**Subthalamic Stimulation improves quality of sleep in Parkinson disease: a 36-month controlled study**

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**Glossary**: **DBS** = deep brain stimulation; **HADS** = Hospital Anxiety and Depression Scale; **LEDD** = levodopa equivalent daily dose; **MED** = standard-of-care medical therapy; **NMS** = nonmotor symptoms; **PD** = Parkinson’s Disease; **PDQ-8** = PD Questionnaire-8; **PDSS** = PD Sleep Scale; **QoL** = quality of life; **STN** = subthalamic nucleus

**Abstract**

**Background:** Sleep disturbances and neuropsychiatric symptoms are some of the most common nonmotor symptoms in Parkinson’s disease (PD). The effect of subthalamic stimulation (STN-DBS) on these symptoms beyond a short-term follow-up is unclear.

**Objective:** To examine 36-month effects of bilateral STN-DBS on quality of sleep, depression, anxiety, and quality of life (QoL) compared to standard-of-care medical therapy (MED) in PD.

**Methods:** In this prospective, controlled, observational, propensity score matched international multicenter study, we assessed sleep disturbances using the PDSleep Scale-1 (PDSS), QoL employing the PDQuestionnaire-8 (PDQ-8), motor disorder with the Scales for Outcomes in PD (SCOPA), anxiety and depression with the Hospital Anxiety and Depression Scale (HADS), and dopaminergic medication requirements (LEDD). Within-group longitudinal outcome changes were tested using Wilcoxon signed-rank and between-group longitudinal differences of change scores with Mann-Whitney *U* tests. Spearman correlations analyzed the relationships of outcome parameter changes at follow-up.

**Results:** Propensity score matching applied on 159 patients (STN-DBS n=75, MED n=84) resulted in 40 patients in each treatment group. At 36-month follow-up, STN-DBS led to significantly better PDSS and PDQ-8 change scores, which were significantly correlated. We observed no significant effects for HADS and no significant correlations between change scores in PDSS, HADS, and LEDD.

**Conclusions:** We report Class IIb evidence of beneficial effects of STN-DBS on quality of sleep at 36-month follow-up, which were associated with QoL improvement independent of depression and dopaminergic medication. Our study highlights the importance of sleep for assessments of DBS outcomes.

**Keywords:** Deep brain stimulation, sleep dysfunction, subthalamic nucleus, quality of life, nonmotor symptoms

**Introduction**

Sleep disturbances and depressive symptoms are amongst the most common nonmotor symptoms (NMS) in patients with Parkinson’s disease (PD) and are major predictors of negative health-related quality of life (QoL).[1] Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is effective in improving medication-refractory motor impairment,[2] QoL,[3] and a wide range of NMS[4] in patients with PD. Long-term effects of STN-DBS on NMS have only been studied to a limited extent. Previous studies have documented beneficial effects of STN-DBS on sleep up to three years postoperatively.[5-7] However, there is a lack of controlled studies comparing effects of STN-DBS on sleep symptoms to standard-of-care medical treatment (MED).

It has been described that in PD patients mood disturbances such as depression and anxiety are associated with sleep disturbances[8] and worse quality of life. Furthermore, sleep problems and depressive symptoms in PD are partly responsive to dopaminergic medication.[9, 10] However, little is known about the long-term effects of STN-DBS on sleep, mood, and dopaminergic medication and their relationship with quality of life.

Therefore, in this study, we aimed to investigate 36-month effects of STN-DBS on these parameters in comparison to patients treated with MED. We hypothesized that STN-DBS improves subjective sleep symptoms at 36-month follow-up independent of mood symptoms and dopaminergic medication and that these sleep improvements are correlated with improvements of quality of life.

**Materials and methods**

**Study design**

We prospectively recruited patients between 03/2011 and 10/2015 in an ongoing, observational, controlled, multicenter international study as part of the DBS and medication arms of the NILS study that investigates NMS in patients with PD.[4] Here, we report the results of the 36-month follow-up. The study was carried out in accordance with the declaration of Helsinki and authorized by the medical ethics committees of the participating centers (master votes for Germany: Cologne, study number: 12-145, German Clinical Trials Register: DRKS00006735, and for the United Kingdom: National Research Ethics Service South East London REC 3, 10/H0808/141; NIHR portfolio, number: 10084). All patients gave written informed consent prior to any study procedures. Enrollment criteria and study procedures have been reported previously[11] and will only described briefly.

**Participants**

PD diagnosis was based on the UK Brain Bank criteria and DBS screening was carried out according to the international guidelines. Patients were eligible for DBS treatment if they were responsive to levodopa (>30% improvement of motor examination assessed by the Unified PD Rating Scale–III). We excluded patients with clinically relevant neuropsychiatric disorders or neuropsychological impairment as assessed in a multidisciplinary team including specialized neuropsychiatrists and neuropsychologists. For the final analysis, we included only patients with advanced PD with dyskinesia, ON/OFF fluctuations or medication-refractory tremor in the MED group, to achieve better comparability between the STN-DBS and MED group. Patients in the MED group selected for the final analyses were regarded as potential candidates for STN-DBS in the multi-disciplinary assessments, but preferred non-surgical treatment at this point in time according to published standard-of-care recommendations.[12] Various parameters may have influenced patients’ informed decisions including patients’ age, disease duration, dopaminergic medication requirements, and severity of motor and non-motor symptoms.[12] Patients in both groups received oral medical therapy, which could include levodopa, dopamine agonists, monoamine oxidase type B inhibitors, catechol-O-methyltransferase inhibitors, amantadine, or other drugs for treatment of PD symptoms. We have published results regarding other non-motor aspects of PD in the same cohort elsewhere.[11]

**Clinical Assessment**

Baseline and follow-up assessments took place in the ON-medication state (MedON). Patients in the STN-DBS group were also in the ON-stimulation state at follow-up (medication and stimulation ON, MedON/StimON). Clinical assessments were carried out using the following scales:

The **Parkinson’s Disease Sleep Scale-1 (PDSS)** is a self-rating visual analogue scale assessing 15 commonly reported symptoms associated with sleep disturbances in PD. The items range from 0 (maximum impairment) to 10 (no impairment) (total score 0–150). Lower scores in the PDSS represent more severe impairment.[13] The PDSS addresses overall quality of night’s sleep (item 1), sleep onset and maintenance insomnia (items 2 and 3), nocturnal restlessness (items 4 and 5), nocturnal psychosis (items 6 and 7), nocturia (items 8 and 9), nocturnal motor symptoms (items 10–13), sleep refreshment (item 14) and daytime dozing (item 15).[13]

The **Hospital Anxiety and Depression Scale (HADS)** comprises subscales for anxiety and depression (HADS-A and -D) with seven items, respectively.[14] Each of the two subscales’ scores range from 0 (no anxiety/depression) to 21 (maximum anxiety/depression) with higher scores indicating more severe impairment.

The **PD Questionnaire (PDQ)-8** is a short-form of the PDQ-39[15] and covers eight dimensions contributing to QoL in PD. The scale is recommended by the Movement Disorders Society Scales Committee and has been commonly used in patients undergoing DBS.[16, 17] The outcome was reported as PDQ-8 Summary Index (PDQ-8 SI) ranging from 0 (no impairment) to 100 (maximum impairment) to help interpreting the results.

We calculated **levodopa equivalent daily dose (LEDD)** according to the method by Tomlinson et al. for recording the therapeutical regimen.[18] Additionally, we calculated the LEDD for dopamine agonists separately.

Motor impairment, activities of daily living and motor complications were assessed with the **Scales for Outcomes in PD (SCOPA),** which was deducted from the Unified Parkinson’s Disease Rating Scale and has been shown to strongly correlate with the corresponding parts.[19, 20] The SCOPA was chosen as motor scale for time efficiency as it can be assessed four times faster than the MDS-Unified PD Rating Scale.[19, 21] The SCOPA includes 25 items with four response options, ranging from 0 (no impairment) to 3 (severe impairment; total score 0­–75). The subscales range from 0 (no impairment) to 42 (SCOPA-motor examination), 21 (SCOPA-activities of daily living), and 12 (SCOPA-motor complications).

**Statistical analysis**

We used SPSS 26.0 (IBM Corporation) for the statistical analysis. Propensity score matching was applied to identify sub-cohorts with balanced baseline characteristics, which is a method of estimating treatment effects in observational studies, when random treatment allocation is difficult to implement.[22] Propensity score matching aims to reduce bias caused by preexisting differences between treatment groups. [23] The technique includes separate logistic regressions to compute propensity scores of the different subjects. The most common implementation of propensity score matching is 1:1, in which pairs of patients with overlapping propensity scores within a predefined calliper are formed.[24] The matching was computed with Propensity Score Matching for SPSS (version 3.04).[25] For matching, we used the following variables: age at baseline, disease duration since diagnosis, dopamine agonist LEDD and preoperative SCOPA total score. We implemented a 1:1 ratio nearest-neighbor matching algorithm with a 0.25 caliper without replacement. Afterwards, balance diagnostics of the entered covariates based on Cohen’s effect size |d|<0.25 were calculated as a threshold for an accurate balance of the covariates.[23]

The assumption of normality distribution was assessed with the Shapiro-Wilk test. Differences of baseline characteristics between the two groups were analyzed using Chi2-test for dichotomous variables and for continuous variables with Mann–Whitney *U* or unpaired *t*-tests, when parametric criteria were fulfilled. To determine outcome changes from baseline to follow-up within each group, Wilcoxon signed-rank or paired sample *t*-tests were calculated. Mann-Whitney *U* tests of change scores between STN-DBS and MED groups (mean testbaseline − mean testfollow-up) were conducted to analyze differences of outcome parameter changes. As we assessed a variety of tests, we employed Benjamini-Hochberg’s procedure for multiple comparisons and report corrected *P*-values (threshold: *P*<0.05). Information on the clinical relevance of the responses can be found in the supplementary table e-3 (relative changes and respective effect sizes Cohen’s *d*). In addition, we explored the relationship between changes of PDQ-8, PDSS, HADS, and LEDD from baseline to 36-month follow-up using Pearson correlations and partial correlations, respectively Spearman correlations and partial correlations if the assumption of normality distribution was violated.

**Results**

A total of 323 patients were screened, of whom 147 patients were excluded as they did not suffer from dyskinesia, ON/OFF fluctuations or medication-refractory tremor and, therefore, were no DBS candidates (see Figure 1). Five patients were excluded because they underwent DBS in the globus pallidus interna or ventral intermediate nucleus of the thalamus, and ten patients because of neuropsychological impairment (Mini Mental State Examination<25). A total of 159 patients with PD (103 male) undergoing STN-DBS (n=75) or MED (n=84) were assessed eligible for this study. The 159 patients in the final sample had a mean age of 64.0 years ±9.6 with mean disease duration of 8.8 years ±5.0. The mean time to follow-up was 3.0 years ±0.5.

**Baseline characteristics in the original and matched cohort**

In the original cohort, patients in the STN-DBS group were significantly younger, had longer duration of PD, higher LEDD, and greater dopamine agonist requirements than the MED group (see Table 1). Also, the STN-DBS group had more severe impairment in all of the clinical scales except for HADS (all *P*<0.05).

Propensity score matching resulted in a sub-cohort of 80 patients (40 patients in each group). Balance diagnostics revealed no significant differences for the demographic and clinical outcome parameters. Baseline motor subscores and Mini-Mental State Examination scores of the matched cohort are reported in the Supplementary table   
e-1. The following results refer to the matched cohort. Additionally, clinical outcomes of the original cohort are presented in the Supplementary table e-2.

**Clinical Outcome Changes at 36-month follow-up**

Between-group longitudinal differences (STN-DBS vs. MED) and longitudinal within-group changes are reported in table 2. The time of follow-up assessment did not differ significantly between the groups (STN-DBS=3.0±0.2 years, MED=3.1±0.4 years; *P*=0.167).

Between-group longitudinal differences of change scores were significant for the PDSS total, PDQ-8 SI, SCOPA-total, LEDD total, and LEDD of dopamine agonists, all favoring STN-DBS. In the STN-DBS group, the PDSS total score significantly improved from baseline to 36-month follow-up. We further observed beneficial effects of STN-DBS on the SCOPA-total score. In contrast, in the MED group, we found a significant worsening of the PDSS total score, whereas the SCOPA total score remained stable. As expected, the LEDD total and LEDD of dopamine agonists were reduced significantly in the STN-DBS group and remained stable in the MED group. In both groups, the HADS total score, as well as its depression and anxiety subscales did not change significantly at 36-month follow-up.

Post-hoc analyses of the different PDSS domains revealed significant beneficial effects of STN-DBS on ‘Overall quality of night’s sleep’, ‘Sleep onset and maintenance insomnia’, ‘Nocturnal restlessness’, and ‘Nocturnal motor symptoms’. In contrast, in the MED group, we observed a significant worsening of ‘Nocturia’ and ‘Nocturnal motor symptoms’. Significant between-group longitudinal differences were found for ‘Overall quality of night’s sleep’, ‘Sleep onset and maintenance insomnia’, ‘Nocturnal restlessness’, ‘Nocturia’, ‘Nocturnal motor symptoms’, and ‘Sleep refreshment’.

**Explorative correlation analyses**

Better PDSS total score outcomes were significantly correlated with better SCOPA total score (=–0.35, *P*=0.002) and PDQ-8 SI (=–0.40, *P*<0.001) outcomes. A partial correlation between changes in PDSS total score and PDQ-8 SI was still significant after controlling for the SCOPA outcome (=–0.34, *P*=0.003). No significant correlations were found between changes of PDSS total score and other parameters. PDQ-8 SI changes were also significantly correlated with changes in HADS total scores (=0.48, *P*<0.001), its anxiety and depression subscales (both (=0.42, *P*<0.001), and with SCOPA total score (=0.28, *P*=0.016). There were no significant correlations between changes in overall LEDD or LEDD dopamine agonists with any other outcome changes including the different PDSS domains.

**Discussion**

In this prospective, controlled, observational, propensity score matched, international multicenter study with a 36-month follow-up in 80 patients with PD, we report beneficial effects of STN-DBS on subjective sleep symptoms which were significantly correlated with improvements of QoL and motor symptoms. Depressive and anxiety symptoms remained unchanged from baseline to 36-month follow-up. Beneficial effects of STN-DBS on subjective sleep disturbances were not associated with changes in depression, anxiety, or dopaminergic medication requirements. The relationship between quality of life and subjective sleep disturbances was still significant when controlling for motor symptoms.

**Motor symptoms, quality of life, and LEDD**

In line with previous studies with up to 36-month follow-up, we observed long-term improvements in motor symptoms and QoL.[2, 3] In the MED group, standard-of-care resulted in stabilized motor symptoms and QoL at 36-month follow-up. As expected, STN-DBS led to a significant LEDD reduction, while medication requirements remained stable in the MED group.

**Specific aspects of sleep**

To our knowledge, this is the first controlled study demonstrating sustained improvements in various aspects of sleep dysfunction in PD patients following STN-DBS at 36-month follow-up. Compared to a control group receiving MED, STN-DBS significantly improved the following specific sleep aspects:

The present work is the first observation, to our knowledge, of a significantly better outcome of symptoms of **sleep onset and maintenance insomnia** in the STN-DBS compared to the MED group at 36-month follow-up. In line with previous studies, we observed sustained beneficial effects of STN-DBS[6] which is supported by polysomnography studies that observed improved total sleep time, sleep continuity and depth.[26, 27]

We observed a significant improvement ofsymptoms of **nocturnal restlessness** in the STN-DBS group, which was also significantly better than in the MED group. This is in line with a study by Klepitsaya and colleagues that reported significant improvements of restless legs syndrome following STN-DBS two years postoperatively.[28] Our study adds to this evidence by extending the time frame of beneficial effects on nocturnal restlessness to 36 months. A decrease of dopaminergic medication may be a possible explanation for the favorable nocturnal restlessness outcome in the STN-DBS group as chronic dopaminergic treatment in high dosages may cause augmentation of restless leg symptoms. However, we did not observe a significant correlation of LEDD and nocturnal restlessness, possibly due to patient-specific augmentation thresholds. Another possible mechanisms of action could be an improvement of bidirectional information flow in the STN-somatosensory cortex loop.[29]

In our study, we observed significant between-group longitudinal differences of symptoms of **nocturia**, which was driven by significant worsening in the MED group, whereas patients in the STN-DBS group experienced a stabilization of nocturia. The stabilization of nocturia in the STN-DBS group at 36-month follow-up was in accordance with previous studies with shorter follow-up periods up to 4-month.[30] Previous results from our cohort have provided evidence for an improvement of “urinary incontinence during motor OFF at night” for up to 5 months and an improvement of urinary symptoms for up to 24 months[4] in patients undergoing STN-DBS. A possible mechanism of action could be an improved processing of sensory information[31] due to improved sensory gating.[32]

The present study shows beneficial effects on **nocturnal motor symptoms** at 36-month follow-up, which is in line with results from Choi et al.[6] In contrast, a significant worsening was found in the MED group and, as a result, the between-group longitudinal difference of nocturnal motor symptoms was significant. A direct modulation of the motor circuitry is likely to be a main contributor of improved motor symptoms at night.[33]

To our knowledge, this is the first study to report significantly favorable effects on self-reported **sleep refreshment** in patients undergoing STN-DBS. This was mainly driven by a worsening of sleep refreshment in the MED group, whereas sleep refreshment stabilized in the STN-DBS group. This observation supports results of a study by Choi et al. which reported no significant change of sleep refreshment.[6]

**Anxiety and Depression**

In the present study, we did not observe significant changes of anxiety and depression at 36-month follow-up. This result is in line with previous studies, on depressive and anxiety symptoms by Weaver et al. and Berney et al. with a follow-up period up to one year.[34, 35] In contrast, Funkiewiez et al. found improvements in depressive symptoms after bilateral STN-DBS one year and three years postoperatively.[36] Recent studies have reported that depression and anxiety depend on the location of active DBS contacts, the volume of tissue activated by DBS or the structural connectivity profiles between the STN and prefrontal cortex.[37]

**Mechanisms of improved sleep following STN-DBS**

Heterogeneous causes may account for improvements of sleep disturbances following STN-DBS. Firstly, enhanced motor function may be an important contributor to improvements in sleep. This is in line with our observation of significantly better nocturnal motor symptoms and the observed significant correlation between changes in motor examination and sleep disturbances. Secondly, a pathophysiologic correlate for a direct DBS effect on sleep could be the modulation of regions in proximity of the STN. In particular, the pedunculopontine nucleus, which is reciprocally connected to the STN, regulates the sleep-wake cycle and serves as a critical ‘mesencephalic locomotor region’.[38] As a reticular structure, the precise topographic boundaries of the pedunculopontine nucleus are indistinct. However, a location 5 mm ventral of the STN with even closer projections has been discussed.[39] Thirdly, reduced LEDD following STN-DBS may enhance sleep symptoms like daytime sleepiness although we observed no linear relationship with changes in LEDD. As a fourth possible explanation, the interplay between anxiety, depression, and sleep symptoms could play an important role. In the present study, improvements of PDSS total score and HADS anxiety and depression subscale scores were not significantly correlated, indicating that sleep and mood disorders could be independently modulated by STN-DBS. This is in line with studies in which we observed distinct ‘sweet spots’ for sleep and mood symptoms connected to specialized functional brain networks.[37, 40]

**Relationship between dopaminergic medication, sleep dysfunction and depression**

Dopamine has a complex role for sleep disturbances in PD. Dopamine receptor agonists can both alleviate and aggravate specific aspects of sleep dysfunction in PD. We observed no association between sleep disturbances and overall LEDD or dopamine agonists LEDD. Ricciardi et al. found a significant relationship between *improvement* of sleep and dopamine agonists dose reduction.[41] On the other hand, there are also sleep-related adverse events caused by dopamine receptor agonists, such as excessive daytime sleepiness and sleep attacks.[42]

The effect on mood of dopamine agonists is still controversial. We found no significant correlations between depressive symptoms and dosages of the other dopamine agonists. Future studies with larger cohorts are needed to investigate the relative effects of DBS and dopaminergic medication contributing to the observed changes.

**Limitations**

Our study has several limitations. The multicenter design of the study reduces bias caused by single center studies, increases external validity, and enables to capture data of large samples. Although the cohort size of the overall study population (n=159) is one of the largest in studies of its kind, the matched treatment groups (STN-DBS n=40; MED n=40), however, were relatively small. This might be explained by the fact that we chose a conservative caliper for the matching procedure (0.25), as we wanted to implement a precise matching of the two groups. A narrower caliper would have resulted in smaller matched cohort sizes. Furthermore, although the controlled design of this study enabled us to separate between effects of PD progression and DBS, the treatment assignment was not randomized. In observational “real-life” studies, groups may differ systematically so that direct group comparisons may be misleading. By using propensity score matching, we aimed to increase causal inference by controlling preexisting differences in demographic and clinical parameters between the STN-DBS and MED group.[23] This method was used because a safe and effective treatment option cannot be withheld for three years from patients in advanced PD stages. Propensity score matching provides a precise method to match patients from two groups in these situations and diagnostic statistics in the present study indicated a well-balanced matching for all baseline parameters. However, inter-group comparisons results might have varied depending on the selection of matching variables. The choice of matching parameters was based on a previous publication of our group,[11] as these variables have led to balanced demographic and clinical baseline parameters between the treatment groups. However, we used dopamine agonists medication requirements instead of the overall LEDD for matching, as dopamine agonists dosage may be specifically important when investigating sleep dysfunction, because dopamine agonists have been observed to influence specific aspects of sleep dysfunction in previous publications.[41, 42] Propensity score matching cannot replace randomized trials, as there may be potentially relevant parameters, which were not assessed in the study, such as apathy or impulse control disorders. To account for this limitation, comparisons between the matched groups were carried out using independent sample tests. In the broader context of treatment choices, in the MED group, patients may have decided against surgical treatment options during the three year course of the study, in part, based on their short disease duration (mean 7.5 years in the original cohort) which was even shorter than in the EARLYSTIM study (7.7 years).[3] Additionally, in the STN-DBS group, the matching led to the selection of less severely affected patients, as there were too few matching partners within the defined caliper in the MED group. Consequently, it cannot be ruled out that the observed effects of STN-DBS may be different in patients with very severe PD. Future studies should examine the dependence of DBS outcomes on the different levels of baseline impairment. Another limitation concerns the fact that medication changes were not resolved by an external panel in the present study, as e.g. in the EARLYSTIM study. However, standard-of-care medical therapy in each participating center was based on the same criteria[12] and motor scores and quality of life did not worsen significantly in the MED group over the 36-month period, indicating an effective medical treatment of these aspects. Moreover, as the minimal clinically important difference has not been reported for the PDSS-1 yet, we calculated Cohen’s effect size to quantify clinical relevance of the responses. Furthermore, we were interested in complex subjective sleep symptoms, such as nocturnal psychosis, sleep refreshment, nocturia, and motor state-related sleep symptoms, which cannot be captured by objective measurements of polysomnography or multiple sleep latency test, which measure parameters concerning sleep architecture. Further long-term studies are needed to investigate the relationship between sleep, depression, and anxiety with other neuropsychiatric symptoms, such as apathy, alexithymia, impulse control disorders, and mania[43] as they can develop late under treatment, have partly overlapping neuroanatomical pathways and may therefore be confounding factors in analyses of long-term outcomes.

**Conclusion**

This study provides Class IIb evidence for beneficial effects of STN-DBS compared to standard-of-care medical therapy on overall quality of nights’ sleep and different specific sleep disturbances, such as sleep onset and maintenance insomnia, nocturia, nocturnal motor symptoms, and sleep refreshment at 36-month follow-up. Sleep improvements were partly mediated by improved motor function. Furthermore, we observed no long-term effect of STN-DBS on depression and anxiety symptoms and no correlation between sleep and mood outcomes, indicating that sleep and mood disorders are separately influenced by STN-DBS. Beyond that, sleep and mood outcomes were significantly correlated with QoL improvement, highlighting their clinical relevance and the importance of holistic assessments of non-motor aspects in PD. Studies comparing different treatment options of PD pave the way to personalized medicine for individual patient profiles to better identify patients with the greatest benefits of each treatment option.

**Authors’ Roles**

Stefanie T. Jost – data acquisition, data analysis, drafting of the manuscript, tables and figures

K. Ray Chaudhuri – study concept and design, data acquisition, critical revision of the manuscript

Keyoumars Ashkan – surgical intervention, critical revision of the manuscript

Philipp A. Loehrer – data acquisition, critical revision of the manuscript

Monty Silverdale – data acquisition, critical revision of the manuscript

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**Financial Disclosure/Conflict of Interest**

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**Table 1 – Baseline characteristics in the original cohort and matched sub-cohort.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Original cohort (n=159)** | | | | | | | | |  | **Matched sub-cohort (n=80)** | | | | | | | | |
|  | **STN-DBS** | | |  | **MED** | | |  | ***p*** *a* |  | **STN-DBS** | | |  | **MED** | | |  | ***p*** *a* |
|  | *n* | *M* | *SD* | *n* | *M* | *SD* |  | *n* | *M* | *SD* |  | *n* | *M* | *SD* |  |
| Age | 75 | 61.9 | 8.2 |  | 84 | 65.8 | 10.4 |  | **.006** |  | 40 | 62.2 | 8.6 |  | 40 | 63.8 | 10.4 |  | .343 |
| Disease duration | 75 | 10.2 | 4.7 |  | 84 | 7.5 | 5.0 |  | **<.001** |  | 40 | 9.7 | 4.7 |  | 40 | 8.3 | 4.9 |  | .114 |
| Sex (female/ male) [%] | 75 | 30/45 | [40.0/ 60.0] |  | 84 | 26/58 | [31.0/ 69.0] |  | .249 |  | 40 | 15/25 | [37.5/ 62.5] |  | 40 | 13/27 | [32.5/ 67.5] |  | .815 |
| LEDD total | 74 | 1151.7 | 523.4 |  | 84 | 780.4 | 410.3 |  | **<.001** |  | 40 | 1066.0 | 468.2 |  | 40 | 885.2 | 355.3 |  | .111 |
| LEDD of dopamine agonists | 74 | 315.7 | 258.7 |  | 84 | 219.5 | 220.2 |  | **.015** |  | 40 | 259.9 | 211.2 |  | 40 | 232.8 | 187.8 |  | .449 |
| PDSS total score | 72 | 93.2 | 24.3 |  | 84 | 106.2 | 24.5 |  | **.001** |  | 40 | 94.0 | 25.5 |  | 40 | 101.9 | 22.8 |  | .117 |
| HADS total score | 75 | 10.6 | 6.8 |  | 84 | 11.3 | 6.0 |  | .333 |  | 40 | 10.8 | 7.1 |  | 40 | 13.0 | 6.1 |  | .097 |
| HADS – Anxiety | 75 | 5.7 | 4.0 |  | 84 | 6.2 | 3.4 |  | .257 |  | 40 | 5.8 | 4.0 |  | 40 | 7.0 | 3.5 |  | .165 |
| HADS – Depression | 75 | 4.9 | 3.3 |  | 84 | 5.2 | 3.2 |  | .631 |  | 40 | 5.0 | 3.6 |  | 40 | 6.1 | 3.3 |  | .127 |
| PDQ-8 Summary Index | 75 | 33.2 | 17.9 |  | 84 | 26.2 | 15.4 |  | **.010** |  | 40 | 32.6 | 19.5 |  | 40 | 30.1 | 14.5 |  | .721 |
| SCOPA total score | 75 | 23.4 | 8.9 |  | 84 | 19.5 | 7.3 |  | **.009** |  | 40 | 23.3 | 9.0 |  | 40 | 21.3 | 7.4 |  | .518 |

**Legend:** Demographic characteristics and outcome parameters at baseline in the original cohort and matched sub-cohort. Significant results are highlighted in bold font.

a Mann-Whitney *U* test or *t* test when parametric test criteria were fulfilled.

**Abbreviations: HADS** = Hospital Anxiety and Depression Scale; **LEDD** = levodopa equivalent daily dose; **MED** = standard-of-care medical treatment; **PDSS** = Parkinson’s Disease Sleep Scale-1; **PDQ-8** = 8-item Parkinson’s Disease Questionnaire; **SCOPA** = Scales for Outcomes in Parkinson’s Disease; **STN-DBS** = subthalamic nucleus deep brain stimulation.

**Table 2 – Outcomes at baseline and 36-month follow-up in the matched sub-cohort.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **STN-DBS** | | | | | | | **MED** | | | | | | | |  | |  | |
|  | *n* | Baseline | |  | 36-MFU | |  | Baseline vs. 36‑MFU |  | *n* | Baseline | |  | 36-MFU | |  | Baseline vs. 36‑MFU |  | STN-DBS vs. MED |
| *M* | *SD* |  | *M* | *SD* |  | *p* a |  | *M* | *SD* |  | *M* | *SD* |  | *p* a |  | *p* b |
| PDSS total score | 40 | 94.0 | 25.5 |  | 106.7 | 19.1 |  | **.003** |  | 40 | 101.9 | 22.8 |  | 92.4 | 20.7 |  | .015 |  | **<.001** |
| Overall quality of night’s sleep | 40 | 4.4 | 3.0 |  | 5.8 | 2.7 |  | **.015** |  | 40 | 5.5 | 2.5 |  | 5.1 | 2.5 |  | .594 |  | **.019** |
| Sleep onset and maintenance insomnia | 40 | 11.0 | 5.9 |  | 14.1 | 4.7 |  | **.001** |  | 40 | 13.6 | 5.4 |  | 13.4 | 5.1 |  | .768 |  | **.012** |
| Nocturnal restlessness | 40 | 10.9 | 6.1 |  | 13.7 | 4.9 |  | **.028** |  | 40 | 11.3 | 5.0 |  | 10.3 | 4.8 |  | .296 |  | **.017** |
| Nocturnal psychosis | 40 | 16.9 | 3.8 |  | 15.4 | 4.7 |  | .070 |  | 40 | 15.2 | 4.9 |  | 14.6 | 4.3 |  | .115 |  | .988 |
| Nocturia | 40 | 11.0 | 5.8 |  | 11.3 | 5.5 |  | .816 |  | 40 | 13.9 | 4.6 |  | 11.4 | 4.9 |  | **.004** |  | **.027** |
| Nocturnal motor symptoms | 40 | 27.5 | 8.6 |  | 32.5 | 7.4 |  | **<.001** |  | 40 | 29.5 | 8.6 |  | 26.1 | 9.0 |  | .087 |  | **<.001** |
| Sleep refreshment | 40 | 6.1 | 3.2 |  | 6.6 | 2.9 |  | .374 |  | 40 | 6.6 | 3.1 |  | 5.2 | 2.7 |  | **.042** |  | **.032** |
| Daytime dozing | 40 | 6.5 | 3.6 |  | 7.2 | 3.1 |  | .342 |  | 40 | 7.2 | 2.8 |  | 6.4 | 3.1 |  | .133 |  | .062 |
| HADS total score | 40 | 10.8 | 7.1 |  | 10.4 | 7.8 |  | .806 |  | 40 | 13.0 | 6.1 |  | 13.6 | 6.6 |  | .663 |  | .953 |
| HADS – Anxiety | 40 | 5.8 | 4.0 |  | 5.4 | 4.5 |  | .796 |  | 40 | 7.0 | 3.5 |  | 6.5 | 3.7 |  | .307 |  | .554 |
| HADS – Depression | 40 | 5.0 | 3.6 |  | 5.0 | 3.7 |  | .504 |  | 40 | 6.1 | 3.3 |  | 7.1 | 3.6 |  | .052 |  | .310 |
| PDQ-8 Summary Index | 40 | 32.6 | 19.5 |  | 28.3 | 20.2 |  | .169 |  | 40 | 30.1 | 14.5 |  | 34.8 | 18.2 |  | .226 |  | **.030** |
| SCOPA total score | 40 | 23.3 | 9.0 |  | 18.2 | 9.2 |  | **.003** |  | 40 | 21.3 | 7.4 |  | 23.1 | 10.6 |  | .318 |  | **.006** |
| LEDD total (mg) | 40 | 1066.0 | 468.2 |  | 664.7 | 436.6 |  | **<.001** |  | 40 | 885.2 | 355.3 |  | 961.3 | 397.8 |  | .456 |  | **<.001** |
| LEDD of dopamine agonists (mg) | 40 | 259.9 | 211.2 |  | 113.0 | 114.1 |  | **<.001** |  | 40 | 232.8 | 187.8 |  | 192.9 | 180.2 |  | .226 |  | **.017** |

**Legend:** Outcome parameters at baseline and follow-up for STN-DBS and MED groups. Multiple comparisons due to multiple outcome parameters were corrected with Benjamini-Hochberg’s method. Post-hoc exploratory analyses were conducted for PDSS domains and HADS subscales. Significant results are highlighted in bold font.

a Wilcoxon signed rank test between baseline and 36-month follow-up to analyze within-group changes of outcome parameters

b Mann-Whitney *U* test to analyze between-group longitudinal differences of change scores between STN-DBS and MED group.

Significant results are highlighted in bold font.

**Abbreviations: 36-MFU** = 36-month follow-up; **HADS** = Hospital Anxiety and Depression Scale, **LEDD** = Levodopa equivalent daily dose; **MED** = standard-of-care medical treatment group; **PDSS** = Parkinson’s Disease Sleep Scale-1; **PDQ-8** = 8-item Parkinson’s Disease Questionnaire; **SCOPA** = Scales for Outcomes in Parkinson’s Disease; **STN-DBS** = subthalamic nucleus deep brain stimulation.

**Figure 1 – Patient selection.**

****

**Abbreviations:** **MMSE** = Mini-Mental State Examination; **MED** = standard-of-care medical treatment group; **STN-DBS** = subthalamic nucleus deep brain stimulation.

**Figure 2 ­– Parkinson’s Disease Sleep Scale domain scores at baseline and 36-month follow-up for the STN-DBS and MED groups in clustered boxplots and radar charts.**



**Legend:** PDSS domain scores at baseline (blue) and 36-MFU (red) for the STN-DBS and MED groups as clustered box plots (A) and radar charts (B). Significant within-group changes of PDSS domains from baseline to 36-MFU are highlighted with a black star and significant between-group differences (STN-DBS vs MED) with a cross. (A) In the clustered box plot, small circles represent outliers (2–3 SD). (B) PDSS domain scores are presented as percentage of maximum domain scores. Smaller areas represent more severe sleep impairment.

In the STN-DBS group, PDSS domains overall quality of night’s sleep, sleep onset and maintenance insomnia, nocturnal restlessness, and nocturnal motor symptoms significantly improved from baseline to 36-MFU. In the MED group, nocturia and sleep refreshment significantly worsened from baseline to 36-MFU. Between-group longitudinal differences in PDSS domain scores were significant for overall quality of night’s sleep, sleep onset and maintenance insomnia, nocturnal restlessness, nocturia, nocturnal motor symptoms, and sleep refreshment.

**Abbreviations: 36-MFU** = 36-month follow-up; **MED** = standard-of-care medical treatment; **PDSS** = Parkinson’s Disease Sleep Scale-1; **STN-DBS** = subthalamic nucleus deep brain stimulation.

**Supplementary Table e-1 – Baseline characteristics in the original cohort and matched sub-cohort.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Original cohort (n=159)** | | | | | | | | |  | **Matched sub-cohort (n=80)** | | | | | | | | |
| **STN-DBS** | | |  | **MED** | | |  | ***p* a** | **STN-DBS** | | |  | **MED** | | |  | ***p* a** |
|  | *n* | *M* | *SD* |  | *n* | *M* | *SD* |  |  | *n* | *M* | *SD* | *n* | *M* | *SD* |  |
|  |
| SCOPA-tremor | 75 | 20.2 | 20.0 |  | 84 | 15.9 | 19.0 |  | .127 |  | 40 | 24.6 | 21.4 |  | 39 | 16.9 | 17.7 |  | .096 |
| SCOPA-axial symptoms | 73 | 28.6 | 17.4 |  | 84 | 27.8 | 17.4 |  | .903 |  | 40 | 26.8 | 16.4 |  | 40 | 30.1 | 18.1 |  | .438 |
| SCOPA-dysphagia and dysarthria | 73 | 23.7 | 14.1 |  | 84 | 18.8 | 12.1 |  | **.021** |  | 40 | 21.4 | 12.7 |  | 39 | 19.7 | 12.6 |  | .444 |
| SCOPA-bradykinesia | 75 | 41.1 | 20.2 |  | 84 | 35.9 | 17.8 |  | .067 |  | 40 | 40.4 | 18.5 |  | 39 | 39.1 | 18.4 |  | .666 |
| SCOPA-dyskinesia | 74 | 37.2 | 31.8 |  | 84 | 17.7 | 22.9 |  | **<.001** |  | 40 | 35.4 | 32.3 |  | 40 | 24.2 | 26.7 |  | .113 |
| SCOPA-ON/OFF fluctuations | 74 | 43.9 | 26.4 |  | 84 | 33.3 | 15.7 |  | **<.001** |  | 40 | 40.8 | 26.7 |  | 40 | 33.8 | 17.9 |  | .098 |
| MMSE (range 0–30) | 75 | 29.0 | 1.1 |  | 83 | 28.7 | 1.5 |  | .438 |  | 40 | 29.2 | 0.90 |  | 40 | 28.9 | 1.30 |  | .394 |

**Legend:** SCOPA subscores are presented as percentage of maximum domain score. Significant results are highlighted in bold font.

a Mann-Whitney *U* test or *t* test, when parametric test criteria were fulfilled.

Tremor subscore was based on items 1 and 2; axial subscore on items 5, 6, 7, 9, 15, and 16; bradykinesia subscore on items 3 and 4; dysphagia and dysarthria subscore on items 8, 10, and 11; dyskinesia subscore on items 18 and 19; and ON/OFF fluctuations subscore on items 20 and 21.

**Abbreviations: MED** =standard-of-care medical treatment; **MMSE** =Mini-Mental State Examination; **SCOPA** = Scales for Outcomes in Parkinson’s disease; **STN-DBS** = subthalamic nucleus deep brain stimulation.

**Supplementary Table e-2 – Outcomes at baseline and follow-up in subthalamic stimulation and medical treatment group in the original cohort.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **STN-DBS (n=75)** | | | | | | | **MED (n=84)** | | | | | | |
|  |  | Baseline | | | 36-MFU | | Baseline vs. 36-MFU a |  |  | Baseline | | 36-MFU | | Baseline vs. 36-MFU a |  | STN-DBS vs. MED b |
| *n* | *M* | *SD* | *M* | | *SD* | *p* |  | *n* | *M* | *SD* | *M* | *SD* | *p* |  | *p* |
| PDSS total score | 72 | 93.2 | 24.3 | 99.1 | | 25.5 | **.032** |  | 84 | 106.2 | 24.5 | 96.4 | 24.2 | **<.001** |  | **<.001** |
| PDSS item scores |  |  |  |  | |  |  |  |  |  |  |  |  |  |  |  |
| Overall quality of night’s sleep | 72 | 4.0 | 2.9 | 5.3 | | 2.8 | **.009** |  | 84 | 5.7 | 2.7 | 5.7 | 2.6 | .765 |  | **.018** |
| Sleep onset and maintenance insomnia | 72 | 11.5 | 5.8 | 13.1 | | 5.1 | **.026** |  | 84 | 14.1 | 5.1 | 13.7 | 5.0 | .414 |  | **.032** |
| Nocturnal restlessness | 73 | 10.4 | 6.2 | 12.8 | | 6.5 | **.007** |  | 84 | 12.2 | 5.1 | 11.6 | 5.0 | .280 |  | **.004** |
| Nocturnal psychosis | 72 | 16.9 | 3.6 | 15.2 | | 4.7 | **.005** |  | 84 | 16.3 | 4.3 | 14.8 | 4.4 | **<.001** |  | .513 |
| Nocturia | 72 | 11.1 | 5.2 | 10.8 | | 5.4 | .604 |  | 84 | 13.6 | 4.5 | 11.6 | 4.7 | **.001** |  | .065 |
| Nocturnal motor symptoms | 72 | 27.2 | 9.0 | 29.4 | | 9.2 | **.031** |  | 84 | 30.5 | 8.2 | 27.3 | 9.4 | **.004** |  | **<.001** |
| Sleep refreshment | 73 | 5.9 | 3.2 | 6.2 | | 2.9 | .233 |  | 84 | 6.7 | 2.8 | 5.9 | 2.8 | .073 |  | **.044** |
| Daytime dozing | 72 | 6.4 | 3.4 | 7.1 | | 3.1 | .077 |  | 84 | 7.1 | 3.2 | 6.4 | 3.0 | **.038** |  | **.007** |
| HADS-T | 75 | 10.6 | 6.8 | 11.2 | | 7.4 | .275 |  | 84 | 11.3 | 6.0 | 12.4 | 6.6 | .130 |  | .940 |
| HADS-A | 75 | 5.7 | 4.0 | 5.6 | | 4.4 | .903 |  | 84 | 6.2 | 3.4 | 6.2 | 3.7 | .855 |  | .826 |
| HADS-D | 75 | 4.9 | 3.3 | 5.5 | | 3.8 | .069 |  | 84 | 5.2 | 3.2 | 6.2 | 3.7 | **.008** |  | .522 |
| PDQ-8 SI | 75 | 33.2 | 17.9 | 31.4 | | 20.6 | .275 |  | 84 | 26.2 | 15.4 | 32.0 | 18.0 | **.014** |  | **.012** |
| SCOPA-T | 75 | 23.4 | 8.9 | 18.1 | | 9.2 | **<.001** |  | 84 | 19.5 | 7.3 | 21.2 | 9.7 | .098 |  | **<.001** |
| LEDD (mg) | 74 | 1151.7 | 523.4 | 720.4 | | 463.8 | **<.001** |  | 84 | 780.4 | 410.3 | 923.6 | 505.2 | **.014** |  | **<.001** |
| LEDD dopamine agonists (mg) | 74 | 315.7 | 258.7 | 140.2 | | 151.5 | **<.001** |  | 84 | 219.5 | 220.2 | 191.2 | 209.8 | .098 |  | **<.001** |

**Legend:** Outcome parameters at baseline and follow-up for STN-DBS and MED groups. Multiple comparisons due to multiple outcome parameters were corrected with Benjamini-Hochberg’s method. Post-hoc exploratory analyses were performed for PDSS domains. Significant results are highlighted in bold font.

a Wilcoxon signed rank test between baseline and 36-month follow-up to analyze within-group changes of outcome parameters

b Mann-Whitney U test to analyze between-group longitudinal differences of change scores between STN-DBS and MED group.

**Abbreviations: 36-MFU** = 36-month follow-up; **LEDD** = levodopa equivalent daily dose; **MED** = standard-of-care medical treatment; **PDQ-8 SI** = 8-item Parkinson’s Disease Questionnaire Summary Index; **PDSS** = Parkinson’s Disease Sleep Scale-1; **SCOPA** = Scales for Outcomes in Parkinson’s disease; **STN-DBS** = subthalamic nucleus deep brain stimulation.

**Supplementary Table e-3 – Change scores, Relative changes and Effect sizes for the matched sub-cohort.**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Change Score** | |  | **Relative change (%)** | | |  | **Effect size** | |
|  | STN-DBS | MED |  | STN-DBS | MED |  | Cohen’s d | Classification |
| PDSS total score | –12.7 | 9.5 |  | –13.5 | 9.3 | |  | 0.91 | large |
| HADS total score | 0.4 | –0.6 |  | 3.7 | –4.6 | |  | 0.15 | – |
| HADS – Anxiety | 0.4 | ­0.5 |  | 6.9 | 7.1 | |  | 0.03 | – |
| HADS – Depression | 0.0 | –1.0 |  | 0.0 | –16.4 | |  | 0.29 | small |
| PDQ-8 Summary Index | 4.3 | –4.7 |  | 13.2 | –15.6 | |  | 0.52 | moderate |
| SCOPA total score | 5.1 | –1.7 |  | 21.9 | –8.0 | |  | 0.83 | large |
| LEDD total (mg) | 401.3 | ­–76.1 |  | 37.7 | –8.6 | |  | 1.14 | large |
| LEDD of dopamine agonists (mg) | 146.9 | 39.9 |  | 56.5 | 17.1 | |  | 0.53 | moderate |

**Legend:** Change scores and relative changes from baseline to 36-month follow-up in the STN-DBS and MED group. Effect sizes of the between-group longitudinal comparison STN-DBS vs. MED (Mann-Whitney *U* test). Effect sizes were favorable for STN-DBS for PDSS total score, SCOPA total score and LEDD total (large effects), PDQ-8 Summary Index and LEDD of dopamine agonists (moderate effects) and HADS depression subscale (small effects) and negligible for HADS total score and anxiety subscale..

Change Score = mean testbaseline – mean testfollow-up

Relative Change = (mean testbaseline – mean testfollow-up) / mean testbaseline x 100

Cohen’s *d* = (mean pre-post changetreatment group – mean pre-post changecontrol group) / SD pretestpooled groups.

Cohen’s *d* was classified as ‘small’ (0.20≥*d*<0.50), ‘moderate’ (0.50≥*d*<0.80) and ‘large’ (*d*≥0.80).

**Abbreviations: HADS** = Hospital Anxiety and Depression Scale, **LEDD** = Levodopa-equivalent daily dose; **MED** = standard-of-care medical treatment group; **PDSS** = Parkinson’s Disease Sleep Scale-1; **PDQ-8** = 8-item Parkinson’s Disease Questionnaire; **SCOPA** = Scales for Outcomes in Parkinson’s Disease; **STN-DBS** = subthalamic nucleus deep brain stimulation.

**Supplementary Figure 1: Parkinson’s Disease Sleep Scale item scores at baseline and 36-month follow-up for the STN-DBS and MED groups in clustered boxplots.**

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**Legend:** PDSS item scores at baseline (blue) and 36-MFU (red) for the STN-DBS and MED groups as clustered box plots. Significant within-group changes of PDSS items from baseline to 36-MFU are highlighted with a black star and significant between-group longitudinal differences (STN-DBS vs MED) with a cross. Outliers are illustrated with dots (2-3 SD) and extreme outliers with colored stars (>3 SD).

In the STN-DBS group, PDSS items overall quality of night’s sleep, sleep onset insomnia, sleep maintenance insomnia, nocturnal restlessness, wakefulness due to numbness/tingling, early waking due to painful posturing, and tremor on wakeup significantly improved from baseline to 36-MFU. In the MED group, urinary incontinence during motor OFF at night and sleep refreshment significantly worsened from baseline to 36-MFU. Between-group longitudinal differences in PDSS items were significant for overall quality of night’s sleep, sleep onset insomnia, nocturnal restlessness, urinary incontinence during motor OFF at night, wakefulness due to numbness/tingling, early waking due to painful posturing, tremor on wakeup, and sleep refreshment.

**Abbreviations: 36-MFU** = 36-month follow-up; **MED** = standard-of-care medical treatment; **PDSS** = Parkinson’s Disease Sleep Scale-1; **STN-DBS** = subthalamic nucleus deep brain stimulation.