Right on track: Towards improving DBS patient selection and care

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CHAPTER 2

Selecting candidates for Deep Brain Stimulation in Parkinson's Disease: the role of patients' expectations

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Abstract

Patients with advanced Parkinson's Disease (PD) may be eligible for Deep Brain Stimulation (DBS) in case of medication-related motor fluctuations or tremor refractory to oral medication. However, several PD symptoms are unresponsive to DBS and constitute relative contra-indications for DBS. Patients referred for DBS undergo an eligibility screening during which motor functioning and contra-indications for surgery are assessed. During this pre-screening the potential benefits and drawbacks of surgery are discussed, together with patients' expectations of the results of DBS. Unrealistic expectations on the benefits of DBS may contribute to reduced patient satisfaction and poor clinical outcomes after surgery. The aim of this multicenter study (289 patients) was to assess the reasons for rejection after an outpatient-based pre-screening visit for DBS referrals, with particular emphasis on the role of patient expectations of DBS. The most frequent reason contributing to rejection was suboptimal oral treatment or satisfying symptom-control with oral medication (50% of rejections). Unrealistic expectations were identified in 38% of rejected patients and were the singular reason for rejection in 4%. Incorporating the assessment of unrealistic expectations increased the accuracy (Area Under the Curve) of determining DBS eligibility from 0.92 ((95% confidence interval (95%CI) 0.88 – 0.97) to 0.97 (95%CI 0.96 – 0.99). Patients' expectations of DBS are easily checked, and better education of patients and treating neurologists with regard to unrealistic expectations of this procedure may improve efficiency of referrals and avoid unnecessary stress and disappointments during screening.

Introduction

Deep brain stimulation (DBS) is considered a highly effective therapy to relieve medication-refractory levodopa-induced motor complications or resistant tremor in Parkinson's disease (PD),[1] generally targeting either the subthalamic nucleus, thalamus or pallidum. The potential benefit of DBS is weighed against possible surgical complications or shortcomings that may compromise its success. Examples of the latter include stimulation-resistant symptoms such as postural instability gait disorder, medication-resistant freezing, speech disturbances, psychiatric and cognitive dysfunction, which do not improve or may even worsen following DBS and therefore constitute relative contra-indications for this treatment. DBS failures are often associated with poor selection of DBS candidates, highlighting the importance of a formal comprehensive screening including brain imaging and formal assessments of motor function, balance, cognition, and psychiatric functioning.[2] However, this extensive screening is stressful, expensive, and time-consuming. Prior to the formal DBS screening, patients are often referred to neurologists experienced in DBS for a 'pre-screening', to assess whether patients are suitable candidates for the full DBS screening procedure. During this pre-screening, patients deemed unsuitable may be rejected at an early stage and thereby avoid participation in the demanding full screening procedure. Several screening algorithms have been proposed to aid in DBS referral, with high sensitivity but low specificity.[3-5] Notably, none of these algorithms considers patients' expectations of DBS. Patients may report various reasons for undergoing DBS which are known to remain unsolved after surgery. Hence, realistic expectations of DBS are considered an important criterion for patients selection,[6] as various studies demonstrated that patients with unrealistic expectations, or with suboptimal education on the benefits of DBS prior to surgery, report lower postoperative satisfaction or QoL.[7-9] Patient-reported expectations of DBS have been scarcely studied;[8-10] the contribution of unrealistic patient expectations to the decision on DBS eligibility is yet unknown.

The aim of our study was to assess the reasons for rejection after an outpatient-based pre-screening visit for DBS referrals, with particular emphasis on the role of patient expectations of DBS in determining eligibility for a full screening for surgical candidacy. Improvement of outpatient-based pre-screening in capturing the patients that are more obviously unsuitable for DBS could contribute to avoid unnecessary participations in a full screening procedure, thereby increasing the efficiency of the screening procedure and reducing overall patient burden. Furthermore, insights on this topic may provide further directions to referring neurologists.

Methods

Study participants

All consecutive PD patients (UK Brain Bank Criteria) referred for DBS between January 2013 and June 2018 to two different Dutch academic DBS centers, the Leiden University Medical Center (LUMC) and the Maastricht University Medical Center (MUMC), were included in the study. Patients already under treatment at the LUMC or MUMC prior to the decision concerning DBS eligibility were excluded. All patients received a formal pre-screening, during which a neurologist experienced in DBS assesses the DBS eligibility based on an extensive patient history and neurological examination during an outpatient visit prior to any formal screening procedure.

Outcome measures

From the electronic patient files, we extracted demographic and clinical variables, as well as indications for DBS (severity of motor fluctuations or presence of refractory tremor) and contra-indications (see table 2.1), as assessed during the initial outpatient visit. At this stage, assessment of outcomes such as motor function and cognition were based on anamnestic data; patients who are selected for the formal pre-operative evaluation would receive the full screening procedures including, among others, cognitive evaluation and levodopa challenge test.

We further extracted expectations of DBS, as reported by the patient after a standardized question. Realistic expectations were defined prior to data-collection as a desire to relief a symptom that is DBS-responsive: 1. Less "OFF"-time, 2. Less dyskinesias, 3. 'Less medication', 4. Relief of therapy-refractory tremor. Unrealistic expectations were defined as a desire to relieve a symptom that is unlikely to be responsive to DBS (e.g. medication-resistant freezing or cognitive symptoms) and was unresponsive to previous adequate dopaminergic therapy exposure.[11] The reasons for rejection for DBS screening were also documented. Patients could be rejected for multiple reasons.

Statistical analysis

Demographic and clinical variables were compared between patients who were accepted and rejected for the DBS eligibility screening with independent Student's T-tests and Pearson $\chi 2$ tests.

A multivariate logistic regression model with a forced entry covariance matrix, including demographic variables, indications, and contraindications for surgery, was used to determine the odds of being accepted for DBS screening (see supplementary table 2.1). A second model

added the factor 'realistic expectations of DBS surgery' to assess its additional contribution in predicting eligibility. The predicted probabilities of both models were plotted on Receiver Operating Characteristic curves to determine the Area Under the Curve (AUC). Significance levels were confirmed using Benjamini Hochberg False Discovery Rate corrections (threshold for significance set at 0.05).

All analyses were performed using IBM Statistical Package for the Social Sciences 23 Software (SPSS Inc., Chicago, Illinois). A formal ethical evaluation of this study was waived by the local medical ethics committees.

Results

Patient characteristics

During the study period, 289 patients were referred to both centers for DBS (LUMC: n=162; MUMC: n=127). Mean (SD) age was 61.0 (8.3) years; mean (SD) disease duration was 9.4 (4.8) years. For 19 patients expectations of DBS were not documented. Further demographic variables are shown in table 2.1.

Table 2.1. Patient characteristics

	Total	Rejected	Accepted	P
N	289	76	213	
% female (n)	90 (31)	23 (30)	67 (31)	0.847
Age in years [a] (mean (SD))	61.0 (8.3)	63.4 (8.4)	60.2 (8.1)	0.003
Disease duration in years [a] (mean (SD))	9.4 (4.8)	8.5 (5.2)	9.7 (4.7)	0.066
Severity "OFF" [b]				
No "OFF"	62 (22)	27 (36)	36 (17)	
1-50% "OFF"	178 (62)	40 (53)	138 (65)	0.003
51-100% "OFF"	48 (17)	9 (12)	39 (18)	
Severity dyskinesias [b]				
No dyskinesias	87 (30)	33 (43)	54 (25)	
1-50% dyskinesias	151 (52)	33 (43)	118 (55)	0.012
51-100% dyskinesias	51 (18)	10 (13)	41 (19)	
Refractory tremor [b]	55 (19)	13 (17)	42 (2)	0.618
Balance impairment or medication-resistant freezing [b]	91 (31)	40 (53)	51 (24)	<0.001
Psychiatric side-effects of dopaminergic medication [b]	105 (36)	33 (43)	72 (34)	0.134
Anamnestic cognitive impairment [b]	97 (34)	39 (51)	58 (27)	<0.001
Sufficient control with current oral treatment or suboptimal treatment [b]	46 (16)	40 (53)	6 (3)	<0.001
Unrealistic expectations [b, c]	62 (23)	54 (67)	28 (8)	<0.001

A higher severity of "OFF", dyskinesias, and refractory tremor were considered good indications for DBS. Balance impairment or freezing during "ON", psychiatric side-effects, cognitive impairment, suboptimal treatment, and unrealistic expectations were considered relative contraindications for surgery.

[a] mean (SD)

[b] valid n (%)

[c] 19 patients missing

Expectations and reasons for undergoing DBS

Several patients reported multiple reasons / expectations. Twenty-three percent of patients (n=63) reported unrealistic expectations of DBS (figure 2.1). There were no differences among referring neurologists and centers in the percentage of referred patients with unrealistic expectations (only LUMC referrals studied).

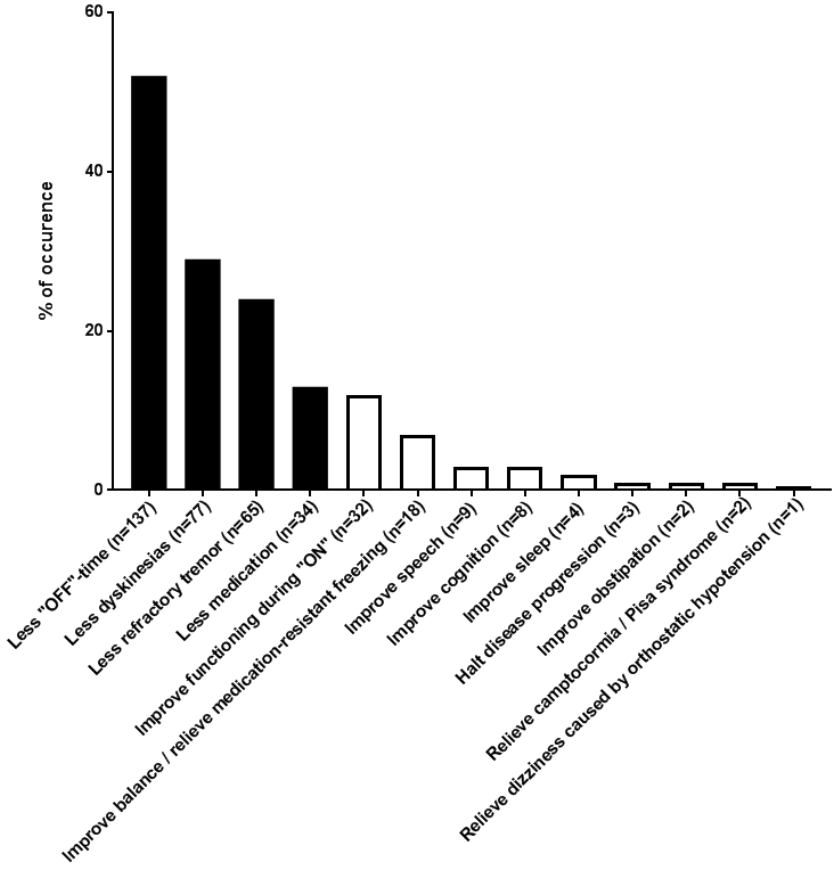

Figure 2.1. Reasons for undergoing DBS
Patient-reported reasons for undergoing DBS, classified as either realistic (black) or unrealistic (white). Data expressed as % of occurence (n). Multiple reasons were possible.

Reasons for rejection

Twenty-six percent of patients (n=76) were rejected for DBS eligibility screening (see supplementary table 2.1). The most-frequent reported reasons that contributed to rejection were sufficient control with oral dopaminergic medication or suboptimal treatment (50%, n=38), unrealistic expectations (38%, n=29), impaired balance or medication-resistant

freezing (36%, n=27), and cognitive impairment (30%, n=23).

Thirty-seven percent of rejections (n=28) were for a single reason. From these, 28% (n=21) was due to sufficient control with oral medication or suboptimal oral treatment, 4% (n=3) due to unrealistic expectations (either improvement of function during "ON", dizziness caused by orthostatic hypotension, or camptocormia), 3% (n=2) due to psychiatric comorbidity (either severe obsessive compulsive disorder prior to PD, or amphetamine-addiction), 1% (n=1) due to severe cognitive impairment, and 1% (n=1) due to medication-resistant freezing.

Contribution of DBS expectations to assessment of eligibility

Analyses were performed on pooled patient data; patients often had several indications or contraindications for surgery. The odds of acceptance for the DBS full screening were significantly reduced (after FDR correction) when balance impairment or medication-resistant freezing (OR=0.06, $p<0.001$), sufficient disease control with oral medication or suboptimal oral treatment (OR<0.01, $p<0.001$), or unrealistic expectations (OR=0.01, $p<0.001$) were present (see supplementary table 2.2). The AUC of the multivariate model without the factor 'realistic expectations of DBS' was 0.92; adding DBS-expectations to the model increased the AUC to 0.97 (see supplementary figure 2.1).

Discussion

In this study we found that the primary reason for rejection was sufficient symptom control with oral medication or suboptimal oral treatment, which contributed in 50% of rejections. Furthermore, 23% of patients referred for DBS surgery had unrealistic expectations of DBS, which was associated with rejection for the DBS screening. Our findings underscore the need to improve what referring health professionals communicate about the effect of DBS. Identification of unrealistic expectations should be an important red flag for referrals to DBS centers.

In 38% of rejections, unrealistic expectations contributed to the decision to reject, although they represented the singular reason in only 4% of rejections, indicating that unrealistic expectations often occur parallel to other contra-indications. Even when patients are good candidates for DBS on medical grounds, unrealistic expectations may result in disappointment with the results of surgery.[6-8] Clinicians should also be aware that patients might be unwilling to reveal their unrealistic expectations in order to favor the selection process, which might result in an underestimation of this issue. Although this factor is not included in current screening algorithms,[4-5] our findings show that it may contribute to better

patient-selection. Patients' needs and wishes concerning DBS-effects can easily be checked in advance and provide an opportunity for patient education and management of expectations prior to referral or screening. In clinical practice, a 'shared decision making' approach in which patients' expectations of treatment are carefully addressed is important, especially when it concerns an invasive and potentially hazardous intervention. Final eligibility is then usually determined based on both clinical grounds and the patients' preferences and desires. Lack of appropriate patient education is often the source of wrong expectations. The results of this study may indeed point to an insufficient or inadequate information procedure done by the treating neurologists. We speculate that two possible scenarios underlie this observation: 1. Patients received suboptimal information on expected outcomes of DBS by their referring neurologists, or 2. Patients received adequate information on DBS but retained unrealistic expectations nonetheless. To what degree unrealistic expectations are retained after proper patient education is unknown and persistent unrealistic desires may still cause postoperative dissatisfaction. Nevertheless, including evaluation of patients' expectations during the pre-screening appears warranted in order to rectify these expectations accordingly during the formal screening. Future studies may investigate whether improved education of both patients and referring neurologists on DBS eligibility improves referring practices, and whether extensive patient education may mitigate previously reported disappointment with DBS surgery.

It is important to notice that all factors were accurately evaluated on an individual basis by movement disorders neurologists experienced with DBS. There may be discussion on which expectations should be considered 'realistic' or 'unrealistic', as, for example, improvement of function during "ON", or improvement of camptocormia may be achieved in some patients, whereas substantial medication reduction is not always achievable.[11] A screening-procedure that is too strict or rigid may lead to withholding patients an effective treatment for at least a subset of their symptoms. Moreover, assessment of treatment-effect was based on anamnestic information rather than formal levodopa-challenge tests, which is suboptimal compared to the full screening procedure. This warrants accurate case-by-case evaluations. Indeed, some of the relative contraindications were also detected in some of the patients who were eventually selected for the full screening. Furthermore, no distinction between DBS targets such as subthalamic, pallidal or thalamic stimulation was made. The decision on DBS targets was made after the initial pre-screening based upon results of the full preoperative evaluation, including a formal levodopa challenge test, neuropsychological evaluation and MRI. For the purpose of this study, we considered improvement of all symptoms unresponsive to dopaminergic treatment (with the exception or tremor) or not directly resulting from medication-related complications to be unrealistic. Only a minority of patients were rejected for a single reason, while in most cases the reason of rejection reflected multiple features

of advanced PD, not expected to respond to DBS. The increase in accuracy of a screening-algorithm after including assessment of expectations provides a minor addition to previously reported algorithms. However, we demonstrate that the error margin of these models can be reduced by more than half and thereby constitutes a relevant addition.

With regard to suboptimal oral treatment, we speculate that patients are often referred at an earlier stage upon their own request, or as an anticipatory strategy on account of the long waiting lists. The positive results of the EARLYSTIM trial [12] may have also prompted neurologists to referring PD patients earlier, although patients without motor complications or with motor complications that can still be controlled by further optimization of medical treatment were not included in that trial. Although it has been speculated that DBS could be beneficial even in the earliest stages of the disease, DBS surgery still bears potentially serious complications, which warrants an adequate patient selection and an accurate weighing of the individual risk/benefit profile.

Strengths of our study include the multicenter design, inclusion of consecutive patients, and near-complete data. Whereas normally a retrospective design constitutes a limitation, in this case this prevented biases by providing an overview of our current clinical practice without opportunity to influence it during data-collection. However, given the retrospective design no exploration of the background of the unrealistic expectations could be performed and the effects of more extensive education on DBS eligibility cannot be estimated. Moreover, both centers reflect Dutch populations and standards of care, and our results require verification in different populations before they can be inferred on a larger scale.

We speculate that our results may contribute to improvement of the DBS referral procedure by providing practical indications for referring neurologists. We suggest incorporating assessment of DBS expectations in the screening for DBS eligibility to verify whether further patient education on the effect of DBS is required. Patients associations and neurological associations might play a role in improving information concerning DBS indications and effects among patients and their treating neurologists.

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References

1. Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol 2009;8:67-81.
2. Martinez-Ramirez D, Okun MS. Rationale and clinical pearls for primary care doctors referring patients for deep brain stimulation. Gerontology 2014;60:38-48.
3. Coleman RR, Kotagal V, Patil PG, Chou KL. Validity and Efficacy of Screening Algorithms for Assessing Deep Brain Stimulation Candidacy in Parkinson Disease. Movement disorders clinical practice 2014;1:342-347.
4. Moro E, Schupbach M, Wachter T, et al. Referring Parkinson's disease patients for deep brain stimulation: a RAND/UCLA appropriateness study. J Neurol 2016;263:112-119.
5. Okun MS, Fernandez HH, Pedraza O, et al. Development and initial validation of a screening tool for Parkinson disease surgical candidates. Neurology 2004;63:161-163.
6. Hariz M. Fulfillment of patients' expectations is the ultimate goal of deep brain stimulation for Parkinson disease. World neurosurgery 2014;82:1037-1039.
7. Agid Y, Schupbach M, Gargiulo M, et al. Neurosurgery in Parkinson's disease: the doctor is happy, the patient less so? Journal of neural transmission Supplementum 2006:409-414.
8. Hasegawa H, Samuel M, Douiri A, Ashkan K. Patients' expectations in subthalamic nucleus deep brain stimulation surgery for Parkinson disease. World neurosurgery 2014;82:1295-1299.e1292.
9. Maier F, Lewis CJ, Horstkoetter N, et al. Patients' expectations of deep brain stimulation, and subjective perceived outcome related to clinical measures in Parkinson's disease: a mixed-method approach. J Neurol Neurosurg Psychiatry 2013;84:1273-1281.
10. Reddy P, Martinez-Martin P, Brown RG, et al. Perceptions of symptoms and expectations of advanced therapy for Parkinson's disease: preliminary report of a Patient-Reported Outcome tool for Advanced Parkinson's disease (PRO-APD). Health and quality of life outcomes 2014;12:11.
11. Almeida L, Deeb W, Spears C, et al. Current Practice and the Future of Deep Brain Stimulation Therapy in Parkinson's Disease. Seminars in neurology 2017;37:205-214.
12. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 2013;368:610-622.

Supplementary material

Supplementary table 2.1. Reasons for rejection

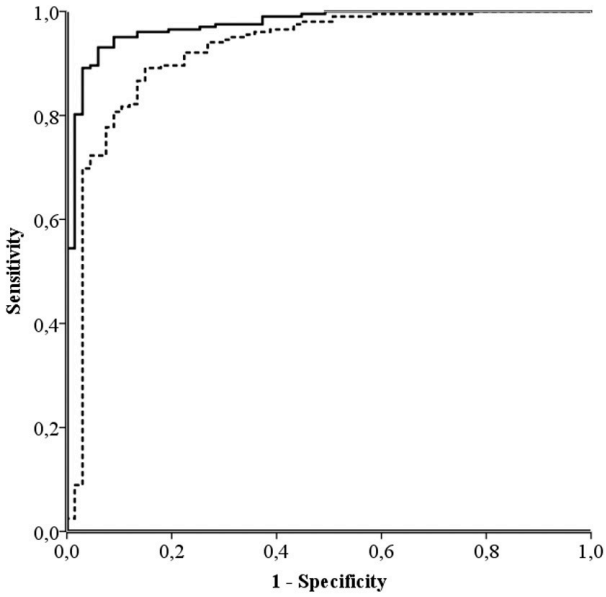
N	76
Sufficient control or suboptimal oral treatment	38 (50)
Unrealistic expectations	29 (38)
Impaired balance / freezing during on	27 (36)
Impaired cognition	23 (30)
Soft speech	14 (18)
Advanced age	10 (13)
Declined	8 (11)
Psychiatric comorbidity	7 (9)
Psychiatric side-effects	4 (5)

Data expressed as valid n (%)
Multiple reasons were possible.

Supplementary table 2.2. Likelihood of acceptance for DBS screening: multivariate analyses

	OR[a]	95%CI	P [b]	ΔR^{2} [c]	P
Age	1.02	0.95 – 1.11	0.562	0.06	0.04
Disease duration	1.13	1.01 – 1.27	0.040		
1 – 50% "OFF" [d]	0.69	0.13 – 3.57	0.656	0.13	<0.001
51 – 100% "OFF" [d]	2.71	0.35 – 20.71	0.337		
1 – 50% dyskinesias [e]	1.24	0.27 – 5.77	0.786		
51 – 100% dyskinesias [e]	3.52	0.51 – 24.38	0.202		
Refractory tremor	0.88	0.16 - 4.49	0.881		
Balance impairment / freezing during "ON"	0.06	0.02 – 0.28	<0.001	0.44	<0.001
Nonmotor side-effects	0.41	0.13 – 1.34	0.140		
Cognitive impairment	0.25	0.07 – 0.87	0.029		
Further treatment options possible	0.00	0.00 – 0.01	<0.001		
Unrealistic expectations	0.01	0.00 – 0.04	<0.001	0.17	<0.001

[a] OR to be accepted for screening
[b] Bold values indicate that significance remained after False Discovery Rate correction
[c] Nagelkerkes R^{2}, [d] significance of ΔR^{2}
[d] Relative to 'no "OFF"-time'
[e] Relative to 'no dyskinesias'
OR: Odds Ratio; 95%CI: 95% Confidence Intervals



Supplementary figure 2.1. Inclusion of DBS-expectations increases the accuracy of predicting the likelihood of acceptance for DBS screening

Dashed line: AUC model without 'realistic expectations': 0.92 (95%CI 0.88 – 0.97). Continuous line: AUC model including 'realistic expectations': 0.97 (95%CI 0.96 – 0.99). AUC: Area Under the Curve.