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Medical management after subthalamic stimulation in Parkinson's disease: a phenotype perspective

Manejo medicamentoso após estimulação subtalâmica na doença de Parkinson: uma perspectiva fenotípica

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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.

RESUMO

A estimulação cerebral profunda do núcleo subtalâmico (ECP NST) é um tratamento estabelecido para doença de Parkinson (DP), que leva à melhora das flutuações motoras, da discinesia e do tremor. Após a cirurgia, deve haver uma estratégia cuidadosa de programação da estimulação e do manejo medicamentoso, pois um desequilíbrio entre eles pode comprometer a qualidade de vida. O gerenciamento clínico não é simples e depende de vários sintomas motores e não motores perioperatórios. Nesta revisão, discutimos os dados da literatura sobre o tratamento clínico agudo após a ECP NST na DP e propomos um algoritmo clínico baseado no perfil fenotípico do paciente no período perioperatório. Em geral, nos estudos clínicos, a dose diária equivalente de levodopa é reduzida em 30 a 50% um ano após a cirurgia. Em pacientes que recebem altas doses de medicações dopaminérgicas ou com alto risco de impulsividade, recomenda-se redução inicial do agonista dopaminérgico após a ECP NST, para evitar síndrome hiperdopaminérgica, particularmente a hipomania. Por outro lado, uma rápida redução de agonistas dopaminérgicos em mais de 70% durante os primeiros meses pode levar à síndrome de abstinência do agonista dopaminérgico, com apatia, dor e disautonomia. Em pacientes com discinesia grave antes da cirurgia, é recomendada redução inicial na dose de levodopa. Finalmente, quando o fenótipo do paciente antes da cirurgia é o parkinsonismo grave (flutuação motora) com ou sem tremor, a redução da medicação após a cirurgia deve ser mais conservadora. O tratamento médico individualizado após a ECP contribui para o sucesso final da terapia.

Palavras-chave: estimulação encefálica profunda; manejo medicamentoso; doença de Parkinson; fenótipo; núcleo subtalâmico.

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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[1,2]. 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 medical management of motor complications, due to the dopaminergic therapy in patients with advanced PD[1].

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[3]. 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[4,5].

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[2,4].

Medical management is not straightforward, because the phenotype of patients undergoing surgery is variable[6]. Some patients have more dyskinesia, 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[2]. 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[6-8]. Parkinsonian motor signs, such as OFF symptoms, dyskinesias, and tremor are the major complaints of the patients refereed for DBS surgery[6-8]. 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[8,9].

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[10,11]. 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[11,12]. 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[13]. 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[1-14]. 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[15]. 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

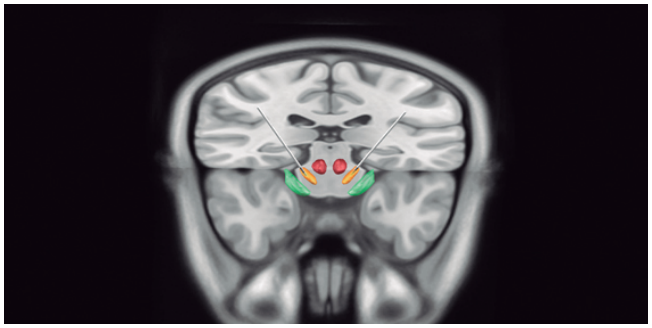
axons could antidromically activate several cortical areas in a retrograde manner, influencing distal sites[6]. Most of the cortical afferents to the STN arise from the primary motor cortex and supplementary motor area and innervate the dorsal aspects of the nucleus (motor part of STN)[16]. The limbic ventromedial portion of the STN receives fibers from the prelimbic-medial orbital areas of the pre-frontal cortex[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[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[19] is reduced by 30 to 50% one year after surgery[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[14]. In this study, the total LEDD was reduced by 53.4% compared to baseline at 6 months and 47.9% at 3 years[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[14]. The complete discontinuation of medication is usually avoided because the lack of dopamine in the limbic system can lead to apathy and depression[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.



Orange: STN; Red: Red Nucleus; Green: Globus Pallidus Internus[47]

Figure 1. Upper view of electrodes implanted in a patient with Parkinson's disease located in the dorsal part of subthalamic nucleus.

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[22]. In the extreme, patients can cycle between disabling dyskinesias during the "ON" state and disabling parkinsonism during the "OFF" state[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[23]. Striatal denervation and subsequent structural alterations of post-synaptic dopaminergic transmission are necessary for LID to develop[24].

STN DBS does not have an appreciable antidyskinetic effect and can even induce dyskinesias, which thwarts an increase in stimulation during programming[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[25,26]. There are experiments suggesting that glutamate neurotransmitter release may underpin stimulation induced dyskinesia, but the exact mechanisms remain unknown[27].

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

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

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.

baseline. The mean reduction in the LEDD was approximately 60%[28,29]. It became clear that the reduction in dyskinesia could be attributed, at least partly, to the reduction in the levodopa dosage[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%[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[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[32]. The microlesion effect results from a transient damage of the STN and usually lasts 3-4 weeks[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[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)[25]. 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[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[25].

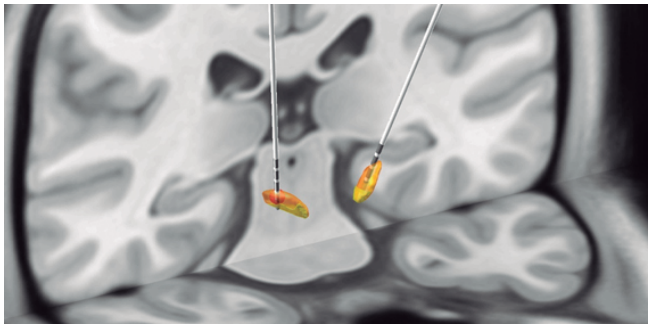
Hyperdopaminergic syndrome

During the few days immediately following surgery, patients usually experience a mild euphoria, hyperactivity, and increased motivation[32]. 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[2] and is directly involved in our decision making, providing a "NoGo" signal that suppresses responses[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[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[2].

Hyperdopaminergic syndrome following the surgery can worsen if the current spreads to the ventral-medial regions (limbic part) of the STN[34]. DBS-induced mania/hypomania appears to occur in 4% of patients[35], but this number increases to 82% with ventromedial electrode placement[36]. 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 hyperdopaminegic 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[37]. In those



Orange: STN sensorimotor region; Yellow: STN limbic region[47].

Figure 2. Electrode reconstruction illustrating the volume of tissue activated (circumferential red circle around the electrode) into the sensorimotor region of the STN (dorsal part). Note the yellow region (limbic region) in the anterior part of the nucleus. The spread of the current to this region could lead to neuropsychiatry symptoms.

patients not taking dopamine agonists, the initial levodopa reduction should be preferable over other drugs, because of its psychostimulant effects1[11]. 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[35]. In the long-term, the reduction of dopaminergic medication leads to progressive disappearance of their long-term effects and to desensitization[38].

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)[15], which uses a structured, standardized interview designed to detect and quantify a wide range of neuropsychiatric symptoms in PD[15,39]. 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 (COMTi), monoamine oxidase inhibitor (MAOi), 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[39]. These symptoms can be observed at all stages of the disease, but are predominant at its onset or when it is undertreated[39]. 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[24-40].

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[11]. 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[2,43]. 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[1]. 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[46]. 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[2].

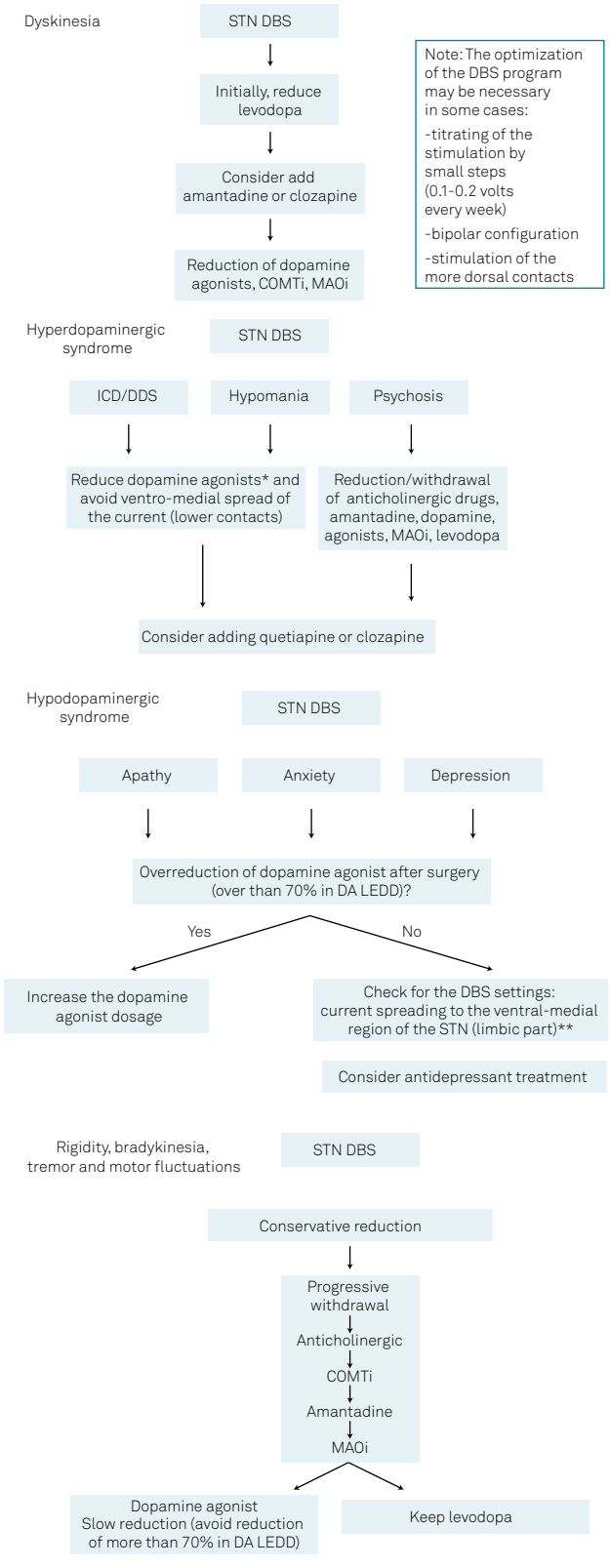
Rigidity, bradykinesia, tremor and motor fluctuations

STN DBS improves rigidity and bradykinesia by 63 and 52%, respectively, 12 months after surgery[1]. With the addition of dopaminergic replacement therapy, these improvements increased to 73 and 69%, respectively[1]. Regarding the tremor, STN stimulation may produce an improvement of 86% in the first year after surgery[1]. 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 COMTi, amantadine, and MAOi[14].

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[31].

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[2]. 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 hyperdopaminergic behaviors. However, an abrupt drastic reduction in dopaminergic drugs (in case of either disabling dyskinesia or



STN DBS: Subthalamic nucleus deep brain stimulation; COMTi/: catechol-O-methyltransferase inhibitor; MAOi: 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[2].

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.

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