Deep Brain Stimulation in Parkinson's Disease – Impact on Quality of Life

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Abstract

Health-related quality of life (HRQoL) is reduced in Parkinson's disease patients. Deep brain stimulation (DBS) is an established treatment for motor problems and motor fluctuations in advanced Parkinson's disease. Three randomised trials were recently conducted to assess the effects of DBS on HRQoL. All studies found improvements in HRQoL after surgery. DBS of the subthalamic nucleus and the globus pallidus interna improved HRQoL to a similar degree. However, in the long-term, such improvements may not be maintained, perhaps because HRQoL is a subjective measure and subjective perceptions of disability may change over time. DBS has proven long-term efficacy on motor symptoms, and the decline in benefit over time may also be explained by progression in the non-motor symptoms of the disease. Several predictors of HRQoL improvements after DBS have been identified, including good levodopa response, young age and good cognitive function.

Keywords

Parkinson's disease, continuous dopaminergic stimulation, deep brain stimulation, health-related quality of life, motor fluctuations

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Health-related Quality of Life in Parkinson's Disease

In general, measures of Parkinson's disease (PD) symptoms, biomedical markers or survival do not cover every aspect of the disease relevant or important to the patient. Health-related quality of life (HRQoL) is defined as the perception and evaluation by the patient of the impact that the illness and its consequences has had on their life. Therefore, it is a subjective measurement, but one that helps in providing a more rounded picture of the effects of a disease on the patient. Several forms and questionnaires have been developed to measure HRQoL, including generic forms such as the Short-Form 36 Health Survey (SF-36), and disease-specific forms such as the 39-item Parkinson's Disease Questionnaire (PDQ-39).

HRQoL is reduced in PD patients. In a study that measured HRQoL using the Nottingham Health Profile in 233 PD patients and 100 healthy elderly people, PD patients had lower HRQoL in all measured dimensions (emotional reactions, energy, pain, physical mobility, sleep, social isolation and total score of the Nottingham Health Profile) compared with the healthy elderly people.[1]

Many factors in PD could impact on HRQoL, such as motor symptoms, non-motor symptoms (NMS), disability, social functioning limitations and drug side-effects. A study showed that a decline in physical mobility was the most important single factor contributing to worsening HRQoL in people with PD during long-term follow-up.[2] It also showed that a deterioration in NMS, when taken together, had a greater impact on overall HRQoL than a decrease in physical mobility. In addition, poor HRQoL was predicted by more advanced disease, greater severity of depressive symptoms and presence of insomnia.

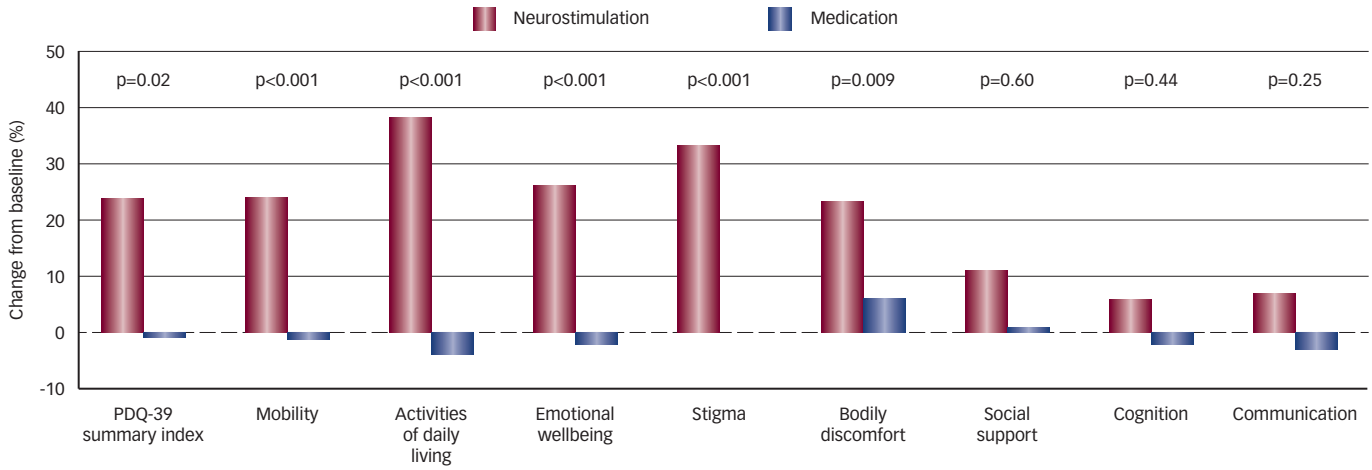
Changes in Health-related Quality of Life after Deep Brain Stimulation

Thousands of patients have been treated with deep brain stimulation (DBS) since the first procedure in 1993, and clinical results on motor symptoms and motor complications have been reported in a large number of publications.[3] In the last few years, there have been three randomised studies that used measurements of HRQoL as important endpoints.[4–6]

One of these trials conducted pairwise comparison of subthalamic nucleus DBS (STN-DBS) plus medication (n=78) and medication alone (n=78).[4] The primary endpoints were the changes from baseline to six months in HRQoL, as assessed by PDQ-39, and the severity of symptoms without medication, as assessed by the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III). Only the STN-DBS group showed significant improvements, which were in five of the eight PDQ-39 domains (see *Figure 1*). The domains that did not improve significantly with STN-DBS were social support, cognition and communication.

Another randomised controlled trial compared DBS (STN-DBS, n=60; globus pallidus interna DBS [GPi-DBS], n=61) and best medical therapy

Figure 1: Changes in 39-item Parkinson's Disease Questionnaire Subscores from Baseline to Six Months in Patients Treated with Subthalamic Nucleus Deep Brain Stimulation plus Medical Therapies or Medical Therapies Alone



PDQ-39 = 39-item Parkinson's Disease Questionnaire. Source: Adapted from The New England Journal of Medicine*, G Deuschl, C Schade-Brittinger, P Krack, et al., A randomized trial of deep-brain stimulation for Parkinson's disease, 355, 896–908.*[4] *Copyright © 2006 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.*

Table 1: Change in Quality of Life from Baseline to 24 Months, as Assessed by the 39-item Parkinson's Disease Questionnaire, in Patients Treated with Pallidal Deep Brain Stimulation or Subthalamic Deep Brain Stimulation

Outcome	Pallidal Stimulation (n=152)		Subthalamic Stimulation (n=147)		Pallidal versus Subthalamic Stimulation	
Quality of Life	Baseline	24 Months	Baseline	24 Months	Difference (95 % CI)	p value†
Score on 39-item Parkinson's Disease Questionnaire (range 0–100)‡:						
• Mobility	57.0 ± 22.3	46.6 ± 25.3	61.6 ± 20.6	54.0 ± 24.5	-2.3 (-7.6 to 3.1)	0.40
• Activities of daily living	55.0 ± 18.6	41.4 ± 20.7	55.7 ± 18.1	46.6 ± 23.7	-4.4 (-9.3 to 0.5)	0.08
• Emotional wellbeing	36.5 ± 18.9	33.4 ± 19.1	41.1 ± 18.6	39.1 ± 21.1	-1.2 (-5.6 to 3.2)	0.58
• Stigma	38.7 ± 25.3	28.2 ± 22.4	42.1 ± 24.6	30.7 ± 25.3	1.0 (-4.5 to 6.4)	0.73
• Social support	23.8 ± 17.2	26.0 ± 18.6	30.1 ± 19.3	29.4 ± 20.1	3.1 (-1.2 to 7.4)	0.16
• Cognition	39.8 ± 16.7	38.9 ± 18.4	44.1 ± 17.0	43.5 ± 19.3	-0.4 (-4.2 to 3.5)	0.85
• Communication	44.7 ± 19.5	48.5 ± 20.5	47.8 ± 18.6	53.1 ± 22.1	-1.5 (-6.3 to 3.3)	0.54
• Bodily discomfort	48.1 ± 21.1	40.5 ± 21.8	52.8 ± 23.4	46.3 ± 24.0	-1.0 (-5.6 to 3.5)	0.65
• Single index	42.8 ± 13.6	38.0 ± 15.3	46.9 ± 12.6	42.7 ± 15.6	-0.6 (-3.6 to 2.4)	0.69

CI = confidence interval. ‡A higher score indicates worse functioning. †p values are for changes in scores from baseline to 24 months in the group undergoing pallidal stimulation compared with those undergoing subthalamic stimulation. Source: Adapted from The New England Journal of Medicine*, KA Follett, FM Weaver, M Stern, et al., Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease, 362, 2077–91.*[5] *Copyright © 2010 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.*

(n=134).[7] Patients were monitored for six months and HRQoL was assessed by PDQ-39. Compared with the best medical therapy group, the DBS group showed significant improvements in the summary measure of HRQoL and in seven of eight PD HRQoL subscores (p<0.001). The social support subscore did not change significantly with either intervention: mean change from baseline to six months for DBS and best medical therapy were -1.7 (95 % confidence interval [CI] -5.1 to 1.7) and 1.5 (95 % CI -1.7 to 4.6), respectively. After completion of six months of medical therapy, the patients proceeded to DBS, with an additional 61 patients assigned directly to DBS after randomisation to medical therapy was closed. Hence, a total of 299 patients underwent randomisation to STN-DBS (n=147) or GPi-DBS (n=152).[5] The patients were monitored for 24 months. The results showed improvements in six of the eight subscales of the PDQ-39 in both groups (see *Table 1*). There was no significant difference between the two surgical therapies for any of the items.

In a third randomised study, the PD SURG trial, 366 patients with PD that was not adequately controlled by medical therapy received immediate surgery (DBS) and best medical therapy (n=183), or best medical therapy alone (n=183).[6] The trial showed that the mean improvement in the PDQ-39 summary index score at one year compared with baseline was significantly higher in the surgery group (5.0 points) than in the medical therapy group (0.3 points) (difference -4.7, 95% CI -7.6 to -1.8; p=0.001).

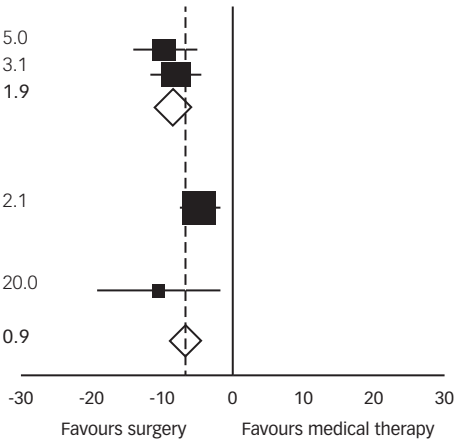
The three randomised trials found similar effects of DBS on HRQoL (see *Figure 2*). The greatest effect was shown in the Deuschl et al.[4] study, which also demonstrated the largest effect of DBS on motor function. This suggests that more effective surgery may lead to greater improvement in HRQoL.

Long-term Data

We have recently assessed the long-term effects of STN-DBS on motor function and mortality in a retrospective study of 144 patients with advanced Parkinson's disease (APD).[8] Off-medication UPDRS-III motor score was improved by a mean of 53 % 12 months after surgery (see *Figure 3*). The subsequent mean annual increase was 3.2 points, most likely caused by natural disease progression. In addition, the daily dose of dopaminergic medication was reduced by a mean of 49 % and increased only marginally in the first five years after surgery. Survival was 97 % three years after initiation of DBS therapy and 90 % after five years. This study demonstrates that DBS has a stable long-term effect on motor function, which may have a positive impact on patients' HRQoL in the long-term.

Figure 2: Meta-analysis of 39-item Parkinson's Disease Questionnaire Summary Index Score in Trials of Deep Brain Stimulation versus Medical Therapy

	Change from Baseline				Difference	Variance	Difference (95 % CI)
	Surgery		Medical Therapy				
	Number	Mean (SD)	Number	Mean (SD)			
6 months							
Deuschl and colleagues[4]	71	-9.5 (1.8)	73	0.2 (1.3)	-9.7	5.0	-14.1 to -5.3
Weaver and colleagues[7]	121	-7.7 (1.3)	134	0.4 (1.1)	-8.1	3.1	-11.6 to -4.6
Subtotal	192		207		-8.7	1.9	-11.4 to -6.0
Test for heterogeneity: X^2_1=0.3; 2p=0.58							
12 months							
PD SURG[6]	160	-5.0 (1.1)	150	-0.3 (0.9)	-4.7	2.1	-7.5 to -1.9
18 months							
Schüpbach and colleagues[12]	10	-6.5 (3.3)	10	4.0 (3.1)	-10.5	20.0	-19.3 to -1.7
Total	362		367		-7.0	0.9	-8.9 to -5.0
Test for heterogeneity (4 trials): X^2_3=5.0; 2p=0.17							
Test for trend between subtotals: X^2_1=1.5; 2p=0.22							



CI = confidence interval; SD = standard deviation. Source: Reprinted from The Lancet Neurology, *9, A Williams, S Gill, T Varma, et al., Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial, 581–91,[6] copyright © 2010, with permission from Elsevier.*

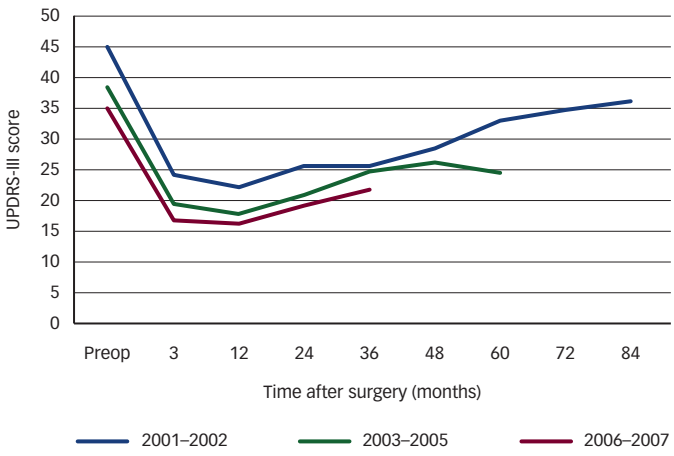
Only one study on the long-term effects of DBS on HRQoL has been published.[9] The study compared the effects of GPi-DBS (n=20) and STN-DBS (n=45) on HRQoL as assessed by Sickness Impact Profile (SIP) questionnaires, before DBS and at six and 36 months after. The SIP provides a physical dimension and a psychosocial dimension sum score and 12 category scores (alertness/intellectual behaviour; ambulation; body care and movement; communication; eating; emotional behaviour; home management; mobility; recreation and pastimes; sleep and rest; social interaction; and work). Improvements in motor functioning were observed up to 36 months with either DBS therapy. Furthermore, STN-DBS and GPi-DBS resulted in significant early improvements in HRQoL (see *Figure 4*). However, part of the initial benefit in HRQoL was lost after 36 months. This may be explained by the fact that HRQoL is a subjective measure and has a strong placebo effect. Subjective impressions of disability may change over time. Another possible reason for the loss of benefit in HRQoL over time is progression of disease-related NMS.

Predictive Factors of Health-related Quality of Life Improvement

Identification of predictive factors of HRQoL improvement may help in selecting the most suitable patients for DBS therapy. Studies have shown that patient groups vary in improvements for the same intervention: change in HRQoL depends on therapy efficacy on motor function,[6] but several patient-related factors are also involved. One of these factors is levodopa response, as shown in a study that compared HRQoL in patients who underwent STN-DBS (n=105) with a control group (n=40).[10] Twelve months after surgery, there was a large improvement in HRQoL in the STN-DBS group compared with controls (Cohen's *d*=0.9). At the individual level, 32 % of the STN-DBS patients showed a substantial improvement in HRQoL. Moreover, HRQoL improvement correlated with levodopa challenge test results. Thus, a patient with severe motor symptoms in the 'off' state and very limited symptoms in the 'on' state (i.e., a high levodopa response) has a good chance of improvement in HRQoL after surgery.

Another predictor of HRQoL improvement is age. Derost et al.[11] showed that STN-DBS reduced motor complications to a similar degree in 'young' (mean age 57.4 ± 4.9 years, n=53) and 'old' patients (mean age 68.8 ± 2.8 years, n=34), but that HRQoL improved only in 'young' patients. This may be explained by differences between the two groups: the 'old' patients had more significant worsening in UPDRS motor score (p<0.0001) and axial score (p=0.0001) under on-medication and on-stimulation conditions during the study.

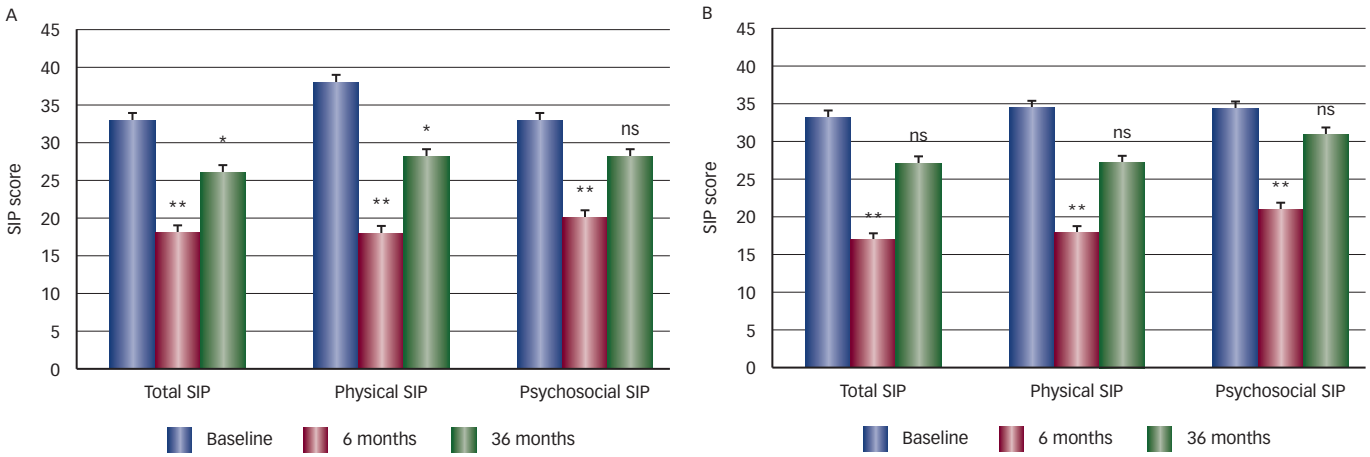
Figure 3: Long-term Effect of Subthalamic Deep Brain Stimulation on Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) Scores



Source: Adapted from Toft M et al., 2011.[8]

Other factors may also be involved. One such factor is cognition, which is related to age in PD; cognitive deficits are not improved by DBS.[4] While patients with cognitive decline may show motor improvements for a short period of time, the progressive deterioration of cognitive symptoms will greatly impair their HRQoL. The development of cognitive deficits in PD is not linear; there is a sharper decline with advancing disease. This has implications for the timing of DBS: if surgery is performed when the patient is on the verge of cognitive deterioration, the benefit in HRQoL is likely to be reduced.

Figure 4: Change in Total Sickness Impact Profile (SIP), Physical SIP and Psychosocial SIP Scores from Baseline to Six and 36 Months after Deep Brain Stimulation of the Subthalamic Nucleus (A) or Globus Pallida Interna (B)



*Mean plus standard error of the mean shown. **p<0.01; *p<0.05; ns = not significant compared with baseline. Source: Adapted from J Volkmann, A Albanese, J Kulisevsky, et al., Long-term effects of pallidal or subthalamic deep brain stimulation on quality of life in Parkinson's disease,* Mov Disord*, 2009;24:1154–61,° copyright © 2009 Movement Disorders Society, with permission from John Wiley and Sons.*

Conclusions

HRQoL is markedly reduced in PD patients. Randomised studies have shown that DBS leads to significant improvement in HRQoL, although only one long-term study has been published. Furthermore, STN-DBS and GPi-DBS appear to have similar effects on HRQoL. Important predictors of HRQoL improvement were found to include levodopa response, age and cognitive function; thus a young patient with well preserved cognitive function and motor symptoms that are highly responsive to levodopa has the best chance to see an improvement in HRQoL after DBS. Trials are needed to further investigate the long-term effects of DBS on HRQoL, and predictors of favourable outcome in terms of HRQoL, in order to optimise patient selection for this therapy. ■

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