April 12, 2022

US. Food and Drug Administration

Citizen's Petition

The undersigned submits this petition under Federal Food, Drug, and Cosmetic Act under CFR 10.30 to request the Commissioner of Food and Drugs to issue an order as described below.

A. **Action Requested**

This Petition requests the FDA to issue an Order regarding the practice of requiring neuropsychological testing prior to DBS surgery. More specifically, the Commissioner should specify that the use of such testing and the weighing of the perceived benefits and risks of DBS surgery, including that gleaned from any neuropsychological assessments, should be left to the patient to decide.

B. **Statement of Grounds**

Direct Brain Stimulation (DBS) for Parkinson's disease (PD) provides durable symptomatic relief and allows many individuals to maintain the activities of daily living for more than 10 years. Furthermore, patient satisfaction with DBS remains high over this time period. See Hitti, et al.

As a potential road block to these benefits, neurologists require that candidates for DBS surgery demonstrate certain cognitive abilities from a neuropsychological assessment before the surgery.

However, no standardized neuropsychological test currently exists for this purpose. Even defining what constitutes an unacceptable cognitive dysfunction prior to DBS surgery remains an open question.

And more importantly, there is no study that compares the decline in specific cognitive conditions from DBS surgery to the decline in those conditions in a control group of patients who did not receive DBS. Both groups are likely to see a decline. But is the difference, if any, statistically significant? Additionally, what is

the magnitude of the difference for particular variables? Over what time period do these effects manifest themselves?

Most studies try to show deterioration after DBS surgery for certain conditions. This is not the proper benchmark, but even so the results are inconsistent.

Thus, there is a lack of delineation of the cognitive conditions appropriate for testing, a lack of a standardized test for these conditions, a lack of statistically significant results from these tests, a lack of reliable estimates of the magnitude of the effect on each condition, and a lack of an identified time period in which any statistically significant differences would occur.

Moreover, neuropsychological assessments are judgmental and can be influenced by factors such as the perception of the patient's physical condition.

As explained by Chad D. Vickery, et al. in an article in Science Direct:

> "…it has been pointed out that neuropsychological tests may be "failed" for a variety of reasons apart from neurological disease, including psychiatric conditions such as depression or anxiety, inattentiveness secondary to various causes, and limited cooperation or poor motivation. Therefore, prior to inferring brain dysfunction on the basis of neuropsychological test results, alternative explanations must be carefully considered and ruled out." (Emphasis added)

At a minimum, doctors and patients should not take the findings of a neuropsychological assessment at face value. Second, in cases of a poor showing, the standard practice should include getting a second, blind opinion. Third, the people doing the assessment should not review the patient's medical history before the assessment. Fourth, the people doing the evaluation should interview the patient's family and/or friends after administrating the test to collaborate the findings. Fifth, the study should be limited to one hour. If there is ambiguity that requires clarification, a second one-hour assessment should occur on another day.

Ali Harati and Thomas Müller in an article in Surgical Neurology International summarize the issue as follows:

> STN DBS in the treatment of PD has resulted in a significant reduction of motor symptoms and improved independence and quality of life in appropriately selected patients. However, it may have isolatable effects on verbal fluency and related function. Case series in the literature reported similar findings. Potential candidates for DBS should be counseled about the risk of mild cognitive declines.

From a patient's vantage point, conditions such as responsiveness to levodopa and the presence of dyskinesia indicate potential significant benefits from DBS. The risk of mild cognitive declines does not compare in scope to these benefits. Moreover, it would appear that the declines are likely to occur even without DBS.

The FDA's standard review process covers a wide range of practices, including approving the veracity of genetic tests before the results are provided to patients. Why hasn't the FDA reviewed the standard industry practice of interjecting neuropsychological testing into the decision-making process for DBS? In the absence of FDA approval, neurologists should not be using these neuropsychological assessments for a go/no go decision on DBS (or any other condition); any more than prescribing cannabis for the recovery from DBS surgery without any verifiable evidence of the risks and rewards.

C. Environmental Impact

There is no environmental impact.

D. Economic Impact

Neuropsychological testing costs about $2500. There are thousands of DBS surgeries performed successfully each year with an extremely low percentage of adverse effects.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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Steven A. Zecola

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