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Synchronized cervical VNS with accelerated theta burst TMS for treatment resistant depression

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Declaration of competing interest

Dr. George is the principal investigator at MUSC which is an enrolling site in a LivaNova coordinated VNS depression trial (RECOVER).

Dear Editor:

Several lines of evidence suggest that vagus nerve stimulation (VNS) triggers transient release of plasticity promoting neuromodulators throughout the cortex, such as acetylcholine and norepinephrine [1]. Cervical VNS can effectively treat medication resistant epilepsy [2,3] and treatment resistant depression over the course of many years [4,5]. In some cases, cervically implanted VNS depression patients continue to have depressive episodes requiring treatment with medications, electroconvulsive therapy (ECT), or prefrontal transcranial magnetic stimulation (TMS). The FDA initially ruled that TMS was contraindicated in patients with VNS, but this was later shown to be safe [6]. At first, TMS providers turned off the VNS device during TMS as they do in ECT. However, as TMS does not need to produce a seizure, a common clinical practice is to simply have the VNS device remain on and deliver the TMS ignoring the VNS firing pattern.

A new development with TMS for depression is the use of intermittent theta burst (iTBS) patterns, and combining multiple treatments in one day in accelerated, high dose protocols [7-10]. While preliminary, these accelerated iTBS treatments have shown clinical promise in even highly treatment resistant patients. We wondered if it would be feasible and safe to pair and synchronously deliver accelerated iTBS with cervically implanted VNS, reasoning that the additional VNS phase dependent plasticity might theoretically improve the antidepressant effects of TMS. Here we describe one patient where we used a simple, clinically feasible approach with good outcome and no adverse events.

The patient was a 55-year-old woman with a long history of treatment resistant depression. Her initial onset was at age 15 with the first medication and counseling treatments at age 24. At age 36, she was hospitalized and required a course of bilateral electroconvulsive therapy (ECT), with good response. She required three more rounds of ECT over the next six years. At age 43 she had cervical VNS implanted, with no further need for hospitalizations or ECT. Her VNS battery died and was replaced at age 50. She stayed on multiple medications for most of this time but was able to continue to work. A year prior to this TMS course, her depression worsened, and she was unable to continue working. Her VNS settings and medications were adjusted with no improvement. Her pre-treatment PHQ-9 was 22 (Fig. 1A).

During this treatment course, the patient's medications were quetiapine 150mg, levetiracetam 1000mg twice daily, lorazepam 3mg nightly, lamotrigine 400mg nightly, and cytomel 37.5 μg each morning. Her VNS device was initially set at 0.75mA intensity, 10Hz, 250 μs pulse width, 7s on, and 108s off. We increased the VNS stimulation intensity to 1mA during paired VNS/iTBS, allowing the patient to notice each VNS train and thus enabling our synchronization of iTBS. We kept the on-time at 7s and reduced the VNS off-time to 12.4s during each TMS session (the minimum allowed by the manufacturer). To effectively turn the VNS device off, the patient positioned a hand-held magnet over her VNS generator between TMS sessions. TMS was delivered using a MagVenture ×100 machine with a Cool B65 figure- 8 coil. We measured her resting motor threshold (rMT) at 55% Maximum Stimulator Output (MSO) and positioned the TMS coil over F3 (left dorsolateral prefrontal cortex) with the coil angled 45° down from the sagittal plane. We stimulated at 50% MSO

(90% rMT) using a standard iTBS pattern of triplet bursts at 50Hz with a carrier frequency of 5Hz. Each iTBS train was 2 seconds on with an intertrain interval of 17.4 seconds. This timing allowed the iTBS and VNS to be synchronized for the first 2 seconds of every VNS/iTBS train (Fig. 1B). We delivered 20 trains of 30 pulses each for a total of 600 pulses per session. We repeated this for 7 sessions each day, with at least 30 minutes between each session. We administered these treatments each Monday for two weeks, and then once again two weeks later for a total of three treatment days (Fig. 1A).

In order to synchronize the onset of TMS and VNS at the beginning of each session, the patient removed her magnet which allowed the VNS device to run freely. The patient then raised her finger when she could feel the VNS firing and we then started the TMS device. (Fig. 1B). Since the minimum on-time for each VNS train was 7 seconds, there were 5 seconds of VNS pulses delivered after the TMS had stopped. However, all TMS pulses were delivered with VNS on. (Fig. 1B).

The patient had no adverse effects from paired VNS/iTBS. About 2 hours after the last session on the first treatment day, her appetite returned, and she ate a full meal at a restaurant for the first time in several months. That evening, she started listening to music, watched a movie, sought out social interactions with neighbors, and all suicidal thoughts had dissipated. Her sleep improved to 6 hours, despite some persistent middle of the night awakenings. Her energy was much improved, and she was able to shop, cook, and walk the next day. Her concentration and anhedonia improved. She opened all her Christmas presents (February 3), which had been ignored in a corner for over a month. These qualitative changes were accompanied by a PHQ-9 score of 11 (meeting criteria for response, with her initial PHQ-9 score of 22) (Fig. 1A). She returned the following week with a PHQ-9 of 15. After a second treatment, her PHQ-9 improved to 9 and remained there through the following two weeks. At the end of the third treatment, her PHQ-9 was 10 (Fig. 1A). Interestingly, the patient's depression has remained stable for the past 5 months, with a PHQ-9 score of 8 at the time of this writing.

This case demonstrates that it is safe, feasible, and potentially effective to synchronize cervical VNS with accelerated, high dose iTBS for highly treatment resistant depression. However, it is difficult to make any further conclusions from a single patient with an open label treatment. Since iTBS was only delivered synchronously with VNS, the patient may have had this response to TMS alone. The timing of paired VNS/iTBS was limited by the boundaries of the patient's VNS device (12.4s minimum intertrain interval), and these parameters could potentially be further optimized. The approach outlined here could be used for any clinician treating a depressed patient who already has a VNS device implanted. Future studies with synchronized VNS/TMS are warranted for treating depression or other neuropsychiatric disorders.

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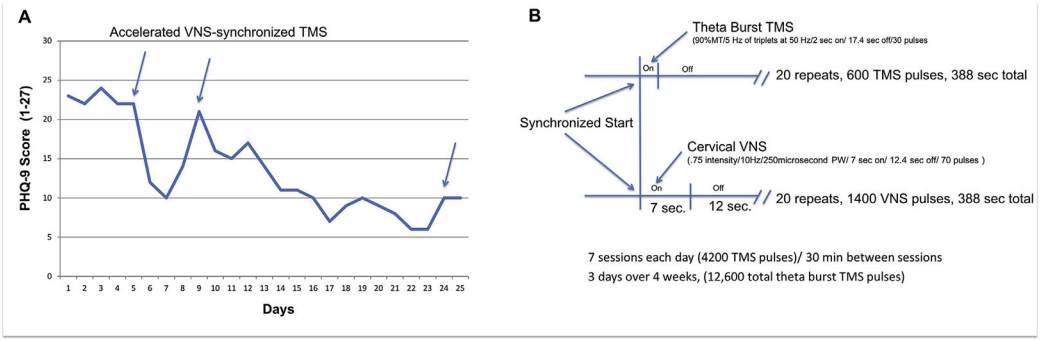

Fig. 1.

1A: PHQ-9 Scores Over Time. After the first accelerated, high dose intermittent theta burst stimulation (iTBS) x VNS treatment was delivered, the patient's PHQ-9 score went from 22 to 11 and met response criteria the next day. Following two additional treatments, the patient's end PHQ-9 score was a 10. **1B: Theta Burst TMS and Cervical VNS Pulse Pattern.** Over 20 trains, 600 iTBS and 1400 VNS pulses were delivered with paired and synchronized onset. This treatment session was repeated 7 times per day, for 3 days over 4 weeks.