Clinical Manifestations of Tolerance to Deep Brain Stimulation

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BACKGROUND

❖ Tolerance to deep brain stimulation (DBS) can be described as
1. tremor rebound with a temporary increase of tremor intensity over the preoperative state after switching off DBS (Kronenbuerger 2006),
2. habituation, which is the loss of sustained tremor control over a short duration of follow-up (Barbe 2011), or
3. late therapy failure that may occur after at least one year of satisfactory control of tremor with DBS (Pilitsis 2008).

❖ Causes not completely understood. Theories include:
- o Natural disease progression
- o Inadequate electrode location
- o Resolution of microthalamotomy effects from surgery
- o Adaptation of neural networks to chronic localized stimulation (Barbe 2011).

❖ Existing research shows:
- o 13-40% of patients with essential tremor (ET) implanted in the thalamus (ViM) develop tolerance, despite proper lead placement (Pilitsis et al, 2008).
- o A prospective studies found 73% of ET patients experienced waning benefit of stimulation, as early as 3months following implantation (Shih et al, 2013)
- o Loss of acute benefit from programming in 54% of electrodes in ET patients with ViM stimulation by 10 weeks (Barbe et al, 2011)
- o Rebound is described in ET and Parkinson's disease (PD) (Hariz 1999) but is not well-characterized.

❖ **Objective: To determine factors and characteristics associated with development of tolerance to DBS across disease states and targets.**

METHODS

❖ Prospective questionnaire study with retrospective chart review in a 3-month cross-sectional population of a tertiary Movement Disorders Center

❖ Inclusion criteria:
- o > 18 years old
- o diagnosis of ET, PD, or dystonia as determined by a movement disorders specialist,
- o lead implantation in the ViM, globus pallidus interna (GPi), or the subthalamic nucleus (STN)

❖ Exclusion criteria
- o Stimulator in place < 6 months

❖ Prospective evaluation included a Clinician-administered survey either in person or by phone consisting of 8-items:
- o whether the patient experienced habituation or rebound,
- o patient rating of their symptom control
- o patient satisfaction with the treatment
- o a patient-rated version of the Clinical Global Impression Scale compared the positive effects of the DBS with the effects of losing the benefit of an adjustment

❖ Retrospective chart review to identify diagnosis, disease onset, stimulator placement date, target and laterality for all patients who agreed to complete surveys

❖ Information was extracted to a database for analysis. Statistical methods included **2-tailed Fisher's exact test** to compare incidence of tolerance across disease states and targets, **Mann Whitney U** to compare self-report measures in patients with and without tolerance, **Kruskal-Wallis** and **ANOVA*** to compare self-report measures among those experiencing tolerance across disease states and targets, and **2-tailed t-test*** to compare patient characteristics.

RESULTS

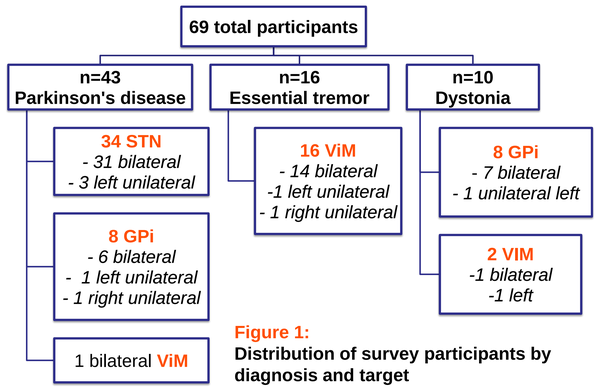

Figure 1: **Distribution of survey participants by diagnosis and target**

Table 1: **Patient Characteristics**

	ViM	STN	GPi
Gender	M: 14 F: 5	M: 20 F: 14	M: 5 F: 11
Current Average Age	70 years	64 years	61 years
Disease treated by DBS	ET: 17 PD: 1 Dystonia: 1	PD: 34	PD: 8 Dystonia: 8
Average Disease duration	33 years	15 years	19 years
Average Duration of DBS implantation	5 years	5 years	5 years
N Bilateral	16	31	13

Table 2: **Characteristics of patients experiencing habituation**

	Mean age (years) at time of survey			Mean disease duration (years) at time of survey			Mean time (years) since DBS at time of survey		
Target	+habit	- habit	P	+habit	- habit	P	+ habit	- habit	P
ViM (n=9)	68.2	74.6	0.2	32.9	39.3	0.4	4.6	6.1	0.5
STN (n=7)	62.3	64.2	0.6	14.6	15.1	0.8	4.7	4.6	0.9
GPi (n=3)	56	62.2	0.3	21.3	17.8	0.5	7.3	3.9	0.2

- ❖ 27.5% (n = 19) reported symptoms of habituation
- ❖ Analysis by target:
  - 20.6% (n = 7) STN
  - 47.4% (n = 9) ViM
  - 18.8% (n = 3) GPi

  (P = 0.103)*
- ❖ Analysis by disease state:
  - 20.9% (n = 9) PD
  - 50% (n = 8) ET
  - 20% (n = 2) dystonia

  (P = 0.107)*

*2-tailed Fisher's exact test

Table 3: **Characteristics of patients experiencing rebound**

	Mean age (years) at time of survey			Mean disease duration (years) at time of survey			Mean time (years) since DBS at time of survey		
Target	+rebound	- rebound	P	+rebound	- rebound	P	+rebound	- rebound	P
ViM (n=10)	68.8	71.9	0.5	34.3	32	0.8	6.1	4.4	0.4
STN (n=11)	62.6	64.3	0.6	15.5	14.8	0.7	5	4.5	0.6
GPi (n=1)	66	60.7	0.6	17	18.6	0.9	3	4.7	0.7

- ❖ 31.9% (n = 22) reported symptoms of rebound
- ❖ Analysis by target:
  - 32.3% (n = 11) STN
  - 52.6% (n = 10) ViM
  - 6.3% (n = 1) GPi

  (P = 0.011)*
- ❖ Analysis by disease state:
  - 25.6% (n = 11) PD
  - 56.3% (n = 9) ET
  - 20% (n = 2) dystonia

  (P = 0.064)*

*2-tailed Fisher's exact test

Table 4: **Patient self-report measures on efficacy, satisfaction, and global impression of change with DBS in patients reporting habituation by stimulator target**

	Overall efficacy of DBS			*Overall satisfaction with DBS*			*Patient global impression of change*		
	+habit	- habit	P	+habit	- habit	P	+ habit	- habit	P
ViM	3	1.4	0.0601	5.1	6.8	**0.012**	6.8	2.4	**0.0048**
STN	3.1	1.5	0.067	5	6.5	0.12	8	2.8	**0.0027**
GPi	1.7	1.4	0.41*	6.3	6.5	0.85*	5.3	2.2	**0.036***
K-W	0.722			0.654			0.811		

Table 5: **Patient self-report measures on efficacy, satisfaction, and global impression of change with DBS in patients reporting rebound by stimulator target**

	Overall efficacy of DBS			*Overall satisfaction with DBS*			*Patient global impression of change*		
	+rebound	-rebound	P	+rebound	- rebound	P	+rebound	- rebound	P
ViM	2.8	1.4	0.142	5.4	6.7	0.112	6.2	2.6	**0.013**
STN	2.3	1.6	**0.01**	5.8	6.3	0.087	4.8	3.4	0.162
GPi	1	1.5	0.4*	6	6.5	0.67*	1	2.9	0.45*
ANOVA*	0.6*			0.8*			0.4*		

*Because of small sample size for GPi and Dystonia patients, a parametric approach (t-test, ANOVA) was used for analysis instead of a nonparametric approach (Mann Whitney U, Kruskal-Willis).

CONCLUSIONS

❖ Presence of habituation and rebound should be considered when performing clinical evaluations on any patient treated with DBS.
- o tolerance to stimulation is not unique to ViM stimulation or ET, though it may be more common in this target and this disease.
- o Factors such as age, disease duration, and duration of DBS therapy do not appear to play a significant role.
- o recurrent symptoms other than tremor (e.g. bradykinesia, rigidity, dystonia) may be experienced.

❖ Tolerance to DBS influences patient perceptions of DBS efficacy and satisfaction
- o Patients experiencing habituation generally seemed to have significantly lower self-reported efficacy of DBS and significantly lesser satisfaction with DBS therapy than those who did not experience habituation.
- o Rebound symptoms led to significantly lower satisfaction and PGI in the ViM group, but did not differ by disease state
  - ✓ However, rebound itself may be a less-recognized phenomenon (by both patients and clinicians) since most patients leave DBS therapy on all the time.

❖ A unique finding in our survey study was the laterality experienced by multiple patients implanted bilaterally.
- o 80% of patients implanted bilaterally who experienced worse tolerance unilaterally did so on the left side.
- o No direct association between handedness and laterality was found.

❖ Study limitations: retrospective nature, lack of objective assessments to confirm patient reports of tolerance, and small sample size, especially among dystonia patients.

❖ Further, prospective studies, including larger Ns of dystonia patients and investigations into laterality of tolerance symptoms, are warranted.

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