Brazilian Journal of Psychiatry
bjp
Revista Brasileira de Psiquiatria

Braz J Psychiatry. 2020 Jul-Aug;42(4):344-346
doi:10.1590/1516-4446-2020-0004
Brazilian Psychiatric Association

EDITORIAL

Why is deep brain stimulation for treatment-resistant depression a needed treatment option?

Patricio **Riva-Posse**

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA.

Treatment-resistant depression (TRD) is an ongoing area of concern in public health, with increasing interest in the psychiatric scientific community, given its great personal and societal costs. Its prevalence is high, and up to a third of patients do not respond to four consecutive antidepressants.[1] Patients with TRD experience significant loss in quality of life, high costs, and hospitalizations, and are estimated to be twice as likely to attempt suicide at least once during their lifetime than non-resistant depressed patients, and 15 times more likely than the general population.[2-5]

Despite multiple antidepressant treatment options, patients with TRD encounter growing difficulties to maintain a relief of symptoms with subsequent episodes. This is true as well for newer treatments such as ketamine and esketamine.[6,7] Electroconvulsive therapy (ECT) is very effective in depression, with remission rates of 60–90% reported in clinical trials, but relapse rates are high, and long courses of ECT have cumulative cognitive side effects that many times become intolerable for patients.[8] Non-pharmacological treatments besides ECT have been available for years, with the main example being repetitive transcranial magnetic stimulation (rTMS); multiple meta-analysis have demonstrated efficacy of rTMS by stimulation of the dorsolateral prefrontal cortex (DLPFC).[9,10] However, rTMS is a burdensome treatment (daily 40-minute sessions for up to 6 weeks), and patients with high levels of treatment resistance are less likely to respond.[11] Vagus nerve stimulation (VNS) was approved for use in TRD in 2005. The device delivers low-frequency, chronic, intermittent-pulsed electrical signals to the left cervical vagus nerve. Studies have described a slow but sustained clinical response, mostly shown by long-term naturalistic follow-up of patients rather than in the primary end points of the clinical trials.[12] Sadly, insurance coverage by third-party payers has been limited; therefore, the number of patients benefitting from this treatment option is low despite 15 years of commercial availability.

Deep brain stimulation (DBS) has the potential to provide a new treatment for TRD once other strategies have ceased to work. DBS may provide faster relief than VNS, as well as a sustained response for extended periods of time. Besides VNS, no other treatment option has been studied in long-term results (over 1 year). The conceptualization of psychiatric disorders as circuit-based, and the formulation of depression as the manifestation of dysfunctional brain networks, with support from neuroimaging, enabled the introduction of DBS in depression, modeled after its success in movement disorders. DBS is the most invasive of the neuromodulatory approaches, requiring neurosurgical implantation of bilateral electrodes in the selected area of interest. However, it provides a unique opportunity to achieve sustained control of symptoms of depression. Since the first report of DBS in depression in 2005, multiple targets have been investigated, with promising results.[13] The largest clinical samples have studied the subcallosal cingulate white matter (SCC), nucleus accumbens (NAc), ventral capsule/ventral striatum (VC/VS), and medial forebrain bundle (MFB).[14] Different open-label case series have reported response in around 40–70% of patients. The enthusiasm of these reports led to large randomized clinical trials (RCTs) in the SCC and VC/VS, which unfortunately did not meet their primary clinical endpoints.[15,16] These trials were terminated early after interim analyses determined low likelihood of a positive result with completion of the desired recruitment goals.

Many opinions were expressed regarding potential causes for these failures. One main concern has been directed at the trial design: primary endpoints were reportedly too early to identify a difference between active stimulation and placebo. Supporting this hypothesis, the results from a different trial showed that discontinuation of stimulation after a period of optimization was better suited to identify a difference between active and sham stimulation. Bergfeld et al. described a 40% overall response rate in 25 patients during the open-label phase; then, a number of participants entered a randomized crossover period, in which all responders experienced return of symptoms within less than 2 weeks once stimulation was discontinued.[17] Other groups identified that the possible reason for failure of larger RCTs was the surgical protocol to determine the ideal region for implantation. Initially through retrospective analysis of white matter connectivity in patients who responded to SCC DBS, and then through prospective identification of the target using diffusion

Correspondence: Patricio Riva-Posse, 101 Woodruff Cir, NE suite 4309, Atlanta, GA, 30322, USA.
E-mail: privapo@emory.edu
Submitted Feb 05 2020, accepted Feb 06 2020, Epub May 11 2020.

How to cite this article: Riva-Posse P. Why is deep brain stimulation for treatment-resistant depression a needed treatment option? Braz J Psychiatry. 2020;42:344-346. http://dx.doi.org/10.1590/1516-4446-2020-0004

tractography, Riva-Posse et al. reported that, albeit in a single center, results from DBS can improve with accurate targeting from 41% to 73% with 6 months of stimulation.[18,19] This is the same approach used for target selection in MFB, as it necessarily requires identification of the white-matter bundle in which DBS leads are to be implanted.[20,21] DBS in the MFB has been reported to yield rapid and effective results in small open-label trials from two separate centers, with around 70% of patients responding.[22,23] Different targets (but within the same mood network) then hint at the possibility that adequate DBS requires accurate implantation. A third explanation that could improve the outcome of future trials, along with protocol design and precise targeting, lies at the problem of heterogeneity in the depressive syndrome. If, as proposed above, DBS is a specific intervention on a predefined circuit, then outcome measurement should address the expected results of modulation of that particular circuit.[24] Consequently, work ahead should focus on trying to identify clinical, imaging, or physiological characteristics of patients that may respond to DBS, or changes that are exerted by the electrical modulation of the target circuit.[25,26] This refinement of patient selection, and biomarker engagement with therapy, has evolved with incremental success in the field of Parkinson disease, even aiding in the determination of target selection depending on clinical characteristics.[27,28]

There are encouraging results in the field of DBS for depression. Patients have experienced sustained antidepressant response for years after surgery with DBS of the SCC, VC/VS, and MFB.[29-31] The keys for success in the near future of DBS for depression will rely on the integration of advances in imaging, neurophysiology, and clinical expertise to plan new multicenter trials that will replicate, on a larger scale, the observations of different research groups, thus ensuring a safe and long-lasting treatment option for the TRD population.[32] The stakes are high, but for clinicians who have had the privilege of observing a life-changing procedure treat depression so effectively when all else has failed, there is no other option.

Disclosure

The author has received consulting fees from Janssen Pharmaceutical.

References

1 Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry. 2006;163:1905-17.

2 Gibson TB, Jing Y, Smith Carls G, Kim E, Bagalman JE, Burton WN, et al. Cost burden of treatment resistance in patients with depression. Am J Manag Care. 2010;16:370-7.

3 Ivanova JI, Birnbaum HG, Kidolezi Y, Subramanian G, Khan SA, Stensland MD. Direct and indirect costs of employees with treatment-resistant and non-treatment-resistant major depressive disorder. Curr Med Res Opin. 2010;26:2475-84.

4 Olchanski N, McInnis Myers M, Halseth M, Cyr PL, Bockstedt L, Goss TF, et al. The economic burden of treatment-resistant depression. Clin Ther. 2013;35:512-22.

5 Dunner DL, Rush AJ, Russell JM, Burke M, Woodard S, Wingard P, et al. Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. J Clin Psychiatry. 2006;67:688-95.

6 Newport DJ, Carpenter LL, McDonald WM, Potash JB, Tohen M, Nemeroff CB, et al. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. Am J Psychiatry. 2015;172:950-66.

7 Daly EJ, Singh JB, Fedgchin M, Cooper K, Lim P, Shelton RC, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry. 2018;75:139-48.

8 Kellner CH, Knapp RG, Petrides G, Rummans TA, Husain MM, Rasmussen K, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). Arch Gen Psychiatry. 2006;63:1337-44.

9 Lam RW, Chan P, Wilkins-Ho M, Yatham LN. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and metaanalysis. Can J Psychiatry. 2008;53:621-31.

10 Gaynes BN, Lloyd SW, Lux L, Gartlehner G, Hansen RA, Brode S, et al. Repetitive transcranial magnetic stimulation for treatment-resistant depression: a systematic review and meta-analysis. J Clin Psychiatry. 2014;75:477-89; quiz 489.

11 Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: a meta analysis. Int J Neuropsychopharmacol. 2002;5:73-103.

12 Aaronson ST, Sears P, Ruvuna F, Bunker M, Conway CR, Dougherty DD, et al. A 5-year observational study of patients with treatment-resistant depression treated with vagus nerve stimulation or treatment as usual: comparison of response, remission, and suicidality. Am J Psychiatry. 2017;174:640-8.

13 Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. Neuron. 2005;45:651-60.

14 Dandekar MP, Fenoy AJ, Carvalho AF, Soares JC, Quevedo J. Deep brain stimulation for treatment-resistant depression: an integrative review of preclinical and clinical findings and translational implications. Mol Psychiatry. 2018;23:1094-112.

15 Holtzheimer PE, Husain MM, Lisanby SH, Taylor SF, Whitworth LA, McClintock S, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant depression: a multisite, randomised, sham-controlled trial. Lancet Psychiatry. 2017;4:839-49.

16 Dougherty DD, Rezai AR, Carpenter LL, Howland RH, Bhati MT, O'Reardon JP, et al. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. Biol Psychiatry. 2015;78:240-8.

17 Bergfeld IO, Mantione M, Hoogendoorn ML, Ruhe HG, Notten P, van Laarhoven J, et al. Deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry. 2016;73:456-64.

18 Riva-Posse P, Choi KS, Holtzheimer PE, Crowell AL, Garlow SJ, Rajendra JK, et al. A connectomic approach for subcallosal cingulate deep brain stimulation surgery: prospective targeting in treatment-resistant depression. Mol Psychiatry. 2018;23:843-9.

19 Riva-Posse P, Choi KS, Holtzheimer PE, McIntyre CC, Gross RE, Chaturvedi A, et al. Defining critical white matter pathways mediating successful subcallosal cingulate deep brain stimulation for treatment-resistant depression. Biol Psychiatry. 2014;76:963-9.

20 Coenen VA, Schlaepfer TE, Allert N, Madler B. Diffusion tensor imaging and neuromodulation: DTI as key technology for deep brain stimulation. Int Rev Neurobiol. 2012;107:207-34.

21 Coenen VA, Sajonz B, Reisert M, Bostroem J, Bewernick B, Urbach H, et al. Tractography-assisted deep brain stimulation of the superolateral branch of the medial forebrain bundle (slMFB DBS) in major depression. Neuroimage Clin. 2018;20:580-93.

22 Schlaepfer TE, Bewernick BH, Kayser S, Madler B, Coenen VA. Rapid effects of deep brain stimulation for treatment-resistant major depression. Biol Psychiatry. 2013;73:1204-12.

23 Fenoy AJ, Schulz P, Selvaraj S, Burrows C, Spiker D, Cao B, et al. Deep brain stimulation of the medial forebrain bundle: distinctive responses in resistant depression. J Affect Disord. 2016;203:143-51.

24 Widge AS, Deckersbach T, Eskandar EN, Dougherty DD. Deep brain stimulation for treatment-resistant psychiatric illnesses: what has gone wrong and what should we do next? Biol Psychiatry. 2016;79:e9-10.
25 Smart O, Choi KS, Riva-Posse P, Tiruvadi V, Rajendra J, Waters AC, et al. Initial unilateral exposure to deep brain stimulation in treatment-resistant depression patients alters spectral power in the subcallosal cingulate. Front Comput Neurosci. 2018;12:43.
26 Veerakumar A, Tiruvadi V, Howell B, Waters AC, Crowell AL, Voytek B, et al. Field potential 1/f activity in the subcallosal cingulate region as a candidate signal for monitoring deep brain stimulation for treatment-resistant depression. J Neurophysiol. 2019;122:1023-35.
27 Paschen S, Deuschl G. Patient evaluation and selection for movement disorders surgery: the changing spectrum of indications. Prog Neurol Surg. 2018;33:80-93.
28 Wingeier B, Tcheng T, Koop MM, Hill BC, Heit G, Bronte-Stewart HM. Intra-operative STN DBS attenuates the prominent beta rhythm in the STN in Parkinson's disease. Exp Neurol. 2006; 197:244-51.
29 Crowell AL, Riva-Posse P, Holtzheimer PE, Garlow SJ, Kelley ME, Gross RE, et al. Long-term outcomes of subcallosal cingulate deep brain stimulation for treatment-resistant depression. Am J Psychiatry. 2019;176:949-56.
30 Fenoy AJ, Schulz PE, Selvaraj S, Burrows CL, Zunta-Soares G, Durkin K, et al. A longitudinal study on deep brain stimulation of the medial forebrain bundle for treatment-resistant depression. Transl Psychiatry. 2018;8:111.
31 van der Wal JM, Bergfeld IO, Lok A, Mantione M, Figee M, Notten P, et al. Long-term deep brain stimulation of the ventral anterior limb of the internal capsule for treatment-resistant depression. J Neurol Neurosurg Psychiatry. 2020;91:189-95.
32 Dougherty DD. Will deep brain stimulation help move precision medicine to the clinic in psychiatry? Biol Psychiatry. 2019;85:706-7.