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Deep Brain Stimulation for Parkinson Disease

An Expert Consensus and Review of Key Issues

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Objective: To provide recommendations to patients, physicians, and other health care providers on several issues involving deep brain stimulation (DBS) for Parkinson disease (PD).

Data Sources and Study Selection: An international consortium of experts organized, reviewed the literature, and attended the workshop. Topics were introduced at the workshop, followed by group discussion.

Data Extraction and Synthesis: A draft of a consensus statement was presented and further edited after plenary debate. The final statements were agreed on by all members.

Conclusions: (1) Patients with PD without significant active cognitive or psychiatric problems who have medically intractable motor fluctuations, intractable tremor, or intolerance of medication adverse effects are good candidates for DBS. (2) Deep brain stimulation surgery is best performed by an experienced neurosurgeon with expertise in stereotactic neurosurgery who is working as part of a interprofessional team. (3) Surgical complication rates are extremely variable, with infection being the most commonly reported complication of DBS. (4) Deep brain stimulation programming is best accomplished by a highly trained clinician and can take 3 to 6 months to obtain optimal results. (5) Deep brain stimulation improves levodopa-responsive symptoms, dyskinesia, and tremor; benefits seem to be long-lasting in many motor domains. (6) Subthalamic nuclei DBS may be complicated by increased depression, apathy, impulsivity, worsened verbal fluency, and executive dysfunction in a subset of patients. (7) Both globus pallidus pars interna and subthalamic nuclei DBS have been shown to be effective in addressing the motor symptoms of PD. (8) Ablative therapy is still an effective alternative and should be considered in a select group of appropriate patients.

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SURGICAL TREATMENT OF PARKINSON disease (PD) was described as early as 1940 and, until recently, had focused on ablative procedures of the thalamus and globus pallidus pars interna (GPi). These surgical treatments (especially pallidotomy) rose to prominence in the era before levodopa (LD) but later reemerged as popular approaches in the 1990s. They were rapidly replaced in the late 1990s by deep brain stimulation (DBS), mainly as a result of concerns for adverse effects resulting from bilateral lesions as well as the irreversible effects resulting from poorly placed lesions. Furthermore, a new target, the subthalamic nuclei (STN) was identified to be an effective target and quickly became the most common site for DBS electrode placement.[1-3]

Since its approval by the Food and Drug Administration for PD in 2002, more than 70 000 patients have undergone DBS surgery, according to Medtronic Inc. Despite the widespread use of this treatment, several aspects of DBS therapy remain controversial. The purpose of this consensus workshop was to bring together many of the leading experts in the field to address certain issues involving the procedure that remain unresolved.

METHODS

Panel Selection

Participants were invited based on their extensive practice at centers that perform a high volume of DBS procedures, having been extensively involved in research in PD and DBS, and have published in peer-reviewed jour-

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nals in the field. Seventy six percent of those invited attended the workshop (33 neurologists, 13 neurosurgeons, a psychiatrist, a speech researcher, 2 neuropsychologists, a rehabilitation specialist, and a research scientist).

Agenda

The organizing committee distributed a proposed agenda, and participants were encouraged to suggest changes. Two topic leaders for each area were selected to review and distribute key focused articles in advance, briefly review the topic, and lead a discussion.

Meeting

Topic leaders introduced their subject and led a discussion open to all participants. Detailed notes of the discussions were taken, and the meeting was recorded. Prior to the end of the meeting, a preliminary statement was prepared by the topic leaders, presented to all attendees, and discussed again to achieve consensus. The final statement was prepared by the organizing committee based on the documented final discussion, and the manuscript was sent to all participants for their review, comments, and approval.

PATIENT SELECTION

The most important step toward consistent DBS outcomes remains careful patient selection. More than 30% of DBS failures can be ascribed to inappropriate indication(s) for surgery.[4] Patient selection is based on an individual risk-benefit evaluation for each patient that, in most expert centers, has been delivered via a multidisciplinary approach involving a movement disorder neurologist, a neurosurgeon, a neuropsychologist, an internist, and in many cases, a psychiatrist. Best results have been reported in patients with advanced PD and (1) excellent LD response, (2) younger age, (3) no or few axial non–LD-responsive motor symptoms, (4) no or very mild cognitive impairment, and (5) absence of or well-controlled psychiatric disease. However, the rigid application of these criteria may lead to the exclusion of a substantial number of persons with PD.[5] While there was consensus on their importance for the selection process, there was less agreement on how to accurately measure them or the cutoff values that should be respected for DBS eligibility.

Diagnosis

Advanced PD complicated by disability from motor fluctuations, dyskinesias, or tremor despite optimal drug therapy is universally accepted as a reasonable indication for DBS.[6-8] Patients with atypical parkinsonism usually have less favorable outcomes and therefore are not generally considered good candidates for DBS.[9]

Age

The value of age as an independent outcome predictor for DBS has been debated,[10,11] although there are insufficient data to establish a clear age cutoff. The major concerns with age have been the associated comorbidities, cognitive decline,[12] higher incidence of LD-resistant symptoms,[13-15] and higher overall risk of surgical complications.[16]

Disease Duration

Disease duration has not been a primary factor in dictating the selection of patients with PD for DBS therapy. There is currently no evidence of a neuroprotective effect of DBS to provide a clear rationale for earlier DBS surgery. Historically, patients with PD who have DBS have had disease durations of 10 to 15 years; however, preliminary evidence suggest that DBS may have a greater beneficial effect on quality of life for patients with less advanced disease.[17] There has been a concern that operating on patients earlier than 5 years following diagnosis would lead to the inclusion of patients with atypical parkinsonism.

Disease Severity

There are data showing that disease severity has been correlated with clinical outcome[11] but there remains no consensus on a specific severity measure and/or cutoff. Disease severity that leads to disability is influenced by individual factors such as professional status and social function and should be considered.

LD Responsiveness

Response to LD has been universally accepted as the single best outcome predictor for response to DBS.[18,19] Most centers use a formal LD challenge, and a 30% improvement in the Unified Parkinson Disease Rating Scale III score has been used as one useful marker of LD responsiveness but should not be considered an absolute criterion. In addition, severe tremor resistance to LD therapy is considered an accepted exception to this.

Cognitive Impairment

Dementia is the most frequent exclusion criterion for DBS surgery. There was no consensus on the type of testing to establish cognitive impairment in patients with PD or on the level of performance including mild cognitive impairment that would exclude patients from receiving DBS. There are limited data suggesting that advanced age may be associated with higher risk of frontal and related executive deterioration following STN DBS.[12]

Psychiatric Issues

There was no consensus on individual psychiatric symptoms as exclusion criteria for DBS surgery.[11] Surgery is generally deferred in patients with unstable psychiatric conditions until their symptoms have been adequately managed. The reported increased rate of suicide in patients with PD who have undergone STN DBS underscores the need for a more accurate preoperative psychiatric assessment and treatment of depression as well as the need for careful and detailed postoperative follow-up.[20]

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TECHNICAL ISSUES

The surgical techniques for implanting DBS devices are constantly evolving, and surgeons select their preferred technique based on training, experience, and the capabilities of their institution. There are few studies that have directly compared the safety or effectiveness of various surgical techniques. Thus, the best technique for performing DBS surgery remains a source of debate. Nevertheless, the experts agreed on the following: (1) DBS surgery is best performed by an experienced surgeon with specific expertise in stereotactic and functional neurosurgery who should be working as part of an interprofessional team that includes a movement disorder neurologist, neuropsychologist, psychiatrist, and neurophysiologist; (2) both frame-based and so-called frameless navigation techniques are acceptable as long as the surgeon is experienced with the chosen method; (3) there is no best means of targeting for DBS surgery. Acceptable imaging modalities for targeting include magnetic resonance imaging (MRI), computed tomography, ventriculography, and various combinations thereof; (4) some form of intraoperative neurophysiological monitoring is useful for guiding proper lead placement (microelectrode recording, semi–microelectrode recording, microelectrode or macroelectrode stimulation, and/or tissue impedance monitoring); (4) some form of postoperative brain imaging (computed tomography or MRI) is performed by most surgeons to check the position of the implanted DBS leads and to evaluate for hemorrhage and pneumocephalus; and (5) the DBS leads may be implanted during 1 surgery or in 2 separate procedures. The extension cables and pulse generators may be implanted on the same day as the electrodes or days to weeks after, depending on the center's preference. The value of staging or doing unilateral-only implants in a subset of patients, particularly elderly patients or those with cognitive impairment, is of interest but currently not known.

SURGICAL COMPLICATIONS

The rates of surgical complications are quite variable in the literature and include intracranial hemorrhage (0%-10%), stroke (0%-2%), infection (0%-15%), lead erosion without infection (1%-2.5%), lead fracture (0%-15%), lead migration (0%-19%), and death (0%-4.4%).[10,21-25] There was consensus that the incidence of symptomatic intracranial hemorrhage is likely less than 2% for most centers and that lead fracture and migration are likely much lower in recent times owing to improved technology. Hardware infection is the most common reported serious surgical complication, although there was no general consensus on methods to reduce the risk despite agreement on the necessity for the use of perioperative antibiotics.

Several potential factors were discussed that might influence surgical complication rates. Although clear data are lacking, there was general consensus that advanced age and comorbidities of the patient add risk but these should not exclude someone from consideration. There was general consensus that the experience of the surgical team is a key factor in lowering the risk of surgical complications and there is a critical need for prospective standardized reporting of complications.

HARDWARE ISSUES

The hardware complications of DBS are not infrequent but the absence of standardized reporting of adverse events makes it impossible to accurately determine the adverse event profile. Although a revision may be limited to part of the system such as the implantable pulse generator, quite often the revision includes the whole DBS system. The most commonly reported hardware-related complications are infection, migration or misplacement of the leads, lead fractures, and skin erosion. While improved surgical techniques may help reduce adverse events, the primary improvement must come from the manufacturer to produce more durable and redundant leads. We also encourage new designs in leads to further improve performance, minimize complications from errant lead placement, and reduce programming time. In addition, the pulse generator should be improved by decreasing its size, increasing the battery life, allowing different patterns of stimulation, and shielding it from electromagnetic interference.

DBS AND MRI SAFETY

The group agreed that MRI procedures are necessary for some patients with DBS systems for evaluation of new or existing intracranial pathology, assessments of DBS lead location in cases with limited benefit or adverse effects, and performing additional DBS surgery. The following areas related to DBS and MRI were considered important considerations: heating, magnetic field interactions and movements, induced currents, and operational/functional disruption of DBS components. Heating was determined to be the most important factor with respect to safety of MRI in patients with DBS implants and have been reviewed elsewhere.[26-30]

The current Food and Drug Administration approved manufacturer (Medtronic) recommendations are interrogation of the system prior to the MRI examination; assessment of impedance to rule out short or open circuits (MRI cannot be performed if the system integrity is compromised); that the DBS system must be turned Off, programmed at 0 V, and to be in a bipolar mode with the magnetic switch disabled; only a 1.5-T MRI and a head transmit/receive coil should be used; and radio frequency power cannot exceed specific absorption rate of 0.1 W/kg in the head.

The group expressed concerns about these recommendations being too restrictive with respect to MR scanning of patients. More common and higher resolution sequences are not allowed, and many centers routinely perform various MR sequences that do not adhere to the manufacturer's criteria and have had a large experience without complications. Larson et al demonstrated safety in more than 1000 MR examinations, many of which were outside the manufacturer's criteria.[31] The National Parkinson Foundation Center of Excellence experience was also discussed and included 3304 patients without any

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safety risks.[32] It was also noted that, at some centers, the radiologists are still prohibiting MR scanning with DBS.

The group discussed the 2 case reports pertaining to safety issues with respect to MRI and DBS.[33] The cases occurred during unique scenarios, and there have been no additional reports of safety-related issues.

The group recommended additional studies and discussions with the Food and Drug Administration and Medtronic to potentially modify the restrictive recommendations and allow for more flexibility in MR scanning. There were no issues of concern with respect to current induction, device functionality, and magnetic field interactions with DBS systems.

PROGRAMMING

Deep brain stimulation programming is best accomplished by a highly trained clinician (eg, neurologist, neurosurgeon, nurse, physician assistant) who understands not only the technical aspects of DBS but also PD-related issues and pharmacological management. While the use of the intraoperative data and postoperative imaging can be useful in guiding choice of electrodes, it is recommended to systematically test the effects of stimulation (adverse and beneficial) for all electrodes during the initial programming session. There was general agreement that the initial parameters of stimulation, which should be studied, are pulse width, frequency, voltage, and electrode configuration. Rigidity and tremor were the most frequent clinical signs targeted for improvement during the first programming session; however, measurement of motor speed and gait assessment may also be useful. Optimization of DBS parameters is usually attained within 3 to 6 months during 4 to 5 programming sessions. Anti-PD medication reduction should be performed gradually and excessive early reduction avoided. Assessment and management of adverse events due to stimulation (speech, gait, balance, neuropsychiatric, etc) is best approached systematically to optimize benefits and minimize adverse effects. Other programming strategies such as low-frequency stimulation and alternative electrode configurations can be considered to treat problems not adequately managed by more standard approaches.[34]

SURGICAL OUTCOMES

Gait and Speech

Balance and gait are gradually and nearly always impaired as PD progresses, resulting in significant disability, decreased quality of life, morbidity, and mortality.[35,36] The effects of DBS on balance and gait are difficult to interpret because they are complex behaviors that may or may not be sensitive to LD or DBS, and many postoperative observations are anecdotal.[37,38] In general, aspects of gait and speech that improve with LD therapy improve with DBS; however, these may later worsen with disease progression. There was consensus that STN DBS can worsen speech and gait in some patients whose symptoms may be improved by altering stimulation parameters. Finally, in the recently reported Veterans Affairs/National Institute of Neurological Disorders and Stroke Cooperative DBS Study (Co-op Study), an increase in the number of falls was reported with STN DBS compared with GPi DBS[39] and medical therapy.[10]

Cognition and Behavior

Recognition of psychiatric and cognitive comorbidities, especially depression, anxiety, apathy, psychosis, and impulsivity prior to surgery is critical because they confound assessment of surgical results. Depression and impulsivity have been reported following DBS and may represent a consequence of stimulation or emergence of symptoms that may have been present preoperatively.[12,40-44] Altering stimulation parameters can often help mitigate stimulation-induced behavioral problems. In the recently reported Co-op Study, depression worsened with STN DBS but was improved with GPi DBS, suggesting that either STN stimulation or reduction of PD medications can contribute to depression.[39] There are also reports of worsened verbal fluency, executive dysfunction,[12,41] and processing speed[39] following STN DBS.

LONG-TERM OUTCOMES

Long-term improvements have been demonstrated for up to 5 years for both STN and GPi DBS, especially on motor fluctuations[45-49] and for tremor with STN, GPi, and ventral intermediate nucleus of the thalamus DBS.[47,50,51] The stimulation parameters in all 3 targets seem to remain relatively stable, and there is little current evidence for tolerance. However, there are 2 preliminary reports of delayed failures of GPi stimulation in a few patients who were improved by STN stimulation, suggesting the possibility that both treatments may have a different efficacy in the long-term.[52]

Despite these positive results, PD continues to progress after DBS, and there is little evidence that DBS alters disease progression. Over time, patients who have DBS often develop LD-resistant symptoms including freezing of gait, postural instability, and cognitive decline.

GPi vs STN

Similar benefits for both STN and GPi DBS have been reported in only a few randomized studies.[53-55] In a recent randomized study, unilateral stimulation of the STN and GPi DBS resulted in similar effects on mood and cognition but GPi stimulation resulted in improved quality of life compared with STN stimulation.[56,57] The most definitive study on this subject comes from the recently reported Co-op Study.[39] Two hundred ninety-nine patients with PD were randomized to STN or GPi DBS with the primary outcome of Unified Parkinson Disease Rating Scale Part III assessed in a blinded manner. Similar improvements were found at 2-year follow-up for both surgical sites. Dopaminergic medication was decreased more for the STN group but visuomotor processing speed declined less after GPi DBS. Furthermore, subjects who had GPi DBS showed improvement in depression, whereas subjects who had STN DBS worsened. Severe adverse events were common but similar for the 2 targets.[39] Taken together, both STN and GPI DBS improve motor func-

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tion but the target selection should be individualized considering the differences in nonmotor outcomes.

ROLE OF STEREOTACTIC ABLATIONS IN PARKINSON DISEASE

Although thalamotomy and pallidotomy have been largely abandoned and replaced by DBS, ablative therapies may yet have a role in certain patients such as those with an increased risk of infection or a history of recurrent infection of their DBS systems; with limited access to centers specializing in DBS surgery; and not desiring implanted hardware, as well as being unwilling to commit to long-term programming. Potential disadvantages of ablative surgery include mistargeted lesions with permanent neurological deficit(s), suboptimal benefits requiring repeat procedures, and risk of bilateral lesions. The effectiveness and risks of ablative surgery are reviewed elsewhere.[58-60]

Radiosurgical ablative surgery such as γ knife surgery is not considered an established or safe therapy for the GPi or STN. In a selected group who have a poor risk/benefit ratio for DBS, unilateral radiosurgical thalamotomy may be performed but the risk/benefit ratio is still being examined.

CONCLUSIONS

In our deliberations, we reached consensus on several issues involving DBS for the treatment of PD. Good candidates are patients with PD with disabling motor fluctuations and/or medically intractable tremor without significant cognitive or psychiatric problems. It is recommended that DBS be performed at centers with an experienced team of experts. Both STN and GPi appear to be equally effective targets for treating motor symptoms; STN DBS allows for greater reduction in medication but may be associated with worsening of nonmotor symptoms and falls. With the exception of tremor, DBS treats primarily LD-responsive symptoms, and the benefits of DBS are sustained for several years. Postoperative brain MRIs can be safely performed and are useful. Finally, there is still a role for ablative lesions for select patients.

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