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Congress of Neurological Surgeons Systematic Review and Evidence-Based Guideline on Subthalamic Nucleus and Globus Pallidus Internus Deep Brain Stimulation for the Treatment of Patients With Parkinson's Disease: Executive Summary

QUESTION 1: Is bilateral subthalamic nucleus deep brain stimulation (STN DBS) more, less, or as effective as bilateral globus pallidus internus deep brain stimulation (GPi DBS) in treating motor symptoms of Parkinson's disease, as measured by improvements in Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) scores?

RECOMMENDATION: Given that bilateral STN DBS is at least as effective as bilateral GPi DBS in treating motor symptoms of Parkinson's disease (as measured by improvements in UPDRS-III scores), consideration can be given to the selection of either target in patients undergoing surgery to treat motor symptoms. (Level I)

QUESTION 2: Is bilateral STN DBS more, less, or as effective as bilateral GPi DBS in allowing reduction of dopaminergic medication in Parkinson's disease?

RECOMMENDATION: When the main goal of surgery is reduction of dopaminergic medications in a patient with Parkinson's disease, then bilateral STN DBS should be performed instead of GPi DBS. (Level I)

QUESTION 3: Is bilateral STN DBS more, less, or as effective as bilateral GPi DBS in treating dyskinesias associated with Parkinson's disease?

RECOMMENDATION: There is insufficient evidence to make a generalizable recommendation regarding the target selection for reduction of dyskinesias. However, when the reduction of medication is not anticipated and there is a goal to reduce the severity of "on" medication dyskinesias, the GPi should be targeted. (Level I)

QUESTION 4: Is bilateral STN DBS more, less, or as effective as bilateral GPi DBS in improving quality of life measures in Parkinson's disease?

RECOMMENDATION: When considering improvements in quality of life in a patient undergoing DBS for Parkinson's disease, there is no basis to recommend bilateral DBS in 1 target over the other. (Level I)

QUESTION 5: Is bilateral STN DBS associated with greater, lesser, or a similar impact on neurocognitive function than bilateral GPi DBS in Parkinson disease?

RECOMMENDATION: If there is significant concern about cognitive decline, particularly in regards to processing speed and working memory in a patient undergoing DBS, then the clinician should consider using GPi DBS rather than STN DBS, while taking into consideration other goals of surgery. (Level I)

QUESTION 6: Is bilateral STN DBS associated with a higher, lower, or similar risk of mood disturbance than GPi DBS in Parkinson's disease?

RECOMMENDATION: If there is significant concern about the risk of depression in a patient undergoing DBS, then the clinician should consider using pallidal rather than STN stimulation, while taking into consideration other goals of surgery. (Level I)

QUESTION 7: Is bilateral STN DBS associated with a higher, lower, or similar risk of adverse events compared to GPi DBS in Parkinson's disease?

RECOMMENDATION: There is insufficient evidence to recommend bilateral DBS in 1 target over the other in order to minimize the risk of surgical adverse events.

The full guideline can be found at: https://www.cns.org/guidelines/deep-brain-stimulation-parkinsons-disease.

KEY WORDS: Deep brain stimulation, Globus pallidus internus, Guidelines, Neuromodulation, Parkinson's disease, Subthalamic nucleus

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The efficacy of bilateral deep brain stimulation (DBS) for the treatment of motor symptoms and levodopa-induced dyskinesias in Parkinson's Disease (PD) patients is well established.[1-7] However, the effectiveness of selecting different stimulation targets is less clear. To date, 2 different targets have been proposed for the treatment of motor symptoms of PD, the subthalamic nucleus (STN) and globus pallidus internus (GPi). While there is evidence to suggest that both are effective when combined with best medical treatment vs best medical treatment alone,[6] the circumstances in which 1 target should be selected over the other are still disputed. It is also unknown whether STN and GPi DBS induce similar benefits.

METHODS

Details of the systematic literature review are provided in the full text of this guideline (https://www.cns.org/guidelines/deep-brain-stimulation-parkinsons-disease). A PubMed search was conducted for articles published between 1966 and February, 2017. Two different search strategies were used and the results were combined, yielding 151 unique abstracts. The selected studies were classified according to criteria for evidence on therapeutic effectiveness as detailed in the Joint Guidelines Committee Guideline Development Methodology.

RESULTS

The combined search queries yielded a total of 151 unique abstracts, which were screened for eligibility. A total of 18 articles were included in the final analysis. For Question 1, 2 Class I,[8,9] 2 Class II,[10,11] and 6 Class III[12-17] studies found no differences between the 2 targets in motor score improvements at various time points, up to 5 yr postoperatively, in various medication and stimulation conditions. In contrast, 2 articles,[18,19] including 1 Class I study,[18] found that STN stimulation is associated with greater improvement in motor scores assessed in the "off" medication/"on" stimulation condition. The advantage seen in the STN cohort in this study persisted at 3-yr follow-up.[11] No study to date has demonstrated a difference in the motor response to STN or GPi DBS in the "on" medication/"on" stimulation state.

With respect to Question 2, compelling evidence was derived from 3 Class I studies,[8,9,18] 2 Class II studies,[11,20] and 6 Class III studies[10,12-15,17] showing greater reduction in dopaminergic medications following STN than GPi DBS. For the third question, a single study provides Class I evidence[18] that the severity of "on" medication dyskinesias, but not the amount of time with dyskinesias, is reduced to a greater extent following pallidal stimulation than subthalamic stimulation. The remaining 2 Class I studies showed no significant differences in the reduction of dyskinesias between these surgical targets.[8,9]

For Question 4, no study demonstrated a significant difference between the 2 targets regarding improvement in quality of life. Class I evidence from 3 studies have shown comparable improvements in quality of life as measured by the Unified Parkinson's Disease Rating Scale, Part II (UPDRS-II) at 1 yr,[8] the composite Parkinson's Disease Questionnaire (PDQ-39) at 2 yr,[9] or a quality of life questionnaire at 1 yr.[18] Three-year follow-up in the veterans affairs (VA) study utilized the PDQ-39 and did not reveal a difference between the 2 surgical targets, as shown by a single Class II study.[20] Six Class III studies[10,12,14,15,21,22] showed improvements in quality of life following DBS without differences between the 2 targets. With respect to Question 5, neurocognitive function was formally assessed using various batteries in 5 studies.[9,18,20,23,24] Class I evidence was provided by 3 of these studies, in which patients and assessors were blinded to the stimulation site.[9,18,23] In 1 of these studies,[9] STN DBS was associated with a significantly greater decline in processing speed and working memory compared to GPi DBS.

For Question 6, Class I evidence from the VA Cooperative Study demonstrated a slight improvement in the GPi group (5.8%) compared to a slight worsening in the STN group (–11.6%) on the Beck Depression Inventory (BDI; $P = .02$).[9] There were no differences between groups when this cohort was assessed for suicidal ideation and suicidal behaviors at 6, 12, and 24 mo postoperatively using the UPDRS-I.[25] The NSTAPS

ABBREVIATIONS: BDI, Beck Depression Inventory; **DBS,** deep brain stimulation; **GPi DBS,** globus pallidus internus deep brain stimulation ; **PD,** Parkinson's disease ; **PDQ,** Parkinson's Disease Questionnaire ; **STN DBS,** subthalamic nucleus deep brain stimulation ; **UPDRS-III,** Unified Parkinson's Disease Rating Scale, Part III ; **VA,** veterans affairs

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3-yr follow-up study found that there were no differences between targets when measuring with a composite of mood, cognitive, and behavioral effects (Class II).[11] Class III evidence comes from 2 trials. A retrospective study of 27 patients demonstrated that both GPi and STN DBS groups were associated with a trend towards reduced Hamilton Depression Scale scores up to 12 mo postoperatively.[17] Another retrospective series demonstrated decreases on the BDI score 12 mo postoperatively in both the STN DBS group (21.1%) and the GPi group (27.0%).[24] Thus, there is Class I evidence from a single study suggesting that, compared to STN DBS, GPi stimulation is associated with better outcomes in terms of depression. For Question 7, no study showed a significantly higher risk of adverse events related to 1 surgical target over another.

DISCUSSION AND CONCLUSION

PD is characterized by many symptoms, which may vary in severity and response to medications and DBS. This clinical heterogeneity can make selection of the appropriate target for DBS somewhat complex. Based on the current literature, there are areas of agreement and disagreement over the question of target superiority in DBS for the treatment of PD. Ultimately, the selection of a specific brain target for stimulation should be tailored to the needs of the individual patient.

Disclosures

These evidence-based clinical practice guidelines were funded exclusively by the Congress of Neurological Surgeons (CNS) and the American Society for Stereotactic and Functional Neurosurgery, which received no funding from outside commercial sources to support the development of this document.

Conflict of Interest

The DBS for Parkinson's Disease Task Force members were required to report all possible COIs prior to beginning work on the guideline, using the COI disclosure form of the American Association of Neurological Surgeons (AANS)/CNS Joint Guidelines Review Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair are given latitude to approve nominations of Task Force members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs. The conflict of interest findings are provided in detail in the full-text introduction and methods manuscript (https://www.cns.org/guidelines/deep-brain-stimulation-parkinsons-disease).

Disclaimer of Liability

This clinical systematic review and evidence-based guideline was developed by a multidisciplinary physician volunteer task force and serves as an educational tool designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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