Topic Brief: Patient Selection for Deep Brain Stimulation for Parkinson's Disease

Date: 11/28/2022
Nomination Number: 994

Purpose: This document summarizes the information addressing a nomination submitted on May 31, 2022, through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue: The nominator is interested in the benefits of harms for deep brain stimulation for individuals with Parkinson's Disease, particularly in subgroups; and in different targets for deep brain stimulation. This will help with patient selection and treatment decisions.

Program decision: The EPC Program will not develop a new systematic review based on this nomination because the evidence is limited.

Key Findings

- We found multiple systematic reviews that address the topic, but they did not assess the breadth of subgroups of interest to the nominator.
- We found few studies comparing DBS to best medical treatment in subgroups, and comparing STN to GPi targets for DBS.

Background

A recent analysis estimated a U.S. prevalence of approximately one million individuals with diagnosed Parkinson's disease in 2017. The estimated economic burden was $51.9 billion which includes direct and indirect medical and non-medical costs for the patient and caregiver. The Medicare program bears the largest share of excess medical costs, as most PD patients are over age 65[1]. Symptoms of Parkinson's disease begin gradually and include tremors of the hands, arms, and legs; stiffness of the arms, legs, and torso; poor balance. As the disease advances people may also experience problems with talking, depression, sleep issues, and difficulties with swallowing[2]. From 1999 to 2017, age-adjusted death rates for Parkinson disease among adults aged ≥65 years increased from 41.7 to 65.3 per 100,000 population[3].

A variety of medicines sometimes help symptoms. Surgery and deep brain stimulation (DBS) can help severe cases. Current clinical practice of patient selection consists of patients with motor symptoms not controlled well with best medical therapy (BMT), while axial, speech, affective, and cognitive symptoms must be normal or minimally affected. Concerns around harms of DBS including impulsivity, cognitive decline[2].

The nominator is the American Academy of Neurology (AAN). They plan to use the proposed AHRQ systematic review to inform a clinical practice guideline. They have guideline on dopaminergic therapy in early Parkinson's disease[4]; they do not have a guideline on deep brain stimulation. AAN affirmed the 2018 guideline from the Congress of Neurological Surgeons on Subthalamic Nucleus and Globus Pallidus Internus Deep Brain Stimulation for the Treatment of Patients With Parkinson's Disease[5] which focused on the target for DBS but not on patient selection. The nominator expanded the initial focus of their nomination to include targets for DBS; they did not wish to expand the scope to include studies that compared subgroups of patient receiving DBS.

CMS covers DBS for Parkinson's disease if patients meet all criteria[6]:

1. Diagnosis of Parkinson's disease based on the presence of at least 2 cardinal features (tremor, rigidity or bradykinesia).
2. Advanced idiopathic Parkinson's disease as determined by the use of Hoehn and Yahr stage or Unified Parkinson's Disease Rating Scale (UPDRS) part III motor subscale.
3. L-dopa responsive with clearly defined "on" periods.
4. Persistent disabling Parkinson's symptoms or drug side effects (e.g., dyskinesias, motor fluctuations, or disabling "off" periods) despite optimal medical therapy.
5. Willingness and ability to cooperate during conscious operative procedure, as well as during post-surgical evaluations, adjustments of medications and stimulator settings.

In 2017, NICE recommended deep brain stimulation for people with advanced Parkinson's disease whose symptoms are not adequately controlled by best medical therapy[7]. Other guidelines have exclusions such as people with dementia, relevant psychiatric or somatic comorbidity such as acute psychosis, major depression, or dementia, and younger age[8].

Scope

1. What is the effectiveness and harms of deep brain stimulation for treatment of Parkinson's disease?
   a. Do outcomes vary by patient subgroups?
2. What is the comparative effectiveness and harms of deep brain stimulation targeting subthalamic nucleus (STN) compared to deep brain stimulation targeting globus pallidus internus (GPi)?

Table 1. PICOs for Questions

PICOs	Patient subgroups	DBS target
Population	Individuals with Parkinson's disease a. Subgroups: age, sex, race/ethnicity, duration of disease, prior treatment, comorbidities	Individuals with Parkinson's disease
Intervention	Deep brain stimulation	Deep brain stimulation targeting globus pallidus internus
Comparator	No deep brain stimulation	Deep brain stimulation targeting subthalamic nucleus
Outcomes	Motor symptoms (MDS-UPDRS III), resource utilization. dyskinesias (MDS-UPDRS IV), ADLs (MDS-UPDRS II), non-motor symptoms (MDS-UPDRS I, cognitive scales, mood scales, apathy	Motor symptoms (MDS-UPDRS III), resource utilization. dyskinesias (MDS-UPDRS IV), ADLs (MDS-UPDRS II), non-motor symptoms (MDS-UPDRS I, cognitive scales, mood scales, apathy

	scales, non-motor scales, etc.), quality of life (PDQ-39), medication reduction. Harms such as include surgical complications (stroke, hemorrhage, infection, cognitive impairment, impulsivity, dysarthria, or balance impairment/falls/freezing of gait.	scales, non-motor scales, etc.), quality of life (PDQ-39), medication reduction. Harms such as include surgical complications (stroke, hemorrhage, infection, cognitive impairment, impulsivity, dysarthria, or balance impairment/falls/freezing of gait.

Assessment Methods

See Appendix A.

Summary of Literature Findings

While we found many systematic reviews addressing question 1, most did not or did not plan to have subgroup of analysis by patient characteristics of interest to the nominator. We identified five in-progress and two completed systematic reviews that included subgroups, though a single review did not look at all subgroups or outcomes of interest: two in-progress reviews and two completed systematic reviews analyzed findings by disease severity[9-12]; three in-progress reviews and one completed systematic reviews will look at age[9-12]; two in-progress reviews on duration of symptoms[10, 12]; one in-progress and one completed systematic review on preoperative levodopa dose[12, 13]; one on sex [11]; and one on baseline cognitive scores[14]. One focused solely [14]on cognitive outcomes, one on economic outcomes[10], one on lower urinary symptoms[11], and one on quality of life[9].

We identified seven systematic reviews comparing DBS of subthalamic nucleus and globus pallidus internus[15-21]. One focused on tremor suppression[16] and one focused only on long-term neuropsychological outcomes[21]. Two included network meta-analysis of multiple targets for DBS[15, 18]. One SR reported using GRADE[21]; and none of the study abstracts included mention of risk of bias assessment. The number of studies included in reviews ranged from 5[16] to 48[21].

We identified a 2022 European Academy of Neurology/Movement Disorder Society - European Section guideline on the treatment of Parkinson's disease[22], applicable to both questions. While not a systematic review we note that the guideline was supported by a systematic review by Cochrane Response UK; and used GRADE. The search ended December 31, 2020. Subgroups included earlier Parkinson's with and without fluctuations; and comparison of STN and GPi DBS.

For question 1 we identified three publications that compared DBS to best medical treatment[23-25]. We also identified 23 additional publications that compared groups receiving DBS; as noted above the nominator did not wish to expand the scope to include studies comparing subgroups receiving the same intervention. Though not directly relevant we have included these in Table 2. Of all publications, two were also included in the 2022 European guideline[23, 26].

For question 2 we identified eight studies comparing STN DBS to GPi DBS[27-34]. None were identified in the review underpinning the 2022 European guideline.

Table 2. Summary of Systematic Reviews and Findings identified in targeted search

	Systematic reviews (August 2019-August 2022)	Primary studies (October 2017-October 2022)

Question 1: subgroups	Total-7 • Age-[9-12] • Sex-[11] • Severity-[9-12, 35] • Levodopa at baseline-[12, 13]; • Duration-[10, 12, 22] • Cognition scores at baseline-[14]	Total-3 • Severity[23, 24,] • Age[25] Total-23 (indirectly relevant) • Multiple subgroups[36-40] • Age[26, 41-44] • Severity[44, 45] • Preop levo-dopa responsiveness[46] • Sex Gender[47-49] • Baseline neuropsych[50-52] • Preop mood symptoms[53] • Rate of progression[54] • Comorbidities[55] • MRI findings[56] • Gait variability[57]
Question 2: STN vs. GPi DBS	Total-8[15-22]	Total-8 • RCT[32-34] • Non-RCT[27-31]

DBS=deep brain stimulation; GPi=globus pallidus internus; KQ=key question; STN=subthalamic nucleus;

Summary of Selection Criteria Assessment

We identified multiple systematic reviews on the topic, though most focused on a single subgroup or outcome. We found few studies comparing DBS to best medical treatment in subgroups, and comparing STN to GPi targets for DBS.

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgements
Caryn McManus
Robin Paynter

This report was developed by staff of Agency for Healthcare Research and Quality (AHRQ), Rockville, MD. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. No statement in this article should be

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We conducted a search for existing systematic reviews. We searched for high-quality, completed or in-process evidence reviews published in the last three years August 2019 to August 2022 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
    - AHRQ Evidence Reports https://www.ahrq.gov/research/findings/evidence-based-reports/index.html
    - EHC Program https://effectivehealthcare.ahrq.gov/
- US Department of Veterans Affairs Products publications
    - Evidence Synthesis Program https://www.hsrd.research.va.gov/publications/esp/
    - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program https://www.healthquality.va.gov/
- Cochrane Systematic Reviews https://www.cochranelibrary.com/
- PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
- PubMed https://www.ncbi.nlm.nih.gov/pubmed/

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a limited Medline search of primary literature published within the last five years from August 2017 through October 2022. We reviewed the entire search yield for relevance.

Publication Date Limits: 2017 – 2022
Publication type limits: see search string at end of search strategy.

(Parkinson Disease[MeSH] **OR** Parkinson **OR** Parkinsons)
AND
(Deep Brain Stimulation[MeSH] **OR** “deep brain stimulation”)
AND
(Treatment Outcomes[MeSH] **OR** Treatment Failure[MeSH] **OR** Therapeutic Index[MeSH] **OR** Outcome Assessment, Health Care[MeSH:noexp] **OR** “outcome” **OR** “outcomes” **OR** Patient Outcome Assessment[MeSH] **OR** Health Status[MeSH] **OR** Functional Status[MeSH] **OR** Quality of Life[MeSH] **OR** Activities of Daily Living[MeSH] **OR** “activities of daily living” **OR** Dyskinesias[MeSH] **OR** dyskinesias **OR** “MDS UPDRS” **OR** “MDSUPDRS” **OR**

“UPDRS” **OR** “disease rating scale” **OR** “motor symptoms” **OR** “motor symptom” **OR** “motor functions” **OR** “motor function” **OR** “motor experiences” **OR** “motor experience” **OR** “nonmotor symptoms” **OR** “nonmotor symptom” **OR** “non motor symptoms” **OR** “non motor symptom” **OR** “nonmotor functions” **OR** “nonmotor function” **OR** “non motor functions” **OR** “non motor function” **OR** “nonmotor experiences” **OR** “non motor experiences” **OR** “cognitive scales” **OR** “cognitive scale” **OR** “mood scales” **OR** “mood scale” **OR** “apathy scales” **OR** “apathy scale” **OR** Cognition[MeSH] **OR** Mental Status and Dementia Tests[MeSH] **OR** Patient Harm[MeSH] **OR** Intraoperative Complications[MeSH] **OR** Postoperative Complications[MeSH] **OR** Postoperative Cognitive Complications[MeSH] **OR** complication* **OR** “adverse” **OR** harm* **OR** dysarthria **OR** hemorrhage **OR** impairments)
AND
(Systematic Review[pt] **OR** Meta-Analysis[pt] **OR** Controlled Clinical Trial[pt] **OR** systematic[tiab] **OR** "meta-analysis"[tiab] **OR** "controlled trial"[tiab])

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for an evidence report?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Approximately 1 million people in the US have Parkinson's disease.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	This is of high interest and affects patients and their caregivers.
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	The burden disease is estimated at $51.9 billion which includes direct and indirect medical and non-medical costs for the patient and caregiver. Much of this cost is borne by Medicare.
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	We identified 14 completed and in-progress systematic reviews, and one guideline. For question 1, no review included all subgroups of interest and the reviews have a variety of methods and search dates. For question 2 the description of methods was limited in the review identified and none included mention of risk of bias assessment. We identified a guideline that was informed by a systematic review from Cochrane Response, though the review was not published separately. The review scope did not include the range of subgroups of interest, and the search for the review ended in 2020.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes the standard of care is unclear. While DBS is used for treatment of refractory movement symptoms for Parkinson's there are concerns about the effects of treatment on cognition and impulsivity. There is therefore uncertainty about which patients will overall benefit most.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	A 2016 survey found high variability on the best approaches for DBS candidate selection, brain target selection, procedure type, and postoperative practices[58].
5. Primary Research	

5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	We identified three studies addressing question 1 and eight studies addressing question 2. There are too few studies to inform a new systematic review.