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The Effectiveness and Risks of Cranial Electrical Stimulation for the Treatment of Pain, Depression, Anxiety, PTSD, and Insomnia: A Systematic Review

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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EXECUTIVE SUMMARY

ABSTRACT

Background

Cranial electrical stimulation (CES) is increasing in popularity as a treatment, yet of uncertain clinical benefit.

Purpose

To review evidence about the effectiveness and harms of CES for patients with chronic painful conditions, depression, anxiety, PTSD, and insomnia.

Data Searches

Searches of multiple databases from inception to 10/10/2017; reference-mining of included articles; recommendations from experts.

Study Selection

Randomized controlled trials of CES versus usual care or sham CES.

Data Extraction

Data extraction was performed in duplicate. The Principal Investigator performed the Strength of Evidence assessment.

Data Synthesis

28 relevant publications from 26 RCTs met eligibility criteria. Two small RCTs compared CES to usual care, neither reported a statistically significant benefit. Four old RCTs and one modern RCT provided low strength evidence of a possible benefit of CES compared to sham in patients with anxiety and depression. RCT results were conflicting for fibromyalgia, headache, other painful conditions, depression and insomnia. There is low strength evidence that CES does not cause serious side effects. All RCTs were judged to be at high risk of bias because of the possibility of unblinding of therapy.

Limitations

All RCTs were judged to be at high risk of bias; there were too few RCTs of the same patient population and intervention to support statistical pooling.

Conclusions

The evidence is insufficient to support conclusions that CES has clinically important effects on headache, fibromyalgia, neuromuscular pain, depression, PTSD, or insomnia. There is low-strength evidence for a possible beneficial effect of modest size in patients who have anxiety with depression. CES is probably safe, in that no serious side effects have been reported in RCTs, although reporting bias is present.

EVIDENCE REPORT

INTRODUCTION

Cranial electrical stimulation (CES) is a non-invasive method of applying low-intensity electrical current to the head. It is related to but distinct from other forms of transcranial electrical stimulation including electroconvulsive therapy, transcranial direct current stimulation (tDCS), and high-definition transcranial direct current stimulation. The different versions of transcranial electrical stimulation vary in the placement of electrodes, the intensity of the current, and the waveform of the current.[1] According to Guleyupoglu and colleagues, CES evolved from the concept of "electrosleep," first investigated at the beginning of the 20th century.[1] Most of the early research and applications occurred in Russia. Beginning in the 1960s, the concept of electrosleep became more popular in the USA. Because of the belief that the treatment did not actually induce sleep, but rather the sleep was a side effect of the relaxing effect of the current stimulation, the name was changed from "electrosleep" to "cranial electrical stimulation."[1] Other proposed names, which have not persisted, included "transcerebral electrotherapy" and "NeuroElectric Therapy." The latter is noteworthy because it gave its name to an early CES device, the Neurotone 101, which was the first device approved by the FDA.[1] All subsequent CES devices have been cleared for marketing by FDA based on the concept of claiming equivalency to the Neurotone 101. The status of cranial electrical stimulation devices and FDA regulation remains a matter of some controversy.

After an initial burst of research activity in the 1970s and early 1980s, published research on CES entered a quiescent phase, but then resumed and accelerated beginning about 2005. CES has been proposed as a therapy for anxiety, pain, insomnia, depression, headache, fibromyalgia, and numerous other conditions.[1] An early meta-analysis by Klawansky and colleagues[2] identified 8 sham-controlled RCTs for anxiety, two RCTs for brain dysfunction, two trials for headache and two trials for insomnia. Employing an effect size approach, which pooled studies across outcomes and types of CES, the authors found a statistically significant effect size of -0.58 (95% CI -0.95, -0.22) favoring active treatment for the anxiety outcome. Pooled effects for the other conditions showed no benefit for insomnia or brain dysfunction and a small beneficial effect for headache. The authors cautioned, however, that the quality of included studies was "quite low", due mostly to inadequate blinding. They concluded that larger, more rigorous studies were needed. Regarding the blinding, a more recent Cochrane review of CES in acute uncomplicated depression by Kavirajan and colleagues[3] restricted their eligibility criteria to RCTs with a convincing sham, diagnosis using standardized criteria, and assessments with validated rating instruments, and reported finding no studies of subjects with depression meeting these criteria.

The most commonly used CES devices in the USA are the Alpha-Stim products and the Fisher-Wallace Cranial Electrical Stimulator.[4] They differ in the location of the electrodes (ear clips in the former, sponge electrodes at the temples in the latter) and in the amount and type of current. Both are FDA-cleared for marketing for the treatment of anxiety, depression, and insomnia.

One driver for the resurgence in interest in CES has been the Department of Defense and Department of Veterans Affairs authorizing practitioners to prescribe CES for anxiety, post-traumatic stress disorder, insomnia, depression and headache. One survey of active duty service members and veterans reported on the responses from 152 subjects (a 10% response) rate, and found that 99% of respondents believed CES was effective and 99% considered CES to be safe.[5] Another VA study, that included CES among a number of alternative treatments for Veterans

with chronic pain, found a statistically significant decrease of 1.0 points (on a 0-10 point pain rating scale) in a pre/post study.[6] Anecdotal evidence suggests that the demand for CES devices among Veterans is increasing. This systematic review was requested by VA to review the RCT evidence for effectiveness in these conditions.

METHODS

TOPIC DEVELOPMENT

This topic was developed in response to a nomination by Joyce Edmondson, PSAS Clinical Program Manager, Office of Rehabilitation and Prosthetic Services (10P4R) and Friedhelm Sandbrink, MD, Deputy National Director, Pain Management, National Pain Management Program, Specialty Care Services (10P4E). Key questions were then developed with input from the topic nominator, the ESP coordinating center, the review team, and the technical expert panel (TEP).

The Key Questions were:

1: Compared to usual care, what is the effectiveness of cranial electrical stimulation (CES) for the following conditions: chronic pain, depression, anxiety, PTSD, and insomnia?

2: Compared to usual care, what are the risks of cranial electrical stimulation (CES) for the following conditions: chronic pain, depression, anxiety, PTSD, and insomnia?

The review was registered in PROSPERO: CRD42016023951.

SEARCH STRATEGY

We searched Cochrane (through 10/10/2017), PsycINFO (through 10/10/2017), and Embase (through 10/10/2017), and PubMed (through 10/10/2017) for relevant literature using key terms relating to the conditions of interest and cranial electrical stimulation intervention. We also searched for similar articles in PubMed through 10/10/2017 for three key publications.[7-9] The full search strategy is available in Appendix A. In addition to these searches, we also included references from expert recommendations, and searches of manufacturer websites or other material.

STUDY SELECTION

All titles were screened for retrieved citations by the Principal Investigator. Abstracts were then screened for relevant citations. For those abstracts deemed relevant, full-text articles were retrieved and screened against the following PICOTS framework, which describes our inclusion criteria:

Study design: Only randomized controlled trials were included

Population(s): Adult patients with one or more of the following conditions: a chronic pain condition, depression, anxiety, insomnia, and posttraumatic stress disorder (PTSD)

Intervention(s): Any cranial electrical stimulation (CES) device used in the home setting

Comparator(s): Usual care including appropriate known treatments

Outcome(s): Chronic pain: pain severity, use of opioid analgesic medication, quality of life, and daily functioning; Depression and anxiety: clinical assessments, scores on standardized

inventories; PTSD: symptom severity, quality-of-life measures, daily functioning; Insomnia: ability to initiate /maintain sleep, resolution of symptoms

Timing: No restrictions

Setting: Home setting, or office-based if needed for the conduct of the trial. Studies of hospitalized patients were excluded.

DATA ABSTRACTION

We abstracted data on the following: condition, description of patients, description of CES, description of sham, sample size, duration of treatment, assessment of blinding, and results. Many studies reported outcomes in multiple domains. We only extracted primary outcomes. In other words, if the study assessed patients with a painful condition, we extracted pain outcomes. If the study assessed patients with anxiety, we extracted anxiety outcomes, etcetera.

QUALITY ASSESSMENT

We assessed all included randomized controlled trials with the Cochrane Risk of Bias tool.[10] Each included study was ranked Low, Unclear, or High (green, yellow, and red, respectively) on seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. A full description of these domains is available in Appendix B. We judged that blinding was Low risk of bias only if a quantitative assessment was made of the blinding and similar proportions of subjects in each group believed they received active CES. We assessed risk of bias for the outcome assessment made nearest the end of the CES treatment.

DATA SYNTHESIS

For continuous outcomes, sample size, mean change, and its standard deviation were extracted for each CES group and comparator group within each trial. If the mean change was not reported for a trial, then data at baseline and follow-up were extracted and a mean change was estimated. To estimate the standard deviation of the mean change, both the baseline and follow-up standard deviations were used and adjusted for the dependence between the two by using a correlation of 0.5 (the midpoint). A standardized mean difference (SMD) and its 95% confidence interval (CI) were estimated comparing the mean change between the CES and comparator group. A SMD less than zero suggests that the CES group performed better than the comparator group. For binary data, the sample size, number or percent of patients with an event were extracted. A risk ratio (RR) and its 95% CI was estimated comparing the CES group to the comparator group.

A forest plot was created that included all studies with data capable of supporting an effect size analysis to facilitate visual comparison of results across studies and outcomes.

There were too few studies in any category of condition and specific CES device treatment to support meta-analysis. Therefore, our synthesis is narrative.

RATING THE BODY OF EVIDENCE

Where possible a summary of findings and quality of evidence table was used to summarize the existing evidence. Based on the GRADE working group,[11] the quality of the evidence was categorized as follows:

High: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Insufficient: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

GRADE evaluates the quality of the evidence across all identified studies contributing to the outcome of interest.

PEER REVIEW

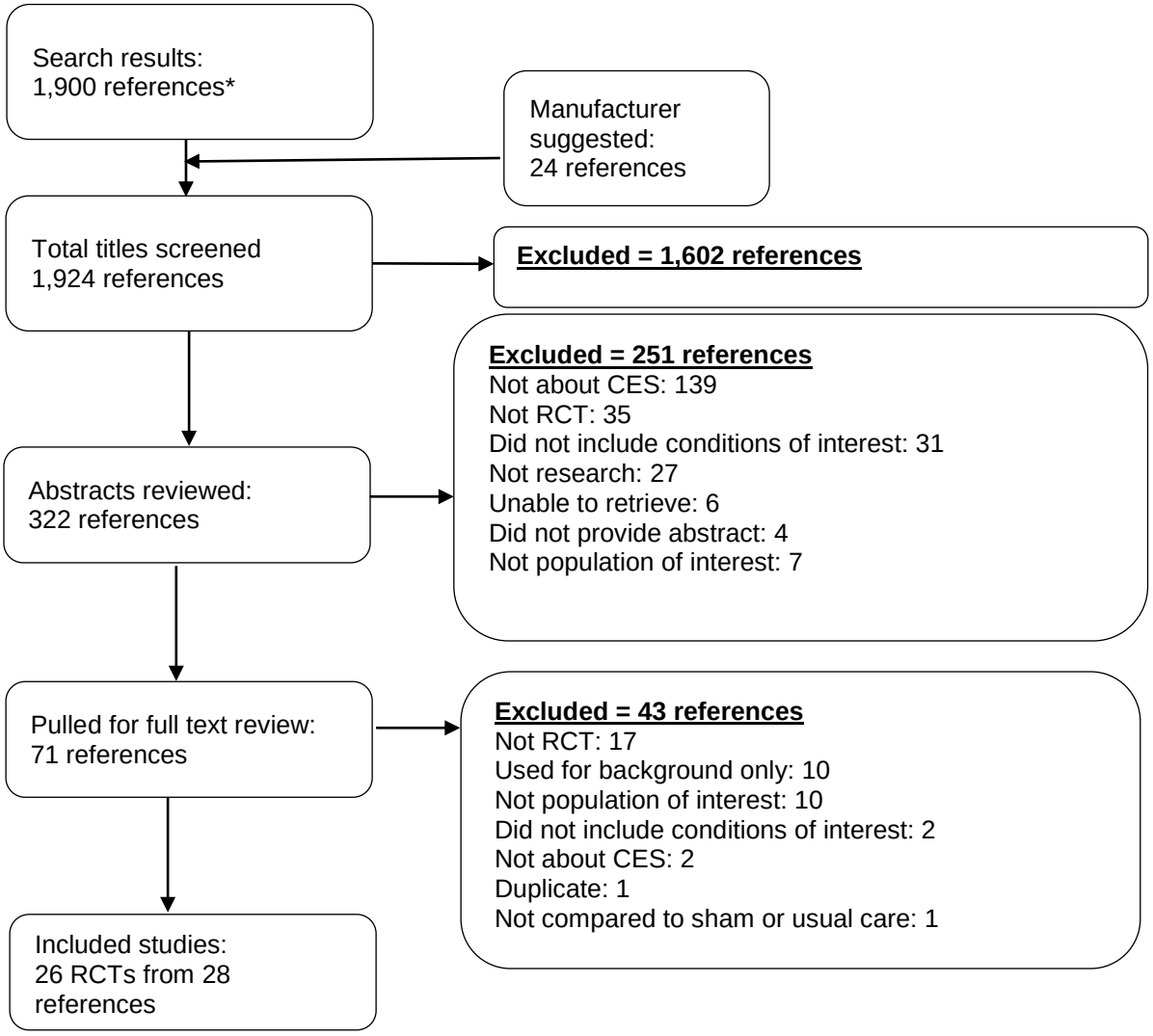
A draft version of the report was reviewed by technical experts and clinical leadership. Reviewer comments and our response are documented in Appendix C.

RESULTS

LITERATURE FLOW

Our literature searches and expert recommendations identified 1,924 potentially relevant citations, including articles screened in Russian, Italian, French, German, and Czech, of which 322 were included by the reviewer at the title screening. Of these, 71 abstracts were included and obtained as full-text publications. Two hundred fifty-one abstracts were excluded as not being about CES (n=139), not describing a RCT (n=35), not including the conditions of interest (n=31), not research (n=27), not population of interest (n=7), unable to retrieve (n=6), not providing any abstract for review (n=4) and not systematic review (n=2). A total of 28 publications met all eligibility criteria. The 43 excluded studies from the full-text review were excluded for the following reasons: 10 publications provided information relevant to background only (*eg*, description of various kinds of CES), 17 were not RCTs, 10 did not describe our population of interest (*eg*, pediatric or inpatient or some other condition), 2 did not include the conditions of interest, 2 were not about CES, one did not compare to sham or usual care, and one was a duplicate of another publication included for review. See Figure 1 for the literature flow. Details of included studies are provided in Appendix D. A full list of studies excluded at full-text review is included in Appendix E.

Figure 1. Literature Flow Chart



* Search results from PsycInfo, Cochrane, and PubMed, as well as expert recommendations

KEY QUESTION 1: Compared to usual care, what is the effectiveness of cranial electrical stimulation (CES) for the following conditions: chronic pain, depression, anxiety, PTSD, and insomnia?

We identified 28 published articles describing 26 RCTs of cranial electrical stimulation for the target conditions. There were 14 RCTs of patients with painful conditions,[9,12-25] 3 RCTs of patients with depression,[26-28] 5 RCTs of patients with depression and anxiety,[7,29-32] 2 RCTs of patients with insomnia,[8,33] and one RCT each of patients with anxiety and insomnia[34] and anxiety alone.[35] There were no RCTs of patients with PTSD. A variety of different cranial electrical stimulation devices were used. The Fisher-Wallace Cranial Stimulator device was used in 3 RCTs,[12,26,27] the Alpha-Stim unit was used in 12 RCTs,[7-9,14-18,20,21,23,28,35] the Pain Suppressor was used in 2 RCTs,[13,19] the Neurotone 101 was used in 3 RCTs,[29,32,34] the Electrosone-50 was used in 2 RCTs,[30,31] the Transcranial ElectroStimulator was used in 2 RCTs,[24,25] the Electrodorm 1 was used in one RCT,[33,36] and a custom-built device was used in one RCT.[22] The full details of each included study are reported in the Evidence Table (Appendix D). For studies providing data that could be used to calculate an effect size, these are presented in a forest plot in Figure 2.

The studies had many methodologic limitations. No RCT was judged to have acceptably blinded patients, as assessed by asking patients after the study was completed whether they believed they had received active therapy or placebo, and finding equivalent proportions in each group. This is consistent with the finding of a Cochrane Review on the topic, which set its inclusion criteria as being properly blinded studies, and finding none.[3] This places all identified RCTs at high risk of bias. Furthermore, 21 of the RCTs enrolled fewer than 30 subjects in each group, limiting confidence that the principal goal of randomization – the balancing between groups of all variables, both measured and unmeasured – had been achieved. Table 1 shows the quality assessments for each included study.

Table 1. Risk of Bias Assessment for Included Studies

Author, year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Barclay et al, 2014[7]	◒	●	◒	◒	●	●	●
Cork et al, 2004[21]	◒	◒	◒	◒	●	●	◒
Feighner et al, 1973[30]	◒	◒	◒	◒	●	●	◒
Gabis et al, 2003[24]	●	●	◒	◒	●	●	○
Gabis et al, 2009[25]	●	●	◒	◒	◒	●	◒
Gibson et al, 1987[35]	◒	◒	◒	◒	●	●	◒
Hearst et al, 1974[29]	◒	◒	◒	◒	◒	●	◒
Heffernan et al, 1997[20]	◒	◒	◒	◒	●	●	○
Katsnelson et al, 2004[22]	◒	◒	◒	◒	●	●	○
Lande et al, 2013[8]	●	●	◒	◒	●	●	●
Lichtbroun et al, 2001[15]	●	●	◒	◒	◒	●	◒
McClure et al, 2015[27]	●	●	◒	◒	◒	●	◒
Mischoulon et al, 2015[26]	●	●	◒	◒	●	●	◒
Moore et al, 1975[34]	◒	◒	◒	◒	◒	●	◒
Rintala et al, 2010	◒	◒	◒	◒	○	●	●
Rosenthal, 1972[31]	◒	◒	◒	●	◒	●	◒
Scallet et al, 1976[32]	◒	◒	◒	◒	●	●	◒
Solomon et al, 1989[13]	◒	◒	◒	◒	●	●	●
Solomon et al, 1985[19]	◒	◒	◒	◒	●	●	◒
Tan et al, 2000[18]	◒	◒	◒	◒	○	●	◒
Tan et al, 2011[16]	●	●	◒	◒	●	●	●
Tan et al, 2006[17]	◒	◒	◒	◒	●	●	◒
Taylor, et al., 2013[14] Taylor, et al., 2013[9]	◒	◒	◒	◒	●	●	◒
Tietjen, et al., 2013[12]	◒	◒	◒	◒	◒	●	◒
Turner, 2016[28]	◒	●	◒	◒	◒	◒	◒
Weiss, 1973[33] Cartwright, 1975[36]	◒	◒	◒	◒	●	●	◒

- ● = Low, ◒ = Unclear, ○ = High

CES Compared to Usual Care

We identified 2 RCTs that compared the use of CES to usual care, that is, not adding a placebo intervention. The first trial was a 3-arm comparison of cranial electrical stimulation using an Alpha-Stim device in 57 patients with fibromyalgia, who were randomized to active CES (N=17 completing the study), sham CES (N=14) or usual care alone (N=15).[9,14] Patients were recruited from community rheumatology practices, and had to meet American College of Rheumatology criteria for fibromylagia, have a pain score of 3 or greater on a 10 point numeric rating scale, and be on stable medications for at least 4 weeks. The enrolled sample was 95% female and 89% white, with a mean age of 50.8 years, with an average pain score of 5.8. Subjects in the active and sham group were instructed to use their machine for 60 minutes a day for 8 weeks. The sham devices had been set by the manufacturer to look and act identical to the active devices except that the sham devices did not deliver any stimulation. Over the 8 week course of the study, pain scores in the sham-treated patients and the usual care patients went up slightly, whereas the pain score of the active CES-treated patients declined (about 1 point). According to the authors' analysis of the slope of the lines of the daily pain scores, the difference between the active CES-treated patients and the other 2 groups was statistically significant (p=.023). However, our analysis of their data did not show a statistically significant difference in average pain between groups (effect size = -0.57, 95% CI -1.28, 0.14).

The second study was a 4-arm study of cranial electrical stimulation using an Alpha-Stim device in 64 persons recruited via newspaper advertisements and scoring over 50 on the state anxiety scale of the State-Trait Anxiety Inventory. Subjects were randomized to a single 20-minute session of CES, relaxation instructions, both, or neither. After a single session, there was no difference in the reduction in state anxiety score between subjects receiving CES or relaxation instructions (22.2 vs 20.7 respectively). Both active treatment groups had greater reductions than patients who got neither (reduction of 1.3). This study was 30 years old.[35]

CES Compared to Treatments Including Sham CES

The remainder of the included studies assessed active CES to a control group receiving sham CES, or in one case, an electrical stimulator believed to be inactive. Almost all the studies included patients who were actively being treated with other therapies for their conditions. However, 7 of the studies are more than 25 years old,[13,29-31,33-35] making any comparison to patients also receiving active treatment subject to the change over time in how these conditions have been treated.

CES for Painful Conditions

We identified 15 published studies describing 14 RCTs of CES for painful conditions. There were 3 RCTs of patients with headache,[12,13,19] 3 RCTs of patients with fibromyalgia (one of these has already been presented in the section above),[9,14,15,21] 2 RCTs of patients with pain following spinal cord injury (SCI),[16,17] 2 RCTs of patients with painful degenerative joint disease,[20,22] 2 RCTs of patients with cervical pain, chronic low back pain, or headaches,[24,25] one RCT of patients with chronic neuromuscular pain [18], and one RCT of Parkinson's patients with chronic musculoskeletal pain.[23] Two studies were more than 25 years old.[13,19,20] In 8 RCTs CES was delivered with the Alpha-Stim device, in 2 headache studies the CES was delivered with the Pain Suppressor unit, in one RCT the CES was delivered with the Fisher Wallace Cranial Stimulator unit, in 2 RCTs the CES was delivered with the Transcranial ElectroStimulator, and in one RCT the CES was delivered with a custom-built device.

All 3 studies of patients with fibromyalgia reported statistically significant benefits in active CES with an Alpha-Stim device as compared to sham treated patients, of modest size in 2 RCTs,[9,14,21] and of larger size in one other.[15] No study reported what constituted the usual care for the patients with fibromyalgia, only that their medication dose was stable for at least 4 weeks or no report at all. In one study our analysis of the reported data did not show a statistically significant difference in average pain between active and sham-treated groups (effect size = -0.27, 95% CI -0.98, 0.44). One study was co-authored by an employee of the manufacturer of the CES device.

In 3 studies explicitly of VA populations, and all with the same first author, use of the Alpha-Stim device was not associated with statistically significantly differences in pain score among patients with SCI-associated pain or chronic neuromuscular pain.[16-18] One study included only 11 patients, however, and was therefore too small to detect anything other than large effects (although the change score in pre-post pain was almost identical between groups, -0.45 vs -0.36 for active and sham-treated patients respectively, which does not suggest a much larger sample size might have detected an effect of at least moderate size). In the second study, while the average pain score on the 0-10 Numeric Pain Scale was no different at the end of the intervention between patients receiving active versus sham CES, the matched pre-post difference in pain rating before and after the CES session did show a statistically significant benefit favoring CES. In the largest of these 3 studies, 105 patients with SCI-associated pain of at least 6 months duration at or below the level of the injury and a pain score of at least 5 (on a 10 point scale) were randomized to receive either one hour of daily CES or sham CES for 21 days.[16] Daily pain scores showed no difference between groups in changes in pain score over time ($p>.90$).

We identified 3 RCTs[12,13,19] involving the use of CES for patients with headache. One RCT, which is 29 years old, evaluated the use of the Pain Suppressor in 100 patients with "tension headaches occurring alone or as part of migraine."[13] The second RCT, by the same first author and 33 years old, enrolled 40 patients with "migraine or muscle contraction headaches or both", and also delivered CES using the Pain Suppressor.[19] The third RCT was published only in abstract form and evaluated the use of the Fisher Wallace Cranial Stimulator in 50 patients with chronic migraine headache.[12] The first two RCTs reported a beneficial effect of CES in terms of the patient's global evaluation (in the first RCT) and on a numeric pain rating scale (in the second RCT, where CES was given only once and during the headache), whereas the latter study reported no statistically significant effects for CES. In the former study, what constituted usual care for the patients with tension headache was not described, other than "patients had a history of tension headaches requiring analgesic agents for at least one year prior to entry."

We identified 5 studies of CES for patients with chronic musculoskeletal pain or painful degenerative joint disease.[20,22-25] In one study, a single 5-minute session of CES produced a greater change on a 5-point pain scale than a 5-minute session with a device that produced a constant 0.5Hz square wave electrical current, which the authors considered a "control".[20] In another study of 13 patients with Parkinson's disease and chronic musculoskeletal pain treated with the Alpha-Stim device or sham found no statistically significant benefit of CES.[23] Gabis and colleagues reported 2 studies involving patients admitted to their pain clinic who received 8 consecutive days of 30-minute treatments with either the Transcranial ElectroStimulator or with an active placebo with a 50-Hz signal delivered with a device described as indistinguishable from the CES device.[24,25] One of these studies enrolling 20 patients with chronic back or cervical pain reported similar decreases in pain levels between groups after the first 30-minute treatment session (longer term outcomes were not reported).[24] The second study by Gabis and colleagues enrolled 119 patients, of whom 75 (63%) had chronic cervical or back pain (n=33), and reported

statistically significant pain improvements of about 1-2 points on a 10-point pain scale between patients treated with CES as compared to active-placebo, measured 3 weeks after the end of treatment.[25] The fifth trial involving 64 adults with hip or knee osteoarthritis found no statistically significant benefit for a CES machine custom built by the investigators compared with a sham device that delivered no current.[22]

Summary

We identified a small number of RCTs of the use of CES for a handful of painful conditions: fibromyalgia, headache, SCI-associated pain, painful degenerative joint disease, cervical pain and chronic low back pain, chronic musculoskeletal pain, and chronic neuromuscular pain. Studies were at high risk of bias, and results were mixed.

CES for Depression

We identified 3 RCTs of CES for patients with depression or depressive symptoms.[26-28] The Evidence Table presents details of these studies (Appendix D). Two studies used the Fisher Wallace Cranial Stimulator unit. One study enrolled patients with major depressive disorder (MDD) that was treatment-resistant, and with an average HAM-D score of 18.4. The other enrolled patients with bipolar depression, not diagnosed as treatment-resistant, and with a mean HAM-D score of 19.6. In both studies, patients were randomized to active CES or to a sham, in one case by having an inactive unit and in the other by having an operator turning off the current after first turning it on so the patient felt a tingling in the scalp. In the first study, treatment was delivered for 20 minutes for 5 days each week for 3 weeks, and could also be self-administered on a daily basis, and in the second study treatment was 20 minutes daily for 2 weeks. Both studies were small, 40 subjects in the study of MDD and 16 subjects in the study of bipolar depression. The study of patients with MDD reported no difference between groups in HAM-D scores over time, with values nearly identical in active and sham-treated patients. The study of patients with bipolar depression found no difference between groups in HAM-D scores at one week, but a non-statistically significant 1.8 point difference in scores at 2 weeks, and a statistically significant 8 point difference in the Beck Depression Inventory at 2 weeks. Both studies were considered to be at high risk of bias. The study of patients with depressive symptoms used the Alpha-Stim unit, and randomized community-recruited volunteers to active versus sham CES.[28] There was no difference between groups in change in Beck Depression Inventory outcomes at 3 weeks (Figure 2). This study was considered to be at high risk of bias.

Summary

Three small studies of CES for patients with depression or depressive symptoms found somewhat different results. However, the studies had differences in their patient populations, the implementation of the sham, and the delivery of the CES (self-administration vs operator-administered), and the degree to which any of these, or chance, contributed to the difference in observed outcomes is unknown. All three RCTs were judged to be at high risk of bias.

CES for Anxiety and Depression

We identified 5 RCTs of CES used for patients explicitly identified as having anxiety and depression.[7,29-32] Four of these RCTs are more than 40 years old, and each studied fewer than 30 patients.[29-32] In general, these trials reported favorable results with use of CES, but as the standard of care of these conditions has changed greatly in the intervening 40 years, the criteria for the diagnosis of anxiety were either vague or no longer in use, and the CES devices used are

no longer available (Neurotone 101 and Electrosone 50), we do not present their results here. Details are in the Evidence Table in Appendix D. The largest study of this patient population enrolled 115 patients meeting DSM-IV criteria for anxiety, confirmed using the SCID-I, and with a baseline Hamilton Anxiety score of > 15. Twenty-three of these patients also had comorbid depression. Usual care for patients included antidepressants as long as the medication and dose were stable for at least 3 months. Benzodiazepine use was only allowed on a PRN basis and not taken more than twice a week. The enrolled population was two-thirds female and had a mean age of 42 years. Prescription medications were being used by 64% of the subjects. Generalized anxiety disorder was diagnosed in 53% and anxiety disorder was diagnosed in 7%. Comorbid depression and PTSD were diagnosed in 20% and 11% respectively. The baseline HAM-A and HAM-D scores were about 29 and 14. Patients were randomly assigned to an active Alpha-Stim 100 CES unit or a unit made inactive by the manufacturer, and told to treat themselves daily for one hour, for 5 weeks. Between 85% and 90% of subjects in both groups completed the 5-week study. Weekly measurements of HAM-A and HAM-D showed a steady decline (improvement) in both groups over time, but the declines were greater for the patients treated with active CES, being about 6.5 points on the HAM-A score and 3.5 points on the HAM-D score at 5 weeks, differences that in both cases were statistically significant. The study authors stated the CES machines were supplied by the manufacturer, and that no funding was obtained for the study, which was conducted in a private practice setting.

Summary

We identified 5 RCTs of patients with anxiety and depression, but 4 were more than 40 years old and probably do not provide evidence relevant for contemporary practice. The most recent study found statistically significant benefits of modest size in standard scales of anxiety and depression severity over a short period of time (5 weeks).

CES for PTSD

We identified no published RCTs that assessed the use of CES for patients with PTSD as the primary diagnosis (some studies, above, did include a small percentage of patients with PTSD as a comorbid diagnosis).

CES for Insomnia

We identified 2 RCTs of CES for the treatment of insomnia.[8,33,36] One study is more than 40 years old, used a CES device that is no longer marketed (the Electrodorm I), and recruited subjects through newspaper advertising for persons who chronically had "trouble falling asleep."[33,36] These patients' usual care, or prior care, for their symptoms was not described, and as the treatment of insomnia has changed during the intervening 40 years we judged we could draw no conclusions from this study about the value of CES compared to contemporary usual care. Details of the study are presented in the Evidence Table in Appendix D. The second RCT was published in 2012, and assessed 57 active-duty military personnel who scored at least 21 on the Pittsburgh Insomnia Rating Scale, and who did not have any of a series of exclusionary conditions (actively suicidal, seizure disorder, pregnancy, cardiac pacemaker, etc.). These subjects' prior care or usual care was not described. CES was delivered with the Alpha-Stim unit, of which the manufacturer supplied 10 active and 10 inactive units. Subjects used the unit for 60 minutes a day for 5 days. There were no statistically significant differences between groups in the time to sleep, the total time slept, and the number of awakenings per night.[8]

Summary

One very old and one more modern RCT do not provide evidence supporting the efficacy of CES for decreasing the symptoms of insomnia compared to usual care.

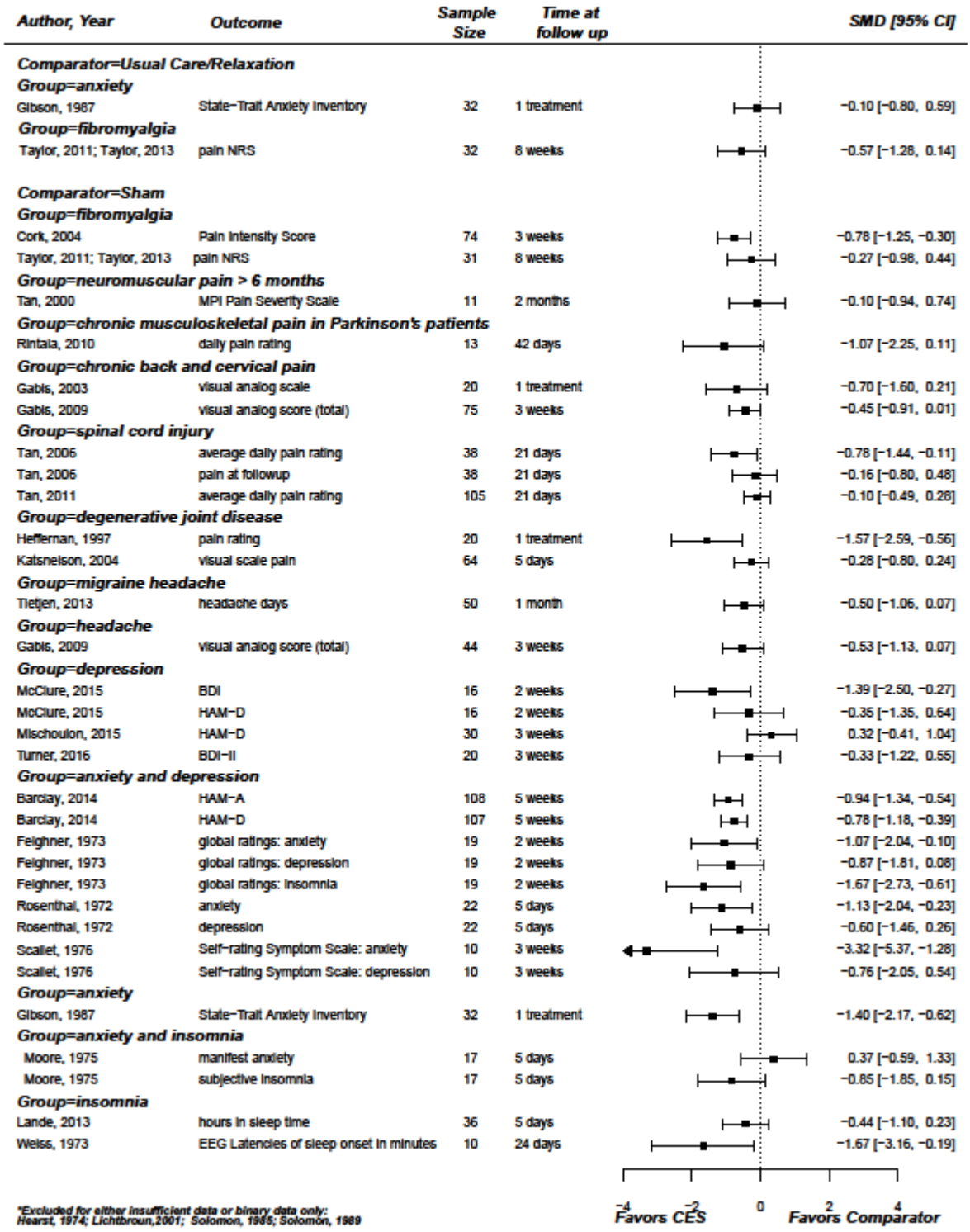
CES for Anxiety and Insomnia

We identified a single RCT of the use of CES for subjects "suffering from persistent anxiety and insomnia" without "evidence of a psychosis, or an organic psychosyndrome."[34] This study was more than 40 years old, and used a CES device which is no longer marketed (the Neurotone). Other than stating that "all subjects who were taking medication before treatment were told that this should remain unchanged for the duration of the trial" these subjects' prior or usual care for their symptoms was not described. Because the treatment of these conditions has changed over the past 40 years, we judged we could draw no conclusions from this study about the value of CES compared to contemporary usual care.

CES for Anxiety

We identified one 30 year old study that compared CES, relaxation instructions, both, or neither, in recruited subjects who scored 50 or higher on the state anxiety scale of the State-Trait Anxiety Inventory, in a single 20-minute session. Compared to receiving nothing, subjects treated with 20 minutes of CES reported a greater reduction in state anxiety score (22.2 vs 1.3).[35] We could draw no conclusions from the trial as a treatment for anxiety since there was no follow-up longer than the single session.

Figure 2. Randomized clinical trials of cranial electrical stimulation for various conditions



Quality of Evidence for Key Question 1

The quality of evidence is presented in Table 2. For most conditions, we judged the quality of evidence as being Insufficient, meaning that we cannot even estimate the measure of effect. For

one clinical situation we judged the quality of evidence as Low, meaning the true effect may be very different than the estimate of effect. This situation was:

CES may have a modest beneficial effect on symptoms of anxiety and depression in selected patients (SOE = LOW).

Table 2. GRADE Quality of Evidence Table

Condition	Number of Studies, Number of participants	Study Limitations	Consistency	Directness	Precision	Quality of Evidence
Painful Conditions						
Headache	3 RCTs; 190	Serious Limitations	Serious Inconsistency	Direct	Serious Imprecision	Insufficient
Fibromyalgia	3 RCTs; 191	Serious Limitations	Serious Inconsistency	Direct	Serious Imprecision	Insufficient
Pain with Spinal Cord Injury	2 RCTs; 143	Serious Limitations	Serious Inconsistency	Direct	Serious Imprecision	Insufficient
Neuromusculoskeletal Pain	4 RCTs; 174	Serious Limitations	Serious Inconsistency	Direct	Serious Imprecision	Insufficient
Degenerative Joint Disease	2 RCTs; 84	Serious Limitations	Serious Inconsistency	Direct	Serious Imprecision	Insufficient
Depression						
MDD Treatment – Resistant	1 RCT; 30	Serious Limitations	N/A	Direct	Serious Imprecision	Insufficient
Bipolar Depression	1 RCT; 16	Serious Limitations	N/A	Direct	Serious Imprecision	Insufficient
Anxiety and Depression	5 RCTs; 198	Serious Limitations	Consistent	Direct	Serious Imprecision	Low
Anxiety & Insomnia						
Insomnia	2 RCTs; 67	Serious Limitations	Serious Inconsistency	Direct	Serious Imprecision	Insufficient
Anxiety and Insomnia	1 RCT; 17	Serious Limitations	N/A	Direct	Serious Imprecision	Insufficient
Anxiety	1 RCT; 64	Serious Limitations	N/A	Indirect	Serious Imprecision	Insufficient

KEY QUESTION 2: Compared to usual care, what are the risks of cranial electrical stimulation (CES) for the following conditions: chronic pain, depression, anxiety, PTSD, and insomnia?

Of the 26 RCTs included in our review, 16 did not report any assessment of adverse events or safety.[7,8,15,17-22,28,29,31-35] Ten RCTs did report data about adverse events or safety.[9,12,13,16,23-27,30] The details of the adverse events that were reported are presented in Table 3. In one early study, 4 patients receiving active CES had worsening depression, including the need for hospitalization for 2 of them.[30] These authors concluded their data suggested that CES may not be appropriate for patients with depression. However, more recent studies of depression, including more than 200 patients studied, have not reported similar results. It is likely the earlier studies findings were due to chance, or less likely perhaps might have been related to the CES unit used – the Electrosone 50 – which is no longer in use. Outside of this one report, the only adverse events that seem to be reported more commonly in actively treated patients than in sham-treated patients are mild tingling or skin irritation, tiredness/malaise/sleepiness, and possibly transient visual symptoms.

Table 3. Adverse Events of CES

Author	Side Effect
Feighner[30]	4 patients, all receiving active treatment, had to be withdrawn from the study due to "massive worsening of depressive symptoms"; 2 required hospitalization.
Gabis[24]	No significant adverse events were noted
Gabis[25]	No adverse events or side effects resulting from treatment have been reported
McClure[27]	No EEG or EKG abnormalities observed. No significant difference in drowsiness, blurred vision, dizziness, or headache between groups
Mischoulon[26]	No withdrawals due to AE. "Poor concentration" and "malaise" were statistically significantly more common in the CES group. 29% of the CES group reported "mild flashing light" in the peripheral vision and/or tingling sensation at the temples, this was not a statistically significant difference from the 0% reporting these symptoms in the control group.
Rintala[23]	Active CES users (n=6) reported pulsing, trickling, or tingling sensations on ears (n=3), tender ears (n=1), pins-and-needles sensation near the bladder (n=1). Sham CES users (n=7) reported drowsiness (n=1), warm ears (n=1), and headache after one session (n=1). No serious study-related adverse events occurred during the study.
Solomon[13]	11% vs 13% of patients in active vs sham-treatment groups reported adverse events
Tan[16]	29% vs 11% and 17% vs 7% of active vs sham-treated patients reported "ears pulse, tingle, sting, itch, small electric feeling, ear clips too tight" and "drowsy, sleepy, fell asleep, relaxing", respectively (not statistically significant different)
Taylor[9]	No difference in blood pressure between groups; investigators were worried about blood pressure effects of CES
Tietjen[12]	Scalp irritation in 1 acute and 2 sham treated patients, dizziness in 2 active treated patients, visual flickering and worsening of headache in 6 and 3 active treated patients. No statistical testing performed.

Quality of Evidence for Key Question 2

Outside of one old study whose findings have not been repeated, there have been no serious adverse events from the use of CES. Minor symptoms, particularly tingling or skin irritation, are common (and are in fact one of the signs used to indicate current is being transmitted by the unit). However, the total number of patients studied is small, and most RCTs of CES have not systematically reported adverse events. We judged the quality of evidence for the conclusion that CES does not cause serious adverse events but does cause certain minor symptoms as low, downgraded from moderate due to the possibility of the reporting bias (less than 50% of studies of effectiveness included any reporting of adverse events).

SUMMARY AND DISCUSSION

The principal conclusions of this systematic review are that the evidence is insufficient to support conclusions that CES has clinically important effects on headache, fibromyalgia, neuromuscular pain, depression, PTSD, or insomnia. There is low-strength evidence for a possible beneficial effect of modest size in patients who have anxiety with depression. CES is probably safe, in that no serious side effects have been reported, although reporting bias is present.

SUMMARY OF EVIDENCE BY KEY QUESTION

Key Question 1: Compared to usual care, what is the effectiveness of cranial electrical stimulation (CES) for the following conditions: chronic pain, depression, anxiety, PTSD, and insomnia?

CES may have a modest beneficial effect on symptoms of anxiety and depression in selected patients (SOE = LOW).

Key Question 2: Compared to usual care, what are the risks of cranial electrical stimulation (CES) for the following conditions: chronic pain, depression, anxiety, PTSD, and insomnia?

CES does not cause serious adverse events but does cause certain minor symptoms (SOE = LOW).

LIMITATIONS

Publication Bias

We were not able to test for publication bias and can make no conclusions about its possible existence.

Study Quality

The principal limitation to this review is the quality of the original RCTs. With all RCTs at high risk of bias, even the few signals of benefits are suspect.

Heterogeneity

Heterogeneity is a limitation of this review as there were too few studies of the same patient and treatment to support statistical pooling.

Applicability of Findings to the VA Population

Several studies were specifically of VA populations and for those studies the applicability of findings is direct. Many other studies, however enrolled populations that differ from VA in gender and probably comorbidities (probably fewer comorbidities than VA populations) rendering their applicability to VA only moderate.

RESEARCH GAPS/FUTURE RESEARCH

The biggest research gap and need for future research is adequately blinded studies of sufficient size to detect clinical benefits of moderate size. While the sample size depends on the specific

outcome being assessed, a reasonable rule-of-thumb would be 60 patients per group. Given that VA has many patients with pain, depression, anxiety, PTSD, and insomnia, and given that these studies may be relatively short in duration (6 months), it should be very feasible for VA to mount a program of research to answer the questions about effectiveness and safety, and answer these questions within a few years (2 – 4 years). As part of this evaluation, it would also be useful to understand whether any possible benefit persists after treatment discontinuation, or whether relapse in symptoms occur, and the timing of relapse. If CES is shown to have benefit compared to sham, then comparative effectiveness studies that assess CES compared to other proven active therapies for these conditions is warranted. Finally, long-term studies of safety may be needed.

CONCLUSIONS

The evidence for the effectiveness and safety of CES is sparse. There is low strength evidence of a modest benefit in patients with anxiety and depression. CES is probably safe, but strength of evidence is low since few RCTs report adverse events. It should be feasible for VA to obtain better quality data to answer these questions through a series of RCTs with adequate blinding.

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APPENDIX A. SEARCH STRATEGIES

CRANIAL ELECTRIC STIMULATION – SEARCH METHODOLOGY

DATABASE SEARCHED: PubMed

SEARCH STRATEGY #1:
TIME PERIOD COVERED: from inception to 2/1/2016
LANGUAGE: English

"cranial electrical stimulation"(tiab) OR cranial electric stimulat*(tiab) OR electrotherap*(tiab) OR fisher wallace stimulat*(tiab) OR alpha-stim(tiab)

SEARCH STRATEGY #1A (update to Search #1):
TIME PERIOD COVERED: 1/1/2016-7/12/2017
LANGUAGE: English

"cranial electrotherapy" OR cranial electric stimulat* OR cranial electrical stimulat* OR alpha-stim OR fisher wallace stimulat*

SEARCH STRATEGY #2:
TIME PERIOD COVERED: from inception to 7/12/2017
LANGUAGE: ALL

Electrosleep OR "Transcerebral electrotherapy" OR "Neuroelectric therapy"

SEARCH STRATEGY #3:
TIME PERIOD COVERED: from inception to 7/17/2017
LANGUAGE: English

Similar Article searches on the following articles:
A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression
Timothy H. Barclay a,n, Raymond D. Barclay b, Journal of Affective Disorders 164 (2014) 171–177

Alfred G. Bracciano , Wen-Pin Chang , Stephanie Kokesh , Abe Martinez ,Melissa Meier & Kathleen Moore (2012) Cranial Electrotherapy Stimulation in the Treatment of Posttraumatic Stress Disorder: A Pilot Study of Two Military Veterans, Journal of Neurotherapy, 16:1, 60-69, DOI: 10.1080/10874208.2012.650100 –
NOT IN PUBMED

Efficacy of cranial electric stimulation for the treatment of insomnia: A randomized pilot study
R. Gregory Lande,∗, Cynthia Gragnanib
Complementary Therapies in Medicine (2013) 21, 8—13

Cranial electrical stimulation improves symptoms and functional status in individuals with fibromyalgia

Cranial electrical stimulation improves symptoms and functional status in individuals with fibromyalgia
Taylor, A. G., Anderson, J. G. Riedel, S. L. Lewis, J. E. Kinser, P. A. Bourguignon, C.
Pain Manag Nurs, (2013) 14(4), 327-335

SEARCH STRATEGY #4:
TIME PERIOD COVERED: from inception to 10/10/17
LANGUAGE: English

"transcranial electrical stimulation"(Title) OR "transcranial electric stimulation"(Title)

DATABASE SEARCHED: PsycINFO

SEARCH STRATEGY #1
TIME PERIOD COVERED: from inception to 2/4/2016
LANGUAGE: English

S1 TI ("cranial electrotherapy" OR "cranial electric stimulation" OR "cranial electrical stimulation") OR SU ("cranial electrotherapy" OR "cranial electric stimulation" OR "cranial electrical stimulation") OR AB ("cranial electrotherapy" OR "cranial electric stimulation" OR "cranial electrical stimulation") OR (SU electrical stimulation AND (brain OR cranial OR transcranial))
AND
TI (pain OR painful OR depression OR depressive OR anxiety OR anxiety disorders(mh) OR post-traumatic stress OR posttraumatic stress OR "post traumatic stress" OR ptsd OR insomnia OR sleep* OR fibromyalgia) OR SU (pain OR painful OR depression OR depressive OR anxiety OR anxiety disorders(mh) OR post-traumatic stress OR posttraumatic stress OR "post traumatic stress" OR ptsd OR insomnia OR sleep* OR fibromyalgia) OR AB (pain OR painful OR depression OR depressive OR anxiety OR anxiety disorders(mh) OR post-traumatic stress OR posttraumatic stress OR "post traumatic stress" OR ptsd OR insomnia OR sleep* OR fibromyalgia)

OR

TI ("fisher wallace stimulation" OR alpha-stim) OR SU ("fisher wallace stimulation" OR alpha-stim) OR AB ("fisher wallace stimulation" OR alpha-stim)

SEARCH STRATEGY #1A (update to Search #1):
TIME PERIOD COVERED: 1/1/2016-7/12/2017
LANGUAGE: English

TI ("cranial electrotherapy" OR "cranial electric stimulation" OR "cranial electrical stimulation") OR SU ("cranial electrotherapy" OR "cranial electric stimulation" OR "cranial electrical

stimulation") OR AB ("cranial electrotherapy" OR "cranial electric stimulation" OR "cranial electrical stimulation") OR SU (electrical stimulation AND (brain OR cranial OR transcranial)) OR TI ("fisher wallace stimulation" OR alpha-stim) OR SU ("fisher wallace stimulation" OR alpha-stim) OR AB ("fisher wallace stimulation" OR alpha-stim)
AND
TI (pain OR painful OR depression OR depressive OR anxiety OR post-traumatic stress OR posttraumatic stress OR "post traumatic stress" OR ptsd OR insomnia OR sleep* OR fibromyalgia) OR SU (pain OR painful OR depression OR depressive OR anxiety OR post-traumatic stress OR posttraumatic stress OR "post traumatic stress" OR ptsd OR insomnia OR sleep* OR fibromyalgia) OR AB (pain OR painful OR depression OR depressive OR anxiety OR post-traumatic stress OR posttraumatic stress OR "post traumatic stress" OR ptsd OR insomnia OR sleep* OR fibromyalgia)

SEARCH STRATEGY #2:
TIME PERIOD COVERED: from inception to 7/12/2017
LANGUAGE: ALL

TI (Electrosleep OR "Transcerebral electrotherapy" OR "Neuroelectric therapy") OR SU((Electrosleep OR "Transcerebral electrotherapy" OR "Neuroelectric therapy") OR AB ((Electrosleep OR "Transcerebral electrotherapy" OR "Neuroelectric therapy")

SEARCH STRATEGY #3:
TIME PERIOD COVERED: from inception to 10/10/17
LANGUAGE: English

TI ("transcranial electrical stimulation" OR "transcranial electric stimulation")

DATABASE SEARCHED: Cochrane databases

SEARCH STRATEGY
TIME PERIOD COVERED: from inception to 2/4/2016
LANGUAGE: English

SEARCH STRATEGY #1
("cranial electrotherapy" or "cranial electric stimulation" or "cranial electrical stimulation":ti,ab,kw) OR (electrical stimulation and (brain or cranial or transcranial)):ti,ab,kw OR ("fisher wallace stimulation" or alpha-stim):ti,ab,kw (Word variations have been searched)
AND
pain or painful or depression or depressive or anxiety or anxiety disorders (mh) or post-traumatic stress or posttraumatic stress or "post traumatic stress" or ptsd or insomnia or sleep* or fibromyalgia:ti,ab,kw (Word variations have been searched)

SEARCH STRATEGY #1A (update to Search #1)
DATABASE SEARCHED: Cochrane CENTRAL

TIME PERIOD COVERED: 1/1/2016-7/12/2017

LANGUAGE: English

'"cranial electrotherapy" or "cranial electric stimulation" or "cranial electrical stimulation" in Title, Abstract, Keywords

SEARCH STRATEGY #2:
TIME PERIOD COVERED: from inception to 10/10/17
LANGUAGE: English

"transcranial electrical stimulation" or "transcranial electric stimulation" in Record Title

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DATABASE SEARCHED: Embase

SEARCH STRATEGY #1:
TIME PERIOD COVERED: From inception to 7/12/2017
LANGUAGE: English

'cranial electrotherapy' OR 'cranial electric stimulation' OR 'cranial electrical stimulation' OR 'fisher wallace stimulation' OR 'alpha stim'/exp OR 'alpha stim'
AND
(humans)/lim

SEARCH STRATEGY #2:
TIME PERIOD COVERED: from inception to 7/12/2017
LANGUAGE: ALL

'electrosleep'/exp OR electrosleep OR 'transcerebral electrotherapy' OR 'neuroelectric therapy'
AND
(humans)/lim

SEARCH STRATEGY #3:
TIME PERIOD COVERED: from inception to 10/10/17
LANGUAGE: English

'transcranial electrical stimulation':ti OR 'transcranial electric stimulation':ti

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NOTE: ADDITIONAL FILTERS FOR ANIMAL-ONLY STUDIES WERE APPLIED IN ENDNOTE

APPENDIX B. CRITERIA USED IN QUALITY ASSESSMENT

The Cochrane Collaboration's Tool for Assessing Risk of Bias*

Domain	Support for judgement	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes).*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

* http://handbook.cochrane.org/ in Table 8.5.a

APPENDIX C. PEER REVIEW COMMENTS AND AUTHOR RESPONSES

Comments	Response
Page 18: Research gaps/future research: It might be useful to highlight the need for understanding whether possible benefits persist after treatment discontinuation or whether relapse in symptoms occur. In addition, there also is a need for comparative effectiveness research (rather that studies of "usual care" which evolves over time. VA is investing in dissemination of interventions for PTSD, depression and insomnia. An important question is whether CES is comparable to other evidence based treatments. Finally, quality of life outcomes should be incorporated into future research. This may be worthy of mention in this section of the review as well.	We have added these helpful suggestions to the future research section.
The study will be of significant value to providers in Pain Management as we discuss with our patients treatment options. Management of chronic pain is founded on a biopsychosocial model of pain. Treatment is often multimodal. While complementary and non-traditional approaches may have their value as one part of the pain management armamentarium, the many choices available nowadays may appear overwhelming to the medical providers and patients. Thus it is important to guide patients to the treatment options that have good evidence of effectiveness and a favorable benefit versus risk ratio. There are evidence-based pain behavioral pain management options (such as Cognitive Behavioral Therapy for Chronic Pain (CBT-CP), as well as physical therapy and other rehabilitation approaches with proven long-term benefit. It is important that “newer” pain management approaches such as CES do no distract patients from engaging in the therapeutic modalities that have much greater evidence of long term benefit. In regard to long-term risks of CES, the current evidence is rather sparse. While this systematic review indicates low evidence that CES does not cause serious side effects. It remains concerning that the older literature reference cited (reference 23, Feighner et al, 1974) reports “massive worsening of depressive symptoms” from so-called “electrosleep therapy”. We need long-term studies include appropriate measurements of mood and cognitive function, with adequate sensitivity for change of time, in order to conclude that gradual changes in these functions and other adverse effects do not occur over time.	We have added to the future research section the need for long-term studies of safety.
The systematic review does not make recommendations about use of CES in daily practice, and it will be interesting to see whether the information of this review will lead to any policy changes in VHA.	
In the reference to the Cochrane review by Kavirajan, page 2 line 44, the author's name is misspelled (should be "Kavirajan"). In addition, the lack of eligible studies in that Cochrane review was not due solely to the lack of trials with credible blinding in the sham group. Rather, some trials were excluded due to failure to use validated diagnostic criteria or rating scales. Additionally, since the review focused on acute major depression, which is the focus of clinical trials of most FDA-approved antidepressant agents, trials examining CES in chronic depression or treatment refractory depression or bipolar depression were excluded. So, the current characterization of the negative findings by Kavirajan et al is somewhat inaccurate. It could be corrected by stating that "a more recent Cochrane review of CES in acute uncomplicated by Kavirajan and colleagues3 restricted their eligibility criteria to RCTs with a convincing sham, diagnosis using standardized criteria, and assessments with validated rating instruments, reported finding no studies meeting these criteria."	We have made this correction.

The discussion of trials for "anxiety and depression" should state what specific anxiety disorders were examined, as anxiety is a symptom of various anxiety disorders and not a diagnosis in itself. The discussion should note which anxiety disorders were diagnosed using which criteria. In most of the trials considered (other than Barclay et al), it is unclear whether formal diagnostic criteria were used in the inclusion criteria and this should be noted in the text.	We have added text about this. Three of these studies were old (more than 40 years) and as noted by the reviewer, the diagnostic criteria used were either not stated or no longer considered current. Only in the study by Barclay and colleagues were formal modern criteria used (DSM-IV, SCID-I and the HAM-A scale).
Finally, there is a typo on page 2, line 19: "become" should be "became".	This was fixed.

APPENDIX D. EVIDENCE TABLE FOR RCTS OF CRANIAL ELECTRICAL STIMULATION BY CONDITION

Author Year	Patients	Description of CES	Description of Sham or Comparison	Sample Size	Duration	Assessment of Blinding	Results
Painful Conditions							
• Migraine Headache o Fisher Wallace							
Tietjen, 2013[12]	"Chronic migraine without satisfactory pain control on medication" (No other details available)	This study used the Fisher-Wallace Cranial Stimulator, a low-intensity alternate current device.	Not described other than "sham".	50	1 month	Assessment of blinding not performed	Pre-Treatment mean headache days CES: 19.4 Sham: 19.6 Post-treatment mean headache days CES: 18.5 Sham: 20.1 (No significant difference)
• Headache o Pain Suppressor							
Solomon, 1985[19]	Adults with migraine or muscle contraction headaches or both. (No other data provided)	This study used the Pain Suppressor. It was a low amperage (maximum 4 mA), high frequency (12,000 to 20,000 Hz rectified to monophasic wave form) and short pulse width (approximately 30 ms).	The subliminal CES used electric current just below the patient's ability to experience the tingling sensation. The placebo had electrodes in place without electrical stimuli.	40	1 treatment	Assessment of blinding not performed	Improved symptoms of headache CES: 10 of 18 (55%) Subliminal CES: 5 of 18 (28%) Sham: 4 of 22 (18%) ($p < .025$)

Author Year	Patients	Description of CES	Description of Sham or Comparison	Sample Size	Duration	Assessment of Blinding	Results
Solomon, 1989[13]	Adults with tension headaches occurring alone or as part of migraine. Patients with a diagnosis of migraine headache, cluster headache, or medication rebound headache were excluded. Mean age = 42 % female = not reported	This study used the Pain Suppressor. The intensity of the electrical current was adjustable from 0-4 mA. Patients were instructed to increase the intensity until a sensation was felt at the electrode site. The intensity was further increased to the maximum tolerable level, defined as that point where the tingling sensation due to the current became uncomfortable. The unit delivered the current for 20 minutes before shutting off automatically. The signal consisted of a monopolar square wave pulse with a duration of 35 µs a peak amplitude of 4 mA. The pulse was repeated at a frequency of 15,000 Hz for 50 ms. The 50 ms pulse train had a repetition rate of 15 Hz.	The placebo current ran for 70 seconds before shutting off, but the current meter registered 1.0 – 4.0 mA for 20 minutes, the same as the active unit.	100	10 weeks	Assessment of blinding not performed	Global evaluation by patient Highly effective CES: 6 (12%) Placebo: 2 (4%) Moderately effective CES: 12 (24%) Placebo: 6 (12%) Minimally effective CES: 13 (26%) Placebo: 20 (20%) Not effective CES: 19 (38%) Placebo: 31 (63%) (p = .006)
• Degenerative Joint Disease o Alpha-Stim							
Heffernan, 1997[20]	30 subjects were chosen, half females, half males, aged 30-65 years, who were experiencing DJD of hip, shoulder, knees, or back, confirmed by x-ray, and whose pain was unresponsive to medication, and lasted for at least 8 hours per day for 2 years or more.	[This] … device provided a variable, averaged, 0.5 Hz, biphasic square wave pulse, at a 50% duty cycle.	The control device was a function generator producing a constant 0.5 Hz square wave, at 50% duty cycle.	30	1 treatment	Assessment of blinding not performed	Pre-treatment mean pain score (0-5) CES: 4.5 Control: 4.6 Post-treatment CES: 2.1 Control: 4.8 (p < .01)

Author Year	Patients	Description of CES	Description of Sham or Comparison	Sample Size	Duration	Assessment of Blinding	Results
	o Custom-built device						
Katsnelson 2004 [22]	Adults with hip or knee osteoarthritis with baseline pain score >4 Mean age = not stated % female = 97%	The device for this study was custom-built by the authors. It can deliver 1-15 mA RMS of a modulated, 100kHz AC waveform. The waveform can be symmetric or asymmetric.	The sham device delivered no therapeutic current	64	5 days	Assessment of blinding not performed	Pre-treatment mean VAS pain score (0-10) Sham: 5.8 Symmetric: 5.8 Asymmetric: 6.0 Post-treatment mean VAS pain score Sham: 3.6 Symmetric: 2.9 Asymmetric: 3.0 (p>0.05)
• Fibromyalgia o Alpha-Stim							
Lichtbroun, 2001[15]	Adults from a single practice diagnosed by one clinician as having fibromyalgia using ACR criteria Mean age = 50 % female = 97%	This study used the Alpha-Stim device. Each device was preset to provide 100-µA, modified square-wave biphasic stimulation on a 50% duty cycle at 0.5 Hz, and to automatically turn off at the end of the hour.	Sham treatment was identical (except) electrodes did not pass current.	60	3 weeks	Assessment of blinding not performed	"The double-blind treated group had significant mean gains on tender point score ($t = 2.27$, $p < .01$), self-rated pain ($t = 3.04$, $p < .002$), quality of sleep ($t = 2.05$, $p < .02$), feeling of well being ($t = 1.67$, $p < .05$), and quality of life ($t = 1.92$, $p < .03$). There were 38 degrees of freedom on each analysis. The sham-tested and placebo-controlled groups had no positive gains during the study." (No two-tailed test of statistical significance was performed comparing active with sham CES treated patients.)
Cork, 2004[21]	Adults 22-75 years of age presenting to a university pain clinic with a diagnosis of fibromyalgia Mean age = 53 % female = 95%	All patients were given an Alpha-Stim CES device. Each devise was preset to provide 1 hour of 100-µA, modified square-wave biphasic stimulation on a 50% duty cycle at 0.5 Hz.	Sham treatment was provided by identical ear clips that did not pass current	74	3 weeks	Assessment of blinding not performed	Pre treatment pain intensity (0-5) CES: 3.4 Sham: 3.6 Post-treatment pain intensity CES: 2.5 Sham: 3.4 (p < .01)

Author Year	Patients	Description of CES	Description of Sham or Comparison	Sample Size	Duration	Assessment of Blinding	Results
Taylor, 2011[9] Taylor, 2013[14]	Adult patients were recruited from local rheumatology practices and were eligible if they met ACR 1990 criteria for fibromyalgia and had a score of 3 or greater on a 10 point number rating scale and were on stable medication for at least 4 weeks. Mean age = 51 % female = 94% Mean pain = 5.8	This study used the Alpha-Stim device. Participants in the CES device group received devices that were active and preset at the factory to provide a maximum of 60 minutes of modified square-wave biphasic stimulation at 0.5 Hz and 100 mA, the lowest setting that has been used in earlier studies with patients with FM and below the level of perception.	Sham devices appeared to be activated, but did not deliver any stimulation.	46	8 weeks 8 weeks	Assessment of blinding not performed	Pre-treatment pain CES: 5.8 Sham: 5.7 Usual care: 6.0 Post-treatment pain CES: 5.0 (estimated) Sham: 5.9 (estimated) (Slope of line was stated as statistically different between groups, but comparison of final outcomes across groups was not performed)
• Spinal Cord Injury o Alpha-Stim							
Tan, 2006[17]	Veterans who were 6 months to 60 years post-SCI with chronic musculoskeletal pain or neuropathic pain, without evidence of substance abuse or severe cognitive or mental disorder. Mean age = 56 % female = 0% 55% had neuropathic pain	This study used the Alpha-Stim 100 with "the amount of electrical stimulation set at a sub-threshold level and could not be changed by the participant."	Sham CES, not otherwise described.	38	21 days	Assessment of blinding not performed	Average daily pain ratings Pre-treatment CES: 6.5 Sham: 6.1 Post-treatment CES: 5.7 Sham: 6.0 (The authors did not do tests of between group ratings)

Author Year	Patients	Description of CES	Description of Sham or Comparison	Sample Size	Duration	Assessment of Blinding	Results
Tan, 2011[16]	VA patients with SCI (any level and any degree of completeness) that had occurred at least 6 months prior, and having at least one chronic pain component at or below the level of the injury that was classified as neuropathic pain and ≥ 5 on a numeric rating scale. Mean age = 52 % female = 14%	This study used the Alpha-Stim SCS. Persons in the treatment group received 1 hour per day of 100 µA sub-sensation active CES.	The control group received sham CES for the same amount of time.	105	21 days	Assessment of blinding not performed	Pre-treatment pain CES: 5.60 Sham: 5.41 Post-treatment pain CES: 5.00 Sham: 5.00 (p > .90)
• Neuromuscular pain lasting > 6 months o Alpha-Stim							
Tan, 2000[18]	VA patients with primarily neuromuscular pain of at least 6 months duration. Patients with fibromyalgia, history of significant exposure to electricity and chronic psychiatric problems were excluded. Mean age = 56 % female = 9% Back pain was the most common symptom.	This study used the Alpha-Stim 100. This equipment uses a battery to deliver 10 to 600 microamperes of adjustable current at selected frequencies of 0.5, 1.5, or 100 Hz. For this study, 0.5 Hz was the selected frequency used.	In the sham, brief electrical stimulation was provided in random order.	11 (28 began treatment, there were 17 dropouts)	12 treatments over a variable period of time	Assessment of blinding not performed	No significant differences in slope of pain scores over time between active and sham CES using ANOVA.

Author Year	Patients	Description of CES	Description of Sham or Comparison	Sample Size	Duration	Assessment of Blinding	Results
• Musculoskeletal pain lasting > 6 months in Parkinson's patients o Alpha-Stim SCS							
Rintala, 2010[23]	VA and non VA patients with Parkinson's disease and chronic musculoskeletal pain or low or extremity pain of at least 6 months duration with average pain intensity of at least 5 of 10.	The CES equipment used was the Alpha-Stim SCS. Active devices provided subsensory stimulation of 100 mA.	Sham devices had no electric current flowing	19	42 days	Assessment of blinding not performed	Differences between active and sham CES before and after the 42 day treatment period were not statistically tested. Pre/post treatments within each treatment day favored active CES treatment.
• Cervical pain, chronic low back pain, or headaches o Transcranial ElectroStimulator							
Gabis, 2003[24]	Adult patients with chronic low back or cervical pain seen in a pain clinic Mean age = 46.2 % female = 55% 85% of patients had back pain	This study used the Transcranial ElectroStimulator Pulsatilla 1000. The stimuli generator emits pulses on a fixed and controlled frequency. The maximal electrode current as measured on the forehead electrode is 4mA. The treatment is asymmetrical, biphasic for zero net charge, 77Hz frequency and 3.3 msec of pulse width	Patients receiving placebo were treated with a 50 Hz signal with maximum current of 0.75 mA. It was designed to give the patient the feeling of being treated	20	8 consecutive days	Assessment of blinding not performed	Mean difference pre-post treatment on VAS pain score CES: 2.2 Sham: 1.2 (not significant)

Author Year	Patients	Description of CES	Description of Sham or Comparison	Sample Size	Duration	Assessment of Blinding	Results
Gabis, 2009[25]	Adult patients with cervical pain, chronic low back pain, or headaches Mean age = 51 % female = 60%	This study used the Transcranial ElectroStimulator Pulsatilla 1000. The stimuli generator emits pulses on a fixed and controlled frequency. The maximal electrode current as measured on the forehead electrode is 4mA. The treatment is asymmetrical, biphasic for zero net charge, 77Hz frequency and 3.3 msec of pulse width	Patients receiving placebo were treated with a 50 Hz signal with maximum current of 0.75 mA. It was designed to give the patient the feeling of being treated	119	8 consecutive days of treatment 3 weeks and 3 months	Assessment of blinding not performed	Pre-treatment VAS pain scores Cervical pain CES: 5.89 Placebo: 5.65 LBP CES: 5.82 Placebo: 7.00 Headache CES: 6.20 Placebo: 4.59 3 week follow up Cervical pain CES: 3.26 Placebo: 4.65 LBP CES: 3.82 Placebo: 5.25 Headache CES: 3.55 Placebo: 3.73 (Comparison of headache pre-post p=0.007, all other differences not significant) At 3 months follow up all comparisons pre-post were statistically significant except patients with LBP

Author Year	Patients	Description of CES	Description of Sham or Comparison	Sample Size	Duration	Assessment of Blinding	Results
Depression							
	o Fisher Wallace						
McClure, 2015[27]	Adults with bipolar depression diagnosed using SCID-P, not diagnosed as treatment-resistant, between HAM-D 13-28, CGI-S $\leq$ 5 Mean age = 48 % female = 50% 80% had comorbid personality disorder Mean HAM-D = 19.6	This study used the Fisher-Wallace Cranial Stimulator. It used alternating current in three frequencies: 5 Hz, 500 Hz, and 15,000 Hz. The CES treatment was delivered by two electrodes covered with damp sponges and placed over the temples bilaterally with 2 mA of alternating current for one 20-minute session per day for the active treatment group.	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, then turning it off.	16	12 weeks (double-blind phase = 2 weeks)	Assessment of blinding not performed	Pre-treatment HAM-D CES: 18.1 Sham: 20.7 Post-treatment HAM-D (2 weeks) CES: 10.9 Sham: 15.1 (p = .5) Pre-treatment BDI CES: 30.6 Sham: 29.6 Post treatment BDI (2 weeks) CES: 17.6 Sham: 25.9 (p=0.02)

Author Year	Patients	Description of CES	Description of Sham or Comparison	Sample Size	Duration	Assessment of Blinding	Results
Mischoulon, 2015[26]	Adults with major depressive disorder, treatment resistant on a stable dose of antidepressant medication HAM-D score of 15-23 Mean age = 48 Mean HAM-D = 18.4 % female = 57%	This study used the FW-100 Fisher Wallace Cranial Stimulator. The device's electronic waveform contains a 15,000 Hz (to traverse the skull) square wave carrier which is rectified, varying from 0 to 4 mA. The first 15 Hz modulating signal (to theoretically influence brain neurochemical activity) provides 50 ms of "on" time and 16.7 ms of "off" time (total pulse period 66.7 ms, 50% duty cycle). A second, 500 Hz modulating signal changes the "on" time series of 15,000 Hz carrier pulses (750 pulses in 50 ms) into 25 smaller bursts of 15 pulses each of the 15,000 Hz carrier signal, for 375 pulses in the same 50 ms. The consecutive positive burst and "off" time is followed by an equal and opposite negative burst and "off" time, balancing the direct current component to zero. Output voltage ranges from 0 to 40 V, first positive and then negative. CES was left at this level until it automatically shut off after 20 minutes.	The sham devices were modified to not deliver current to the headset.	30	3 weeks 3 weeks	Double Assessment of blinding not performed	Pre-treatment HAM-D CES: 18.1 Sham: 18.7 Post-treatment HAM-D CES: 15.8 Sham: 14.5 (no significant difference)

Author Year	Patients	Description of CES	Description of Sham or Comparison	Sample Size	Duration	Assessment of Blinding	Results
	o Alpha-Stim						
Turner, 2016[28]	Adults self-referred by response to community advertisements with BDI-II of 14 or greater. Mean age = 60 Mean BDI-II = not stated % female = 90%	The cranial electrotherapy stimulation devices used in this study were furnished by Electromedical Products International. (The manufacturer) coded the devices prior to shipment. CES stimulation was administered for 60 minutes at an intensity of 2 V, which produced 100 mA at 0.5Hz random biphasic square wave form.	The placebo treatment earclips did not pass current	20	3 weeks	Assessment of blinding not performed	Average reduction in BDI, post-treatment compared to pre-treatment CES: 14.1 Sham: 11.1 (p=0.46)
• Anxiety & Depression o Alpha-Stim							
Barclay, 2014[7]	Adults meeting DSM-IV criteria for anxiety disorder and comorbid depression confirmed using SCID-I, HAM-D > 15, benzodiazepine use only if PRN and no more than 2 per week, patients with any other Axis I diagnosis were excluded, or at risk for suicide or attempted suicide in the prior 12 months. Mean age = 42 % female = 67.8% Mean HAM-A = 28.5 Mean HAM-D = 13.9	This study used the Alpha-Stim 100. The device provides electrical stimulation by generating bipolar, asymmetric, rectangular waves with a frequency of 0.5Hz and a current intensity that was preset and locked by the manufacturer at its lowest therapeutic doseat100 µA, a subsensory level.	The sham CES devices were identical to the active device, except the ear clip electrodes and did not transmit electricity.	115	5 weeks	Assessment of blinding not performed	Pre-treatment HAM-A CES: 29.5 Sham: 27.6 Post-treatment HAM-A CES: 13.4 Sham: 20.0 (p = 0.001) Pre-treatment HAM-D CES: 14.5 Sham: 13.2 Post-Treatment HAM-D CES: 6.5 Sham: 10.0 (p = 0.001)

Author Year	Patients	Description of CES	Description of Sham or Comparison	Sample Size	Duration	Assessment of Blinding	Results
	o Neurotone 101						
Hearst, 1974[29]	Adult outpatients at a University psychiatric clinic who had been ill for at least two years without obtaining a definitive remission despite chemotherapy and psychotherapy, and with no change in treatment for at least 1 month. Psychotic patients were excluded. 50% had depression, 40 % had anxiety, and 36% had hypochondriasis. Mean age = 38 % female = 86%	This study used the Neurotone 101. Burst rate was 100 Hz/second with a burst width of 2 ms. This current was used to treat the alternating current treatment group.	The sham group consisted of altering the current from the Neurotone 101 to direct current, rectified and filtered to force positive square wave pulses of the same width and frequency.	28	5 days	Assessment of blinding not performed	Number of patients reporting greater than median improvement Depression CES: 79% Sham: 21% Anxiety CES: 29% Sham: 50% Hypochondriasis CES: 29% Sham: 43% (* $p < 0.05$ as reported in article) Number of patients "completely well" on overall global rating CES: 79% Sham: 50% (no significant difference)
Scallet, 1976[32]	Patients were included if they attended a university psychiatry outpatient clinic, had no change in medication, attending psychiatric or psychotherapeutic approach for at least 1 month, had a diagnosis of chronic hysteria, and no evidence of active medical or neurologic disease. Mean age and gender no reported.	The Neurotone 101 was used. The burst rate was 100 Hz/second with a burst width of 2 ms. The output was rectified and filtered to form positive square wave pulses of the same width and frequency.	All patients received relaxation technique instructions. The sham group had the amplitude of current reduced over 30 seconds and then discontinued, and was told that patients often develop a tolerance to the tingling sensation.	17	3 weeks	Assessment of blinding not performed	Change in symptom scores at 1 week Anxiety Relaxation + central stimulation CES: 5.4 Relaxation + peripheral stimulation CES: 7.7 Relaxation + sham: 1.4 ($p < 0.05$) Depression Relaxation + central stimulation CES: 5.4 Relaxation + peripheral stimulation CES: 77.3 Relaxation + sham: 3.4 ($p > 0.05$)

Author Year	Patients	Description of CES	Description of Sham or Comparison	Sample Size	Duration	Assessment of Blinding	Results
	o Electrosone-50						
Rosenthal, 1972[31]	Patient selected from psychiatric outpatient clinics. 18 of 22 patients had a diagnosis of neurosis and personality disorder with prominent anxiety, depression, and insomnia. Mean age = 43 % female = not recorded	This study used an American-made machine modeled after the Russian Electrosone. A frequency of 100 positive pulses per second and a pulse duration of 1 ms with no base line d-c bias current. The current was regulated so that the patient felt a slight but not uncomfortable tingling sensation over his or her eyes or mastoid processes. This was usually produced by a current reading of 0.1 to 0.25 mA on the machine dial. Independent measurement, however, indicated that the true current was 0.5 to 1.2 mA.	Not described other than the sham patients did not feel the tingling sensation.	22	5 days	Assessment of blinding not performed	Psychiatrist-assessed outcomes Pre-treatment anxiety CES: 4.3 Sham: 4.4 Post-treatment anxiety CES: 1.4 Sham: 3.2 Pre-treatment sleep disturbance CES: 4.2 Sham: 4.2 Post-treatment sleep disturbance CES: 0.8 Sham: 3.5 Pre-treatment depression CES: 2.8 Sham: 3.6 Post-treatment depression CES: 1.0 Sham: 2.7 (All differences between CES and sham were statistically significant)

Author Year	Patients	Description of CES	Description of Sham or Comparison	Sample Size	Duration	Assessment of Blinding	Results
Feighner, 1973[30]	Adults "ill for a minimum of 2 years with prominent anxiety, insomnia, and depressive symptoms. All had received extensive prior psychiatric care including psychotherapy, pharmacotherapy remissions, and in 4 cases ECT without significant recession" Mean age = 41 % female = 79%	This study used the Electrosone-50. A machine setting of 100 positive pulses/second of direct current was used, with a duration of 1/ms and zero bias baseline current. Amplitude was gradually raised to tolerance for each patient until the prickling sensation over the eyes became moderately uncomfortable (average meter reading ranged from 0.1 to 0.25 mA).	Sham treatments were identical including the brief raising of amplitude to reach a moderately painful prickling sensation, after which the amplitude was slowly turned to zero.	23	2 weeks 2 weeks	Double Assessment of blinding not performed	Pre-treatment Global ratings CES: Anxiety = 4.5 Depression = 4.0 Insomnia = 4.6 Sham: Anxiety = 4.4 Depression = 3.8 Insomnia = 4.6 Post-treatment Global ratings CES: Anxiety = 2.5 Depression = 2.8 Insomnia = 1.9 Sham: Anxiety = 4.0 Depression = 3.9 Insomnia = 4.4 (no between-group comparisons were performed)

PTSD – No studies of cranial electrical stimulation to treat PTSD were identified

Author Year	Patients	Description of CES	Description of Sham or Comparison	Sample Size	Duration	Assessment of Blinding	Results
Insomnia							
	o Alpha-Stim						
Lande, 2013[8]	Subjects were active-duty military personnel who had a score of 21 or greater on the Pittsburgh Insomnia Rating Scale Mean age = not reported, but 77% of patients were less than age 41 % female = 19% Mean Pittsburgh Insomnia Rating Scale score = 36	This study used the Alpha-Stim SCS. The manufacturer set the active devices at 100 µA, an imperceptible level of stimulation.	Sham was described as a non-functional CES device.	57 (13 did not complete all 5 sessions)	5 days	Assessment of blinding not performed	No statistically significant difference between groups in time to sleep, total time slept, and number of awakenings
	o Electrodorm 1						
Weiss, 1973[33] Cartwright, 1975[36]	"Insomniacs" recruited in a newspaper advertising, who had reported a latency to sleep onset of at least 60 minutes at least 3 times per week. Subjects underwent study in the sleep laboratory and only those that did not reach stage 2 sleep within 20 minutes and stage 4 sleep within 60 minutes were included. (No details about age, sex, or other demographics provided)	This study used the Electrodorm 1.	The sham treatment discontinued the current after the tingling sensation was felt.	10	24 days	Assessment of blinding not performed	Pre-treatment Latency of sleep onset CES: 60.8 Sham: 60.5 Post-treatment Latency of sleep onset CES: 10.6 Sham: 58.5 (No between group comparisons were performed) Two-year follow up of 5 patients reported 4 were able to fall asleep with little difficulty

Author Year	Patients	Description of CES	Description of Sham or Comparison	Sample Size	Duration	Assessment of Blinding	Results
• Anxiety & Insomnia o Neurotone 101							
Moore, 1975[34]	"Subjects were selected because they were suffering from persistent anxiety and insomnia and did not have evidence of a psychosis" Mean age = 38 % female = 47%	This study used the Neurotone, which gave an output of 100 positive pulses per sec, with a pulse duration of 2 ms, and a maximum potential of 20 v. The current was turned on and slowly increased until a tingling sensation was felt. It was increased until it became uncomfortable, then turned back until the sensation stopped. The latter reading was between the former two. For treatment, the current was maintained just below the threshold of the tingling sensation.	Sham treatment was conducted identically to active treatment except the current was turned back to zero.	17	5 days	Assessment of blinding not performed	Patient-completed Taylor's Manifest Anxiety Scale change between pre and post-treatment CES: -0.75 Sham: 2.55 (No statistical difference) Subjective anxiety CES: 0.37 Sham: 0.55 (No statistical difference) Subjective insomnia CES: 1.87 Sham: 0.44 (p reported as < 0.05)
• Anxiety o Alpha-Stim							
Gibson, 1987[35]	Subjects were non-paid volunteers who responded to advertisements in local newspapers…who scored 50 or above on the state anxiety scale of the State-Trait Anxiety Inventory and were considered as "anxious". Mean age = 37 % female = 50%	This Alpha-Stim 350 was selected for use because it uses a microampere, randomized biphasic direct current through remote electrodes.	These were 2 comparison groups: 1) 20 minutes of pre-recorded relaxation instructions 2) control of 20 minutes of neutral tape with the CES device turned off	64	1 treatment	Assessment of blinding not performed	State anxiety scores pre-treatment CES: 52.3 Relaxation: 52.9 Control: 53.2 Post-treatment CES: 30.1 Relaxation: 32.2 Control: 51.9 (p < 0.001)

APPENDIX E. CITATIONS OF FULL-TEXT EXCLUDES

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