REVIEW ARTICLE doi: 10.2176/nmc.ra.2016-0002

Neurol Med Chir (Tokyo) 56, 236–248, 2016 Online April 6, 2016

Update on Deep Brain Stimulation for Dyskinesia and Dystonia: A Literature Review

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Abstract

Deep brain stimulation (DBS) has been an established surgical treatment option for dyskinesia from Parkinson disease and for dystonia. The present article deals with the timing of surgical intervention, selecting an appropriate target, and minimizing adverse effects. We provide an overview of current evidences and issues for dyskinesia and dystonia as well as emerging DBS technology.

Key words: deep brain stimulation, dyskinesia, Parkinson disease, dystonia

Introduction

The 30th anniversary of deep brain stimulation (DBS) will come around in 2017.[1)] In these three decades, DBS has become an established surgical option for dyskinesia in Parkinson disease (PD) and various types of dystonia.[2)] Major guidelines for PD[3–5)] and dystonia[6)] confirm the evidence levels of DBS as effective. In addition, reviewing recent clinical trials of patients with PD or with dystonia help us define therapeutic efficacy of DBS and its adverse effects more clearly than in the past.[7,8)] Furthermore, emerging stimulation technology has advanced to overcome clinical difficulties encountered during DBS treatment. In this review, the authors summarize the current evidence of DBS for dyskinesia in PD and for dystonia, list relevant clinical issues, and then present recent advances of DBS technology.

Methods

The authors searched literatures published from 1 January 2014 to 31 October 2015 on Pubmed database. The search terms and syntax were [(Parkinson or Parkinson's or dystonia) and "deep brain stimulation"]. The search yielded 949 articles. We excluded 28 non-English articles, 10 articles not focusing on PD or dystonia, and 66 non-human studies. We classified the remaining 845 articles into guidelines and reviews, meta-analyses, clinical trials, other outcome analyses, expert opinions, DBS technology, surgical techniques, and miscellaneous. Searching our personal files and the reference listed on the retrieved articles identified additional articles.

The classified articles were grouped according to the following themes: current evidences with guidelines and meta-analyses, randomized trials examining efficacy of DBS, stimulation targets, complication management, advances in surgery and technology.

Received January 4, 2016; Accepted March 1, 2016

Results

I. Current evidences of DBS for dyskinesia of PD and for dystonia

1. Guidelines from the American Academy of Neurology (AAN), the Movement Disorder Society (MDS), and the European Academy of Neurology (EAN)

There are three guidelines for management of PD[3–5)] and two for dystonia[6,9)] available from the leading neurological societies (Table 1). These PD guidelines refer to efficacy and safety of DBS based on the landmark clinical trials (Table 2). Comparing to the studies on DBS for PD, there are fewer randomized controlled trials (RCTs) of DBS on dystonia; thus, evidence level of using DBS for dystonia is relatively low. Here we briefly summarize these guidelines chronologically.

The AAN published practice parameter for motor complications of PD in 2006.[5)] It recommends that DBS of the subthalamic nucleus (STN) is a treatment option to improve motor function, to ameliorate motor fluctuation and dyskinesia, and to reduce medication dosage (Level C, Table 1). The recommendation for

Table 1 Recommendation for deep brain stimulation in guidelines from neurological societies

Guidelines and year	Recommendations		
	Therapeutic effects	Predictive factors	Safety
AAN, 2006	STN-DBS • a possible treatment option to improve motor function and to reduce motor fluctuations, dyskinesia, and medication usage (Level C)	STN-DBS • preoperative response to levodopa (Level B) • younger age and shorter disease duration (less than 16 years) (Level C)	STN-DBS • need to be counseled regarding the risks and benefits
	GPi- and VIM-DBS • insufficient evidence to make any recommendations (Level U)	GPi- and VIM-DBS • insufficient evidence to make any recommendations (Level U)	GPi- and VIM-DBS n/a
MDS, 2011	STN- or GPi-DBS • efficacious and clinically useful as symptomatic adjunct to levodopa and as treatment for motor complications	n/a	Any DBS acceptable risk with specialized monitoring
	VIM-DBS • likely efficacious and possibly clinically useful as symptomatic adjunct to levodopa		
EFNS/MDS-ES, 2013	STN- or GPi-DBS • effective against sever motor fluctuations and dyskinesia, biphasic dyskinesia, unpredictable ON-OFF, Off-period and early-morning dystopias (Level A) • reduction in dopaminergic treatment (Level A)	n/a	STN- or GPi-DBS • recommended for patients below the age of 70 without major psychiatric or cognitive problems • depression improved with GPi and worsened with STN DBS • visuomotor processing worsened with STN DBS
	VIM-DBS • improves tremor but not akinesia		VIM-DBS n/a

AAN: American Academy of Neurology, DBS: deep brain stimulation, ES: European section, EFNS: European Federation of Neurological Society, GPi: globus pallidus interna, MDS: Movement Disorder Society, n/a: not available, STN: subthalamic nucleus, VIM: ventral intermediate nucleus of the thalamus. Level A: established as effective, ineffective, or harmful for the given condition in the specified population (requiring at least two consistent class I studies), Level B: probably effective, ineffective, or harmful for the given condition in the specified population (requiring at least one class I study or at least two consistent class II studies), Level C: possibly effective, ineffective, or harmful for the given condition in the specified population (requiring at least one class II study or two consistent class III studies), Level U: data inadequate or conflicting; given current knowledge, treatment is unproven.

STN-DBS were based on the four class III studies[10–13] (Table 2). Younger age, shorter disease duration, and response to levodopa are considered to be predictive factors for the preferred surgical outcome of STN-DBS from two class II studies[14,15] (Table 2). For safety concern, it recommends that patients should have appropriate preoperative counseling (Table 1). As for DBS of the globus pallidus interna (GPi) or of the ventral intermediate (VIM) nucleus of the thalamus, this guideline concluded that there was insufficient evidence for any recommendation of these two targets at that time.

Five years later with more evidences from further clinical trials including several RCTs, the MDS published an updated guideline.[4] This update assessed seven class I trials of DBS published from 2005 to 2010[16–23] (Table 2) and confirmed that bilateral DBS of STN or GPi are efficacious as an adjunct to levodopa, and also efficacious for the treatment of both dyskinesia and motor fluctuation. They assessed the referred clinical trials with their quality scores (Table 1). DBS of the VIM is evaluated as likely efficacious and possibly clinically useful as symptomatic adjunct to levodopa.

Table 2 Landmark studies for AAN, MDS, and EFNS guidelines

Author and year	Guidelines	Therapeutic class (AAN)	Prognostic class (AAN)	MDS class	MDS quality score	EFNS class
Deep Brain Stimulation for Parkinson's Disease Study Group, 2001	AAN, EFNS	III	IV			II
Østergaard et al., 2002	AAN	III	IV			
Pahwa et al., 2003	AAN	III	IV			
Welter et al., 2002	AAN	IV	II			
Kleiner-Fisman et al., 2003	AAN, EFNS	IV	II			n/a
Anderson et al., 2005	MDS			I	58%	
Deuschl et al., 2006	MDS, EFNS			I	80%	I
Esselink et al., 2006, 2009	MDS			I	86%, 93%	
Schüpbach et al., 2006	MDS			I	74%	
Follett et al., 2010	MDS, EFNS			I	90%	I
Williams et al., 2010	MDS			I	80%	
Weaver et al., 2009	MDS, EFNS			I	n/a	I
Krack et al., 2003	EFNS					III
Schüpbach et al., 2005, 2007	EFNS					III
Volkmann et al., 2004	EFNS					III
Lang et al., 2006	EFNS					n/a
Limousin et al., 1999	EFNS					n/a

AAN: American Academy of Neurology, DBS: deep brain stimulation, ES: European section, EFNS: European Federation of Neurological Society, GPi: globus pallidus interna, MDS: Movement Disorder Society, n/a: not available, STN: subthalamic nucleus, VIM: ventral intermediate nucleus of the thalamus.

In 2013, just before the organization of the EAN, the former European Federation of Neurological Societies (EFNS) and MDS-European section (MDS-ES) published a guideline,[3] which also confirmed the efficacy of DBS of the STN or the GPi for advanced PD motor symptoms with referring to further five articles[24–28] (Table 2). The EFNS/MDS-ES guidelines describe the DBS effects in detail, by focusing on respective symptoms of motor fluctuation and motor complications as well as non-motor and cognitive symptoms. As for DBS-VIM, they conclude it improves tremor but not akinesia.[29] Recommendations from these three guidelines are listed in Table 1. The recent two guidelines from MDS and from EFNS/MDS-ES describe that DBS of STN or of GPi are similarly effective to control motor symptoms of the advanced PD. The guidelines also referred to safety concerns of DBS.

As for dystonia, EFNS and MDS published guidelines in 2011.[6,9] The EFNS guidelines[6] recommended DBS of the GPi as a good option for primary generalized and segmental dystonia (Level A), and for cervical dystonia (Level B). For secondary dystonia, pallidal DBS is less effective (Level C) and the AAN guidelines for tardive dystonia concluded that there is insufficient data to recommend DBS to control tardive dystonia.

The MDS guidelines[9] indicate the inclusion and exclusion conditions regarding the patient characteristics as age, comorbidities, disease duration; clinical features as mobility, activity of daily scores, pain status, specific types of dystonia, predictor of response, target selection, motor and non-motor features; previous medical and surgical treatments; and genetic causes. Throughout an exhaustive literature analysis, the guideline suggested that DBS should be considered before musculoskeletal deformity and complication are fixed. There is no data in children younger than 7 years of age and no strict restriction of upper age limit. Screening for psychiatric comorbidities and systematic evaluation for older patients are recommended. DBS of

the GPi was recommended for primary generalized dystonia who do not respond well to medical therapy, for cervical dystonia without adequate response to botulinum toxin. DBS may be considered for tardive dystonia, hyperkinetic cerebral palsy. As described in the next section, there are fewer meta-analyses on DBS for dystonia. The following is a common agreement about the DBS for dystonia: for generalized or segmental dystonia patients, DBS is considered as an option after failure of medical treatment and botulinum toxin. However, there is no consensus about the types of medications and length with botulinum toxin treatment before surgery. Patients with disabling symptoms which significantly deteriorate activity of daily life may consider DBS before these symptoms become fixed. For cervical dystonia, pallidal DBS is suggested as second line, while peripheral denervation surgery can be also another second line option.

2. Meta-analyses

In 2005 and 2006, two meta-analyses examining the general outcome of DBS for PD were published.[30,31] These meta-analyses covered 48 articles, only 2 of them were RCTs.[11,32] These meta-analyses showed 40–50% improvement in motor function after DBS of the STN or the GPi and performance of activities of daily living. Medication requirements were significantly reduced following DBS of the STN but not of the GPi.

In 2014, three meta-analyses of RCTs of DBS for PD were published.[33–35] A meta-analysis[35] of six RCTs (n = 1,184)[16,17,19,22,36–38] compared DBS versus medication (Table 3). Most cases analyzed in this meta-analysis had undergone DBS of bilateral STN (n = 65 for DBS of the GPi). The meta-analysis demonstrated that DBS significantly improved motor function and quality of life. The results also showed that DBS reduced the medication dose and its associated complications, possibly because most analyzed cases were treated with bilateral STN stimulation. As for cognitive effects, analyses on language, mental status, dementia rating, semantic and phonemic fluencies, and Stroop test favored medication alone, while analyses on mental health and depression rating favored DBS.[35]

Two other meta-analyses were on RCTs comparing DBS of the STN and of the GPi.[33,34] They analyzed four to six such RCTs[18,23,39–42] (Table 3). The total sample sizes were 502–563 patients. Both DBS of the STN and of the GPi were similarly effective to improve motor functions. However, if a heterogeneous

Table 3 Randomized controlled trials examined in the recent meta-analyses

Author and year	Number of patients		Stimulation
DBS vs. BMT	DBS	BMT	
Deuschl et al., 2006; Witt et al., 2008	76	76	bilateral STN-DBS
Williams et al., 2010	183	183	bilateral STN-DBS (include other surgery in 2%)
Weaver et al., 2009	60 STN 61 GPi	134	bilateral DBS of STN or GPi
Schüpbach et al., 2007	10	10	bilateral STN-DBS younger than 50 years old
Okun et al., 2012	101	35	bilateral STN-DBS constant current stimulation vs. without stimulation for 3 months
Schüpbach et al., 2013	124	127	bilateral STN-DBS, EARLY-STIM study
DBS, STN vs. GPi	STN	GPi	
Anderson et al., 2005	10	10	
Rothlind et al., 2007	19	23	unilateral or staged bilateral stimulation
Zahodne et al., 2009	20	22	unilateral stimulation
Follett et al., 2010	147	152	
Rocchi et al., 2012	15	13	
Odekerken et al., 2013	63	65	

BMT: best medical therapy, DBS: deep brain stimulation, GPi: globus pallidus interna, STN: subthalamic nucleus.

study is eliminated, motor function during off period may favor STN stimulation in patients with advanced PD.[33] In addition, short-term outcome up to 12 months was in favor of DBS of the STN. Activities of daily living improved equally in both DBS groups. As for mental status, depression may improve from baseline in GPi stimulation group[34] and postoperative depression was significantly more frequent in patients with STN stimulation than with GPi stimulation.[33]

As for dystonia, there have been few RCTs those examined clinical effects of DBS for primary and secondary dystonia: a class I study of primary generalized/segmental dystonia;[43] a class II study for primary generalized dystonia;[44] four class III studies for cervical dystonia;[45–48] and individual class III study for tardive dyskinesia,[49] secondary dystonia,[46] and cerebral palsy,[50] respectively. A single meta-analysis study had been published before 2010.[51] Recently, several meta-analyses showed effects of DBS for various types of dystonia[52,53] including cervical dystonia[54] and hyperkinetic cerebral palsy.[55] Comparing to the studies on DBS for PD, the results from the literature is heterogeneous and difficult to draw a definite conclusion from meta-analyses.

II. Clinical issues in DBS for dyskinesia from PD and for dystonia

While guidelines and meta-analyses propose general criteria for surgical indication and indicate considerable risks in patients with PD, reviews and expert opinions pointed out that several controversial issues of importance as follows: the timing of surgical intervention, the selection of stimulation target, adverse effects of stimulation and refractory symptoms. These clinical issues are also critical points to consider DBS for patients with dystonia. Herein, we provide an overview of such clinical issues by reviewing the relevant articles.

1. Expanding therapeutic time windows for early and late timings

Patients with advanced PD may consider DBS as their treatment options. Common disease duration at surgery of these patients was reported to be 13–14 years.[31] Considering that the average age of onset for idiopathic PD is around 60 years old,[56] and also regarding that aging is the risk factor for surgical complications and co-morbidity,[57,58] therapeutic time window of DBS for PD is relatively small (Fig. 1). There have been several trials investigating benefits of surgical interventions at early and late timings.

There are two studies examining the effects of early DBS for PD. EARLY-STIM trial[37] is a 2-year, multi-center prospective, randomized, and controlled study in 251 patients (18–60 years old, a mean age of 52 years old) with PD for 4 years and fluctuation or dyskinesia for 3 years (mean disease duration: 7 years). Bilateral STN-DBS plus best medical therapy (BMT) had been significantly superior to BMT alone

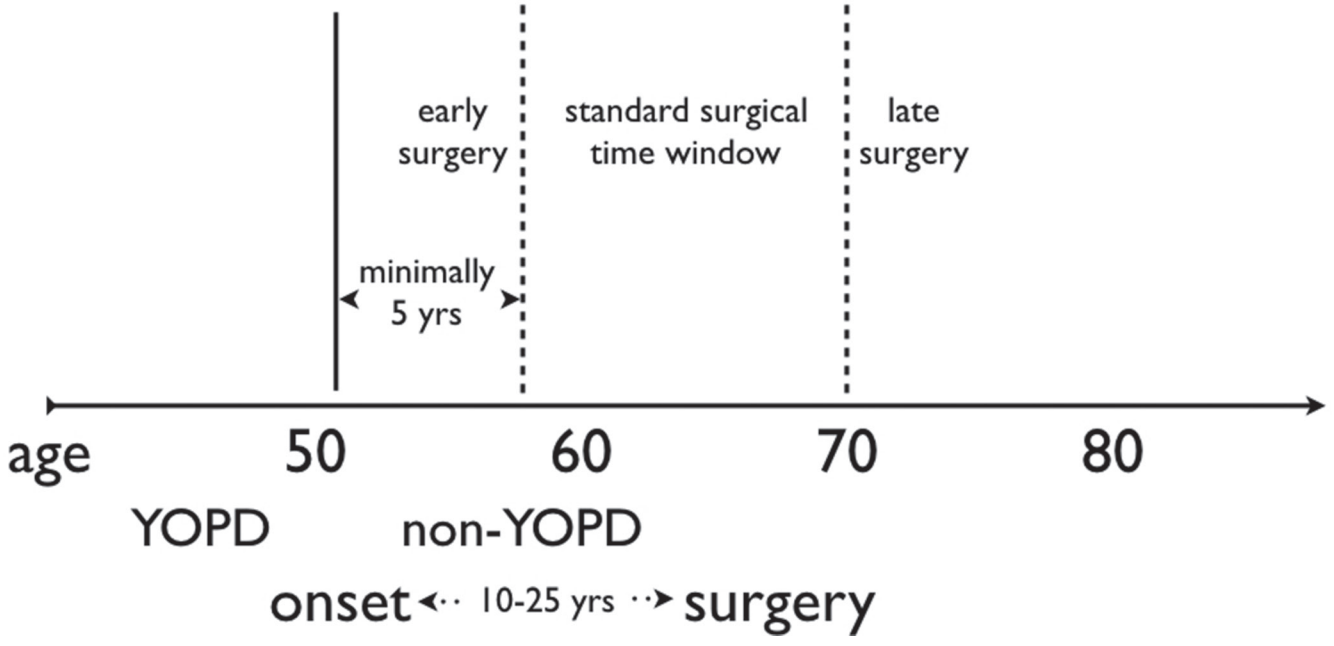

Fig. 1 A graphical representation for disease onset and surgical therapeutic time window in Parkinson disease. YOPD: young onset Parkinson disease.

in improving quality of life and motor function for up to 2 years. Mean scores on a Parkinson's disease questionnaire (PDQ-39), improved by 7.8 points in patients who received DBS and worsened by 0.2 points in those who received BMT alone. The maximum effect was reached at 5 months and remained stable for up to 24 months. The levodopa-equivalent daily dose was reduced by 39% in patients who received STN-DBS and increased by 21% in those who received BMT alone. EARLY-STIM trial results showed significant and clinically meaningful improvements in quality of life, motor disability, activities of daily living, and levodopa-induced motor complications after 2 years of follow-up. These advantages need to be considered because serious adverse events during surgery and stimulation occurred in 18% of patients. There were two suicides in the neurosurgical group and one in the BMT group.[26]

Another RCT from Vanderbilt University[59] examined the effects of further early DBS intervention on 30 patients with PD before the onset of motor fluctuations (disease duration within 4 years). STN-DBS and BMT were compared to BMT alone in very early PD patients with a mean age of 60 years and their mean disease duration of 2 years. These patients were on Hoehn and Yahr stage II during off medication, and did not suffer from motor fluctuations or dyskinesia. The authors found no differences between DBS group and BMT alone group in the motor function outcomes or the change in levodopa equivalent daily dose from baseline to 24 months. Two of the 15 operated patients had serious adverse events (one postoperative stroke and one device infection and removal). The long-term outcome is not clear to show disease modifying effect on clinical progression of PD.[60]

As "late" application of stimulation, DBS for elderly patients was examined in a large retrospective cohort study.[61] The study examined 1,757 patients who underwent DBS for PD. The main outcomes were length of hospital stay and complications within 90 days following surgery. The results showed 7.5% of patients experienced at least one complication within 90 days, including wound infections (3.6%), pneumonia (2.3%), hemorrhage/hematoma (1.4%), or pulmonary embolism (0.6%). Their analysis concluded that increasing age did not significantly affect the overall 90-day complication rates. The authors discussed expanding of the therapeutic window for elderly patients. However, the study lacks several critical analyses on motor and cognitive outcomes. Previous studies have shown worsening of activities of daily living scores and axial motor scores in the ON medication state in older patients despite improvement in motor complications.[57,58] Unlike younger patients, older patients were not able to reduce medication doses and their several quality of life items were worsening or unchanged. Thus, indication for elderly patients should be carefully examined.

Dystonia patients are generally younger than patients with PD. For children with primary generalized dystonia, DBS should be considered before they develop mobile deficit and joint deformity.[62,63] Short disease duration is also a predictive factor for postoperative control of dystonia, especially in DYT1 mutation carriers.[64,65]

2. Target selection

The guidelines from MDS[4] and EFNS[3] showed that DBS of both STN and GPi has been designated as efficacious symptomatic adjuncts to levodopa for the treatment of dyskinesia and/or motor fluctuations in advanced PD patients. Multiple RCTs comparing STN and GPi DBS and their meta-analyses showed less substantial difference for efficacy and safety profiles between these two targets.[18,33,34,39] The motor benefits can be similar with each target. Each component has slightly different responses dependent on the target. Medication reduction[18] and control of rigidity[66] and bradykinesia[33] favor STN.[67] Reductions in levodopa dosage may be maintained for several years after STN-DBS.[68] Suppression of dyskinesia and dystonia,[18] cognition,[69] mood, apathy,[33] and long-term effects on stability[70] and cognitive favor GPi.[67] Target selection should be based on the detailed multi-disciplinary preoperative assessment including non-motor, cognitive, and psychological/psychiatric status.

As for dystonia, in both adults and children, as well as with generalized and segmental types including cervical and craniofacial dystonia, DBS of the postroventral lateral GPi has been shown to be efficacious. In some studies, STN has been reported as a useful target for dystonia[71–73] including some patients who had been treated with pallidotomy.[74] As a feature of STN stimulation, immediate relief of symptoms and lower intensities of stimulation are reported.[75,76] A prospective double-blind cross-over study comparing DBS of the STN and the GPi for various types of dystonia showed the results favor STN.[77] In addition, there are number of publication reporting that the motor thalamus, particularly ventral oralis anterior and posterior, has also been used as a target of stimulation.[78–82] Thalamic stimulation has been shown to be effective for dystonic tremor, myoclonic dystonia, and writer's clamp.[83,84]

3. Adverse effects of stimulation and refractory symptoms

Dopa-responsive motor symptoms and motor complications as dyskinesia are well-treated with DBS in

long term. In addition, some non-motor symptoms such as pain[85] may respond well to DBS. However, even with successful surgery, decreased verbal fluency and a variety of psychosocial problems have occurred.[19,31] Additionally postural instability, freezing of gait, and cognitive problems do not improve with the procedure and may become worse.[68] In patients with pre-existing intellectual impairment and in patients over 70 years old, cognitive decline after DBS is common.[86] Furthermore, DBS can increase the incidence of falls and may increase impulsivity. Even in a recent trial as EARLY-STIM study, depression was commonly observed with neurostimulation than with BMT alone (4.8% vs. 0.8%).[37] Non-motor and psychiatric evaluation constitutes vital part of the preoperative evaluation.

In patients with dystonia, pallidal stimulation can cause adverse effects, especially if deep pallidal contact is used.[87,88] Bradykinesia with slowing of finger tap, hypokinetic gait disturbance with freezing of gait, and stimulation-induced Parkinsonism may occur in patients with dystonia, even in unaffected limbs.[87,88] STN stimulation tends to cause dyskinesia rather than bradykinesia, and does not influence cognition significantly.[72,77,89]

III. Emerging techniques of DBS

1. Advances of surgical management

Surgical complications of DBS include intracranial hemorrhage, hemiparesis, infection, depression, confusion, attention/cognitive deficits, dysarthria, and death.[31] Such major complications still occurred in about 10% of patients who received DBS.[37] Reduction of surgical morbidity and enhancing accuracy are of importance. Hence, various surgical management and techniques have been reported.

Intraoperative imaging is being proposed for real-time guidance of the electrode placement, combined with new "mini-frames." Skull-mounted device systems (e.g., NexFrame, Medtronic, Minnesota, USA; STarFix, FHC Inc., Maine, USA) used in conjunction with intraoperative magnetic resonance imaging (MRI) or computed tomography scans, which may be fused to the preoperative scans to allow real-time verification and navigation.[90] Source of inaccuracy of targeting may come from brain-shift during the operation.[91] Intraoperative MRI may be in conjunction with procedures under general anesthesia. Surgery under general anesthesia would be beneficial for patients with severe discomfort or with severe motor conditions. The impact of intraoperative MRI on safety and accuracy is being investigated currently, as other trials comparing the outcomes of awake versus asleep DBS for PD are also currently ongoing.

2. Novel DBS technology

Recent advances of DBS technology introduce newly designed electrodes, novel implanted pulse generators (IPGs), and innovative on-demand stimulation systems.

Newly designed directional multipolar electrode can shape and steer the current spread with certain topographical directions to optimize stimulation effects.[92–96] Such electrode designs consistently showed a significant widening of the therapeutic range of stimulation topographically, compared to the conventional spherical stimulation.[95,96]

Furthermore, advanced stimulation techniques have added new mode of neurostimulation. Medtronic Activa system has interleaving stimulation mode, which enables dual stimulation from different electrodes with variable amplitudes and pulse widths. This interleaved stimulation can allow the clinician to shape the various spherical electrical fields.[97] Boston Scientific (Marlborough, Massachusetts, USA) Vercise™ is capable of providing completely different stimulation including frequency parameter.[92] In addition, this IPG allows the use of low pulse widths to reduce the incidence of side effects. These IPG programming options enable us in further shaping of the current along the vertical axis of the electrode. To support these electrodes and IPG advances, image guidance system simulating the current spread on the MRI and atlases will guide visually to plan an appropriate stimulation setting (Boston Scientific, Guide DBS; Medtronic, Optivise). For the availability of postoperative MRI, new DBS system is compatible with 1.5T MRI machine[98] enabling both improvement in targeting and verification of electrode location.[99] Rechargeable IPGs are also available. The rechargeable IPG battery life is up to 9 years (Activa RC), 10 years (BRIO from St. Jude, Saint Paul, Minnesota, USA), or 25 years (Vercise). Finally, new IPGs can deliver constant-current stimulation, which will minimize fluctuation of current according to changes of hardware or stimulated tissue.[36,100]

Besides these electrodes and IPG innovations, a new concept of stimulation has emerged as on-demand stimulation system, which is called closed-loop or adaptive stimulation, comparing to the classic system as open-loop. Recent neural network and connectivity studies revealed that basal ganglia network activity in PD are dynamic conditions and a constant stimulation may cause adverse effects depending on the particular state. By using electrodes implanted in the STN as both probe and modulator of neural circuitry, preliminary study with adaptive DBS using non-implantable device on eight patients with PD has adaptive DBS triggered by the beta-frequency activity, is superior to standard stimulation.[101]

Discussion

Updated guidelines, clinical trials, and long-term follow-up studies refine the clinical evidences to apply DBS for PD and dystonia effectively and safely. Recent researches focus on the therapeutic time window and suggest that the relatively early indication of DBS may be beneficial for certain patients. Benefits of early surgery for patients with PD are as follows: DBS can improve levodopa responsive symptoms, while symptoms appearing in the late stage are often unresponsive;[102] elderly patients are liable to surgical complication and worsening of axial motor functions;[103] the alleviation of motor symptoms has great socioeconomic impact on patients and their caregivers. However, the risk of surgical procedure should be considered significantly. The decision to perform DBS always needs to weigh the balance between potential benefits and possible risks of DBS in each patient, including selection of an appropriate target, STN, or GPi. For patients with dystonia, especially with secondary dystonia, more clinical and neurophysiological study will define the predictive factor and alternative DBS targets to refine clinical outcomes.

Major risks possible for relatively young patients who consider DBS are severe complications such as vital intraparenchymal hemorrhage and vital psychiatric sequel. Thus, improving the safety and accuracy of DBS procedure should be prioritized for functional neurosurgeons.

Even in the elderly patients, the short-term complication seems not to be significantly high, however, these elderly patients tend to have co-morbidity and risk of cognitive impairment.[104] Therefore, application of DBS for elderly patient also should be discussed for the needs of surgical intervention individually. For elderly or patients at high risk, there are options as utilizing unilateral or staged operations, or selecting thalamic target if patients suffer tremor dominant symptoms.

Finally, recent advances of surgical management and DBS technology improve the safety and accuracy of procedures. These therapeutic procedures may explore further opportunity of surgical intervention for unresolved clinical issues of advanced PD.

Conflicts of Interest Disclosure

The authors have declared no conflicts of interest.

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