# Perspectives on the Earlier Use of Deep Brain Stimulation for Parkinson Disease from a Qualitative Study of U.S. Clinicians

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BACKGROUND: **In November 2015, the U.S. Food and Drug Administration (FDA) approved the use of deep brain stimulation (DBS) therapy in people with Parkinson's disease (PD) "of at least four years duration and with a recent onset of motor complications, or motor complications of longer-standing duration that are not adequately controlled with medication." Although the full implications of this more recent approval are yet to be determined, to date, there are no strict criteria defining appropriate earlier use of DBS. As such, confusion remains regarding the actual meaning of early DBS initiation. To better inform responsive policy, we sought the perspectives of movement disorder neurologists and neurosurgeons regarding the earlier use of DBS. Insights from these clinicians are key to developing appropriate clinical guidelines and determining how early is too early. The objective of this study is to explore attitudes among clinicians toward the earlier use of DBS for PD.**

METHODS: **Twelve Michigan-based clinicians were interviewed both about DBS referral/use processes and their perspectives regarding the earlier use of DBS in PD. We used a structured interview with closed- and open-ended questions. All interviews were transcribed verbatim and analyzed using a mixed-method approach.**

RESULTS: **We found that most clinicians considered earlier use not solely to be time dependent but instead determined by patient symptoms. Only 16.8% were aware of the FDA's recent indication of early use of DBS, with 25% of our respondents being unsure as to whether it should be seen as an early treatment modality. On average, neurologists suggested DBS as the next treatment option, after medications have been exhausted, typically 6 years after diagnosis.**

CONCLUSIONS: **There remain wide variations in terms of clinicians' parameters for referrals and timing of DBS. Larger studies are needed to support or refute our findings.**

## INTRODUCTION

As the evidence for deep brain stimulation (DBS) providing good symptomatic control and improvement in quality of life for patients with Parkinson's disease (PD) continues to grow,[1,2] a paradigm shift toward earlier diagnosis and comprehensive treatment is increasingly being considered by members of the movement disorders community.[3] Today, DBS is regarded as a suitable earlier treatment option in PD, once patients are no longer benefitting from medication,[2,4] or are having significant medication side effects.[5] As part of this shift in DBS timing, in November 2015, the U.S. Food and Drug Administration (FDA) gave approval for the use of DBS therapy in people with PD "of at least four years duration and with a recent onset of motor complications, or motor complications of longer-standing duration that are not adequately controlled with medication" (https://www.meddeviceonline.com/doc/fda-approves-medtronic-parkinson-s-disease-with-recent-motor-complications-0001) (from here on it is referred to as earlier use). Several groups were investigating the appropriateness of DBS earlier in the progression of the disease even before FDA approval.[3,6-9] Currently, there are groups investigating the potential benefit of DBS prior to the onset of motor complications, perhaps as a disease modifying strategy.[7,10,11] The core question of timing in

**Key words**
- Deep brain stimulation
- Parkinson disease
- Perspectives

**Abbreviations and Acronyms**
**AAN**: American Academy of Neurology
**DBS**: Deep brain stimulation
**FDA**: Food and Drug Administration
**GPi**: Globus pallidus interna
**PD**: Parkinson's disease

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the DBS debate is: How early is too early? This question is particularly salient because it can impact patient care.

### Clinician Referrals

Patient selection has been discussed in the scientific literature. Important considerations include levodopa response, intractable tremor, psychiatric comorbidities, balance problems with on-gait freezing, age, unremarkable brain magnetic resonance imaging, good cognition, and realistic expectations.[12-15]

Katz et al.[14] found that when compared with prior studies, the quality of DBS referrals has improved, with more uniformly accepted referral criteria: 1) diagnosis of advanced idiopathic idiopathic Parkinson's disease, with symptom duration of 5 years or longer; 2) documented positive response to levodopa therapy; 3) history of motor fluctuations; 4) marked disability in the off-medication state that substantially interferes with the patient's quality of life and functionality; 5) realistic expectations; 6) ability and willingness to participate in regular follow-up visits; and 7) absence of comorbidities that are contraindications to DBS (e.g., disabling psychiatric illness). Although some criteria overlap, there still is no overarching consensus about recommendations for DBS referral. This in turn is reflected in the wide-ranging algorithms for patient selection for DBS found in practice.

A recent web-based survey of the Parkinson's Foundation Centers of Excellence in the United States revealed that the average minimum duration of PD expected before offering DBS was 5–6 years; however, surprisingly, some sites indicated no minimum disease duration. In 77% of those centers, the decision to proceed with DBS was a consensus decision of a multidisciplinary team, including for example a neurologist, neurosurgeon, and a neuropsychologist. In 96% of the polled centers, a formal neurocognitive battery was required. Most of the centers did not use an overall rating scale to determine DBS candidacy.[16]

Current clinical guidelines for the use of DBS in PD[11,17] were released prior to The Effect of Deep Brain Stimulation of the Subthalamic Nucleus (STN-DBS) on Quality of Life in Comparison to Best Medical Treatment in Patients With Complicated Parkinson's Disease and Preserved Psychosocial Competence (EARLYSTIM) trial[2] and the related recent FDA approval, and those guidelines have not been updated.[18] For example, in 2006, the American Academy of Neurology (AAN)[17] recommended that subthalamic nucleus DBS be considered as an appropriate treatment option in younger patients with shorter disease duration to improve motor function and reduce motor fluctuations, dyskinesia, and medication usage, possibly resulting in greater improvement than that of older patients with longer disease duration (level of evidence C). There was insufficient evidence regarding globus pallidus interna (GPi) and ventral intermediate nucleus of the thalamus stimulation for PD. A few years after the AAN recommendations, an expert consensus provided guidance to patients, physicians, and other health care providers on several issues involving DBS for PD.[11] Regarding timing, the expert consensus suggested that disease duration should not be a major factor in patient selection noting that there is no evidence for the neuroprotective effects of DBS to support its earlier use.

Neither of these recommendations established a definitive timing for DBS, but instead were open to interpretation. Regardless, the FDA's recent approval for DBS using a Medtronic device establishes a clear timeline. For Boston Scientific (Marlborough, Massachusetts, USA, https://www.prnewswire.com/news-releases/boston-scientific-receives-us-fda-approval-for-the-vercise-deep-brain-stimulation-system-300569763.html) and Abbott systems (Little Canada, Minnesota, USA, https://parkinsonsnewstoday.com/?s=st+jude), which recently entered the market of neurostimulation for PD, duration of symptoms was not mentioned in their letters of approval.

The differences in clinicians' referral criteria, and the shift in time frame for considering DBS, highlight the need for development of consensus criteria determining appropriate timing for this intervention.[18] To date, a systematic analysis of clinicians' attitudes and views regarding the timing of DBS has not been undertaken. To start gaining understanding, we carried out an empirical investigation in Michigan with clinicians to shed light on their current practices for selecting DBS candidates, their perspectives on whether the new FDA approval is regarded as early for the procedure, and their views on risks and benefits.

## METHODS

We carried out a pilot study in Michigan to explore clinicians' attitudes toward earlier use of DBS. We used structured interviews with closed- and open-ended questions.

Interview questions were based on prior research[18] and on discussions with other researchers. All interviews were conducted by the first author either via zoom or face-to-face interactions in the clinicians' offices. Each interview lasted 30–45 minutes and was digitally recorded and transcribed verbatim. Interviews were analyzed using a qualitative content analysis approach.[19-21] Qualitative analysis of the interviews was combined with the use of descriptive statistics to present demographics and compare categories. All subjects provided informed consent prior to the interview. This study received institutional review board approval from Michigan State University (x17-1144e).

We contacted clinicians identified either by us (C. S. and L. Y. C.) or by an online search of individuals who were either movement disorder neurologists or functional neurosurgeons with expertise in DBS for PD and who worked in relatively high-volume PD tertiary care centers in the Michigan area. The structured interview included questions about the number of DBS procedures or referrals, the earliest time in the disease course they have referred or implanted patients with PD with DBS, the main criteria used to select surgical candidates, their thoughts on the timeline of the recent FDA approval being too early or not, their views on risks and benefits of earlier DBS versus later intervention in the disease progression, and finally, their thoughts on whether the FDA approval will have a negative or beneficial impact in their practice. Clinicians were contacted both via e-mail and telephone to arrange a time and location for the interview. Interviews took place during the second half of 2017.

## RESULTS

Twelve clinicians (1 clinical coordinator, 3 neurosurgeons, and 8 movement disorder neurologists; 5 women) with an average of 9.4 years of experience with DBS for PD from 4 different clinics were

**Table 1.** Clinicians' Experience

| Physicians Experience with DBS | Neurosurgeons | Movement Disorder Neurologist |
|---|---|---|
| Years of experience (overall mean, 9.4 years) | 16 ± 6.08 (9–20) | 7.22 ± 4.52 (2–15)* |
| Surgeries/referrals since beginning of practice | Range of surgeries, 270–600 | Range of referrals, 5–200 |
| Earliest in the disease progression they have implanted/referred patients | 3.83 ± 1.75 (2–5.5) | 3.77 ± 1.56 (2–17) |

Values are mean ± SD (range) or as otherwise indicated.
*Includes clinical coordinator.

interviewed about DBS use/referral and their perspectives regarding earlier use of DBS in PD (Table 1).

Regarding target, the subthalamic nucleus was the most frequent site for implantation (73%, n = 8/11), with the GPi being the second most common target (36.4%, n = 4/11). Only 1 clinician considered the GPI as the main target, and only 1 participant mentioned the ventral intermediate nucleus as a site that is also considered for intervention. This reflects a wide variability compared with previous U.S. estimates.[22]

We found that the criteria used to determine when to refer or perform DBS was variable, with levodopa responsiveness being the most frequently mentioned criteria (50%, n = 6), followed by disease severity, average years of disease progression, and quality of life. The least important criterion when considering DBS was the age of the patient (75%, n = 9). Some clinicians noted that a rigorous algorithm was used in their clinics to select patients (n = 2/11); however, in most cases that was not the case. To accurately evaluate the presence of disabling motor fluctuations, 11 clinicians spoke about the importance of involvement of the patient, the neurologist, other DBS team members, and in some cases the family. Five clinicians reported the presence of a multidisciplinary team consisting of some combination of the following in their routine DBS management: neurology, neurosurgery, neuropsychology, rehabilitation, and social work.

Interestingly, we found that most clinicians considered earlier use not to be time dependent but instead viewed it as patient dependent and based on symptoms. Only 16.8% (n = 2) saw the FDA's new indication as early use of DBS and 25% were unsure (n = 3). The remaining clinicians welcomed the time suggested by the FDA approval, with comments such as "the 4-year cutoff is reasonable because there are multiple papers showing that" (clinician 1); and "we think that the EARLYSTIM study was very well done and probably accurately reflects the optimal timing of DBS. But, you know, the question is really going to be whether even earlier than that has benefit" (clinician 3). One clinician mentioned that the FDA timing is midstage and that early DBS would be when patients "don't have motor fluctuations and medications are controlling their symptoms (clinician 10)."

Most (54%, n = 6/11) considered the earlier use of DBS as less risky, perhaps with fewer associated surgical complications. The remainder thought it had a similar risk profile (36.4%, n = 4/11). For example, one clinician noted the following: "If someone has early Parkinson's disease and they're 40 years old, obviously they are going to have less of a risk than someone who is 60. But I think if you have someone who's 60 who has early Parkinson's disease and you have someone else who is 60 who has later stage Parkinson's disease, their risks are going to be equivalent" (clinician 2). Other clinicians noted that the patient ultimately has to make the decision, and needs to do so based on the risk-benefit ratio of the timing of the procedure. A number of clinicians seemed puzzled by the need to decide when the risk-benefit ratio is equitable, or when there had been a sufficient number of medication trials before considering surgical options. Only one of our participants reported that earlier DBS has more risk.

Regarding whether earlier DBS provided patients with expanded opportunities for improved quality of life compared with DBS later in the disease course, three quarters (75%, n = 9/12) thought that that indeed was the case, 2 answered that the timing did not matter in outcome, and only 1 answered that it is premature to answer that.

More than half of respondents (63.6%, n = 7/11) saw the earlier use of DBS as having the potential to have a positive impact on their practice (increased number of patients in total and increased number of better surgical candidates). Thirty-six percent of our participants thought that because people generally are afraid of brain surgery, the FDA approval for earlier DBS would not impact their practice. As one clinician aptly noted, "I just think it's going to be hard to ever convince patients to do that as the first line therapy, unless we prove that it slows down disease progression" (clinician 9). An additional barrier mentioned for earlier DBS to have a beneficial impact was the lack in surge of neurologist referrals despite the new FDA indication. Therefore, even with the FDA approval for earlier DBS, it remains uncertain as to whether or not surgeons will have a growth in their practices.

## DISCUSSION

The aim of this study was to explore attitudes and views about the timing of DBS for PD among clinicians. The more interesting findings were connected to referral considerations and perceptions around timing of DBS.

### Referral/Implantation Considerations

Although some studies report that the quality of DBS referrals has improved,[15] there is no established consensus on referral practices. Our study found great variability regarding referral considerations and they appeared to vary on an individual basis, with only a few mentioning an established protocol for making such decisions. There was no agreement on the most important reasons for referrals; however, most clinicians mentioned the importance of levodopa response, disease severity, and disabling motor fluctuations. A point of agreement among clinicians was that age is not a major factor when considering someone's candidacy for DBS. Overall, our results do not suggest a conservative approach of referring physicians regarding brain surgery. Although some clinicians mentioned the EARLYSTIM literature, the wide variability found in our sample regarding referral criteria might be the result of an overall limited

awareness of DBS for PD treatment and the FDA and AAN recommendations and guidelines.

Although surgical outcomes are likely linked to optimal selection of patients, it would be beneficial to have specific consensus selection criteria among different centers.

### Timing of DBS

Prior to the EARLYSTIM study, patients were required to have a PD diagnosis for a minimum of 5 years before being considered surgical candidates.[15] An important study documenting the shift toward earlier DBS was the international survey performed by Christen et al.[22] In their multinational survey of tertiary DBS centers, they found that DBS is not considered to be a treatment of last resort (67.0%) and clinicians seemed to feel that it should be offered even when the disease is still manageable by medications (60.4%). Our results are similar to this survey-based study in that most of our participants did not consider the timing of DBS as being dependent on the duration of the disease but rather on disease severity and medication response. For example, even when the FDA provided a timeline for the earlier use of the Medtronic neurostimulator (Minneapolis, Minnesota, USA), our study demonstrated that clinicians do not necessarily follow this time frame in their referral practices, evidenced by the mean referral timing being less the 4 years. Although it is true that these earliest referrals might be for patients with unusual presentations and disease course, the fact that most clinicians do not consider the FDA approval as early DBS emphasized a shift in timing of DBS compared with previous years.

Some clinicians have argued that early DBS could affect disease progression[6]; however, only one of our participants mentioned this consideration as a potential benefit for earlier DBS. Still, three quarters of our participants viewed earlier DBS as providing beneficial opportunities to patients. In general, our participants made relatively balanced arguments weighing the pros and cons of earlier DBS, and those arguments were consistent with the scientific and neuroethical literature on the topic. For example, our participants mentioned the risk of selecting patients who do not have idiopathic PD as candidates for DBS if they are selected too early in the disease course.[23] They also mentioned setbacks, such as loss of work, increased anxiety, or increased likelihood of other comorbidities observed in advanced disease, as negative effects of delaying surgical intervention for appropriate candidates.[18]

### Other Relevant Findings

Regarding multidisciplinary team involvement in determining surgical candidacy, nearly half of our participants noted that at least 2 additional disciplines were needed. This then parallels results by Christen et al.,[22] who found that 60.7% of DBS centers used a multidisciplinary team. In an expert consensus document,[11] it was agreed that DBS surgery is best performed by an experienced surgeon with specific expertise in stereotactic and functional neurosurgery working as part of a multiprofessional team that includes a movement disorder neurologist, neuropsychologist, psychiatrist, and neurophysiologist. Therefore, there is room for improvement in those centers where such a multidisciplinary team is not used.

### Study Limitations

Participants in this study were all practicing clinicians in central Michigan; as such, the results may not be applicable elsewhere. The fact that we only included movement disorders neurologists and not general neurologists is also a limitation because most patients with PD in the United States do not see a movement disorder neurologist during their disease course. The use of semi-structured interviews makes comparison between clinicians difficult because each person answers questions according to their own perception and experience. However, the fact that we have closed-ended questions allows for making comparisons while using the open-ended responses to provide background and richness to the findings. More research is needed to examine clinicians' perceptions and attitudes about earlier use of DBS and different factors shaping discrepancies in referral practices.

## CONCLUSIONS

At this point in time, it is difficult to accurately assess the effects of the FDA's approval for earlier DBS in PD in terms of its economic, social, and individual patient implications. However, our study suggests there are no established standard referral criteria used across providers. There also are stark differences regarding timing of DBS among clinicians. Research is needed to better understand what factors shape clinicians' willingness to refer or not refer patients to DBS earlier in the disease course. Equally, it is vital to create a consensus statement regarding appropriate candidacy of patients that would take into account the safety and efficacy of different targets, genetics, and other psychosocial factors which have a role in shaping how individuals potentially respond to the DBS therapy.

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