

## LETTERS TO THE EDITORS

# Concomitant deep brain stimulation and vagus nerve stimulation for treatment-resistant depression: a case report

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Depression is one of the main causes of disability worldwide.<sup>1</sup> It is estimated that about 30% of patients diagnosed with depression do not achieve and sustain remission following two or more adequate evidence-based treatments,<sup>2</sup> which characterizes treatment-resistant depression (TRD).<sup>3</sup> TRD is associated with several poorer outcomes, from individual risk of suicide to high direct and indirect societal costs.<sup>4,5</sup> Among the pharmacological and non-pharmacological interventions for TRD, vagus nerve stimulation (VNS) and deep brain stimulation (DBS) are invasive brain stimulation techniques that have shown positive efficacy and safety results.<sup>6,7</sup> Concomitant treatment with both interventions has not yet been reported in the literature. This report presents a case in which DBS and VNS were co-administered in a patient with TRD.

In this letter to the Editor we present the case of a 58-year-old man with major depressive disorder onset at age 13. The patient has undergone several pharmacological trials since his diagnosis, in addition to electroconvulsive therapy, and inpatient treatment due to suicide attempts. In 2010, the patient underwent VNS device implantation and responded well to VNS therapy. In 2014, after four years of good response to VNS therapy, the symptoms recurred and the patient's current depressive episode began. In 2018, the patient decided to join a clinical trial of medial forebrain bundle DBS (MFB-DBS) treatment. The VNS device was turned off about 6 weeks before DBS device implantation. At some point during DBS treatment, the patient concomitantly used ketamine with no symptom remission. In December 2020, after 27 months in DBS therapy, the participant was still experiencing significant symptoms, and a decision was made to reactivate his VNS device. From that point, DBS and VNS were concomitantly administered. The patient's Montgomery-Asberg Depression Rating Scale (MADRS) scores were obtained beginning at 67 weeks before VNS device reactivation and up to 30 weeks after initiating DBS-VNS therapy, totaling seven assessments (six before and one after initiation of DBS-VNS therapy).

The patient's MADRS scores are shown in Figure 1. The MADRS scores at 67 weeks, 65 weeks, 60 weeks, 51

weeks, 38 weeks, and 12 weeks before VNS reactivation were 18, 16, 29, 36, 27, and 13 respectively. After 30 weeks of joint stimulation with DBS and VNS, his MADRS score was 7. No severe side effects attributable to DBS-VNS treatment were reported.

In this case report, the lowest level of depressive symptoms (MADRS scores = 7) was observed during the concomitant use of two modalities of invasive neurostimulation, with no severe side effects. However, it is important to note that the patient's depressive symptom scores were already decreasing prior to concomitant VNS-DBS stimulation.

We hypothesize that concomitant VNS and MFB-DBS may lead to greater improvement than each therapy alone due to possible complementary mechanisms of action. Studies suggest that VNS may act by modulating levels of dopamine, norepinephrine, gamma-aminobutyric acid, homovanillic acid, 5-hydroxyindoleacetic acid, and their metabolites.<sup>8</sup> In addition, VNS has been associated with increased neuroplasticity markers, such as brain-derived neurotrophic factor.<sup>7</sup> In MFB-DBS, the impact on the reward pathway seems to have played a role in the response. Stimulation of the reward pathway in MFB-DBS is associated with activation of dopamine receptors in the prefrontal cortex<sup>9</sup> and increased dopamine D1 and D2 receptor mRNA expression.<sup>7</sup> Furthermore, higher brain-derived neurotrophic factor levels have been described in MFB-DBS.<sup>7,10</sup>

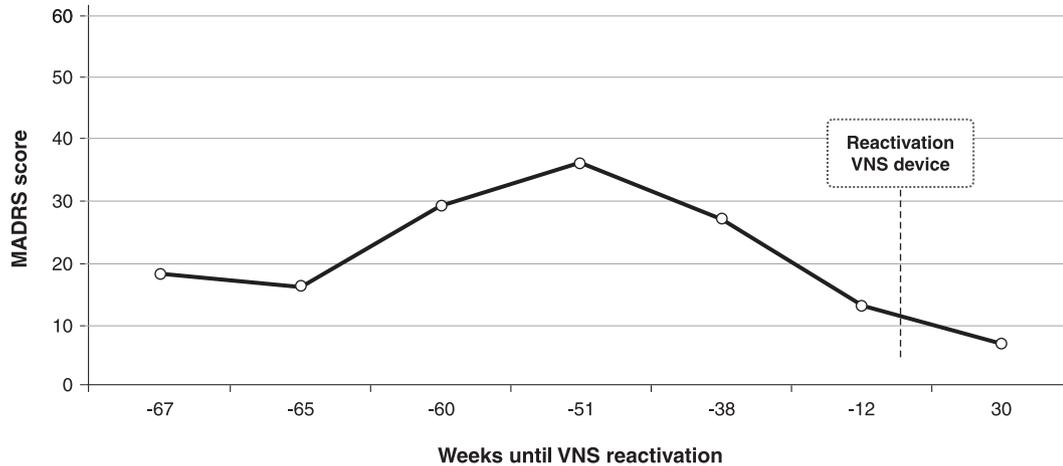
Further follow-up is needed to verify whether the patient's improvement is sustained and no safety concerns arise.

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## Disclosure

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**Figure 1** MADRS scores during the observation period (week 0 corresponds to VNS device reactivation).

Pharmaceuticals, and Abbvie; is a consultant for Eurofarma; is a stockholder at Instituto de Neurociencias Dr. Joao Quevedo; and receives copyrights from Artmed Editora, Artmed Panamericana, and Elsevier/Academic Press.

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## Clinical perspective on antipsychotic receptor binding affinities

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The interactions between antipsychotic drugs and cell receptors can be measured as binding affinity values, expressed in terms of the dissociation constant,  $K_d$ ; the inhibition constant,  $pK_i$  ( $-\log K_i$ ); and the half-maximal inhibitory concentration,  $IC_{50}$ . The affinity constant values ( $K_i$ ) of each ligand are experimentally measured, calculated from the Cheng-Prusoff equation:  $K_i = IC_{50}/(1 + C/K_d)$ , where  $C$  is the concentration of ligand and  $K_d$  is its