AMERICAN ACADEMY OF NEUROLOGY

EVALUATION OF SURGERY FOR PARKINSON'S DISEASE

A Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

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PD is a common disorder affecting on average 100 per 100,000 population. Despite the large number of medications available for the treatment of early and moderately advanced PD, options specifically designed for the patient with advanced disease are limited. Surgery for PD dates from 1939-1940, when Bucy and Case[1] and Klemme[2] excised parts of the cerebral cortex to treat tremor and dystonia, but this type of surgery produced hemiparesis. Surgical basal ganglia lesions were introduced a few years later by Meyers,[3,4] who found that pallidotomy produced significant relief of tremor, rigidity, and dyskinesias, but with considerable mortality. Stereotaxic techniques to coagulate the globus pallidus in PD were introduced in the 1950s by Spiegel and Wycis,[5,6] and Cooper was an early advocate of pallidal surgery.[7] Based on the anatomic connections between the pallidum and the thalamus, Hassler introduced the concept of surgery on the ventrolateral nucleus of the thalamus.[8,9] Microelectrode recording allowed Narabayashi[10,11] to find that lesioning the ventral intermediate (Vim) nucleus of the thalamus was the most specific target to control the tremor in PD. Neurosurgery reached its peak in the 1960s, but declined after the introduction of levodopa.

The recent resurgence of surgery was initiated by adrenal medullary transplantation. The premise of adrenal medullary transplants was that these cells, when transplanted into patients with advanced PD, would survive and function as a new source of dopamine. The theoretical advantages of adrenal tissue include that the tissue comes from the patient, eliminating the issue of immunologic rejection; dopamine is a normal intermediate compound made by the chromaffin cells; and chromaffin cells may have neuritic morphology when grown in culture. The disadvantages include the non-neuronal source and the rather modest survival rates of cells in laboratory transplantation studies. Isolated case reports of effective treatment of advanced PD with unilateral transplantation of adrenal medullary cells into the striatum in the 1980s led to several clinical trials testing the safety and efficacy of this procedure.

Fetal mesencephalon transplantation was introduced subsequently and is based on several considerations. First, PD is associated with relatively selective degeneration of dopaminergic cells located in the substantia nigra, a portion of the mesencephalon. Second, replacement of dopaminergic activity by means of precursor drugs, receptor agonists, or inhibitors of dopamine catabolism improves the signs and symptoms of PD. Third, laboratory evidence in experimental animals has demonstrated that grafts of dopamine-containing neurons improve behavioral models of PD. Fourth, in these animal models, grafts reinnervate the striatum and form synaptic connections with host neurons. As a result, a small number of research teams have developed programs for human fetal mesencephalic cell grafts in PD patients. Several published reports exist, although each has a small number of cases, and often multiple reports pertain to the same patients, followed for varying periods of time or studied with different ancillary research protocols. Fetal transplantation poses several challenges not encountered with adrenal medullary transplants, including questions of the proper age of the fetus, preservation and implantation techniques, immunosuppression, and finally the ethical issues related to use of fetal material.

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* Members of the Task Force on Surgery for Parkinson's Disease are listed in Appendix 1 on page 1918.

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With better knowledge of the physiology of the basal ganglia and thalamus as a result of advances in electrophysiologic techniques and animal investigations, combined with the advance of neuroimaging techniques, there has also been a renaissance of functional surgery. Thalamotomy is frequently employed particularly for tremor. Theory suggested that the subthalamic nucleus and globus pallidus are overactive in PD; animal models were consistent and human studies confirmed this to be true. With the rationale of reducing this overactivity, pallidotomy has become a frequent procedure.

Deep brain stimulation (DBS) of the Vim nucleus of the thalamus, as an alternative to thalamotomy, was approved by the Food and Drug Administration in 1997 for the treatment of contralateral tremor in PD and essential tremor. DBS of the thalamus was introduced in Europe in 1987 and approved there in 1993. More recently, DBS of other brain structures, particularly the globus pallidus and subthalamic nucleus, has been studied in the treatment of PD, and this received European approval in 1998.

Because surgery is being performed more frequently, the American Academy of Neurology (AAN) Therapeutics and Technology Assessment Subcommittee requested that a task force review its role, safety, and indications in the treatment of PD. Four working groups were formed to evaluate the safety and indications of thalamotomy, pallidotomy, adrenal and fetal transplant, and DBS, following the guidelines of the AAN. The field is rapidly evolving, and the current document is based on the published literature up to December 1998.

Methods. This study was based on a Medline, Embase, and Biosis bibliographic search from 1991 through 1998. The terms used for the search included: parkinsonism or PD and pallidotomy or thalamotomy or thalamus surgery, globus pallidus surgery, or subthalamic nucleus surgery; brain stimulation or electrostimulation or electrical stimulation; cell transplantation or cell transplant or tissue transplant or tissue transplantation; and therapy as a modifier. Articles selected for evaluation by each working group had at least four patients, except for studies on fetal transplantation and DBS of the globus pallidus and subthalamic nucleus, which required at least two patients because studies with at least four patients were limited. Citations identified were then evaluated by at least two members of each working group, who read the whole article and made the decision to include or exclude according to AAN guidelines as well as CONSORT guidelines.[12]

Each working group classified each paper based on the type of evidence it provided. Almost all papers finally included were Class III (see Appendix 2), peer reviewed, used validated methods of assessment, and provided consistent, clinical (rather than technical) data. Although most studies considered were prospective, only two included a concurrent control group, a requirement necessary to meet Class II evidence.[13,14]

For *thalamotomy*, 18 articles were found, but only four studies met criteria.[15-18] For *pallidotomy*, of the 40 identified papers, 22 were included.[14,19-39] Of the 38 articles identified for *DBS of the thalamus*, 16 articles met criteria.[40-55] The review of *DBS of the globus pallidus* consisted of all 10 articles identified,[56-65] and *DBS of the subthalamic nucleus* was based on all 6 articles identified.[62,66-70] There were 52 articles for *adrenal medullary* transplantation, but the review includes only the 9 that met criteria.[71-79] For *human fetal mesencephalon transplantation*, 19 papers were found and all were included.[13,75,80-96]

Once the evidence regarding all the articles reviewed was classified, each working group summarized all the collected data and indicated the quality of evidence of all citations contributing to their recommendations. A draft of this document was circulated among all the study participants for their final review and comments. Recommendations were made according to AAN definitions (Appendix 3), and the strength of the recommendation was based on the class of evidence of the data (Appendix 4).

Results and summary statement. *Comments applicable to all procedures.* The procedures require neurosurgeons with a high level of expertise in stereotactic techniques. The majority of reporting centers have multidisciplinary teams of neurosurgeons, neurologists, neurophysiologists, psychiatrists, psychologists, and neuroradiologists with expertise in the diagnosis, assessment, and treatment of movement disorders. The surgical technique is not yet optimized and varies in the different centers; this is one source of variability of results. Inexperienced centers will likely have less favorable results and more adverse side effects.

In general, cognitive impairment is a predictor of poor outcome and patients of advanced age derive decreased benefit. Significant coexisting medical conditions, psychiatric disease, or focal abnormalities on brain imaging are relative contraindications.

Thalamotomy. *Indications and technical components.* Thalamotomy directed to the Vim nucleus is indicated for asymmetric, severe, medically intractable tremor, particularly when the tremor is not associated with important symptoms from other features of PD. Data collection was retrospective (Class III). Thalamotomy is not effective

for treatment of bradykinesia, micrographia, or difficulty with gait or speech,[97] but targeted to the ventral oral posterior nucleus it may have value for rigidity and dyskinesia.[98] We will emphasize the operation directed to the Vim target here.

Thalamotomy on the second side has a good chance at decreasing tremor but a high incidence of speech problems. Therefore, if surgery is considered, Vim-DBS is the treatment of choice for the second side.

The operation is generally not appropriate for atypical parkinsonism, including multiple system atrophy, but in the rare patient with severe disabling tremor, thalamotomy might be beneficial.

Two studies employed CT scanning for at least part of the study[16,18] and the same two employed microelectrode or semi-microelectrode recording for physiologic localization. These methods seem important for proper localization within the thalamus, but controlled observations on this point are not available.

Key study results. Results of Class III studies of thalamotomy using current techniques[15,16,18] reported moderate to good effect on contralateral tremor in 79 to 85% of cases (total 97 patients) at mean follow-ups of 17 to 41 months. The duration of benefit is good, as demonstrated by a study that found a significant long-term (>3 years; mean, 11 years) reduction in contralateral resting tremor.[17]

Transient complications (less than 3 months) were noted in 36 to 61% of cases, and included contralateral weakness, confusion, aphasia, dysarthria, contralateral ataxia, contralateral dystonia, and sensory change. Permanent complications occurred in 14 to 23% of cases, and included aphasia, dysarthria, apraxia, abulia, and death (the latter at 7 days from a pulmonary embolism).

Four staged operations were carried out on the second side with good effect on tremor, but with two permanent complications—hypophonia and dysarthria.

Recommendation. It is recommended that thalamotomy be offered to the PD patient for surgical treatment of asymmetric, severe, and medically intractable tremor, but not for bradykinesia or difficulty with gait or speech. For this purpose, thalamotomy is reasonably safe and effective, with a type C recommendation based on Class III evidence. Contraindications include atypical parkinsonism, multiple system atrophy, and high surgical risk from medical disease. Computerized imaging should be employed for radiologic localization and microelectrode recording for physiologic localization is likely helpful. Thalamotomy is an option for operation of the second side if the patient is willing to accept the possibility of dysarthria, but because of this significant risk, bilateral thalamotomy would have to be considered doubtful—a type D recommendation based on minimal evidence. If an operation on the second side is desirable, then DBS of the thalamus may well be the treatment of choice because it can be better controlled, but there are no published data to support this view.

Pallidotomy. *Indications and technical components.* Unilateral pallidotomy is indicated for advanced PD with motor fluctuations and drug-induced involuntary movements (dyskinesias) along with significant bradykinesia and rigidity, with or without tremor. The improvements in these cardinal features of PD last at least 2 years, as documented by following a total of 22 patients from two studies.[22,27] The effects and duration of benefit of unilateral pallidotomy on gait and postural disturbances are less striking. Because of the risks associated with the surgery and the unknown long-term benefit, pallidotomy should be offered to patients who continue to have significant motor disability interfering with normal activities of daily living despite optimal medications. The magnitude of the improvement appears to be greatest for drug-induced dyskinesias. There is the suggestion that responsiveness to levodopa should be a criterion for inclusion. There is also evidence that hypermetabolism in the globus pallidus as assessed by fluoro-deoxyglucose uptake in the pallidal complex is a predictor of a beneficial response to pallidotomy. Symptoms persisting in the "on" state (e.g., freezing, falls, dysarthria) do not respond well to pallidotomy. Benefits are predominantly contralateral, suggesting that asymmetric patients stand to improve the most with pallidotomy.

There are insufficient reliable data on the indications, safety, or benefits of bilateral pallidotomy. The available data, however, suggest that bilateral pallidotomy is associated with a higher incidence of neurologic adverse effects, particularly speech complications.[31,34]

Preliminary evidence from some of the groups who have published the evaluable studies indicates that patients with other parkinsonian disorders failing to respond to levodopa do not substantially benefit from pallidotomy.

CT or MRI targeting is most widely used. All papers evaluated in this report used physiologic mapping in addition to aid in target selection. Both macroelectrode stimulation mapping and microelectrode recording/stimulation mapping are being used. It is impossible to assess which imaging or mapping procedure is superior with the available data. Microelectrode recording mapping requires more equipment and experienced personnel. A study comparing the benefits and adverse effects of pallidotomy using microelectrode versus macroelectrode mapping is not available.

Studies utilizing radiosurgical, nonphysiologically guided pallidotomy (gamma knife) could not be adequately evaluated. Whereas there is one report of comparable benefit to radiofrequency lesioning,[99] others report limited benefits[100] and substantial complications.[101] Thus, this method cannot be recommended at the present time as standard care.

Although the posterior ventral portion of the internal division of the globus pallidus is the common target, there is not yet certainty of the optimal target.

Key study results. Striking improvements in motor function are reported in L-DOPA-responsive patients in whom no further improvement was possible with medical therapy. The improvements include: 1) marked amelioration of contralateral drug-induced dyskinesias, reaching over 90%; 2) total Unified Parkinson Disease Rating Scale (UPDRS) and contralateral UPDRS motor improvements in the "off" state of approximately 30%; and 3) substantial decrease in contralateral tremor score (approximately 50 to 60%). The motor improvements are most pronounced contralaterally and are of greater magnitude in the "off" than the "on" state. Measures of activities of daily living improve in both the "on" and "off" states with unilateral pallidotomy. Pallidotomy can restore functional independence in certain patients with advanced and disabling disease. To some extent, at least in some patients, bradykinesia is improved by virtue of the fact that the L-DOPA dose can be increased without producing dyskinesias.

The bulk of the data suggest that younger patients derive more benefit from pallidotomy than older patients.[21,27] The choice of pallidotomy for young patients, however, has to be balanced with the uncertainty of the long-term consequences of the procedure and the possibility that surgery may diminish therapeutic benefits of future medical or surgical treatments.

Adverse effects with pallidotomy are common. For many centers, these are new procedures requiring the acquisition of new technical, anatomic, physiologic, and neurosurgical knowledge. The reports that have been reviewed represent the initial experience of several groups with variable experience in functional neurosurgery. The pallidotomy procedure requires the use of specialized imaging and surgical tools and considerable knowledge and expertise of the surgical team. Overall, the articles reviewed report an approximately 10 to 15% incidence of persistent adverse effects with unilateral pallidotomy. The majority of these complications are mild and well tolerated and appear to be far outweighed by the motor benefits of pallidotomy.

The initial publications in the 1992-1998 epoch reported that the major complications of pallidotomy were visual field deficits related to lesions encroaching upon the optic tract and facial weakness due to lesions or edema of the capsular fibers for the face. The incidence of these complications appears to have dropped in subsequent studies. The reasons for this are most likely an increased awareness of the potential for this complication and modifications in the surgical technique to optimize the lesion.

The most serious complications reported in the 19 papers are intracerebral hematomas related to the penetration of electrodes in the brain. The incidence ranges from 0% to 15% with a mean of approximately 2% (11 of 554 patients). A similar incidence of intracranial hemorrhage is encountered in all functional neurosurgical procedures as reported by centers with a large volume of cases. Several of the patients died. The overall incidence of death from pallidotomy is approximately 0.3%. Other serious reported complications include worsening of cognitive function, most commonly transient postoperative confusion. Neuropsychological evaluations have demonstrated either no or mild deficits, most commonly decreased verbal fluency, particularly after left-sided pallidotomy.[34,37-39]

Recommendation. Based on our survey, unilateral pallidotomy is safe and effective with a Type C recommendation (positive recommendation based on Class III evidence). Unilateral pallidotomy is recommended for patients with PD with bradykinesia, rigidity, and tremor who experience significant drug-induced dyskinesia. The greatest benefit seems to be in ameliorating the dyskinesia. There is less benefit to gait and postural disturbance than other features of PD. The ideal candidate is young, cognitively intact, has asymmetric disease with dyskinesias, and is responsive to L-DOPA. The benefits of pallidotomy are maintained for at least 2 years; further long-term follow-up is required. Pallidotomy requires considerable expertise in stereotactic and functional neurosurgery. Physiologic mapping with either microelectrode recordings and stimulation or macroelectrode stimulation may improve the results. Although the optimal lesion location and volume are yet to be determined, there is increasing evidence that precise lesion placement within the internal segment of the globus pallidus is critical and that lesions outside this area are less effective. Because little data on the cognitive consequences of pallidotomy are available, it is recommended that patients undergo a pre- and postoperative neuropsychological assessment. The benefits of pallidotomy are predominantly contralateral.

No reliable data are available on the indication, safety, or efficacy of bilateral pallidotomy. Preliminary reports, however, suggest a high incidence of speech complications with bilateral pallidotomy. Bilateral procedures may

carry significant risk and would have to be considered doubtful, with type D negative recommendation based on minimal data.

DBS of the Vim nucleus of the thalamus. *Indications and technical components.* The indication for high-frequency stimulation of the Vim thalamic nucleus is severe and disabling tremor that is unresponsive to medical therapy. Good candidates for the procedure are patients with functional disability due to tremor and not to other motor symptoms such as bradykinesia. Rest, postural (proximal and distal), and kinetic tremor improve with DBS; improvement in disability correlates with improvement in postural tremor.[102] Most experience has been in patients with PD or essential tremor, although other miscellaneous tremors related to midbrain and cerebellar disease have also been studied.

Tremor may not be well controlled pharmacologically in 20 to 30 % of PD patients. However, because for most of these patients the tremor is not the major cause of disability, they are not candidates for thalamic DBS. This leaves a small group of patients (<5%) who may be suitable for surgery.

Severe bilateral tremor may be an indication for bilateral procedures—either thalamotomy on one side followed by DBS on the other or bilateral DBS. Owing to its low morbidity, DBS of Vim can be performed bilaterally in patients with severe bilateral tremor, often during one surgical session.

Dementia is a relative contraindication because the patient must be able to cooperate in the operating room and because dementia may be exacerbated by any further brain disturbances. Age, per se, is not a contraindication and the procedure has been performed in patients up to 81 years of age. Activities in certain occupations may induce the repetitive turning on and off of the device and may contraindicate this procedure.

A stereotactic frame is attached to the patient's head under local anesthesia. The Vim nucleus of the thalamus is targeted by various methods using CT and MRI localization. In the operating room, a burr hole is made under local anesthesia. The electrode is advanced to the Vim under stereotactic guidance. Stimulation through the electrode is used to find the site that produces the best suppression of tremor with the least paresthesias or other unwanted side effects. The final position of the electrode tip is selected to provide maximum tremor suppression at the lowest stimulation intensity with only transient paresthesia in the arm and face at the initiation of stimulation. At the time of surgery or several days later, the impulse generator is placed in the subcutaneous tissue of the infraclavicular area, connected subcutaneously by an extension wire to the implanted electrode, and programmed to yield the greatest tremor suppression with the least side effects. Other groups[103] use microrecording first in order to localize the optimal site for macroelectrode implantation. In essence, the size of the affected region and location may be specified by modifying stimulation parameters. Stimulation parameters and contact selection are programmed by telemetry. The adjustable parameters include contact selection (with quadripolar electrodes), pulse rate, pulse width, and pulse amplitude. Patients are able to switch their impulse generator on or off by means of a hand-held magnet, but cannot alter the settings.[50]

The procedure can be done bilaterally, in either one or two sessions.

DBS of the thalamus is effective only in reducing parkinsonian tremor and does not affect bradykinesia. For this reason, there is much interest in stimulation of the globus pallidus interna and the subthalamic nucleus in an effort to control the other symptoms of PD as well as the tremor.

One member of the team must become familiar with programming the impulse generator and adjusting the stimulation parameters for optimal response. Programming the stimulator is very time-consuming in the first few months for some patients, and is an ongoing problem in others. Continuing surveillance is needed, and the impulse generator needs to be changed every 3 to 5 years.

Key study results. An immediate response even without the stimulation through the implanted electrode, which may last for a couple of weeks, occurs in some patients and is attributed to a "micro-thalamotomy effect."[54] Brain stimulation of the Vim has proved effective in reducing contralateral tremor, both in the short term (3 to 12 months) and long term (up to 8 years). Based on 148 PD patients, up to 90% have significant tremor reduction and as many as 50% may have complete tremor resolution. There may be a minor loss of efficacy over years but generally tremor remains markedly reduced for periods up to 8 years.

Response of tremor to contralateral stimulation has generally been scored on a 0 to 4 scale with 0 representing no change in tremor, 3 being a significant reduction of tremor (75%), and 4 representing total abolition of tremor. More than 80% of PD patients have a significant reduction (3 or 4 on the scale) in tremor contralateral to stimulation. Over 90% of the patients rated their outcome as moderately to markedly improved after unilateral DBS of the thalamus. Patients are generally much more receptive to the idea of chronic stimulation than the idea of ablative lesions, although the hardware may be somewhat intimidating.

There has been no prospective comparison of chronic high-frequency stimulation of Vim with thalamotomy. It is a general impression of clinicians experienced with both that the effect on tremor is very comparable between ablative lesions and chronic stimulation but that adverse effects are less frequent in DBS because of the ability to adjust stimulation parameters.

The effect of stimulation on disability depends on whether patients are selected in whom tremor is a major contributor to disability. If, as in most people with PD, the major disability is caused by bradykinesia, the operation will not improve the patient's function, as rigidity and bradykinesia are not improved by thalamic stimulation. Thus, improvement in tremor does not necessarily reduce disability,[104] because disability does not necessarily correlate with tremor.[102] Some investigators find activities of daily living measured by UPDRS improved by thalamic stimulation; others do not. One group found thalamic stimulation reduced contralateral levodopa-induced dyskinesia.[48] Subsequent analysis suggested that the electrode tips were placed slightly more medial so that stimulation may have affected centromedian and parafasicular nuclei as well as Vim.[52]

Complications of implantation of DBS electrodes have included subdural hematomas, microhematomas at the tip of the electrode, brain infarcts, seizures, permanent paresthesias, cardiac ischemia, and lead displacement requiring reoperation. As a whole, surgical complications are relatively uncommon and easily managed and rarely result in serious permanent problems.

A common complication of stimulation occurring in most patients is transient (seconds) paresthesias when the stimulator is turned on. Other complications of stimulation that occur infrequently (<10%) are paresis, dysarthria, dysequilibrium, ataxia, dystonia, chorea, persistent paresthesias, and headache. These adverse effects can be reduced or abolished by changing the stimulation parameters. Upon turning off the stimulator, there may be a rebound worsening of tremor, which prevents patients from turning off the stimulator at night to conserve the battery and reduce tolerance to chronic stimulation.

Device/battery failures have occurred in a few patients. The life of the battery should be 3 to 5 years depending upon the stimulation parameters and whether the stimulation is continuous around the clock or is used just during waking hours. Infection or erosion around the subcutaneous leads may occur.

A postmortem examination was obtained in a patient with therapeutically efficacious left thalamic stimulating electrode in place for 43 months who died of a right middle cerebral infarct. There were small areas of spongiosis and gliosis within 1 mm of the electrode track and increased lymphoid cells within 2 mm of the electrode track. No damage attributable to stimulation was observed.[45]

The real advantage of DBS of the thalamus becomes apparent when bilateral procedures are employed. Bilateral thalamotomies have a complication rate of up to 25%.[51] Because of the ability to adjust stimulation parameters, the prevalence of these complications with bilateral DBS is almost nil.[50]

Recommendations. DBS of the thalamus for tremor in PD patients is rated as safe and effective with a type C recommendation based on Class III evidence. Bilateral thalamic DBS appears safe and effective also, but remains investigational as there are only limited data.

DBS of the globus pallidus. *Indications and technical components.* Virtually all patients selected for surgery had advanced disease, Hoehn and Yahr stages 3 and 4, with associated motor fluctations and dopa dyskinesias. Two patients had multiple system atrophy.[105] There are no formal discussions of contraindications, but most patients have been in reasonably good health and not cognitively impaired.

The technical aspects are similar to those reported in the prior discussion of DBS of the thalamus and will not be repeated here. Considerable time is needed to optimize the programming of the device.

Key study results. Correcting for multiple reports of the same patients in different publications, there have been 64 patients reported, 33 operated bilaterally and 31 unilaterally. Patients have been followed for up to 42 months. Results are similar in all reports and are, in general, favorable. There are benefits to all aspects of parkinsonism including bradykinesia, speech, walking, rigidity, and tremor. Particularly dramatic is the marked reduction in dyskinesias. In more detail, there is a clear antiparkinsonian effect seen in the drug off state, but only a marginal improvement, if any, in the drug on state. However, the dyskinesias are largely gone and the on state is much more sustained. Clear comparisons between unilateral and bilateral stimulation have not been made, although unilateral stimulation affects mostly the contralateral side. Most reports note that the dopaminergic medication requirement is not changed, and over time the doses even increased. Although the follow-up is typically not long in these reports, the benefits seem to be lasting. One report notes a slight deterioration beginning at about 1 year.[63]

Two reports came to the same conclusions about the location of the stimulation within the pallidum.[61,65] Ventral stimulation is particularly effective against the dyskinesias and improves rigidity, but has a weak effect on bradykinesia. Indeed, it may even reduce the effectiveness of levodopa. Dorsal stimulation improves the

bradykinesia, but may worsen the dyskinesias. The authors suggest that a compromise location between these two extremes would be appropriate.

A few reports neither mention nor minimize complications. Transient complications seem common; these include confusion, dysarthria, and hemiparesis, which generally fade in a few weeks. Asymptomatic hemorrhages have been noted on postsurgery MRI scanning. There are also complications from having the stimulation parameters too high, such as paresthesias, but these are quickly controlled. Long-term complications include decrease in speech fluency, dysarthria, and hypophonia, but none of the problems have been severe. One report notes decreased anxiety and depression and increased vigor.[60]

The two patients with multiple system atrophy had no antiparkinsonian effect.

Recommendations. Results are largely favorable, and complications are typically transient. The targeted group is patients with severe PD with fluctuations and dyskinesias. There are only limited data reported for other parkinsonian states, but for multiple system atrophy, at least, the procedure does not seem indicated. The indications are much the same as for pallidotomy, and the considerations of the choice between pallidotomy and DBS of the pallidum is similar to that of the choice between thalamotomy and DBS of the thalamus. However, another alternative is DBS of the subthalamic nucleus. There has been one report comparing the efficacy of the two targets, and this has suggested that DBS of the subthalamic nucleus is more effective.[62] Because the indications for DBS of the pallidum are, therefore, not certain, the procedure is best considered still investigational.

DBS of the subthalamic nucleus. *Indications and technical components.* Although this procedure is being widely done, only two groups, from Grenoble and Toronto, have reported their results in the peer-reviewed literature. Indications have been limited to patients with severe PD with fluctuations. Dyskinesias, although originally not considered an indication, are now included. All cases have been done bilaterally. Most patients have been in reasonably good health and not cognitively impaired, and there is a suggestion that older patients might not do as well.[68]

The technical aspects are similar to those reported in the prior discussion of DBS of the thalamus and will not be repeated here. Considerable time is needed to optimize the programming of the device. In comparison with the globus pallidus, the subthalamic nucleus is a smaller target.

Key study results. Attempting to correct for multiple reports of the same patients in different publications, there have been 34 patients studied. Many have been followed for 12 months and some for more than 36 months. Limousin et al.[70] reported on 24 cases and gave the most comprehensive review of the Grenoble experience. Virtually all patients improved substantially in all aspects, including tremor, akinesia, postural stability, and gait. Comparing the "off" states before surgery and with DBS postoperatively, there was a 60% improvement in motor score and score for activities of daily living. Comparing the "on" states, there was a 10% improvement with DBS, but the time spent in the "on" state was markedly increased; the UPDRS score for the duration of off time was reduced from 2.2 ± 0.7 to 0.6 ± 1.0. There was a marked and significant improvement in both the intensity and duration of dyskinesias, and the painful "off"-period dystonia disappeared in 12 of 16 patients and diminished in the other 4. The levodopa dose was reduced by about half, a result clearly different from DBS of the globus pallidus. An additional difference is that the dyskinesias were eradicated early with DBS of the globus pallidus but only after some months with DBS of the subthalamic nucleus. It is likely that the beneficial effect on the dyskinesias is due, at least in part, to the reduction in levodopa dose. In fact, dyskinesias can be an early transient problem with DBS of the subthalamic nucleus and need to be managed with careful adjustment of the stimulation parameters.

As noted, the best "on" state with drug is improved during stimulation, but by a relatively small amount. The drug response was used by Krack et al.[62] to predict the effect of the stimulation.

In the report comparing DBS of the globus pallidus and subthalamic nucleus, all patients had disease onset before age 40 years.[62] The improvement during the "off" drug state in the motor portion of the UDPRS was 71% for subthalamic nucleus stimulation and only 39% for globus pallidus stimulation.

Limousin et al.[70] followed 20 patients for 1 year, 10 patients for 2 years, and 5 patients for more than 3 years, and the benefits appear stable. Kumar et al.[68] have studied seven patients for up to 12 months with a double-blind evaluation procedure (stimulation on or off) and found similar significant benefit.

A number of side effects have been reported. In the Grenoble experience, one patient developed a large intracerebral hematoma during surgery with permanent severe paralysis and aphasia. Another developed an infection at the site of the extension lead, requiring removal of the hardware, although she was subsequently reimplanted. Eight of the 20 patients followed for at least 1 year had transient mental status changes after surgery, but these did not last more than 2 weeks. Eighteen patients gained weight, and five developed eyelid-opening apraxia. Mild dystonia can be a consequence of the stimulation, but is accepted by the patients. Several patients

reported decreased energy and increased anxiety, and these were thought to be possibly due to the reduction in levodopa dose.[62] A number of complications were also reported by the Toronto group.[68] Two of the patients entered into the study never reached an evaluation point. One, who was slightly cognitively impaired before surgery, became paranoid during surgery and the procedure was discontinued. The other developed an infection of the hardware and it was removed. Of the seven who were evaluated, one had a cortical venous thrombosis with infarction and resultant worsening of hypophonia, one had a decline in verbal memory, one had a personality change, and one had a cognitive decline.

Recommendations. There is insufficient experience reported to date with DBS of the subthalamic nucleus to come to a definite conclusion, and it must be considered still investigational. The beneficial effects for all aspects of PD are impressive, but there are a number of complications that have occurred. Most complications have been transient or mild, but some have been significant, and this will have to be weighed against the possible benefit. As noted above, the risk for younger patients may be significantly less. There seems to be considerable enthusiasm for this procedure, particularly in Europe, where it has already been approved for the treatment of PD, and new results will be appearing soon that may allow a positive recommendation.

In relation to approaches to the subthalamic nucleus, subthalamotomy is also being investigated in a few centers and preliminary results have been reported.[106]

Adrenal medullary transplants. *Indications and technical components.* The studies focused on patients with idiopathic PD who were increasingly unresponsive to medication and who had motor fluctuations. Patients were examined to identify that they had two adrenal glands preoperatively. In all cases, the operation was performed once and not repeated on the other side. Contraindications were patients without two adrenal glands and those without clinically definite PD.

The prototypic surgery involved an adrenalectomy, either abdominal or retroperitoneal, and a simultaneous craniotomy with transplantation of dissected adrenal medullary tissue into one (usually right-sided) caudate nucleus (i.e., into the nondominant hemisphere). Some studies used an open frontal craniotomy and others used stereotaxic guidance.

Three ideas for modified protocols have evolved from these studies: first, special perfusion techniques aimed at increasing cell survival[75]; second, the addition of trophic factors or peripheral nerve cotransplants to enhance cell survival; and third, the grafting of fetal adrenal medullary cells. Cotransplantation procedures combining adrenal medullary tissue with peripheral nerve fragments have been performed in two small series (<5 subjects each), and in each, selected patients improved.[75,107]

The primary problem with adrenal surgery was the double procedure, abdominal and cerebral, involving two teams, long intraoperative time, and long recovery.[72] Morbidity was less with retroperitoneal surgery than frontal-abdominal and less with stereotaxic than open craniotomy. Surgical and perisurgical complications included pulmonary, abdominal, psychiatric, and neurologic, and late sequelae included persistent hemiparesis, seizures, and behavior disinhibition in some patients.

These studies were all begun before the development of the Core Assessment Protocol for Intracerebral Transplantation (CAPIT), so there were individual variations in the scale selected.

No assessments were blinded.

Key study results. In most series, the numbers were relatively small, ranging from 7 to 20, with registry data on 61 patients collected from the United States and Canada. Follow-up ranged from 6 months to 2 years. In all groups that focused on motor efficacy, there was documented clinical improvement (up to 2 years), usually in the form of improved function during the off state and more hours of on time. In some, but not all cases, doses of L-DOPA were reduced. No study aimed at assessing motor efficacy had a control group or even a comparison group retrospectively matched, but the studies suggest that these patients fared better than they would have without surgery in terms of their motor disability. One study suggested neuropsychological improvement.[71]

In addition to the clinical studies, a few well-analyzed pathologic reports were also reviewed. As a group, these reports showed either no or very few surviving cells. Although there was no report of an autopsy performed at the time that a patient was clinically improved after surgery, these reports suggest that very little adrenal medullary tissue survived long term in patients.

Most groups reported that morbidity and mortality were high. There were significant neurologic difficulties with the procedure, including several deaths, cerebrovascular accidents, and long- and short-term mental sequelae. Waxman et al.'s[77] report focused on medical complications and documented serious complications, most notably cardiopulmonary in origin. This report developed a comparison group of other patients undergoing either craniotomies or adrenalectomies, but not both, and found morbidity to be much higher in the PD study patients.

They suggested that the PD and the complicated double surgery were the reasons for the serious medical difficulties. In the registry data of Goetz et al.,[76] operative complications were less frequent in the patients undergoing retroperitoneal adrenalectomy and in those undergoing stereotaxically guided grafts. These observations have been supported by other studies, although the numbers were too small to show statistical significance. Unacceptable morbidity and mortality were hallmarks of most series.

Recommendation. Based on the cited studies, adrenal medullary transplant in PD appears to be a difficult double operation procedure when performed on severely advanced PD patients. Most studies suggested efficacy but morbidity was high. There have been no controlled studies. At the current time, the procedure should be considered unacceptable for safety reasons. The quality of the data is Class III, and the strength of the recommendation is Type D.

To the committee's knowledge, the procedure is not being currently investigated further.

Human fetal mesencephalic cell transplants. *Indications and technical components.* The studies focused on patients with idiopathic PD who were poorly controlled with medication and who had motor fluctuations. Patients with secondary parkinsonism from toxin exposure with MPTP or other degenerative conditions are not considered in this report. In most series, the numbers were relatively small, ranging from 2 to 12. In most patients, immunosuppression was used for varying periods of time pre- and postoperatively. In unilateral cases, one operation was performed. With the bilateral procedures, staging of operations with intervals approximating 1 to 3 weeks was usual. Follow-up ranged from 6 months to 5 years.

In most instances, significant other medical illnesses precluded entry into the study. Some groups had age restrictions.

Whereas in the adrenal transplants there were basically two types of adrenalectomy and two types of cranial surgery, the number of variables is much larger with fetal transplantation. In terms of the tissue preparation, there are two principal choices, either dissection of blocks of tissue or creation of a suspension of dissociated cells**.** Usually the donor (i.e., the mother) is screened for HIV-I; HIV-II; HTLV-1; hepatitis A, B, and C; cytomegalovirus; toxoplasmosis; syphilis; and herpes simplex virus. In addition, fetal tissue is cultured for aerobic and anaerobic bacteria, yeast, herpes simplex virus, and cytomegalovirus. Not much testing can be done on the fetus, because there is such a short period of time available. Dopamine production is assessed by a few teams, but cooling of the tissue (a necessary technical aspect) slows metabolism and gives a false reading. Viability testing by trypan blue staining is more standard. Other variables are donor age, immunosuppression, and tissue storage techniques. Open or stereotaxic surgery can be used, although open surgery is usually unilateral and stereotaxic procedures can be either unilateral or bilateral. The site of transplantation varied among studies, focusing on caudate nucleus, putamen, or both. Within the putamen itself, investigators differed in placing the transplant diffusely or aiming selectively to the anterior or posterior putamen. Likewise, donor tissue age varied from 5 to 17 weeks postconception. Basic science studies suggest that tissue older than 10 weeks has largely differentiated and already sent out neuritic processes. This maturation prior to transplant reduces survival of cells and integration with host tissue in experimental animals. Additionally, the number of mesencephalons transplanted has varied from one to four per side, making the full range in unilateral and bilateral cases from one to eight. Finally, the issue of immunosuppression is not uniform in these studies, some having none at all, some having only cyclosporin for short periods, and others having more complete and more protracted treatment.

With the number of potential technical variables, protocols to test the effect of each one could be envisioned. However, in the United States, a significant difficulty with implementation has been the political and ethical pressures against such research efforts. The limitation of available human fetal tissue in North America and Europe suggests that large-scale evaluations of each possible operative variable will not likely occur. For the future, other possible cell sources, such as porcine xenografts, and engineered cells are being investigated.

All included studies used standardized rating scales to measure outcomes. These studies primarily used the UPDRS and assessed motor fluctuations. Some used the CAPIT, which includes responses to a standard L-DOPA dose. Two studies focused on psychometric changes and used standard scales for these measures.[91,92] PET scanning was used in approximately half of the groups, but data were often incomplete and performed only on a subsample.

Key study results. In all groups motor performance improved in at least some of the patients studied, usually in the form of improved function during the off state and more hours of on time. In some, but not all cases, doses of L-DOPA were reduced. Improvement generally started after 3 to 6 months and lasted up to 5 years. Only one study focusing on motor efficacy[13] had a control group and none examined a comparison group retrospectively matched. No study was blinded and placebo effects were never tested. For the neuropsychological evaluations, Price et al.[91]

found more psychiatric complications after surgery, but could not conclude whether these were more frequent or severe than for comparable advanced PD patients without transplant. Sass et al.[92] used a comparison group of patients without surgery and found that no improvement in cognition occurred after surgery.

In regard to PET scans, the general pattern was an increased fluorodopa uptake in the area of transplantation with continued loss of uptake in the areas that did not receive transplantation. These data have been presented in descriptive form in some studies and in specific detail in others.[90] The findings have been interpreted as signs of reinnervation and healthy activity of transplanted or host neurons, or both.

In addition to the clinical studies, pathology reports from two patients who died 18 and 19 months after surgery from unrelated events demonstrated healthy appearing graft tissue with large numbers of dopaminergic cells that had extensive reinnervation patterns in a patch-matrix configuration.[89,108] There was no evidence of host rejection.

In contrast to the experience with adrenal medulla transplants, patients tolerated the fetal transplant well. Morbidity and mortality have been very low. Patients have only the cranial surgery and therefore severe and persistent medical complications occurred in very few subjects. However, in cases where long-term immunosuppression occurred,[109] opportunistic pneumonia did occur. Occasional morbidity included confusion, usually transient after surgery, and small hemorrhages near the implantation or needle-track sites.

Recommendations. Based on the cited Class III studies, human fetal transplantation into the striatum in PD appears to be an encouraging procedure when performed on severely advanced PD patients. Because of the absence of controlled studies, it is investigational as a procedure for advanced PD at a research center. It is promising, because its efficacy appears to be good in the published reports, and its associated morbidity and mortality are low. Further modifications in surgical, dissection, and preservation techniques; the possibility of supplementation with trophic factors; or combination with other neurosurgical procedures such as pallidotomy and thalamotomy are areas of future potential research with controlled studies. Several prospective controlled trials are currently in progress, and further data should be available soon.

Table *Summary of recommendations**

Procedure	Bradykinesia	Tremor	Dyskinesia	Recommendation	Strength of recommendation
Unilateral thalamotomy	No	Yes	No	Safe, effective	C
Bilateral thalamotomy	No	Yes	No	Doubtful	D
Unilateral pallidotomy	Yes	Yes	Yes	Safe, effective	C
Bilateral pallidotomy	Yes	Yes	Yes	Doubtful	D
Unilateral DBS thalamus	No	Yes	No	Safe, effective	C
Bilateral DBS thalamus	No	Yes	No	Investigational	
DBS pallidum†	Yes	Yes	Yes	Investigational	
DBS subthalamic nucleus†	Yes	Yes	Yes	Investigational	
Adrenal implant	Yes	Yes	Yes	Unacceptable	D
Fetal implant	Yes	Yes	Yes	Investigational	

* A yes or no in the bradykinesia, tremor, or dyskinesia column reflects whether the procedure affects these symptoms.
† Deep brain stimulation of the pallidum and subthalamic nucleus are typically done bilaterally.

Conclusion. Surgery for PD is rapidly becoming an important therapeutic consideration in the management of medication-resistant disease (table), based on a strong consensus of Class III evidence (i.e., provided by nonrandomized, historical controls or case series). In carefully selected cases, thalamotomy and DBS of the thalamus can safely and effectively control tremor. It is clear, however, that they cannot help bradykinesia, which typically is, or will become over time, the most important symptom. Hence, other procedures should always be considered even if tremor is the main symptom. When the problem is severe dyskinesias and on-off fluctuations, unilateral pallidotomy has been demonstrated to be effective and reasonably safe. For bilateral pallidotomy, the risks are substantial, limiting its potential utility. Pallidal DBS may well be demonstrated to be a good alternative, and it can be done bilaterally more safely. The influence of pallidal surgery on bradykinesia, however, seems limited, at least when compared to the levodopa-induced "on" state. For improvement of bradykinesia, fetal implantation surgery seems promising, but remains investigational. Implantation with other types of cells, including engineered cells, will be employed in the future. Adrenal implantation surgery has been abandoned. For bradykinesia, DBS of the subthalamic nucleus, typically done bilaterally, appears very promising, although it too is currently investigational. Other considerations are that procedures such as thalamotomy and pallidotomy are immediate in effect and essentially complete at the time of operation, but irreversible. DBS makes no major lesion,

but requires intensive postoperative adjustments and lifelong maintenance. Implants are not immediate in their effect and may require immunosuppression. In making a decision about any type of surgery, the risks should be weighted against any possible benefit. Because these procedures are under intense investigation, new knowledge is expected to accrue rapidly and the recommendations concluded here will evolve.

Note. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

Appendix 1

Members of the Task Force on Surgery for Parkinson's Disease include: *Coordinators:* M. Hallett, MD, I. Litvan, MD. *Thalamotomy Working Group*—Chair: F. Lenz, MD; Members: E. Ahlskog, MD, R. Grossman, MD, J. Jankovic, MD, H. Narabayashi, MD, R. Tasker, MD. *Pallidotomy Working Group*—Chair: A.M. Lozano, MD; Members: M. DeLong, MD, A.E. Lang, MD, J.A. Obeso, MD, C. Waters, MD. *Deep Brain Stimulation Working Group*—Chair: W.C. Koller, MD; Members: A.L. Benabid, MD, D. Caparros-Lefebvre, MD, J.G. Nutt, MD, P. Pollak, MD, J. Siegfried, MD. *Adrenal and Fetal-Nigral Implants Working Group*—Chair: C. Goetz, MD; Members: G.L. Defer, MD, J.J. Lopez-Lozano, MD.

American Academy of Neurology Therapeutics and Technology Assessment Subcommittee members: Chair: Douglas S. Goodin, MD; Members: Elliot Mark Frohman, MD, PhD, Robert Goldman, MD, John Ferguson, MD (facilitator), Philip B. Gorelick, MD, MPH, Chung Hsu, MD, PhD, Andres Kanner, MD, Anne Marini, MD, PhD, Carmel Armon, MD, David Hammond, MD, Edward Westbrook, MD.

Appendix 2

Classes of evidence.

Class I: Evidence provided by one or more well-designed randomized controlled clinical trials.

Class II: Evidence provided by one or more well-designed clinical studies such as prospective open, case-controlled studies, etc.

Class III: Evidence provided by expert opinion, non-randomized historical controls, or case reports of one or more patients.

Appendix 3

Possible recommendations.

Safe: A judgment of the acceptability of risk in a specified situation, e.g., for a given medical problem, by a provider with specified training, at a specified type of facility.

Effective: Producing a desired effect under conditions of actual use.

Established: Accepted as appropriate by the practicing medical community for the given indication in the specified patient population.

Possibly useful: Given current knowledge, this technology appears to be appropriate for the given indication in the specified patient population. If more experience and long-term follow-up are accumulated, this interim rating may change.

Investigational: Evidence insufficient to determine appropriateness, warrants further study. Use of this technology for given indication in the specified patient population should be confined largely to research protocols.

Doubtful: Given current knowledge, this technology appears to be inappropriate for the given indication in the specified patient population. If more experience and long-term follow-up are accumulated, this interim rating may change.

Unacceptable: Regarded by the practicing medical community as inappropriate for the given indication in the specified patient population.

Appendix 4

The possible strengths of recommendations.

Type A: Strong positive recommendation, based on Class I evidence or overwhelming Class II evidence when circumstances preclude randomized clinical trials.

Type B: Positive recommendation, based on Class II evidence.

Type C: Positive recommendation, based on strong consensus of Class III evidence.

Type D: Negative recommendation, based on inconclusive or conflicting Class II evidence or consensus of Class III evidence.

Type E: Strong negative recommendation, based on evidence of ineffectiveness or lack of efficacy, based on Class I or Class II evidence.

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