Ms. Ref. No.: 65152, Systematic Reviews
Title: Deep Brain Stimulation for Obsessive-Compulsive Disorder: worldwide experience after 20 years.
World Journal of Psychiatry

Professor Rajesh R. Tampi,
Editor-in-Chief
World Journal of Psychiatry

Dear Prof. Tampi,

Please find attached a revised version of our manuscript “Deep Brain Stimulation for Obsessive-Compulsive Disorder: worldwide experience after 20 years”. We have addressed all reviewers’ comments and suggestions, and hope that it is now acceptable for publication in World Journal of Psychiatry. We wish to thank the reviewers for their comments, as we think that the manuscript has been considerably improved after including all the recommended modifications.

The detailed answers to the reviewers are listed below.

Sincerely,

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Reviewer #1:

This systematic review presents the worldwide experience in the use of deep brain stimulation (DBS) in severe resistant patients with Obsessive-Compulsive Disorder (OCD) in the last twenty years, comparing short- (ST) (230 patients) and long-term (LT) response (155 patients). Both ST and LT studies report a similar and stable reduction in severity (47.4%). The authors conclude that DBS is a safe and well-tolerated technique and no clear predictors of response can be established yet. Although the authors should be applauded for collecting and analyzing a large sample of references, the study has some weaknesses which need be addressed before publication:

1. The reasons why perform this review need to be strengthened. You'd better focus on the treatment-refractory OCD including the limitation of medicine and CBT.

Following the reviewer's suggestion, we have added two paragraphs to the Introduction of the article, strengthening the reasons to perform this systematic review.

Page 5, 1st paragraph:

"However, about 10% of patients continue to present chronic and severe obsessive-compulsive symptoms despite exhausting all available pharmacological strategies and carrying out intensive behavior therapy[4,5]. In this group of severely disabled OCD patients, neurosurgical interventions have been considered a potential treatment for decades, although not without risks."

Page 6, 1st paragraph:

"In addition, data on the long-term outcome of these patients have recently begun to be published[18–22]. Despite all these advances and 20 years after the first DBS implantation in a patient with OCD, knowledge on the benefits and risks of DBS use in OCD is still limited due to small sample sizes, lack of adequate control conditions, and heterogeneity in the anatomical targets and stimulation parameters. In this sense, the systematic and critical review of all the data published to date can help us resolve

some of the existing unknowns on the extension and probability of treatment response to DBS, the need of concomitant pharmacological or behavioral treatments after implantation, the recommended duration of stimulation both in responding and non-responsive patients or the risk of severe adverse effects."

2. For the Eligibility criteria 3: The primary outcome was variation in symptoms of OCD measured by the Y-BOCS, please have check whether other scales for the assessment of OCD was used in DBS studies. If have, please added them to your studies.

We appreciate the reviewer's comment, but the Y-BOCS scale is the gold standard used to assess changes in response to any type of treatment in OCD, whether pharmacological, behavioral, or as in our review, neurostimulation. In this sense, there is no published article on DBS in OCD for therapeutic use that does not employ the Y-BOCS to define the response, although some studies use, in addition to Y-BOCS, other scales such as the OCI-R (Obsessive Compulsive Inventory-Revised) to provide additional information on the different dimensions of patients' symptoms.

We have added a statement clarifying this point to Eligibility criteria 3 (page 7):

"The Y-BOCS is the gold standard for OCD symptom assessment and was employed in all studies assessing response to DBS in OCD."

3. If available, add some statement of imaging studies of DBS for OCD, that is will be interesting.

Although studies whose main objective was neuroimaging were specifically excluded from this review, as specified in the inclusion criteria, following the reviewer's suggestion we have modified the presentation of the data on predictive biomarkers of response and differentiated a specific section for neuroimaging findings (page 17, 1st paragraph):

"With respect to neuroimaging data, Van Laere et al[66] found that higher preoperative activity in the subgenual ACC assessed by positron emission tomography with fluorodeoxyglucose integrated with computed tomography (^{18}F-FDG PET/CT) has been correlated with greater response to DBS in a small sample of six patients. Abelson et al[67] reported that such scans detected decreased OFC activity in only two of four patients who responded to bilateral ALIC stimulation, suggesting that DBS improves OCD symptoms only when it restores the inhibitory function of the ventral cortico–striato–thalamo–cortical pathway. Le Jeune et al[68] similarly reported a Y-BOCS reduction after DBS that correlated with decreased metabolic activity in the ventro-medial prefrontal region of the OFC. Regarding connectivity, Figee et al[69] detected that clinical improvement after DBS correlated with a normalization of functional connectivity in the NAcc prefrontal cortex, and Baldermann et al[70] recently showed that response to DBS was predictable by analyzing the effects of stimulation on structural connectivity to prefrontal and frontal regions. Modulation of structural connectivity to the right middle frontal gyrus with DBS was identified to be associated with a better clinical response in a sample of six patients, whereas changes on connectivity to the OFC was associated with nonresponse. The same group has recently reported that response to ALIC and STN in four OCD cohorts predicted whether electrodes could or could not stimulate a fiber bundle connecting medial prefrontal regions to the STN[71]."

4. There are so much Y-BOCS data was extracted, why not perform a meta-analysis?

We really appreciate the reviewer's comment, but as it is known to carry out a meta-analysis it is necessary to estimate the absence of heterogeneity between the studies included in the analysis. In our case, as it is shown in Tables 3, 4 and 5, since we decided to consider all available information on OCD patients treated with DBS, including both randomized controlled trials and observational studies, studies were extremely heterogeneous on their design, sample size (from 1 to 70 patients), duration of DBS trial (from 7 to 36 months for short term studies and from 38 to 98,5 months

for the long term ones), stimulations parameters and neuroanatomical targets (anterior limb on internal capsule, bed nucleus of stria terminalis, inferior thalamic peduncle, ventral caudate/ventral striatum, anteromedial globus pallidus internus, caudate nucleus, medial dorsal and the ventral anterior nucleus of the thalamus, medial forebrain bundle and nucleus accumbens). For this reason we decided to carry out a qualitative systematic review, noting in the limitations section of the difficulty in interpreting even these data due to such heterogeneity (pag 20, 2nd paragraph):

"Our review has several limitations. We decided not to limit our search to RCTs and we included open studies, series, and published clinical cases, representing 79% and 91% of studies in the ST and LT studies, respectively. Although we consider that this makes our results more representative, it also limits their methodological validity because we could not adequately control for biases and the risk of a placebo response. The marked heterogeneity among the reviewed studies, including sample size, study design, stimulation parameters, anatomical targets, and psychometric tools for defining primary and secondary outcomes, make any meaningful comparison difficult. Finally, many groups concomitantly use other therapeutic approaches (e.g., CBT) concurrently with DBS or do not define whether pharmacological treatments are interrupted after DBS implantation. As such, we cannot exclude the possibility that the beneficial effects attributed to DBS were in fact attributable to a multimodal treatment approach."

5. Programming was also an important issue for DBS, you can add some information about it.

Following the recommendation of the reviewer we have added a statement to the Results section summarizing the existing data on the programming parameters and highlighting their heterogeneity (Results, Page 9, 1st paragraph)

"There was great variability in the programming parameters reported in each study, with both monopolar and bipolar stimulation being used, average frequency of stimulation ranging from 100-130 Hz, average pulse width from 60-450 µsec and average voltage from 2-7,4 V."

6. Please polish Figure 1. Please check whether there is overlapped sample for included studies.

We thank the reviewer for his comment on Figure 1. We have checked and corrected the information on full-text articles assessed for eligibility and studies included in synthesis.

We have carefully checked the overlapping of samples as it is mentioned in the Methods section (page 8, Study selection and outcome measures, 1st paragraph: "Data were double-checked to exclude duplication. If a patient was included in more than one study, only their most recent/detailed data were considered.").

In the results section it is mentioned the number of patients included in short term studies for whom long-term information was afterwards available (page 8, last paragraph)

"Some LT studies described the LT follow-up of patients who had previously been included in ST studies (41 cases)."

7. Nearly all the included sample are adults, is there any study focus on DBS for young patients with OCD.

Following the reviewer's comment we have added a paragraph to the Discussion (page 19, 1st paragraph), underlining that given the strict existing criteria for DBS, published results are limited to the adult population, with highly evolved forms of the disease, without specific references to younger subjects or those with a reduced time of illness.

"Results from published studies are limited to adult patients with OCD. Candidates to DBS must meet strict criteria to be considered for electrode implantation: they must suffer from severe to extreme OCD according to Y-BOCS scores and must be seriously impaired in daily functioning for more than 5 years despite a minimum of three adequate pharmacological trials and cognitive-behavioral therapy. Even for those

patients with early-onset OCD in childhood or adolescence, it takes years to meet these criteria. In this sense, mean illness duration before DBS implantation was around 24 years according to our results. It is unknown at this time if younger patients or patients with shorter disease progression might be better candidates for DBS."

Reviewer #2:

This a timely comprehensive review, I read with great interests. It could have the potential to become an important and high-cited publication. Only one small suggest, it's helpful to include DBS target information in Table 6 and 7

We greatly appreciate the positive evaluation of the reviewer on our article. We agree with him/her that information on DBS target is important to interpret the results of the different studies. To avoid presenting our results on too long tables, we have divided the information about the included studies in different tables: 4 and 6 for short-term studies and 5 and 7 for long-term ones. To avoid the repetition of information, data on DBS target for each study is provided just in Tables 4 (short-term) and 5 (long-term).