Personalized Medicine in Psychiatry 17–18 (2019) 1–3

Contents lists available at ScienceDirect

Personalized Medicine in Psychiatry

journal homepage: www.elsevier.com/locate/pmip

Are modern neuromodulation therapies too precise?

William M. McDonald

Emory University Department of Psychiatry and Behavioral Sciences, Atlanta, Georgia, USA

In this issue of Personalized Medicine in Psychiatry, leaders in the field of neuromodulation review the extant evidence on the efficacy of the most innovative neuromodulation techniques in treatment resistant depression (TRD). And while the evidence is clear that the field has become increasingly precise in focusing neuromodulation stimulation down to a millimeter of tissue, it is not clear that these modern neuromodulation treatments will supplant an innovative treatment from the 1930s, electroconvulsive therapy (ECT), as the gold standard for treatment resistance [1–5].

There is a clear need to develop new treatments for TRD. Up to one in five depressed patients will fail pharmacotherapy and/or psychotherapy, meet criteria for TRD and account for over 100 billion dollars a year in lost productivity and medical costs [6]. TRD is also associated with approximately half the annual depression treatment costs and associated with a higher medical comorbidity and an increased risk of dying by suicide [7].

Although antidepressants are now safer and have fewer side effects, it is hard to make a persuasive argument that the "newer" antidepressant treatments are more effective than the first tricyclics, imipramine and amitriptyline, which were developed in the 1950's (see for example [8]). The NIMH funded Sequenced Treatment Alternatives to Relieve Depression (STAR*D) showed that only 67% of patients remitted in an evidenced based trial using an algorithm for sequencing psychotherapy, antidepressants (ranging from monoamine oxidase inhibitors to serotonin reuptake inhibitors) and augmenting strategies [9]. In fact, if a patient failed the first two antidepressant trials in STAR*D, their chances of remitting to the third trial was only about 15%; And even if patient remitted on their third antidepressant trial, they had only a 5% chance of staying well for one year [1].

In this issue, Yao et al., [10] conclude that many of the positive clinical predictors of response to ECT are the same factors that complicate treatment with pharmacotherapy and require a more immediate response: severity of depression, suicidal ideation and psychosis in the depressive episode. And, although the response to ECT is decreased in patients with multiple antidepressant failures, the remission rates after ECT are reliably in the 50%- 80% range with about half the patients on maintenance therapy remaining well in the year after ECT [11–13].

In fact, given the proven safety and efficacy of ECT, some have rightly questioned the placement of ECT in algorithms only after multiple antidepressant trials with the entreaty: "no need to save the best for last" [14]. But for many clinicians, families and patients the answer is obvious: the stigma associated with ECT, fear of permanent memory loss as well as the cost and availability of the treatment. Yao et al. delineate biomarkers that are now being refined in preclinical models as markers for ECT response. These biomarkers could add precision to an ECT recommendation and, with that precision, may come acceptance that this treatment is the treatment of choice, even early in the treatment course.

One approach to decreasing the cognitive side effects of ECT has been to investigate a more focused convulsive stimulus. Models of the ECT-induced seizure with standard electrode configurations produce a stimulation that activates up to 94% of the brain volume and expose the hippocampi (and other memory structures) to a suprathreshold electrical field [15]. Kallioniemi et al. [16] outline the recent research in magnetic seizure therapy (MST). MST uses an electrical field to create more focal seizures which could potentially decrease the cognitive side effects of convulsive therapy (i.e., less effect on memory areas such as the hippocampus and amygdala) and focus the seizure on circuit specific targets.

Compared to ECT, MST activates only 21% of the brain volume [15]. Ongoing randomized controlled trials (RCT's) are designed to confirm earlier findings that MST has a similar antidepressant efficacy to ECT, with fewer cognitive side effects. And, while ECT stimulates large cortical and subcortical areas, the precision of MST in targeting a specific neuroanatomic area comes with the possibility that the efficacy of MST may be decreased relative to ECT, unless research can clearly define the "right" circuit to stimulate. And there is no doubt that if MST can be shown to have the efficacy of ECT with fewer cognitive side effects, and a more precise target based on the individual's neurophysiology, MST has the potential for providing individualized treatments for TRD.

Another strategy to match the efficacy of ECT with fewer potential side effects, has been to investigate subconvulsive neuromodulation therapies. Both repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) do not require anesthesia and have minimal cognitive or other side effects. tDCS has low cost and can potentially be administered by a patient at home with remote supervision [17]. The question is, are tDCS treatments as effective as ECT, or at least more effective than a third trial of an antidepressant?

Jog et al. [18] review the efficacy of conventional F3 anodal tDCS

E-mail address: wmcdona@emory.edu.

https://doi.org/10.1016/j.pmip.2019.08.001

Available online 17 October 2019

which to date has shown only small to moderate effect sizes in depression studies, albeit with heterogenous patient populations. Their detailed analysis of the literature shows that the types of depressive symptoms that respond preferentially to tDCS are core depressive features (i.e., psychomotor retardation and dysphoria) as opposed to vegetative symptoms. And, they point out that there are current studies underway to optimize tDCS by changing the technical parameters, combining pharmacology and psychotherapy and employing sophisticated modeling to target circuits.

The accumulating data is quite different for the safety and efficacy of rTMS. RTMS was approved by the FDA in 2008 for the treatment of patients with resistant major depression. With the FDA approval of the theta burst protocol in 2018, and the decrease in the treatment time from 38″ to closer to 3″, comes the potential to accelerate the treatment course from weeks to days [19,20] making rTMS increasingly accessible for TRD patients. Garnaat et al. [21] point out that 25%- 50% of the TRD patients respond to rTMS, and research is underway to optimize the response by investigating novel protocols and neuronavigation techniques. Some of these techniques are quite sophisticated and use imaging to identify cortical sites with intrinsic connections to subcortical targets (e.g., subgenual cingulate). This strategy has proven successful in improving the response to TMS [22]. While ECT remains the treatment of choice in a severely suicidal or psychotic patients needing a more immediate response, rTMS has the potential to precisely target specific brain regions and circuits and has no cognitive side effects. Unlike MST this focal stimulation does not require anesthesia. And the public perception of TMS has generally been very positive.

Vagal nerve stimulation (VNS) was first approved by the FDA for treatment resistant depression but the clinical application of VNS was limited by the cost and the fact that the Center for Medicare and Medicaid Services (CMS) and other insurance companies have been slow to provide coverage for the procedure. However, as the review by de Leon et al. [23] clarifies the evidence that highly treatment resistant patients (I.e., failure of eight or more medications) have a significant response to VNS and have a sustained response over time. Recent data, including a publication in the American Journal of Psychiatry on the 5-year efficacy of VNS [24], has led CMS to revaluated coverage for VNS in TRD and approve a CMS protocol to evaluate the safety and efficacy of VNS in TRD [25].

Investigational trials in deep brain stimulation (DBS) for TRD have also shown efficacy using very specific neuroanatomical targets (e.g., subgenual cingulate cortex) in some of the most treatment resistant patients (e.g., patients who failed ECT). Conroy and Holtzheimer et al. [26] review the available data on the use of the most precisely targeted neuromodulation therapy. Research in DBS received a setback when the Broaden trial was halted due to a lack of efficacy. An analysis of DBS data showed how critical electrode placement can be when your target is only a few millimeters of tissue [27] and may provide lessons for future trials. Kilian et al. [28] review the emerging treatments using DBS as a starting point, and cover the range of innovative strategies from ultrasound to gamma knife radiation surgery. These techniques have the potential to further advance the field by targeting the network of connected centers involved in treatment resistant depression.

Research in neuromodulation devices is advancing rapidly with more focal treatments that target specific neuroanatomic circuits. Unfortunately, what has not kept pace is the research that uses demographic, clinical, biomarker and neuroanatomic data to identify which patients are likely to benefit, where precisely the clinician should stimulate for an individual patient and which device would be most appropriate. The investigators in this issue describe the present state of this research.

ECT may be one of the most successful neuromodulation devices precisely because it is less focal: That is, if you don't know exactly where to stimulate, you may be better with a nonfocal treatment. Neuromodulation therapy offers the opportunity to stimulate a specific neuroanatomic target. The challenge will be to personalize the target to the individual patient.

Conflict of interest

Dr. McDonald reports research supported by the National Institute of Mental Health, National Institute of Neurological Disease and Stroke, National Institute of Aging, Patient-Centered Outcomes Research Institute, Stanley Foundation, Soterix, Neuronetics, NeoSync and Cervel Neurotherapeutics.

He has a contract with Oxford University Press to co-edit a book on the Clinical Guide to Transcranial Magnetic Stimulation in the Treatment of Depression and section editor for Current Psychiatry Reports. He is a consultant for Signant Health.

References

[1] Conway CR, George MS, Sackeim HA. Toward an evidence-based, operational definition of treatment-resistant depression: when enough is enough. JAMA Psychiatry 2017;74(1):9–10.
[2] Sackeim HA, Aaronson ST, Bunker MT, Conway CR, Demitrack MA, George MS, et al. The assessment of resistance to antidepressant treatment: Rationale for the Antidepressant Treatment History Form: Short Form (ATHF-SF). J Psychiatr Res 2019;113:125–36.
[3] Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. J Clin Psychiatry 1997;58(Suppl. 13):23–9.
[4] Oquendo MA, Malone KM, Ellis SP, Sackeim HA, Mann JJ. Inadequacy of antidepressant treatment for patients with major depression who are at risk for suicidal behavior. Am J Psychiatry 1999;156(2):190–4.
[5] Chandler GM, Iosifescu DV, Pollack MH, Targum SD, Fava M. RESEARCH: validation of the Massachusetts general hospital antidepressant treatment history questionnaire (ATRQ). CNS Neurosci Ther 2010;16(5):322–5.
[6] Mrazek DA, Hornberger JC, Altar CA, Degtiar I. A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996–2013. Psychiatr Serv 2014;65(8):977–87.
[7] Greden JF. The burden of recurrent depression: causes, consequences, and future prospects. J Clin Psychiatry 2001;62(Suppl. 22):5–9.
[8] Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 2018;391(10128):1357–66.
[9] Fava M, Rush AJ, Trivedi MH, Nierenberg AA, Thase ME, Sackeim HA, et al. Background and rationale for the sequenced treatment alternatives to relieve depression (STAR*D) study. Psychiatr Clin North Am 2003;26(2). pp. 457–94, x.
[10] Yao Z, McCall WV, Essali N, Wohl E, Parker C, Rosequist PB, et al. Precision ECT for major depressive disorder: a review of clinical factors, laboratory, and physiologic biomarkers as predictors of response and remission. Personalized medicine. Psychiatry 2019.
[11] Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. [see comments.]. JAMA 2001;285(10):1299–307.
[12] O'Connor MK, Knapp R, Husain M, Rummans TA, Petrides G, Smith G, et al. The influence of age on the response of major depression to electroconvulsive therapy: a C.O.R.E. Report. Am J Geriatric Psychiatry 2001;9(4):382–90.
[13] 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(12):1337–44.
[14] Beale MD, Kellner CH. ECT in treatment algorithms: no need to save the best for last. J Ect 2000;16(1):1–2.
[15] Lee WH, Lisanby SH, Laine AF, Peterchev AV. Comparison of electric field strength and spatial distribution of electroconvulsive therapy and magnetic seizure therapy in a realistic human head model. Eur Psychiatry 2016;36:55–64.
[16] Kallioniemi E, McClintock SM, Deng Z, Husain MM, Lisanby SH. Magnetic seizure therapy: towards personalized seizure therapy for major depression. Precision Med Psychiatry 2019. https://doi.org/10.1016/j.pmip.2019.04.003 in this issue.
[17] Shaw MT, Kasschau M, Dobbs B, Pawlak N, Pau W, Sherman K, et al. Remotely supervised transcranial direct current stimulation: an update on safety and tolerability. J Vis Exp 2017;128.
[18] Jog M, Wang D, Narr KL. A review of transcranial direct current stimulation (tDCS) for the individualized treatment of depressive symptoms. Precision Med Psychiatry 2019. https://doi.org/10.1016/j.pmip.2019.03.001 in this issue.
[19] Trevizol AP, Blumberger DM. An update on repetitive transcranial magnetic stimulation for the treatment of major depressive disorder. Clin Pharmacol Ther 2019.
[20] Williams NR, Sudheimer KD, Bentzley BS, Pannu J, Stimpson KH, Duvio D, et al. High-dose spaced theta-burst TMS as a rapid-acting antidepressant in highly refractory depression. Brain 2018;141(3):e18.
[21] Garnaat SL, Fukuda AM, Yuan S, Carpenter LL. Identification of clinical features and biomarkers that may inform a personalized approach to rTMS for depression. Precision Med Psychiatry 2019. https://doi.org/10.1016/j.pmip.2019.09.001 in this issue.

[22] Fox MD, Liu H, Pascual-Leone A. Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connectivity. Neuroimage 2013;66:151–60.
[23] de Leon VC, Drysdale AT, Conway CR, Aaronson ST. Predictors of response for vagus nerve stimulation in treatment-resistant depression. Precision Med Psychiatry 2019. https://doi.org/10.1016/j.pmip.2019.05.001 in this issue.
[24] 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(7):640–8.
[25] Services. CfMM. Decision Memo for Vagus Nerve Stimulation (VNS) for Treatment Resistant Depression (TRD) (CAG-00313R2). CMS.GOV: CMS; 2019. p. https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=292.
[26] Conroy SK, Holtzheimer PE. Deep brain stimulation for treatment-resistant depression: predicting response and optimizing treatment. Precision Med Psychiatry 2019. https://doi.org/10.1016/j.pmip.2019.10.002 in this issue.
[27] 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(12):963–9.
[28] Kilian HM, Meyer DM, Schlaepfer TE. Emerging treatments. Precision Med Psychiatry 2019. https://doi.org/10.1016/j.pmip.2019.07.002 in this issue.