ARTICLE CLASS OF EVIDENCE

Deep brain stimulation improves restless legs syndrome in patients with Parkinson disease

Olga Klepitskaya, MD, Ying Liu, MD, Saloni Sharma, MBBS, Stefan H. Sillau, PhD, Jean Tsai, MD, PhD, and Arthur S. Walters, MD

Neurology® 2018;91:e1013-e1021. doi:10.1212/WNL.0000000000006162

Correspondence
Dr. Klepitskaya
olga.klepitskaya@ucdenver.edu

Abstract

Objective

To study the effect of subthalamic nucleus (STN) deep brain stimulation (DBS) in patients with Parkinson disease (PD) and moderate to severe restless legs syndrome (RLS) on their RLS symptoms.

Methods

Patients undergoing STN DBS surgery for PD completed the International RLS Study Group Rating Scale (IRLS) and RLS Quality of Life (QoL) questionnaires preoperatively and postoperatively at 6 months, 1 year, and 2 years. The primary outcome measure was IRLS sum score and subscales (severity and impact) and the secondary measure was RLS QoL scores. Differences among the mean scores over time were analyzed using mixed model regression.

Results

Twenty-two patients were enrolled. The preoperative IRLS sum scores were 19.59 ± 6.95, severity subscale 12.91 ± 4.33, impact subscale 4.45 ± 2.72, and transformed RLS QoL score 68.30 ± 20.26. The differences between preoperative and averaged postoperative scores were IRLS sum score −7.80, severity subscale −5.50, impact subscale −1.20, and RLS QoL 4.73. The overall F tests demonstrated differences among the times for the means of the IRLS sum and subscales: $p < 0.05$. There were no correlations between RLS symptoms improvement and PD motor symptoms improvement or reduction in PD medications. Half of the patients had at least 50% improvement and 27% had resolution of their RLS symptoms (IRLS = 0).

Conclusions

STN DBS significantly decreased RLS symptoms in patients with PD despite a decrease in dopaminergic treatment. This improvement was sustained over a 2-year period.

Classification of evidence

This study provides Class IV evidence that for patients with PD and moderate to severe RLS, STN DBS improves RLS symptoms.

MORE ONLINE

→ **Class of Evidence**
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

From the Department of Neurology (O.K., Y.L., S.H.S., J.T.), University of Colorado Denver, Aurora; University of Rochester (S.S.), NY; and Division of Sleep Medicine (A.S.W.), Vanderbilt University School of Medicine, Nashville, TN.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

DBS = deep brain stimulation; **GPi** = globus pallidus; **IRLS** = International RLS Study Group Rating Scale; **LE** = levodopa equivalents; **PD** = Parkinson disease; **RLS** = restless legs syndrome; **RLS QoL** = RLS Quality of Life Questionnaire; **STN** = subthalamic nucleus; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Restless legs syndrome (RLS) is more common in Parkinson disease (PD) (10%–50%)[1,2] compared to the general population (2.5%–10%).[3,4] Deep brain stimulation (DBS) is a well-established modality for the treatment of dopamine-responsive motor symptoms in advanced PD.[5,6] It is reasonable to postulate that because RLS responds well to dopaminergic therapy, it would improve with DBS as well. However, literature on this topic is limited and existing publications demonstrate conflicting results.[7–14] Two studies reported improvement in RLS symptoms after subthalamic nucleus (STN) DBS in patients with PD. Chahine et al.[7] reported significant improvement in International RLS Study Group Rating Scale (IRLS) scores in 6 patients; Driver-Dunckley et al.[9] reported a mean of 84% improvement in IRLS scores in 6 patients with complete resolution of symptoms in three of them. In addition, DBS and lesioning of the globus pallidus (GPi) have been reported to improve RLS symptoms.[11–13] Ondo et al.[12] reported a case of an extremely severe idiopathic RLS refractory to all medical therapy that improved after implantation of bilateral GPi DBS. Okun et al.[13] reported a case of a patient with generalized dystonia whose RLS resolved after bilateral GPi DBS and recurred unilaterally after an infection required removal of one of the devices. In contrast, emergence of RLS after STN DBS was demonstrated in 2 studies. Kedia et al.[8] reported emergence of new problematic RLS symptoms in 11 out of 195, and Marques et al.[10] in 6 out of 31 patients with PD after STN DBS. One study showed no effect on RLS symptoms among 9 patients with essential tremor who were treated with thalamic ventral intermediate nucleus (Vim) DBS.[14]

Methods

The aim of this study was to evaluate the effect of STN DBS on RLS symptoms in patients with PD and RLS. This retrospective clinical cohort study included all patients who underwent STN DBS for PD at the University of Colorado Hospital from January 2008 to December 2013.[15] This study was approved by the Institutional Review Board at University of Colorado (COMIRB 16-1127).

All patients were evaluated in the University of Colorado movement disorder clinic, completed comprehensive presurgical workup, and were approved for DBS surgery for PD by the multidisciplinary team of experts. The diagnosis of RLS was made according to the latest diagnostic criteria for RLS, based on 4 essential criteria and exclusion of the RLS mimics, such as peripheral neuropathy, radiculopathy, leg cramps, positional discomfort, and akathisia.[16] The diagnosis was made by experienced movement disorders neurologists using detailed history and thorough neurologic examination, as well as additional testing where appropriate. Clinical assessments were done per routine DBS program protocol preoperatively and postoperatively at 6 months, 1 year, and 2 years after surgery. All patients were asked to complete the IRLS[17] and the RLS Quality of Life Questionnaire (RLS QoL)[18] among other clinically relevant assessments. Only data from the patients with idiopathic PD who reported moderate to severe RLS (IRLS sumscores >10) and completed questionnaires preoperatively and at least one time point postoperatively were included in the analysis. It is a common standard for all therapeutic studies in RLS, in particular those that resulted in the Food and Drug Administration approval of medications to treat RLS, to exclude patients with mild RLS (IRLS score <15 or <10, depending on the protocol) to avoid a floor effect.

General data were collected through medical record chart review, including demographics, Unified Parkinson's Disease Rating Scale (UPDRS), and medications preoperatively and at each postoperative time point. Dopaminergic medications were converted into levodopa equivalents (LE), according to the accepted formula[19] (LE = immediate-release levodopa × 1 + controlled-release levodopa × 0.75 + pramipexole × 100 + ropinirole × 20 + rotigotine × 30 + selegiline × 10). The use of concomitant medications that can potentially affect RLS symptoms was analyzed as well. These medications were grouped in the benzodiazepines, opioids, and gabapentinoids. All data were deidentified.

The primary outcome measures were the IRLS sumscore and subscales (severity of symptoms and effect of the symptoms). IRLS is a validated 10-question instrument for measuring severity of RLS.[17] The scale reflects subjective assessment of the primary features (questions 1, 2, 3, and 6), intensity and frequency of symptoms (questions 7 and 8), and associated sleep problems (questions 4 and 5). The scale also includes questions that probe the effect of symptoms on the patient's mood and daily functioning (questions 9 and 10).[17] Each question has a choice of 5 response options graded from no RLS (score = 0) to very severe RLS (score = 4). This produces a total score ranging from 0 to 40. IRLS sum and subscale scores (symptoms severity in questions 1, 2, 4, and 6 through 8; symptoms impact in questions 5, 9, and 10) were recorded at every time point. Item 3 was used for the total score for overall RLS severity.[17] IRLS scores were analyzed as changes from preoperation (baseline) to postoperation (6 months, 1 year, or 2 years).

The secondary outcome measures were the RLS QoL scores. RLS QoL is a questionnaire specifically developed to assess the effect of RLS on the quality of life among patients with RLS.[18] It has been validated in a clinical setting and shows sensitivity to change with treatment in a clinical trial setting and it is the only scale designated as "recommended for use in cross-sectional assessments and treatment-related changes in RLS quality of life" by the Movement Disorders Society Committee on Rating Scales.[20] The total score of RLS QoL (sum over items 1–5, 7–10, and 13) was recorded at baseline preoperatively and 6 months, 1 year, and 2 years postoperatively[21] and was transformed to a 100% interval, with 100 representing optimal status.

This study is an uncontrolled retrospective clinical cohort study that uses the IRLS scores, a subjective outcome measurement, as the primary outcome, and the RLS QoL scores, a subjective patient assessment of RLS-related QoL, as a secondary outcome measure. This study design provides Class IV evidence in regards of the effect of STN DBS on RLS symptoms on patients with PD and moderate to severe RLS.

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Statistical analysis

All statistical analyses were performed on an available case basis in SAS 9.4. The default α was 0.05. The primary independent variable was time (baseline, 6 months, 1 year, and 2 years follow-up). The primary dependent variables were the IRLS and the RLS QoL scales. No covariates were included, nor were subgroup analyses or interaction tests feasible, because of the sample size and the lack of control. Since the data were longitudinal, they were analyzed with mixed model regression with time as a categorical and an unstructured covariance matrix for repeated measures on patient-provided maximum flexibility. Longitudinal correlation was used to compensate for at random missingness for all patients with at least one measurement. Because longitudinal correlation compensates for missingness at random, and because of the limitations of the sample and the absence of a reliable imputation model, no missing data imputation was attempted. Regression methods were used because they are relatively robust to deviations for normally distributed data, as long as the data are not strongly skewed.

Changes in the IRLS and the RLS QoL scales were assessed by estimating and testing linear contrasts among the time points in the mixed regression model. A protective omnibus F test simultaneously compared all follow-up times to baseline. A statistically significant F test permits pairwise comparisons among time points without further adjustment for multiple comparisons, within a single model. A statistically nonsignificant F test means none of the pairwise comparisons among time points can be truly statistically significant, regardless of their univariate p values. An equally weighted average of the 3 follow-up times compared to baseline was also constructed as a summary measure.

Tukey-Kramer adjustment controlled the familywise error rate for all pairwise comparisons among time points within the model results for a single outcome, a more conservative approach than relying solely on the protective F test. For adjusting for multiple comparisons across multiple models and outcomes, both the Benjamini Hochberg method and the Bonferroni method were considered. The Benjamini Hochberg method controls the false discovery rate at $\alpha = 0.05$ and the Bonferroni method controls the familywise error rate at $\alpha = 0.05$, but is ultraconservative. Spearman and Pearson correlations were calculated between changes in IRLS and RLS QoL scores and change in LE for each follow-up time and change in UPDRS before and after surgery. Spearman was used to detect any monotonic trend, while Pearson was used because it is more powerful for linear relationships. Multiple comparison adjustment was not performed for the tests of correlation because we wanted to be anticonservative in investigating whether there was any evidence of correlation.

Result

The retrospective search yielded 22 patients with idiopathic PD and RLS who met the inclusion criteria: 13 female and 9 male. The mean patient age at first interview was 58.3 ± 7.4 years (table 1). Mean PD disease duration was 10.2 ± 4.9 years. The baseline mean UPDRS III (motor) scores before surgery were 17.25 (SD 14.03) "on" medication and 41.57

Table 1 Demographic characteristics at baseline (before deep brain stimulation surgery, n = 22)

Variable	Mean (SD)
Age, y	58.3 (7.4)
Male/female	9/13
Age at onset, y (PD)	48.4 (6.8)
Years since symptoms onset	10.2 (4.9)
UPDRS III "on"	17.25 (14.03)
UPDRS III "off"	41.57 (12.40)
IRLS sum	19.59 (6.95)
IRLS severity	12.91 (4.33)
IRLS impact	4.45 (2.72)
RLS QoL	68.30 (20.26)
LE	1203.2 (657.5)

Abbreviations: IRLS = International RLS Study Group rating scale; LE = levodopa equivalents; "off" = 12 hours "off" short-acting and 24 hours "off" long-acting PD medications; "on" = typical functional state when patients are receiving medication and have a good response; PD = Parkinson disease; RLS QoL = RLS Quality of Life Questionnaire; UPDRS III = Unified Parkinson's Disease Rating Scale part III, motor score.

(SD 12.40) "off" medication. The baseline mean IRLS score, reflecting RLS severity, was 19.59 (SD 6.95). Fifteen patients had moderate (IRLS score between 10 and 20) and 7 severe (IRLS scores >20) RLS. Bilateral STN DBS was performed in 21 out of 22 patients (95% bilateral). Because the sample in this study was a sample of convenience, only subsets of the patients were available for each follow-up visit. There were 17 patients with visits at the 6-month follow up, 13 with visits at the 1-year follow up, and 10 with visits at the 2-year follow-up. Nine patients had 1 follow-up, 8 had 2 follow-ups, and 5 had all 3 follow-ups. The data missingness is believed to be mostly random, because patients filled out multiple questionnaires related to their PD and several other symptoms frequently encountered in PD at their own will and were not required to do so. The most common reason for loss of follow-up was the change in clinical provider due to relocation or change in insurance. All of the 22 patients, however, were required to have at least 1 follow-up.

From the overall *F* tests, there was evidence of differences between preoperative and postoperative IRLS scores, demonstrating significant improvement after DBS: *p* value for the sumscore is 0.0109, for the severity subscale 0.0126, and for the symptoms impact subscale 0.0003. For the IRLS sumscores and severity subscale, all of the postoperative time differences were individually statistically significant when compared to baseline, even after applying the Tukey-Kramer adjustment for controlling the familywise error rate for all pairwise time comparisons within a model. For the IRLS impact subscale, the only individually statistically significant postoperative time compared with baseline was 1 year (tables 2 and 3 and figure 1A). There was no evidence of difference among 3 postoperative time points for the IRLS sumscores and severity subscale, demonstrating no change in RLS symptoms between 6 months to 2 years postoperatively: *p* values = 0.2535 and 0.1549, respectively. Estimates suggest stability or continued improvement after initial improvement, and there are no indications of worsening. The IRLS impact subscale improved significantly between 6 months and 1 year postoperatively: estimated change = −1.01, univariate *p* value = 0.0032, Tukey-Kramer adjusted *p* value = 0.0155, overall *F* test for differences among follow-up times *p* value = 0.0053. The secondary outcome measure, RLS QoL scale, according to estimates, improved postoperatively, but did not reach significance: there was no statistical evidence of mean differences preoperatively and postoperatively ($p = 0.3627$) or among any of the pairwise time comparisons, or for time-averaged change (table 3). For estimation of the mean differences between preoperative and postoperative, the postoperative scores were averaged over the 3 time points (table 3 and figure 1B).

Applying the Benjamini Hochberg procedure to control the false discovery rate at $\alpha = 0.05$ among all of the contrasts of the individual follow-up times with baseline, across the models all IRLS scales and the RLS QoL scale, 12 tests, we found that all of the univariately statistically significant tests remained statistically significant. Applying the Bonferroni procedure to control the familywise error rate at $\alpha = 0.05$, we found that the contrasts of 1 year to baseline for the IRLS sumscore (adjusted *p* value = 0.0120) and 1 year vs baseline (adjusted *p* value = 0.0120) and 2 years vs baseline (adjusted *p* value = 0.0276) for the IRLS severity score remained statistically significant.

Table 2 Mean scores on the IRLS and RLS QoL at baseline, 6 months, 1 year, and 2 years post–subthalamic nucleus deep brain stimulation

Variable	No. of observations	Mean	SD
IRLS sumscore			
Baseline	22	19.59	6.95
6 mo	17	14.53	12.27
1 y	13	11.74	8.08
2 y	10	12.83	11.26
IRLS severity score[a]			
Baseline	22	12.91	4.33
6 mo	17	9.53	7.86
1 y	13	7.82	5.39
2 y	10	8.12	7.17
IRLS impact score[b]			
Baseline	22	4.45	2.72
6 months	17	3.41	3.61
1 year	13	2.62	2.29
2 years	10	3.50	3.47
RLS QoL transformed score[c]			
Baseline	22	68.30	20.26
6 mo	16	72.26	24.17
1 y	13	76.15	20.07
2 y	10	78.75	22.15
LE			
Baseline	22	1203.2	
6 mo	16	370.8	−69.2
1 y	13	499.7	−58.5
2 y	10	787.7	−34.5

Abbreviations: IRLS = International RLS Study Group Rating Scale; LE = levodopa equivalents; RLS QoL = RLS Quality of Life Questionnaire.
[a] IRLS severity scores, 6 items, 1, 2, 4, 6, 7, 8. Higher score = higher severity.
[b] IRLS impact scores, 3 items, 5, 9, 10. Higher scores = higher impact.
[c] RLS Quality of Life transformed scores = [(actual raw score – lowest possible raw score)/possible raw score range] × 100. Higher score = better quality of life.

Table 3 Longitudinal model estimated differences on the IRLS and RLS QoL scores between baseline and 6 months, 1 year, and 2 years post–subthalamic nucleus deep brain stimulation

Contrast	Estimate	Standard error	*p* Value	Adjusted *p* value[a]
IRLS sumscore				
All postoperatives vs baseline			0.0109	
6 months vs baseline	−5.97	1.96	0.0059	0.0279
1 year vs baseline	−7.07	1.88	0.0010	0.0051
2 years vs baseline	−10.36	3.43	0.0066	0.0308
Postoperatives (averaged) vs baseline	−7.80	2.18	0.0017	
IRLS severity score[b]				
All postoperatives vs baseline			0.0126	
6 months vs baseline	−4.12	1.36	0.0066	0.0311
1 year vs baseline	−5.04	1.32	0.0010	0.0052
2 years vs baseline	−7.35	2.11	0.0023	0.0112
Postoperatives (averaged) vs baseline	−5.50	1.39	0.0007	
IRLS impact score[c]				
All postoperatives vs baseline			0.0003	
6 months vs baseline	−0.70	0.70	0.3276	0.7500
1 year vs baseline	−1.71	0.55	0.0049	0.0235
2 years vs baseline	−1.19	1.01	0.2626	0.6534
Postoperatives (averaged) vs baseline	−1.20	0.65	0.0824	
RLS QoL transformed score[d]				
All postoperatives vs baseline			0.3627	
6 months vs baseline	3.32	4.86	0.5024	0.9024
1 year vs baseline	5.11	4.38	0.2569	0.6547
2 years vs baseline	5.77	6.06	0.3580	0.7780
Postoperatives (averaged) vs baseline	4.73	4.06	0.2579	

Abbreviations: IRLS = International RLS Study Group Rating Scale; RLS QoL = RLS Quality of Life Questionnaire.
[a] Tukey-Kramer adjustment for all pairwise comparisons.
[b] IRLS severity scores, 6 items, 1, 2, 4, 6, 7, 8. Higher score = higher severity.
[c] IRLS impact scores, 3 items, 5, 9, 10. Higher scores = higher impact.
[d] RLS QoL transformed scores = [(actual raw score − lowest possible raw score)/possible raw score range] × 100. Higher score = better QoL.

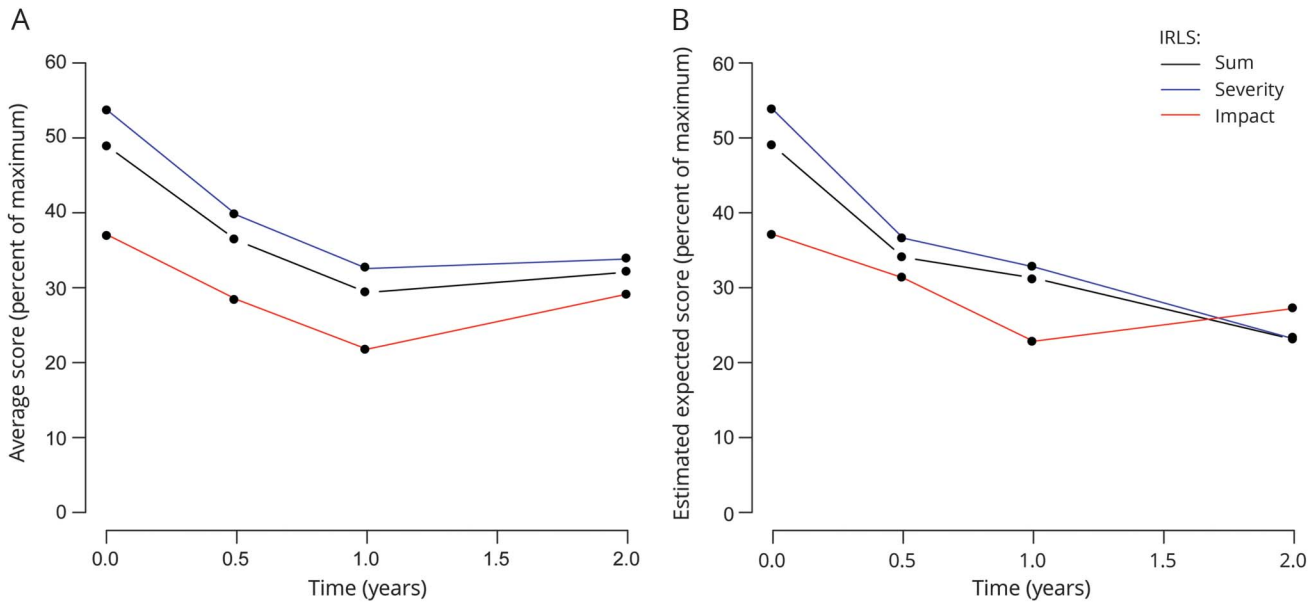
Out of the 22 patients, half had at least 50% improvement, and 27% had resolution of the symptoms (IRLS = 0) at least at one available observation time.

The reduction in mean LE postoperatively was 69.2% at 6 months, 58.5% at 1 year, and 34.5% at 2 years compared to preoperatively, respectively. At $\alpha = 0.05$, there were no statistically significant correlations between changes in the IRLS or the RLS QoL scores and changes in LE (table 4).

The mean improvement in motor symptoms after DBS was 20.07 points on UPDRS III "off" medication (from 37.57 to 17.50) (n = 15, mean −20.07, SD 7.55, $p < 0.0001$). There were no statistically significant correlations between changes in the IRLS or the RLS QoL scores and the degree of improvement in UPDRS III between preoperative "off" medication and postoperative "off" medication/"on" stimulation (table 5). The tests for correlations between changes between preoperative and postoperative LE and IRLS and UPDRS and IRLS change were not statistically significant; however, data collection was not uniform and usable sample sizes were small (9–15), especially for the later times, so power was small (tables 4 and 5).

The majority of the patients in this study (19/22) were using concomitant medications that could potentially affect RLS symptoms. Preoperatively, 8 (36%) patients used

Figure Mean and expected scores



(A) Mean scores on the International RLS Study Group Rating Scale (IRLS) sumscores, severity and impact subscores at baseline, 6 months, 1 year, and 2 years post– subthalamic nucleus deep brain stimulation. (B) Model estimates of expected scores of IRSL sum, severity, and impact. The overall *F* tests demonstrated differences among the times for the means of the IRLS scales: *p* value for the sum score 0.0109, severity subscale 0.0126, and impact subscale 0.0003.

benzodiazepines, 7 (32%) used opiates, and 4 (18%) used both. None of the patients were using gabapentinoids. The most common indications for benzodiazepines were anxiety, insomnia, and REM sleep behavioral disorder, and for opioids, pain. None of the patients were taking these medications specifically for the indication of RLS. There were variety of changes in these medications postoperatively; all of them were made based on other medical issues, not RLS symptoms. No pattern of changes and no correlation with RLS symptoms were noted (table 5, supplementary data links.lww.com/WNL/A666).

Discussion

This study demonstrated a significant improvement of the IRLS sum score and severity and impact subscales in 22 patients with PD and moderate to severe RLS after STN DBS. These improvements lasted for up to 2 years after surgery despite a significant reduction in dopaminergic therapy (34.5%–69.2%). Half of the patients improved to only mild degree of RLS symptoms (<10 on IRLS score), and almost one-third (27.3%) had complete resolution of symptoms. RLS QoL scale also improved postoperatively, although not statistically significantly.

RLS and PD share several features, such as responsiveness to dopaminergic pharmacotherapy, exacerbations by dopaminergic antagonists, and association with periodic limb movements of sleep.[22] There are also differences between RLS and PD. Neuroimaging and pathologic data show normal presynaptic nigrostriatal dopaminergic function and substantia nigra histology in patients with idiopathic RLS compared with abnormal function in the nigrostriatal pathway and neuronal loss in the substantia nigra in patients with PD.[23] Nevertheless, the dopaminergic dysfunction is crucial in pathophysiology of both conditions. Recent literature on the pathophysiology of RLS has implicated central dopaminergic dysfunction in several regions including the substantia nigra, striatum, putamen, and downstream disinhibition of the sensory dorsal horn and the intermediolateral nucleus of the spinal cord.[24,25] DBS is a powerful treatment of dopamine-responsive symptoms of PD, therefore, it is reasonable to expect that DBS can alleviate symptoms of other dopamine-responsive conditions, such as RLS. Although, just like in PD, the exact mechanism of improvement of RLS symptoms after DBS is not known, it had been postulated that STN stimulation modulates the basal ganglia outflow, which decreases the downstream disinhibition at the spinal level, thus alleviating abnormal sensations and motor restlessness.[2,7,13,26]

One crucial variable in examining the effect of DBS on RLS in patients with PD is dopaminergic therapy. Because STN DBS dramatically improves PD motor symptoms, it allows for substantial reduction in the dosage of dopaminergic medications.[27–29] Worsening or emergence of RLS post-DBS, reported in prior studies, might be explained by preoperative masking of RLS symptoms by dopaminergic therapy and re-emergence of symptoms after abrupt decrease or discontinuation of dopaminergic treatment.[8,10] For example, in a series of 195 patients with PD who underwent STN DBS, a greater reduction in antiparkinsonian medication was found in the 11 patients who developed RLS postoperatively compared to those who did not (79% vs 40%).[8] In another study, patients

Table 4 Correlation between IRLS total, severity, and impact subscores or RLS QoL score and changes in LE

Time	No. of observations	Spearman correlation	*p* Value	Pearson correlation	*p* Value
IRLS score					
6 mo	16	−0.20339	0.4499	−0.18566	0.4912
1 y	13	0.06052	0.8443	0.0799	0.7953
2 y	10	0.10303	0.777	0.08439	0.8167
IRLS symptom score					
6 mo	16	−0.26991	0.312	−0.23965	0.3713
1 y	13	0.01653	0.9573	0.04645	0.8802
2 y	10	0.10334	0.7763	0.08739	0.8103
IRLS impact score					
6 mo	16	0.19585	0.4673	0.02188	0.9359
1 y	13	0.30237	0.3153	0.25151	0.4072
2 y	10	0.03087	0.9325	0.09866	0.7863
RLS QoL score					
6 mo	15	−0.10027	0.7222	0.04127	0.8839
1 y	13	−0.15385	0.6158	−0.12174	0.692
2 y	10	0.16413	0.6505	0.14094	0.6977

Abbreviations: IRLS = International RLS Study Group Rating Scale; LE = levodopa equivalents; RLS QoL = RLS Quality of Life Questionnaire.

with emergence of RLS after STN DBS took a higher dose and had a more significant reduction of dopamine agonists compared to patients without emergence of RLS.[10] In our study, patients achieved a reduction of LE 69.2% at 6 months, 58.5% at 1 year, and 34.5% at 2 years after surgery, and yet, they were experiencing significant improvement in their RLS symptoms.[7,9] Moreover, no correlation was found between degree of medication reduction and RLS symptoms improvement (table 4). This supports the notion that DBS has a direct effect on the brain dopaminergic systems rather than affecting symptoms indirectly through change in medications. On the other hand, we cannot absolutely exclude a role of dopaminergic augmentation in the development of RLS symptoms in our patients before surgery and, therefore, the possibility that the postoperative improvement in RLS symptoms observed in our study represents a result of withdrawal of dopaminergic medications in patients who had augmentation. Clinically, we do not believe that many patients had augmentation, because they did not have a rapid spread of the RLS symptoms from the night into the day, which is the key feature of augmentation. However, further studies are needed to determine whether the extent and the rate of dopaminergic agents reduction, specifically dopamine agonists, postoperatively increases the risk of emergence of RLS or improves symptoms in case of augmentation. Until the effect of DBS and effect of medication reduction on RLS symptoms is clarified further, for patients with advanced PD and preexisting RLS, dopaminergic therapy should be reduced gradually after STN DBS with close monitoring of RLS symptoms.

Another important question raised by this and other studies is the characterization of RLS in patients with PD. Idiopathic RLS, RLS occurring in patients with PD, and for that matter, other RLS subtypes, associated with other medical conditions, could possibly have different pathogenesis; therefore, treatment success in one subtype might not be directly applicable to treatment of idiopathic RLS. In the 5 STN DBS studies (including the present study), patients were diagnosed with RLS based on their symptoms, without differentiation between idiopathic vs secondary RLS.[7–10] The difference in the pathogenesis of RLS may contribute to the conflicting reports. Future studies should characterize RLS in their patients in greater detail to address the possibility that different pathogenic mechanisms in a given cohort can affect the outcomes after DBS.

The other important concern about this study, as well as other published studies of the effect of DBS on RLS symptoms, is the lack of placebo control. Consideration of the placebo response is important in establishing effectiveness of any treatment, but it is even more important in this study, because both disease states, PD and RLS, are known to have a high magnitude of placebo response. The fact that RLS responds to both dopaminergic and opioid agents, both acting on the

Table 5 Correlation between IRLS total, symptom, and impact scores or RLS QoL score and UPDRS III score (preoperative "off" medication and postoperative "off" medication/"on" stimulation)

Time	No. of observations	Spearman correlation	*p* Value	Pearson correlation	*p* Value
IRLS score					
6 mo	15	−0.45961	0.0848	−0.35636	0.1923
1 y	12	0.28722	0.3654	0.14649	0.6496
2 y	9	−0.1	0.798	−0.0688	0.8604
IRLS symptom score					
6 mo	15	−0.39408	0.1461	−0.33706	0.2192
1 y	12	0.27369	0.3894	0.12899	0.6895
2 y	9	−0.20084	0.6044	−0.05146	0.8954
IRLS impact score					
6 mo	15	−0.36721	0.1782	−0.23935	0.3903
1 y	12	0.42405	0.1695	0.18877	0.5568
2 y	9	−0.05985	0.8784	−0.01628	0.9669
RLS QoL score					
6 mo	14	0.47351	0.0872	0.33667	0.2392
1 y	12	−0.23077	0.4705	0.02611	0.9358
2 y	9	0.1	0.798	0.15897	0.6829

Abbreviations: IRLS = International RLS Study Group Rating Scale; RLS QoL = RLS Quality of Life Questionnaire.

reward mechanism pathways, has been implicated in the high physiologic response of RLS symptoms to a placebo. A meta-analysis of pharmacologic studies in the treatment of RLS confirmed a large placebo effect on IRLS; matched with a large treatment effect, the pooled placebo response rate was 40.09% (95% confidence interval 31.99–48.19).[30] PD, being a disease of dopamine, is also considered to have one of the highest magnitudes of placebo response,[31] with a placebo response rate between 9% and 59%.[31–35] It is also well-known that the magnitude of the placebo effect is directly related to the cost and the nature of the procedure: the placebo effect increases with increased cost of the intervention and is higher with more invasive procedures (thus, highest with surgeries).[36] All of these make the data regarding the effect of DBS on RLS vulnerable.

We, as well, cannot exclude a placebo effect on RLS symptoms in patients with PD after DBS in our study. However, this effect would unlikely play a substantial role for several reasons. First, by definition, the placebo effect is a therapeutic benefit related to the expectation of benefit in a given therapeutic context. Patients in our center were educated about realistic expectations from surgery and expected improvements of the motor symptoms of PD and not symptoms of RLS. Patients were given RLS-related questionnaires, among many others, as a part of a large battery of tests and scales administered per clinical outcomes protocol and were not in any way "cued" towards improvements in their RLS. In fact, patients much more likely would expect the worsening in RLS symptoms after DBS due to postoperative decrease in medications known to treat RLS. The placebo effect would be unusual in this context. Second, the placebo effect is known to be short-living, having more significant effect on short-term (up to 3 months) than long-term results.[37] Our study demonstrated improvement in RLS symptoms for up to 2 years after surgery. By that time, the placebo effect is usually nonexistent. Nevertheless, the possibility of the placebo effect on RLS symptoms after DBS has to be eliminated in future studies. This highlights the importance of a prospective controlled trial of DBS in RLS, specifically idiopathic RLS, with greater power. Methodologies such as sham stimulation, blinding of "on" and "off" stimulation, and crossover study should be considered in order to account for factors that can affect the outcome.[38]

In our study, STN DBS significantly decreased the symptoms of moderate to severe RLS in patients with PD despite a decrease in dopaminergic treatment. This improvement was sustained over a 2-year period. There was no correlation between the degree of RLS symptoms improvement and degree of medications reduction or improvement of PD motor symptoms after DBS. These results suggest that DBS could be effective for treatment of RLS in patients with PD and, possibly, in severe medication-refractory idiopathic RLS as well. The

study underscores the importance of further investigations and provides directions for future research to clarify the effect of DBS on RLS symptoms.

Author contributions

Dr. Klepitskaya contributed to study concept, design, data collection, and interpretation, preparation of first draft of manuscript and subsequent revisions. Dr. Liu contributed to data entry, preparation of first draft of manuscript and subsequent revisions. Dr. Saloni Sharma contributed to initial data entry. Dr. Sillau contributed statistical analysis. Dr. Tsai contributed to preparation of first draft of manuscript and subsequent revisions. Dr. Walters contributed to study concept, design, and manuscript revisions.

Acknowledgment

The authors thank Nicole Leith for assistance in compiling, editing, and submitting the article and the patients who participated in this study.

Study funding

Supported by donations for research support from Elizabeth and Gregory Gerhard and Edwin and Donna Brand.

Disclosure

O. Klepitskaya received a research grant from Davis Phinney Foundation; serves as an investigator on clinical trials sponsored by Neuroderm, Abbott, Pharma2B, USWorldMeds, and Intec; serves as a consultant at Schlesinger Associates and Olson Research Group, Inc.; performs DBS in her practice (50% effort); received honoraria for a presentation from Medtronics; received institutional support from the University of Colorado and Colorado Department of Public Health and Environment; and received funding for trips to investigator meetings from Neuroderm. Y. Liu received support from Colorado Department of Public Health and Environment and David Phinney Foundation. S. Sharma, S. Sillau, and J. Tsai report no disclosures relevant to the manuscript. A. Walters has received research funding from MundiPharma and Xenoport/Arbor for studies on restless legs syndrome and is coinvestigator on 2 funded NIH R01 grants on restless legs syndrome. Go to Neurology.org/N for full disclosures.

Received January 25, 2018. Accepted in final form June 14, 2018.

References

1. Fereshtehnejad SM, Shafieesabet M, Shahidi GA, Delbari A, Lokk J. Restless legs syndrome in patients with Parkinson's disease: a comparative study on prevalence, clinical characteristics, quality of life and nutritional status. Acta Neurol Scand 2015;131:211–218.
2. Rijsman RM, Schoolderman LF, Rundervoort RS, Louter M. Restless legs syndrome in Parkinson's disease. Parkinsonism Relat Disord 2014;20(suppl 1):S5–S9.
3. Garcia-Borreguero D, Egatz R, Winkelmann J, Berger K. Epidemiology of restless legs syndrome: the current status. Sleep Med Rev 2006;10:153–167.
4. Allen RP, Walters AS, Montplaisir J, et al. Restless legs syndrome prevalence and impact: REST general population study. Arch Intern Med 2005;165:1286–1292.
5. 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.
6. Follett KA, Weaver FM, Stern M, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med 2010;362:2077–2091.
7. Chahine LM, Ahmed A, Sun Z. Effects of STN DBS for Parkinson's disease on restless legs syndrome and other sleep-related measures. Parkinsonism Relat Disord 2011;17:208–211.
8. Kedia S, Moro E, Tagliati M, Lang AE, Kumar R. Emergence of restless legs syndrome during subthalamic stimulation for Parkinson disease. Neurology 2004;63:2410–2412.
9. Driver-Dunckley E, Evidente VG, Adler CH, et al. Restless legs syndrome in Parkinson's disease patients may improve with subthalamic stimulation. Mov Disord 2006;21:1287–1289.
10. Marques A, Fantini ML, Morand D, et al. Emergence of restless legs syndrome after subthalamic stimulation in Parkinson's disease: a dopaminergic overstimulation? Sleep Med 2015;16:583–588.
11. Rye DB, DeLong MR. Amelioration of sensory limb discomfort of restless legs syndrome by pallidotomy. Ann Neurol 1999;46:800–801.
12. Ondo WG, Jankovic J, Simpson R, Jimenez-Shahed J. Globus pallidus deep brain stimulation for refractory idiopathic restless legs syndrome. Sleep Med 2012;13:1202–1204.
13. Okun MS, Fernandez HH, Foote KD. Deep brain stimulation of the GPi treats restless legs syndrome associated with dystonia. Mov Disord 2005;20:500–501.
14. Ondo W. VIM deep brain stimulation does not improve pre-existing restless legs syndrome in patients with essential tremor. Parkinsonism Relat Disord 2006;12:113–114.
15. Klepitskaya OS, Liu Y, Sillau SH, Tsai J, Walters AS. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) improves restless leg syndrome (RLS) in patients with Parkinson's disease (PD). Movement Disord 2015;30:S486–S487.
16. Allen RP. Restless legs syndrome/Willis Ekbom disease: evaluation and treatment. Int Rev Psychiatry 2014;26:248–262.
17. Walters AS, LeBrocq C, Dhar A, et al. Validation of the International Restless Legs Syndrome Study Group Rating Scale for Restless Legs Syndrome. Sleep Med 2003;4:121–132.
18. Abetz L, Vallow SM, Kirsch J, Allen RP, Washburn T, Earley CJ. Validation of the Restless Legs Syndrome Quality of Life Questionnaire. Value Health 2005;8:157–167.
19. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;25:2649–2653.
20. Walters AS, Frauscher B, Allen R, et al. Review of quality of life instruments for the restless legs syndrome/Willis-Ekbom disease (RLS/WED): critique and recommendations. J Clin Sleep Med 2014;10:1351–1357.
21. Winkelman JW, Sethi KD, Kushida CA, et al. Efficacy and safety of pramipexole in restless legs syndrome. Neurology 2006;67:1034–1039.
22. Suzuki K, Miyamoto M, Miyamoto T, Hirata K. Restless legs syndrome and leg motor restlessness in Parkinson's disease. Parkinson's Dis 2015;2015:490938.
23. Iranzo A, Comella CL, Santamaria J, Oertel W. Restless legs syndrome in Parkinson's disease and other neurodegenerative diseases of the central nervous system. Mov Disord 2007;22(suppl 18):S424–S430.
24. Earley CJ, Kuwabara H, Wong DF, et al. The dopamine transporter is decreased in the striatum of subjects with restless legs syndrome. Sleep 2011;34:341–347.
25. Godau J, Schweitzer KJ, Liepelt I, Gerloff C, Berg D. Substantia nigra hypoechogenicity: definition and findings in restless legs syndrome. Mov Disord 2007;22:187–192.
26. Zhao H, Zhu W, Pan T, et al. Spinal cord dopamine receptor expression and function in mice with 6-OHDA lesion of the A11 nucleus and dietary iron deprivation. J Neurosci Res 2007;85:1065–1076.
27. Saleh S, Swanson KI, Lake WB, Sillay KA. Awake neurophysiologically guided versus asleep MRI-guided STN DBS for Parkinson disease: a comparison of outcomes using levodopa equivalents. Stereotact Funct Neurosurg 2015;93:419–426.
28. Weaver FM, Stroupe KT, Cao L, et al. Parkinson's disease medication use and costs following deep brain stimulation. Mov Disord 2012;27:1398–1403.
29. Ostrem JL, Ziman N, Galifianakis NB, et al. Clinical outcomes using ClearPoint interventional MRI for deep brain stimulation lead placement in Parkinson's disease. J Neurosurg 2016;124:908–916.
30. Fulda S, Wetter TC. Where dopamine meets opioids: a meta-analysis of the placebo effect in restless legs syndrome treatment studies. Brain 2008;131:902–917.
31. de la Fuente-Fernandez R, Stoessl AJ. The placebo effect in Parkinson's disease. Trends Neurosci 2002;25:302–306.
32. Parkinson Study Group. Safety and efficacy of pramipexole in early Parkinson disease: a randomized dose-ranging study. JAMA 1997;278:125–130.
33. Diamond SG, Markham CH, Treciokas LJ. Double-blind trial of pergolide for Parkinson's disease. Neurology 1985;35:291–295.
34. Frisaldi E, Carlino E, Zibetti M, et al. The placebo effect on bradykinesia in Parkinson's disease with and without prior drug conditioning. Mov Disord 2017;32:1474–1478.
35. Goetz CG, Leurgans S, Raman R, Stebbins GT. Objective changes in motor function during placebo treatment in PD. Neurology 2000;54:710–714.
36. de la Fuente-Fernandez R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Science 2001;293:1164–1166.
37. Mestre TA, Shah P, Marras C, Tomlinson G, Lang AE. Another face of placebo: the lessebo effect in Parkinson disease: meta-analyses. Neurology 2014;82:1402–1409.
38. Mestre TA, Lang AE, Okun MS. Factors influencing the outcome of deep brain stimulation: placebo, nocebo, lessebo, and lesion effects. Mov Disord 2016;31:290–298.

Deep brain stimulation improves restless legs syndrome in patients with Parkinson disease

Olga Klepitskaya, Ying Liu, Saloni Sharma, et al.

Neurology 2018;91;e1013-e1021 Published Online before print August 15, 2018
DOI 10.1212/WNL.0000000000006162