Cranial Electrotherapy Stimulation for Major Depressive Disorder

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Q. What is cranial electrotherapy stimulation?

A. Cranial electrotherapy stimulation (CES), also known as 'transcranial electrostimulation,' 'electrosleep therapy,' and 'electronarcosis,' is a Food and Drug Administration (FDA)-approved, non-invasive treatment for insomnia, anxiety and depression. CES involves the transcranial application of electrical magnetic fields to the scalp, at levels that do not induce seizure (Rosa & Lisanby, 2012). CES includes a range of techniques, but all methods use low-level alternating electrical signals applied to the scalp or earlobes. In the United States, CES devices require a prescription from a licensed health care practitioner, though the treatment itself is self-administered using hand-held, electrical devices, and there is significant variation in frequency and duration of treatment (Kavirajan et al., 2014).

Q. What is the potential mechanism of action underlying CES?

A. While the mechanism of action of CES is unclear, CES devices provide a weak alternating electrical current, which is thought to modulate cortical excitability. CES is hypothesized to enhance naturally occurring neurological activity (Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). Research has shown that weak cranial currents applied during sleep can affect memory; weak electric fields can affect neural function; and, additionally, changes in neurotransmitters and hormones have been found, including increased levels of monoamines in the brain (Rosa & Lisanby, 2012; Kavirajan et al., 2014).

Q. Is CES recommended as a treatment for major depressive disorder (MDD) in the Military Health System (MHS)?

A. No. The *2016 VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder* does not include CES as a treatment for MDD.

The MHS relies on the VA/DoD clinical practice guidelines (CPGs) to inform best clinical practices. The CPGs are developed under the purview of clinical experts and are derived through a transparent and systematic approach that includes, but is not limited to, systematic reviews of the literature on a given topic and development of recommendations using a graded system that takes into account the overall quality of the evidence and the magnitude of the net benefit of the recommendation. A further description of this process and CPGs on specific topics can be found on the VA clinical practice guidelines website.

Q. Do other authoritative reviews recommend CES as a treatment for MDD?

A. No. Other authoritative reviews have not substantiated the use of CES for MDD.

Several other recognized organizations conduct systematic reviews and evidence syntheses on psychological health topics using similar grading systems as the VA/DoD CPGs. These include the Agency for Healthcare Research and Quality (AHRQ) and Cochrane.

- AHRQ: CES was not included in a 2011 comparative effectiveness review (Gaynes et al., 2011) of nonpharmacologic interventions for treatment-resistant depression in adults, though other somatic treatments were included.
- Cochrane: A 2014 systematic review (Kavirajan et al., 2014) found no high quality clinical trials of CES in people with acute depression. This review excluded trials of CES in chronic or refractory depression.

Q. Is there any recent research on CES as a treatment for MDD?

A. A February 2020 literature review identified a single trial of CES conducted with individuals diagnosed with MDD. This trial, a double blind pilot study of CES as an add-on intervention for treatment-resistant MDD, compared CES to sham CES (Mischoulon et al., 2014). No significant differences were found between groups on measures of depression symptoms or remission rates. In addition to the limitation of a small sample size (n = 30), the sham CES condition in this trial did not include a tingling

sensation, possibly compromising blinding. As an augmentation trial, results may not provide evidence on the use of CES as a monotherapy.

Other trials on CES for depression looked at depressive symptoms in patients without a primary diagnosis of MDD as we define it today, with many of the studies conducted in the 1960s and 1970s (e.g., Barclay & Barclay, 2014; Greenblatt, Grosser, & Wechsler, 1964; Hearst, Cloninger, Crews, & Cadoret, 1974; Lyon et al., 2015).

Q. What conclusions can be drawn about the use of CES as a treatment for MDD in the MHS?

A. FDA approval of CES for the treatment of MDD was obtained in 1979, before the requirement for submission of clinical trial data on safety and efficacy. Since then, new CES devices have been cleared for marketing without submission of this data due to an FDA provision permitting that new devices be granted marketing approval if deemed "substantially equivalent" to an existing, approved device (Hines et al., 2010).

Much of the existing research done on CES for depression suffers from methodological shortcomings, including failure to use standardized diagnostic criteria to diagnose depression, lack of a sham comparator condition, or compromised blinding due to the sham CES not producing a local tingling sensation (Kavirajan et al., 2014). A single double-blind pilot trial has been conducted on CES as a treatment for MDD, using modern diagnostic criteria. This trial marks an improvement in the methodology from previous trials, though the sample size is small, and blinding may not have been maintained in the sham condition. The current state of the CES evidence base is not mature enough to recommend CES as an evidence-based treatment for use during a major depressive episode in patients with MDD in the MHS.

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