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Five-Year Follow-Up of Bilateral Epidural Prefrontal Cortical Stimulation for Treatment-Resistant Depression

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ABSTRACT

Background: Epidural prefrontal cortical stimulation (EpCS) represents a novel therapeutic approach with many unique benefits that can be used for treatment-resistant depression (TRD).
Objective: To examine the long-term safety and efficacy of EpCS of the frontopolar cortex (FPC) and dorsolateral prefrontal cortex (DLPFC) for treatment of TRD.
Methods: Adults ($N = 5$) who were 21–80 years old with severe TRD [failure to respond to adequate courses of at least 4 antidepressant medications, psychotherapy and ≥20 on the Hamilton Rating Scale for Depression (HRSD24)] were recruited. Participants were implanted with bilateral EpCS over the FPC and DLPFC and received constant, chronic stimulation throughout the five years with Medtronic IPGs. They were followed for 5 years (2/1/2008–10/14/2013). Efficacy of EpCS was assessed with the HRSD24 in an open-label design as the primary outcome measure at five years.
Results: All 5 patients continued to tolerate the therapy. The mean improvements from pre-implant baseline on the HRSD24 were [7 months] 54.9% (±37.7), [1 year] 41.2% (±36.6), [2 years] 53.8% (±21.7), and [5 years] 45% (±47). Three of 5 (60%) subjects continued to be in remission at 5 years. There were 5 serious adverse events: 1 electrode 'paddle' infection and 4 device malfunctions, all resulting in suicidal ideation and/or hospitalization.
Conclusion: These results suggest that chronic bilateral EpCS over the FPC and DLPFC is a promising and potentially durable new technology for treating TRD, both acutely and over 5 years.

Introduction

Depression is a severely disabling disorder of extreme sadness or melancholia that affects a person's activities of daily life as well as social functioning [1]. Depression is a major public health problem and is the second leading cause of disability worldwide [2]. Although pharmacotherapeutic approaches to depression treatment are effective for some, they have demonstrated limited success in large clinical studies [3]. When depression fails to remit after adequate treatment, it is labeled treatment-resistant depression (TRD) [4]. TRD represents a spectrum that is often quantified by the number and type of failed adequate trials of treatments. This typically ranges from a minimum of a single failed trial of pharmacological monotherapy to more treatment-resistant forms of TRD that fail numerous trials of pharmacological monotherapies as well as pharmacological augmentation strategies, and to the most resistant forms of TRD that fail treatment with electroconvulsive therapy (ECT) [5].

Approximately 72% of patients will fail to remit after treatment with a single pharmacological monotherapy and thus meet criteria for some degree of TRD [6]. For these patients, an interventional

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psychiatric approach may be considered [7,8], with several options being available, depending in part on how many and what types of adequate trials of treatments that the patient has received. For example, transcranial magnetic stimulation (TMS) [9] is FDA-approved to treat patients who have failed treatment with a single antidepressant medication, and although no FDA recommendations currently exists for ECT, typical guidelines limit use to patients who have failed one or more antidepressant trials and/or require a rapid antidepressant response [10,11]. In contrast, the FDA recommends treatment with vagal nerve stimulation (VNS) only for patients who have failed treatment with at least 4 antidepressants or ECT [12]. Unfortunately, many patients experience a particularly resistant form of TRD with no current FDA-approved treatment options once all treatments have failed [8]. For these patients with the most treatment-resistant form of TRD, a more invasive approach using devices implanted into the encephalon is warranted. For example, deep brain stimulation (DBS) of several structures, including the ventral striatum [13] and subgenual cingulate, is currently being developed for TRD [14]. Although DBS was initially a promising treatment option for these patients [14], large, controlled clinical trials have failed thus far to demonstrate efficacy [15,16].

One promising target for the treatment of patients with highly treatment-resistant TRD using implanted devices is the prefrontal cortex [17,18]. Studies have suggested that in depression, the left dorsolateral prefrontal cortex (DLPFC) is hypoactive and the right DLPFC may be hyperactive [19]. The relationship between left DLPFC activity and depression is likely causal, as repetitive TMS (rTMS) over left DLPFC has been shown to be effective and is a US Food and Drug Administration (FDA)-approved intervention for TRD [9,20]. Furthermore, there is emerging data of utilizing transcranial direct current stimulation over DLPFC for treatment of depression [21]. Another region of the prefrontal cortex, the frontopolar cortex (FPC), specifically BA 10, is also a promising depression target. The FPC has gained attention as an important node in the mood regulatory circuitry [22], and is consistently found to have increased resting-state activity in patients with depression [23]. Thus, the FPC and DLPFC represent promising targets for neuromodulation as treatment for TRD [8].

Epidural cortical stimulation (EpCS) represents a novel therapeutic approach that can be used to stimulate the DLPFC and FPC to treat TRD [24,25]. EpCS involves placing stimulating electrodes directly on the dura mater dorsal to the cortical areas to be stimulated [26]. Chronic EpCS of sensory or motor areas has demonstrated efficacy in managing intractable pain syndromes [27–30], improving recovery from stroke [31], and addressing Parkinson's disease and other motor disorders [26].

We have previously reported outcomes up to 7 months in 5 patients with TRD that were implanted with bilateral EpCS over the DLPFC and FPC in an open-label design [24]. We continued to assess the long-term safety and efficacy of chronic intermittent EpCS for treatment of TRD and report outcomes for all 5 of these patients 5 years following initial implantation. During this time an expanded array of stimulation parameters was investigated and additional treatments were combined with EpCS during this unrestricted phase of the investigation. The efficacy and safety of EpCS endured during this follow-up period and several trends in stimulation parameters were observed and are discussed herein.

Methods and materials

This long-term follow-up study was conducted at the Medical University of South Carolina (MUSC) in compliance with the original Investigational Device Exemption issued to Z.N. and later transferred to E.B.S. under the guidance of the FDA. For the original study, the inclusion criteria limited enrollment to individuals with definite histories of depression with substantial treatment-resistance in order to address the ethical concerns of providing an experimental and untested intervention that required surgery. The MUSC Institutional Review Board approved the research protocol. Written consents were obtained at the onset before the initial implantation and included permission for further ratings at these extended time-points. All subjects underwent comprehensive assessments including detailed neuropsychological testing at baseline, after implantation, and at the 5-year follow-up.

Participants

For the original study, all 5 participants presented with a nonpsychotic, nonatypical major depressive episode (MDE) as part of either bipolar (I or II) disorder or major depressive disorder (MDD), defined by DSM-IV criteria [32]. For the initial enrollment, all participants scored ≥20 on the 24-item Hamilton Rating Scale for Depression (HRSD24) [33,34] before implantation [24]. We retained all 5 of our original study patients in this 5-year follow-up study. All 5 of our patients had not benefited sufficiently from trials of at least 4 classes of antidepressant medications or other somatic treatments as defined by the Antidepressant History Treatment Form (ATHF) criteria [5] as well as a minimum of 6 weeks of prior psychotherapy during any MDE prior to surgical intervention. During the long-term follow-up study time-period, both stimulation parameters and medications could be modified in both type and dose. For 3 of the 5 patients, VNS was reactivated after the initial 1-year mark and the VNS device stayed on chronically. ECT, TMS, and DBS could not be provided to any of the patients after EpCS implantation. The majority of treatment changes during the study consisted of EpCS stimulation parameter modifications (e.g., current, frequency, duty cycle, different leads stimulated) with minimal changes in medications (primarily removal of medications in the remitters) across the entire 5 years.

Chronic stimulation parameters

For the last 2–3 years, patients received chronic, bilateral stimulation of the left and right FPC and DLPFC using a total of 4 paddle leads at 130 Hz, 4.5–6.5 V, 210 μs (except one patient with a pulse width of 90 μs), double bipolar (0–/1+/2–/3+) across all 4 paddles for each lead. These settings evolved over time and parameters were selected on a trial and error basis during the final 4 years of therapy. The pulse width and frequency settings were altered from the original protocol during years 2–5 and the recent pulse width and frequency settings were based on DBS obsessive-compulsive disorder (OCD) treatment trial parameters [35]. Eventually all patients' frequency settings were reprogrammed from an initial 60 Hz to 130 Hz, which represents a difference from another study utilizing a single paddle [25] and reflects a programming strategy similar to DBS [36].

Assessments

Unmasked clinical outcome measures included the HRSD24, the 10-item Montgomery-Asberg Depression Rating Scale (MADRS) [37], Inventory of Depressive Symptoms – Self-Report (IDS-SR) [38], the 11-item Young Mania Rating Scale (YMRS) [39], the Clinical Global Impression: Severity (CGI-S) and Clinical Global Impression: Improvement (CGI-I) ratings. These measurements were obtained at pretreatment (baseline), weekly for the first 3 months, biweekly for the next 2 months and monthly after that for the first year. Follow-up assessments were completed within ±1 week of scheduled visits. Functional outcomes were assessed with the Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES) [40], Medical