Deep Brain Stimulation Target Selection in an Advanced Parkinson’s Disease Patient with Significant Tremor and Comorbid Depression

Amar S. Patel*
Department of Neurology, Yale School of Medicine, Yale University, New Haven, CT, USA

Abstract

Clinical Vignette: A 67-year-old female with advanced Parkinson’s disease (PD), medically refractory tremor, and a history of significant depression presented for evaluation of deep brain stimulation (DBS) candidacy.

Clinical Dilemma: Traditionally, the subthalamic nucleus (STN) has been preferred over the globus pallidus interna (GPi) as a DBS target for PD patients with levodopa-responsive fluctuations in rigidity and akinesia, for whom tremor is also a significant source of impairment. However, STN stimulation is avoided in patients with a significant pre-surgical history of mood disorder.

Clinical Solution: Bilateral DBS of the GPi led to significant short-term improvement in PD motor symptoms, including significant tremor reduction.

Gap in Knowledge: There is insufficient evidence to support or refute clinicians’ traditional preference for STN stimulation in treating refractory PD tremor. Similarly, the available evidence for risk of worsening depression and/or suicidality after STN DBS is mixed. Both questions require further clarification to guide patient and clinician decision-making.

Keywords: Parkinson’s disease, tremor, depression, deep brain stimulation, subthalamic nucleus, globus pallidus interna

Citation: Patel AS. Deep brain stimulation target selection in an advanced Parkinson’s disease patient with significant tremor and comorbid depression. Tremor Other Hyperkinet Mov. 2017; 7. doi: 10.7916/D8KD23NZ

*To whom correspondence should be addressed. E-mail: amar.patel@yale.edu

Editor: Elan D. Louis, Yale University, USA

Received: December 30, 2016 Accepted: March 16, 2017 Published: April 11, 2017

Copyright: © 2017 Patel. This is an open-access article distributed under the terms of the Creative Commons Attribution-Noncommercial-No Derivatives License, which permits the user to copy, distribute, and transmit the work provided that the original authors and source are credited; that no commercial use is made of the work; and that the work is not altered or transformed.

Funding: None.

Financial Disclosures: None.

Conflict of Interest: The author reports no conflict of interest.

Ethics Statement: All patients that appear on video have provided written informed consent; authorization for the videotaping and for publication of the videotape was provided.

Clinical Vignette

A 67-year-old right-handed female presented for evaluation of deep brain stimulation (DBS) surgery candidacy for advanced Parkinson’s disease (PD). She had developed PD 18 years prior to evaluation, with rest tremor of the left hand. Her symptoms progressed to include severe bilateral tremor with mild rigidity, bradykinesia, and shuffling gait. She had a robust levodopa response that waned over time, such that each dose of carbidopa–levodopa gave her approximately 2 hours of medication-on time. Her tremor remained significant in spite of medication and interfered with daily activities such as cooking, using utensils, and holding cups. Her medications included carbidopa–levodopa, amantadine, rotigotine, and pramipexole (levodopa daily dose equivalent 920mg). Her history was complicated by depression with two prior episodes of suicide attempt. The last episode occurred 5 years prior to her evaluation. She saw a therapist regularly and did not require pharmacologic treatment for depression. She had a remote history of discrete episodes of hallucinations, related to medication effect or concurrent urinary tract infection. Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) in the off-medication state was 54. This improved to 28 in the on-medication state. Neuropsychological testing revealed robust abilities across all cognitive domains, including attention, processing speed, language, visuospatial abilities, memory and executive functioning. Testing did reveal a concern for her history of suicide attempt and her insight into its causes.

Clinical Dilemma

Correct target selection for DBS in PD is a critical step in delivering efficacious treatment. Although stimulation of the ventral intermediate...
(Vim) nucleus of the thalamus can address unilateral tremor in PD, it does not impact rigidity, akinesia, or levodopa-induced dyskinesia meaningfully.\(^1,2\) Bilateral Vim stimulation also raises concern for exacerbating speech impairment and gait imbalance.\(^3\) To address the totality of motor fluctuations in advanced PD with DBS, clinicians have favored the implantation of the globus pallidus interna (GPi) and subthalamic nucleus (STN), although at varying rates over time. Traditionally, of these two targets, the STN is thought to provide greater tremor control.\(^4\) Indeed, STN stimulation was shown to be equivalent to Vim stimulation for PD tremor in a small series of patients with significant rest and action tremor.\(^5\) However, STN stimulation has also been associated with a concern for worsening depression and higher rates of suicide attempt.\(^6\)

The patient under discussion suffered from significant resting and postural tremor, and has a concerning history of depression and suicide attempt, making the ideal surgical target unclear based on these perhaps dogmatic views. Should Vim be selected at the risk of leaving akinesia and rigidity unaddressed? If the STN is targeted, will the patient be exposed to an unacceptable increased risk of suicidality or depression in the name of tremor reduction? If GPi is selected to avoid possible worsening of mood disorder with STN stimulation, can the patient be assured that her significant tremor will respond to DBS?

**Clinical Solution**

The patient was discussed extensively within the multidisciplinary DBS team, consisting of a movement disorders neurologist, functional neurosurgeon, and neuropsychologist. Her therapist provided supporting information regarding the stability of her depression. The patient was counseled extensively regarding the risks and benefits of DBS, and the concerns of exacerbating neuropsychiatric deficits with STN stimulation, or failing to address non-tremor symptoms with Vim stimulation. A decision was made to offer the patient magnetic resonance imaging-guided bilateral GPi DBS. She underwent surgery without complication. Initial programming showed an improvement in her MDS-UPDRSIII of 53% in the on-stimulation/off-medication state compared with her off-stimulation/off-medication state (MDS-UPDRSIII scores of 24 and 53, respectively), with significant improvement in tremor severity and constancy (Video 1). Long-term follow-up is not yet available.

**Gap in Knowledge**

The debate over the merits of GPi and STN stimulation in PD have been extensively catalogued. Ultimately, the collective body of evidence suggests that the two targets are similar in their motor benefits, but STN may be superior to GPi in regards to economic profile (fewer battery replacements) and medication reduction; GPi is superior to STN in regards to dyskinesia control and medication flexibility.\(^7\) These considerations were not the most pressing sources of debility or risk for the patient under discussion. Informal discussions with DBS clinicians would suggest that of these two targets, STN treatment remains the preferred choice for PD patients in need of significant tremor control, and a target to avoid in patients with significant comorbid psychiatric illness. What evidence supports these biases?

There are limited reports on the effect of GPi stimulation in cases of severe PD tremor or benign tremulous PD. A review of cases of rigorously defined benign tremulous PD implanted at the Mayo Clinic over a 14-year period showed no cases of GPi stimulation (15 patients with Vim and STN stimulation were identified).\(^8\) This likely reflects a target selection bias stemming from the historical use of Vim stimulation for tremor, and STN stimulation for PD tremor. This is in spite of evidence of improvement in severe tremor in patients undergoing pallidotomy.\(^9\) Retrospective reviews provide some support for GPi and STN target equivalency in tremor reduction. Katz et al.\(^10\) reviewed the Veterans Administration (VA) Cooperative Studies Program #468 by analyzing the response of different PD motor subtypes to GPi and STN stimulation. They analyzed tremor dominant (TD), postural instability gait difficulty, and intermediate subtypes. TD subtype was determined by a cumulative UPDRS tremor subscale score 1.5 times greater than that of the subscale items for balance and gait. TD patients experienced greater mean overall improvement, as measured by the UPDRSIII, after GPi DBS than after STN DBS. However, the discrepancy in improvement was mainly accounted for by improvement in gait. Tremor subscales showed no significant difference in improvement based on target.\(^10\)

A few prospective randomized trials have attempted to compare GPi and STN stimulation directly. A single-center study of 23 patients randomized to GPi and STN stimulation, with blinded assessment after 1 year, found UPDRS tremor subscores in either group showed no statistical difference.\(^11\) Larger, more recent studies have shown a similar equivalency in tremor reduction. The aforementioned VA study found that stimulation at either target provided similar overall motor benefits.\(^12\) However, no analysis of tremor subscale was provided in the initial reports of outcomes at 6 and 24 months after DBS. A subset of these patients was followed at 36 months and showed similar overall UPDRSIII improvement, while specifically reporting...
tremor subscale scores which showed equal improvement between STN and GPi groups.\textsuperscript{13}

Other large prospective randomized trials provide conflicting evidence regarding target equivalency for improving PD motor symptoms. The COMPARE trial analyzed cognition and mood changes between STN and GPi stimulation as its primary outcome, but in secondary analysis UHDRS motor scores showed no significant difference between groups.\textsuperscript{14} The NSTAPS study, did find a greater mean improvement in the secondary outcome measure of UHDRS\textsubscript{III} motor scores in the off-medication state after STN DBS than GPi.\textsuperscript{15} However, neither prospective study commented on GPi and STN benefit for tremor specifically. When the evidence of clinical outcomes is reviewed, clinicians’ preference in treating severe PD tremor with STN DBS has little support.

Perhaps tremor should not be regarded as a guiding feature of target selection as our clinical dilemma suggests. What then of our perception of the adverse psychiatric effects of STN stimulation? In a large, multicenter survey of patients with STN DBS, Voon et al.\textsuperscript{6} found that the risk of suicide in the first postoperative year is elevated. Attempted suicides were associated with postoperative depression, being single, and a prior history of suicide attempt and impulse control disorder.\textsuperscript{5} The association of STN stimulation and increased suicide risk is controversial. A careful analysis of the VA cooperative study found no increased risk of suicidal ideation postoperatively, nor between STN and GPi groups.\textsuperscript{16}

Postoperative depression, as a risk factor for suicidality, has also been evaluated with mixed results. The VA cooperative study did suggest a small but statistically significant worsening of depressive symptoms 2 years after STN DBS, but those with GPi DBS showed slight improvement.\textsuperscript{12} The aforementioned COMPARE trial found no difference in visual analog mood subscales between GPi and STN groups.\textsuperscript{14} Two retrospective studies investigated whether a history of preoperative depression was more likely to lead to postoperative depression. A 2002 retrospective review of 24 STN DBS patients, 12 of whom had depressive episodes prior to surgery, found five patients with a persistent depressive episode postoperatively, in spite of significant motor benefit.\textsuperscript{17} Four of these patients were among those with presurgical depression. A larger retrospective review of 110 patients with DBS, to either the STN or GPi, showed that those with a history of presurgical depression had higher postsurgical Beck Depression Inventory scores than those without a history of depression.\textsuperscript{18} The study was not designed to detect a difference between the surgical targets.

Additionally, aggressive medication reduction in the postoperative period appears to be related to the incidence of apathy and depression, suggesting that if there is a correlation between STN DBS and worsening depression, it may be a result of aggressive medication reduction and not the stimulation per se.\textsuperscript{19} Indeed, four out of five of the patients in the 2002 review of STN DBS who experienced postoperative depression were noted to have had a >60% reduction (and in one case complete withdrawal) of their levodopa.\textsuperscript{17} Other studies have shown an improvement in depressive symptoms in the first 6 months after STN DBS, suggesting that effective stimulation and careful postoperative medication management should not be expected to have negative consequences on mood.\textsuperscript{20}

In conclusion, further research is needed to provide evidence-based guidelines for target selection for DBS in advanced PD. The available evidence suggests that STN and GPi DBS are equivalent for PD tremor reduction. Clinicians’ bias towards STN targeting for tremor reduction either fails to recognize that equivalency, or represents a practical experience that has failed to be recognized in the literature. Similarly, a more definitive understanding of the effects of stimulation targets on depression and suicidality would offer clinicians and patients a more accurate assessment of possible psychiatric risk when deciding to proceed with an elective invasive surgery.

References

1. Tarsy D, Scollins L, Corapi K, O’Herron S, Apetauerova D, Norregaard T. Progression of Parkinson’s disease following thalamic deep brain stimulation for tremor. Stereotact Funct Neurosurg. 2005;83(222–227. doi: 10.1159/000091953

2. Hariz MI, Krack P, Alesch F, et al. Multicentre European study of thalamic stimulation for parkinsonian tremor: a 6-year follow-up. J Neurol Neurosurg Psychiatry. 2008;694–699. doi: 10.1136/jnnp.2007.118653

3. Pahwa R, Lyons KE, Wilkinson SB, et al. Long-term evaluation of deep brain stimulation of the thalamus. J Neurol 2006;104:506–512. doi: 10.3171/jn.2006.4.506

4. Tagliati M. Turning tables: should GPi become the preferred DBS target for Parkinson disease? Neurology 2012;79:19–20. doi: 10.1212/WNL.0b013e31825dc96

5. Pairhar R, Alterman R, Papavassiliou E, Tarsy D, Shih LC. Comparison of Vim and STN DBS for parkinsonian resting and postural/act. J Neurol Neurosurg Psychiatr. 2015;5; doi: 10.7916/D81V3D35

6. Voon V, Krack P, Lang AE, et al. A multicenter study on suicide outcomes following subthalamic stimulation for Parkinson’s disease. Brain 2016;131:2720–2728. doi: 10.1093/brain/awv214

7. Williams NR, Foote KD, Okun MS. STN vs. GPi deep brain stimulation: translating the rematch into clinical practice. Mov Disord Clin Pract 2014;1:24–35. doi: 10.1002/mdc.312004

8. Savica R, Matsumoto JY, Josephs KA, et al. Deep brain stimulation in benign tremulous parkinsonism. Arch Neurol 2011;68:1033–1036. doi: 10.1001/archneurol.2011.160

9. Väck JL, Bakay RA, Freeman A, et al. Randomized trial of pallidotomy versus medical therapy for Parkinson’s disease. Ann Neurol 2003;53:550–569. doi: 10.1002/ana.1057

10. Katz M, Luciano MS, Carlson K, et al. CSP 468 study group. Differential effects of deep brain stimulation target on motor subtypes in Parkinson’s disease. Ann Neurol 2015;77:710–719. doi: 10.1002/ana.24374

11. Anderson VC, Burchiel KJ, Hogarth P, Favre J, Hammerstad JP. Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease. Arch Neurol 2005;62:534–540. doi: 10.1001/archneur.62.4.534

12. Follett KA, Weaver FM, Stern M, et al. CSP 468 Study Group. Pallidal versus subthalamic deep-brain stimulation for Parkinson’s disease. N Engl J Med 2010;362:2077–2091. doi: 10.1056/NEJMoa0907083
13. Weaver FM, Follet KA, Stern M, et al. Randomized trial of deep brain stimulation for Parkinson disease: thirty-six-month outcomes. *Neurology* 2012;79:55–65. doi: 10.1212/WNL.0b013e31825dcde1

14. Okun MS, Fernandez HH, Wu SS, et al. Cognition and Mood in Parkinson Disease in STN versus GPi DBS: The COMPARE Trial. *Ann Neurol* 2009;65:586–595. doi: 10.1002/ana.21596

15. Odekerken VJ, van Laar T, Staal MJ, et al. Subthalamic nucleus versus globus pallidus deep brain stimulation for advanced Parkinson’s disease (NSTAPS study): a randomised controlled trial. *Lancet Neurol* 2013;12:37–44. doi: 10.1016/S1474-4422(12)70264-8

16. Weintraub D, Duda JE, Carlson K, et al. Suicide ideation and behaviours after STN and GPi DBS surgery for Parkinson’s disease: results from a randomised, controlled trial. *J Neurol Neurosurg PS* 2013;84:1113–1118. doi: 10.1136/jnnp-2012-304396

17. Houeto JL, Mesnage V, Mallet L, et al. Behavioural disorders, Parkinson’s disease and subthalamic stimulation. *J Neurol Neurosurg PS* 2002;72:701–707. doi: 10.1136/jnnp.72.6.701

18. Okun MS, Wu SS, Foote KD, et al. Do stable patients with a premorbid depression history have a worse outcome after deep brain stimulation for Parkinson disease? *Neurosurgery* 2011;69:357–361. doi: 10.1227/NEU.0b013e3182160456

19. Lhomme E, Klinger H, Thobois S, et al. Subthalamic stimulation in Parkinson’s disease: restoring the balance of motivated behaviors. *Brain* 2012;135:1463–1477. doi: 10.1093/brain/aws078

20. Chopra A, Abulseoud OA, Sampson S, et al. Mood stability in Parkinson disease following deep brain stimulation: a 6-month prospective follow-up study. *Psychosomatics* 2014;55:478–484. doi: 10.1016/j.psym.2013.09.003