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ORIGINAL COMMUNICATION

Patient-adjusted deep-brain stimulation programming is time saving in dystonia patients

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Abstract

Background Deep-brain stimulation (DBS) programming for dystonia patients is a complex and time-consuming task.
Objective To analyze whether programming a programming paradigm based on patient's self-adjustment is practical, effective and time saving in dystonia.
Methods We retrospectively compared dystonia rating scales as well as the time necessary to optimize programming and the number of in-hospital visits in all patients ($n=102$) operated at our center who used simple mode (SM) or advanced mode (AM) programming; the latter uses groups of different stimulation parameters and allows the patient and their caregiver to change stimulation groups at home, using the patient remote control.
Results Both AM- and SM-allocated patients improved clinically to the same extent after DBS, as assessed by the Burke–Fahn–Marsden (BFM) and the Toronto Western Spasmodic Torticollis (TWSTRS) dystonia rating scales. All subscores improved after DBS without statistically significant differences in improvement between AM and SM (BFM: −43% vs. −53%, $p=0.569$; TWSTRS: −63% vs. −72%, $p=0.781$). AM and SM patients reached optimization within a similar median time [5.5 months (95% CI 4.6–6.3) for AM vs. 6.2 months (4.2–7.6) for SM, $p=0.674$] but patients on advanced programming needed fewer in-hospital visits to achieve the same improvement [median of 5 visits (95% CI 4–7) for AM vs. 8 visits (7–9) for SM, $p=0.008$].
Conclusions Advanced DBS programming based on patient's self-adjustment under the supervision of the treating physician is feasible, practical and significantly reduces consultation time in dystonia patients.

Keywords Dystonia · Deep-brain stimulation · Shared decision making · Time saving · Advanced stimulation modes

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Introduction

Treatment of dystonia is based on a variety of strategies including deep-brain stimulation (DBS) [1]. Programming DBS is challenging as the worldwide experience is limited and the therapeutic effects of parameters adjustments are often detectable with a delayed time latency.

Our group developed an algorithm to guide initial DBS programming in dystonia [2]. According to the algorithm, the same initial settings (130 Hz frequency, 60 µs pulse width and amplitude at 3.0–3.5 V or 10–20% below the threshold for side effects) were used for four groups of bilateral monopolar stimulation. Each setting involved one pair of corresponding contacts on each side of the brain aligned along the same axial plane (e.g., the lowest contact on both electrodes, unless post-operative imaging shows a clear asymmetry on electrodes' depth). Patients were then given instructions on how to use their remote control to allow testing of each of the four groups for at least 1 week, while taking notes of subjective therapeutic and adverse effects. At the end of the 4 weeks trials, patients were instructed to go back to the settings which were judged as the best or the two best groups and try them until the next appointment, usually scheduled around 6 weeks after initial programming. If side effects occurred while using a given group, patients could stop it sooner and move to the next one. At the next outpatient follow-up visit, the patient reported a hierarchy of efficacy of the four different groups. Subsequently, the best pair of contacts was kept active and the three other groups were further tested by exploring higher amplitude/frequency/pulse width and/or the combination of the two most effective pairs of contacts.

In this study, we assessed whether this method is practical, clinically effective and less time consuming by retrospectively analyzing the charts of all dystonia patients operated at our center.

Methods

We conducted a retrospective study on all dystonia patients operated at Toronto Western Hospital ($n = 128$). The manuscript is a retrospective review from our Movement Disorders Center database and as such there was neither ethics committee nor patients' consent specific to this study. Only patients with informative clinical data and electrodes symmetrically placed (in case of bilateral implants) were included. The vast majority of patients received DBS in the postero-ventral globus pallidus internus (GPi), in a minority variably combined with subthalamic nucleus (STN) or ventral intermedius nucleus of the thalamus (VIM, see "Results" for details). All patients were implanted with Medtronic devices (Minneapolis, MN-US) using the lead model 3387. Implantable pulse generators (IPGs) used included Kinetra or Activa, the latter being available at our center since 2008. The two primary outcomes consisted of number of days and number of visits to our clinic between first programming and optimization visit. The Optimization visit was arbitrarily defined as *the visit immediately preceding 60 days without DBS parameters adjustments AND with EITHER a report of good benefit on the following visit AND/OR no change in the DBS settings on thefollowing visit*. Specifically, the patient and their caregiver as well as the treating physician were satisfied with the improvement. The database was closed on December 31st, 2016. Patients could fail meeting optimization due to: DBS failure, no follow-up, not meeting optimization criteria on closing date (Fig. 1).

All included cases were classified into two groups: a 'simple mode' (SM) group in which patients either had no influence on their stimulation parameters or could manipulate only one parameter (usually amplitude) within a precise range judged by the physician; an 'advanced mode' (AM) group in which patients were given different groups of stimulation according to the algorithm described above [2]. All AM patients started with four Activa Groups corresponding to each pair of contacts aligned along the same axial plane. A patient could only be included in the AM group if the device was an Activa, whereas SM group patients could have either Kinetra or Activa devices. Consequently, patients operated between 2001 and 2008 all had SM programming, patients operated from 2008 to 2012 had either SM or AM, and all had AM after summer 2012. Surgery was consistently performed according the same method, as detailed elsewhere [3]. Of note, since the implementation of our stimulation algorithm, we consistently went through the details and rationale of our approach with each patient (i.e., AM patients were not blinded to this information).

We recorded the Burke–Fahn–Marsden (BFM) dystonia rating scale and the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) scores at four different time points: "Worst score before DBS"; "Best score after DBS", which could be recorded any time after DBS operation; "optimization score", defined as the score recorded on the clinical visit immediately following the optimization visit (and as such reflects the changes done during the optimization visit); "3 months score", defined as the score obtained 3 months after first programming visit, within a maximum range of 30 days. Of note, the "Best score after DBS" could occasionally be the same as the "optimization score", but in most cases it was recorded later on, keeping the well-established notion that dystonia tends to slowly improve over time, also while keeping the parameters constant (or just fine tuned).

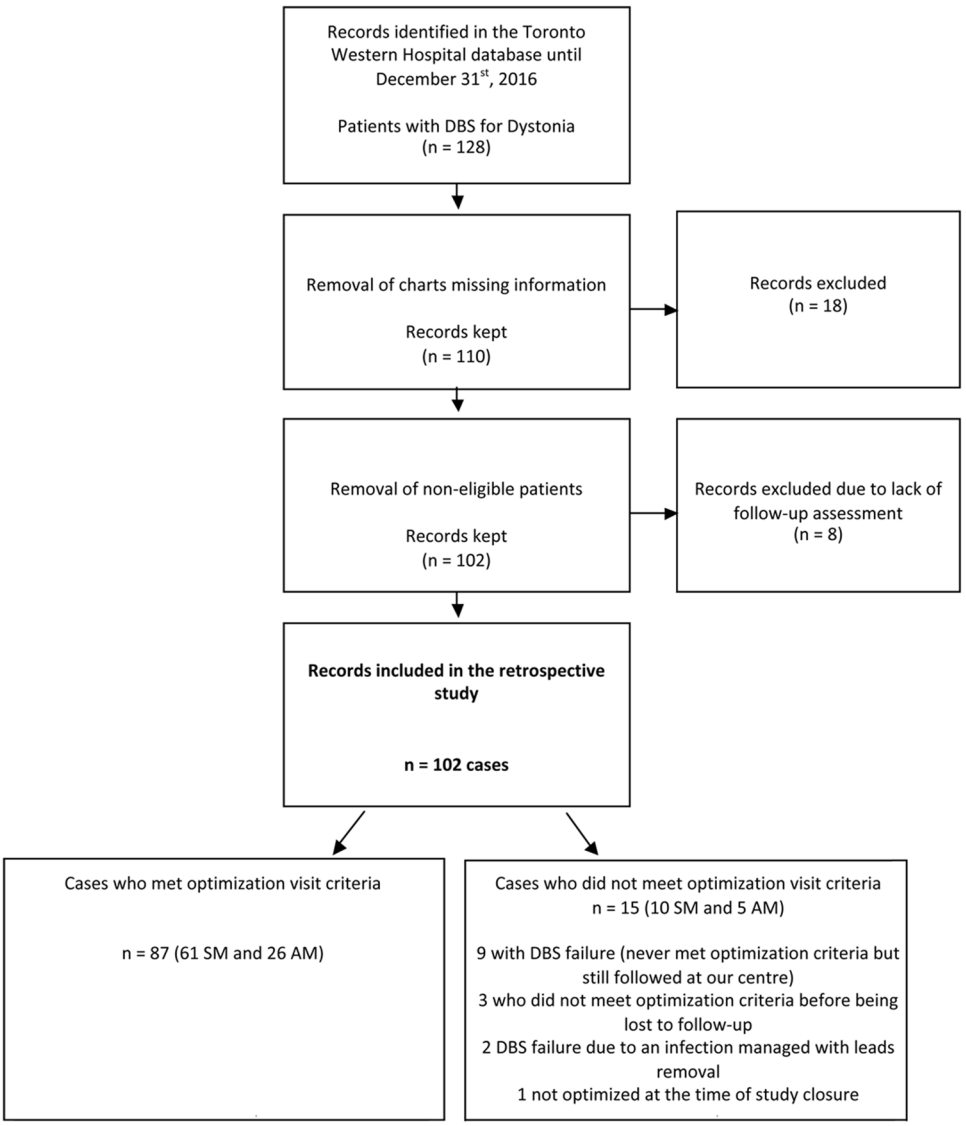

Fig. 1 Flowchart for including the patients in the retrospective review

Statistical analyses

Patients' characteristics were described as frequency and percentage for qualitative parameters and as mean ± SD for quantitative parameters. Differences were assessed using Chi-square test or Fisher exact test, as appropriate, for qualitative parameters and using Welch Student test for quantitative parameters. Optimization-free survival (expressed as time—in month—in one analysis, and as number of visits in a second analysis, between first programming visit and optimization visit) was estimated by the Kaplan–Meier method and compared between groups using a logrank test. BFM and TWSTRS subscores were compared between groups using the Welch student tests. We performed a linear regression model to compare the mean change score between the two groups relating each score to the worst score. The model was: optimization score (respectively, the 3-month score and the best score) = constant + a*worst score + b*group, the coefficient b being the effect of interest (the estimated difference between the two groups).

All analyses were assessed at a two-sided alpha level of 5%. Analyses were performed using softwares R-3.3.1 (https://www.R-project.org) and STATA 15.0.

Results

Out of the 128 identified patients with DBS for dystonia in our database, a total of 102 patients [64 females (63%), mean age at DBS: 45.4 ± 17.3 years (range 8–74), mean disease duration at DBS: 17.6 ± 11.9 years (range 1–50)] were included for analyses (Fig. 1 and Table 1). Of these 102 patients, two were operated in the ventral intermedius nucleus (VIM) of the thalamus and 100 in the globus

Table 1 Patients' characteristics

	All ($n=102$)	SM ($n=71$)	AM ($n=31$)	p
Gender				
Female, *N* (%)	64 (63%)	48 (68%)	16 (52%)	0.189
Male, *N* (%)	38 (37%)	23 (32%)	15 (48%)	
Body distribution*				
F, *N* (%)	33 (32%)	20 (28%)	13 (42%)	0.182
MF/S, *N* (%)	24 (24%)	20 (28%)	4 (13%)	
G, *N* (%)	45 (44%)	31 (44%)	14 (45%)	
Etiology*				
Isolated, *N* (%)	59 (58%)	39 (56%)	20 (65%)	0.688
Combined, *N* (%)	5 (5%)	4 (6%)	1 (3%)	
Complex, *N* (%)	14 (14%)	9 (13%)	5 (16%)	
Acquired, *N* (%)	18 (18%)	13 (19%)	5 (16%)	
Unknown, *N* (%)	5 (5%)	5 (7%)	–	
Age at disease onset				
Years, mean ± SD	27.8 ± 19.3	26.6 ± 19.2	30.6 ± 19.5	0.386
Missing data	*15*	*10*	*5*	
Age at DBS				
Years, mean ± SD	45.4 ± 17.3	44.9 ± 17.4	46.4 ± 17.3	0.690
Missing data	*4*	*4*	*0*	
Years from onset to DBS				
Years, mean ± SD	17.6 ± 11.9	17.4 ± 11.6	18.0 ± 12.9	0.846
Missing data	*19*	*14*	*5*	

**F* focal, *MF/S* multifocal or segmental, *G* generalized, *Isolated* inherited or idiopathic dystonia, *combined* inherited dystonia combined with other movement disorders, *complex* inherited dystonia with other co-occurring neurological/systemic manifestations, *acquired* acquired dystonia

pallidus internus (GPi), 4 of whom also had VIM-DBS (including two patients with unilateral right GPi and right VIM-DBS) and 2 also STN-DBS. As such, 94 cases had GPi-DBS alone, all but 1 with bilateral procedures. Concerning DBS programming, 71 (70%) patients were programmed by means of SM and 31(30%) using AM. Patients' characteristics are detailed in Table 1. Of note, except one case with combined STN-GPi-DBS, whose GPi programming was allocated to AM, all other combined cases and the two cases with VIM-DBS alone were allocated to SM (as they were all operated before 2012 when our algorithm was implemented).

Optimization

By the end of the study, 87 patients met our optimization criteria. The median time to reach DBS optimization was 5.5 months [95% CI 4.6–6.3] for AM and 6.2 months [4.2–7.6] for SM ($p=0.674$, Fig. 2a and Table 2a). The number of visits was significantly lower in AM compared to SM with a median of 5 [95% CI 4–7] visits for AM versus 8 visits for SM [1–3] ($p=0.008$, Fig. 2a and Table 2b). Optimization-free survivals expressed in month and in number of visits are represented in Fig. 2b, c, respectively. Figure 3 shows the number of visits needed to achieve optimization, during the time-window analyzed, i.e., from year 2000 to 2016, for both SM (left panel) and AM (right panel) groups.

BFM and TWSTRS scores

All BFM and TWSTRS subscores improved after DBS without statistically significant differences in improvement between AM and SM (Supplemental Tables S1 and S2): BFM movement subscore improved by 43% for AM and 53% for SM ($p=0.569$); BFM disability subscore improved by 31% for AM and 39% for SM ($p=0.479$); TWSTRS severity subscore improved by 63% for AM and 72% for SM

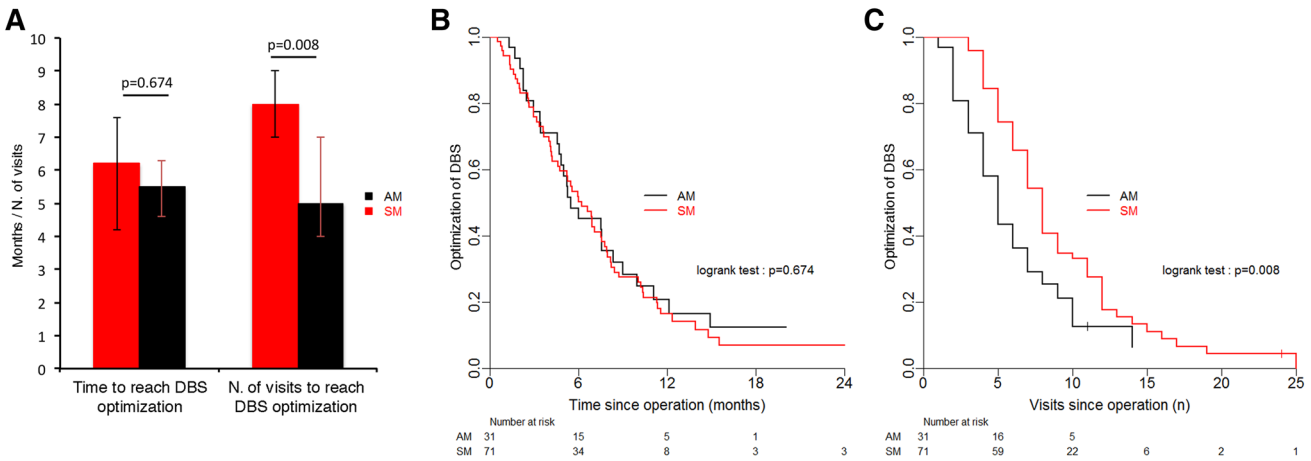

Fig. 2 **a** Time (months, median and 95% CI) and number of visits (median and 95% CI) to reach DBS optimization in patients allocated to simple or advanced mode (SM and AM, respectively). **b** Survival curves depicting the time (in months) from first programming visit to optimization visit. **c** Survival curves depicting the number of visits during the same time interval

Table 2 **a** Survival time expressed in months until the event "meeting the optimization visit criteria" for the AM and SM groups. **b** Survival time expressed in number of visits until the event "meeting the optimization visit criteria" for the AM and SM groups

Mode	Time at risk	Incidence rate	No. of subjects	Survival time		
				25%	50%	75%
Survival time expressed in months until the event						
AM	222.0	0.1171	31	3.4	5.5	10.0
SM	542.3	0.1125	71	3.2	6.2	10.2
Total	764.2	0.1138	102	3.4	6.0	10.2
Survival time expressed in number of visits until the event						
AM	174	0.1494	31	3	5	9
SM	601	0.1015	71	5	8	12
Total	775	0.1123	102	5	7	11

AM advanced mode, *SM* simple mode

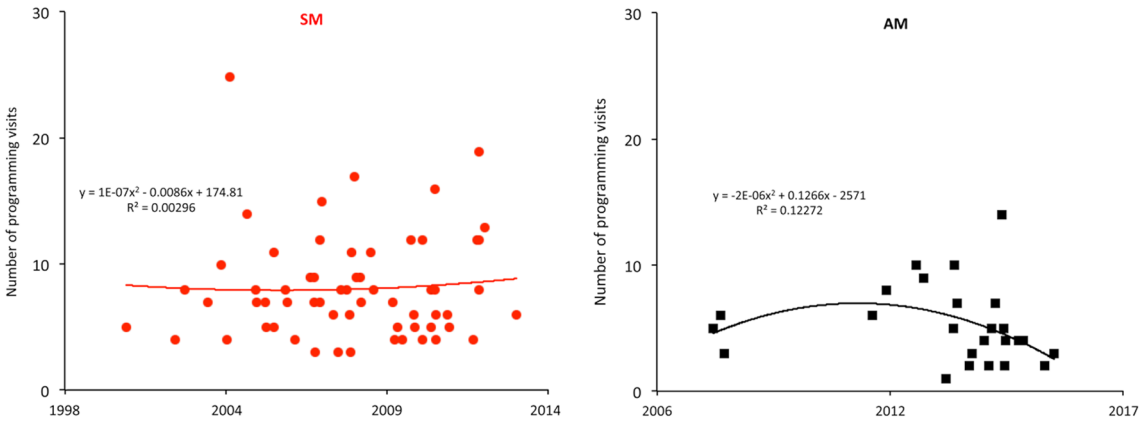

Fig. 3 Number of visits needed to achieve optimization, during the time-window analyzed, i.e., from year 2000 to 2016, for both simple mode (SM; left panel) and advanced mode (AM; right panel) groups. Statistical analysis did not show a significant learning curve effect in both groups

($p=0.781$); TWSTRS disability subscore improved by 74% for AM and 77% for SM ($p=0.665$); TWSTRS pain subscore improved by 60% for AM and 73% for SM ($p=0.870$).

Stimulation parameters

At the most recent clinical visit 62% of AM cases and 59% of SM cases ($p=0.826$) had a symmetrical stimulation, i.e., with the same contacts functioning as cathodes on one side aligned with the contralateral contacts functioning as cathodes (supplemental Figure S3). Voltage averaged 3.6 V in the AM group and 3.2 V in the SM group.

Discussion

This study supports our hypothesis that flexible programming based on the use of the patient's programmer is feasible and practical for both the patient and the treating physician.

Furthermore, this study on a large number of dystonia patients also confirms the results of previous studies regarding clinical effectiveness of DBS for dystonia, with an average improvement of 50% or more of different dystonia scores (BFM and TWSTRS) after DBS [3–10].

Patients in our study were easily able to change their stimulation settings at home by switching groups without traveling back to the clinic. This is not only useful in case the newly implemented stimulation parameters are ineffective, but it is also more practical in the case of side effects elicited by a given stimulation group. For the treating physician, we consider this flexible programming as time saving compared to standard programming carried out solely during in-hospital visits. In particular, we found that fewer visits between first programming visit and DBS optimization date were needed for the AM group, which saves consultation time and could potentially diminish the overall costs of DBS programming. In contrast, SM patients needed more hospital visits because all adjustments were done in the clinic. Although AM patients did neither improve faster nor with more clinical improvement than those who underwent SM programming, our findings confirm the validity of our previously published programming algorithm [2]. Of course this algorithm based on AM must be used according to the discretion of the treating physician, considering the capabilities

and needs of the patients and their family, e.g., dystonic children might need to undergo all DBS changes in the clinic.

Noteworthy, the "shared decision-making" approach at the basis of our AM-based algorithm allows patients and their caregivers to be active participants in the 'DBS journey', a hot topic in medicine [11–13] and movement disorders [14].

Many centers worldwide regularly use the AM for their DBS patients. AM is indeed used for other targets and diseases other than dystonia, e.g., Parkinson's disease. Our general impression is, however, that programming DBS using AM and following a standardized protocol is especially useful for diseases not responding immediately to parameter adjustment, such as dystonia or epilepsy.

As for the limitations of our study, due to its retrospective nature, quality of data derived from charts was heterogeneous, clinical scores were not comprehensively recorded on every clinical visit, and programming procedures changed during the long time course of the study, particularly before the implementation of our standardized stimulation algorithm. Missing data on clinical scores were mainly due to (1) precise time restriction for recording the "3 months score" and (2) patients' heterogeneity, with generalized dystonia patients being assessed mainly or only with BFM and cervical dystonia patients only with TWSTRS. In addition, the main BFM subscore ("movement") and the main TWSTRS subscore ("severity") were recorded much more frequently than the other BFM ("disability") and TWSTRS ("disability" and "pain") subscores.

Although this is not a prospective randomized trial, no selection bias can be hypothesized as the technological development accounted for assigning the patients in either group. Indeed, AM programming became the standard procedure only in 2012, while Activa device was not available at our center before 2008, restricting earlier patients to SM programming. For the same reasons, patients belonging to SM had a longer follow-up after DBS. As such, SM patients have had more follow-up time to benefit from additional treatments and the fact that we detected similar overall outcomes between groups further strengthens the validity of our programming protocol.

We did not observe a learning curve explaining why AM patients needed less visits than SM patients to achieve optimization (Fig. 3). Indeed, we did not observe a learning curve effect for SM patients ($R^2 = 0.00296$), as opposed to AM patients in which a possible inverted-U shape learning curve is depicted ($R^2 = 0.12272$).

Stimulation parameters were unfortunately recorded only at last clinical visit, but not specifically at optimization visit. Therefore, we are not able to extract robust conclusions from this analysis. Most patients in both groups had symmetrically aligned stimulated contacts (supplemental Table S3) with a voltage slightly lower for SM group. However, as impedances were not recorded, we could not calculate the total electrical energy delivered (TEED).

Finally, the dystonia patients included had quite heterogeneous diseases. However, the different etiologies were equally distributed in the two groups and the analysis-stratifying patients according to etiology and distribution of dystonia did not yield significant results (data not shown).

In conclusion, our algorithmic strategy relying on physician-programmed stimulation groups and patients' program changes at home, proved to be feasible and practical, allowing fewer in-hospital visits. This results in significant reduction in the consultation time necessary for the programming of dystonia patients treated with DBS. Furthermore, although this was not designed as a health-economic study, fewer visits likely led to a reduction of costs for the health system and a burden reduction for the patients and their caregivers (e.g., due to less traveling and days off). Finally, our findings mark a first step towards a shared-decision approach even in such complex procedures such as DBS programming.

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Author contribution (1) Research project: A. conception, B. organization, C. execution; (2) statistical analysis: A. design, B. execution, C. review and critique; (3) manuscript: A. writing of the first draft, B. review and critique. JFB: 1B, 1C, 2A, 2B, 3A. MR: 1B, 1C, 3B. MRL: 1C, 3B. VP: 1C. RPM: 3B. MH: 1C, 3B. SKK: 1C, 3B. AML: 1C, 3B. PRB: 3B. AP: 2A, 2B, 3B. AF: 1A, 1B, 2C, 3B.

Compliance with ethical standards

Conflicts of interest The manuscript has not been previously published and is not under review at any other journal. No other related work is under submission elsewhere. All the authors of the paper have participated to the study, revised the manuscript and approved the final version of the manuscript. There is no ghost writer. AF and AML received research funding and honoraria from Medtronic. The other authors (JFB, MR, MRL, VP, RPM, MH, SKK, PRB, and AP) have no disclosure of conflict of interest related to this work.

Ethical approval The manuscript is a retrospective review from our Movement Disorders Center database and as such there was neither ethics committee nor patients' consent specific to this study.

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