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Original Articles

Safe Use of Repetitive Transcranial Magnetic Stimulation in Patients With Implanted Vagus Nerve Stimulators

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ABSTRACT

Vagus nerve stimulation (VNS) and repetitive transcranial stimulation (rTMS) devices are FDA cleared for therapeutic use in treatment resistant depression. Since VNS systems have ferromagnetic components and large-scale safety testing has not been done, the implanted VNS device is considered a contraindication for rTMS therapy. This contraindication should not be considered absolute, as VNS components typically lie outside the electromagnetic field generated by an rTMS treatment coil. We solicited information from clinicians at several academic medical centers through an informal survey about their use of rTMS for depressed patients with implanted VNS systems, and reviewed relevant safety issues with one rTMS device manufacturer. rTMS clinical practices may use special consent procedures and take additional precautions to enhance safety in these situations. Specific recommendations are provided for minimizing risks (heating or movement of VNS components and unintended change in VNS stimulation parameters) when delivering rTMS to patients with implanted VNS systems.

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Introduction

Electroconvulsive Therapy (ECT) and Vagus Nerve Stimulation (VNS) are device-based treatments approved for episodes of major depression that do not remit with pharmacotherapy (commonly referred to as treatment resistant depression [TRD]). Cyberonics' surgically implanted device for stimulation of the left cervical vagus nerve was approved by the U.S. FDA in 2006, after open-label data showed superior 1-year outcomes in a TRD sample with adjunct VNS therapy, compared to a similar cohort receiving naturalistic treatment [1]. Owing to specific inclusion criteria used in the pivotal clinical trials and the surgical nature of the treatment, VNS patients tend to have a relatively high degree of treatment resistance and illness chronicity compared to other samples. While many VNS patients report partial or substantial reduction in depressive symptoms, the majority still does not show 50% improvement after one year [1]. These VNS "non-responders" often face relatively few remaining treatment options, as most have already failed multiple antidepressant medication trials (and perhaps ECT) prior to electing surgical implantation of the VNS device.

The use of repetitive transcranial magnetic stimulation (rTMS) to alleviate symptoms of depression is a rapidly growing area of psychiatric clinical practice and research. Two devices are currently U.S. FDA cleared to deliver rTMS therapy for TRD. The first such device, Neuronetics' NeuroStar®, became commercially available in 2008 following pivotal trials demonstrating efficacy and safety for stimulation of the left prefrontal cortex with a fixed set of parameters and use of a simple fixed-distance measurement to determine coil placement on the patient's head [2,3]. Recent data on naturalistic outcomes since the NeuroStar device has been incorporated into real-life clinical practices confirms efficacy and safety of rTMS delivery with this device [4].

A second device (Brainsway "Deep" TMS System) was FDA cleared for the treatment of depression in early 2013 [5]. Commercial launch of this system in the US remains in relatively early stages at present. The introduction and availability of rTMS devices for clinical (*i.e.*, nonresearch) use in the US offers new hope for

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many VNS nonresponders – a group likely to be eager to try a promising new method of noninvasive brain stimulation using electromagnetic field pulses to gain relief from severe and disabling depressive symptoms.

Published literature to date suggests that concurrent use of VNS and rTMS should be safe. Schrader et al. [6] investigated induction of current in VNS lead wires placed in conductive gel phantom tissue by single TMS pulses delivered by a Magstim TMS coil. They applied maximal intensity TMS 5 mm from the VNS wire, and induced only a 200 nA, 1.0 ms current. For reference, the peak induced current they measured was below the 0.25–3.5 mA current range programmed for delivery to the vagus nerve during standard VNS therapy. Furthermore, both during and after direct application of TMS pulses over the VNS pulse generator, the VNS system continued to function normally. In an experiment designed to evaluate whether VNS stimulation changed cortical excitability in 5 patients with refractory epilepsy, Di Lazzaro et al. [7] applied single and paired TMS pulses to the motor cortex in patients with implanted VNS systems at baseline and after a month of chronic VNS therapy. They did not report any adverse outcomes or safety considerations related to concurrent TMS and VNS device operation in that study. A TMS consensus safety guidelines document published by Rossi et al. [8] summarized nearly 30 *ex vivo* or small human sample studies that used TMS in patients with implanted stimulation or recording electrodes. Based on the limited available evidence, the consensus group concluded that TMS is safe in individuals with VNS systems "…as long as the TMS coil is not activated near the components located in the neck or chest," but they did not provide specific guidance regarding what comprises a safe distance between the two device components. Moreover, they recommended that TMS should only be done in VNS patients "if there are scientifically or medically compelling reasons" to do so, since "unintended neural stimulation" could results from "potentially significant voltages and currents" induced between electrode leads and an internal pulse generator (IPG) if a TMS coil were discharged close to the implanted wires that connected them.

Based upon these theoretical safety considerations, patients with intracranial (head and neck) metal objects (including implanted VNS systems) or cardiac pacemakers were systematically excluded from participation in the rTMS registration clinical trials. Therefore, rTMS safety data for this patient population has never been collected. Accordingly, device labeling for the rTMS devices includes warning language based on the theoretical risk of discharging the rTMS coil in close proximity to ferromagnetic metal components.

In recognition of the lack of device compatibility data, the FDA issued a Class II Special Controls Guidance Document: Repetitive Transcranial Magnetic Stimulation (rTMS) Systems (26 July 2011) that requires all commercial rTMS devices approved for therapeutic use to carry the following statement as part of their device labeling: "*Implanted Stimulator Devices in or near the Head: rTMS devices are contraindicated for use in patients who have active or inactive implants (including device leads), including deep brain stimulators, cochlear implants, and vagus nerve stimulators. Contraindicated use could result in serious injury or death*" [9]. Reflecting this requirement, the "Depression Patient's Manual" distributed with the NeuroStar device describes a general contraindication for use "in patients who have magnetic-sensitive metals implanted in their head or are non-removable and near (within 12 inches) the NeuroStar treatment coil" and cautions further that the device should "not be used in patients who have an implanted device that may not properly function in the presence of the NeuroStar TMS System, even if the device is located outside this (12 inch) distance" [10].

To our knowledge, there are no published reports describing use of rTMS to treat depression in patients with an implanted VNS device. Nevertheless, the practice is carried out in some academic and nonacademic clinical practice centers. We therefore sought to review and clarify the safety issues surrounding this practice, informed by survey data from academic clinical practices offering treatment with both VNS and rTMS modalities.

Methods

To generate descriptive data, we reached out via email to clinicians at 20 academic centers that were known to have conducted clinical research with VNS and/or rTMS treatment modalities. There was no incentive or compensation for sites participating in the survey, and no specific patient data were requested or provided. The survey included questions about how referrals of VNS nonresponders to their TMS clinic were received or processed, and how many VNS patients the center had treated thus far. Other items in the survey included an inquiry about the rTMS informed consent process for VNS patients, and also whether the site had ever encountered any adverse events or VNS-specific safety problems when treating with rTMS. We solicited descriptions from each practice about how they managed concurrent delivery of stimulation with both VNS and rTMS, and we asked them to estimate the overall response rate observed for VNS patients treated with rTMS.

Results

We were able to confirm receipt of the email survey by 17 (85%) academic medical centers. Data from these 17 centers were pooled with experience from our own clinic. Survey respondents consistently identified the potential safety issues for this group as 1) *heating or movement of implanted VNS lead wires and coils* due to proximal electromagnetic fields from rTMS coil on ferromagnetic components and 2) *potential change in the VNS stimulation parameters* (settings previously programmed into the internal pulse generator), *from induced electrical current* in the lead wires. Six sites confirmed they had past experience with delivery of rTMS to one or more VNS patients, six had never declined to treat VNS patients but had no experience to date, and one site had declined to treat a VNS patient due to concern of interaction between the TMS magnet and VNS device. Of the six sites with experience using rTMS in VNS patients, three exclusively used the NeuroStar device, one used both Magstim and NeuroStar devices, and two sites utilized either a Magstim or Magventure device. Pooled experience described by the six experienced sites represented rTMS treatment of 20 VNS patients. None of the sites had experienced any unique adverse events during treatment of VNS patients with rTMS therapy. All of the sites continue to receive referrals for rTMS therapy delivery to patients who remain depressed after a trial of VNS and have implanted VNS device components.

Some of the sites we surveyed employ a distinct consent process prior to treating VNS patients than they use for other rTMS patients. Some consent forms incorporate additional language highlighting the unique risks for VNS patients. At least one site had developed a separate consent form especially for patients with implanted metal. All sites indicated their routine procedures involve documentation in the medical record about steps taken to educate VNS patient about risks during rTMS therapy (see Supplemental information for a consent form example).

Regarding VNS management during the 4–6 week course of rTMS therapy, most practices indicated they routinely discontinue VNS therapy, *i.e.*, set stimulation intensity to 0 mA prior to starting rTMS and leave it off for the duration of the course of TMS. One group described a practice of turning the VNS stimulator off prior to, and on again immediately following, each individual rTMS session, based on the possibility that the two treatments might act