Dopaminergic Dose Adjustment and Negative Affective Symptoms after Deep Brain Stimulation

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Abbreviations

PD: Parkinson's disease; NAS: Negative Affective Symptoms; DBS: Deep brain Stimulation; DA: Dopamine Agonist; LEDD: levodopa daily equivalent dose.

Dear Editor,

With over 40,000 patients with Parkinson disease (PD) treated in the United States and more than 140,000 worldwide, deep brain stimulation (DBS) has demonstrated long-term efficacy in the management of advanced PD.

While DBS has been shown to increase the quality-adjusted life expectancy in PD [1], important complications have also been reported, including severe depression, often associated with apathy, and collectively described within the construct of negative affective symptoms (NAS) [2]. This complex psychiatric condition has been observed in PD patients after DBS [3, 4] but its prevalence and relationship with changes in dopaminergic medications remain unclear.

We retrospectively reviewed the prevalence of DBS-induced NAS in a cohort of consecutive PD patients treated at the University of Cincinnati between 2008 and 2016. Inclusion criteria for the study enrollment were idiopathic PD and full availability of clinical, neuropsychological, and treatment data, at baseline (pre-DBS) and for at least 12 months following DBS. Exclusion criteria were major psychiatric diseases, such as bipolar depression, schizophrenia, personality disorders, and mood disorders triggered by external events or circumstances, including but not limited to death of a family member, divorce, or workplace harassment.

Our primary endpoint was the presence or absence of DBS-induced NAS based on the documentation of onset of depression and apathy reported in clinical notes at each follow-up visit within 12 months after DBS and requiring treatment with antidepressant therapy. In order to account for the effect of dopamine agonists (DA) on mood and behavior, patients were divided according to whether their post-DBS management was centered on the reduction of DA, when part of the pre-DBS regimen (DA+), or whether it was centered on the reduction of levodopa

because DA was not part of the pre-DBS regimen (DA-). DA were always preferentially reduced post-operatively when part of the pre-operative therapeutic regimen. Dopaminergic dose was quantified as levodopa equivalent daily dose (LEDD). Secondarily, we examined demographic, motor, and neuropsychological variables, including pre-DBS history of apathy or depression, as well as DBS targets.

Continuous data were reported as mean ± standard deviation and compared between NAS+ and NAS- using the Mann-Whitney non-parametric test. Categorical data were reported as percentage and compared between NAS+ and NAS- using the Fisher's exact test. Pearson's correlation analyses were conducted to examine the association between NAS and LEDD changes between pre- and post-surgical conditions. All p-values were two-tailed with 0.05 as statistical threshold of significance. The local Institutional Review Board approved this study.

Inclusion criteria were met by 156 out of the 198 PD patients treated with DBS at the University of Cincinnati during 2008-2016. NAS was ascertained in 26.7% (n= 19) of DA+ and in 18.8% (n= 16) of DA- (p= 0.25) after 4.83 ± 3.62 and 4.73 ± 3.59 months, respectively. DA+ patients developing post-DBS NAS had greater DA LEDD reduction (p= 0.042), but not greater total-LEDD reduction (p= 0.257). DA- patients with post-DBS NAS were older at PD onset (p= 0.018) and had nonsignificant total-LEDD reduction (p= 0.878). No other significant differences were observed in clinical, demographic, or neuropsychological variables in DA+ and DA- groups, with a trend towards a higher prevalence of males with NAS in the DA+ group (p: 0.071) (Table 1). Pearson's correlations showed a moderate trend towards NAS and a reduction in DA-LEDD and Total-LEDD which, however, did not meet the significant threshold (p: 0.142, and p: 0.167, respectively).

Behavioral and mood disorders have been consistently reported as possible complications of DBS and frequently associated with post-surgical adjustment in pharmacological therapies [3]. Convergent evidence suggests a role for the mesolimbic tegmental pathway, which projects to the ventral striatum (nucleus accumbens) and to the limbic cortex (medial prefrontal, cingulate and entorhinal areas) [2, 5]. Still, the complex modulation exerted by pharmacological and non-pharmacological treatments on mood and behavior remains poorly defined in PD.

We found that NAS may affect one-fourth of PD patients treated with DBS. Moreover, our data suggest that NAS may be more frequent when DA dose is reduced. Older patients not on pre-DBS DA may also develop NAS (19% prevalence) but without a clear role for LEDD reduction. Altogether, these findings suggest that different pathogenic mechanisms may account for the onset of post-DBS NAS, potentially implying DA reduction, age, and (plausibly though unexamined) the effect of stimulation itself.

The strength of our observations is limited by several limitations. First, the lack of neuropsychological data or systematic clinical interview. Second, the retrospective study design based on a chart review of medical records. Third, the relatively small sample size, which might have limited the statistical power to detect other group differences. Fourth, the difference in DA reduction between patients with and without NAS is only slightly below the threshold for significance and may be less robust when adjusting for multiple comparisons.

Pending confirmation of these results in larger, multicenter clinical studies, we cautiously suggest that NAS represents a frequent complication of DBS, with greater risk among older patients and in those reducing or discontinuing DA.

ETHICAL STANDARD

The authors declare that they acted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The ethical committee approval was obtained and patients provided written informed consent.

FINANCIAL DISCLUSURES

Dr. Tareen has nothing to disclose

Dr. Artusi has nothing to disclose

Dr. Rodriguez-Porcel has nothing to disclose.

Dr. Sheikh has nothing to disclose

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CONTRIBUTORSHIP STATEMENT

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

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All Authors fulfilled the Authorship criteria and approved the final version of the article. The order of authors listed in the manuscript has been approved by all of them.

DATA ACCESS AND RESPONSIBILITY STATEMENT

A Merola had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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	Patients DA+ (n= 71)				Patients DA- (n= 85)		
	NAS + (n= 19)	**NAS - (n= 52)**	**P-Value**		**NAS + (n= 16)**	**NAS - (n= 69)**	**P-Value**
DEMOGRAPHIC FEATURES							
Sex *(males/females)*	16 / 3	32 / 20	0.071		11 / 5	40 / 29	0.765
Age at DBS *(years)*	64.59 ± 9.47	60.96 ± 8.96	0.149		64.61 ± 6.47	61.17 ± 7.30	0.107
Age at PD onset *(years)*	52.94 ± 8.50	51.06 ± 9.11	0.498		55.46 ± 6.54	50.19 ± 7.10	0.018
PD Duration at DBS *(years)*	11.59 ± 3.80	9.87 ± 3.11	0.119		9.08 ± 3.77	11.02 ± 4.26	0.138
CLINICAL FEATURES							
NAS onset latency *(months)*	4.83 ± 3.62	NA	NA		4.73 ± 3.59	NA	NA
MDS-UPDRS-III Med-ON *(pre-surgery)*	22.53 ± 10.01	26.42 ± 28.08	0.672		24.13 ± 12.11	21.31 ± 8.02	0.513
MDS-UPDRS-III Med-ON/Stim-ON *(post-surgery)*	31.62 ± 12.12	30.31 ± 14.43	0.583		34.25 ± 12.94	29.63 ± 11.41	0.104
Surgical Target *(STN/GPi)*	18 / 1	47 / 5	0.559		15 / 1	60 / 9	0.447
History of Depression	26.3 % (n=5)	38.5% (n=20)	0.342		43.7% (n=7)	47.8% (n=33)	0.858
History of Apathy	0% (n=0)	5.8% (n=3)	0.284		0% (n=0)	11.5% (n=8)	0.152
NEUROPSYCHOLOGICAL FEATURES*							
Prevalence of amnestic MCI	26.3% (n=5)	48.1% (n=25)	0.107		37.5% (n=6)	43.5% (n=30)	0.662
Prevalence of non-amnestic MCI	26.3% (n=5)	26.9% (n=14)	0.959		37.5% (n=6)	26.1% (n=18)	0.360
MEDICATION							
Total-LEDD reduction (%)	31.88 ± 21.39	24.94 ± 25.04	0.257		28.44 ± 27.14	26.93 ± 23.89	0.878
DA LEDD reduction (%)	73.78 ± 34.45	50.23 ± 39.74	0.042		NA	NA	NA

Table 1. Demographic, Clinical, Neuropsychological and Treatment data

DA+: pre-surgical therapeutic regimen including DA; DA-: pre-surgical therapeutic regimen not including DA; NAS: Negative Affective State; DBS: Deep Brain Stimulation; PD: Parkinson disease; MDS-UPDRS: Movement Disorders Society Unified Parkinson disease rating scale; STN: Subthalamic nucleus; GPi: Globus pallidus pars interna; NA: not applicable.

* Neuropsychological features were assessed in the pre-operative phase.