Is improvement in the quality of life after subthalamic nucleus stimulation in Parkinson's disease predictable?

Daniels, Christine; Krack, Paul; Volkmann, Jens; Raethjen, Jan; Pinsker, Marcus; Kloss, Manja; Tronnier, Volker; Schnitzler, Alfons; Wojtecki, Lars; Botzel, Kai; Danek, Adrian; Hilker, Rudiger; Sturm, Volker; Kupsch, Andreas [**and 3 more**]

How to cite

DANIELS, Christine et al. Is improvement in the quality of life after subthalamic nucleus stimulation in Parkinson's disease predictable? In: Movement disorders, 2011, vol. 26, n° 14, p. 2516–2521. doi: 10.1002/mds.23907

This publication URL: https://archive-ouverte.unige.ch//unige:95924

Publication DOI: 10.1002/mds.23907

RESEARCH ARTICLE

Is Improvement in the Quality of Life After Subthalamic Nucleus Stimulation in Parkinson's Disease Predictable?

Christine Daniels, MD,[1] Paul Krack, MD, PhD,[1] Jens Volkmann, MD, PhD,[1] Jan Raethjen, MD, PhD,[1] Markus O. Pinsker, MD, PhD,[2] Manja Kloss, MD,[3] Volker Tronnier, MD, PhD,[4] Alfons Schnitzler, MD, PhD,[5] Lars Wojtecki, MD,[5] Kai Bötzel, MD, PhD,[6] Adrian Danek, MD, PhD,[6] Rüdiger Hilker, MD, PhD,[7] Volker Sturm, MD, PhD,[8] Andreas Kupsch, MD, PhD,[9] Elfriede Karner, MPsych,[10] Günther Deuschl, MD, PhD,[1] and Karsten Witt, MD, PhD[1]*

[1]*Department of Neurology, Christian-Albrechts-University, Kiel, Germany*
[2]*Department of Neurosurgery, Christian-Albrechts-University, Kiel, Germany*
[3]*Department of Neurology, Heidelberg University, Heidelberg, Germany*
[4]*Department of Neurosurgery, Heidelberg University, Heidelberg, Germany*
[5]*Department of Neurology, Heinrich Heine University, Dusseldorf, Germany*
[6]*Department of Neurology, Ludwig-Maximilians-University, Munich, Germany*
[7]*Department of Neurology, Cologne University, Cologne, Germany*
[8]*Department of Neurosurgery, Cologne University, Cologne, Germany*
[9]*Department of Neurology, Charité Hospital, Humboldt University, Berlin, Germany*
[10]*Department of Neurology, Innsbruck Medical University, Innsbruck, Austria*

ABSTRACT: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) significantly improves quality of life (QoL) in PD. However, QoL fails to improve in a relevant proportion of patients. We studied clinical baseline and progression parameters associated with improvement in QoL after DBS. Data from a German randomized, controlled study comparing DBS (60 patients) with best medical treatment (59 patients) were analyzed. Changes in patients' QoL were assessed using the Parkinson's Disease Questionnaire (PDQ-39) at baseline and at the 6-month follow-up. For the STN-DBS patients, the changes in PDQ-39 were correlated with predefined clinical preoperative and progression parameters. Scores for QoL improved after STN-DBS for 57% of the patients, and for 43% patients, they did not improve. Patients with improvement in QoL showed significantly higher cumulative daily "off" time. Changes in the PDQ-39 showed a significant positive correlation with the cumulative daily off time at baseline. Logistic regression analysis revealed that 1 additional hour off time at baseline increases the odds for improvement on PDQ-39 by a factor of 1.33 (odds ratio). In the postoperative course, changes in the PDQ-39 significantly correlated with the reduction of cumulative daily off time, an improvement on the UPDRS (UPDRS III off), and positive mood changes. Among the baseline parameters, the cumulative daily off time is the strongest predictor for improvement in disease-related QoL after DBS. Improvement in QoL after STN-DBS is also correlated with changes in motor functions and changes in depression and anxiety.

Key Words: Parkinson's disease; deep brain stimulation; quality of life

***Correspondence to:** Dr. Karsten Witt, Department of Neurology, University of Schleswig-Holstein, Campus Kiel, Schittenhelmstrasse 10, D-24105 Kiel, Germany; k.witt@neurologie.uni-kiel.de

Funding agencies: This study was supported by the Parkinson Foundation Europe and the German Ministry of Research and Technology (01GI0201) Kompetenznetz Parkinson, TP3.
Relevant conflicts of interest/financial disclosures: Drs. Bötzel, Deuschl, Krack, Krause, Kupsch, Pinsker, Schnitzler, Sturm, Tronnier, Volkmann, and Wojtecki report having received speaking fees from Medtronic; Drs. Deuschl, Tronnier, Volkmann, and Wojtecki report having received consulting fees from Medtronic; Drs. Deuschl, Kupsch, Krause, Krack, and Volkmann report having received research grants from Medtronic; and Dr. Sturm reports owning stock options from Medtronic. No other potential conflict of interest relevant to this article was reported.
Full financial disclosures and author roles may be found in the online version of this article.

Received: 26 February 2010; **Revised:** 23 June 2011; **Accepted:** 15 July 2011
Published online 25 August 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23907

The beneficial effect of bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) on motor symptoms and on quality of life (QoL) in advanced PD has been shown by randomized, controlled studies.[1,2] QoL significantly improves in the majority of patients after STN-DBS, but not in all.[3] The reasons for this may be multidimensional, but their identification seems to be important for optimized treatment results. STN-DBS mainly improves motor functions, but nonmotor functions, such as anxiety, depression,[4] bladder function,[5] and ''off''-period–associated pain,[6] are also improved. QoL depends strongly on a lack of nonmotor symptoms of PD, such as depression and cognitive impairment, and is influenced by motor symptoms, such as the signs and symptoms of postural disability, gait abnormalities, freezing, unpredictable ''on-off'' fluctuations, dyskinesias, and falls.[7] In the present study, we evaluated motor and nonmotor baseline parameters that can predict the benefit of STN-DBS for QoL. Moreover, we studied the changes in motor and nonmotor symptoms responsible for changes in QoL after STN-DBS. Clinical data of 121 patients from a randomized, controlled study were analyzed.[1] Patients undergoing DBS for advanced PD were investigated in a prospective, multicenter trial over 6 months to evaluate postoperative changes in motor functions, cognition, psychiatric symptoms, and QoL.

Patients and Methods

Patients and Study Design

Our study included 121 patients from a randomized trial of DBS for PD.[1] Complete data for all PDQ-39 parameters were compiled for all patients (apart from item 28, which was not filled out by some patients who were single and did not answer the question concerning their partners). We randomized 60 PD patients into a control group that received best medical treatment (BMT) for 6 months. The other 61 patients in the study received DBS surgery within 6 weeks after enrollment and completed the study per protocol. Inclusion criteria for the trial were a clinical diagnosis of idiopathic PD for at least 5 years, age younger than 75 years, and PD motor symptoms or dyskinesias that limited the patient's daily activities, despite optimal medical therapy.[1] Exclusion criteria were dementia (Mattis dementia rating scale [MDRS]; sum score, $\leq$130), a major psychiatric illness, or surgical contraindications. The study protocol and peri- and postoperative procedures have been reported in detail elsewhere.[1,4] The study protocol was approved by the ethics committee at each participating centere, and all patients gave written informed consent. All clinical assessments (except the UPDRS III off assessment and the levodopa [L-dopa]-challenge test) were performed under medication on at baseline and after 6 months with neurostimulation on and medication on.

Clinical Evaluation/Data Analysis/Statistics

QoL was assessed by the disease-specific Parkinson's Disease Questionnaire (PDQ-39)[8] and the generic SF-36 questionnaire.[9] Outcome parameters were the PDQ-39 summary index (SI) and the physical (PCS) and mental health composite scores (MCS) of the Short-Form Health Survey (SF-36). In each group, 1 outlier was excluded, so 60 patients from the STN-DBS group and 59 patients from the BMT group were included in the following analyses. The differences between the follow-up 6 months after STN-DBS (x_2) and baseline scores collected immediately before the electrode implantation (x_1) were calculated for each outcome parameter (x_2–x_1). For the disease-specific PDQ-39, the Reliable Change Index (RCI) was computed by multiplying the standard error of the difference (standard deviation of test distribution at baseline multiplied by the square root of 2-2r with r = retest-reliability of the test instrument; r = 0.9) by 1.65, which gave the RCI for a critical change threshold with a *P* value of 5% (one tailed). This threshold was considered to be indicative of a change in QoL and was used for splitting the patient sample into two groups of ''improved'' or ''non-improved.''[10] The STN-DBS group was compared with the BMT group, regarding the number of patients whose QoL scores improved or did not improve based on RCI criteria applied to the PDQ-39, using a chi-squared test.

Changes in QoL scores were correlated with the following baseline parameters: age, disease duration, baseline MDRS total score, baseline psychiatric scores (Beck Depression Inventory [BDI], Beck Anxiety Inventory [BAI], Montgomery-Asberg Depression Rating Scale [MADRS]), baseline motor scores (UPDRS III total score on/off, cumulative daily off-time, and UPDRS VI dyskinesia score on), L-dopa equivalence dosage (LED) at baseline, and an L-dopa challenge test (% effect) at baseline (Spearman's correlation).

Further, baseline characteristics were compared between the improved and nonimproved groups in terms of PDQ-39 using the Mann-Whitney U-test. *P* values <0.05 (two-tailed) were regarded as significant. We did not correct the level of significance for multiple correlations/comparisons because of the exploratory character of this analysis with multiple hypotheses. To evaluate changed motor and nonmotor parameters associated with improvement in QoL, we correlated changes in QoL scores with changes (x_2–x_1) in the following parameters: MDRS total score, psychiatric scores (BDI, BAI, and MADRS), motor scores (UPDRS III total score off, cumulative daily off-time, and UPDRS VI dyskinesia score on), and LED (Spearman's correlation). *P* values <0.05 (two tailed) were regarded as significant. In a second step, baseline parameters and

TABLE 1. Mean Scores (SD) At Baseline and Mean Change Scores (SD) of the PDQ-39 Summary Index (PDQ-39 SI) and the Physical/Mental Composite Scores of the SF-36 (SF-36 PCS/ SF-36 MCS)

	STN Baseline	STN Change	BMT Baseline	BMT Change
PDQ-39 SI	41.1 (13.8)	−11.8 (11.9)	39.9 (15.8)	−0.2 (9.0)
SF-36 PCS	30.3 (7.9)	6.8 (7.9)	30.7 (8.1)	0.2 (6.4)
SF 36 MCS	41.7 (10.4)	4.1 (11.5)	41.2 (10.0)	0.0 (8.5)

Abbreviations: standard deviation; PDQ-39, Parkinson's Disease Questionnaire; SF-36, Short-Form Health Survey; PCS, physical health composite score; MCS, mental health composite score; STN, subthalamic nucleus; BMT, best medical treatment.

the changes in scores that had an impact on changes in QoL, as revealed by the first-step analyses (less strictly selected: $p \leq 0.10$, one tailed), were included in a logistic regression analysis as independent variables with the dichotomous variable improved/nonimproved corresponding to the changes in the PDQ-39 as the dependent variable. Statistical analysis was performed using the SPSS 17 software package (SPSS, Inc., Chicago, IL).

Results

Mean scores at baseline and mean change scores of QoL scales of the STN-DBS goup and the BMT group are given in Table 1. RCI analysis showed a threshold of 10.9 points for the PDQ-39, indicative of a change in QoL. According to this RCI analysis of the PDQ-39, 57% (35 of 60 STN-DBS patients) showed improvement in QoL values 6 months after STN-DBS. For 43% (25 of 60 STN-DBS patients), an unchanged or worse PDQ-39 total score, as compared with the baseline, was evident, indicating no benefit of STN-DBS on QoL. In the BMT group, QoL scores improved in 7% (4 of 59 patients) and did not improve in 93% (55 of 59 patients). The number of improvers, based on the RCI criteria, was higher in the STN-DBS group, compared with the BMT group (χ^2, 35.6; $P < 0.000$, two tailed) (Fig. 1).

Splitting patients into improvers and nonimprovers in regard to PDQ-39 summary score after STN-DBS, as assessed by the RCI analysis, the Mann-Whitney U test revealed that improvers had longer cumulative daily off-time (mean, 6.9 hours; SD 3.4 for improvers versus mean 4.3 hours, SD 2.5 for nonimprovers).

The PDQ-39 change score also was significantly correlated with the cumulative daily off time. Higher scores are associated with greater improvement on the PDQ-39 (Table 2). The changes in PCS are negatively correlated with the UPDRS dyskinesia score on at baseline, so fewer dyskinesia are associated with greater QoL improvement. Among the progression parameters, a change in the BAI, BDI, MADRS, UPDRS III off, and the cumulative daily off time each significantly correlated with a change in Qol (improvement of psychiatric scales and improvement of motor function are associated with improvement of QoL). Changes in QoL were negatively correlated with changes in UPDRS VI, so a reduction of dyskinesias after STN-DBS worsens QoL (Table 3).

In a logistic regression analysis with the dichotomous variable improved/nonimproved corresponding to the RCI for the PDQ-39, the cumulative daily off time at baseline was accepted as the explanatory variable in the model (odds ratio [OR], 1.33; confidence interval [CI], 1.06–1.67 [1 additional hour of off time at baseline increases the odds for improvement on PDQ-39 by the factor of 1.33]). Among the change scores for the PDQ-39, the change in the BDI and the change in the dyskinesia score were accepted (BDI: OR, 1.27; CI, 1.07–1.51; change in dyskinesias: OR, 0.77; CI, 0.62–0.96 [1 additional point of improvement in the BDI score increases the odds of QoL improvement by the factor of ∼1.3; 1 additional point of improvement in the dyskinesia score decreases the odds of QoL improvement by the factor of ∼0.8]).

Discussion

Most of the PD patients' QoL scores improved considerably after STN-DBS.[1,2,11,12] We found that the disease-specific PDQ-39 identified no improvement in QoL for 43% of our patients. Smeding et al. reported a relevant lower rate of patients (21%) whose scores did not improve on the PDQ-39 after STN-DBS.[3] The different rates resulting from the studies can most likely be explained by the different definitions for improvement (or lack of improvement) in QoL. Moreover, results depend on the test instruments used for the measurement

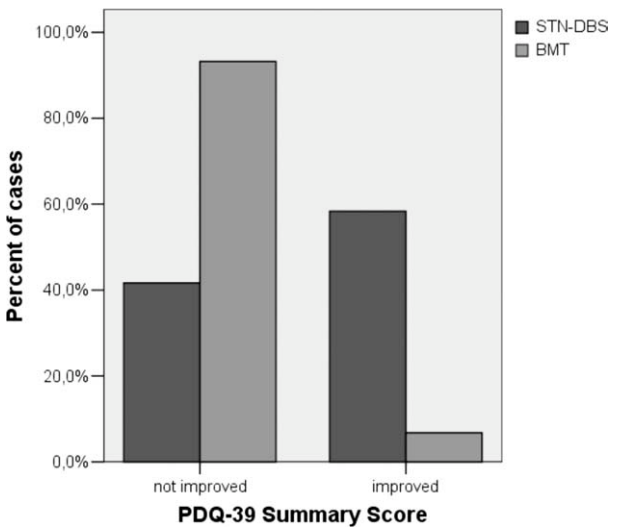

FIG. 1. For the PDQ-39 summary score, improvers and nonimprovers are shown in percent of cases of the STN-DBS group (blue) and the BMT group (grey). Groups differed significantly ($P < 0.001$, two tailed).

TABLE 2. Spearman Correlations of Changes in QoL With Baseline Parameters

	Value at Baseline (SD)	Changes in PDQ-39 Summary Index	Changes in SF-36 Physical Composite Score (PCS)	Changes in SF-36 Mental Composite Score (MCS)
Age (years)	59.7 (7.2)	r = −0.226†	r = −0.153	r = −0.153
		P = 0.083	P = 0.283	P = 0.284
Disease duration (years)	13.0 (6.2)	r = −0.108	r = −0.010	r = −0.024
		P = 0.423	P = 0.948	P = 0.874
MDRS total score	139.7 (3.6)	r = 0.117	r = 0.083	r = 0.036
		P = 0.372	P = 0.564	P = 0.803
BDI summary score	11.5 (5.7)	r = 0.234†	r = 0.066	r = 0.232
		P = 0.075	P = 0.651	P = 0.104
BAI summary score	23.1 (11.4)	r = −0.009	r = −0.247	r = 0.245
		P = 0.949	P = 0.094	P = 0.097
MADRS	8.6 (5.3)	r = 0.068	r = −0.064	r = 0.240
		P = 0.606	P = 0.653	P = 0.090
UPDRS III total score (on)	18.8 (9.2)	r = 0.209†	r = 0.099	r = 0.172
		P = 0.109	P = 0.487	P = 0.227
UPDRS III total score (off)	47.7 (13.2)	r = 0.193†	r = −0.163	r = 0.170
		P = 0.143	P = 0.259	P = 0.239
Cumulative daily off-time	5.7 (3.3)	r = 0.372*,†	r = −0.254	r = 0.131
		P = 0.012	P = 0.114	P = 0.421
UPDRS VI dyskinesia score (on)	6.7 (5.4)	r = −0.213†	r = −0.349*	r = −0.241
		P = 0.102	P = 0.012	P = 0.088
L-dopa equivalence dosage (LED, mg)	1232.3 (536.6)	r = 0.017	r = −0.184	r = −0.034
		P = 0.895	P = 0.197	P = 0.815
L-dopa challenge test (% effect)	61.3 (14.2)	r = 0.201†	r = 0.251	r = 0.160
		P = 0.126	P = 0.078	P = 0.267

*P values $\leq$0.05 (two-tailed) were regarded as significant.
†For the logistic regression analysis, baseline parameters were less strictly selected with $P \leq 0.10$ (one tailed).
Abbreviations: QoL, quality of life; SD, standard deviation; PDQ-39, Parkinson's Disease Questionnaire; SF-36, Short-Form Health Survey; MDRS, Mattis Dementia Rating Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; MADRS, Montgomery-Asberg Depression Rating Scale; LED, L-dopa equivalence dosage.

of QoL. The PDQ-39 has a focus on disease-specific factors that influence QoL, whereas the SF-36 is a generic questionnaire with emphasis on assessing physical and mental domains. With our definition of improvement, QoL improved in only 7% of the BMT group, which corresponds to a significantly lower number, compared with the DBS group. Using the RCI analysis, we chose a more conservative method to detect change in QoL after STN-DBS, because previous studies report a lower threshold for a clinically important difference in QoL.

TABLE 3. Spearman Correlation of Changes in QoL With Change Scores of Progression Parameters

	Mean Change (SD)	Changes in PDQ-39 Summary Index	Changes in SF-36 Physical Composite Score (PCS)	Changes in SF-36 mental composite score (MCS)
MDRS total change score	1.7 (4.7)	r = −0.002	r = −0.028	r = 0.057
		P = 0.990	P = 0.844	P = 0.691
BDI change score	1.9 (6.6)	r = 0.397*,†	r = 0.202	r = 0.372*
		P = 0.002	P = 0.164	P = 0.009
BAI change score	11.0 (10.6)	r = 0.313*,†	r = 0.022	r = 0.313*
		P = 0.029	P = 0.887	P = 0.041
MADRS change score	1.0 (6.7)	r = 0.327*,†	r = 0.241	r = 0.340*
		P = 0.014	P = 0.095	P = 0.017
UPDRS III off change score	21.4 (14.2)	r = 0.285*,†	r = 0.351*	r = 0.074
		P = 0.029	P = 0.012	P = 0.612
Change in cumulative daily off time	4.8 (3.5)	r = 0.370*,†	r = −0.187	r = −0.094
		P = 0.037	P = 0.323	P = 0.620
Change in UPDRS VI dyskinesia score on	3.7 (4.4)	r = −0.222†	r = −0.283*	r = −0.362*
		P = 0.090	P = 0.047	P = 0.015
Change in LED	639.6 (550.0)	r = −0.064	r = −0.150	r = 0.016
		P = 0.632	P = 0.298	P = 0.914

*P values $\leq$0.05 (two tailed) were regarded as significant.
†For the logistic regression analysis, baseline parameters were less strictly selected with $P \leq 0.10$ (one tailed).
Abbreviations: SD, standard deviation; PDQ-39, Parkinson's Disease Questionnaire; SF-36, Short-Form Health Survey; MDRS, Mattis Dementia Rating Scale; BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; MADRS, Montgomery-Asberg Depression Rating Scale; LED, L-dopa equivalence dosage.

Improvement in QoL after STN-DBS is influenced by the factors of motor functioning (cumulative off time, UPDRS III on/off, UPDRS dyskinesia score on). The cumulative daily off time proved to be the strongest, most important predictor. This is plausible, because it was assessed by using the PDQ-39, which has the advantages of a tool for disease-specific measurement. The change in QoL after STN-DBS is not only correlated with cumulative daily off time values at baseline, but also with its change 6 months after STN-DBS. Moreover, the high impact of the daily off time, which is regarded to be one of the most relevant parameters of motor functioning in advanced PD, is supported by an OR of 1.3 in the logistic regression analysis for the dichotomy improved/nonimproved. In the motor domain, changes in the UPDRS III score in the off state were significant and positively correlated with QoL changes after STN-DBS. Together with the predictor cumulative daily off state, these values might indicate that among improvers, preoperative motor functions cannot be restored by medication in an optimal way. STN-DBS quantitatively mimics the effect of L-dopa, so the best predictor of changes in motor function after STN-DBS is the efficiency of a preoperative L-dopa test.[14] The efficiency of an L-dopa test at baseline in our study only shows a tendency to a positive correlation with changes in QoL, but is the strongest predictor for improvement in QoL in the study by Smeding et al.[3] In conclusion, the cluster of predictors in the motor domain characterize a patient as an improver when good L-dopa response is present, but motor symptoms are not sufficiently controlled by medication, expressed in a high cumulative off-time over the day.

Changes in PCS score showed a significantly negative correlation with the dyskinesia scores in the on state, indicating that lower dyskinesia scores at baseline are associated with greater improvement in QoL. Further, both subscores of the SF-36 showed a significantly negative correlation between the change in dyskinesias and the improvement of QoL (less improvement in dyskinesias after STN-DBS is associated with greater QoL improvement). This result is surprising and contrary to our hypothesis that patients with strong dyskinesias in the on state should experience a marked benefit in QoL through DBS. One reason might be that higher dyskinesia scores reflect an advanced stage of disease progression, making it much harder to see improvement in QoL after STN-DBS in these patients. Another reason points to the fact that patients with peak-dose dyskinesias often report nonmotor fluctuations during on periods, and in these periods, patients can experience an elevated mood that is associated with alertness and euphoria.[15] These patients might overrate their QoL in the on periods, a phenomenon that disappears after reducing medication after STN-DBS. These data also might indicate that patients with a fast postoperative reduction of L-dopa (that reduces dyskinesias) have a lack of QoL improvement because of the lack of its psychotropic effects. However, a change in L-dopa equivalence dosage is not a significant predictor for an improvement in QoL.

Changes in the psychiatric scales (BAI, BDI, and MADRS) also correlated with changes in both PDQ-39 and MCS. Nonmotor symptoms may contribute to QoL improvement, as symptoms of depression in PD account for 40% to 60% of the variability in QoL.[7] This strong connection between QoL and depression is also reflected in the present study, where the two change values of depression and the change of the anxiety scale were significantly correlated.

As indicated, our study only showed one important baseline parameter that predicts improvement in QoL after STN-DBS. Despite the large number of very homogeneously investigated patients, our cohort may not be large enough to detect small effects. If they exist, their clinical significance may be questionable. We included a lot of clinical baseline and progression parameters in our analysis. Nevertheless, there might be additional individual factors, such as subtle personality traits, social networks, family background, and job-related issues, but, possibly, also subtle differences in electrode location that were not investigated in the present study and yet might be relevant for improvement in QoL after STN-DBS. Additionally, the exact time course of changes in QoL after STN-DBS is not known, and the time interval of 6 months might be too short to find predictors. Further studies are needed to assess the time course of changes in QoL after STN-DBS. ■

Acknowledgments: We thank Carmen Schade-Brittinger and the Koordinationszentrum für Klinische Studien, Marburg, for data management. The study is registered at clinicaltrials.gov (identifier: NCT00196911).

References

1. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N Engl J Med 2006;355:896–908.
2. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. Jama 2009;301:63–73.
3. Smeding HM, Speelman JD, Huizenga HM, Schuurman PR, Schmand B. Predictors of cognitive and psychosocial outcome after STN DBS in Parkinson disease. J Neurol Neurosurg Psychiatry 2011;82:754–760.
4. Witt K, Daniels C, Reiff J, et al. Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomised, multicentre study. Lancet Neurol 2008;7:605–614.
5. Herzog J, Weiss PH, Assmus A, et al. Subthalamic stimulation modulates cortical control of urinary bladder in Parkinson's disease. Brain 2006;129:3366–3375.
6. Witjas T, Kaphan E, Regis J, et al. Effects of chronic subthalamic stimulation on nonmotor fluctuations in Parkinson's disease. Mov Disord 2007;22:1729–1734.
7. Schrag A. Quality of life and depression in Parkinson's disease. J Neurol Sci 2006;248:151–157.
8. Berger K, Broll S, Winkelmann J. Reliability analysis of the German translation of the PDQ-39: A questionnaire to measure health-related quality of life in Parkinson patients. Akt Neurol 1999;26(26):180–184.

9. Bullinger M, Kirchberger I. SF-36, Manual of the Health Survey 36. Göttingen, Germany: Hogrefe; 1998.

10. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol 1991;59:12–19.

11. Ferrara JM, Diamond A, Hunter C, Davidson A, Almaguer M, Jankovic J. Impact of STN-DBS on life and health satisfaction in patients with parkinson disease. J Neurol Neurosurg Psychiatry 2010;81:315–319.

12. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349: 1925–1934.

13. Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the Unified Parkinson's Disease Rating Scale. Arch Neurol 2010;67: 64–70.

14. Volkmann J, Allert N, Voges J, Weiss PH, Freund HJ, Sturm V. Safety and efficacy of pallidal or subthalamic nucleus stimulation in advanced PD. Neurology 2001;56:548–551.

15. Nissenbaum H, Quinn NP, Brown RG, Toone B, Gotham AM, Marsden CD. Mood swings associated with the 'on-off' phenomenon in Parkinson's disease. Psychol Med 1987;17:899–904.