ABSTRACT
Subthalamic nucleus deep brain stimulation (STN DBS) is an established treatment that improves motor fluctuations, dyskinesia, and tremor in Parkinson's disease (PD). After the surgery, a careful electrode programming strategy and medical management are crucial, because an imbalance between them can compromise the quality of life over time. Clinical management is not straightforward and depends on several perioperative motor and non-motor symptoms. In this study, we review the literature data on acute medical management after STN DBS in PD and propose a clinical algorithm on medical management focused on the patient’s phenotypic profile at the perioperative period. Overall, across the trials, the levodopa equivalent daily dose is reduced by 30 to 50% one year after surgery. In patients taking high doses of dopaminergic drugs or with high risk of impulse control disorders, an initial reduction in dopamine agonists after STN DBS is recommended to avoid the hyperdopaminergic syndrome, particularly hypomania. On the other hand, a rapid reduction of dopaminergic agonists of more than 70% during the first months can lead to dopaminergic agonist withdrawal syndrome, characterized by apathy, pain, and autonomic features. In a subset of patients with severe dyskinesia before surgery, an initial reduction in levodopa seems to be a more reasonable approach. Finally, when the patient’s phenotype before the surgery is the severe parkinsonism (wearing-off) with or without tremor, reduction of the medication after surgery can be more conservative. Individualized medical management following DBS contributes to the ultimate therapy success.

Keywords: deep brain stimulation; medical management; Parkinson’s disease; phenotype; subthalamic nucleus.

Medical management after subthalamic stimulation in Parkinson’s disease: a phenotype perspective
Manejo medicamentoso após estimulação subtalâmica na doença de Parkinson: uma perspectiva fenotípica

Ana Paula BERTHOLO, Carina FRANÇA, Wilma Silva FIORINI, Egberto Reis BARBOSA, Rubens Gisbert CURY

1Universidade de São Paulo, Faculdade de Medicina, Departamento de Neurologia, Centro de Distúrbios do Movimento, São Paulo SP, Brazil.
2Universidade de São Paulo, Instituto de Psiquiatria, Centro de Psicologia, São Paulo SP, Brazil.

Correspondence: Rubens Gisbert Cury; Av. Dr. Enéas de Carvalho Aguiar, 255 / 5º andar / sala 5.084 – Cerqueira César; 05403-900 São Paulo SP, Brazil; E-mail: rubens_cury@usp.br

Conflict of interest: There is no conflict of interest to declare.

Received on August 27, 2019; Received in its final form on October 16, 2019; Accepted on November 6, 2019
Parkinson's disease (PD) is a progressive neurodegenerative disorder, which affects several regions of the central and peripheral nervous system, leading to both motor and non-motor manifestations along the disease course. Surgical treatments for PD, specifically stereotactic ablations (conventional thalamotomy and pallidotomy), were developed before the introduction of levodopa, and reemerged later as a means to overcome difficulties in the management of motor complications, due to the dopaminergic therapy in patients with advanced PD.

Deep brain stimulation (DBS) has been shown to have several advantages compared to traditional lesions, including adaptability, reversibility, and the possibility to be performed bilaterally in the same surgical session. The subthalamic nucleus (STN) is the preferred target among centers and is an established and effective form of treatment that improves motor fluctuations, dyskinesia, and quality of life in well-selected patients with PD.

The success of deep brain stimulation does not rely only on the surgery itself, but also on a whole process, that encompasses several preoperative and postoperative issues. There are key factors in the success of the therapy, starting with the rigorous and standardized selection of patients and meticulous surgical planning to optimize the placement of electrodes. After the procedure, electrode programming strategies and medical management, in both the early and the long-term follow-up, are crucial, given that an unbalancing between them can compromise motor and non-motor functions over time.

Medical management is not straightforward, because the phenotype of patients undergoing surgery is variable. Some patients have more dyskinesias, tremor, or motor fluctuations, or a combination thereof. Additionally, the range of non-motor symptoms varies among candidates, and this may influence how medications are managed. Therefore, the way we change the medication after surgery should be tailored to the individual characteristics of each patient.

In view of the importance of standardized medical management after surgery, the present study aims to:
- Evaluate literature data on acute medical management after DBS in PD.
- Propose a clinical algorithm on medical management focused on the patient’s phenotypic profile at the perioperative period.

**SEARCH STRATEGY AND SELECTION CRITERIA**

References for this review were identified by searches on PubMed, published up to August 2019, and references from relevant articles. We searched for the terms “hyperdopaminergic syndrome”, “hypodopaminergic syndrome”, “apathy”, “cognition”, “dementia”, “depression”, “dopamine agonist”, “impulse control disorders”, “psychosis”, “dyskinesia”, “medication”, “levodopa” and “non-motor symptoms” in combination with the terms “deep brain stimulation” and “Parkinson’s disease”. There were no language restrictions. The final reference list was generated based on the relevance to the topics covered in this article.

**WHO ARE THE PATIENTS REFERRED FOR DBS?**

Patient eligibility for DBS is determined by standardized evaluation in specialized movement disorder centers, using a comprehensive selection process, including a levodopa challenge test, brain imaging, and assessment of neuropsychological and psychiatric functions, with the purpose of achieving the best clinical results and minimizing side effects and complications. Parkinsonian motor signs, such as OFF symptoms, dyskinesias, and tremor are the major complaints of the patients referred for DBS surgery. Pre-operative levodopa-responsiveness has been universally accepted as the single best outcome predictor for response to DBS; with the exception of levodopa-unresponsive tremor, all motor signs that improve with levodopa prior to surgery are expected to improve postoperatively.

Besides the impairment in motor functions, patients undergoing DBS often present a range of non-motor symptoms. In a large cohort of PD patients referred to DBS, half of them fulfilled diagnostic criteria for hyperdopaminergic behavioral disorders, encompassing dopamine dysregulation syndrome and impulse control disorders. Patients undergoing DBS present bothersome disease-related symptoms (motor and non-motor symptoms) associated with high doses of dopaminergic drugs (total levodopa equivalent daily dose - LEDD-greater than 1000 mg), frequently including a dopamine agonist. As detailed below, when we “add” the STN stimulation to patients who are already under high doses of dopaminergic drugs, there is an over-inhibition of the STN activity. This inhibition, in turn, may ‘release the horses’ and culminates in a worsening of dyskinesias and increases the risk of hyperdopaminergic syndrome, such as impulse control disorders during the short-term period after surgery. Thus, a careful and individualized medical management strategy is needed to ‘hold the horses’.

**THE SUBTHALAMIC NUCLEUS IN THE CONTEXT OF DEEP BRAIN STIMULATION**

The STN is a small nucleus that projects fibers to the pallidum and to the substantia nigra and uses glutamate to mediate its function. Deep brain stimulation interferes with the function of the STN and reduces its output, alleviating parkinsonian symptoms (orthodromic effect). In addition, DBS exerts its activity by modulating afferent terminals, including those from the cortex (antidromic effect). The stimulation of afferent...
axons could antidromically activate several cortical areas in a retrograde manner, influencing distal sites\textsuperscript{6}. Most of the cortical afferents to the STN arise from the primary motor cortex and supplementary motor area and innervate the dorsal aspects of the nucleus (motor part of STN)\textsuperscript{16}. The limbic ventromedial portion of the STN receives fibers from the prelimbic-medial orbital areas of the pre-frontal cortex\textsuperscript{17}. Electrode contacts used for chronic DBS in PD are supposed to target the dorsolateral part of the STN (Figure 1), but limbic spread of the current could lead to neuropsychiatry symptoms\textsuperscript{18}.

**PRACTICAL RECOMMENDATIONS IN THE ACUTE PHASE FOLLOWING STN DBS**

The concerns that clinicians should be aware of after surgery are:

- The *amount* of medication that should be reduced (total LEDD).
- *Which* medication, in a logical order, should be tapered.

Several studies have shown that the LEDD\textsuperscript{19} is reduced by 30 to 50% one year after surgery\textsuperscript{14-21} (Table 1 defines the ‘total’ and the ‘dopamine agonist’ LEDD). One study demonstrated that the major modifications in medication dosage occurred during the initial postoperative period - the first 6 months\textsuperscript{14}. In this study, the total LEDD was reduced by 53.4% compared to baseline at 6 months and 47.9% at 3 years\textsuperscript{14}. They evaluated 150 patients and showed that 56% of patients were on monotherapy at 6 months and 41.3% at 3 years. Furthermore, 9.3% patients were free from medication at 6 months, and 7% were free at 3 years\textsuperscript{14}. The complete discontinuation of medication is usually avoided because the lack of dopamine in the limbic system can lead to apathy and depression\textsuperscript{2,14}. The order of medication tapering will depend on the clinical phenotype before the surgery and the patient’s profile following the surgery. Details are provided in the following sections.

**Dyskinesias**

Levodopa-induced dyskinesia (LID) occurs in nearly all patients with PD after 10 years of chronic dopaminergic treatment, it is secondary to early treatment with high doses and chronic pulsatile stimulation of dopamine receptors\textsuperscript{22}. In the extreme, patients can cycle between disabling dyskinesias during the “ON” state and disabling parkinsonism during the “OFF” state\textsuperscript{23}. Risk factors for the development of dyskinesias are young-onset PD, female gender, high UPDRS part II scores at baseline, lower weight, and high dose of levodopa\textsuperscript{23}. Striatal denervation and subsequent structural alterations of post-synaptic dopaminergic transmission are necessary for LID to develop\textsuperscript{24}.

STN DBS does not have an appreciable antidyskinetic effect and can even induce dyskinesias, which thwarts an increase in stimulation during programming\textsuperscript{1}. In most cases, when stimulation-induced dyskinesia occurs it has been interpreted as a good prognostic sign, indicating that the optimal lead location has been achieved\textsuperscript{25,26}. There are experiments suggesting that glutamate neurotransmitter release may underpin stimulation induced dyskinesia, but the exact mechanisms remain unknown\textsuperscript{27}.

Dyskinesia reduction has been consistently reported after STN implantation, due to the reduction of postoperative dopamine replacement therapy\textsuperscript{1}, in particular levodopa. Russmann et al. found that LED was reduced by 74% after 21 months of STN DBS, along with a reduction in antiparkinsonian medication during this time\textsuperscript{22}.

In a prospective study of 91 patients, a robust improvement in all motor signs in the OFF condition (the percentage of time with good mobility and no dyskinesia and mean dyskinesia score) was observed. Six months after DBS, 74% of patients were without dyskinesia in “ON” state compared to 27% at baseline, and 7% of patients were with dyskinesias in “ON” state compared to 23% at

| Parkinsonian Drug              | Conversion factor |
|-------------------------------|------------------|
| Immediate release L-dopa dose | x 1              |
| Controlled release L-dopa dose| x 0.75           |
| Entacapone                    | x 0.33           |
| Pramipexole                   | x 100            |
| Ropinirole                    | x 20             |
| Rotigotine                    | x 30             |
| Selegiline                    | x 10             |
| Rasagiline                    | x 100            |
| Amantadine                    | x 1              |

Total LEDD is the sum of all drugs (Actual total daily dose x Conversion factor). Dopamine agonist (DA) LEDD represents the Pramipexole, Ropinirole or Rotigotine daily dose x Conversion factor.

---

**Table 1** Protocol for calculating levodopa equivalent daily dose for antiparkinsonian agents.

---

**Figure 1.** Upper view of electrodes implanted in a patient with Parkinson’s disease located in the dorsal part of subthalamic nucleus.
baseline. The mean reduction in the LEDD was approximately 60%\textsuperscript{28,29}. It became clear that the reduction in dyskinesia could be attributed, at least partly, to the reduction in the levodopa dosage\textsuperscript{28}. A comprehensive meta-analysis of 921 patients who underwent STN DBS between 1993 and 2004 noted an average reduction in dyskinesia of 69.1%, with an average reduction in LEDD of 55.9%\textsuperscript{28,30}.

Vingerhoets et al. evaluated 20 patients with PD with motor fluctuations and dyskinesia, who underwent bilateral STN DBS. The medication was reduced by 79% and was completely withdrawn in 10 patients. Fluctuations and dyskinesia showed an overall reduction of 90%, disappearing completely in patients without medication\textsuperscript{31}.

In patients referred for DBS treatment due to severe dyskinesia, an initial reduction in levodopa (mainly the plasmatic peak) soon after the surgery seems to be reasonable and can be considered as the best approach. It is worth mentioning that although the DBS stimulation is usually kept turned off during the first weeks after surgery, a microlesion effect is a commonly observed phenomenon after the electrode insertion and mimics the DBS stimulation effect\textsuperscript{32}. The microlesion effect results from a transient damage of the STN and usually lasts 3-4 weeks\textsuperscript{32}.

In patients who maintain dyskinesias, even after a reduction of levodopa following DBS, other strategies may be considered, such as: a concomitant reduction of dopaminergic agonist, introduction of amantadine and/or clozapine, and also programming techniques (not the aim of this article), such as titrating of the stimulation by small steps (0.1-0.2 volts every week), bipolar stimulation, and stimulation of the more dorsal contacts. This later approach allows the current to spread into the dorsally adjacent lenticularis fasciculus, which exerts an effect similar to that of pallidal stimulation and ultimately suppresses dyskinesia, mimicking the antidyskinetic effect of globus pallidus internus stimulation\textsuperscript{1}.

An infrequent but nonetheless potential complication of STN DBS is a permanent stimulation-induced dyskinesia following the surgery. A small subset of patients experiences troublesome dyskinesia after STN DBS, despite optimal programming and medication adjustments (called ‘brittle’ dyskinesia)\textsuperscript{35}. Young onset of PD may play a role in the genesis of this post-STN DBS ‘brittle’ dyskinesia. Other risk factors, such as longer disease duration, longer duration of levodopa therapy, and female patients with a low body weight have been suggested, although the number of patients reported so far is small\textsuperscript{27,28}. The emergence of this troublesome dyskinesia post-STN DBS is challenging. Rescue GPi DBS can be effective in ‘brittle’ dyskinesia and was previously reported\textsuperscript{35}.

**Hyperdopaminergic syndrome**

During the few days immediately following surgery, patients usually experience a mild euphoria, hyperactivity, and increased motivation\textsuperscript{22}. Overall, this “disinhibition” is overlooked by patients and their relatives, and it naturally improves within a few weeks. However, in a few patients, a more robust hyperdopaminergic syndrome may arise, and generally results from a combination of the lesioning effect of the electrode, the high frequency stimulation itself (which has an inhibitory effect over the nucleus), and a high dopaminergic load.

The STN is a key player in the inhibitory control of complex motivated behavior\textsuperscript{2} and is directly involved in our decision making, providing a “NoGo” signal that suppresses responses\textsuperscript{13}. Accordingly, some evidence from pre-clinical studies shows that STN lesions impair the response selection processes, and lead to premature responding in high-conflict choice selection paradigms\textsuperscript{13}. Taken together, in the acute phase after surgery, the synergistic activity of both high frequency stimulation and the persistent effect of dopaminergic drugs over-inhibit the STN, releasing the brake and disinhibiting behavior\textsuperscript{2}.

Hyperdopaminergic syndrome following the surgery can worsen if the current spreads to the ventral-medial regions (limbic part) of the STN\textsuperscript{34}. DBS-induced mania/hypomania appears to occur in 4% of patients\textsuperscript{35}, but this number increases to 82% with ventromedial electrode placement\textsuperscript{26}. Therefore, slow titration of the stimulation and avoidance of the most medial and inferior contacts are recommended (Figure 2).

Reducing dopaminergic medication load might lead to an improvement in behavioral features. In patients with a high risk of hyperdopaminergic syndrome (male sex, young age at onset, previous history of ICD, and dopamine agonist LEDD over 150 mg) an initial reduction of dopaminergic agonists - even before the surgery - is recommended. The amount of reduction is not established, but a reduction of 15-30% of dopamine agonists LEDD during the first months following the surgery seems reasonable (which represents the Pramipexole, Ropinirole or Rotigotine daily dose x Conversion factor - see Table 1). An aggressive reduction (more than 70% in dopamine agonists LEDD) can be associated with severe apathy and depression and should be discouraged\textsuperscript{22}. In those
patients not taking dopamine agonists, the initial levodopa reduction should be preferable over other drugs, because of its psychostimulant effects\(^1\). A short course of clozapine or quetiapine may be necessary in some cases during the first weeks following surgery, along with neuropsychologist evaluation and cognitive behavioral therapy\(^2\).

It is important to highlight that a dopaminergic drug decrease does not instantly lead to a reduction in the behavioral effects, because the drugs also have long-term effects\(^3\). In the long-term, the reduction of dopaminergic medication leads to progressive disappearance of their long-term effects and to desensitization\(^4\).

Despite being uncommon, the presence of hyperdopaminergic syndrome after STN DBS can be reduced if a detailed preoperative assessment is performed. In our center, the neuropsychology team routinely applies the Ardouin Scale of Behavior in Parkinson's Disease (ASBPD)\(^5\), which uses a structured, standardized interview designed to detect and quantify a wide range of neuropsychiatric symptoms in PD\(^6,9\). The scale assesses 'behavioral addictions' to classify repetitive behaviors found in patients with PD, including impulse control disorder, punding, and excessive hobbyism. Every item is rated on a five-point scale from 0 (absence of disorder or change compared to usual behavior) to 4 (severe behavioral disorder) by accounting for the severity and the frequency of the disorder compared to premorbid usual functioning and its psychosocial effect. When any item on the ASBPD scores 3 or 4 the patient is not referred for DBS until the symptom is compensated.

Finally, psychosis, characterized by short-lasting transient hallucinations and delusions, are described shortly after surgery. In these cases, the first medications to be generally reduced or discontinued are the anticholinergic drugs, followed by amantadine, dopaminergic agonists, catechol-O-methyltransferase inhibitor (COMT\(_\alpha\)), monoamine oxidase inhibitor (MAO\(_\alpha\)), and, lastly, levodopa. The prescription of antipsychotics for short-term use can be necessary\(^2\).

The other side of the coin: Hypodopaminergic syndrome

Apathy and depression are common neuropsychiatric disorders in PD, with the prevalence reaching 50% for depression, and from 17 to 70% for apathy\(^9\). These symptoms can be observed at all stages of the disease, but are predominant at its onset or when it is undertreated\(^9\). Postoperatively, apathy and depression may emerge and have been attributed to direct stimulation effects of the STN for apathy or of adjacent zones for depression, but most importantly, due to inadvertent overreduction of levodopa and dopamine agonists inducing dopamine withdrawal syndromes\(^9,40\).

Apathy

Apathy is one of the most common symptoms found in PD and is defined as a lack of motivation accompanied by reduced goal-directed cognition, behavior, and emotional involvement\(^1\). It may be observed at all stages of PD, in isolation or more frequently in association with dementia, depression, or anxiety\(^41\). Postoperative apathy is frequently associated to anxiety or depression and seems to be the tip of the iceberg of a larger spectrum of hypodopaminergic symptoms\(^42\).

Apathy occurs after a mean of 4-7 months following DBS\(^1\) and is associated with rapid reduction of dopaminergic therapy, which leads to a postoperative deactivation of dopaminergic receptors within the mesocortical and mesolimbic pathways\(^1\). Thobois and some colleagues showed that after a forceful 82% reduction of dopaminergic medication within 2 weeks after surgery, half of patients developed apathy. Furthermore, postoperative apathy has been considered in the spectrum of dopamine withdrawal syndrome (DAWS). A PET study at baseline revealed that the greater the mesocorticolimbic dopaminergic denervation, the higher the odds of developing apathy after surgery\(^43\).

Apathy following STN DBS responds to dopamine agonist treatment\(^43\). Czernecki et al. showed that apathy dramatically improved with ropinirole, a D2 and D3 dopaminergic agonist, in all but one of the 8 patients who became apathetic after complete withdrawal of dopaminergic medication following STN stimulation\(^44\). In the present study, the average score on the Starkstein Apathy scale showed an improvement of 54% (+24%), and the improvement in mood was not correlated to the effect on apathy\(^44\). Thobois et al. also showed that piribedil, another D2/D3 dopaminergic agonist, significantly alleviates postoperative apathy in patients with PD after STN DBS\(^42\).

Because of the risk of hyperdopaminergic syndrome, dopamine load should not be reduced sharply after surgery, since this could lead to patients becoming apathetic. The presence of apathy after surgery can “block” the beneficial effect of DBS on motor symptoms. Whereas clinicians are happy with the motor outcome, the patient’s global impression does not change after surgery or, in some cases, it even worsens. This is why apathy should be detected after surgery and treated early on with dopaminergic drugs to prevent postoperative depression with suicidal risk\(^2,41\). Practical recommendations indicate that, overall, dopaminergic medications, especially dopamine agonists, should be reduced during the months following STN DBS, but a reduction of more than 70%, or a complete discontinuation, must be avoided.

Depression

In patients with bilateral chronic STN stimulation, depressive features improved, remained unchanged, or even worsened compared to the preoperative condition\(^20,45\). Postoperative improvement of depression might result from a psychological response to the alleviation of disabling motor symptoms or from the effects of STN stimulation on neural circuits involved in mood\(^20,45\). On the other hand, suicidal tendencies have been reported in
some patients with PD after STN DBS. Occurrence of suicide has been linked to hypodopaminergic features secondary to acute post-surgical withdrawal of medications, which, as discussed, is a common practice in the initial phase of DBS treatment. We recommend a very close follow-up and repetitive psychological assessment, if needed, throughout the first postoperative year to detect a delayed onset hypodopaminergic syndrome, which requires cautious as to the re-introduction of dopaminergic medications and antidepressant treatment.

Rigidity, bradykinesia, tremor and motor fluctuations

STN DBS improves rigidity and bradykinesia by 63 and 52%, respectively, 12 months after surgery. With the addition of dopaminergic replacement therapy, these improvements increased to 73 and 69%, respectively. Regarding the tremor, STN stimulation may produce an improvement of 86% in the first year after surgery. When the patient’s phenotype before surgery is the severe parkinsonism (wearing-off) with or without tremor, the reduction of the medication can be more conservative. In such cases, the add-on of DBS plus medication are beneficial. Overall, we keep the levodopa unchanged and decrease the dopaminergic agonist when the DA LEDD is greater than 150 mg, due to potential neuropsychiatric side effects, as previously discussed. Sequentially, when the stimulation reaches a stable value, there is a gradual reduction in anticholinergic medications, followed by COMT inhibitors, amantadine, and MAOIs.

**FINAL REMARKS**

In patients referred for DBS surgery, it is important to evaluate the patient’s main phenotype at baseline, because it directly influences the drug management soon after surgery (Figure 3 summarizes the algorithm). This assessment of motor and non-motor symptoms, which predominate in each individual, allows a more individualized reduction in the amount of dopaminergic drugs and a logical sequence of reduction to minimize potential postoperative risks. Hyperdopaminergic and hypodopaminergic syndromes, together with severe dyskinesia, are the most challenges issues.

A multidisciplinary approach with the systematic assessment of non-motor dopamine-dependent symptoms is essential to screen for changes in motivation and mood, and to manage and prevent hypodopaminergic and hyperdopaminergic episodes. The reduction in dopaminergic drugs afforded by STN DBS, and the consequent striatal desensitization, enable long term reversal, not only of dyskinesia but also of hypodopaminergic behaviors. However, an abrupt drastic reduction in dopaminergic drugs (in case of either disabling dyskinesia or

---

**STN DBS:** Subthalamic nucleus deep brain stimulation; COMT: catechol-O-methyltransferase inhibitor; MAO: monoamine oxidase inhibitor; ICD: impulse control disorder; DDS: dopamine dysregulation syndrome; DA LEDD: dopamine agonist levodopa equivalent daily dose. *Overreduction can lead to dopamine agonist withdrawal syndrome. **Although the limbic spread of the current usually leads to hyperdopaminergic syndrome, negative symptoms, such as apathy can happen and dramatically improve after DBS adjustment.

**Figure 3.** Algorithm for medical management in the acute phase after subthalamic stimulation, according to the most prevalent patient's phenotype.
pathologic hyperdopaminergic syndrome) may lead to complications ranging from isolated apathy up to a full-blown hypodopaminergic syndrome, highlighting apathy as the core symptom in association with anxiety, depression, and pain, in various combinations.

A slow, progressive, and orchestrated increase of STN DBS intensity parallel to a reduction in dopaminergic drugs according to patient’s characteristics is the more logical approach. However, systematic studies addressing medical management following DBS are still needed and will contribute to the ultimate success of DBS in PD.

References

1. Fasano A, Daniele A, Albanese A. Treatment of motor and non-motor features of Parkinson's disease with deep brain stimulation. Lancet Neurol. 2012 May;11(5):429–42. https://doi.org/10.1016/S1474-4422(12)70049-2
2. Castrioto A, Lhomme E, Moro E, Krack P. Mood and behavioural effects of subthalamic stimulation in Parkinson's disease. Lancet Neurol. 2014;13(3):287–305. https://doi.org/10.1016/S1474-4422(13)70294-1
3. Schuurman PR, Bosch DA, Bossuyt PMM, Bonsel GJ, van Someren EJW, de Bie RMA, et al. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med. 2000;342(7):461–8. https://doi.org/10.1056/NEJM200002173420703
4. Fasano A, Appel-Cresswell S, Jog M, Zurovskis M, Duff-Canning S, Cohn M, et al. Medical Management of Parkinson's disease after initiation of deep brain stimulation. Can J Neurol Sci. 2016 Sep;43(5):626–34. https://doi.org/10.1017/cjn.2016.274
5. Brandão P, Gripe TC, Modesto LC, Ferreira AGF, Silva FMD, Pereira FF, et al. Decisions about deep brain stimulation therapy in Parkinson's disease. Arq Neuropsiquiatr. 2018 Jun;76(6):411–20. https://doi.org/10.1590/0004-282X20180064.
6. Moro E, Schüpbach M, Wächter T, Allert N, Eleopra R, Honey CR, et al. Referring Parkinson's disease patients for deep brain stimulation: a RAND/UCLA appropriateness study. J Neurol. 2016 Jan;263(1):112–5. https://doi.org/10.1007/s00415-015-7942-x
7. Moro E, Allert N, Eleopra R, Houeto J-L, Phan T-M, Stoevelaar H, et al. International Study Group on Referral Criteria for DBS. A decision tool to support appropriate referral for deep brain stimulation in Parkinson's disease. J Neurol. 2009 Jan;256(1):83–8. https://doi.org/10.1007/s00415-009-0069-1
8. Moro E, Lang AE. Criteria for deep-brain stimulation in Parkinson's disease: review and analysis. Expert Rev Neurother. 2006;6(11):1695–705. https://doi.org/10.1586/14737175.6.11.1695
9. Bronstein JM, Tagliati M, Alterman RL, Lozano AM, Volkmann J, Stefani A, et al. Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues. Arch Neurol. 2011 Feb;68(2):165. https://doi.org/10.1001/archneurol.2010.260
10. Lhomme E, Klinger H, Thobois S, Schmitt E, Ardouin C, Bichon A, et al. Subthalamic stimulation in Parkinson's disease: restoring the balance of motivated behaviours. Brain. 2012 May;135(Pt 5):1463–77. https://doi.org/10.1093/brain/aw2078
11. Delport B, Lhomme E, Klinger H, Schmitt E, Bichon A, Fraix Y, et al. Psychostimulant effect of dopaminergic treatment and addictions in Parkinson's disease. Mov Disord. 2017 Nov;32(15):2649–53. https://doi.org/10.1002/mds.23429
12. Lim S-Y, O’Sullivan SS, Kotschet K, Gallagher DA, Lacey C, Lawrence AD, et al. Dopamine dysregulation syndrome, impulse control disorders and punding after deep brain stimulation surgery for Parkinson’s disease. J Clin Neurosci. 2009 Sep;16(9):1148–52. https://doi.org/10.1016/j.jocn.2008.09.004
13. Frank MJ, Samanta J, Moustafa AA, Sherman SJ. Hold your horses: impulsivity, deep brain stimulation, and medication in Parkinsonism. Science. 2007 Nov 23;318(5854):1309-12. https://doi.org/10.1126/science.1146157
14. Alexoudi A, Shalash A, Knudsen K, Witt K, Mehdorn M, Volkmann J, et al. The medical treatment of patients with Parkinson's disease receiving subthalamic neurostimulation. Parkinsonism Relat Disord. 2015 Jun;21(6):555–40; discussion 555. https://doi.org/10.1016/j. parkreldis.2015.03.003
15. Ardouin C, Chéreau I, Llorca P-M, Lhomme E, Durif F, Pollak P, et al. Assessment of hyper- and hypodopaminergic behaviors in Parkinson's disease. Rev Neurol. 2009;165(11):845–56. https://doi.org/10.1016/j.neurol.2009.06.003
16. Eusebio A, Witjas T, Cohan J, Fluchère F, Jouve E, Régis J, et al. Subthalamic nucleus stimulation and compulsive use of dopaminergic medication in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2013 Aug;84(8):868–74. https://doi.org/10.1136/jnnp-2012-302387
17. Häßig TD, Tse W, Frisina PG, Baker BR, Hollander E, Shapiro H, et al. Subthalamic deep brain stimulation and impulse control in Parkinson’s disease. Eur J Neurol. 2009 Apr;16(4):493–7. https://doi.org/10.1111/j.1468-1331.2008.02509.x
18. Hamani C, Florence G, Heinsen H, Plantinga BR, Temel Y, Uludag K, Ahlo E, et al. Subthalamic nucleus deep brain stimulation: basic concepts and novel perspectives. eNeuro. 2017 Sep 22;4(5). pii: ENEURO.0140-17.2017. https://doi.org/10.1523/ ENEURO.0140-17.2017
19. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord. 2010;25(15):2649–53. https://doi.org/10.1002/mds.23429
20. Cury RG, Gaihardoni R, Fonoff ET, dos Santos Ghilardi MG, Fonoff F, Arnaut D, et al. Effects of deep brain stimulation on pain and other nonmotor symptoms in Parkinson disease. Neurology. 2014 Oct 14;83(16):1403–9. https://doi.org/10.1212/ WNL.0000000000000887
21. Hacker ML, Currie AD, Molinari AL, Turchar M, Millan SM, Heusinkveld LE, et al. Subthalamic nucleus deep brain stimulation may reduce medication costs in early stage Parkinson’s disease. J Parkinsons Dis. 2016;6(1):125–31. https://doi.org/10.3233/JPD-150712
22. Russmann H, Ghika J, Combrement P, Villemure J-G, Bogousslavsky J, Burkehard PR, et al. L-dopa-induced dyskinesia improvement after STN-DBS depends upon medication reduction. Neurology. 2004 Jul;63(1):153–9. https://doi.org/10.1212/01.wnl.0000139107.72829.9d
23. Warren Olanow C, Kieburtz K, Rascol O, Poewe W, Schapira AH, Emre M, et al. Factors predictive of the development of Levodopa-induced dyskinesia and wearing-off in Parkinson’s disease. Mov Dis. 2013 Jul;28(8):1064–71. https://doi.org/10.1002/mds.25364
24. Fasano A, Appel-Cresswell S, Jog M, Zurovskis M, Duff-Canning S, Cohn M, et al. Medical management of Parkinson's Disease after initiation of deep brain stimulation. Can J Neurol Sci. 2016 Sep;43(5):626–34. https://doi.org/10.1017/cjn.2016.274
25. Sriram A, Foote KD, Oyama G, Kwak J, Zeilman PR, Okun MS. Brittle dyskinesia following STN but not GPi deep brain stimulation. Tremor Other Hyperkinet Mov (N Y). 2014;4:242. https://doi.org/10.7916/D8KS6PPR
26. Zheng Z, Li Y, Li J, Zhang Y, Zhang X, Zhuang P. Stimulation-induced dyskinesia in the early stage after subthalamic deep brain stimulation. Stereotact Funct Neurosurg. 2010;88(1):29–34. https://doi.org/10.1159/000260077
27. Espay AJ, Morgante F, Merola A, Fasano A, Marsili L, Fox SH, et al. Levodopa-induced dyskinesia in Parkinson disease: Current and evolving concepts. Ann Neurol. 2018 Dec;84(6):797–811. https://doi.org/10.1002/ana.25364

28. Munhoz RP, Cerasta A, Okun MS. Surgical treatment of dyskinesia in Parkinson's disease. Front Neurol. 2014;5:65. https://doi.org/10.3389/neurol.2014.00065

29. Deep-Brain Stimulation for Parkinson's Disease Study Group, Obeso JA, Olanow CW, Rodríguez-Oroz MC, Krack P, Kumar R, et al. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med. 2001 Sep 27;345(13):956–63. https://doi.org/10.1056/NEJMoa000827

30. Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. Mov Disord. 2006 Jun;21 Suppl 14:S290-304. https://doi.org/10.1002/mds.20962

31. Vingerhoets FJ, Villemure J-G, Temperli P, Pollo C, Pralong E, Ghika R, et al. Microlesion Effect as a Predictor of the Effectiveness of Subthalamic Deep Brain Stimulation for Parkinson's Disease. Stereotactic and Functional Neurosurgery. 2014;5:65. https://doi.org/10.3389/fneur.2014.00065

32. Tykocki T, Nauman P, Koziara H, Mandat T. Microlesion Effect as a Predictor of the Effectiveness of Subthalamic Deep Brain Stimulation for Parkinson's Disease. Stereotactic and Functional Neurosurgery. 2014;5:65. https://doi.org/10.3389/fneur.2014.00065

33. Mallet L, Schupbach M, N’Diaye K, Remy P, Bardinet E, Czernecki V, et al. Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior. PNAS. 2007 Jun;104(25):10661–6. https://doi.org/10.1073/pnas.0610849104

34. Chopra A, Tye SJ, Lee KH, Sampson S, Matsumoto J, Adams A, et al. Underlying neurobiology and clinical correlates of mania status after subthalamic nucleus deep brain stimulation in Parkinson's disease: a review of the literature. J Neuropsychiatry Clin Neurosci. 2012 Winter;24(1):102–10. https://doi.org/10.1176/appi.neuropsych.10070109

35. Temel Y, Kessels A, Tan S, Topdag A, Boon P, Visser-Vandewalle V. Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: A systematic review. Parkinsonism Relat Disord. 2006 Jun;12(5):265–72. https://doi.org/10.1016/j.parkreldis.2006.01.004

36. Herzog J, Reff J, Krack P, Witt K, Schrader B, Müller D, et al. Manic episode with psychotic symptoms induced by subthalamic nucleus stimulation in a patient with Parkinson's disease: Manic Episode After STN-DBS. Mov Disord. 2003 Nov;18(11):1382–4. https://doi.org/10.1002/mds.10530

37. Tareen TK, Artusi CA, Rodríguez-Porcel F, Devoto JL, Sheikh H, Mandybur GT, et al. Dopaminergic dose adjustment and negative affective symptoms after deep brain stimulation. J Neurol Sci. 2018 Jul;390:33–5. https://doi.org/10.1016/j.jns.2018.04.002

38. Castrioto A, Kistner A, Klinger H, Lhomée M, Schmitt E, Fraix V, et al. Psychostimulant effect of levodopa: reversing sensitisation is possible. J Neurol Neurosurg Psychiatry. 2013 Jan;84(1):18–22. https://doi.org/10.1136/jnnp-2012-302444

39. Rieu I, Martinez-Martín P, Pereira B, De Chazeron I, Verhagen Metman L, Jahnshahi M, et al. International validation of a behavioral scale in Parkinson's disease without dementia. Mov Disord. 2015 Apr;30(5):705–13. https://doi.org/10.1002/mds.26223

40. Lhomée M, Wojtecki L, Czerniecki V, Witt K, Maier F, Tonder L, et al. Behavioural outcomes of subthalamic stimulation and medical therapy versus medical therapy alone for Parkinson's disease with early motor complications (EARLYSTIM trial): secondary analysis of an open-label randomised trial. Lancet Neurol. 2018 Mar;17(3):223–231. https://doi.org/10.1016/S1474-4422(18)30035-8

41. Aarsland D, Marsch L, Schrag A. Neuropsychiatric symptoms in Parkinson's disease. Mov Disord. 2009 Nov;24(19):2175–86. https://doi.org/10.1002/mds.22899

42. Thobois S, Lhomée E, Klinger H, Ardouin C, Schmitt E, Bichon A, et al. Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. Brain. 2013 May;136(Pt 5):1568–77. https://doi.org/10.1093/brain/aws077

43. Thobois S, Ardouin C, Lhomée E, Klinger H, Lagrange C, Xie J, et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. Brain. 2010 Apr;133( Pt 4):1111–27. https://doi.org/10.1093/brain/awt032

44. Czernecki V, Schüpbach M, Yasi S, Lévy R, Bardinet E, Yelnik J, et al. Apathy following subthalamic stimulation in Parkinson disease: a dopamine responsive symptom. Mov Disord. 2008 May;23(7):964–9. https://doi.org/10.1002/mds.21949

45. Zibetti M, Torre E, Cinquepalmi A, Rosso M, Ducati A, Bergamasco B, et al. Motor and nonmotor symptom follow-up in parkinsonian patients after deep brain stimulation of the subthalamic nucleus. Eur Neurol. 2007;58(4):218–33. https://doi.org/10.1159/000107943

46. Antonini A, Moro E, Godeiro C, Reichmann H. Medical and surgical management of advanced Parkinson's disease. Management of Advanced Parkinson's Disease. Mov Disord. 2018 Jul;33(8):900–8. https://doi.org/10.1002/mds.27340

47. Horn A, Kuhn AA. Lead-DBS: a toolbox for deep brain stimulation electrode localizations and visualizations. Neuroimage. 2015 Feb;107:127–35. https://doi.org/10.1016/j.neuroimage.2014.12.002

Bertholo AP et al. Drug management after DBS in Parkinson's disease