in the GPi group.

That therapeutic effect of GPi stimulation upon dyskinesia is durable is suggested by Ghika and colleagues (1998). Among 6 patients whose dyskinesias improved (mean UPDRS dyskinesia score improvement of 66%) at 12 months after bilateral GPi electrode implantation, there was a persisting, though somewhat diminished, beneficial effect after 24 months (mean UPDRS dyskinesia score improvement of 33%)

D. Levodopa dosage reduction. Whether GPi DBS merely fails to permit therapeutic reductions in levodopa dosage or, in fact, allows dosage to be increased to a therapeutic level without causing dyskinesia complications is not clear.

In 5 studies, including both multicenter trials, there was no significant change in the daily levodopa requirement. In 3 other studies, the mean daily levodopa dose requirement increased with GPi stimulation. In one trial (Krack et al. 1998), bilateral DBS of the GPi was associated with a mean dose increase of nearly 30%.

Kumar and colleagues (2000) suggest that such contradictory outcomes may be attributed to stimulation of functionally distinct sites in the pallidum. Stimulation of a more ventral region appears to have the greatest therapeutic effect upon dyskinesia and rigidity, while simultaneously blocking the beneficial effect of levodopa and resulting in greater akinesia (Krack et al. 1997; Bejjani et al. 1997). Stimulation of a more dorsal pallidal region may have greater antiparkinsonian effect, but has also been found to cause stimulation-induced dyskinesia (Krack et al. 1997).

E. Cardinal symptoms. Six studies report moderately improved scores in tremor, rigidity, and bradykinesia, during the off-medication state (Krack et al. 1998; Krause et al. 2001; Volkmann et al. 2001; Kumar et al. 2000; Burchiel et al. 1999), but these improvements reached statistical significance in only in the DBS Study Group trial and in the smaller trial by Burchiel and colleagues.

Duration of DBS GPi treatment effect. The effect of GPi DBS appears to be durable for at least 2 years. Ghika and colleagues (1998) report persisting beneficial effects in terms of major

improvement in mean motor scores, ADL scores, and reductions in “off” time, lasting more than 2 years, even though, beginning at 12 months after surgery, these authors reported some signs of decreasing efficacy.

Adverse effects and morbidity. Morbidity and adverse effects associated with DBS GPi appear in Table 8. They consist of worsening of hypophonia, stimulation-resistant gait ignition failure (freezing), new unilateral hand tremor, and stimulation-induced hand posture, transient stimulation side-effects (optic sensations, dystonia, choreoathetosis), subtle loss of verbal fluency, mild worsening of dysarthria, and stimulation-induced apraxia of lid opening . Other adverse effects not specific to GPi DBS included surgery-related wound infection, skin erosions, lead displacement, and acute battery failure.

Summary of Bilateral DBS of the GPi trials

In summary, evidence from 9 studies provides outcomes data for GPi DBS among at least 53 patients. Eight of the 9 studies were non-randomized, open-label clinical series. One small study (n=10) randomized patients prospectively to DBS of either the STN or the GPi. Two studies were larger multicenter trials.

The magnitude of change and reproducibility of results demonstrate a clinically important improvement in motor symptoms of PD and reduction in levodopa-induced dyskinesia can be achieved with pallidal DBS.

Although only one small study is properly designed to compare the two targets for DBS, in general, these studies seem to indicate that bilateral stimulation of the GPi yields a less-marked improvement in off-medication motor symptoms than does bilateral stimulation of the STN. Furthermore, clinical response is achieved using more conservative stimulation parameters with bilateral STN of the DBS than with bilateral DBS of the GPi, a factor important for prolonging battery life. Kumar and colleagues report that response to DBS is less complex with the STN target than the GPi target, making programming easier and less time-consuming in STN DBS (Kumar et al. 1998b).

As noted in the “Review of Evidence” section for bilateral DBS of the STN, a surgical alternative for patients with medically refractory Parkinson’s disease is pallidotomy. Table 5 summarizes the pallidotomy literature. Five studies published between 1995 and 1998 demonstrated only modest motor improvements (14 to 30%) in most patients (115 of 133) after pallidotomy, with more positive motor improvements recorded in only in the study published by Dogali and colleagues (1995; 71% motor improvement among 18 of 133). A contralateral dyskinesia reduction of 70–92% can be obtained with pallidotomy. However, pallidotomy is limited to a unilateral procedure because of unacceptably high risk of adverse neuropsychological outcomes if performed bilaterally.

Table 8: Adverse effects of DBS GPi, published literature

Author Year	Number of patients	Mortality	Significant morbidity Adverse effects
DBS Study Group 2001	41	none	<p>related to procedure: 4 intracranial hemorrhage 3 hemiparesis secondary to hemorrhage 1 seizures 1 dysarthria</p> <p>related to device: 2 migration 1 infection 1 lead break 1 seroma</p> <p>related to stimulation: 3 dyskinesia 2 dystonia 1 abdominal pain (some patients had more than one adverse effect)</p>
Volkman et al. 2001	11	none	<p>procedure related: 3 confusion (transient) 2 infection of lead or generator (1 transient, 1 serious) 2 lead dislodgment (1 transient, 1 serious) 4 skin erosion (2 transient, 2 serious) 1 neuralgia (transient)</p> <p>system related: none</p> <p>therapy related: 1 more frequent falls (transient) 6 weight gain >10 kg (3 transient, 3 ongoing) (more than one complication may have occurred in a single patient)</p>
Krause et al. 2001	6		<p>1 withdrawal because of severe depression 2 reports of strong increase in libido, requiring psychiatric inpatient treatment in some cases 1 report of visual irritation at certain stimulation intensity levels, but reduction in visual field (via Goldmann perimetry) 2 severe dysarthria, in one case so severe that the patient became permanently unable to speak understandably 1 report of severe psychosis that developed one year after stimulator implantation</p>
Scotto di Luzio et al. 2001	5	none	<p>2 mild transient confusion immediately after surgery 2 transient dysarthria 1 subcutaneous infection, requiring lead and IPG removal</p>
Krack et al. 1998a	5	none	<p>2 worsening hypophonia 1 mild unilateral hand tremor 1 stimulation-induced mild dystonic hand posture 1 apraxia of lid opening 1 loss of on-time duration and worsening of on-medication akinesia</p>

Table 8: Adverse effects of DBS GPi, published literature (cont'd)

Author Year	Number of patients	Mortality	Significant morbidity Adverse effects
Ghika et al. 1998	6	none	3 neuropsychological worsening (speech fluency, dysarthria) 1 worsening of Beck's depression inventory 1 wound infection 3 acute failure of stimulator after passing through security magnets in department stores 1 battery failure at one year
Kumar et al. 2000 (Multicenter)	17	none	(reported for all unilateral and bilateral patients) Transient adverse effects as optimal stimulation parameters were being sought (paresthesias, tonic contraction, dysarthria, photopsia, nausea – in almost all patients. 2 scalp cellulitis, one requiring removal of electrode, 1 chest wall infection; 2 hardware fractures requiring surgical replacement 3 battery failure in less than one year bilateral GPi: 1 apraxia of eyelid opening
Burchiel et al. 1999	10	none	1 severe dyskinesia during intraoperative stimulation 1 infraclavicular hematoma after generator placement, resolved spontaneously adverse events during stimulation parameter adjustment (transient paresthesia, balance impairment, dysarthria, dysphagia, hypomimia) occurred in both GPi and STN groups facial dystonia and limb dyskinesia occurred in STN patients, subsided immediately with stimulation parameter adjustment; unintentional switching off of stimulators by external electromagnetic fields (theft detectors, high-power transmitters) occurred on multiple occasions, leading to spontaneous cessation of stimulation
Pahwa et al. 1997	3	none	1 asymptomatic intracranial hemorrhage seen on routine postop CT 1 transient speech difficulty and hemiparesis resolving in 5 minutes in the operating room 1 facial dystonia and paresthesia requiring surgical repositioning of a lead 6 weeks after initial implantation 1 transient visual disturbance 1 choreiform movement of foot related to stimulation
Comparison with complications reported with ablative pallidal surgery for Parkinson's disease			
(1) Samuel et al. 1998		0-8% (1,3)	confusion 4-10% (1,2) intracranial hemorrhage 1.5-12% (1,3,4)
(2) Lang et al. 1997			infection 0.5-2.7% (3) dysarthria 0.6-27% (1-4)
(3) Tasker 1998			cognitive difficulty 0.8-12.5% (2,3)
(4) Vitek et al. 1998			seizures 0.5-8.0% (1,3,4)

There are no studies directly comparing chronic bilateral DBS of the GPi with unilateral pallidotomy. Unlike the pallidal ablative procedure, stimulation of the GPi has advantages of being reversible and adjustable. Furthermore, the fact that stimulation of the GPi, unlike pallidotomy, can be offered bilaterally is advantageous, since Parkinson's disease most often affects both sides of the body. Finally, it is possible that bilateral DBS of the GPi may be preferable to DBS STN for some patients, particularly those in whom levodopa-induced dyskinesia is the primary obstacle to an otherwise optimal drug effect.

Definitive determination of which stimulation target, the STN or GPi, provides most effective therapy requires a well-designed randomized clinical trial. Such a trial is scheduled to begin in 2002. A Veterans Administration/National Institutes of Health (VA/NIH) Cooperative trial, involving 6 Parkinson's disease centers and their university affiliates, will enroll 300 patients beginning in the first quarter of 2002. Patients will be randomized to either immediate DBS surgery or delayed DBS surgery after a 6 month trial of best medical management. Each surgical group will be further randomized to either STN or GPi target. All patients will be followed-up for 2 years.

Results of the trial can be expected in approximately 5 years (personal communication, Matt Stern, M.D., University of Pennsylvania, November 6, 2001).

Neuropsychological outcomes of bilateral DBS of the STN or the GPi

Whether neurobehavioral effects of bilateral DBS of the STN or GPi are similar to the effects of ablative procedures has not been determined. There are no studies directly comparing the effects of unilateral or bilateral stimulation and ablation and only few studies examining the neurobehavioral outcomes of stimulation (Table 9).

Observations from patients with hemiparkinsonism suggest that the right and left basal ganglia have distinctly different roles in mediation of verbal and visuospatial abilities. Patients with right hemiparkinsonism (disease involvement of the left basal ganglia) show greater deficits in verbal abilities, especially in work-list memory performance and verbal fluency, than patients with left hemiparkinsonism (Green and Barnhart 2000; Blonder et al. 1989; Spicer et al. 1988; Starkstein et al. 1987; Taylor et al. 1986). Conversely, though less consistently, patients with left hemiparkinsonism have more profound visuospatial deficits (Green and Barnhart 2000; Blonder et al. 1989; Starkstein et al. 1987; Taylor et al. 1986; Spicer et al. 1988).

Evidence shows that laterality of a surgically created lesion is a significant determinant of neuropsychological sequelae after unilateral pallidotomy. Most patients with bilateral PD are right-handed. To maximize improvement in motor control of their dominant hand, these patients are often treated with a left pallidotomy. Green and Barnhart (2000) note that the convention of providing such patients, as well as those with predominant right-sided parkinsonian symptoms, with a left pallidotomy lesion may place patients with already mildly impaired verbal ability at greater risk for significant postsurgical loss of verbal function.

Table 9: Neuropsychological Outcomes after bilateral STN DBS or bilateral GPi DBS

Author Center Year	N	Evaluation condition Domain assessed (Assessment method)	Improved (gain, improvement)	Worsened (Decline)	Authors' Conclusions
Alegret et al. 2001 Barcelona	15 patients consecutive all STN all bilateral	Examinations were performed 3 days before and 3 months after surgery, between 8–9:00 a.m. with patients free of medication for a minimum of 12 hours. Declarative memory (Rey Auditory Verbal Learning Test RAVLT) Visuo-spatial function (Line Orientation Test of Bent et al. Prefrontal functions (Trail-Making Test) Phonetic and semantic verbal fluency (Stroop and word-color tests) Obsessive-compulsive traits (Maudsley Obsessional Compulsive Inventory (MOCI)	Prefrontal function (Trail-making A Test) Obsessive-compulsive traits (MOCI)	Phonetic and semantic verbal fluency (Stroop color test, Declarative memory (RAVLT) Visuo-spatial function (Line Orientation Test performance);	“This study shows that bilateral STN-DBS, which provides impressive motor benefits in patients with medically intractable PD, produces both beneficial and detrimental neuropsychological changes.” “All surgical procedures (for PD) involving the left of both hemispheres seem to negatively influence verbal memory. Since pallidotomy, GPi stimulation, sub-thalamotomy and STN-DBS produce functional changes of the GPi and thalamus, and since these nuclei are related to memory processes (such as associative memory), changes in learning ability are to be expected”
Pillon et al. 2000 Grenoble and Paris	76 patients Group 1: 56 patients from Grenoble: STN: 48 GPi: 8 Group 2: 20 patients from Paris: STN: 15 GPi: 5 all bilateral	Group 1: Assessed before surgery and at 3 months and 12 months, with stimulator turned “on” and “off”, without levodopa (after 12 hours’ withdrawal): Wisconsin Card Sorting Test, Verbal fluency tests, Graphic and motor series, role of control of attention on task performance: (Stroop Tests, Trail Making Test) Group 2: Assessed before surgery and at 3 and 12 months, with stimulators “on” Global intellectual efficiency (Mathis Dementia Rating) Verbal learning (Grober and Buschke Test) Mood (Beck Depression Inventory) Group 2: Assessed at 6 months, with stimulator turned “on and “off,” with levodopa dose maintained: Tests of executive function previously shown to be sensitive to levodopa therapy: From the Cambridge Neuropsychological Tests Automated Battery (CANTAB), simple and choice reaction times (Motor Screening and Big Little Circle) cognitive flexibility, spatial Working Memory Verbal working memory: Digit Ordering Tests	Among STN patients: STN Group 1: Increased psychomotor speed (seen in word and color condition of the Stroop tests, and forms A (simple tracking) and B (cognitive shifting) of Trail Making Tests; STN Group 2: Improvement in the reaction time tests (simple and choice) from CANTAB STN Group 2: Spatial working memory (significant improvement); STN Group 2: Verbal working memory (trend toward significant improvement) “These positive changes were less than one SD for most patients”	Among Group 1 STN patients: Category fluency (significant long-term decrease in performance) Literal fluency (trend toward deficit)	Group 1: “Our results showed <ul style="list-style-type: none"> • cognitive improvement in psychomotor speed and working memory in STN patients with stimulator turned “on”; • no overall differential effect between STN and GPi stimulation, • no cognitive long-term effect of DBS at 12 months, except for a mild lexical fluency deficit in STN patients. Group 2 Evaluations “suggest a greater improvement under stimulation for STN patients, but there was no group effect and no interaction between group and stimulation conditions given high between-subject variability.”

Table 9: Neuropsychological Outcomes after bilateral STN DBS or bilateral GPi DBS (cont'd)

Author Center Year	N	Evaluation condition Domain assessed (Assessment method)	Improved (gain, improvement)	Worsened (Decline)	Authors' Conclusions
St. Cyr et al. 2000 Toronto	11 patients (all STN) 67 years all bilateral	Evaluation with stimulator on, in the medication "best on" state, at 3-6 months and at 9-12 months: Attention (Digit Span B and F, Trail Making Test A, Paced Auditory Serial Addition Test) Visual learning and memory (Batterie D'efficence mnesique) Executive function (Conditional Associative Learning Test, Trail Making Test B) Verbal learning and memory (California Verbal Learning Test) Language fluency (FAS/CFL) Mood (Frontal Lobe Personality Scale, Geriatric Depression Inventory) Personality (Frontal Lobe Personality Scale) Functional MRI Fine motor (Purdue Pegboard, grip strength, coin sorting while finger tapping) Motor UPDRS	Mood (NS except for elderly subgroup which improved transiently until 12 months postop)	Attention Visual learning and memory (at 3-6 months, recovered at 9-12 months) Executive function Verbal learning Language fluency Personality	Declines were more consistently observed inpatients who were older than 69 years, leading to a mental state comparable with progressive supranuclear palsy. "Frontal" behavioral dyscontrol without the benefit of insight was also reported by half (3/6) of the caregivers of the elderly subgroup. At 9-12 months postoperative, only learning based on multiple trials had recovered. Tasks reliant on the integrity of frontal striatal circuitry either did not recover or gradually worsened over time. Bilateral STN DBS can have a negative impact on various aspects of frontal executive functioning, especially in patients older than 69 years.
Trepanier et al. 2000 Toronto	9 (same patients as described in Kumar et al. 1998, 1999, and St. Cyr et al. 2000) all bilateral	Same evaluation as above, comparison with patients treated with unilateral pallidotomy [total (n= 42), left side (n=18), right side (n=24)], bilateral STN DBS [total (n=9), age >69 (n=5)], and bilateral GPi DBS ((n=4)	For STN DBS group, see above St Cyr et al. For GPi DBS group: No improvements	For STN DBS group, see St Cyr et al. For GPi DBS group: Attention Language fluency (1/1)	Neuropsychological sequelae of posteroventral pallidotomy (n=42), bilateral STN DBS (n=9), and bilateral GPi DBS (n=4). "Our four GPi DBS patients (all less than 70 years old) showed fewer of the deleterious effects (working memory, executive functioning, long delay free and cued recall on the CVLT, FAS, RIE-BEM) seen in the other groups but these observations are too preliminary to draw any conclusions." "In our limited experience, staged bilateral PV pallidotomy appears to be the most psychologically toxic procedure. Two of three patients suffered major cognitive decompensation across all domains, but especially in area of executive functioning..." "Patients with unilateral PV pallidotomy can experience improvements in allocation of attentional resources but can also suffer declines in working memory, certain aspects of executive functioning, and lateralized declines in verbal learning and fluency post-left [lesions] and visuo-constructional abilities in post- right lesions."

Table 9: Neuropsychological Outcomes after bilateral STN DBS or bilateral GPi DBS (cont'd)

Author Center Year	N	Evaluation condition Domain assessed (Assessment method)	Improved (gain, improvement)	Worsened (Decline)	Authors' Conclusions
Burchiel et al. 1999	9 (5 STN, 4 GPi) all bilateral	Visuo-motor processing (Symbol Digits Modalities Test) Memory (Controlled Oral Work Association Test, Hopkins Verbal Learning Test, Memory Assessment Scale: Names and Faces) Attentional capacity (Digit Span), Cognitive impairment (Cognitive Difficulties Scale) Auditory span (Sentence Repetition) Mood (Beck Depression Inventory)	Among all patients, the Cognitive Difficulties Scale, which measures everyday inefficiencies caused by lapse of memory or attention were improved compared with on-LD baseline.	Beck Depression Inventory score improved 49%, from 14.3 +/-6.2 at baseline to 7.3 +/- 3.2 at 12 months	Memory attention, and visuomotor processing unchanged at 12 months;
Ardouin et al. 1999 Grenoble and Paris	62 patients (49 STN, 13 GPi) 54.6 years all bilateral	Evaluation with optimal doses of levodopa in some cases only , and with stimulator on in all cases, at 3 months (n=41, Grenoble group) and 6 months (n=8, Paris group) Global intellectual efficiency (Mattis Dementia Rating Scale) Verbal learning (Grobe and Buschke Test) Executive function (simplified version of Wisconsin Card Sorting Test) Inhibition of interference aspects of control of attention on task performance (Stroop Test) Set shifting aspects of control of attention on task performance (Trail Making Test) Mood assessment (Beck Depression Inventory)	Control of attention (Trail Making Test, parts A,B) Mood	Literal and total lexical fluency	Under stimulation, only 4 of 25 cognitive variables were affected by DBS. Literal and total lexical fluency worsened significantly in the entire population and in patients with STN DBS, but not in patients with GPi DBS. "Stimulation of the STN or GPi does not change the overall cognitive performance in Parkinson's disease and does not greatly affect the functioning of subcortical loops involved in cognition in humans."
Moro et al. 1999 Rome	15 (all STN) all bilateral	General mental status (Mini-Mental State Examination) Verbal memory (Rey's Auditory Verbal learning test), Verbal fluency and intelligence (Raven's progressive matrices)			Nonsignificant improvements in MMSE score and Raven's matrices, trend toward improvement for Rey's delayed recall, trend toward worse performance for verbal fluency (mean - 17.3%, p=0.109)
Krack et al. 1998a Grenoble	13 "young-onset PD" (8 STN, 5 GPi) all bilateral	Method of assessment not specified			"None of the patients experienced permanent adverse effects related to the surgical procedure. In particular, there was no permanent change detected in the neuropsychological follow-up examinations (data not shown).
Kumar et al. 1998a Toronto	9 elderly late stage PD (all STN) all bilateral	Method of assessment not specified			1 "mild reduction in verbal memory" with postop MRI evidence of a new thalamic lesion 1 "mild personality change" 1 patient with preop "progressive cognitive decline experienced an abrupt decline in most areas of cognition after surgery"

The hypothesis that lesion laterality is associated with specific patterns of adverse neuropsychological sequelae finds support in a number of studies (Green and Barnhart 2000). For example, Trepanier and colleagues (1998) examined neuropsychological consequences among 42 Parkinson's disease patients treated with unilateral pallidotomy. They found that left lesions led to a loss of verbal learning (-2.2 SD) and of verbal fluency (-1.6 SD) among 60% of 18 patients so treated. None of these patients recovered verbal-learning ability by 12 months after surgery. Among 24 patients treated with right pallidotomy, there was a loss of visuo-spatial constructional abilities (-3.5 SD), which however, fully resolved by 12 months after surgery. Behavioral changes of a "frontal nature" were reported in 25% to 30% of all patients.

Thus some patients, who were generally pleased with the motor outcomes of the pallidotomy procedure, were often "restricted in their ability to function properly at work or in social settings" by adverse postsurgical neuropsychological effects. Similarly, Stebbins and colleagues (2000) reported significant declines in performance on all measures sensitive to frontostriatal integrity among a group of 11 Parkinson's disease patients treated with pallidotomy, but no such changes in a control group of patients with Parkinson's disease, matched to the treatment group for age, education, UPDRS motor score, and Hoehn and Yahr score during the on-medication period.

Ten studies addressing whether bilateral DBS poses this same risk are presented in Table 9. There is great variation among these studies in terms of design, extent to which patients were characterized at preoperative baseline, the neuropsychological and psychiatric measures employed, the frequency of and interval between examinations, the inclusion of a control group, and methods used for statistical analysis.

If only the most recent publication from each medical center is considered, neuropsychological evaluation for 139 patients with advanced Parkinson's disease treated with DBS of either the STN or the GPi are available. Although the studies vary in their assessment of the degree of neuropsychological risk associated with DBS, there appears to be some consensus that the risk, while present, is minimal. Common to nearly all studies is a finding of some degree of compromise in the realm of verbal learning and/or language fluency after implantation of DBS electrodes.

For example, in the recently published and particularly carefully designed trial by Alegret and colleagues (2001), memory, visuo-spatial and frontal function are evaluated in 15 patients with Parkinson's disease before and 3 months after bilateral implantation of DBS STN stimulators. These investigators found that bilateral STN DBS produced a mixture of beneficial changes (moderate improvement in a prefrontal task and obsessive-compulsive traits) and detrimental changes (moderate deterioration of verbal memory).

Noting that, in general, all surgical procedures (for Parkinson's disease) involving the left or both hemispheres appear to negatively affect verbal memory, they conclude that, since the involved nuclei are related to memory processes, some change in learning ability after these surgical procedures is to be expected.

Although the studies vary in their assessment of the degree of neuropsychological risk associated with DBS, many of the studies are meticulously detailed and some include relatively large study populations. Considered together, there appears to be, among these 10 studies, some degree of consensus that neurocognitive risk, while present, is minimal.

Preliminary data published by Morrison and colleagues (200), using a new protocol, the Program for Neuropsychological Investigation of Deep Brain Stimulation (PNIDBS) supports this consensus. Their preliminary results suggest that the DBS procedure has a minimal impact on cognitive functioning in most patients studied.

It appears, from the available evidence, that the impressive motor benefits achieved with bilateral DBS may be accompanied by some adverse neurocognitive effects. However, it also appears that this negative impact upon neurobehavioral function is not as clinically meaningful to most patients as the potential motor improvement. In other words, at this time, for most investigators and patients, the motor benefits of DBS appear to outweigh the neuropsychological risks.

SUMMARY ACCORDING TO APPLICATION OF THE TECHNOLOGY EVALUATION CRITERIA

Based on the available evidence, the Blue Cross and Blue Shield Medical Advisory Panel made the following judgments about whether bilateral DBS of the STN or the GPi for the treatment of advanced Parkinson's disease meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

In August 1997, the U.S. Food and Drug Administration (FDA) approved the premarket application (PMA) for the Aactiva® Tremor Control System (Medtronic, Inc., Minneapolis, MN) for use in patients with essential tremor or tremor caused by Parkinson's disease. In March 2000, the FDA's Neurological Devices Panel Advisory Committee unanimously recommended for final FDA approval the bilateral use of the Medtronic device via supplemental PMA for the treatment of advanced Parkinson's disease (U.S. Food and Drug Administration 2000). The supplemental PMA for the Aactiva® Parkinson's Control Therapy system received final FDA approval on January 14, 2002 (U.S. Food and Drug Administration 2002). As a condition of approval, the company has agreed to conduct a 3-year, post-approval study of the system to assess its long-term clinical results.

Bilateral DBS of the STN or GPi for the treatment of symptoms of advanced Parkinson's disease, therefore, meets the first criterion.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

There are no large prospective randomized studies with long-term follow-up of bilateral DBS for treatment of advanced Parkinson's disease. In no published studies are patients randomized to

treatment arms to compare bilateral DBS with best medical management. Only one small pilot study compares the STN and GPi targets for bilateral DBS using prospective randomization.

Nevertheless, the published scientific evidence is compelling because of the numbers of consecutively treated patients described, the consistency of the findings across studies, and the magnitude of clinical improvements observed on standardized rating scales of neurologic function.

Fourteen published trials present motor outcomes following bilateral STN DBS among 186 patients, with follow-up for at least 6 months for 151 patients and for at least 12 months for 116 patients. Nine published trials present motor outcomes following bilateral GPi DBS among at least 53 patients, with follow-up for at least 3 months (n=53) and for as long as 30 months (n=6).

In addition, 10 trials examine neuropsychological function following bilateral DBS of either nucleus among at least 139 patients.

3. The technology must improve the net health outcome.

Parkinson's disease is a chronic, progressive neurodegenerative disease. Pharmacologic therapy generally relieves symptoms early in the course of the disease, but does not halt disease progression. Most patients, after a time, experience a progressive loss of benefit from levodopa. After 5–10 years of pharmacologic therapy, 50–90% of patients experience motor fluctuations. Motor fluctuations are sudden shifts from the “on” state (during which the effect of levodopa facilitates motor control) to the “off” state (during which medication is not working). In the “off” state, the patient may suddenly become rigid, unable to walk, or even akinetic or “frozen.” Patients with advanced disease may also experience dyskinesias, involuntary movements of the head, neck, torso, or limbs, which are often painful. Thus, advanced disease is characterized by ever-longer “off” periods, and disruption of “on” periods by medication-induced dyskinesia. None of these symptoms can be expected to resolve spontaneously with continued pharmacologic treatment.

In the studies examined in this Assessment, improvement in motor function with bilateral DBS of either the STN or the GPi is consistently demonstrated in each study.

The published studies demonstrate statistically significant improvement in treated patients, as measured by standardized rating scales of neurologic function. The most frequently observed improvements consist of: increased waking hours spent in a state of mobility without dyskinesia; improved motor function during “off” periods; reduction in frequency and severity of levodopa-induced dyskinesia during “on” periods; and improvement in cardinal symptoms of Parkinson's disease during “off” periods. With bilateral DBS of the STN, reduction in the required daily dosage of levodopa and/or its equivalents is observed.

The magnitude of these changes is both statistically significant and clinically meaningful. In the most recent multicenter trial, “on” time without dyskinesia increased from 27% of waking hours at baseline to 74% of waking hours 6 months after bilateral implantation of electrodes in the STN and to 64% of waking hours with bilateral implantation in the GPi. Similarly, motor scores in the

“off” medication state improved by 51% in the STN group and by 35% in the GPi group. In the same trial, a global assessment by both patients and physicians indicated a reduction of severe disability from approximately 75% at baseline to 15% (physician assessment) and 23% (patient assessment) 6 months after surgery. The reduction in disability was due largely to less-frequent and less-severe “off” periods and increased “on” time free of dyskinesia. Other smaller trials report similar outcomes. Among smaller studies, mean “off” period motor scores improved by 34% to 74% in the STN groups. In studies that included patients undergoing bilateral GPi DBS, mean “off” period motor scores improved by 26% to 65% in the GPi groups, with the exception of one small German study, which showed no significant change in motor scores.

The beneficial treatment effect lasts at least for the 6–12 months observed in most trials. The available data with longer term follow-up are generally positive. For example, among 110 patients followed for 1–83 months in a French study, persisting significant motor improvement was observed in 16 patients at 3 years and in 4 patients up to 5 years after bilateral implantation of DBS electrodes.

Adverse effects and morbidity associated with bilateral DBS of the STN or GPi are similar to those known to occur with thalamic stimulation. They include complications related to the procedure, to the device itself, and to the effects of stimulation. In the multicenter DBS Study Group trial, 2.8% of patients had persistent neurologic deficits due to intracranial hemorrhage. Other common adverse effects include infection (n=4 of 143), lead migration (n=5 of 143), and dyskinesia requiring adjustment of stimulation parameters (n=5 of 143). Case reports have shown that inadvertent turning off of the device may bring on a sudden return of severe symptoms and the medical emergency condition of parkinsonian crisis.

Ten studies address the possibility neuropsychological sequelae of bilateral DBS. Altogether, these studies present evidence gathered from 139 patients. Common to nearly all studies is some degree of compromise in the realm of verbal learning and/or language fluency after bilateral implantation of DBS electrodes. For example, in a carefully designed trial examining memory, visuo-spatial and frontal function in 15 patients before and 3 months after implantation, bilateral STN DBS produced both beneficial and detrimental changes. Beneficial changes were moderate improvement in prefrontal task performance and obsessive-compulsive traits, but moderate deterioration of verbal memory was also observed.

In general, all surgical procedures for Parkinson’s disease involving the left or both hemispheres appear to negatively affect verbal memory. Therefore, some change in learning ability after these surgical procedures is to be expected, as the involved nuclei are related to memory processes.

4. The technology must be as beneficial as any established alternatives.

Unilateral pallidotomy is an established surgical alternative for treatment of advanced Parkinson’s disease. The improvements in “off” period motor function following bilateral DBS of the GPi or STN appear to be as great as, or perhaps greater than, those seen after unilateral pallidotomy. The DBS Study Group reports motor improvements of 34% and 51% for bilateral DBS of the GPi and STN respectively among 127 patients. Studies of pallidotomy offer an

indirect comparison: “off” period motor improvements ranged from 14–30% among a total of 115 patients in 5 studies, and a sixth study of 18 patients found 71% improvement.

DBS has other advantages. Unlike pallidotomy, which is no longer recommended as a bilateral procedure because of high risk of serious postoperative neuro-cognitive dysfunction, DBS can be performed as a bilateral procedure. Furthermore, DBS is not an ablative procedure. Unlike an ablative procedure, which cannot be undone, DBS electrodes can be removed. Finally, there appears to be less operative morbidity associated with DBS than with pallidotomy, possibly because the final step of the pallidotomy surgery, thermocoagulation, is unnecessary.

The currently available data suggest that bilateral DBS of the STN may provide a more consistent and more positive improvement than bilateral DBS of the GPi. Using the DBS Study Group data as the most representative evidence, bilateral DBS of the STN resulted in a mean 51% improvement in “off” period motor scores, a 44% improvement in “off” period ADL scores, a 25.8% improvement in “on” period motor scores, and a 57% reduction in “on” period dyskinesia. All of these changes were significant (each with $p < 0.001$).

For bilateral GPi DBS, the magnitude of change is less marked and, for certain measures, reaches a lesser degree of statistical significance. During GPi DBS, mean “off” period motor scores improved by a 32%, “off” period ADL scores by 38%, “on” period motor scores by 26.8%, and “on” period dyskinesia was reduced by a mean of 66%. The changes following GPi DBS reached a statistical significance of $p < 0.001$ only for the “off” period motor and ADL scores.

Reduction in daily levodopa dosage was possible only with bilateral DBS of the STN. The mean levodopa dosage reduction from about 1,200 mg per day preoperatively to about 760 mg per day at 6 months with bilateral DBS of the STN was highly significant ($p < 0.001$). In no studies has the dosage of levodopa been reduced following bilateral DBS of the GPi.

Despite these apparent differences, there are important issues that warrant further examination of GPi DBS. First, the DBS Study Group data indicate that cardinal symptoms of Parkinson’s disease (i.e., tremor, rigidity, bradykinesia, gait disturbance) are ameliorated by stimulation of either target, with statistical significance $p < 0.001$ for each symptom.

While a reduction in daily levodopa dosage may be a beneficial health outcome in most cases, it may not always be so. During bilateral DBS of the STN, a reduction in levodopa is often necessary to reduce the dyskinesia that may accompany the procedure. Observations from a study of bilateral DBS of the STN in 8 patients with early onset Parkinson’s disease indicate levodopa reduction may have some negative aspects. Despite the fact that stimulation provided off-period motor function similar to their best on-drug periods, some of these patients complained of a lack of energy and initiative during off-drug periods and other off-drug symptoms such as anxiety following major decreases in levodopa dosage.

Patients who have undergone unilateral pallidotomy represent another subset in whom DBS of the STN may be contraindicated because postoperative levodopa dose reduction that may be required to prevent dyskinesia on the stimulated side may make any further levodopa treatment of parkinsonian symptoms of the ablated side impossible.

Finally, preliminary studies of bilateral DBS of the GPi reveal that each cardinal symptom of Parkinson's disease appears to have a unique topography and pathophysiology within the GPi. Thus, depending upon the topography of the DBS electrode, further study may demonstrate stimulation of the GPi target to be more effective for those patients in whom a specific symptom, such as dyskinesia, is a dominant complaint.

In summary, bilateral DBS of either the STN or GPi have consistently resulted in significant therapeutic response in 14 (n=186) and 9 trials (n=153), respectively. It is unknown whether some of the apparent differences in effectiveness are due to differences in study design (randomization versus consecutive cases), patient selection (age, disease severity, and duration), clinical and technical methodology (location of DBS electrodes, setting of stimulation parameters), or other factors. Judgment about the superiority of one target over the other in the absence of a well-designed, prospective, randomized clinical trial is premature at this time.

At present, only one small trial compares the two targets in a prospective, randomized, blinded study design. Definitive determination of which stimulation target, the STN or GPi, provides most effective therapy may be provided by a recently approved trial. The Veterans Administration/National Institutes of Health Cooperative Trial, involving 6 Parkinson's disease centers and their university affiliates, will enroll 300 patients beginning in the first quarter of 2002.

5. The improvement must be attainable outside the investigational settings.

The results for bilateral DBS for advanced Parkinson's disease that are reported in the literature have been achieved at experienced centers. Bilateral DBS meets this criterion when performed at centers that can demonstrate comparably low procedure-related morbidity and mortality.

Based upon the above, bilateral deep brain stimulation of the subthalamic nucleus or the globus pallidus interna for patients with advanced Parkinson's disease meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

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APPENDIX

Table A. Definitions of terms used in studies of Parkinson’s disease

“off” periods	Has been used to refer to a variety of conditions, ranging from brief periods when patients experience certain parkinsonian symptoms, such as immobility and loss of dexterity, due to a temporary loss of medication effect to the condition that occurs after a prolonged withdrawal of anti-parkinsonian medication
“off” condition	Also known as the “practically defined ‘off’ condition”, the term “off condition” is now defined as that condition observed after a patient has received no antiparkinsonian medications for 12 hours. An operational definition, the term “off” condition ignores what true off is, or that there may be several types of off. This term was adopted as a working definition at the recommendation of the CAPIT committee in 1992 in order to promote standardization and comparability of PD studies. In studies of Parkinson’s disease, the term “off” usually refers to a standard “practically defined ‘off’ condition” created for purposes of the study by withdrawal of medication for 12 hours.
“worst off”	A condition that both the patient and physician agree is about as severe as their parkinsonism ever gets. This term was recommended by the CAPIT committee to account for the fact that the practically defined off may not always reflect the patient’s most severe off periods
“end-of-dose deterioration” or “wearing off” phenomenon	“Wearing off” episodes occur when the benefit of a given dose of levodopa lasts less than 4 hours. “Wearing off” is perceived by the patient as a loss of mobility or dexterity, usually taking place gradually (over minutes to one hour), and having a close temporal relationship to timing of medications. “Wearing off” episodes may be treated by modifications of pharmacologic treatment, such as increasing the dose of levodopa if the patient does not have dyskinesia, increasing the frequency and using smaller doses if the patient does have dyskinesia, adding a dopamine agonist, adding a COMT inhibitor, using a sustained-release formulation of levodopa (if the patient does not have dyskinesia or psychosis), switching to liquid levodopa/carbidopa for fine titration, or adding selegiline.
motor fluctuations	Alternations between “on” periods, during which the patient experiences a good response to antiparkinsonian medication (that is, experiences good mobility and dexterity) and “off” periods, during which parkinsonian symptoms become worse. Patients are said to experience “motor fluctuations” once the benefit of a dose of levodopa lasts less than 4 hours. Most patients treated with levodopa experience predictable “off” periods as the effect of the most recent dose wears off (see “end-of-dose” or “wearing off” above). Some patients experience unpredictable “off” periods that occur suddenly without warning, over a period of seconds or minutes, last minutes to hours, and appear to have no relationship to the time of levodopa administration or the plasma levodopa concentration.
freezing or “motor blocks”	Hesitancy or freezing of motor behavior, particularly involving gait. In most patients, freezing or “motor blocks” are later treatment-resistant symptoms that occur independently of medication and are not responsive to manipulation of levodopa. In some patients, freezing may be a manifestation of an inadequate or an excessive dopamine effect.
“on”	The period of maximum mobility and smooth motor function occurring in response to a dose of levodopa and/or other antiparkinsonian medication
“best on”	That condition that the patient and physician both agree represents the maximal therapeutic benefit from medication

Table A. Definitions of terms used in studies of Parkinson’s disease (cont’d)

dyskinesia	<p>Abnormal involuntary movements, usually choreiform or dance-like, but may also have the appearance of dystonia, myoclonus, tics.</p> <p>Levodopa-induced dyskinesia tends to affect the head, neck, torso, limbs, respiratory muscles, are reversible, and rapidly disappears with reduction of withdrawal of levodopa;</p> <p>Anticholinergic induced dyskinesia involves the oro-facial-lingual muscles, as with tardive dyskinesia</p> <p>Peak dose dyskinesia (improvement-dyskinesia-improvement or I-D-I): the earliest and most common form of dyskinesia, occurring at the time of maximum or “peak-dose” levodopa response</p> <p>D-I-D dyskinesia: a diphasic pattern of adventitious dyskinetic movements which appear before a therapeutic response to levodopa has begun, disappear during the “on” period, then re-emerge as the beneficial effect of levodopa wears off. (dyskinesia – improvement – dyskinesia)</p>
dystonia	<p>An increased muscle tone resulting in fixed abnormal postures. Dystonia appears in some patients as abnormal involuntary irregular forceful twisting movements of the trunk and extremities producing bizarre movements and positions of the body.</p> <p>Dystonic movements may increase during volitional motor activity and emotional stress, and disappear during sleep.</p> <p>In PD, dystonia tends to involve the distal extremities.</p> <p>Is also seen in untreated Parkinson’s disease.</p> <p>May be the earliest manifestation of levodopa-induced dyskinesia</p> <p>Important to distinguish whether dystonia occurs during “off” period in patients who have motor fluctuations, or during “on” periods and is due to medication.</p> <p>Dystonia in Parkinson’s disease is more commonly associated with “off” periods among patients with motor fluctuations.</p>
Hemiballismus	<p>A hyperkinetic movement disorder characterized by violent flinging motions in the arm contralateral to a lesion in or near the subthalamic nucleus. May also include a rotary movement at the shoulder and hip, and flexion and extension movements in the hand and foot.</p>

From Lang and Lozano 1998; Obeso et al. 2000a.

Data Elements of the Unified Parkinson's Disease Rating Scale (UPDRS) Data Form

I. MENTATION, BEHAVIOR AND MOOD

1. Intellectual Impairment

0 = None.

1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.

2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.

3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.

4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)

0 = None.

1 = Vivid dreaming.

2 = "Benign" hallucinations with insight retained.

3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.

4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. Depression

1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.

2 = Sustained depression (1 week or more).

3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).

4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative

0 = Normal.

1 = Less assertive than usual; more passive.

2 = Loss of initiative or disinterest in elective (nonroutine) activities.

3 = Loss of initiative or disinterest in day to day (routine) activities.

4 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING (for both "on" and "off")

5. Speech

0 = Normal.

1 = Mildly affected. No difficulty being understood.

2 = Moderately affected. Sometimes asked to repeat statements.

3 = Severely affected. Frequently asked to repeat statements.

4 = Unintelligible most of the time.

6. Salivation

0 = Normal.

1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.

2 = Moderately excessive saliva; may have minimal drooling.

3 = Marked excess of saliva with some drooling.

4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

0 = Normal.

1 = Rare choking.

2 = Occasional choking.

3 = Requires soft food.

4 = Requires NG tube or gastrostomy feeding.

8. Handwriting

0 = Normal.

1 = Slightly slow or small.

2 = Moderately slow or small; all words are legible.

- 3 = Severely affected; not all words are legible.
- 4 = The majority of words are not legible.

9. Cutting food and handling utensils

- 0 = Normal.
- 1 = Somewhat slow and clumsy, but no help needed.
- 2 = Can cut most foods, although clumsy and slow; some help needed.
- 3 = Food must be cut by someone, but can still feed slowly.
- 4 = Needs to be fed.

10. Dressing

- 0 = Normal.
- 1 = Somewhat slow, but no help needed.
- 2 = Occasional assistance with buttoning, getting arms in sleeves.
- 3 = Considerable help required, but can do some things alone.
- 4 = Helpless.

11. Hygiene

- 0 = Normal.
- 1 = Somewhat slow, but no help needed.
- 2 = Needs help to shower or bathe; or very slow in hygienic care.
- 3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
- 4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes

- 0 = Normal.
- 1 = Somewhat slow and clumsy, but no help needed.
- 2 = Can turn alone or adjust sheets, but with great difficulty.
- 3 = Can initiate, but not turn or adjust sheets alone.
- 4 = Helpless.

13. Falling (unrelated to freezing)

- 0 = None.
- 1 = Rare falling.
- 2 = Occasionally falls, less than once per day.
- 3 = Falls an average of once daily.
- 4 = Falls more than once daily.

14. Freezing when walking

- 0 = None.
- 1 = Rare freezing when walking; may have start hesitation.
- 2 = Occasional freezing when walking.
- 3 = Frequent freezing. Occasionally falls from freezing.
- 4 = Frequent falls from freezing.

15. Walking

- 0 = Normal.
- 1 = Mild difficulty. May not swing arms or may tend to drag leg.
- 2 = Moderate difficulty, but requires little or no assistance.
- 3 = Severe disturbance of walking, requiring assistance.
- 4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)

- 0 = Absent.
- 1 = Slight and infrequently present.
- 2 = Moderate; bothersome to patient.
- 3 = Severe; interferes with many activities.
- 4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism

- 0 = None.
- 1 = Occasionally has numbness, tingling, or mild aching.

- 2 = Frequently has numbness, tingling, or aching; not distressing.
- 3 = Frequent painful sensations.
- 4 = Excruciating pain.

III. MOTOR EXAMINATION

18. Speech

- 0 = Normal.
- 1 = Slight loss of expression, diction and/or volume.
- 2 = Monotone, slurred but understandable; moderately impaired.
- 3 = Marked impairment, difficult to understand.
- 4 = Unintelligible.

19. Facial Expression

- 0 = Normal.
- 1 = Minimal hypomimia, could be normal "Poker Face".
- 2 = Slight but definitely abnormal diminution of facial expression.
- 3 = Moderate hypomimia; lips parted some of the time.
- 4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)

- 0 = Absent.
- 1 = Slight and infrequently present.
- 2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
- 3 = Moderate in amplitude and present most of the time.
- 4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of Hands

- 0 = Absent.
- 1 = Slight; present with action.
- 2 = Moderate in amplitude, present with action.
- 3 = Moderate in amplitude with posture holding as well as action.
- 4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

- 0 = Absent.
- 1 = Slight or detectable only when activated by mirror or other movements.
- 2 = Mild to moderate.
- 3 = Marked, but full range of motion easily achieved.
- 4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)

- 0 = Normal.
- 1 = Mild slowing and/or reduction in amplitude.
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succession.)

- 0 = Normal.
- 1 = Mild slowing and/or reduction in amplitude.
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)

- 0 = Normal.
- 1 = Mild slowing and/or reduction in amplitude.
- 2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
- 3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
- 4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY (in the past week)

A. Dyskinesias

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)
0 = None.
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.

3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?

0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)

0 = No
1 = Yes

B. Clinical Fluctuations

36. Are "off" periods predictable?

0 = No
1 = Yes

37. Are "off" periods unpredictable?

0 = No
1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?

0 = No
1 = Yes

39. What proportion of the waking day is the patient "off" on average?

0 = None.
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

C. Other Complications

40. Does the patient have anorexia, nausea, or vomiting?

0 = No
1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?

0 = No
1 = Yes

42. Does the patient have symptomatic orthostasis?

(Record the patient's blood pressure, height and weight on the scoring form)

0 = No
1 = Yes

V. MODIFIED HOEHN AND YAHR STAGING

STAGE 0 = No signs of disease.

STAGE 1 = Unilateral disease.

STAGE 1.5 = Unilateral plus axial involvement.

STAGE 2 = Bilateral disease, without impairment of balance.

STAGE 2.5 = Mild bilateral disease, with recovery on pull test.

STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.

STAGE 4 = Severe disability; still able to walk or stand unassisted.

STAGE 5 = Wheelchair bound or bedridden unless aided.

VI. SCHWAB AND ENGLAND ACTIVITIES OF DAILY LIVING SCALE

100% = Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.

90% = Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.

80% = Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.

70% = Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.

60% = Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.

50% = More dependent. Help with half, slower, etc. Difficulty with everything.

40% = Very dependent. Can assist with all chores, but few alone.

30% = With effort, now and then does a few chores alone or begins alone. Much help needed.

20% = Nothing alone. Can be a slight help with some chores. Severe invalid.

10% = Totally dependent, helpless. Complete invalid.

0% = Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Bedridden.

Adapted from Fahn S et al. and Members of the UPDRS Development Committee.

In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent Developments in Parkinson's Disease, Vol 2. Florham Park, NJ. Macmillan Health Care Information 1987, pp 153-163, 293-304