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# Efficacy and safety of a form of cranial electrical stimulation (CES) as an add-on intervention for treatment-resistant major depressive disorder: A three week double blind pilot study

David Mischoulon*, Marasha F. De Jong, Ottavio V. Vitolo, Cristina Cusin, Christina M. Dording, Albert S. Yeung, Kelley Durham, Susannah R. Parkin, Maurizio Fava, Darin D. Dougherty

*Depression Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA*

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ABSTRACT

We examined efficacy and safety of one specific cranial electrical stimulator (CES) device at a fixed setting in subjects with treatment-resistant major depressive disorder (MDD). Thirty subjects (57% female, mean age 48.1 ± 12.3 years) with MDD and inadequate response to standard antidepressants were randomized to 3 weeks of treatment with CES (15/500/15,000 Hz, symmetrical rectangular biphasic current of 1–4 mAmp, 40 V) or sham CES (device off) for 20 min, 5 days per week. The primary outcome measure was improvement in the 17-item Hamilton Depression Rating Scale (HAM-D-17). Adverse effects (AEs) were assessed using the Patient Related Inventory of Side Effects (PRISE). Completion rates were 88% for CES, 100% for sham. Both treatment groups demonstrated improvement of about 3–5 points in HAM-D-17 scores ($p < 0.05$ for both), and no significant differences were observed between groups. Remission rates were 12% for CES, and 15% for sham, a nonsignificant difference. CES was deemed safe, with good tolerability; poor concentration and malaise were the only distressing AEs that differed significantly between CES and sham ($p = 0.019$ and $p = 0.043$, respectively). Limitations include a small sample and lack of an active comparator therapy. Although both treatment groups improved significantly, this CES at the setting chosen did not separate from sham in this sample. Thus we cannot rule out that the benefit from this setting used in this particular form of CES was due to placebo effects. Since this form of CES has other settings, future studies should test these settings and compare it against other CES devices.

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## 1. Introduction

Cranial Electrical Stimulation (CES) has been used for more than a half century in Europe and the US for various indications (Smith, 2008). The device transmits a small electrical pulse through the surface of the head and into the brain, often below threshold level of sensation (Smith, 2008). The general and psychotropic mechanisms are unknown. Various models have been proposed, including increasing/rebalancing of endorphins, neurotransmitters and neurohormones; regulation of body energy flow; effects on the limbic system, reticular activating system, and hypothalamus; vascular effects; positive impact on brain neural firing patterns and default network connectivity; circadian regulation; and adaptogenic function (assisting the body to battle effects of chronic stress). All these putative mechanisms may be relevant to CES's psychotropic effects, with the adaptogenic mechanism appearing to be the most favored, as it is the sum total of all the other mechanisms mentioned, and considering the role of stress in psychiatric illness (Feusner et al., 2012; Gunther and Phillips, 2010; Kavirajan et al., 2014; Smith, 2008).

Effectiveness of CES is supported by hundreds of clinical and mechanistic studies. Adverse effects occur at rates of less than 1% and tend to be mild (skin irritation at the electrode site, and headaches) (Kirsch and Nichols, 2013). Given its safety and

* Corresponding author. 1 Bowdoin Square, 6th Floor, Massachusetts General Hospital, Boston, MA 02114, USA.
*E-mail address:* dmischoulon@partners.org (D. Mischoulon).

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tolerability, the United States Food and Drug Administration (FDA) grandfathered the device for approval in the 1970s (Smith, 2008). There are 11 different approved CES devices in the US, and probably many other unregistered devices (Kavirajan et al., 2014).

Despite many published studies, rigorous randomized controlled trials (RCTs) of CES are lacking (Kavirajan et al., 2014; Kirsch and Nichols, 2013; Smith, 2008). Several systematic reviews and meta-analyses have emerged over the past 2 decades. Klawansky et al. (1995) focused on anxiety and other conditions, but not depression. Kirsch and Gilula (2007) examined CES in depression, but their meta-analysis had several limitations: they did not specify a search strategy or study inclusion criteria; their summary effect size was based only on active CES treatment, and did not compare CES versus sham; they combined data from open uncontrolled trials and blinded RCTs, which likely overestimated effect sizes; they included trials with heterogenous primary diagnoses, which limits generalizability; and one negative trial with heavily medicated inpatients was excluded because improvement in the sham group "invalidated" the study (Kirsch and Gilula, 2007). This study, conducted in 1974 and later invalidated in a Cochrane review (Kavirajan et al. 2014), probably had an inefficient CES device.

A monograph by Smith (2008) summarized different meta-analyses covering various human clinical trials of CES for various conditions, including 18 depression studies comprising 853 subjects. Seven of these studies were double-blind, two single blind, two crossover, and seven open-label. Various types of depression were included. In many studies, depression was specifically a symptom within another syndrome, such as fibromyalgia or substance abuse. Few, if any, of these studies examined major depressive disorder (MDD) as the primary disorder, which significantly limits this work.

A recent Cochrane Review (Kavirajan et al. 2014), the most comprehensive thus far, examined 270 RCTs comparing efficacy and tolerability of CES versus sham CES for depressive disorders in adults. Only 7 studies (Feighner et al., 1973; Greenblatt et al., 1964; Hearst et al., 1974; Levitt et al., 1975; Marshall and Izard, 1974; Passini et al., 1976; Rosenthal, 1972) were judged rigorous enough for full eligibility assessment, but were ultimately excluded for various reasons: failing to use (or not reporting) specific diagnostic criteria (5 studies); focus on subjects with chronic (>2 years duration) rather than acute depression (2 studies); lack of appropriate comparator groups (4 studies); and sham CES that (unlike the active CES) did not produce tingling, potentially compromising the blind (3 trials). These results emphasize the dearth of rigorously designed trials of CES in depression.

In an RCT not mentioned in the Cochrane Review, Rose et al. (2009) examined CES versus sham in 38 subjects with sleep disturbances and depressive symptoms. While both groups improved after 4 weeks, no significant differences between the two groups were observed for depressive symptoms, though a trend favored CES for sleep. More recently, Barclay and Barclay (2014) performed a 5-week double-blind RCT of CES in 115 primary care patients with anxiety disorders and comorbid depression. Results based on the Hamilton Anxiety and Depression scales showed a significant difference between CES and the sham intervention for anxiety ($p = 0.001$, $d = 0.94$) and depression ($p = 0.001$, $d = 0.78$), favoring active CES, with good tolerability.

Smith's (2008) and other systematic reviews (Shealy, 2003; Shealy et al., 1989), as well as an email poll of 152 veterans who used CES for various indications (Kirsch et al., 2014) suggest an overall average symptomatic improvement of about 50% for depression, a figure comparable to standard antidepressants. Reports often described symptomatic improvement after one week (5 daily treatments), and clinical symptom reduction by two weeks (10 daily treatments) (Smith, 2008). Yet these encouraging studies are limited by small samples, symptom heterogeneity, and overlap of conditions, though they may better reflect "real world" populations in which comorbidity is often the norm.

Interpreting these findings is also difficult due to the wide variety of marketed CES devices, different treatment protocols, and because published trials do not always provide detailed stimulation parameters. Treatment typically involves 20–60 min of daily stimulation for three weeks based on a current strength that is comfortable to the patient, followed by less frequent treatments that may go on indefinitely (Gilula and Kirsch 2005). Frequencies used range from 0.5 Hz to 167 kHz, and current flow amplitude from 100 μA to 4 mA (Kavirajan et al., 2014); duration of stimulation and/or continuous application may vary from five minutes to six consecutive days (Zaghi et al., 2010).

Given the accessibility of CES, and the growing demand for alternatives to conventional antidepressants and somatic therapies, we carried out a pilot, double-blind, randomized controlled trial of CES in subjects with treatment-resistant MDD who were not responding adequately to standard antidepressants. We sought to generate preliminary evidence of the efficacy and safety of a particular CES device as adjunctive therapy for MDD. We hypothesized that subjects who received active as opposed to sham CES would have a significantly greater improvement in their depression symptoms. Due to the small sample, we could not hypothesize an effect size, but would calculate one to determine signal strength to guide the design of a larger, more rigorous study. As an exploratory aim, we examined whether CES would benefit sleep.

## 2. Materials and methods

The investigation was carried out per the latest version of the Declaration of Helsinki, and approved by our institutional review board (IRB). We screened 53 potential participants, and enrolled 30 adults of both genders, with major depressive disorder (MDD) diagnosed by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) (First et al., 1995). Severity of depression was determined by Structured Interview for the 17-item Hamilton Depression Rating Scale (SIGH-D HAM-D 17; Hamilton, 1960; Williams, 1988). Subjects were required to be taking any current antidepressant and not responding in a satisfactory manner. See Fig. 1 for subject characteristics.

Subjects were recruited by general and community advertisement from our Depression Clinical and Research Program (DCRP). Informed consent was obtained per IRB guidelines. Investigators who screened subjects to ascertain relevant psychiatric, medical, and neurological history, were our program's psychiatrists and psychologists, trained and certified in the use of appropriate diagnostic instruments such as the SCID and HAM-D. Our program holds regular re-training sessions to ensure inter-rater reliability.

Inclusion criteria were: age 18–65; good general health; meeting criteria for MDD based on the DSM-IV; a HAM-D-17 score $\geq$15 and $\leq$23; treatment-resistance, defined as meeting the above DSM-IV and HAM-D criteria while taking an approved antidepressant at minimum adequate and stable dose for $\geq$6 weeks with <50% response per MGH-Antidepressant Treatment Response Questionnaire (ATRQ; Chandler et al., 2010). Per our IRB, the HAM-D score eligibility range was set to include subjects who were partial or non-responders (HAM-D 15–18) but not too severely depressed (HAMD $\leq$ 23), given CES's experimental nature.

Subjects were excluded for any of the following: unstable health conditions that in the opinion of the investigators represented a risk to the subject; having any electrical stimulation implants – i.e. pacemaker, deep brain stimulators (e.g. vagal nerve stimulator, deep brain stimulator), or transcutaneous electrical nerve