Chapter 24
A Role of Deep Brain Stimulation in Advanced Parkinson's Disease

Vladimira Vuletić and Valentino Rački

Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disease characterized with motor symptoms and non-motor symptoms. Bradykinesia, rigidity, rest tremor, postural instability are well-known motor symptoms, while pain, autonomic dysfunction, cognitive decline, depression, fatigue, apathy, and sleep disturbances are some of frequent non-motor symptoms [1]. We have few groups of antiparkinsonian drugs, with levodopa being a gold standard, to manage disease symptoms. The medications are very functional in an early stage, called the first honey-moon period, but in the advanced phase, we can witness the shortening of time when there is adequate symptom control. Management of advanced Parkinson's disease is challenging. In that stage, we can see motor fluctuation, severe non-motor symptoms, and insufficient control of motor symptoms with falls, freezing, festination, and sudden ON and OFF periods. Non-motor symptoms, especially neuropsychiatric problems, exert the most influence over quality of life in patients and their caregivers [2]. Proper DBS patient selection and management depends on a multidisciplinary approach that encompasses many specialties, including neurologists, neurosurgeons, neuroradiologists, psychologists, speech pathologists and physiotherapists.

Deep brain stimulation (DBS) has been used in the field of movement disorders for the last 33 years. From previous studies we know that DBS is an effective therapy for Parkinson's disease patients in their advanced state [3]. Subthalamic nucleus is the most widely used target, with individual advantages and disadvantages

V. Vuletić (✉) · V. Rački
Department of Neurology, UHC Rijeka, Rijeka, Croatia

Department of Neurology, Faculty of Medicine, University of Rijeka, Rijeka, Croatia
e-mail: Valentino.racki@uniri.hr

V. Demarin et al. (eds.), *Mind, Brain and Education*,
https://doi.org/10.1007/978-3-031-33013-1_24

influencing patient selection, followed by internal globus pallidus (GPi) that also has a beneficial effect [4]. Potential DBS patients are selected using the existing guidelines and the role of an interdisciplinary team is very important. Educated multidisciplinary team reviews each individual's risk–benefit profile for DBS. It is important to mention that DBS is not a cure and it does not stop disease progression and is not the only therapy for advanced PD, therefore, a clear explanation of possible benefits and side effects should be given to patients and their family member during the evaluation process. Their expectations should be realistic and clearly defined. The period after DBS has been lately called as a second honeymoon period by our patients. These advances have led researchers to put DBS among the most important advances in the clinical neurosciences in the past two decades, with ever-growing research. In this review, we will present the role of DBS in advanced Parkinson's disease.

Definition of Advanced Parkinson's Disease and the Indication for DBS

The definition of advanced Parkinson disease is still unclear. There are different definitions based on expert opinions, although it is clear that advanced PD begins when conventional treatment does not provide an adequate level of symptoms control [2]. Some consensus has been met, with a clear focus on both motor and non-motor symptoms, and include disease duration, motor fluctuation with dyskinesia, Hoehn and Yahr staging and specific clinical phenotypes like axial symptoms, cognitive decline or levodopa resistance [5].

Today, all recommendation for adequate management of Parkinson's disease include a multidisciplinary team of health professionals, including the neurologist or geriatrician, Parkinson's disease nurse specialist, physiotherapist, occupational therapist, speech and language therapist, dietitian, clinical psychologist, social worker, urologist, sex therapist, among many others. A multidisciplinary team approach has been shown to improve the quality of life and motor function for people with Parkinson's disease, and is also helpful for their caregivers [6–11]. Additionally, in the DBS team we also have a neurosurgeon, who is crucial to the success of therapy [6]. Finally, we also have studies that have shown beneficial effect of DBS in moderate early PD [12].

The definition of advanced PD is a moving target, but clear guidelines are now emerging on the benefits of DBS in both advanced and early PD patient groups. A recently published guideline using the GRADE methodology by Deuschl et al. had two main research questions and delivered several key recommendations. Most importantly, regarding DBS, there are clear recommendations that it should be preferentially offered to patients suffering from advanced PD with fluctuations bilaterally in the subthalamic nucleus (STN) or GPi, pending proper patient selections. Furthermore, we can consider offering STN-DBS to early PD patients with early fluctuations, as well as those with refractory tremor. The evidence so far does not recommend offering DBS to early PD patients without fluctuation [13].

Effect of DBS in PD

Evidence from previous studies has shown that DBS of either the subthalamic nucleus (STN) or the GPi have beneficial effect on motor fluctuations and dyskinesia associated with advanced PD. Benefits include increased ON time without troubling dyskinesia by a mean of 4.6 hours per day, reducing medications more than 50%, reducing OFF time for 67%, reducing dyskinesias for 70% and increasing quality of life by 50–70% [3]. The exact mechanism is still unknown, while it is thought that stimulation modulates neural circuits, improving transmission of signal and reducing oscillations [14]. DBS makes no major brain lesion, and is both adjustable and reversible. Greatest benefit requires proper adjustments in the whole disease course, which includes often visits to centers of excellence to manage parameter stimulation and adjustment of medical treatments. It is considered as a safe method and adverse events recorded during first 6 months were generally not serious when compared to the groups on best medical therapy [15]. Most commonly, the adverse events are due to operative procedure like intracerebral hemorrhage, infections etc., but cognitive and behavioral complications were infrequent and not significantly different between DBS and medical treatment groups when patients are properly selected [3]. The long term studies have shown persistent effect after 5, 10 and even 15 years [16–18]. Factors that predict benefit of DBS are: preoperative levodopa responsiveness, age, duration of OFF time, dyskinesias and psychiatric symptoms [19]. Comparing different targets, STN-DBS or GPi-DBS are both effective in advanced and early PD, although STN-DBS led to significantly greater improvements compared with GPi-DBS in mean change in the UPDRS motor examination score, disability score, and levodopa equivalent drug reduction in the off-drug phase. However, in the on-drug phase assessment, GPi-DBS was associated with a greater reduction in dyskinesia compared to STN-DBS. Generally it seems that STN as a target is better for more medication reduction, less-frequent battery changes, and has a more favorable economic profile, while GPi is better for more-robust dyskinesia suppression, easier programming, and greater flexibility in adjusting medications. There are also slight differences in the cognitive impact of DBS, with STN-DBS impacting cognitive deterioration more often than GPi-DBS, even though the risks are low for both [20]. In the end, the decision of target (STN or GPi) has to be tailored towards each patients [21, 22].

Research has shown that DBS has beneficial effects on non-motor symptoms at 24-month follow-up [23]. Generally, the impact of DBS is varied, and it can negatively impact cognitive function, especially if patients beforehand already have mild or severe cognitive impairments [20]. On the other hand, beneficial effects of DBS can be seen in autonomic dysfunction, sleep, seonsory function and mood disorder [24]. STN-DBS can improve anxiety in PD patients [25, 26] and impulse control disorders due to a reduction of the dopaminergic drugs after DBS [27]. Consequently, these improvements lead to improved quality of life and treatment satisfaction of patients [28]. There are some investigations in place to find good targets for DBS in PD dementia, such as the stimulation of the cholinergic nucleus basalis of Meynert, although further research is required [29].

Future Perspectives: New Technologies in DBS

The ability to improve advanced PD patient outcomes in intrinsically linked to the advancement of DBS systems. Two key improvements to DBS can be seen in the development of directional and local field potential systems, which have entered routine clinical practice. Research has already shown that directional programming brings many benefits to patients via more flexible stimulation options and can lead to greater therapeutic width and is preferred both by physicians and patients [30]. This is mostly achieved by increasing the threshold for side effects, as the clinical benefits are comparable to conventional DBS [31]. This has been shown in routine practice, with a majority of patients receiving some form of directionality in stimulation for 36 months, mainly for ameliorating side effects [32]. However, longer-term studies are required to see whether the benefits over conventional DBS hold in time.

Another novel approach to DBS programming is using local field potentials for guided stimulations catered to every patient [33]. Local field potentials are biosignals that have been previously used in DBS for confirming correct placements intraoperatively [34]. Furthermore, they are also used for insights into the pathophysiology of the disease from a functional perspective [35]. It's use in clinical practice is still being evaluated, and the greatest promise comes from the ability to reduce initial programming time. Conventional DBS programming is still based on a trial-and-error approach, while personalized measurements of oscillations point to clear targets in each patients. Pilot studies have shown that LFP based programming can streamline the whole process and limit the amount of time spent [36].

Furthermore, looking forward, we can expect further innovation in the field with adaptive closed loop stimulation. Current DBS systems function in an open loop environment, meaning they are programmed beforehand and do not respond to any feedback from the patient. There are several devices in development that could use biomarkers of brain activity and change stimulation settings automatically, leading to the most precise stimulation possible for each patient and each situation [37].

Conclusion

Treatment of advanced PD with invasive methods is becoming more developed each day. DBS has been routinely used for years, and with accumulating experience it is now clear that it should be the first choice for properly selected patients. This is reflected in the most recent guidelines, with STN and Gpi holding strong recommendations for treatment, which lead to a significant improvement to quality of life and functioning.

DBS expert centers are preferentially multidisciplinary and can provide holistic approaches to each patient to facilitate the best possible outcomes. Future perspectives of DBS are bright, with novel systems entering routine clinical practice that offer greater flexibility and effectiveness with less side effects.

References

1. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. JAMA. 2020;323(6):548–60.
2. Coelho M, Ferreira JJ. Late-stage Parkinson disease. Nat Rev Neurol. 2012;8(8):435–42.
3. Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Bötzel K, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med. 2006;355(9):896–908.
4. Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med. 2010;362(22):2077–91.
5. Luquin MR, Kulisevsky J, Martinez-Martin P, Mir P, Tolosa ES. Consensus on the definition of advanced Parkinson's disease: a neurologists-based Delphi study (CEPA study). Parkinsons Dis. 2017;2017:4047392.
6. Pedersen SW, Suedmeyer M, Liu LWC, Domagk D, Forbes A, Bergmann L, et al. The role and structure of the multidisciplinary team in the management of advanced Parkinson's disease with a focus on the use of levodopa-carbidopa intestinal gel. J Multidiscip Healthc. 2017;10:13–27.
7. Carne W, Cifu D, Marcinko P, Pickett T, Baron M, Qutubbudin A, et al. Efficacy of a multidisciplinary treatment program on one-year outcomes of individuals with Parkinson's disease. NeuroRehabilitation. 2005;20(3):161–7.
8. Carne W, Cifu DX, Marcinko P, Baron M, Pickett T, Qutubuddin A, et al. Efficacy of multidisciplinary treatment program on long-term outcomes of individuals with Parkinson's disease. J Rehabil Res Dev. 2005;42(6):779–86.
9. van der Marck MA, Bloem BR, Borm GF, Overeem S, Munneke M, Guttman M. Effectiveness of multidisciplinary care for Parkinson's disease: a randomized, controlled trial. Mov Disord. 2013;28(5):605–11.
10. van der Marck MA, Munneke M, Mulleners W, Hoogerwaard EM, Borm GF, Overeem S, et al. Integrated multidisciplinary care in Parkinson's disease: a non-randomised, controlled trial (IMPACT). Lancet Neurol. 2013;12(10):947–56.
11. Martinez-Martin P, Rodriguez-Blazquez C, Forjaz MJ. Quality of life and burden in caregivers for patients with Parkinson's disease: concepts, assessment and related factors. Expert Rev Pharmacoecon Outcomes Res. 2012;12(2):221–30.
12. Deuschl G, Schüpbach M, Knudsen K, Pinsker MO, Cornu P, Rau J, et al. Stimulation of the subthalamic nucleus at an earlier disease stage of Parkinson's disease: concept and standards of the EARLYSTIM-study. Parkinsonism Relat Disord. 2013;19(1):56–61.
13. Deuschl G, Antonini A, Costa J, Śmiłowska K, Berg D, Corvol JC, et al. European Academy of Neurology/Movement Disorder Society - European Section guideline on the treatment of Parkinson's disease: I. Invasive therapies. Eur J Neurol. 2022;29(9):2580–95.
14. Chiken S, Nambu A. Mechanism of deep brain stimulation: inhibition, excitation, or disruption? Neuroscientist. 2016;22(3):313–22.
15. Weaver FM, Follett K, Stern M, Hur K, Harris C, Marks WJ, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. JAMA. 2009;301(1):63–73.

16. Rodriguez-Oroz MC, Moro E, Krack P. Long-term outcomes of surgical therapies for Parkinson's disease. Mov Disord. 2012;27(14):1718–28.
17. Castrioto A, Lozano AM, Poon YY, Lang AE, Fallis M, Moro E. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. Arch Neurol. 2011;68(12):1550–6.
18. Bove F, Mulas D, Cavallieri F, Castrioto A, Chabardès S, Meoni S, et al. Long-term outcomes (15 years) after subthalamic nucleus deep brain stimulation in patients with Parkinson disease. Neurology. 2021;97(3):e254–62.
19. Welter ML, Houeto JL, Tezenas du Montcel S, Mesnage V, Bonnet AM, Pillon B, et al. Clinical predictive factors of subthalamic stimulation in Parkinson's disease. Brain. 2002;125(Pt 3):575–83.
20. Rački V, Hero M, Rožmarić G, Papić E, Raguž M, Chudy D, et al. Cognitive impact of deep brain stimulation in Parkinson's disease patients: a systematic review. Front Hum Neurosci. 2022;16:867055.
21. Odekerken VJ, van Laar T, Staal MJ, Mosch A, Hoffmann CF, Nijssen PC, et al. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson's disease (NSTAPS study): a randomised controlled trial. Lancet Neurol. 2013;12(1):37–44.
22. Williams NR, Foote KD, Okun MS. STN vs. GPi deep brain stimulation: translating the rematch into clinical practice. Mov Disord Clin Pract. 2014;1(1):24–35.
23. Klingelhoefer L, Samuel M, Chaudhuri KR, Ashkan K. An update of the impact of deep brain stimulation on non motor symptoms in Parkinson's disease. J Parkinsons Dis. 2014;4(2):289–300.
24. Vuletic V, Racki V, Chudy D, Bogdanovic N. Deep brain stimulation in non-motor symptoms of neurodegenerative diseases [Internet]. In: Neurostimulation and neuromodulation in contemporary therapeutic practice. London: IntechOpen; 2019. https://www.intechopen.com/chapters/68407. [cited 2022 Jan 13].
25. Parsons TD, Rogers SA, Braaten AJ, Woods SP, Tröster AI. Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. Lancet Neurol. 2006;5(7):578–88.
26. Castelli L, Perozzo P, Zibetti M, Crivelli B, Morabito U, Lanotte M, et al. Chronic deep brain stimulation of the subthalamic nucleus for Parkinson's disease: effects on cognition, mood, anxiety and personality traits. Eur Neurol. 2006;55(3):136–44.
27. Shotbolt P, Moriarty J, Costello A, Jha A, David A, Ashkan K, et al. Relationships between deep brain stimulation and impulse control disorders in Parkinson's disease, with a literature review. Parkinsonism Relat Disord. 2012;18(1):10–6.
28. Gruber D, Calmbach L, Kühn AA, Krause P, Kopp UA, Schneider GH, et al. Longterm outcome of cognition, affective state, and quality of life following subthalamic deep brain stimulation in Parkinson's disease. J Neural Transm (Vienna). 2019;126(3):309–18.
29. Gratwicke J, Kahan J, Zrinzo L, Hariz M, Limousin P, Foltynie T, et al. The nucleus basalis of Meynert: a new target for deep brain stimulation in dementia? Neurosci Biobehav Rev. 2013;37(10 Pt 2):2676–88.
30. Schnitzler A, Mir P, Brodsky MA, Verhagen L, Groppa S, Alvarez R, et al. Directional deep brain stimulation for Parkinson's disease: results of an international crossover study with randomized, double-blind primary endpoint. Neuromodulation. 2022;25(6):817–28.
31. Dembek TA, Reker P, Visser-Vandewalle V, Wirths J, Treuer H, Klehr M, et al. Directional DBS increases side-effect thresholds—a prospective, double-blind trial. Mov Disord. 2017;32(10):1380–8.
32. Karl JA, Joyce J, Ouyang B, Verhagen ML. Long-term clinical experience with directional deep brain stimulation programming: a retrospective review. Neurol Ther. 2022;11(3):1309–18.
33. Rosa M, Marceglia S, Barbieri S, Priori A. Local field potential and deep brain stimulation (DBS). In: Jaeger D, Jung R, editors. Encyclopedia of computational neuroscience [Internet]. New York, NY: Springer; 2013. p. 1–20. https://doi.org/10.1007/978-1-4614-7320-6_547-1. [cited 2022 Sep 30].

34. Yin Z, Zhu G, Zhao B, Bai Y, Jiang Y, Neumann WJ, et al. Local field potentials in Parkinson's disease: a frequency-based review. Neurobiol Dis. 2021;155:105372.
35. Telkes I, Jimenez-Shahed J, Viswanathan A, Abosch A, Ince NF. Prediction of STN-DBS electrode implantation track in Parkinson's disease by using local field potentials. Front Neurosci. 2016;10. https://www.frontiersin.org/articles/10.3389/fnins.2016.00198. [cited 2022 Sep 30].
36. Fasano A, Gorodetsky C, Paul D, Germann J, Loh A, Yan H, et al. Local field potential-based programming: a proof-of-concept pilot study. Neuromodulation. 2022;25(2):271–5.
37. Frontiers | Deep brain stimulation programming 2.0: future perspectives for target identification and adaptive closed loop stimulation [Internet]. https://www.frontiersin.org/articles/10.3389/fneur.2019.00314/full. [cited 2022 Sep 30].