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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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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

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┌─────────────────────┐
│ Search results:     │
│ 1,900 references*   │
└─────────────────────┘          ┌─────────────────────┐
          │                      │ Manufacturer        │
          │◄─────────────────────│ suggested:          │
          ▼                      │ 24 references       │
┌─────────────────────┐          └─────────────────────┘
│ Total titles        │
│ screened            │────────► ┌──────────────────────────────────────┐
│ 1,924 references    │          │ Excluded = 1,602 references          │
└─────────────────────┘          └──────────────────────────────────────┘
          │
          │                      ┌──────────────────────────────────────┐
          │                      │ Excluded = 251 references            │
          │                      │ Not about CES: 139                   │
          │                      │ Not RCT: 35                          │
          ▼                      │ Did not include conditions of        │
┌─────────────────────┐          │   interest: 31                       │
│ Abstracts reviewed: │────────► │ Not research: 27                     │
│ 322 references      │          │ Unable to retrieve: 6                │
└─────────────────────┘          │ Did not provide abstract: 4          │
          │                      │ Not population of interest: 7        │
          │                      └──────────────────────────────────────┘
          │
          │                      ┌──────────────────────────────────────┐
          ▼                      │ Excluded = 43 references             │
┌─────────────────────┐          │ Not RCT: 17                          │
│ Pulled for full     │────────► │ Used for background only: 10         │
│ text review:        │          │ Not population of interest: 10       │
│ 71 references       │          │ Did not include conditions of        │
└─────────────────────┘          │   interest: 2                        │
          │                      │ Not about CES: 2                     │
          │                      │ Duplicate: 1                         │
          │                      │ Not compared to sham or usual        │
          ▼                      │   care: 1                            │
┌─────────────────────┐          └──────────────────────────────────────┘
│ Included studies:   │
│ 26 RCTs from 28     │
│ references          │
└─────────────────────┘
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*   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]	Unclear	Low	Unclear	Unclear	Low	Low	Low
Cork et al, 2004[21]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Feighner et al, 1973[30]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Gabis et al, 2003[24]	Low	Low	Unclear	Unclear	Low	Low	High
Gabis et al, 2009[25]	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
Gibson et al, 1987[35]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Hearst et al, 1974[29]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Heffernan et al, 1997[20]	Unclear	Unclear	Unclear	Unclear	Low	Low	High
Katsnelson et al, 2004[22]	Unclear	Unclear	Unclear	Unclear	Low	Low	High
Lande et al, 2013[8]	Low	Low	Unclear	Unclear	Low	Low	Low
Lichtbroun et al, 2001[15]	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
McClure et al, 2015[27]	Low	Low	Unclear	Unclear	Unclear	Low	Unclear
Mischoulon et al, 2015[26]	Low	Low	Unclear	Unclear	Low	Low	Unclear
Moore et al, 1975[34]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Rintala et al, 2010	Unclear	Unclear	Unclear	Unclear	High	Low	Low
Rosenthal, 1972[31]	Unclear	Unclear	Unclear	Low	Unclear	Low	Unclear
Scallet et al, 1976[32]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Solomon et al, 1989[13]	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Solomon et al, 1985[19]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Tan et al, 2000[18]	Unclear	Unclear	Unclear	Unclear	High	Low	Unclear
Tan et al, 2011[16]	Low	Low	Unclear	Unclear	Low	Low	Low
Tan et al, 2006[17]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Taylor, et al., 2013[14] Taylor, et al., 2013[9]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Tietjen, et al., 2013[12]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Turner, 2016[28]	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear
Weiss, 1973[33] Cartwright, 1975[36]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear

- ● = 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

Author, Year	Outcome	Sample Size	Time at follow up	SMD [95% CI]
Comparator=Usual Care/Relaxation				
Group=anxiety				
Gibson, 1987	State–Trait Anxiety Inventory	32	1 treatment	−0.10 [−0.80, 0.59]
Group=fibromyalgia				
Taylor, 2011; Taylor, 2013	pain NRS	32	8 weeks	−0.57 [−1.28, 0.14]
Comparator=Sham				
Group=fibromyalgia				
Cork, 2004	Pain Intensity Score	74	3 weeks	−0.78 [−1.25, −0.30]
Taylor, 2011; Taylor, 2013	pain NRS	31	8 weeks	−0.27 [−0.98, 0.44]
Group=neuromuscular pain > 6 months				
Tan, 2000	MPI Pain Severity Scale	11	2 months	−0.10 [−0.94, 0.74]
Group=chronic musculoskeletal pain in Parkinson's patients				
Rintala, 2010	daily pain rating	13	42 days	−1.07 [−2.25, 0.11]
Group=chronic back and cervical pain				
Gabis, 2003	visual analog scale	20	1 treatment	−0.70 [−1.60, 0.21]
Gabis, 2009	visual analog score (total)	75	3 weeks	−0.45 [−0.91, 0.01]
Group=spinal cord injury				
Tan, 2006	average daily pain rating	38	21 days	−0.78 [−1.44, −0.11]
Tan, 2006	pain at followup	38	21 days	−0.16 [−0.80, 0.48]
Tan, 2011	average daily pain rating	105	21 days	−0.10 [−0.49, 0.28]
Group=degenerative joint disease				
Heffernan, 1997	pain rating	20	1 treatment	−1.57 [−2.59, −0.56]
Katsnelson, 2004	visual scale pain	64	5 days	−0.28 [−0.80, 0.24]
Group=migraine headache				
Tietjen, 2013	headache days	50	1 month	−0.50 [−1.06, 0.07]
Group=headache				
Gabis, 2009	visual analog score (total)	44	3 weeks	−0.53 [−1.13, 0.07]
Group=depression				
McClure, 2015	BDI	16	2 weeks	−1.39 [−2.50, −0.27]
McClure, 2015	HAM−D	16	2 weeks	−0.35 [−1.35, 0.64]
Mischoulon, 2015	HAM−D	30	3 weeks	0.32 [−0.41, 1.04]
Turner, 2016	BDI−II	20	3 weeks	−0.33 [−1.22, 0.55]
Group=anxiety and depression				
Barclay, 2014	HAM−A	108	5 weeks	−0.94 [−1.34, −0.54]
Barclay, 2014	HAM−D	107	5 weeks	−0.78 [−1.18, −0.39]
Feighner, 1973	global ratings: anxiety	19	2 weeks	−1.07 [−2.04, −0.10]
Feighner, 1973	global ratings: depression	19	2 weeks	−0.87 [−1.81, 0.08]
Feighner, 1973	global ratings: insomnia	19	2 weeks	−1.67 [−2.73, −0.61]
Rosenthal, 1972	anxiety	22	5 days	−1.13 [−2.04, −0.23]
Rosenthal, 1972	depression	22	5 days	−0.60 [−1.46, 0.26]
Scallet, 1976	Self−rating Symptom Scale: anxiety	10	3 weeks	−3.32 [−5.37, −1.28]
Scallet, 1976	Self−rating Symptom Scale: depression	10	3 weeks	−0.76 [−2.05, 0.54]
Group=anxiety				
Gibson, 1987	State−Trait Anxiety Inventory	32	1 treatment	−1.40 [−2.17, −0.62]
Group=anxiety and insomnia				
Moore, 1975	manifest anxiety	17	5 days	0.37 [−0.59, 1.33]
Moore, 1975	subjective insomnia	17	5 days	−0.85 [−1.85, 0.15]
Group=insomnia				
Lande, 2013	hours in sleep time	36	5 days	−0.44 [−1.10, 0.23]
Weiss, 1973	EEG Latencies of sleep onset in minutes	10	24 days	−1.67 [−3.16, −0.19]

*Excluded for either insufficient data or binary data only:
Hearst, 1974; Lichtbroun, 2001; Solomon, 1985; Solomon, 1989

−4　−2　0　2　4
Favors CES　　　Favors Comparator

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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