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Deep Brain Stimulation for Obsessive-Compulsive Disorder: Systematic Review and Evidence-Based Guideline Sponsored by the American Society for Stereotactic and Functional Neurosurgery and the Congress of Neurological Surgeons (CNS) and Endorsed by the CNS and American Association of Neurological Surgeons

BACKGROUND: It is estimated that 40% to 60% of patients with obsessive-compulsive disorder (OCD) continue to experience symptoms despite adequate medical management. For this population of treatment-refractory patients, promising results have been reported with the use of deep brain stimulation (DBS).

OBJECTIVE: To conduct a systematic review of the literature and develop evidence-based guidelines on DBS for OCD.

METHODS: A systematic literature search was undertaken using the PubMed database for articles published between 1966 and October 2012 combining the following words: "deep brain stimulation and obsessive-compulsive disorder" or "electrical stimulation and obsessive-compulsive disorder." Of 353 articles, 7 were retrieved for full-text review and analysis. The quality of the articles was assigned to each study and the strength of recommendation graded according to the guidelines development methodology of the American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Guidelines Committee.

RESULTS: Of the 7 studies, 1 class I and 2 class II double-blind, randomized, controlled trials reported that bilateral DBS is more effective in improving OCD symptoms than sham treatment.

CONCLUSION: Based on the data published in the literature, the following recommendations can be made: (1) There is Level I evidence, based on a single class I study, for the use of bilateral subthalamic nucleus DBS for the treatment of medically refractory OCD. (2) There is Level II evidence, based on a single class II study, for the use of bilateral nucleus accumbens DBS for the treatment of medically refractory OCD. (3) There is insufficient evidence to make a recommendation for the use of unilateral DBS for the treatment of medically refractory OCD.

KEY WORDS: Deep brain stimulation, Guidelines, Obsessive-compulsive disorder, Neuromodulation, Psychiatry

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Congress of Neurological Surgeons
GUIDELINES

ABBREVIATIONS: AANS, American Association of Neurological Surgeons; **CNS,** Congress of Neurological Surgeons; **DBS,** deep brain stimulation; **OCD,** obsessive-compulsive disorder; **YBOCS,** Yale and Brown OCD Scale

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Obsessive–compulsive disorder (OCD) is characterized by unwanted recurrent, intrusive, anxious thoughts (obsessions) and repetitive ritualized behaviors aimed at preventing or reducing distress (compulsions).[1] Although many patients respond to medications and/or psychotherapy, 40% to 60% continue to experience symptoms despite adequate medical management.[2,3] In the late 1990s, Nuttin et al[4] carried out the first study using deep brain stimulation (DBS) to treat OCD. The promising findings of that study generated great interest in the field, with a series of studies being published thereafter.[5-26] Although most of the literature on DBS for OCD comprises small case series, well-designed high-quality studies have also been conducted.

DBS targets investigated for the treatment of OCD include the anterior limb of the internal capsule,[4,14] the ventral caudate,[27] the subthalamic nucleus,[20] the inferior thalamic peduncle,[18] and the nucleus accumbens.[10] These structures have been selected as they are considered to be part of the OCD circuitry, have been used as targets for stereotactic lesions, and improved comorbid OCD symptoms in patients undergoing DBS surgery for other indications (eg, Parkinson disease).[4,10,28] Overall, studies published to date have used similar inclusion criteria, that is, surgery was offered to adult patients in whom medical therapy, who did not have major contraindications to the procedure, and who had severe OCD symptoms. In OCD trials, disease severity is often scored with the Yale and Brown OCD Scale (YBOCS), a 40-item scale in which patients answer 20 questions related to obsessions and 20 related to compulsions. In the YBOCS, high scores are associated with more severe OCD symptoms.

We reviewed the literature on DBS for OCD for efficacy focusing on study design. Level of evidence was assigned to each study and the strength of recommendation graded according to the American Association of Neurological Surgeons (AANS)/Congress of Neurological Surgeons (CNS) criteria.[29]

Question Addressed in the Systematic Review and Evidence-Based Clinical Practice Guideline

Is DBS effective for the treatment of OCD?

METHODS

Search Strategy

This systematic review was conducted and reported according to PRISMA (see PRISMA Checklist, **Supplemental Digital Content** http://links.lww.com/NEU/A656).[30] A literature search was undertaken using the PubMed database for articles published between 1966 and October 2012 combining the following words: "Deep Brain Stimulation and obsessive-compulsive disorder" or "electrical stimulation and obsessive-compulsive disorder." These searches resulted in 353 abstracts, which were reviewed by three independent investigators. The flow of information through the different phases of the review is presented in the Figure. Relevant articles were selected for full-text review and had to meet the following article inclusion and exclusion criteria:

Inclusion

- Clinical series with 6 or more patients treated with DBS. This limit was chosen because, due to the small number of subjects included, studies with fewer than 6 patients often reported the outcomes of individual patients rather than analyzing data for the whole population. In addition, with small sample sizes, the presence of outliers can significantly compromise the analysis of data.
- Clinical series with a minimum postoperative follow-up of 6 months. Although ideally longer follow-up intervals would be desirable, the 6-month timeline was selected because it was the most common follow-up interval reported in the studies pooled for analysis in our review.

Exclusion

- Studies including only preclinical data.
- Review articles.
- Letters to the editor.
- Clinical series with fewer than 6 patients.
- Clinical series with a follow-up shorter than 6 months.
- Articles reporting on patient populations other than those with OCD.
- Clinical series in which ablative surgery was used instead of DBS.
- Reports that mainly addressed aspects related to surgical technique.

Of 352 articles, 7 original articles were retrieved for analysis.[10,13-17,20] A total of 345 studies were excluded for the following reasons: 188 were review articles, 22 included only preclinical data, 51 were letters to the editor or had fewer than 6 patients, 44 addressed other diseases (eg, Parkinson disease, Tourette syndrome), 6 reported on the effects of ablative procedures instead of DBS, and 34 addressed questions pertinent to targeting or surgical technique. One article was common to both search lists and was included only once.

AANS/CNS Evidence Levels and Levels of Recommendations

For each of the articles included, evidence classification and strength of recommendations were graded according to the AANS/CNS criteria (Table 1).[29] The level of evidence (ie, Level I, II, or III) assigned to each article was based on study design, data analysis, and follow-up. The strength of recommendation (ie, Level I, II, or III) was linked to the level of evidence supporting the recommendation. The level of a recommendation could be decreased if there were methodological concerns regarding the studies that provided evidence for that particular recommendation. For each of the studies included, our opinion regarding the limitations is discussed.

Special Considerations

Crossover studies are common in neuromodulation. After being implanted with stimulation systems, patients are often randomized to receive active ("on") or sham ("off") stimulation for a period of time, followed by the inverse treatment.

Confounder effects in DBS studies include a carryover effect (ie, the persistence of a clinical improvement after stimulation is discontinued) and an insertional effect (ie, improvement in clinical scores due to the implantation of electrodes and not the delivery of stimulation per se). In addition, in some of the applications of DBS, the clinical benefits of this therapy are known to accrue with time. Finally, one has to acknowledge the possible influence of a placebo response. Bearing these aspects in mind, we only considered as Level I evidence those studies that are prospective, randomized, controlled trials in which patients received active or sham

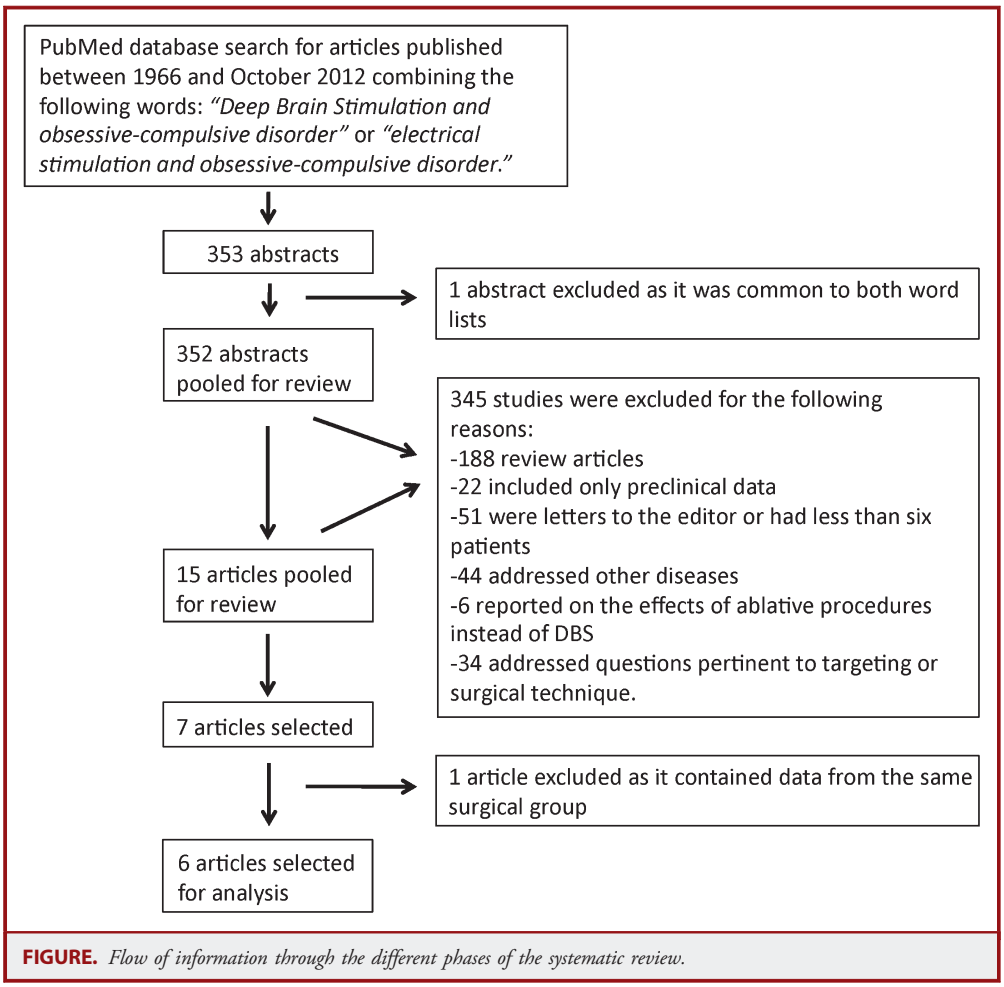

FIGURE. *Flow of information through the different phases of the systematic review.*

stimulation with a washout period (ie, stimulation discontinued) in between crossover arms. Studies in which an open-label phase was included before blinded evaluations (ie, comparing active and sham treatment) were downgraded. Under these circumstances, patients would have been exposed to the therapy and know what to expect from the therapy before the blinding.

Defining Response

In most open-label studies, response to DBS in OCD is defined by 35% or greater improvement in YBOCS scores when postoperative values are compared with those recorded at baseline.[31,32] Partial response is considered when postoperative YBOCS scores are reduced by 25% to 35%.

Double-blind studies report a response when "on" stimulation YBOCS scores are significantly lower (improved) than those recorded in the "off" DBS condition. In functional neurosurgery, results from double-blind studies often vary from those recorded in open-label trials. For the purpose of these guidelines, the following were defined as a significant improvement:

1. In double-blind studies comparing active ("on") vs sham stimulation ("off"), the differences between "on" and "off" scores (ie, DBS "on" vs sham treatment) reached statistical significance AND had a magnitude of at least 25%; this percentage was selected as it has been commonly used in randomized, controlled trials comparing the effects of selective serotonin reuptake inhibitors and placebo in OCD.[33]
2. In open-label studies, there was a minimum 35% improvement when postoperative "on" stimulation scores were compared with those recorded before surgery.

RESULTS

Of the 7 studies included as evidence to support the topic (Table 2),[10,13-17,20] 3 had a double-blind phase in which active stimulation was compared with sham treatment.[10,16,20] Only 1 of them, however, fulfilled criteria to be classified as a class I study.[20] The remaining 2 studies either did not include a washout segment or had a short crossover phase. Both were classified as Level II evidence.[10,16]

Level I

Mallet et al[20] conducted a study in which bilateral electrodes were implanted in a region of the subthalamic nucleus that was 2 mm anterior and 1 mm medial to the target commonly used in Parkinson disease. Surgical candidates were between 18 and 60 years of age with at least 5 years of disease duration. The diagnosis of OCD was established according to Diagnostic and

TABLE 1. American Association of Neurological Surgeons/ Congress of Neurological Surgeons Evidence Levels and Levels of Recommendation

Evidence Classification
Level I: evidence provided by ≥1 well-designed, randomized, controlled clinical trials, including overview (meta-analyses) of such trials
Level II: evidence provided by well-designed observational studies with concurrent controls (eg, case-control and cohort studies)
Level III: evidence provided by expert opinion, case series, case reports, and studies with historical controls
Levels of recommendation
Level I: generally accepted principles for patient management that reflect a high degree of clinical certainty (usually this requires Level I evidence that directly addresses the clinical questions or overwhelming Level II evidence when circumstances preclude randomized clinical trials)
Level II: recommendations for patient management that reflect clinical certainty (usually this requires Level II evidence or a strong consensus of Level III evidence)
Level III: other strategies for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion)

Statistical Manual Fourth Edition criteria. Severity of the disease was characterized by YBCOS scores higher than 25 (or 15 on 1 subscale), global assessment of function scores of less than 40, and clinical global impression scores higher than 4. Patients were refractory to selective serotonin reuptake inhibitors, augmentative strategies, and behavioral therapy.

The study consisted of double-blind and open-label phases. The former had a crossover design with patients undergoing 3-month periods of active or sham stimulation, followed by the inverse treatment. Between treatments, the authors included a 1-month washout period. Assignment to treatment was conducted randomly in a 1:1 ratio with a blocking scheme and a centralized procedure. Primary outcome was considered a change in YBOCS at the end of the "on" and "off" periods.

A total of 18 patients were enrolled at 10 academic centers. Sixteen were randomized to start the trial by receiving active or sham stimulation. Overall, the authors found statistically significantly lower YBOCS scores at the end of the "on" vs "off" phases (19 vs 28; 32%, P = .01).

Level II

Two studies generated Level II evidence. In both, electrodes were implanted in the nucleus accumbens. Inclusion criteria had no key differences from those described in the previously mentioned study.

Denys et al[10] designed a trial that included 3 segments. The first was an 8-month open-label phase that commenced after DBS devices were programmed. In the second phase, patients underwent crossover, blinded assessments while receiving bilateral stimulation or sham treatment for 2 weeks. The third phase consisted of a 12-month maintenance open-label period. Block randomization was used to select those who would receive active or sham stimulation first during the second phase of the trial.

Of the 16 patients included, 14 had agreed to participate in the blinded phase. A significant 8.8-point reduction in the YBOCS score was observed when patients were treated with active vs sham stimulation (30%, P = .003; 8.3 points after correction for a carryover effect).

In the second trial that generated Level II evidence, Huff et al[16] studied the effects of right nucleus accumbens DBS in patients with OCD. The study consisted of 3 stages. In the operating room, four 7-minute blocks of test stimulation were conducted to assess optimal DBS settings. After the pulse generator was implanted, a 6-month double-blind, crossover phase was carried out. Patients were given active or sham stimulation for 3 months followed by the inverse treatment. The last portion of the study was an open-label phase. Overall, no significant differences were recorded when "on/off" stimulation scores were compared during the blinded phase of the trial.

Level III

Level III data were generated by 4 original studies[13-15,17] as well as the open-label segments of the Level I/II studies described. Two studies from the same group included similar data.[14,15] Only 1 of those studies is shown in Table 2.[14]

DBS targets in these studies were the nucleus accumbens, ventral capsule/ventral striatum (which includes the nucleus accumbens), subthalamic nucleus, and inferior thalamic peduncle. Follow-up varied from 12 to 36 months. Overall, DBS was found to be effective in all the targets described except when unilaterally administered to the nucleus accumbens. In studies using bilateral DBS, more than 50% of the patients had a good surgical response (ie, ≥35% improvement in YBOCS scores). The average reduction in YBOCS scores across trials was between 39% and 51%.

DISCUSSION

The effectiveness of DBS for OCD has been reported in randomized, controlled trials comparing active and sham stimulation. Based on the literature, the following recommendations can be made: (1) There is Level I evidence, based on a single Level I study, for the use of bilateral subthalamic nucleus DBS for the treatment of medically refractory OCD. (2) There is Level II evidence, based on a single Level II study, for the use of bilateral nucleus accumbens DBS for the treatment of medically refractory OCD. (3) There is insufficient evidence to make a recommendation for the use of unilateral DBS for the treatment of medically refractory OCD.

As most patients with OCD respond to medical treatment, the number of subjects recruited in surgical trials is small. Despite this caveat, with a Level I study and a Level II study showing success, a Level II recommendation may be made that bilateral DBS is

TABLE 2. Summary of Studies Pooled for Review[a]

Author, year	Level	Description of the Study	Conclusions	Comments
Mallet et al[20]	I	Bilateral STN DBS in 17 patients, 10 academic centers; 10-mo study with double-blind crossover and open-label phases; crossover phase had randomized 3-mo periods of active or sham stimulation followed by the reverse with an interim 1-mo wash out	Lower YBOCS scores with active vs sham DBS (19 vs 28; 32%, $P = .01$)	16 randomized to active/sham stimulation
Denys et al[10]	II	Bilateral nucleus accumbens DBS in 16 patients; open-label period for 8 mo followed by double-blind crossover phase, 2 wk on and 2 wk off stimulation. Thereafter, patients underwent a 12-mo maintenance open-label phase	8.3 ± 2.3 point reduction in the YBOCS with active vs sham stimulation $P = .004$; in the open phase, 9 of 16 patients were responders with YBOCS scores decreased from 33.7 (3.6) to 16.2 (8.6) at 21 mo ($P < .001$)	Crossover data in 14/16; no wash-out period
Huff et al[16]	II	Right nucleus accumbens DBS in 10 patients; the study comprised a double-blind crossover with 3-mo on/3-mo off periods, followed by a 6-mo open phase	No difference between active and sham stimulation ($P = .205$); at 12 mo, mean YBOCS decreased from 32.2 ± 4 to 25.4 ± 6.7 ($P = .012$)	
Greenberg et al[14,15]	III	Case series of 26 patients from 4 centers treated with bilateral Vc/Vs DBS; mean 31.4-mo follow-up (range, 3-36)	16 of 26 were responders. Mean YBOCS score decrease from 34 ± 0.5 to 20.9 ± 2.4 ($P = .002$)	The same patients were included in the 2 studies
Goodman et al[13]	III	Case series of 6 patients treated with bilateral Vc/Vs DBS followed for at least 12 mo; also reported were results from a blinded 1-mo on and 1-mo off crossover phase in 3 patients	4 of 6 were responders; YBOCs scores decreased significantly at 12 mo ($P = .04$); no differences between active and sham stimulation	
Jiminez et al[17]	III	Case series of 6 patients with bilateral inferior thalamic peduncle DBS with a 12-mo minimum follow-up (range, 12-36 mo)	100% had >40% response ($P = .026$)	Does not specify criteria for responses

[a]STN, subthalamic nucleus; DBS, deep brain stimulation; YBOCS, Yale Brown Obsessive Compulsive Disorder Scale; Vc/Vs, ventral capsule/ventral striatum.

a "reasonable therapeutic option" in patients with severe, treatment-refractory OCD.

Studies included in our analysis were not without limitations. The trial by Mallet and et al[20] was very well designed. The inclusion of only 18 patients from 7 centers, however, speaks to the fact that only a small number of patients was treated per center. The trial by Denys et al[10] was a single-center study, which means that the benefits obtained need to be replicated in different centers. In addition, it had a short blinded phase (ie, intercalated weekly periods of active vs sham stimulation). Also problematic was the fact that the study had an open-label phase before the blinded evaluations. Under these circumstances, patients may know what to expect from the therapy before undergoing blinded assessments. The study by Huff et al[16] was also conducted by a single center. As only right-sided DBS was conducted, it is unclear whether the stimulation of the left nucleus accumbens might have yielded similar findings. Further, no washout phase was included between active and sham treatment segments of the blinded phase.

Over the years, there have been numerous publications regarding the kinetics of the clinical effects of DBS. Immediately after surgery, an insertional effect has been documented in several conditions, including OCD and depression. Although in some instances, the effects of DBS are immediate (eg, tremor control), in others they occur over weeks to months (eg, dystonia). The timeframe for an improvement with DBS in OCD is still unclear. Based on the studies published to date, however, the evidence suggests that the effects of DBS may build up with time. In this context, short periods of stimulation (eg, <1 month) may not be adequate during crossover trials in which one wants to fully appreciate differences between stimulation and sham treatment. Another important aspect is the inclusion of a washout phase in studies using an "on/off" crossover design. Carryover effects of DBS have long been demonstrated and may contaminate data recorded when patients initially receive active followed by sham stimulation. Future studies should take these factors into account and recruit enough patients to generate powerful data from a statistical perspective.

Although the efficacy of the procedure has been reported, various questions remain unanswered, including those related to the proper target. The most important topic for further clarification is the location of the most effective target. In the study classified as Level I evidence, Mallet et al[20] investigated bilateral subthalamic stimulation. Level II studies examined the effects of unilateral or bilateral DBS in the nucleus accumbens. Based on active vs sham stimulation comparisons, bilateral accumbens DBS[10] appears more effective than only right-sided stimulation.[16] Whether subthalamic or accumbens DBS is more efficacious has not been explored. Both appear to use similar programming parameters (up to 4 V, 130 Hz, 60 μs for subthalamic nucleus; up to 5 V, 130 Hz, 90 μs for accumbens) and induce comparable improvements in YBOCS scores. Further investigation is certainly required to better understand the relative role of these 2 targets and whether 1 target will prevail.

The next in need of further study is the determination of the patient groups who are most suitable candidates for this operation. OCD comprises different clinical phenotypes. It is possible that particular patient subgroups may respond differently to DBS and that specific targets may be more suitable to treat a specific set of symptoms. For instance, it has been noted that "hoarders" do not respond as well to DBS for OCD.

Finally, we certainly need to develop predictors that may forecast a good prognosis after DBS treatment. These can be electrophysiological, morphological (neuroimaging), functional, or clinical. Success in treating Parkinson disease with DBS derives from our precise knowledge regarding who are the best candidates, when the surgery needs to be done, and where the electrodes should be placed. These questions need to be answered in OCD.

CONCLUSION

Although approved by the US Food and Drug Administration under a humanitarian device exemption, DBS for OCD remains more time-consuming to manage than DBS for movement disorders. Under the humanitarian device exemption approval process in the United States, OCD DBS must be carried out after receiving approval from the local institutional review board and having patients sign separate study consents. Additionally, a treating psychiatrist must be involved in the case and attest to the patient's being a proper candidate. These safeguards are valuable in preventing overuse of the therapy. However, we suspect that rather than achieving its proposed goal, these additional steps are impeding patients who would really benefit from the therapy. We, as functional neurosurgeons, have used DBS for movement disorders within the confines of multidisciplinary committees, sharing decisions with our colleagues. A similar situation occurs in OCD DBS so that we may ensure access to therapy for refractory patients.

Disclosure

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The information in these guidelines reflects the current state of knowledge at the time of completion. The presentations are 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 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.

CME QUESTIONS:

1. Which deep brain structure commonly targeted for deep brain stimulation (DBS) in patients with movement disorders has been studied as a potential target DBS in obsessive-compulsive disorder OCD?
   A. Ventral intermediate nucleus of the thalamus
   B. Globus pallidus interna
   C. Subthalamic nucleus
   D. Pedunculopontine nucleus
   E. Nucleus accumbens

2. In most open-label studies of deep brain stimulation (DBS) for obsessive-compulsive disorder, what is the minimum reduction in Yale Brown Obsessive-Compulsive Scale (YBOCS) scores necessary to be considered a meaningful response?
   A. 15%
   B. 35%
   C. 55%
   D. 75%
   E. 95%

3. When considering DBS for patients with treatment resistant OCD, what is the only DBS treatment protocol that is supported by class I evidence?
   A. Unilateral nucleus accumbens
   B. Bilateral nucleus accumbens
   C. Unilateral subthalamic nucleus
   D. Bilateral subthalamic nucleus
   E. Bilateral inferior thalamic peduncle