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Quality of life predicts outcome of deep brain stimulation in early Parkinson disease

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Abstract

Objective

To investigate predictors for improvement of disease-specific quality of life (QOL) after deep brain stimulation (DBS) of the subthalamic nucleus (STN) for Parkinson disease (PD) with early motor complications.

Methods

We performed a secondary analysis of data from the previously published EARLYSTIM study, a prospective randomized trial comparing STN-DBS (n = 124) to best medical treatment (n = 127) after 2 years follow-up with disease-specific QOL (39-item Parkinson's Disease Questionnaire summary index [PDQ-39-SI]) as the primary endpoint. Linear regression analyses of the baseline characteristics age, disease duration, duration of motor complications, and disease severity measured at baseline with the Unified Parkinson's Disease Rating Scale (UPDRS) (UPDRS-III "off" and "on" medications, UPDRS-IV) were conducted to determine predictors of change in PDQ-39-SI.

Results

PDQ-39-SI at baseline was correlated to the change in PDQ-39-SI after 24 months in both treatment groups ($p < 0.05$). The higher the baseline score (worse QOL) the larger the improvement in QOL after 24 months. No correlation was found for any of the other baseline characteristics analyzed in either treatment group.

Conclusion

Impaired QOL as subjectively evaluated by the patient is the most important predictor of benefit in patients with PD and early motor complications, fulfilling objective gold standard inclusion criteria for STN-DBS. Our results prompt systematically including evaluation of disease-specific QOL when selecting patients with PD for STN-DBS.

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Glossary

BDI = Beck Depression Inventory; **BMT** = best medical treatment; **DBS** = deep brain stimulation; **MÅDRS** = Montgomery-Åsberg Depression Rating Scale; **MDRS** = Mattis Dementia Rating Scale; **PD** = Parkinson disease; **PDQ-39-SI** = 39-item Parkinson's Disease Questionnaire summary index; **QOL** = quality of life; **STN** = subthalamic nucleus; **UPDRS** = Unified Parkinson's Disease Rating Scale.

High-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a powerful treatment in selected patients with Parkinson disease (PD) and levodopa-induced motor complications. The benefit of STN-DBS has first been shown in advanced PD with severe motor fluctuations and dyskinesia[1–3] but more recently, improvement of quality of life (QOL) and motor function have been shown with STN-DBS at an earlier stage.[4–6] The EARLYSTIM study[6] addressed STN-DBS in patients with PD under 61 years of age who had a good (i.e., ≥50%) response to levodopa but had had motor complications for up to 3 years (mean 1.5 ± 0.8 SD years). Intentionally permissive inclusion criteria were chosen that allowed a rather broad population of patients with PD with early motor complications to be included. This was decided to enable recruitment of a large cohort and to build a study population from which one would be able to draw conclusions for a clinical population of a reasonably broad range.

This, however, resulted in a study population of patients with PD with a range from early mild complications to moderately severe and advanced motor complications close to those for the conventional indication for DBS. Therefore, the question came up whether the beneficial effect of DBS in the EARLYSTIM cohort was (mainly or only) driven by a subgroup of the entire population, i.e., the relatively advanced patients. Doubts were uttered by critics of the study whether patients with milder motor complications would benefit from DBS. Indeed, it is possible that the more advanced patients contributed more to the overall beneficial effect of DBS found in the study than patients with very mild and early motor complications.

We therefore performed subgroup analyses to understand the effects of DBS in function of different variables prone to be related to outcome of STN-DBS. In particular, the relative contributions of age, duration of disease, and severity of disease to the effect of DBS on QOL were analyzed.

Methods

The EARLYSTIM study[5,6] was a prospective randomized study comparing STN-DBS with best medical treatment (BMT) to BMT alone over 2 years' follow-up with QOL measured with 39-item Parkinson's Disease Questionnaire summary index (PDQ-39-SI) as the primary endpoint. The protocol and statistical plan of the main study are available at nejm.org/doi/suppl/10.1056/NEJMoa1205158/suppl_file/nejmoa1205158_protocol.pdf. Hypotheses of predicting factors for outcome were formulated before secondary analyses were carried out. Baseline characteristics, including age, disease duration, duration of motor complications (motor fluctuations and dyskinesia), severity of motor parkinsonian signs "off" and "on" medication as measured with the Unified Parkinson's Disease Rating Scale (UPDRS) motor part (III), severity of motor complications (UPDRS-IV), levodopa response, and baseline QOL (PDQ-39-SI) were expected to contribute to the outcome of QOL. To control for contribution of cognition and mood to the outcome in QOL, the baseline ratings for the Mattis Dementia Rating Scale (MDRS), the Beck Depression Inventory (BDI), and the Montgomery-Åsberg Depression Rating Scale (MÅDRS) were also analyzed as potential predictors for change on QOL. Univariate linear regression analyses of these baseline characteristics vs the change in QOL (PDQ-39-SI) were conducted. p Values ≤0.05 were considered statistically significant and no adjustments were made for multiple comparisons. A multivariate linear regression analysis of the STN-DBS group was then performed including the factors with a $p < 0.25$ in the univariate analysis.

A post hoc subgroup analysis was performed for the correlation of baseline PDQ-39-SI with the change in PDQ-39-SI over the 2 years using 4 subgroups of baseline PDQ-39-SI (<15, 15–30, 30–45, >45).

Data availability statement and protocol standards

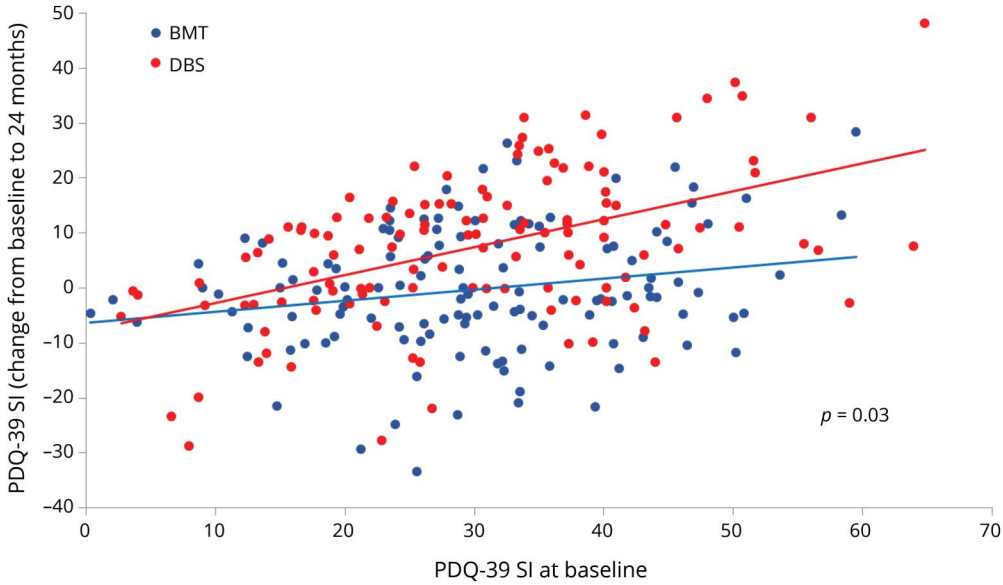
The study protocol and statistical plan is available at nejm.org/doi/suppl/10.1056/NEJMoa1205158/suppl_file/nejmoa1205158_protocol.pdf. Data will not be available on the web. Researchers can submit proposals for collaborative studies. The study has been approved by the Kiel and Paris University ethics committees. The trial is registered at ClinicalTrials.gov number, NCT00354133.

Results

The change in QOL over the 2 years correlated with the baseline value of the PDQ-39-SI in a regression model for each treatment group (STN-DBS $p < 0.001$, medical group $p < 0.001$). However, this effect was more pronounced among patients who were treated with STN-DBS than in patients in the medical control group ($p = 0.0262$ for interaction) (figure 1).

If baseline PDQ-39-SI was used to define categories of severity of impairment due to PD, patients with very mild impairment of QOL, i.e., PDQ-39-SI values under 15, as a group did not benefit from STN-DBS as compared to

Figure 1 Correlation between 39-item Parkinson's Disease Questionnaire summary index (PDQ-39-SI) at baseline and change to 24 months



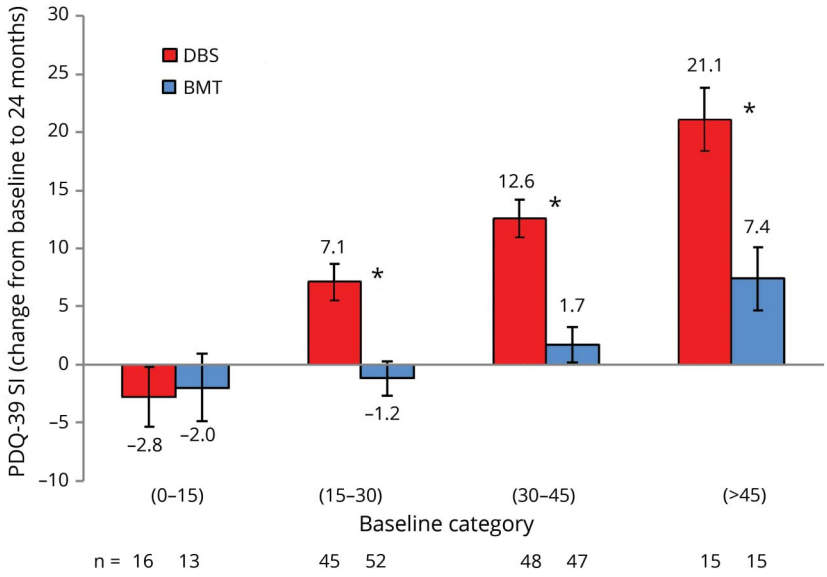
The relation between PDQ-39-SI at baseline and the improvement PDQ-39-SI between baseline and 24 months is shown. The correlation is more pronounced for the deep brain stimulation (DBS) group than for the best medical treatment (BMT) group.

patients in the control group with best medical treatment alone. However, in this group, patients with a very favorable as well as unfavorable outcome in terms of PDQ-39-SI were found. For the other categories with PDQ-39-SI ratings >15 at baseline, STN-DBS resulted in better QOL than best medical treatment alone (figure 2). The change from baseline to 5, 12, and 24 months for each patient with a change at each point (n = 241/251) by treatment group is shown in figure 3.

The change of QOL over the study duration of 2 years was independent of age, duration of PD, and duration of motor complications (motor fluctuations, dyskinesia) at baseline in a regression model. This was the case when analyzed separately by treatment group as well as in a multiple regression model including allocation to the treatment group.

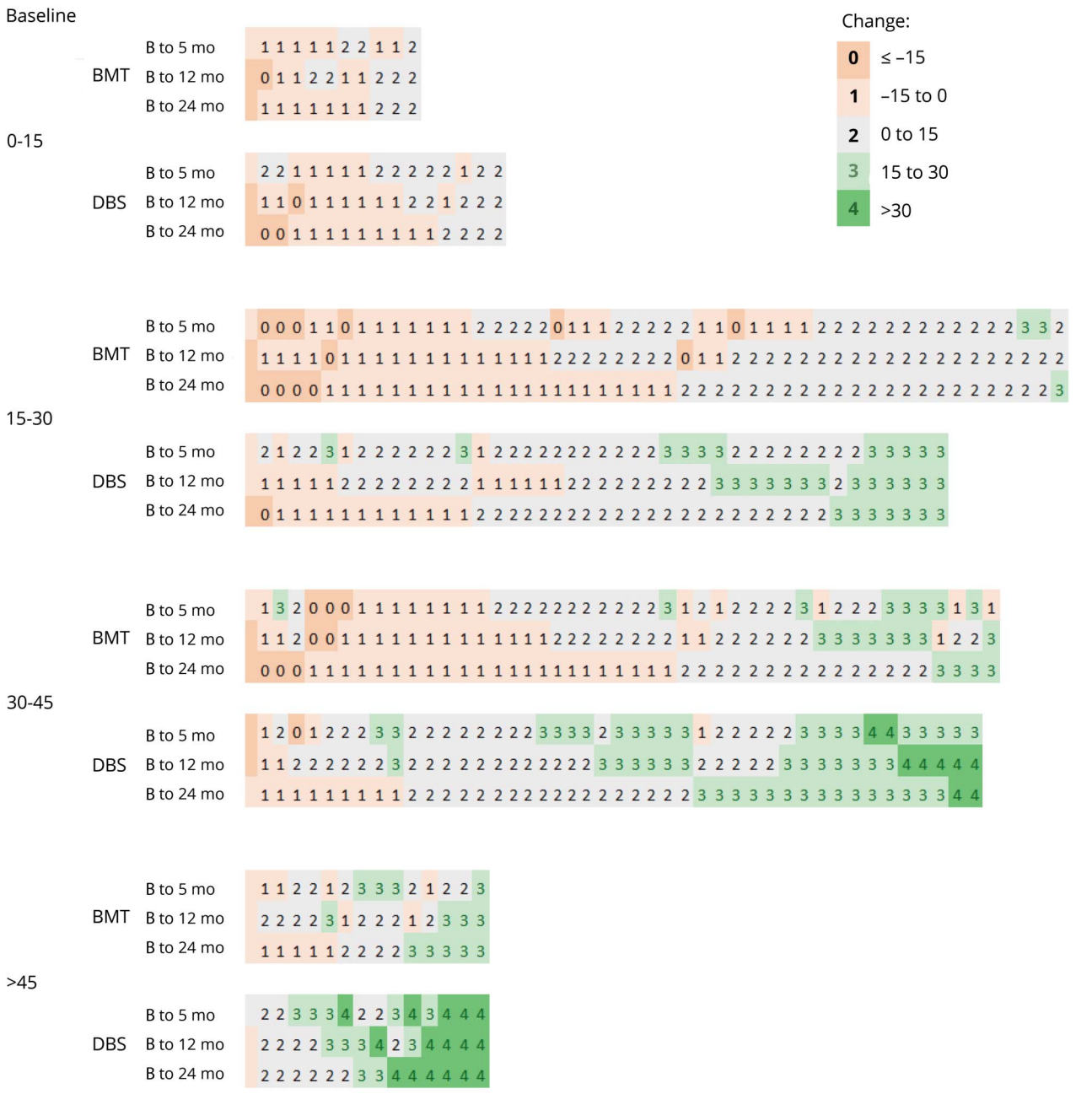
The change of QOL over the 2 years was also independent of the severity of parkinsonian motor signs in the condition

Figure 2 39-Item Parkinson's Disease Questionnaire summary index (PDQ-39-SI) by baseline category



Four categories of PDQ-39-SI baseline values were formed: 0–15, 15–30, 30–45, and >45 points. Higher values on the PDQ-39 scale mean worse quality of life. The ordinate indicates the change of PDQ-39-SI over the 2 years of the EARLYSTIM study period; negative values mean worsening of quality of life, positive values mean improvement. BMT = best medical treatment (i.e., control group); DBS = deep brain stimulation of the subthalamic nucleus plus best medical treatment; n = number of patients in each group. *DBS vs BMT statistically significant (adjusted model-based *p* values <0.05).

Figure 3 Individual 39-item Parkinson's Disease Questionnaire summary index (PDQ-39-SI) change



Change of quality of life (PDQ-39) depending on the baseline PDQ-39 (B). All data at the 3 visits (5, 12, and 24 months) of all patients are shown depending on the baseline value of the PDQ-39 (left column). The response is highlighted by colors (green, better; red, no change). Patients with higher PDQ-39 values at baseline show a better improvement.

"off" and "on" medications as measured with the UPDRS-III, and independent of the severity of levodopa-induced complications measured with the UPDRS-IV, as well as "off" time at baseline. This was the case when analyzed separately by treatment group as well as in a multiple regression model including allocation to the treatment group.

The levodopa response of the motor score (UPDRS III) at baseline was not predictive for the change of the QOL outcome between baseline and 24 months in the DBS-group or in the BMT control group.

Cognitive assessment at baseline with the MDRS was not predictive of change in QOL in either treatment group. Self-assessment of mood using the BDI at baseline did not predict change of the PDQ-39-SI after 2 years among patients in the BMT group. However, higher baseline ratings on the BDI correlated with larger improvement of QOL among patients with STN-DBS. The same was

observed for mood assessed by the examiner as rated with the MÅDRS in patients with STN-DBS. On the other hand, lower ratings on the MÅDRS correlated with better improvement of the PDQ-39-SI in patients with BMT.

The multivariate regression model in patients with STN-DBS included 4 baseline factors with $p < 0.25$ in the univariate analysis: PDQ-39-SI ($p < 0.0001$), BDI ($p < 0.001$), MÅDRS ($p = 0.018$), and UPDRS-III "off" medication ($p = 0.216$). Only the PDQ-39-SI remained significant ($p < 0.0001$) as a baseline predictor for change in QOL in the multivariate model.

Discussion

The EARLYSTIM cohort was intended to broadly represent the group of relatively young patients with PD and early motor complications as seen in daily practice. In such a cohort, the potential for improvement may be more modest than in more advanced PD and patients' expectations are high for STN-DBS. Weighing surgery against BMT, knowledge about predictive factors for the improvement of QOL with either treatment is important. Moreover, in view of negative results of STN-DBS in patients with PD before the onset of motor complications,[7] STN-DBS at a very early stage has been challenged, as the relative contributions of age, disease duration, and duration of presence of motor complications have so far not been disentangled.[8]

QOL at baseline was positively correlated with the improvement of the PDQ-39-SI. This was true for both treatment groups, i.e., patients with worse QOL at baseline improved more over the 2 years' study period. This was, however, very much more pronounced among patients with STN-DBS than with BMT alone. Baseline impairment of QOL is therefore a reasonable aspect to consider for the decision to treat with STN-DBS. We wondered if there was a floor effect for the benefit from STN-DBS with a minimal PD-related suffering required to have a potential advantage from the intervention. Among patients with PDQ-39-SI ratings under 15, there was as a group no difference for the outcome in QOL between the treatment groups, and patients with STN-DBS even tended to have worse average outcomes. However, this post hoc secondary analysis must be taken with reserve, especially since the subgroup with PDQ-39-SI ratings under 15 was very small and some individuals in this group had an excellent improvement of QOL with STN-DBS and would wrongly have been barred from a beneficial treatment if a strict cutoff level for the indication of STN-DBS had been applied. In patients with very low baseline ratings on the PDQ-39-SI, the natural progression of impairment of QOL may outweigh the improvement achieved by STN-DBS. On the other hand, some patients with very modest impairment of their QOL seem to have less to gain from STN-DBS. If they choose to undergo neurosurgery, they may do it for the wrong reasons and have expectations that are unrealistic. Therefore they may end up disappointed with the result and show worse ratings on the PDQ-39-SI. Especially thorough assessment of the reasons to undergo neurosurgery and the expectations from STN-DBS are therefore needed if the impairment of QOL is very modest. For all other categories with higher PDQ-39-SI at baseline, STN-DBS resulted in improved QOL as compared to best medical treatment alone.

In contrast to the strong prediction of improvement of QOL by baseline PDQ-39-SI ratings, the change of QOL after 2 years is independent from age, disease duration, duration of motor complications, and severity of motor signs and motor complications at baseline. This finding differs from the observation in more advanced PD in patients with a higher age after 5–6 months where baseline cumulative daily "off" time was a predictor for improvement of the PDQ-39-SI[9] and younger age was associated with better improvement of the PDQ-8.[10] This difference could be partly related to the longer observation period of 2 years, the different patient profile (younger age, shorter disease duration at surgery) in the EARLYSTIM study, and to a lower variance as a result of the narrower inclusion criteria.

The discrepancy between health-related QOL and motor disease severity at baseline as predictors for the outcome of QOL can be explained by the individual amount of suffering attributed to a given motor impairment. Objective motor improvement does not equal subjective improvement of overall disease-specific QOL.[11] Moreover, the PDQ-39 not only assesses motor aspects of PD, but affective, behavioral, cognitive, nonmotor, and psychosocial issues are also weighed with this instrument. It is known that motor signs are not the most important determinant of QOL in patients with PD.[12–14] Indeed, nonmotor aspects also strongly influence the PDQ-39-SI[15] and thus contribute decisively to the changes of QOL after STN-DBS. This is likely the reason why the L-dopa response of the UPDRS motor score at baseline is predictive for the motor outcome[16,17] but not necessarily for the QOL outcome after 2 years.[9,18,19] It has been shown that patients without dementia with borderline preoperative cognitive scores improve less in QOL than those with better cognitive ratings.[20] However, only patients without dementia without severe depression were included in the EARLYSTIM study. It is therefore not surprising that baseline assessments of cognition (MDRS) and mood (BDI, MÅDRS) were not predictive for outcome. The association of higher ratings on the depression scales with better improvement of QOL among STN-DBS patients may indicate that these patients have a potential for nonmotor improvement to gain from surgery. However, the association was present only in univariate analyses and lost in the multivariate model, in which the PDQ-39-SI baseline score dominated all other factors.

An important limitation of our findings regarding generalization is the highly selected patient population. Indeed, the EARLYSTIM cohort consisted of young patients under 61

with a levodopa response of at least 50% as an inclusion criterion. STN-DBS has been established as a treatment for motor symptoms in advanced PD.[1,21–24] Importantly, the response of motor parkinsonian signs to levodopa is an established predictor of the motor outcome of STN-DBS.[16,25] Parkinsonism that does not respond to L-dopa will not benefit from STN-DBS.[26] In other words, it is not the severity of the motor signs that predicts motor outcome, but their response to L-dopa. In the present study, levodopa response at baseline was not a predictor of improvement in QOL. Part of the explanation may be related to the fact that the same objective motor sign will not lead to the same subjective suffering, and in the same way improvement of motor symptoms that do not bother a patient will not lead to improvement in QOL, which by definition is subjective. A ceiling effect may also partly explain that no such association was found among our patients with STN-DBS, given the fact that levodopa response of at least 50% was defined as an inclusion criterion and that the operated patients in the EARLYSTIM study had an excellent average baseline levodopa response of 63.5% ± 16.2%. Therefore, poor QOL in patients with PD in the absence of L-dopa-responsive motor symptoms should not be regarded as an indication for surgery.

The relation between age, disease duration, and outcome may be different in older patients and in patients with a less pronounced response to levodopa. Better outcome of STN-DBS has been suggested among younger patients with shorter disease duration,[25] and outcome among older patients has been reported as unfavorable.[27] However, these patients were operated at a later stage for severe advanced PD. Our data cannot answer the question whether STN-DBS at an earlier stage will remain advantageous over BMT beyond the 2 years of the duration of the EARLYSTIM study. Uncontrolled open long-term observations on patients with STN-DBS, however, show benefits that last up to a decade.[28]

The lack of correlations of age, disease duration, and disease severity with the change of QOL after STN-DBS leaves only baseline ratings of the PDQ-39-SI as a predictor for change of QOL. All patient groups above 15 points of PDQ-39-SI at baseline have on average a clinically meaningful improvement of their QOL (figure 2), which has been estimated to be ≥1.6 points.[29] The majority of these patients is in the range of PDQ-39-SI >15 (n = 114). We therefore consider it very unlikely that the overall favorable outcome of STN-DBS in the EARLYSTIM study has been driven by only a subgroup of patients corresponding to the traditional indication with severe long-standing advanced complicated PD. The major and decisive explanation of the improvement of QOL comes from STN-DBS, i.e., the treatment itself across a broad range of patient age and clinical profiles within the EARLYSTIM inclusion criteria.

STN-DBS improves QOL in patients with PD and early motor complications who fulfil the EARLYSTIM inclusion criteria independently of age, disease duration, and disease severity. The subjective individual suffering as measured with the PDQ-39-SI should be taken into account as a predictive factor for outcome when selecting patients with early motor complications for STN-DBS.

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Timmerman received funds from Medtronic, Boston Scientific, Sapiens, St Jude Medical, Bayer Healthcare, UCB, and Archimedes Pharma; grants from M&U Müller Foundation, NBIA Foundation, and German Parkinson Foundation; and payments for lectures from TEVA, Lundbeck, Bracco, Gianni PR, Medas, UCB, Desitin, Boehringer, GSK, Eumecom, and Orion Pharm. G. Deuschl received lecture fees from Boston Scientific and has been serving as a consultant for Boston Scientific; received royalties from Thieme; is a government employee; and receives through his institution funding for his research from the German Research Council, the German Ministry of Education and Research, and Medtronic. Go to Neurology.org/N for full disclosures.

Publication history

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Appendix 2 *(continued)*

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Appendix 2 *(continued)*

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Quality of life predicts outcome of deep brain stimulation in early Parkinson disease

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