REVIEW ARTICLE

Medical Management of Parkinson's Disease after Initiation of Deep Brain Stimulation

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ABSTRACT: In this review, we have gathered all the available evidence to guide medication management after deep brain stimulation (DBS) in Parkinson's disease (PD). Surprisingly, we found that almost no study addressed drug-based management in the postoperative period. Dopaminergic medications are usually reduced, but whether the levodopa or dopamine agonist is to be reduced is left to the personal preference of the treating physician. We have summarized the pros and cons of both approaches. No study on the management of cognitive problems after DBS has been done, and only a few studies have explored the pharmacological management of such DBS-resistant symptoms as voice (amantadine), balance (donepezil) or gait disorders (amantadine, methylphenidate). As for the psychiatric problems so frequently reported in PD patients, researchers have directed their attention to the complex interplay between stimulation and reduction of dopaminergic drugs only recently. In conclusion, studies addressing medical management following DBS are still needed and will certainly contribute to the ultimate success of DBS procedures.

RÉSUMÉ: Traitement médical de la maladie de Parkinson lors du début de la stimulation cérébrale profonde. Nous avons effectué une revue de toutes les données disponibles afin de guider la gestion de la médication lors du début de la stimulation cérébrale profonde (SCP) dans la maladie de Parkinson (MP). De façon surprenante, nous avons constaté qu'il existait très peu d'études sur le sujet en période post-opératoire. Le dosage des médicaments dopaminergiques est habituellement diminué, mais le choix de diminuer celui de la lévodopa ou des agonistes de la dopamine est laissé à la préférence personnelle du médecin traitant. Nous avons fait le sommaire du pour et du contre de ces deux stratégies de traitement. Aucune étude sur la gestion des problèmes cognitifs n'a été effectuée après le début de la SCP et peu d'études ont exploré le traitement pharmacologique des symptômes réfractaires à la SCP, tels la dysphonie (amantadine), les troubles de l'équilibre (donépézil) ou de la démarche (amantadine, méthylphénidate). En ce qui concerne les problèmes psychiatriques qui sont fréquemment signalés chez les patients atteints de la MP, ce n'est que récemment que les chercheurs ont porté leur attention sur des interactions complexes entre la SCP et la diminution de la posologie des agents dopaminergiques. En conclusion, il est nécessaire d'effectuer des études portant sur le traitement médical de la MP après le début de la SCP. De telles études contribueront certainement au succès optimal du traitement par la SCP.

Keywords: Parkinson's disease, Deep brain stimulation, Subthalamic nucleus, Globus pallidus internus, Medication

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INTRODUCTION

Several studies and randomised controlled trials have investigated the effectiveness of deep brain stimulation (DBS) for Parkinson's disease (PD) (for a review, see Fasano et al.[1]). Twenty-five years after the beginning of the DBS era, new issues need to be addressed. Some of them relate to management of medical treatment following DBS, as currently there are no guidelines or studies specifically addressing this topic. Therefore, physicians dealing with DBS adjust medications on the basis of their preference,

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personal experience or studies on patients who did not receive DBS. The issue of medical management following DBS is an important one because it greatly contributes to the success of a DBS procedure in both the early phase (e.g., post-op apathy) and at long-term follow-up (e.g., managing disease progression or DBS-induced complications).

In this review, we have summarized all the available evidence to guide medication management before and after DBS, and the current areas of controversy are highlighted to suggest future directions for research.

Search Strategy and Selection Criteria

The data for this review were identified from personal files and textbooks and from PubMed searches, including items published up to the end of 2014 with the terms "apathy", "axial motor symptoms", "balance", "cognition", "dementia", "depression", "dopamine agonist", "dysarthria", "freezing of gait", "impulse control disorders", "levodopa", "non-motor symptoms", "psychosis" and "suicide" coupled with the term "deep brain stimulation" and "Parkinson's disease". The final list of references was selected by including only those papers considered to be of specific relevance, published in English and for the most part during the previous 10 years.

Dopaminergic Treatment in PD before and after DBS

DBS of the subthalamic nucleus (STN) in PD is mainly indicated to reduce motor fluctuations and off-time as well as levodopa-induced dyskinesias. There is emergent evidence that STN DBS might also be helpful for impulse control disorders (ICDs) in PD, although not all studies are in agreement on this. The benefit of STN DBS for dyskinesias is largely due to its ability to significantly reduce dopaminergic medication dosages, whereas the positive effects on ICDs are thought to be secondary to reductions in dopamine agonists, the main culprits in ICDs.[2] After STN DBS, the levodopa equivalent daily dose (LEDD) can usually be reduced by 30 to 50% for best motor outcomes,[3-6] or up to 56% according to a meta-analysis of uncontrolled case series.[7] On the flip side, a frequent adverse event following a reduction in dopaminergic therapy after STN DBS is a non-motor dopamine withdrawal syndrome characterized by apathy and depression, which can in large part be viewed as dopaminergic understimulation, particularly in the limbic and associative circuits.[8] Other targets for DBS in PD usually do not result in significant medication changes (globus pallidus internus [GPi] or thalamus) and are thus not a topic of this review.

Evidence (What We Know)

There are no studies formally examining how to adjust medications *before* DBS treatment. An informal poll among Canadian neurologists and neurosurgeons revealed that practices differ widely between centres: some have general guidelines for stopping all dopamine agonist 2-6 months before the planned procedure, whereas others try to have as many patients as possible on dopamine agonists. Other centres report a more tailored approach depending on a patient's main problem (e.g., dyskinesias vs. excessive OFF time vs. ICDs), thus optimizing medical therapy to fit individual needs. Some centres aim for simplification of medication before DBS and thus maintain patients on levodopa only, some centres prefer controlled release levodopa with the idea of more continuous dopaminergic stimulation, while others prefer immediate release due to the more consistent and reliable effect favouring ease of adjustment.

In the first few weeks after DBS implantation, dyskinesias due to the microlesioning effect might require a temporary reduction in levodopa dose. Further differences in the timing of medication adjustments result from varying protocols regarding when stimulation is switched on: some centres start programming in the immediate postoperative period, usually when patients are still admitted and can be observed closely, while others start programming several weeks after the initial lesioning effect has subsided and a stable clinical picture has emerged.

Apathy is one of the most frequent psychiatric side effects after STN DBS, and one study suggested that apathy might occur after DBS of either the STN or the GPi independent of medication changes.[9] Most studies, though, find a correlation of apathy after DBS with the level of dopaminergic medication. Apathy is especially common in those patients who exhibit significant preoperative non-motor fluctuations and ICDs. A small study suggested that apathy following DBS improved in 7 of 8 subjects with reintroduction of a D2/D3 agonist after prior complete withdrawal from dopaminergic medication following DBS.[10] Thobois et al.[11] reported on 63 patients undergoing STN DBS who had a mean reduction in LEDD of 82% post-DBS, with dopamine agonists discontinued immediately after surgery. In this cohort, 54% developed apathy and 27% developed depression. 12 months after surgery, the apathy had resolved in half the patients after dopamine agonists were reintroduced.[11] It is of interest that 17 of the 63 patients also met the criteria for depression (Beck Depression Inventory score >20, moderate to severe). Associated raclopride PET studies with a methylphenidate challenge suggest a role of increased degeneration in the mesolimbic areas in development of dopamine withdrawal syndrome.[11] The same group more recently published a prospective, randomised, placebo-controlled 12-week trial with the D2/D3 dopamine agonist piribedil at 300 mg per day in 37 subjects presenting with apathy after STN DBS. They found that the piribedil led to a significant improvement in terms of apathy compared to placebo, and there was a trend for improvements in depression, anxiety, anhedonia and quality of life (QoL).[12]

The impact of STN DBS on hyperdopaminergic states presenting with ICDs and dopamine dysregulation syndrome (DDS) has previously been examined in retrospective case series. The outcomes were mixed with both resolution and new onset of ICDs and DDS.[13-15] Two prospective studies have since shed more light on the question of whether DBS and an associated significant reduction in dopaminergic medication can successfully treat ICDs and DDS. Lhommée et al.[16] assessed 63 subjects before and up to one year after STN DBS for non-motor fluctuations, behavioural addictions (ICDs, punding), DDS and overall functioning in appetitive or apathetic modes.[16] The study protocol prescribed the immediate postoperative discontinuation of dopamine agonists in all patients and a reduction in levodopa dose as tolerated to optimize motor function, resulting in a comparatively large 73% reduction in mean levodopa equivalent dose. Preoperative DDS resolved in 4 of 4 patients, behavioural addictions in 17 of 17 and compulsive dopaminergic drug use in 9 of 9. Of note, pre-DBS, 29 patients were assessed to operate in a predominantly appetitive mode and 3 in an apathetic mode, whereas postoperatively the numbers reversed to 2 and 13, respectively. There were two suicide attempts post-DBS.

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The authors also observed a postoperative reduction in non-motor fluctuations likely related to a direct effect of the stimulation of non-motor STN areas, whereas reduction in hyperdopaminergic symptoms was mainly thought to be due to the significant postoperative reduction in dopaminergic medications.[16]

A second prospective observational study without a predetermined medication protocol found that compulsive dopaminergic medication use resolved in 17 of 18 patients post-DBS. Most behavioural addictions were significantly reduced post-DBS, with the exception of binge eating, which newly occurred after DBS in some misusers of dopaminergic medication as well as in some non-misusers. Interestingly, some patients who preoperatively misused levodopa described that they did not experience the same stimulating effect of levodopa post-DBS.[17]

The results of these studies support a major role of dopaminergic medication in the postoperative management of hyperdopaminergic as well as hypodopaminergic symptoms, but they also suggest a direct effect of STN stimulation on non-motor domains and thus a more complex interaction between stimulation and medication, the details of which need to be studied further.

Areas of Controversy and Future Directions

Currently, there are widely varying dopaminergic treatment strategies among experts. There is a paucity of studies directly comparing dopaminergic agents—most importantly levodopa and dopamine agonists or combinations thereof—before and/or after DBS for both motor and non-motor outcomes. The latter play a crucial and increasingly recognized role in the adjustment of dopamine replacement therapy after DBS, and study populations will need to be matched for preoperative motor as well as non-motor symptoms. Likewise, the best medical therapy for an individual after STN DBS might be predicted by algorithms based on such preoperative clinical indices as motor fluctuations with severe OFFs, dyskinesias, ICDs, depression, apathy, etc., reflecting variable degrees of pathology and sensitization in the implicated brain circuits.[11,18]

The post-DBS dopamine withdrawal syndrome is at least (partially) dopamine-responsive, whereas hyperdopaminergic behaviours improve secondary to a reduction in dopaminergic medication. The direct effect of STN DBS on the limbic and associative circuits needs to be further investigated and disentangled from medication effects. Behavioural problems in PD might become a future indication for STN DBS, a topic that requires further investigation. In addition to measurements of mood, apathy and behaviours, QoL scores in both patients and caregivers should be included as study outcomes.

The Management of Axial Symptoms with Non-Dopaminergic Drugs

Parkinson's disease continues to progress after DBS, and over time axial disability predominates. In fact, disorders of posture, gait and balance are often levodopa- or DBS-resistant.[19] Postural difficulties in PD are well known and lead to increased risk of falling. Difficulties with postural control occur in all phases of movement, including sit to stand, quiet stance, reactive postural adjustments, anticipatory commencement of gait, and walking. Quiet stance is worsened with L-dopa and STN DBS, while it is improved with GPi DBS. Reactive postural adjustments that occur in response to an unknown perturbation are worsened in all situations—namely, L-dopa, STN and GPi DBS. L-dopa may

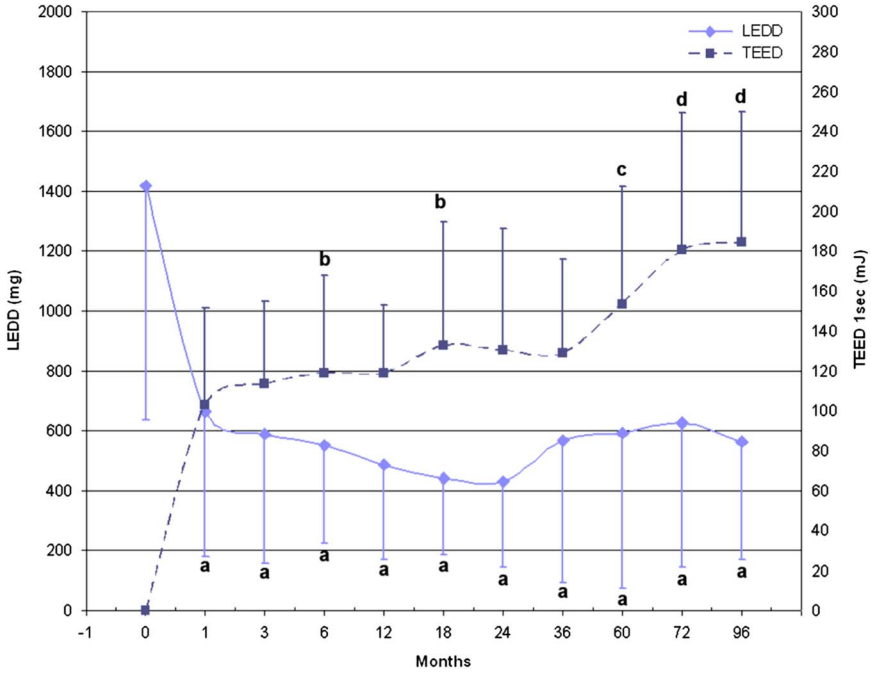

Figure 1: *The trade-off between levodopa equivalent daily dose (LEDD) and total electrical energy delivered (TEED) is achieved within six months after surgery. However, over long-term follow-up, TEED is stable while LEDD begins increasing again. Abbreviations: a = p < 0.001 vs. baseline; b = p < 0.05 vs. 1, 3, 6 and 12 months; c,d = p < 0.05 vs 1, 3, 6, 12, 18, 24 and 36 months (unpublished figure; data from Fasano et al.[21]).*

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improve the ability to move to anticipated perturbations, but both STN and GPi DBS have been shown to potentially worsen this feature. Finally, actual walking assessment shows mixed results, with some improvement, at least initially, for all treatments.[20] Increased fall risk, resistance of gait dysfunction despite improvement in overall motor function and resistance to levodopa treatment have been extensively reported. In fact, worsening of gait function where there was none preoperatively has also been reported. There is no consensus as to how this problem of gait dysfunction can be resolved (for a review, see Fasano et al.[19]). In other instances, DBS itself might worsen these symptoms, and sometimes a reduction of the total energy delivered is required. Accordingly, patients may require increased dosages of dopaminergic medications in spite of the initial reduction (Figure 1).[21] Nevertheless, dopaminergic drugs are very often unsuccessful, and drugs modulating different neurotransmitters are then considered.

Medical treatment for gait impairment is at present limited. In a multicentre, parallel, double-blind, placebo-controlled, randomised trial, PD patients (aged <80 years) with severe gait disorders and freezing of gait, despite optimised treatment of motor fluctuations, with dopaminergic drugs and STN stimulation, were randomly assigned to receive methylphenidate (1 mg/kg per day) or placebo for 90 days. All patients were assessed during an acute L-dopa challenge. The primary outcome was a change in the mean number of steps during the stand–walk–sit (SWS) test without levodopa at baseline and at 90 days. A total of 81 patients were screened, and 35 (33 completed) were assigned to receive methylphenidate and 34 (32 completed) to receive placebo. Analysis was reported on completers. Patients in the methylphenidate group made fewer steps at 90 days (median = 31 steps [*IQR* = 26-42], $F(1, 62) = 6.1$, $p = 0.017$) in comparison with patients in the placebo group (median = 33 steps [*IQR* = 26-45]). Significantly more adverse events—including increased heart rate and decreased weight—were reported in the methylphenidate group compared with placebo.[22]

A prospective multicentre observational study evaluated the effects of amantadine on speech, gait and balance in PD patients with STN DBS who had persistent axial symptoms. The Unified Parkinson's Disease Rating Scale (UPDRS) items were employed as primary outcomes, and changes in speech, gait and postural stability were recorded in those patients on concomitant amantadine compared to their baseline. Subjective measurements reported by patients were the secondary outcome measures. A total of 46 PD patients with STN DBS were enrolled in the study and followed for 10.35 ± 8.2 months (median = 9.0; range = 1-31). The mean daily dose of amantadine was 273.44 ± 47.49 mg. There was a statistically significant improvement in gait scores with amantadine treatment, while postural stability and speech scores did not change. Interestingly, 35 patients (76.1%) reported an improvement in speech, gait or balance, and 30 patients (65.2%) reported improvement in gait and balance on amantadine.[23] Such other options as cholinesterase inhibitors (donepezil 10 mg[24]), rasagiline[25] and SSRIs[26] may be tried, but there are minimal data as to their usefulness.

Psychosocial and Psychiatric Issues

More than 60% of patients report one or more psychiatric symptoms at some point in the course of their PD.[27] Common symptoms include depression, anxiety, apathy, psychosis and cognitive decline. There are also symptoms associated with treatment of PD, including ICDs, DDS and fluctuations in mood and anxiety based on dopaminergic state. The relationship of these symptoms to PD is unclear. For example, depressive symptoms often begin before the onset of PD and may in fact involve systems independent of the motor pathways. Dopamine, for instance, has been implicated in mood, hedonistic drive and reward in non-PD populations.

As PD progresses, there is a growing sense of loss of control and failure as symptoms progress. Choices become more limited. Cracks also appear in relationships with caregiver fatigue and a growing sense of isolation and the need to cope with this illness alone while affirming the importance of a past and no longer present self. The later stages are exemplified by increased physical frailty that overwhelms routines. Patients become very dependent on caregivers and lose their sense of self, shifting to "being us" to the detriment of "being me". They experience a recurrent crisis of meaningful relationships as caregivers fatigue and strangers become increasingly involved in assisting with daily functioning. It is somewhere along this progression that patients undergo DBS.

Evidence (What We Know)

DBS is meant to temporarily halt and reverse the progressive symptomatic decline of PD. A good outcome of the procedure is for patients to not only move better but also to facilitate their participation in meaningful activities and enhance their relationships.[28] Studies have shown good outcomes in some of these measures. However, some qualitative studies have found that, despite a substantial improvement in motor symptoms and relative stability of cognitive status, only 9 of 16 patients who had a professional activity before DBS went back to work after surgery; there was marital conflict in 17 of 24 couples; and there was also a feeling of strangeness expressed by 19 of the 29 patients studied, with expressions of "I don't feel like myself anymore" and "I haven't found myself again after the operation".[28] Fourteen patients (48%) also expressed a sense of helplessness looking back at the damage PD had done: "Now I can live a normal life, go out, see friends, go to the swimming pool, have a sexual life. But PD has destroyed everything. Today, my life is like a forest without trees: I don't have any friends or places to see. What's the use?".[28] Subsequent research[29] has supported these findings in demonstrating that 27% of patients give a negative assessment of the outcome of STN DBS at 3 months. These results are not at odds with those that have shown the positive results of DBS. They represent different methodologies and parameters being assessed in a subset of patients who did not have a positive outcome from the procedure. Patients exhibiting these negative results tend to be more preoperatively depressed and apathetic.

There is also a subset of patients who are at risk of developing postoperative apathy and depression, both of which have been described following DBS (see above). Symptoms of increased depression are of particular concern, as a retrospective study has found increased rates of attempted and completed suicide during the first postoperative year, remaining elevated through the fourth year.[30] Postoperative depression, being single and a previous history of ICDs or DDS were identified as risk factors for attempted suicide. These findings have not been substantiated by a

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Table 1: Synopsis of the effects of DBS on PD motor and non-motor symptoms and medications commonly used during the postoperative period (see text for details), and different mechanisms thought to be responsible are annotated*

		STN DBS	GPi DBS	Medications for post-op management
Motor signs	Appendicular signs	+[a]	+[a]	● Levodopa ● Dopamine agonists
	Axial signs	0/+[a]	0/+[a]	● Levodopa ● Dopamine agonists ● Amantadine (speech and gait) ● Methylphenidate (freezing of gait) ● Donepezil (balance)
	Motor fluctuations	+[a]	+[a]	● Usually not needed
	Dyskinesias	+[c]	+[a]	● Amantadine (usually not needed)
Cognition	Memory	0/+[c]	0	● Donepezil ● Rivastigmine ● Galantamine?
	Executive functions	–[a,c]	0	● Donepezil ● Rivastigmine ● Galantamine?
Mood disorders	Apathy	–[a,c]	0	● Dopamine agonists ● Antidepressants ● Methylphenidate ● Donepezil (in demented patients) ● Rivastigmine (in demented patients)
	Depression	–[a,c]	0/–[a]	● Dopamine agonists ● Antidepressants
	Anxiety	±[a,b,c]	0/+[a]	● Benzodiazepines ● Antidepressants
Behaviour and other psychiatric issues	ICD	0/+[c]	0	● None available
	Delusions and hallucinations	0/+[c]	0	● Quetiapine ● Clozapine
	DDS	–/+[a,c]	0/+[a]	● None available
	Punding	–/+[a,c]	0/+[a]	● Amantadine
Autonomic dysfunction	Drooling	0/+[b,c]	0/+[b]	● Botulinum neurotoxin injected into salivary glands (OnabotulinumtoxinA, AbobotulinumtoxinA, RimabotulinumtoxinB) ● Topical, sublingual or oral anticholinergics (atropine, ipratropium bromide, tropicamide) ● Systemic anticholinergics (glycopyrrolate) ● Systemic alpha-2 agonists (clonidine) ● Systemic alpha-1 agonists (modafinil)
	Sweating	+[b]	0/+[b]	● None available
	Urinary function	+[a,b]	0/+[b]	● Levodopa ● Antimuscarinic (darifenacin, fesoterodine, solifenacin, oxybutynin, tolterodine, trospium) ● β3 agonist (mirabegron)
	Constipation	0/+[b,c]	0/+[b]	● See Figure 2
	Cardiovascular dysautonomia	0/+[b,c]	0	● Droxidopa ● Fludrocortisone ● Midodrine ● Pyridostigmine?
Sleep	Sleep quality	+[a,b,c]	+[b]	● Melatonin ● Clonazepam
	Sleep architecture	0	0	None
	RBD	0/+[c]	0	● Melatonin ● Clonazepam

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Table 1. *Continued*

		STN DBS	GPi DBS	Medications for post-op management
	RLS	–[c]	0	• Levodopa controlled release • Dopamine agonists • Pregabalin
	Daytime sleepiness	+[c]	0	• Methylphenidate • Modafinil
Pain		+[a,b]	0/+[b]	• Levodopa • Dopamine agonists • Pregabalin • Gabapentin

0 = no effect; + = improvement; – = worsening; 0/– or 0/+ = variable outcome; [a] = due to direct effect of stimulation; [b] = secondary to motor improvement; [c] = secondary to drug reduction; ICD = impulse control disorders; DBS = deep brain stimulation; DDS = dopamine dysregulation syndrome; NMS = non-motor symptoms; PD = Parkinson's disease; RBD = REM sleep behaviour disorder; RLS = restless leg syndrome.
*Modified from Fasano et al.[1]

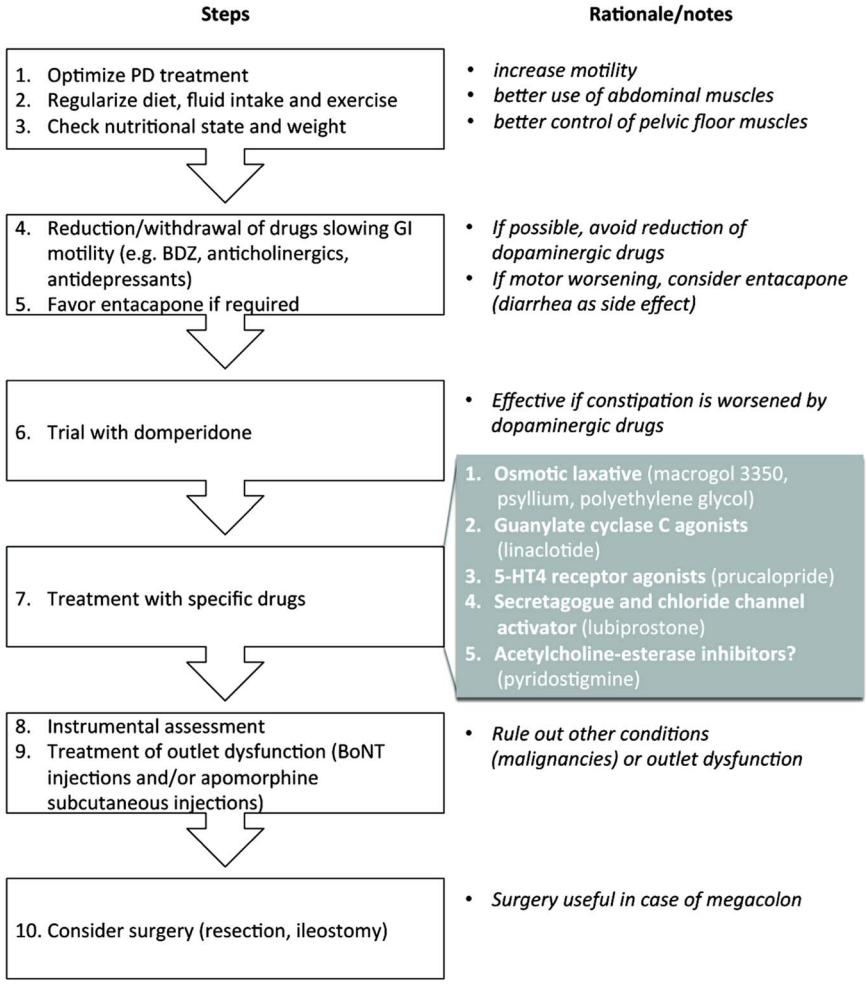

Figure 2: *Ten steps to manage constipation in PD patients. Abbreviations: BDZ = benzodiazepine; BoNT = botulinum neurotoxin; GI = gastrointestinal.*

more recent prospective study[31] that did not show elevated suicidal ideation following STN or GPi DBS.

On the other end of the spectrum, hypomania or mania,[32] as well as increased impulsiveness,[33] have been described after STN DBS. Although possible, medication adjustments play a limited role in these cases because the causative mechanisms are related to stimulation of the limbic portions of the STN; therefore, the best management of these problems relies on adjustment of parameters

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(typically a reduction of the amplitude of stimulation or the use of more dorsal contacts).[1]

Finally, psychosis is also reported in DBS patients, and it is mainly related to disease progression.[1] Its management relies on further reduction or withdrawal of anti-PD medications (particularly amantadine, selegiline, dopamine agonists) followed by the use of antipsychotics (clozapine or quetiapine) or cholinesterase inhibitors (ChEIs; see below).

Areas of Controversy and Future Directions

We have become very successful in optimizing the motor results of patients with PD. In those who are not actively depressed or have forms of dopamine dysregulation, STN DBS is an effective treatment strategy. However, in many patients STN DBS is not successful from a psychosocial or psychiatric perspective. These are the patients who we need to examine further to see if they can safely be helped by the procedure or if GPi DBS is a more favourable option for them. There may also be room to optimize patient outcomes by using more comprehensive evaluations, and not just motor scores, when selecting DBS settings. Beyond DBS, alternative treatments (i.e., infusional therapies) should also be considered, as there is preliminary evidence that intrajejunal levodopa infusion may be associated with good outcomes with respect to ICDs.[34]

Cognitive Issues

While STN DBS is considered generally safe from a cognitive standpoint, especially given the careful selection of surgical candidates and exclusion of individuals with existing PD dementia (PDD), there is considerable individual variability with respect to cognitive outcome. About 41% of patients experience some degree of cognitive decline postoperatively.[35] Typically, mild decline in verbal memory and executive functioning as well as moderate decline in verbal fluency are observed following STN DBS,[35-37] but these changes do not appear to impact QoL negatively.[38,39] In some instances, however, patients develop serious cognitive deterioration in the form of dementia, which by definition carries significant functional disability. The rate of PDD after STN DBS varies considerably across studies, likely due to differences in assessment techniques, diagnostic criteria and patient characteristics, and it remains unclear whether surgery contributes to this cognitive outcome above and beyond disease progression. Some studies have reported rates up to 9.4% in the months following surgery,[40] up to 32% at 2 years[41] and up to 17% at 10 years follow-up.[42] Although rates were lower in several other studies, these illustrate that PDD is relatively common and supports the CAPSIT–PD recommendation to monitor cognition postoperatively.[43] Repeated postoperative neuropsychological assessments can assist in distinguishing lesional from disease-related effects, providing the opportunity to educate patients and their families with respect to cognitive difficulties and future planning, and to readily initiate appropriate therapy.

Evidence (What We Know)

To our knowledge, there are no studies that have examined medical management of cognitive impairment and dementia specifically in surgical PD cohorts. Therefore, current practice is best informed by guidelines developed for non-surgical PD patients (for a recent review, see Emre et al.[44]). A Cochrane review of studies concluded that the available evidence supports the use of ChEIs for treatment of PDD, with positive impact on global assessment, cognition, behavioural disturbances and ADL.[45] At present, the strongest evidence is for rivastigmine, an inhibitor of both acetylcholinesterase (AChE) and butrylcholinesterase (BuChE). A more recent review concluded that both ChEIs and memantine, a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors, improve clinicians' impressions of global change but that only ChEIs enhance cognitive function.[46] Treatment with ChEIs should take into account the potential risks and benefits to patients.[44] Abrupt cessation of ChEIs has been associated with rapid cognitive and behavioural deterioration.[47] Consequently, it has been recommended that patients who are responding be maintained on treatment long term, or that a cautious approach to withdrawal should be taken, if necessary.[44,48] The treatment of PD patients with cognitive impairment but no dementia (e.g., PD–MCI) is controversial, as there is only one level I evidence study supporting the use of cognitive-enhancing medication in this subgroup of patients.[45,49]

Areas of Controversy and Future Directions

Further research is required to improve our ability to identify individuals at risk for cognitive decline post-DBS. At present, management of cognitive impairment and dementia in PD is solely informed by studies in non-surgical cohorts. Studies examining cognitive-enhancing medications in surgical cohorts are required in order to determine whether the same approaches are optimal for DBS patients. The literature to date has primarily used DSM–IV criteria for defining PDD. Future studies should employ MDS Task Force diagnostic criteria for PDD and PD–MCI in order to improve comparisons of efficacy across intervention types. Although conventional psychometric measures (e.g., the Alzheimer's Disease Assessment Scale–Cognitive Subscale [ADAS–cog]) have been the norm in clinical trials, use of additional outcome measures that are more meaningful for patient and caregiver QoL may play a valuable role in determining the efficacy of future treatments. Finally, non-pharmacological interventions are showing some promise in the treatment of cognitive impairment in PD (e.g., exercise[50] or cognitive training[51]) and should continue to be explored.

Conclusions

In this review, we have gathered all the available evidence to guide medication management before and after DBS (see Table 1). Surprisingly, despite the numerous randomised controlled trials (RCTs) focusing on the outcome of DBS, we found that almost no study addressed drug-based management in the postoperative period. For instance, no study on the management of cognitive problems after DBS have been done so far, and only a few studies (the vast majority open-label and retrospective) have explored the pharmacological management of such DBS-resistant symptoms as voice, balance and gait disorders. As for the psychiatric problems so frequently reported in PD patients (e.g., depression or ICD), researchers have only recently directed their attention to the complex interplay between stimulation and reduction of dopaminergic drugs. To date, the best way to manage PD motor progression and non-motor symptoms while balancing levodopa and a dopamine agonist is largely unknown, and an RCT

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is about to start recruiting patients.[52] Many other RCTs are needed and will certainly contribute to the ultimate success of DBS procedures in terms of QoL and psychosocial functioning.

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Disclosures

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