

## Effectiveness of Low Frequency Noninvasive Brain Stimulation Therapy for Improving Neuropsychological and Neurophysiological Functions: A Systematic Review

Zainab Khan, Ashi Saif, and Adila Parveen\*

Centre of Physiotherapy and Rehabilitation Sciences, Jamia Millia Islamia, New Delhi, India

### Abstract

**Introduction.** Cranial electrotherapy stimulation (CES) is a technique used to address various mental disorders symptoms. However, it is recently concluded that the quality of clinical trials involving CES is not standardized and lacks sufficient evidence to support its use for improving mental health. The purpose of this study was to undertake a systematic examination of evidence of CES in improving mental health. **Method.** From inception to April 2022, systematic review was conducted using electronic databases MEDLINE (accessed via PubMed), CENTRAL (Cochrane Library Central Register of Controlled Trials), and Web of Science to retrieve relevant studies. Methodology of all the identified randomized controlled trials (RCTs) was assessed using an 11-point PEDro scale by two independent reviewers. **Results.** Sixteen RCTs were identified to be relevant and their characteristics were evaluated. Thirteen studies concluded CES has favorable effect on variety of mental disorders, particularly on anxiety and depressed symptoms in varied groups. **Conclusions.** While these positive effects were observed, limitations included insufficient detail about existing treatments, lack of using standardized objective outcome measures for quantifying mental health dysfunction, and uneven representation of CES limiting the generalizability and making it difficult to carry out the pooled quantification and meta-analysis. Despite its shortcomings, literature suggests that CES warrants more research.

**Keywords:** cranial electrotherapy stimulation (CES); mental disorders; mental health; psychological health; cognitive health

**Citation:** Khan, Z., Saif, A., & Parveen, A. F. (2023). Effectiveness of low frequency noninvasive brain stimulation therapy for improving neuropsychological and neurophysiological functions: A systematic review. *NeuroRegulation*, 10(3), 186–206. <https://doi.org/10.15540/nr.10.3.186>

\*Address correspondence to: Dr. Adila Parveen, Assistant Professor, Centre for Physiotherapy and Rehabilitation Sciences, Jamia Millia Islamia, New Delhi – 110025, India. Email: [aparveen1@jmi.ac.in](mailto:aparveen1@jmi.ac.in)

**Copyright:** © 2023. Khan et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (CC-BY).

**Edited by:**  
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA

**Reviewed by:**  
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA  
Tanya Morosoli, MSc: 1) Clínica de Neuropsicología Diagnóstica y Terapéutica, Mexico City, Mexico; 2) ECPE, Harvard T. H. Chan School of Public Health, Boston, MA, USA

Mental disorders are an all-time high as a more important topic in the world, particularly in most of the developed countries (Murray et al., 2012). Common mental health disorders (CMD) are mainly comprised of depressive disorders and anxiety disorders (World Health Organization, 2017). Following depression and anxiety, mood disorders have been demonstrated as a highly prevalent disorder among the general population by numerous large epidemiologic surveys in developed countries (Kessler, Berglund, et al., 2005). The high prevalence estimates of these mental disorders are associated with a heavy burden on the health of the community and disruption to their daily life (Kessler,

Chiu, et al., 2005), and are the leading cause of disability worldwide (Vos et al., 2012). In addition, it has been found that these mental disorders are associated with cognitive dysfunctions, and there is an invariable and mutual association between cognitive dysfunction and mental disorders such as depression, anxiety (Castaneda et al., 2008), and mood disorders (Wolf et al., 2010), affecting each other in a bidirectional manner.

The trend is such that, even among the most serious disorders, people are left untreated. In industrialized countries, 36–50% of serious cases remain untreated, whereas in developing countries the

situation is even worse, with 76–86% are left untreated. It has been proposed that treatment services need to be expanded to reduce the prevalence and impact of mental disorders (Wang et al., 2007), as they seem to impact significantly both the patient's functioning and quality of life as well as increase the risk of recurrence of CMD (Perini et al., 2019). Despite this, relatively few interventions for the condition have been developed in recent years. Although there are many pharmacological interventions for improving mental health, they are quite exorbitant or present with considerable side effects. Up to half of such population do not respond to first-line antidepressant treatment and one-third do not respond to two or more treatments (Trivedi et al., 2006), making it prevalent and therefore resulting in added patient suffering, disability, and suicide risk (Crown et al., 2002). These relatively poorer clinical outcomes and limitations with pharmacotherapy heighten the need to optimize and develop brain modulation treatments, which have the potential to modulate brain activity and which may constitute safe and efficacious treatment options for mentally disturbed individuals in the future. Such established treatments include neuromodulation techniques and ablative neurosurgery. A number of new neuromodulation techniques over the past several years have been investigated with the goal of achieving efficacy of established mental disorder treatments with better neurocognitive safety. Noninvasive brain stimulation (NIBS) is a technique to achieve neuromodulation without surgical treatment through safe local stimulation of specific brain areas using magnetism or electricity (In et al., 2017). Reports in animals and humans have described changes in certain neurotransmitters, neurochemicals, and brain activity on electroencephalography as a mechanism of action of these NIBS techniques (Antal & Paulus, 2008; Kirsch, 2002; Zaghi et al., 2010). Repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and cranial electrotherapy stimulation (CES) are used clinically for the improvement of brain functioning and mental health (Fregni & Pascual-Leone, 2007; Kirsch & Nichols, 2013).

Of these, CES has been approved by the US Food and Drug Administration (FDA) as a noninvasive, prescriptive medical intervention for treating insomnia, depression, anxiety, stress, (Rosa et al., 2011, Sevilla-Llewellyn-Jones et al., 2018) and mood-related symptoms as well (Kirsch, 2002). While on the one hand the relatively stronger current modalities such as electroconvulsive therapy (ECT) that are being used as adjuncts to pharmacological

and psychotherapeutic treatment plans have both cardiovascular complications and cognitive side effects (Andrade et al., 2016) and TMS adverse effects including headaches (O'Connell et al., 2018) and seizures (Rossi et al., 2009), CES on the other hand tends to be a more efficient, user-friendly, cost-effective, and easily tolerable noninvasive type of device that can be safely used by patients at home. It is being used as an adjunct to medication or psychotherapy or as a stand-alone treatment (George, 2019). CES now has a foundation of more than 50 years of research and clinical use in the USA which proves its safety and effectiveness (Price et al., 2021).

### Rationale for Systematic Review

An issue recently concluded by Cochrane review is that there are no high-quality clinical trials comparing CES with sham-CES in people with mental disorders such as depression and that there is insufficient evidence to support the use of CES in the treatment of depression (Kavirajan et al., 2014; Price et al., 2021; Shekelle et al., 2018) and low strength evidence to support the use of CES in the treatment of anxiety (Shekelle et al., 2018). However, numerous systematic reviews and meta-analyses have appeared over the past two decades. Klawansky and colleagues focused on anxiety and other conditions but not on other mental disorders (Klawansky et al., 1995). Kirsch and Gilula (2007) investigated CES in depression, but their meta-analysis had several flaws: they did not specify the search strategy or specific study eligibility criteria; their summary effect size was based only on active CES treatment and did not compare CES to sham; they combined data from open uncontrolled trials and blinded randomized control trials (RCTs), which likely overestimated effect sizes; and they included trials with a variety of primary diagnoses, which limits generalizability (Kirsch & Gilula, 2007). A study by Kavirajan and colleagues, led in 1974 and later invalidated in a Cochrane review, possibly had inefficient CES equipment (Kavirajan et al., 2014). Shekelle et al. (2018) focused on anxiety, depression, insomnia, and pain but did not cover the other mental health aspects. Their study lacked explicit study inclusion, and for a few other studies the data was insufficient to determine an effect size, preventing a quantitative assessment of publication bias. As a result, the likelihood of its occurrence remains hypothetical.

Small samples, symptom and demographic variability, overlap of diseases, large variety of marketed CES devices, varied treatment regimens, and the fact that published trials do not usually offer

detailed stimulation settings make it challenging to interpret these findings. Given the gaps in the current literature, the goal of this study was to conduct a systematic assessment of the evidence and provide a clear picture of the usefulness of CES in improving mental health. Furthermore, to our knowledge, this is the first time that the body of evidence in favor of CES (RCTs) for the treatment of the majority of mental diseases has been comprehensively investigated. We believe that the work's uniqueness adds to our understanding of various mental health treatment techniques.

## Methods

### Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards were followed for this review, and it is registered in Prospero with the registration number CRD42021273171. To find papers on the impact of CES on mental health, we devised the following search strategy. A systematic search was performed on the electronic databases MEDLINE (accessed via PubMed), CENTRAL (Cochrane Library Central Register of Controlled Trials), and Web of Science starting from the earliest records available. Random search items used were a combination of keywords (i.e., cranial electrotherapy stimulation, cranial electrical stimulation, cranial electrostimulation, CES, mental health, psychological health, cognitive health, depression, anxiety, stress, mood, brain drive neurotrophic factor, and BDNF) in various combinations. To provide more concentrated results and to widen or narrow the search, the keywords were joined with Boolean operators 'OR' and 'AND' from inception to April 2022. Figure 1 shows a diagram of the PRISMA flowchart.

### Eligibility Criteria

The inclusion criteria involved RCTs, the CMD pathology, or any other mental health disorder diagnosed in the subjects. This review included RCTs investigating the effect of CES with one or more treatment sessions on mental disorders assessed by either qualitative measures (e.g., clinical observation, questionnaires, self-report), quantitative measures (e.g., neuropsychological battery test [NBT], electroencephalography [EEG], event-related potentials [ERP, P300]), or any

biomarkers such as cortisol, adrenocorticotrophic hormone [ACTH], brain-derived neurotrophic factor [BDNF], nerve growth factor [NGF] or any other peripheral biomarkers supported by convincing and highly suggestive evidence across major mental disorders. Studies examining the effect of CES on other conditions such as sleep, pain, incontinence, and fibromyalgia were excluded. Furthermore, studies on healthy subjects or animal models using other forms of neuromodulation, such as ECT and TMS, or other forms of invasive spinal stimulation, were excluded. There was no limit on the number of samples taken. This review did not include studies conducted and reported in languages other than English.

### Selection of Studies

To retrieve records to be reviewed, 206 duplicates were deleted from the total records (392) identified. Two reviewers (ZK and AS) independently read the titles and abstracts of 58 records during the screening procedure. Based on the predesigned eligibility criteria, 16 papers (RCTs) were deemed to be relevant and were examined for study features by two independent reviewers (ZK and AS) who assessed the quality of each of the 16 RCTs' methodology (Figure 1). Conflict at any stage during the process was resolved by consensus with the third reviewer (AP).

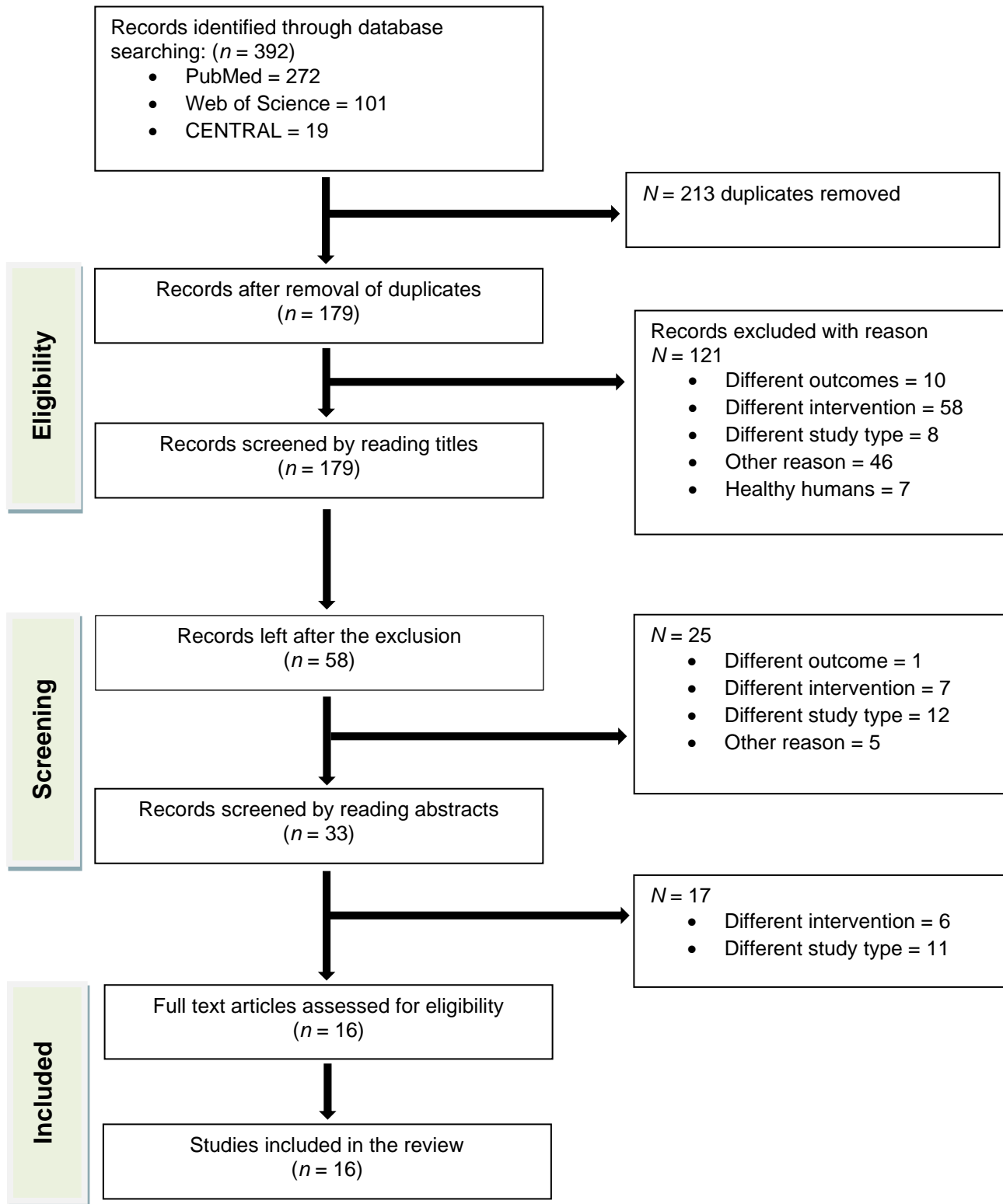
### Data Extraction

Two of the authors (ZK and AS) extracted data on trial characteristics (e.g., author, year of trial conduction, design, duration), the participants (e.g., age, information on other medical comorbidities), and the intervention (e.g., device used, duration, dosimetry, safety, follow-up), and their results are summarized in Table 2. If any of the reported data was ambiguous, then it was resolved in consultation with the third reviewer (AP).

### Measurement of the Treatment Effect

Effect size for the predecided outcome measures (eligibility criteria) was calculated for the RCT reporting point measures and variability using Cohen's *d* (Barclay & Barclay, 2014), two-tailed test (Padjen et al., 1995; Wu et al., 2020), and nQuery power analysis software (Rose et al., 2009).

**Figure 1.** PRISMA Flowchart Showing Identification and Selection of Trials for the Systematic Review.



**Table 1**  
*Quality Scoring of Randomized Controlled Trials (RCTs) Including Pilot RCTs (n = 16).*

Study	Eligibility Criteria	Random Allocation	Concealed Allocation	Group Similarity at Baseline	Blinding of Subjects	Blinding of Therapist	Blinding of Assessor	Dropouts < 15%	Intention to Treat Analysis	Between-Group Differences Reported	Point Estimate and Variability Reported	Total Score	Quality
Barclay & Barclay, 2014	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	Yes	Yes	8	Excellent
Kang et al., 2020	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	No	5	Good
Lee et al., 2013	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	No	5	Good
Lyon et al., 2010	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	Yes	No	7	Good
McClure et al., 2015	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	9	Excellent
Michoulon et al., 2015	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	9	Excellent
Padjen et al., 1995	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	8	Excellent
Roh & So, 2017	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	No	5	Good
Rose et al., 2009	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	No	6	Good
Scherder et al., 2003	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	6	Good
Scherder et al., 2006	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	6	Good
Schmitt et al., 1986	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	Yes	No	7	Good
Smith et al., 1994	Yes	Yes	No	No	Yes	Yes	No	Yes	No	No	No	5	Good
Southworth et al., 1999	Yes	Yes	No	No	Yes	Yes	No	Yes	No	No	No	5	Good
Winick, 1999	Yes	Yes	No	No	Yes	Yes	No	Yes	No	Yes	No	6	Good
Wu et al., 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	9	Excellent

**Table 2**Quality Scoring of Randomized Controlled Trials (RCTs) Including Pilot RCTs ( $n = 16$ )

Study	Participants; $N$	Design	CES Mode, Safety and Dropouts	Patient Evaluation and Follow-up	Interventions	Duration of Intervention	Area of Application of CES and CES Parameters (current density, frequency) in Experimental/Active CES Group	Outcome	Results
Barclay & Barclay, 2014	$N = 115$ ; both males and females, 18–65 years old, with anxiety and comorbid depression.	Double-blind, randomized sham-controlled trial.	Alpha-Stim CES device.  Safety reported: FDA approved.  6% dropout.	At baseline, week 1, week 3, and week 5.  No follow-up.	Two arms:  Group 1 – EG ( $n = 60$ ).  Group 2 – SCG ( $n = 55$ ).	60-min daily CES treatment for 5 weeks.	CES was placed at both earlobes, with a frequency of 0.5 Hz and a current intensity at 100 $\mu$ A, a subsensory level.	Anxiety measured using HAM-A.  Depression measured using HAM-D17.	Significant reduction in anxiety symptoms.  Improved depressive symptoms.
Kang et al., 2020	$N = 80$ ; both male and female patients undergoing general anesthesia.	Computer generated RCT.	Alpha-Stim CES device.  Safety not reported.  11% dropout.	3 times: day before the surgery, pre-operative and on the day of surgery.  No follow-up.	Two arms:  Group 1 – CG ( $n = 40$ ).  Group 2 – EG ( $n = 40$ ).	20-min preoperative CES, 2 sessions, both on the day before and morning of day of surgery.	A clip-type electrode of a microcurrent stimulator was attached to the earlobe, and a microcurrent of less than 200 $\mu$ A and 0.5 Hz was delivered via the electrode.	Anxiety scores measured using 5-point Likert scale.	Reduced both preoperative anxiety levels.
Lee et al., 2013	$N = 50$ ; female patients undergoing thyroidectomy.	Prospective RCT.	Alpha-Stim CES device.  Safety not reported.  0 to 1% dropout.	Before and after the surgery.  No follow-up.	Group 1 – CG ( $n = 25$ ).  Group 2 – EG ( $n = 25$ ).	20-min CES, 2 sessions, between 20:00–22:00 on day before surgery, and between 07:00–09:00 on day of surgery.	All treatments were given via electrodes clipped to the patients' ear lobes. A CES was preset to provide microcurrents of 100 $\mu$ A intensity and frequency of 0.5 Hz.	Anxiety scores measured using a 5-point Likert scale.  Stress level measured using ACTH and cortisol.	Reduced level of preoperative anxiety.  No effects on stress hormone responses.

**Table 2**

Quality Scoring of Randomized Controlled Trials (RCTs) Including Pilot RCTs (n = 16)

Study	Participants; N	Design	CES Mode, Safety and Dropouts	Patient Evaluation and Follow-up	Interventions	Duration of Intervention	Area of Application of CES and CES Parameters (current density, frequency) in Experimental/Active CES Group	Outcome	Results
Lyon et al., 2010.	N = 36; women with stage I-IIIa breast cancer scheduled to receive chemotherapy.	Prospective, three-group, randomized, double-blinded, longitudinal <i>pilot</i> feasibility study	Alpha-Stim CES device.  Safety reported: FDA approved.  0 to 1% dropout.	At baseline, week 3 and week 6.  After completing the protocol, participants completed a follow-up interview.	3 groups:  Group 1 – EG.  Group 2 – SCG.  Group 3 – Usual comparison group.	For participants receiving chemotherapy every 3 weeks (total CES duration use of 8 weeks, daily for 60 min) and for every 2 weeks (total CES duration use of 6 weeks, daily for 60 min).	CES delivers the electrical stimulation via electrodes attached to the earlobes, with a stimulus intensity of less than 1.0 $\mu$ A at 100 Hz frequency from a 9-volt battery source. CES in this study were set at a subsensory intensity.	Depression was measured using HADS.	Decreased depressive symptoms.
McClure et al., 2015	N = 16; male and female outpatients aged 23–71 years diagnosed with bipolar II disorder.	<i>Pilot</i> double-blind, sham-controlled study	Alpha-Stim CES device.  Safety reported: FDA approved.  0 to 1% dropout.	At baseline, weeks 1, 2, 4, and 12.  Follow-up of participants at weeks 4 and 12.	2 Groups:  Group 1 – EG (n = 7).  Group 2 – SCG (n = 9).	20-min CES treatments, 5 days per week for 2 weeks.	The CES treatment was delivered by two electrodes covered with damp sponges and placed over the temples bilaterally with 2 $\mu$ A of alternating current, with a frequency ranging from 5 Hz to 15,000 Hz.	Cognitive functions measured by CFQ, 3MS, and AMI.  Depression measured by BDI, HAM-D-17, and YMRS, at baseline, weeks 2, 4, and 12.  Mood measured by PANAS subscale.	Improved cognitive functioning was found on CFQ.  Decreased symptoms of bipolar depression.  No significant changes on PANAS score.



**Table 2**Quality Scoring of Randomized Controlled Trials (RCTs) Including Pilot RCTs ( $n = 16$ )

Study	Participants; $N$	Design	CES Mode, Safety and Dropouts	Patient Evaluation and Follow-up	Interventions	Duration of Intervention	Area of Application of CES and CES Parameters (current density, frequency) in Experimental/Active CES Group	Outcome	Results
Mischoulon et al., 2015	$N = 30$ ; adults of both genders, with MDD and inadequate response to standard antidepressants.	Double-blind sham-controlled <i>pilot</i> study.	FW-100 Fisher-Wallace device.  Safety reported: FDA approved.  6.6% dropout.	At baseline, weeks 1, 2, and 3.  No follow-up.	2 Groups:  Group 1 – EG ( $n = 17$ ).  Group 2 – SCG ( $n = 13$ ).	20-min CES treatments, 5 days per week for 3 weeks.	The headset of CES (15/500/15,000 Hz, symmetrical rectangular biphasic current of 1–4 $\mu$ A and 40 V) was placed on the scalp (one current applicator on each side), over the two dorsolateral prefrontal cortex areas.	Depression measured using HAM-D-17.	Improved depressive symptoms.
Padjen et al., 1995	$N = 64$ ; alcohol-dependent males (25 and 60 years, younger alcoholics with antisocial personalities and 60 above older alcoholics having too frequent cognitive impairment).	<i>Pilot</i> double-blind randomization sham-controlled study.	N-S, Inc. C stimulator.  Safety not reported.  7.4% dropout.	Baseline, weeks 1, 2, 3, and 4.  No follow-up.	2 Groups:  Group 1 – EG ( $n = 28$ ).  Group 2 – SCG ( $n = 34$ ).	30-min CES treatment, between 5:00 and 8:00 p.m., for 5 days per week for 4 weeks.	CES was administered by placing 4 electrodes; 2 at frontal and 2 at each mastoid with a current intensity of less than 100 $\mu$ A and frequency of 100 Hz at 50% duty cycle.	Depression measured using Hamilton Depression Scale, Montgomery Asberg Scale, and SCL-90-R39.  Anxiety measured by Hamilton Anxiety Scale and the SCL-90-R39.	Significant reduction in depressive symptoms.  Significant improvement in anxiety symptoms.
Roh & So, 2017	$N = 50$ ; healthy postmenopausal women.	Randomized sham-controlled trial study.	Alpha-Stim CES device.  Safety reported: FDA approved.  0 to 1% dropout.	Baseline and after 8 weeks.  No follow-up.	2 Groups:  Group 1 – SCG ( $n = 25$ ).  Group 2 – EG ( $n = 25$ ).	20-min CES treatments, 3 times per week for 8 weeks.	Clip-shaped electrodes were attached to both earlobes of patients with a current of 100 $\mu$ A and frequency of 0.5 Hz.	Cognition measured by BDNF and NGF levels.  Stress measured by ACTH and cortisol.  Mood measured by POMS.	No changes in BDNF and NGF or stress levels were found.  Significant reduction in Tension-Anxiety and Depression-Dejection scores on the POMS; however, no changes were seen on other mood measures.



**Table 2**  
Quality Scoring of Randomized Controlled Trials (RCTs) Including Pilot RCTs (n = 16)

Study	Participants; N	Design	CES Mode, Safety and Dropouts	Patient Evaluation and Follow-up	Interventions	Duration of Intervention	Area of Application of CES and CES Parameters (current density, frequency) in Experimental/Active CES Group	Outcome	Results
Rose et al., 2009	N = 38; AD patients of both genders, age 65 years or older.	Randomized, double-blind, controlled <i>pilot</i> study.	Alpha-Stim CES device.  Safety not reported.  0 to 1% dropout.	Baseline, weeks 2 and 4.  No follow-up.	2 Groups:  Group 1 – EG (n=19).  Group 2 – SCG (n=19).	60-min CES intervention each day for 4 weeks.	A single cable attaches the CES device to two ear clips worn by the participant. The device was preset at an intensity level of electrical stimulation 100 $\mu$ A; timer was preset at 60 min and the pulse rate at 0.05 pps.	Depressive symptoms measured by GDS.	Reduced depressive symptoms.
Scherder et al., 2003	N = 16; AD patients of both genders, with clinical symptoms of dementia present for at least 6 months.	RCT	Alpha-Stim CES device.  Safety not reported.  0 to 1% dropout.	Before and after 6 weeks of intervention.  No follow-up.	2 Groups:  Group 1 – EG (n = 8).  Group 2 – SCG (n = 8).	30-min CES stimulation each day, 5 days per week for 6 weeks.	CES applied involved the bipolar asymmetric rectangular waves, with an intensity between 10 and 600 $\mu$ A and frequency of 0.5 Hz. The electrodes were clipped to the earlobes.	Cognition measured by neuropsychological tests including digit span, visual memory, face and picture recognition, and word fluency test.  Stress level measured using salivary cortisol level.	No beneficial effects on cognitive functions.  Increase instead of a decrease in the level of cortisol.
Scherder et al., 2006	N = 21; patients of AD of both genders with mean age of 84 years.	RCT	Alpha-Stim CES device.  Safety not reported.  0 to 1% dropout.	Before and after 6 weeks of intervention.  No follow-up.	2 Groups:  Group 1 – EG (n = 11).  Group 2 – CG (n = 10).	30-min CES stimulation administered each day, 5 days per week, for 6 weeks.	CES applied involved the bipolar asymmetric rectangular waves, with an intensity between 10 and 600 $\mu$ A and frequency of 100 Hz. The electrodes were clipped to the earlobes.	Cognition measured by neuropsychological tests including digit span, visual memory, face and picture recognition, and word fluency test.  Mood measured by SCL-90, BDI and the BOP.	No improvement in cognition status.  No significant effects for any of mood and behavior scales.

**Table 2**

Quality Scoring of Randomized Controlled Trials (RCTs) Including Pilot RCTs (n = 16)

Study	Participants; N	Design	CES Mode, Safety and Dropouts	Patient Evaluation and Follow-up	Interventions	Duration of Intervention	Area of Application of CES and CES Parameters (current density, frequency) in Experimental/Active CES Group	Outcome	Results
Schmitt et al., 1986	N = 40; inpatient alcohol or poly drug users of both genders.	Double-blind, RCT	Alpha-Stim CES device.  Safety not reported.  0 to 1% dropout.	Before and after 3 weeks of intervention.  No follow-up.	2 Groups:  Group 1 – EG (n = 30).  Group 2 – SCG (n = 10).	30-min CES stimulation each day, 5 days per week for 3 weeks.	The current with a series of low intensity, sinusoidal electric impulses at 100 pps on a 20% duty cycle with current variable from 0.0 to 1.0 mA was applied to the head of the patient through two ear stethoscope electrodes placed just behind the earlobe at the maxillo-occipital juncture.	Cognition measured by revised beta examination, subscales of WAIS including digit span, digit symbol, object assembly.  Anxiety measured by STAI and IPAT.  Mood measured by POMS.	CES improved all WAIS subscales.  Significantly greater improvement in all anxiety measures.  No significant gains on any POMS measures.
Smith et al., 1994	N = 10; CHI patients, both genders with average age of 30 years.	Double-blind, RCT	CES Lab device.  Safety not reported.  0 to 1% dropout.	Before and after 3 weeks of intervention.  No follow-up.	Group 1 – PCG.  Group 2 – SCG.  Group 3 – EG.	45-min CES intervention daily, 4 days per week for 3 weeks.	CES intervention used, involves the alternating current, pulsing 100 times per second (100 Hz) on a 20% duty cycle, with a maximum of 1.5 mA output.	Mood measured by POMS.	Significant reduction in all the negative mood factors of mood states.
Southworth, 1999	N = 21; non-clinical healthy participants (age 18–60 years).	RCT	LISS Body Stimulator Bipolar Model No. SBL-502-B.  Safety reported: FDA approved.  0 to 1% dropout.	Before and after 20–60 min single CES intervention session.  No follow-up.	Group 1 – CG.  Group 2 – EG.	Single session, 20-min CES intervention.	For giving CES intervention, the electrodes were placed below the temples to deliver the CES.  Frequency and intensity not mentioned.	Cognition measured using neuropsychological tests including continuous performances task.	CES intervention improved the attention on continuous performances task.

**Table 2**Quality Scoring of Randomized Controlled Trials (RCTs) Including Pilot RCTs (*n* = 16)

Study	Participants; <i>N</i>	Design	CES Mode, Safety and Dropouts	Patient Evaluation and Follow-up	Interventions	Duration of Intervention	Area of Application of CES and CES Parameters (current density, frequency) in Experimental/Active CES Group	Outcome	Results
Winick, 1999	<i>N</i> = 33; subjects of both genders who underwent to dental procedures in last 1 month.	RCT	Alpha-Stim CES device.  Safety not reported.  0 to 1% dropout.	Before and after the single stimulation.  No follow-up.	2 Groups:  Group 1 – EG ( <i>n</i> = 17).  Group 2 – Placebo control group ( <i>n</i> = 16).	Active CES treatment given 5 min before starting dental procedure.	CES applied during routine dental procedure, using micro-current cranial electrotherapy stimulator to deliver the modified byphasic square waveform of varying pulse width at 50% of duty cycle. Clip-shaped electrodes were attached to both earlobes with a current of 200 $\mu$ A at a frequency of 0.5 Hz.	Anxiety measured by VAS (rated as not anxious at the left and very anxious at the right by 7-point Likert scale).	Improved anxiety symptoms.
Wu et al., 2020	<i>N</i> = 53; patients of both the genders, aged 6–17 years with TD and lack of clinical response to 4 weeks of pharmacotherapy.	Randomized, double-blind, sham-controlled trial.	CES American neuro-fitness by LLC.  Safety not reported.  17% dropout.	Before and after 4 weeks of intervention.  No follow-up.	2 Groups:  Group 1 – EG ( <i>n</i> = 29).  Group 2 – SCG ( <i>n</i> = 24).	30-min CES stimulation therapy, 40 sessions applied for 4 weeks (twice daily on weekdays from Monday to Friday).	The devices used in this study provided the bipolar, asymmetric, rectangular waves.  Frequency and intensity not mentioned.	Anxiety measured by HAMA-14.	Significant reduction in the anxiety symptoms.

**Note.** RCT = randomized controlled trial; % = percent; Hz = hertz;  $\mu$ A = microampere; mA = milliamper; min = minutes; pps = pulses per second; V = volt; MDD = major depressive disorder; AD = Alzheimer's disease; CHI = closed head injuries, TD = tic disorder; CES = cranial electrical stimulation; EG = experimental group; SCG = sham control group; CG = control group; HAMA = Hamilton Rating Scale for Anxiety; HAM-D17 = Hamilton Rating Scale for Depression - 17 items; ACTH = adrenocorticotrophic hormone; HADS = Hospital Anxiety and Depression Scale; BDI = Beck Depression Inventory; YMRS = Young Mania Rating Scale; CFQ = Cognitive Failures Questionnaire; 3MS = Modified Mini-Mental State; AMI = autobiographical memory inventory; SCL-90-R39 = Symptom Check List; BDNF = brain-derived neurotrophic factor; NGF = nerve growth factor; POMS = Profile of Mood States; GDS = Geriatric Depression Scale; BOP = behavior observation scale; WAIS = Wechsler Adult Intelligence Scale; STAI = State Trait Anxiety Index; IPAT = Institute for Personality and Ability Testing Anxiety Scale; VAS = visual analogue scale; HAMA 14 = Hamilton Anxiety Scale - 14 items; FDA = Food and Drug Administration.

### Quality Assessment of Included Trials

The authors utilized an 11-point PEDro scale with a set of general core elements for quality assessment of RCTs to assess the methodological quality of all the collected RCT evidence (Verhagen et al., 1998). The two authors separately rated the quality of the trials (ZK and AS). If there was a disagreement on a criterion, each reviewer separately reevaluated it. Unresolved issues were found and discussed in a meeting in order to obtain a final agreement. Ten out of 11 criteria (when giving ratings, factors regarding the specification of eligibility criteria in the paper were not taken into account because all of the included studies had stated their inclusions and exclusions) were used for quality assessment on PEDro and each criterion was rated either Yes (score = 1) or No (score = 0) to minimize ambiguity in responses. The total score for the methodological quality of each included study was calculated by summing all the responses (maximum score = 10). Studies were then classified as *poor* (score of < 4), *fair* (score of 4–5), *good* (score of 6–8), and *excellent* quality (score of > 8) based on total scores obtained on PEDro scale (Harjohm et al., 2015). In Table 1, the overall score for methodological quality is shown.

### Quality of Trials

Quality scoring was performed for all the RCTs included in the review. Average PEDro score for all the trials was approximately 7/10 (good quality). Three trials scored 9/10 (McClure et al., 2015; Mischoulon et al., 2015; Wu et al., 2020), two scored 8/10 (Barclay & Barclay, 2014; Padjen et al., 1995), three scored 7/10 (Lyon et al., 2010; Scherder et al., 2003; Schmitt et al., 1986), three scored 6/10 (Rose et al., 2009; Scherder et al., 2003; Winick, 1999), and five scored 5/10 (Kang et al., 2020; Lee et al., 2013; Roh & So, 2017; Smith et al., 1994; Southworth et al., 1999). All of the studies randomly allocated the subjects into groups, but only one maintained a concealed allotment (Wu et al., 2020). Four of the trials (Lee et al., 2013; Roh & So, 2017; Scherder et al., 2003; Scherder et al., 2006) did not blind either of the subject, the therapist, or the assessor; however, six studies followed the double-blind procedure with blinding the subject and therapist (Lyon et al., 2010; Rose et al., 2009; Schmitt et al., 1986; Smith et al., 1994; Southworth et al., 1999; Winick, 1999). Four studies carried out triple-blinding for the subjects, the therapist as well as the assessor in their carefully conducted trials (McClure et al., 2015; Mischoulon et al., 2015; Padjen et al., 1995; Wu et al., 2020). Five out of 6 RCTs reported very well about the between-group differences postintervention with point estimates and

measures of variability (Barclay & Barclay, 2014; McClure et al., 2015; Mischoulon et al., 2015; Scherder et al., 2003, Scherder et al., 2006). On the other hand, except two (Lyon et al., 2010; Mischoulon et al., 2015) no other studies applied intention to treat analysis on dropouts (Table 1).

## Results

We devised a search technique that comprised three databases, and we found 392 studies, including 272 in PubMed, 19 in CENTRAL, and 101 in Web of Science. There were 179 articles left after the 213 duplicates were removed. After screening the titles and abstracts, the remaining articles were culled for full texts, and 16 were chosen based on the inclusion criteria. The summarized results of the selected articles are shown in Table 2.

### Characteristics of the Studies

The important characteristics of the selected articles are shown in Table 2.

**Study Design.** Randomized controlled trial (RCTs) including pilot RCTs.

**Participants.** Fifteen included RCTs consisted of 690 participants with different types of pathologies: 115 subjects with anxiety and comorbid depression in one study (Barclay & Barclay, 2014), 30 patients with depression only (Mischoulon et al., 2015), 28 subjects undergoing general anesthesia (Kang et al., 2020), 25 patients undergoing thyroidectomy (Lee et al., 2013), 36 breast cancer patients (Lyon et al., 2010), 16 bipolar disorder patients (McClure et al., 2015), 124 patients were alcoholics and drug abusers (Padjen et al., 1995; Schmitt et al., 1986), 50 postmenopausal women (Roh & So, 2017), 70 Alzheimer's patients (Rose et al., 2009; Scherder et al., 2003; Scherder et al., 2006), 21 patients of close head injuries (CHI; Smith et al., 1994), 33 dental patients (Winick, 1999), 62 tic disorder patients (Wu et al., 2020), and 21 nonclinical healthy participants (Southworth, 1999). However, a common limitation in all studies was the lack of information on sample size and power calculation, except for four studies (Barclay & Barclay, 2014; Padjen et al., 1995; Rose et al., 2009; Wu et al., 2020). The majority of studies included all age groups (6–88 years old) and both genders, with one study assessing only females (Lee et al., 2013; Lyon et al., 2010; Roh & So, 2017) and another study assessing only males (Padjen et al., 1995).

**CES Mode and Safety.** All studies investigated the effect of cranial electrical stimulation using different commercially available devices, like various derivative models of Alpha-Stim (Barclay & Barclay, 2014; Kang et al., 2020; Lee et al., 2013; Lyon et al., 2010; McClure et al., 2015; Roh & So, 2017; Rose et al., 2009; Scherder et al., 2003; Scherder et al., 2006; Schmitt et al., 1986; Winick, 1999), FW-100 Fisher-Wallace device (Mischoulon et al., 2015), N-S, Inc. C stimulator (Padjen et al., 1995), CES Lab device (Smith et al., 1994), CES American by Neuro-Fitness by LLC (Wu et al., 2020), and LISS Body Stimulator Bipolar Model No. SBL-502-B (Southworth, 1999). Some of these studies reported on safety of the CES intervention (Kang et al., 2020; Lee et al., 2013; Lyon et al., 2010; McClure et al., 2015; Mischoulon et al., 2015; Wu et al., 2020; Winick, 1999). However, few of these studies have reported if the device was FDA approved or not (Barclay & Barclay, 2014; Lyon et al., 2010; McClure et al., 2015; Mischoulon et al., 2015; Roh & So, 2017; Southworth, 1999).

**Duration.** Duration of CES treatment ranged from a single session to 8 weeks, with each session varied from 20 min to 1 hr. One study involved a single 20-min CES session (Southworth, 1999). Other studies involved treatment sessions as: 1 hr daily for 5 weeks (Barclay & Barclay, 2014); 20 min on day before surgery and 20 min on morning of surgery (Kang et al., 2020; Lee et al., 2013); 1 hr daily for 6–8 weeks (Lyon et al., 2010); 20 min per day for 5 days each week for 2 weeks (McClure et al., 2015); 20 min per day for 5 days each week for 3 weeks (Mischoulon et al., 2015); 30 min per day for 5 days each week for 4 weeks (Padjen et al., 1995); 20 min per day for 3 days each week for 8 weeks (Roh & So, 2017); 60 min per day for 4 weeks (Rose et al., 2009); 30 min per day for 5 days each week, for 6 weeks (Scherder et al., 2003; Scherder et al., 2006); 30 min per day for 5 days each week, for 3 weeks (Schmitt et al., 1986); 45 min per day for 4 days each week, for 3 weeks (Smith et al., 1994); 30 min twice per day for 5 days each week, for 4 weeks (Wu et al., 2020); and one study did not reported any details regarding the duration for which current was used (Winick, 1999).

**Frequency.** Frequency was used between 0.5 and 15,000 Hz. Frequency of 0.5 Hz was set in most of the studies (Barclay & Barclay, 2014; Kang et al., 2020; Lee et al., 2013; Roh & So, 2017; Rose et al., 2009; Scherder et al., 2003; Scherder et al., 2006; Winick, 1999). A few studies reported the frequency of 100 Hz (Lyon et al., 2010; Padjen et al., 1995; Smith et al., 1994). Whereas two studies have used

frequency ranging between 5 Hz and 15,000 Hz (McClure et al., 2015; Mischoulon et al., 2015), one study used three frequency ranges 0.5 Hz, 1.5 Hz, or 100 Hz (Wu et al., 2020). However, two studies failed to give details of the frequency of current utilized during the experiment (Schmitt et al., 1986; Southworth, 1999).

**Intensity.** Intensity of current used for giving intervention, ranged from 10  $\mu$ A to 2 mA. Intensity of less than 100  $\mu$ A was used in two studies by (Lyon et al., 2010; Padjen et al., 1995). Intensity of 100  $\mu$ A was used in majority of the studies (Barclay & Barclay, 2014; Lee et al., 2013; Roh & So, 2017; Rose et al., 2009). Intensity of 200  $\mu$ A was used in three studies (Kang et al., 2020; McClure et al., 2015; Winick, 1999). One study reported the range of intensity between 100–400  $\mu$ A (Mischoulon et al., 2015), another study set the intensity between 500  $\mu$ A – 2 mA (Wu et al., 1992, 2020). Two studies used the intensity of current between 10–600  $\mu$ A (Scherder et al., 2003; Scherder et al., 2006), whereas one study reported an intensity of 1.5 mA (Smith et al., 1994). However, two studies failed to give details of the intensity of current utilized during the experiment (Schmitt et al., 1986; Southworth, 1999).

**Electrode Placement.** The placement of electrodes varied between the studies, however, majority of the studies used clip electrodes and attached them to earlobes (Barclay & Barclay, 2014; Kang et al., 2020; Lee et al., 2013; Lyon et al., 2010; Roh & So, 2017; Rose et al., 2009; Scherder et al., 2003; Scherder et al., 2006; Winick, 1999; Wu et al., 2020), whereas in one study electrodes were placed at ear temples (McClure et al., 2015) and in another study, the electrodes were placed below the temples (Southworth, 1999). One study applied the stimulation through headsets with wet electrodes sponges (Mischoulon et al., 2015), another one uses the four electrodes (two at frontal and two on each mastoid) for delivering the stimulation. Two studies did not mention any details regarding the electrode placement (Schmitt et al., 1986; Smith et al., 1994).

**Sham Group and Other Comparison Group Protocols.** In all 15 selected studies, the experimental or active group was either compared with the control group (Kang et al., 2020; Lee et al., 2013; Scherder et al., 2003; Scherder et al., 2006; Southworth, 1999), with other intervention groups such as sham CES group (Barclay & Barclay, 2014; McClure et al., 2015; Mischoulon et al., 2015; Padjen et al., 1995; Roh & So, 2017; Rose et al., 2009; Schmitt et al., 1986; Wu et al., 2020), or with a

placebo CES group (Winick, 1999). Further, in studies having three groups, the experimental group was compared with two other stimulation groups such as a sham CES and usual comparison group (Lyon et al., 2010), or with a sham CES and placebo CES group (Smith et al., 1994). However, protocol parameters for other stimulation, such as sham CES stimulation (Barclay & Barclay, 2014; Roh & So, 2017; Rose et al., 2009), control CES stimulation (Kang et al., 2020; Lee et al., 2013; Scherder et al., 2003, Scherder et al., 2006), and placebo CES stimulation (Winick, 1999), were identical to the active CES stimulation, and the electrodes were attached in the same way as in the CES group except the ear clip electrodes did not emit electricity, the power was turned off, or the current was not given (Barclay & Barclay, 2014; Kang et al., 2020; Lee et al., 2013; Roh & So, 2017; Rose et al., 2009; Scherder et al., 2003, Scherder et al., 2006; Winick, 1999). Interestingly, in one study, SCS (sham Alpha-Stim Stress Control System) CES devices were constructed for the placebo treatment with nonconductive wires; otherwise, the device, settings, and batteries were identical in both the active and the sham groups. Further, no details regarding the usual control group were mentioned (Lyon et al., 2010). In another study, the sham CES treatment was performed by a trained technician who did not take part in any other aspect of the study, by turning the current on until the patient experienced a tingling sensation on the scalp and then turning it off. The treatment itself was a subthreshold for the above sensation (McClure et al., 2015). In another study, the sham CES devices were identical to the active device except that the sham devices were modified to not deliver current to the headset (Mischoulon et al., 2015). In a study by Padjen and colleagues, the treatment group involved the flow of the current between the frontal and mastoid electrodes; whereas, in the sham group, the current was arranged to flow between the adjacent frontal electrodes so that the stimulation was limited to the frontal skin and there was no transcranial current flow (Padjen et al., 1995). In a study by Schmitt, the treatment procedure was exactly the same in both active CES group and sham group except that the current was turned off completely for the patients who were in the sham treatment condition (Schmitt et al., 1986). In a study by Smith and colleagues, Group 1 served as placebo controls and continued in their ordinary activities during the study with no access to CES devices; whereas Group 2 served as sham treatment controls and were placed on CES devices via double-blinding boxes but received no treatment (Smith et al., 1994). In a study by Wu and colleagues, the sham CES device was identical to

the active device, except the ear clip electrodes emitted electricity of intensity lower than 100  $\mu$ A (Wu et al., 2020).

**Patient Evaluation and Follow-Up.** Patient evaluation varied in all the studies. In one study the patient evaluation was done before and after 20–60 min after a single session of CES intervention (Southworth, 1999); however, in a study by Kang et al. (2020), the evaluation was done three times per day before the surgery, preoperative, and on the day of surgery. In another study, the assessment was done before and after the surgery (Lee et al., 2013). In other studies, the evaluation was done before the intervention and 3 weeks postintervention (Lyon et al., 2010); at baseline, weeks 1, 3, and 5 (Barclay & Barclay, 2014); at baseline, weeks 2, 4, and 12 (McClure et al., 2015); at baseline, weeks 1, 2, and 3 (Mischoulon et al., 2015); at baseline, weeks 1, 2, 3, and 4 (Padjen et al., 1995); at baseline and after 8 weeks (Roh & So, 2017); at baseline, weeks 2 and 4 (Rose et al., 2009); before and after 6 weeks of intervention (Scherder et al., 2003; Scherder et al., 2006); before and after 3 weeks of intervention (Schmitt et al., 1986; Smith et al., 1994); before and after a single stimulation (Winick, 1999); and before and after 4 weeks of intervention (Wu et al., 2020). However, only two studies took the follow-up of participants postintervention (Lyon et al., 2010; McClure et al., 2015).

**Dropouts and Side Effects.** Discontinuations of the study by the subjects were quite rare overall (Table 1), with proportions of subjects completing each study around 99–100% with only 0–1% dropout in some studies (Lee et al., 2013; Lyon et al., 2010; McClure et al., 2015; Roh & So, 2017; Rose et al., 2009; Scherder et al., 2003; Scherder et al., 2006; Schmitt et al., 1986; Smith et al., 1994; Southworth, 1999; Winick, 1999) for both active and control groups. Some studies had dropout in between 5–17%, such as 6% (Barclay & Barclay, 2014), 7.4% (Padjen et al., 1995), 11% (Kang et al., 2020), and 17% (Wu et al., 2020). However, discontinuations of the study by the subjects were either due to personal issues or some other issues and not because of the side effects of CES.

### Outcome Measures

**Cognition.** Cognitive measures included questionnaires or a self-rating scale such as the Cognitive Failures Questionnaire (CFQ), Modified Mini-Mental State (3MS) exam, and autobiographical memory inventory (AMI; McClure et al., 2015). In another study, neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve



growth factor (NGF) levels for cognitive assessment were used (Roh & So, 2017). Whereas three studies utilized the neuropsychological tests like digit span and visual memory span, the eight-words test, face and picture recognition, and word fluency (Scherder et al., 2003, Scherder et al., 2006) and continuous performance test (Southworth, 1999) for quantifying the changes in cognitive functions parameters.

**Depression and Anxiety.** The most common outcome measures used by the majority of studies for quantifying depression level were questionnaires and self-rating such as the Hamilton Depression Rating Scale 17 (HAM-D17; Barclay & Barclay, 2014; Mischoulon et al., 2015); Hospital Anxiety and Depression Scale (HADS; Lyon et al., 2010), Hamilton Depression scale (HDS) and Montgomery Asberg Scale (Padjen et al., 1995), and the Geriatric Depression Scale (GDS; Rose et al., 2009).

Similar to depression, many studies rely on questionnaires or a self-rating scale for measuring anxiety levels. A study by Barclay and colleagues used the Hamilton Rating Scale for Anxiety (HAM-A) for measuring anxiety (Barclay & Barclay, 2014), whereas another study quantified anxiety levels by using a 5-point Likert scale (1 = *not at all*; 2 = *mild*; 3 = *intermediate*; 4 = *moderate*; 5 = *severe*; Kang et al., 2020). Lyon and colleagues incorporated the Hospital Anxiety and Depression Scale (HADS) for quantifying anxiety level (Lyon et al., 2010). On the other hand, Padjen and colleagues used the Hamilton Anxiety Scale for measuring anxiety levels (Padjen et al., 1995). Another study by Schmitt utilized a variety of scales for assessing anxiety levels such as the State Trait Anxiety Index (STAI) and Anxiety scale of the Institute for Personality and Ability Testing (IPAT; Schmitt et al., 1986). One study incorporated the visual analogue scale (VAS), a 7-point Likert scale (Winick, 1999), whereas the study by Wu and colleagues utilized the Hamilton Anxiety Scale - 14 items (HAMA-14) for quantifying anxiety levels (Wu et al., 2020). A study by Lee and colleagues incorporated the 5-point Likert scale (Lee et al., 2013).

**Mood and Stress.** Mood measures were assessed with the Beck Depression Inventory (BDI), Hamilton Rating Scale for Depression (HAM-D17), Young Mania Rating Scale (YMRS), and Positive and Negative Affect Schedule (PANAS) in a study by McClure and colleagues (McClure et al., 2015). Three studies incorporated the Profile of Mood States (POMS) for the assessment of mood (Roh & So, 2017; Schmitt et al., 1986; Smith et al., 1994). However, one study utilized the behavior

observation scale (BOP), Anxiety and Depression subscales of the Symptom Checklist (SCL-90), and the Beck Depression Inventory (BDI) for measuring the mood status (Scherder et al., 2006).

For quantifying stress, stress-related hormone such as adrenocorticotrophic hormone (ACTH) and cortisol were used by two studies (Lee et al., 2013; Roh & So, 2017), whereas one study involved only salivary cortisol for assessing the stress level (Scherder et al., 2003).

### Effect of CES Intervention On

**Cognition.** A study by McClure and colleagues demonstrated an improved cognitive functioning on one of their cognitive function scales (Cognitive Failures Questionnaire [CFQ]), from baseline to week 4 in an active group ( $p = .045$ ) compared to sham group (McClure et al., 2015). Similarly, a study by Schmitt and colleagues showed improved in all the subscales of WAIS including digit span, digit symbol, object assembly CES following CES intervention of 30 min each day, 5 days a week, for a period of 3 weeks (Schmitt et al., 1986). Along the same lines, one study reported improved continuous performances task for attention following 60 min of CES intervention (Southworth et al., 1999). In contrast, a study by Roh and So revealed no significant changes ( $p > .05$ ) with regard to levels of serum BDNF and serum NGF, or interaction between time and groups following 8 weeks of CES treatment (Roh & So, 2017). Likewise, another study demonstrated no beneficial effects on neuropsychological tests including digit span test, visual memory, recognition, and word fluency following CES treatment for a period of 6 weeks (Scherder et al., 2003). The same authors showed no significant interaction effects between the groups over time during the study for any of the neuropsychological tests after treating with CES for a period of 6 weeks (Scherder et al., 2006).

**Depression.** Majority of the studies stated the reduced depression symptoms after CES treatment. Barclay and colleagues revealed a significant reduction in depressive symptoms (HAM-D17) in active CES group ( $p = .001$ ,  $d = .78$ ) as compared to sham group following an intervention of 5 weeks, suggesting CES as an efficient tool for treating symptoms of depression (Barclay & Barclay, 2014). Likewise, there was significantly greater improvement (end score – baseline) in depressive symptoms in the active treatment group ( $t = -2.56$ ,  $df = 60$ ,  $p = .013$ ) compared to sham group after an intervention of 4 weeks, suggesting results again in favor of the CES for treating depression (Padjen et



al., 1995). However, Mischoulon and colleagues showed improvement in 3 to 5 points in HAM-D17 scores ( $p < .05$ ) and reduced depression remission rates in both the treatment groups without any significant differences between these groups following 3 weeks of CES treatment (Mischoulon et al., 2015). Additionally, in a study (of over 4 weeks) by Rose and colleagues, decreased depressive symptoms scores with final depressive scores falling below baseline were seen in both groups without any significant differences between the groups ( $F = 9.022$ ,  $p = .224$ ; Rose et al., 2009). In a study by McClure and colleagues, following 2 weeks of intervention, active CES but not sham treatment was associated with significant decrease in BDI and HAM-D scores, from baseline to the second week ( $p = .003$ ), maintaining significance until week 4 ( $p = .002$ ), and then reducing to a trend ( $p = .09$ ) by week 8. However, there was no significant difference between the groups for HAM-D scores. For YMRS, the total and subscale scores did not change through the study, and no significant differences were found between and within the groups at any of the time points (McClure et al., 2015). In contrast, in a study of a 6- to 8-week period of intervention by Lyon and colleagues, the symptoms of depression increased over time ( $p = 0$ ), as the depressive symptoms went from mild to a potentially clinically significant level in week 6. However, greater increases (not statistically significant) occurred in the depression symptoms in sham and standard care groups than occurred in CES group from baseline at 3 weeks (Lyon et al., 2010).

**Anxiety.** Most of the studies showed lower anxiety scores in the CES group as compared to other groups following CES intervention (Barclay & Barclay, 2014; Kang et al., 2020). A study by Barclay, revealed a significant reduction in anxiety symptoms in the CES group ( $p = .001$ ,  $d = .94$ ) as compared to sham group, after an intervention of 5 weeks (Barclay & Barclay, 2014). Further, a study by Kang and colleagues signified lower anxiety scores and a smaller number of patients with higher anxiety levels in the CES group as compared to control group, following 20 min of CES stimulation, both on the day before surgery and on the morning of the day of surgery (Kang et al., 2013). Additionally, a study by Padjen and colleagues reported greater improvement (end score – baseline) in the active CES group (not statistically significant) as compared to sham group in anxiety subscales following CES treatment of over 4 weeks (Padjen et al., 1995). A study by Schmitt and colleagues showed that both the alcoholic and polydrug abusers responded significantly and

experienced the same level of improvement in anxiety symptoms with CES, but the control group did not show any improvement in the same, following 3 weeks of intervention (Schmitt et al., 1986). Furthermore, a study by Winick and colleagues (in which CES treatment was administered during a dental procedure) exhibited significant improvement on anxiety symptoms in active CES group compared to placebo group at the conclusion of various dental procedures (Winick, 1999). Likewise, a study by Wu and colleagues demonstrated a significant difference in anxiety scores between the groups over time during the study of 4 weeks of treatment ( $F = 10.64$ ,  $p = .001$ ). Anxiety scores at week 4 decreased significantly according to baseline in active group ( $t = 1.01$ ,  $p = .001$ ), and not in the sham group ( $F = 1.11$ ,  $p = .34$ ; Wu et al., 2020). Lyon and colleagues demonstrated no significant increase in the level of anxiety symptoms in any of the three groups (active, sham, and usual care group) from baseline at 3 weeks, with no statistically significant differences between the groups (Lyon et al., 2010).

**Mood and Stress.** Three (Roh & So, 2017; Schmitt et al., 1986; Smith et al., 1994) out of six studies showed positive results of CES for improving the mood status. Following a 3-week intervention program, Schmitt and colleagues reported that the CES group significantly reduced on every anxiety subscale of the POMS used, the sham-treated CES group improved on only two of the six scales of the POMS, and the normal treatment program controls did not post significant gains on any measure of POMS (Schmitt et al., 1986). In another study, the pretreatment and posttreatment means of the three groups were compared, in which the CES treatment group showed significant improvement on every subtest of the POMS while control groups (placebo and sham group) did not, following 3 weeks of intervention (Smith et al., 1994). Further, in a study by Roh and So, following CES treatment of 8 weeks, the CES group exhibited a significant decline in depression-dejection subscores ( $p < .05$ ) of POMS as compared to sham group (Roh & So, 2017). In contrast, a study by Scherder and colleagues showed no significant interaction effects ( $p > .05$ ), between the groups for any of the mood and behavior scales following 6 weeks of CES therapy (Scherder et al., 2006). The same authors showed no significant effect on mood functions measures following a 6-week CES intervention (Scherder et al., 2003). Additionally, in a study by McClure and colleagues, following 2 weeks of CES intervention, PANAS subscale scores and total score did not change appreciably and no significant differences

were found between and within the groups ( $p > .05$ ) at any of the time points (at weeks 2, 4, and 8; McClure et al., 2015).

None of the included studies showed a positive effect of CES on improving stress level. In one study by Lee and colleagues, there were no significant differences in serum ACTH and cortisol levels in between the patients undergoing thyroidectomy given with CES and patients undergoing thyroidectomy without CES, measured at 1-, 4-, 12-, and 24-hr postsurgery (Lee et al., 2013). A study by Roh and So, revealed no significant differences with regard to levels of plasma cortisol and plasma ACTH or interaction between time and groups following CES treatment of 8 weeks ( $p > 0.05$ ; Roh & So, 2017). In addition, a study by Scherder and colleagues demonstrated that low-frequency CES did not reduce stress in AD patients. Further, both groups showed an increase instead of a decrease in the level of cortisol, following 6 weeks of CES stimulation therapy (Scherder et al., 2003, Scherder et al., 2006).

## Discussion

Prior systematic reviews, found in our literature searches up to April 2022, revealed beneficial results for anxiety and depression but suggest that there is an inadequate literature for methodologically eligible or high-quality trials for anxiety (Shekelle et al., 2018) or depression (Kavirajan et al., 2014; Shekelle et al., 2018). In addition, to the best of our knowledge, the advantages of CES on other outcome parameters such as mood functions, stress levels, and cognitive functions in a range of settings were not studied in the prior review. As a result, our analysis adds fresh research, additional settings, and extra outcome characteristics to these previous reviews. Based on data from 669 participants, this is the first systematic review to provide full information on the findings, features, and quality of RCTs, investigating the effect of CES on variety of mental health conditions such as cognitive dysfunction, depression, anxiety, mood, and stress disorder in various populations. We have mixed findings from different results and therefore limited evidence to support the use of CES for treating variety of mental disorders, as indicated by various qualitative and quantitative methods.

### Cognitive Functions, Depression, and Anxiety

In the present review, we found limited evidence to support the use of CES for improving the cognitive function parameters, as three out of six RCTs reported no changes or improvement in cognitive

functions parameters after using CES (Roh & So, 2017; Scherder et al., 2003, Scherder et al., 2006). However, three studies demonstrated an improved cognitive functioning on one of their cognitive function scales (McClure et al., 2015; Schmitt et al., 1986; Southworth, 1999). Therefore, our overall result has inconclusive findings regarding the effect of CES on cognitive functions.

We examined the efficacy of CES for the treatment of depressive disorders in a methodological review of six RCTs. Most of the studies on different population show that CES is an effective treatment and a useful adjunctive to other ongoing treatments, including pharmacotherapy and psychotherapy for treating depression (Barclay & Barclay, 2014; McClure et al., 2015; Mischoulon et al., 2015; Padjen et al., 1995; Rose et al., 2007). However, a study by Lyon and colleagues showed no significant changes and therefore no improvement in depressive symptoms (Lyon et al., 2010). Overall, our review suggests that CES helps in improving the depressive symptoms in a variety of population. The findings from this systematic review are in line with a prior review: CES as an effective treatment for depression, showing a cumulative treatment effect with repeated use and observable improvements following the first course of treatment (Kirsch & Nichols, 2013); a meta-analysis of CES for the treatment of depression (Price et al., 2021); and a systematic review showing low strength evidence suggesting modest benefit in patients with anxiety and depression (Shekelle et al., 2018).

Regarding anxiety, preceding systematic reviews identified in our literature searches to November 2021 reported beneficial effects for anxiety but with inadequate evidence (Shekelle et al., 2018). We analyze the effect of CES for the treatment of anxiety in a precise review of seven RCTs. The majority of RCTs demonstrated improvement in anxiety symptoms post-CES intervention (Barclay & Barclay, 2014; Kang et al., 2020; Lyon et al., 2010; Schmitt et al., 1986; Winick, 1999) but not significant enough (Padjen et al., 1995; Wu et al., 2020) to report any convincing results.

### Mood and Stress

Three RCTs (Roh & So, 2017; Schmitt et al., 1986; Smith et al., 1994) showed positive results of CES for improving mood status. In contrast, the study by Scherder and colleagues showed no significant effects of CES for the improvement of any of the mood and behavior parameters (Scherder et al., 2003). Another study by the same authors revealed no improvement in mood status following CES

intervention (Scherder et al., 2006). Additionally, a study by McClure and colleagues showed no improvement on any of the mood total scores and mood subscale scores throughout the study period (McClure et al., 2015). In total, findings were not substantial to make any conclusive results concerning mood treatment by CES. Concerning stress, none of the included RCTs (Lee et al., 2013; Roh & So, 2017; Scherder et al., 2003, Scherder et al., 2006) showed any positive changes on stress level quantified by serum or plasma ACTH and cortisol levels, following 6 weeks of CES stimulation therapy (Scherder et al., 2003; Scherder et al., 2006), therefore warranting further research for making any conclusion.

### Speculated Underlying Mechanism

CES mechanism of action on mental health is a topic of discussion, as a growing body of evidence advocated different theories and approaches for explaining the same. The mechanisms underlying the effect of CES are not well understood, but several theories can be used in an attempt to explain the scientific findings and clinical usefulness of CES in treating various mental diseases. A review of early literature (Bystritsky et al., 2008) stated that neurotransmitter levels are affected as a result of CES therapy; however, the animal studies had difficulties in scaling from exam animal anatomy to human neuroanatomy, and thus acquaintances were incomparable. Others have speculated that CES devices might interpose ongoing (pathologic) brain activity by introducing “cortical noise” and that this may impede with electrical oscillatory performance within the brain (Zaghi et al., 2010). Functional magnetic resonance imaging was used in recent research of the mechanistic effects of CES on brain activity on healthy adult volunteers to assess short-term effects (Feusner et al., 2012). Significant deactivation of the midline frontal and parietal regions, as well as changes in connectivity within the default mode network, were discovered by the researchers. Nonetheless, according to one study, the mechanisms of action of externally applied CES have been found in the limbic system (which is involved in emotional regulation and memory), as well as in the cingulate gyrus, insula, and prefrontal cortex (which is involved in pain processing; Taylor et al., 2013) by a variety of process including: transcranial and cranial nerve stimulation, pathways like cortical and subcortical region activation, effects on endogenous brain oscillations and cortical excitability, impact on neurotransmitters, hormones and endorphins, and impact on autonomic nervous system in the desired frequency (Mindes et al., 2014). Overall, it's unclear if CES has a single

mechanism of action or whether clinical effects are caused by different methods of action of different CES devices in different disorders; therefore, more thorough research is needed to resolve these questions.

### Limitations and Future Implications of Research

The widely held studies included in this review revealed improvements in anxiety, depression, and mood functioning to some level. However, in addition to the limitations already mentioned in terms of the quantity and quality of trials in previous literature, this study contains a number of other flaws. For a few research studies, the data was insufficient to compute an impact size; hence, those studies contributed less to the overall outcome. Because the data did not support a quantitative assessment of publication bias, its existence is still questionable. Importantly, many of the published RCTs were pilot studies, had uncertain validity and power, and were restricted by a lack of blinding assessment. Many studies reported small effects or did not provide sufficient detail about patients' existing treatments, such as two studies that did not mention any details regarding the electrode placement (Schmitt et al., 1986; Smith et al., 1994), two studies that failed to give details of the intensity and frequency of current utilized during the experiment (Schmitt et al., 1986; Southworth, 1999), and one study that did not describe any information regarding the duration for which current was used (Winick, 1999). Besides, some studies included single gender in their studies, with only females (Lee et al., 2013; Lyon et al., 2010; Roh & So, 2017) or only males (Padjen et al., 1995). Importantly, the number of treatment sessions of CES was significantly less in two studies (Kang et al., 2020; Lee et al., 2013). To end, all the included studies used a diverse population, mixed symptoms, overlapping conditions, variety of outcome measures and treatment program, making it difficult to perform meta-analysis. As a result, future studies should take into account the aforementioned constraints to back up their conclusions and to carry out the further pool analysis.

### Conclusions

The evidence from this systematic review for the effectiveness of CES is sparse. None of the studies favored the use of CES for improving cognitive function or treating stress. Due to the paucity of RCTs, limited evidence supports the use of CES for treating mood disorder and an average amount of evidence suggests a beneficial effect of CES for treating anxiety and depression symptoms.

Therefore, proof of benefit requires larger RCTs of higher quality, better execution, and longer follow-up. In addition, more gold standard and objective outcome measures such as EEG, ERPs, NBT, BDNF, serotonin, cortisol, and ACTH level to quantify mental health dysfunction are required to provide us with more high-level evidence regarding the efficacy of this treatment. Such standardized outcome measures would also allow an appropriate meta-analysis of future studies in this field. To give clear proof for the same, more trials with optimum controls and randomization protocols are required.

### Author Disclosure

There was no grant support for this review. There is no financial interest. The authors declare no conflict of interest.

### References

- Andrade, C., Arumugham, S. S., & Thirhalli, J. (2016). Adverse effects of electroconvulsive therapy. *Psychiatric Clinics of North America*, 39(3), 513–530. <https://doi.org/10.1016/j.psc.2016.04.004>
- Antal, A., & Paulus, W. (2008). Transcranial direct current stimulation and visual perception. *Perception*, 37(3), 367–374. <https://doi.org/10.1068/p5872>
- Barclay, T. H., & Barclay, R. D. (2014). A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression. *Journal of Affective Disorders*, 164, 171–177. <https://doi.org/10.1016/j.jad.2014.04.029>
- Bystritsky, A., Kerwin, L., & Feusner, J. (2008). A pilot study of cranial electrotherapy stimulation for generalized anxiety disorder. *The Journal of Clinical Psychiatry*, 69(3), 412–417. <https://doi.org/10.4088/jcp.v69n0311>
- Castaneda, A. E., Tuulio-Henriksson, A., Marttunen, M., Suvisaari, J., & Lönngqvist, J. (2008). A review on cognitive impairments in depressive and anxiety disorders with a focus on young adults. *Journal of Affective Disorders*, 106(1–2), 1–27. <https://doi.org/10.1016/j.jad.2007.06.006>
- Crown, W. H., Finkelstein, S., Berndt, E. R., Ling, D., Poret, A. W., Rush, A. J., & Russell, J. M. (2002). The impact of treatment-resistant depression on health care utilization and costs. *The Journal of Clinical Psychiatry*, 63(11), 963–971. <https://doi.org/10.4088/JCP.v63n1102>
- Feusner, J. D., Madsen, S., Moody, T. D., Bohon, C., Hembacher, E., Bookheimer, S. Y., & Bystritsky, A. (2012). Effects of cranial electrotherapy stimulation on resting state brain activity. *Brain and Behavior*, 2(3), 211–220. <https://doi.org/10.1002/brb3.45>
- Fregni, F., & Pascual-Leone, A. (2007). Technology insight: Noninvasive brain stimulation in neurology—perspectives on the therapeutic potential of rTMS and tDCS. *Nature Clinical Practice Neurology*, 3(7), 383–393. <https://doi.org/10.1038/ncpneuro0530>
- George, M. S. (2019). Whither TMS: A one-trick pony or the beginning of a neuroscientific revolution? *The American Journal of Psychiatry*, 176(11), 904–910. <https://doi.org/10.1176/appi.ajp.2019.19090957>
- Hariohm, K., Prakash, V., & Saravankumar, J. (2015). Quantity and quality of randomized controlled trials published by Indian physiotherapists. *Perspectives in Clinical Research*, 6(2), 91–97. <https://doi.org/10.4103/2229-3485.154007>
- In, M.-H., Cho, S., Shu, Y., Min, H.-K., Bernstein, M. A., Speck, O., Lee, K. H., & Jo, H. J. (2017). Correction of metal-induced susceptibility artifacts for functional MRI during deep brain stimulation. *NeuroImage*, 158, 26–36. <https://doi.org/10.1016/j.neuroimage.2017.06.069>
- Kang, H. W., Kim, H. J., Kim, W. Y., Min, W. K., Min, T. J., Lee, Y. S., & Kim, J. H. (2020). Effects of cranial electrotherapy stimulation on preoperative anxiety and blood pressure during anesthetic induction in patients with essential hypertension. *Journal of International Medical Research*, 48(8), 0300060520939370. <https://doi.org/10.1177/0300060520939370>
- Kavirajan, H. C., Lueck, K., & Chuang, K. (2014). Alternating current cranial electrotherapy stimulation (CES) for depression. *Cochrane Database of Systematic Reviews*, (7), CD010521. <https://doi.org/10.1002/14651858.CD010521.pub2>
- Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*, 62(6), 593–602. <https://doi.org/10.1001/archpsyc.62.6.593>
- Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, 62(6), 617–627. <https://doi.org/10.1001/archpsyc.62.6.617>
- Kirsch, D. L. (2002). [Review of the book *The science behind cranial electrotherapy stimulation*, by W. G. Collins]. *NeuroRehabilitation*, 14(2), 123. <https://doi.org/10.3233/NRE-2000-14207>
- Kirsch, D. L., & Gilula, M. F. (2007). CES in the treatment of insomnia: A review and meta-analysis. *Practical Pain Management*, 7(8), 28–39. <https://www.practicalpainmanagement.com/treatments/interventional/stimulators/ces-treatment-insomnia-review-meta-analysis>
- Kirsch, D. L., & Nichols, F. (2013). Cranial electrotherapy stimulation for treatment of anxiety, depression, and insomnia. *Psychiatric Clinics of North America*, 36(1), 169–176. <https://doi.org/10.1016/j.psc.2013.01.006>
- Klawansky, S., Yeung, A., Berkey, C., Shah, N., Phan, H. A. I., & Chalmers, T. C. (1995). Meta-analysis of randomized controlled trials of cranial electrostimulation. Efficacy in treating selected psychological and physiological conditions. *The Journal of Nervous and Mental Disease*, 183(7), 478–484. <https://doi.org/10.1097/00005053-199507000-00010>
- Lee, S.-H., Kim, W.-Y., Lee, C.-H., Min, T.-J., Lee, Y.-S., Kim, J.-H., & Park, Y.-C. (2013). Effects of cranial electrotherapy stimulation on preoperative anxiety, pain and endocrine response. *Journal of International Medical Research*, 41(6), 1788–1795. <https://doi.org/10.1177/0300060513500749>
- Lyon, D. E., Schubert, C., & Taylor, A. G. (2010, July). Pilot study of cranial stimulation for symptom management in breast cancer. *Oncology Nurse Forum*, 37(4), 476–483. <https://doi.org/10.1188/10.ONF.476-483>
- McClure, D., Greenman, S. C., Koppolu, S. S., Varvara, M., Yaseen, Z. S., & Galynker, I. I. (2015). A pilot study of safety and efficacy of cranial electrotherapy stimulation in treatment of bipolar II depression. *The Journal of Nervous and Mental Disease*, 203(11), 827–835. <https://doi.org/10.1097/NMD.0000000000000378>
- Mindes, J., Dubin, M. J., & Altemus, M. (2014). Cranial electrical stimulation. In H. Knotkova, & D. Rasche (Eds.), *Textbook of neuromodulation: Principles, methods and clinical applications* (pp. 127–150). New York, NY: Springer New York. <https://doi.org/10.1016/j.brs.2014.01.047>
- Mischoulon, D., De Jong, M. F., Vitolo, O. V., Cusin, C., Dording, C. M., Yeung, A. S., Durham, K., Parkin, S. R., Fava, M., & Dougherty, D. D. (2015). 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. *Journal of Psychiatric Research*, 70, 98–105. <https://doi.org/10.1016/j.jpsychires.2015.08.016>
- Murray, C. J., Vos, T., Lozano, R., Naghavi, M., Flaxman, A. D., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J. A., Abdalla, S., Aboyans, V., Abraham, J., Ackerman, I., Aggarwal, R., Ahn, S. Y., Ali, M. K., AlMazroa, M. A., Alvarado, M., Anderson, H. R., Anderson, L. M., ... Lopez, A. D. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*, 380(9859), 2197–2223. [https://doi.org/10.1016/S0140-6736\(12\)61689-4](https://doi.org/10.1016/S0140-6736(12)61689-4)
- O'Connell, N. E., Marston, L., Spencer, S., DeSouza, L. H., & Wand, B. M. (2018). Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database of Systematic Reviews*, 3(3), CD008208. <https://doi.org/10.1002/14651858.CD008208.pub5>
- Padjen, A. L., Dongier, M., & Malec, T. (1995). Effects of cerebral electrical stimulation on alcoholism: A pilot study. *Alcoholism: Clinical and Experimental Research*, 19(4), 1004–1010. <https://doi.org/10.1111/j.1530-0277.1995.tb00981.x>
- Perini, G., Ramusino, M. C., Sinfioriani, E., Bernini, S., Petrachi, R., & Costa, A. (2019). Cognitive impairment in depression: Recent advances and novel treatments. *Neuropsychiatric Disease and Treatment*, 15, 1249–1258. <https://doi.org/10.2147/NDT.S199746>
- Price, L., Briley, J., Haltiwanger, S., & Hitching, R. (2021). A meta-analysis of cranial electrotherapy stimulation in the treatment of depression. *Journal of Psychiatric Research*, 135, 119–134. <https://doi.org/10.1016/j.jpsychires.2020.12.043>
- Roh, H.-T., & So, W.-Y. (2017). Cranial electrotherapy stimulation affects mood state but not levels of peripheral neurotrophic factors or hypothalamic-pituitary-adrenal axis regulation. *Technology and Health Care*, 25(3), 403–412. <https://doi.org/10.3233/THC-161275>
- Rosa, M. A., Abdo, G. L., Lisanby, S. H., & Peterchev, A. (2011). Seizure induction with low-amplitude-current (0.5 A) electroconvulsive therapy. *The Journal of Electroconvulsive Therapy*, 27(4), 342. <https://doi.org/10.1097/YCT.0b013e31822149db>
- Rose, K. M., Taylor, A. G., & Bourguignon, C. (2009). Effects of cranial electrical stimulation on sleep disturbances, depressive symptoms, and caregiving appraisal in spousal caregivers of persons with Alzheimer's disease. *Applied Nursing Research*, 22(2), 119–125. <https://doi.org/10.1016/j.apnr.2007.06.001>
- Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & The Safety of TMS Consensus Group. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, 120(12), 2008–2039. <https://doi.org/10.1016/j.clinph.2009.08.016>
- Scherder, E., Knol, D., van Someren, E., Deijen, J. B., Binnekade, R., Tilders, F., & Sergeant, J. (2003). Effects of low-frequency cranial electrostimulation on the rest-activity rhythm and salivary cortisol in Alzheimer's disease. *Neurorehabilitation and Neural Repair*, 17(2), 101–108. <https://doi.org/10.1177/0888439003017002004>
- Scherder, E., Knol, D., van Tol, M.-J., van Someren, E., Deijen, J.-B., Swaab, D., & Scheltens, P. (2006). Effects of high-frequency cranial electrostimulation on the rest-activity rhythm and salivary cortisol in Alzheimer's disease: A pilot study. *Dementia and Geriatric Cognitive Disorders*, 22(4), 267–272. <https://doi.org/10.1159/000095108>
- Schmitt, R., Capo, T., & Boyd, E. (1986). Cranial electrotherapy stimulation as a treatment for anxiety in chemically dependent persons. *Alcoholism: Clinical and Experimental Research*, 10(2), 158–160. <https://doi.org/10.1111/j.1530-0277.1986.tb05064.x>
- Sevilla-Llewellyn-Jones, J., Santesteban-Echarri, O., Pryor, I., McGorry, P., & Alvarez-Jimenez, M. (2018). Web-based mindfulness interventions for mental health treatment: Systematic review and meta-analysis. *JMIR Mental Health*, 5(3), Article e10278. <https://doi.org/10.2196/10278>
- Shekelle, P. G., Cook, I. A., Mlake-Lye, I. M., Mak, S., Booth, M. S., Shanman, R., & Beroes, J. M. (2018). The effectiveness and risks of cranial electrical stimulation for the treatment of pain, depression, anxiety, PTSD, and insomnia: A systematic review. Washington D.C.: Department of Veteran Affairs (US).
- Smith, R. B., Tiberi, A., & Marshall, J. (1994). The use of cranial electrotherapy stimulation in the treatment of closed-head-injured patients. *Brain Injury*, 8(4), 357–361. <https://doi.org/10.3109/02699059409150986>
- Southworth, S. (1999). A study of the effects of cranial electrical stimulation on attention and concentration. *Integrative Physiological and Behavioral Science*, 34(1), 43–53. <https://doi.org/10.1007/BF02688709>
- Taylor, A. G., Anderson, J. G., Riedel, S. L., Lewis, J. E., & Bourguignon, C. (2013). A randomized, controlled, double-blind pilot study of the effects of cranial electrical stimulation on activity in brain pain processing regions in individuals with fibromyalgia. *Explore*, 9(1), 32–40. <https://doi.org/10.1016/j.explore.2012.10.006>
- Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., Ritz, L., Norquist, G., Howland, R. H., Lebowitz, B., McGrath, P. J., Shores-Wilson, K., Biggs, M. M., Balasubramani, G. K., Fava, M., & Star\* D Study Team. (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR\* D: implications for clinical practice. *The American Journal of Psychiatry*, 163(1), 28–40. <https://doi.org/10.1176/appi.ajp.163.1.28>
- Verhagen, A. P., de Vet, H. C., De Bie, R. A., Kessels, A. G., Boers, M., Bouter, L. M., & Knipschild, P. G. (1998). The Delphi list: A criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *Journal of Clinical Epidemiology*, 51(12), 1235–1241. [https://doi.org/10.1016/s0895-4356\(98\)00131-0](https://doi.org/10.1016/s0895-4356(98)00131-0)
- Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., Shibuya, K., Salomon, J. A., Abdalla, S., Aboyans, V., Abraham, J., Ackerman, I., Aggarwal, R., Ahn, S. Y., Ali, M. K., AlMazroa, M. A., Alvarado, M., Anderson, H. R., Anderson, L. M. ... Murray C. J. L. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *The Lancet*, 380(9859), 2163–2196. [https://doi.org/10.1016/S0140-6736\(12\)61729-2](https://doi.org/10.1016/S0140-6736(12)61729-2)
- Wang, J., Adair, C., Fick, G., Lai, D., Evans, B., Perry, B. W., Jorm, A., & Addington, D. (2007). Depression literacy in Alberta: Findings from a general population sample. *The Canadian Journal of Psychiatry*, 52(7), 442–449. <https://doi.org/10.1177/070674370705200706>
- Winick, R. L. (1999). Cranial electrotherapy stimulation (CES): A safe and effective low cost means of anxiety control in a dental practice. *General Dentistry*, 47(1), 50–55.
- Wolf, F., Brüne, M., & Assion, H.-J. (2010). Theory of mind and neurocognitive functioning in patients with bipolar disorder. *Bipolar Disorders*, 12(6), 657–666. <https://doi.org/10.1111/j.1399-5618.2010.00854.x>
- World Health Organization. (2017). *Depression and other common mental disorders: Global health estimates*. Geneva: World Health Organization, 24. <https://www.who.int/publications/i/item/depression-global-health-estimates>
- Wu, W.-J., Wang, Y., Cai, M., Chen, Y.-H., Zhou, C.-H., Wang, H.-N., & Cui, L.-B. (2020). A double-blind, randomized, sham-controlled study of cranial electrotherapy stimulation as an add-on treatment for tic disorders in children and adolescents.

*Asian Journal of Psychiatry*, 51, 101992. <https://doi.org/10.1016/j.ajp.2020.101992>

Zaghi, S., Acar, M., Hultgren, B., Boggio, P. S., & Fregni, F. (2010). Noninvasive brain stimulation with low-intensity electrical currents: Putative mechanisms of action for direct and alternating current stimulation. *The Neuroscientist*, 16(3), 285–307. <https://doi.org/10.1177/1073858409336227>

**Received:** June 15, 2023

**Accepted:** July 25, 2023

**Published:** September 30, 2023