Deep brain stimulation for treatment-resistant depression: optimizing interventions while preserving valid trial design

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Major depressive disorder is a leading cause of disability worldwide, and nearly a third of patients do not respond to psychotherapy and trials of multiple medications (1). For these patients with treatment resistant depression (TRD), deep brain stimulation (DBS) has emerged as a possible therapeutic option. Several small, open-label studies have demonstrated encouraging results with DBS targeting various structures involved in the neurobiology of depression, including the subcallosal cingulate (2-5), ventral capsule/ventral striatum (VC/VS) (6), nucleus accumbens (7), and medial forebrain bundle (8). Despite these promising early studies, two recent randomized, sham-controlled trials were halted after interim analyses showed low likelihood of meeting endpoints, one targeting the VC/VS (9), and the other targeting the subcallosal cingulate (10). At the same time, randomized trials targeting the nucleus accumbens (11) and the ventral anterior limb of the internal capsule (vALIC) (12) for obsessive-compulsive disorder (OCD) observed a significant benefit for co-morbid depression. These disparate results suggest that we need to develop a better understanding of the circuitry that we are targeting in order to obtain more consistent outcomes.

Bergfeld *et al.* (13) assessed the efficacy of vALIC DBS in patients with TRD. This trial began with a 1-year open-label period in which all 25 patients underwent implantation of bilateral DBS and received stimulation adjustments until the response was optimized. Only then were patients randomized to a 12-week double-blind crossover phase comparing active stimulation to sham. In effect, the researchers performed a 1-year open-label study followed by a trial comparing outcomes on and off stimulation.

The open-label portion of the study reported a comparable response rate to that found in other observational series of DBS for depression. Ten (40%) of 25 patients were responders, defined as a decrease of at least 50% on the 17-item Hamilton Depression Rating Scale (HAM-D-17) compared to baseline. The response rate was in the range of observational studies targeting the subcallosal cingulate (28.6–62.5%) (2-5), VC/VS (53.3%) (6), and nucleus accumbens (45.5%) (7) with enrollments ranging from 8 to 21 patients. Only a small, short-term follow-up series of medial forebrain bundle DBS reported a notably higher rate of response (6 of 7 patients, 85.7%, at 12–33 weeks) (8). However, observational studies, particularly those in psychiatry, are subject to significant placebo effects; therefore, the double-blind on *vs.* off stimulation phase of this trial provides important information.

Sixteen patients entered the second phase of the trial, in which they were assigned to either active or sham stimulation arms in a double-blind, randomized fashion. After a period of up to 6 weeks, they were crossed over to the other arm to serve as their own controls. During active stimulation, patients scored significantly lower on the HAM-D-17 (13.6, 95% CI: 9.8–17.4) than with sham stimulation (23.1, 95% CI: 20.6–25.6). Similar results were

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found for the other symptom metrics. Thus this randomized crossover trial reported a benefit from stimulation rather than sham for the first time in a dedicated, controlled trial of DBS for TRD.

Compared to the design of the previous aborted DBS for TRD trials, these authors made several modifications that may have led to the observed positive results. First, the slightly more ventral and anterior position of the vALIC targeted in this study as compared to the previous VC/VS target may be partially responsible. Stimulation of the vALIC was previously shown to have an antidepressant effect in one of the aforementioned randomized trials for OCD. The consequent difference in white matter fibers included in the stimulation field, and therefore the difference in downstream cortical and subcortical areas modulated with DBS therapy, may have engaged a more effective network.

Second, Bergfeld *et al.* (13) added a longer optimization phase prior to randomization. Previous DBS trials implanted all patients with DBS, conducted a randomized trial comparing stimulation to sham, and then allowed all patients to enter an open-label continuation phase. One shortcoming of such an approach is that it may not allow sufficient opportunity to find the optimal stimulation parameters that might permit patients in the treatment arm to receive the maximum potential benefit of the therapy. Programmers can adjust multiple stimulation parameters including voltage, frequency, pulse width, and which of the four contacts on the electrode receive stimulation. Ideal parameters have not been established and may vary from patient to patient. Furthermore, acute response may not predict long-term treatment effects. Thus the relatively short optimization phase of 4 weeks in Dougherty *et al.* (9) may have been insufficient to identify optimal settings, compared to the 52-week optimization phase in Bergfeld *et al.* (13).

Unfortunately, the long open-label phase used for optimization may have contributed to the high dropout rate of non-responders, selection bias, and an overestimation of efficacy in the trial. As the author observed, 8 of the 9 patients who withdrew before the crossover phase were non-responders in the open-label study, leading to a biased selection of responders for the 16 patients in the randomized phased. Dropout always has the potential to introduce selection bias in trials, but this study's long open-label phase preceding randomization led to a substantial bias favoring selection of responders for initial enrollment in the randomized trial. The 100 percent retention of the 16 patients through both crossover phases is commendable, but does not mitigate the initial selection bias in this case.

Crossover designs are primarily used in bioequivalence trials and are rarely feasible in surgery where the effect of a single treatment is irreversible. They ideally require that the disease being treated is chronic and stable and that the treatments alleviate the condition without causing lasting benefit or complete cure. The ability to turn stimulation on and off made a crossover design feasible, but it also could have unblinded patients and contaminated the control population. After a year of stimulation and programming sessions for optimization, patients were more likely to be able to detect when stimulation was turned off. As the authors note, ten patients had an abrupt increase in symptoms during the sham phase. This observation suggests that these individuals realized that stimulation was being withheld and experienced a nocebo effect (worsening of symptoms due to expectation of lack of benefit). This phenomenon may have overestimated the difference between active and sham stimulation and thus artificially inflated the results. Furthermore, patients who have their stimulation turned off after a year are not equivalent to a stimulation naïve control population and may not be an ideal comparison for efficacy.

Despite the limitations mentioned above, the study by Bergfeld *et al.* (13) remains an extremely important contribution to the field of psychiatric neurosurgery, as it represents the first example of Class I evidence regarding the efficacy of ventral ALIC DBS for TRD. Even beyond the promising outcomes, several aspects of study design provide valuable information for future work. The authors' experience highlights the importance and the challenge of designing trials that simultaneously optimize the intervention under evaluation, uphold ethical standards, and maintain validity. Some have argued that trial timelines need to be more flexible to accommodate individual variability in the response to treatment (14). Many are also focused on selecting the appropriate target for each patient based on more recent understanding of individual variability in cognitive and symptom phenotypes (15) or neuroimaging findings (16). Future work will no doubt take into consideration the important lessons learned in this study.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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