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Research Article

A Meta-Analyses of Cranial Electrotherapy Stimulation in the Treatment of Insomnia

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- Insomnia; Cranial Electrotherapy Stimulation (CES); Meta-Analysis; Randomized Controlled Trials (RCTs); Non-Randomized Studies on Interventions (NRSIs)

Abstract

Increasing evidence supports the bidirectional relationship between physical and psychological well-being, morbidity, and mortality. Sleep disorders, especially insomnia, are a pervasive presenting symptom in patients with a range of psychiatric disorders. The sars-cov-2 pandemic has resulted in a historic 73% of the US population reporting disordered sleep, attributed to anxiety (48%), safety concerns (26%), and loneliness (23%). With insomnia as a moderating factor for suicide, the need for efficacious treatment for insomnia has never been more immediate. The mainstay insomnia treatments are often inadequate or contraindicated, resulting in increased demand for complementary or alternative treatments. In clinical trials since the 1970s, brain stimulation, in particular cranial electrical stimulation (CES), has shown efficacy in the treatment of insomnia. We have conducted, what we believe to be, the first 2 meta-analyses of CES as a treatment for insomnia. Methods: Fixed and random effects models, inclusive of homogeneity of Cohen's d effect sizes are reported on 8 studies found in the Cochrane Central Register of Controlled Trials (CENTRAL), using Cooper's Taxonomy of Literature Reviews. Results: A large (d = -0.83), average effect size for the 3 RCTs is shown, in addition to a small (d = -0.38), average effect size for 5 NRSI studies in favor of the active treatment group. Conclusion: CES has a significant effect in the treatment of moderate to severe insomnia across a variety of patient populations.

ABBREVIATIONS

CES: Cranial Electrotherapy Stimulation; RCTs: Randomized Controlled Trials; NRSIs: Non-Randomized Studies on Interventions; TCAs: Tricyclic Antidepressants; SSRIs: Selective Serotonin Reuptake Inhibitors; SNRIs: Serotonin-Norepinephrine Reuptake Inhibitors; SARS-CoV-2 or COVID-19: Severe Acute Respiratory Syndrome Coronavirus 2; CBT: Cognitive Behavioral Therapy; CBT-1: Cognitive Behavioral Therapy for Insomnia; CENTRAL: Cochrane Central Register of Controlled Trials; rTMS: Transcranial Magnetic Stimulation; HAM-A: Hamilton Anxiety Scale; HAM-D: Hamilton Depression Scale; STAI: State/Trait Anxiety Inventory; ZAS: Zung Anxiety Scale; ZDS: Zung Depression Scale; POMS: Profile of Mood States; EEG: Electroencephalogram; FFS: Federal Supply Schedule; NRS: Numerical Ratings Scale; ESAS: Edmonton Symptom Assessment; HADS: Hospital Anxiety and Depression Scale; GSDS: General Sleep Disturbance Scale; TAU: Treatment as Usual; PIRS: Pittsburgh Insomnia Rating Scale; AIS: Athens Insomnia Scale; PHQ-9; Patient Health Questionnaire; GAD-7: Generalized Anxiety Disorder Scale-7; WSAS: Work and Social Adjustment Scale; EQ5D-5L: EuroQol.

INTRODUCTION

Primary insomnia is an umbrella term for a range of various types of disordered sleep that are characterized by difficulty falling (onset insomnia), or staying asleep (maintenance insomnia), which impacts daily functioning [1,2]. The absence of underlying physical, mental, or substance-related etiology predicates the diagnosis and duration of at least 3 months or more occurring 3 or more times per week. The prevalence of insomnia ranges between 6% to 10% of the US population, with women and older adults over-represented [3]. With an estimated annual cost around $100 billion for treatments related to insomnia [4], and resulting in $60 million in loss of productivity [5]. Insomnia is increasingly becoming a public health issue, particularly as a consequence of COVID-19 with general insomnia rates having doubled to 20% and clinical insomnia to 37% [6]. With research by Sleep Standards (2020), reporting that 73% of Americans reported disrupted sleep during the pandemic, attributed to anxiety (48%), safety concerns (26%) and loneliness (23%) [7,8].

The pathophysiology of insomnia is associated with cognitive and physiological arousal, with research indicating an increased level of arousal in patients with primary insomnia both during the day and night [9]. The etiology of insomnia incorporates an interplay between genetic predispositions estimated at between 42% to 57% in twin studies to levels of arousal. In addition, medical and psychosocial stressors that perpetuate the sleep-related behavior, and behaviors such as rumination and worry that maintain and exacerbate the disordered sleep [10,11]. Insomnia is typically classified as acute or chronic depending on the length of occurrence and contributing factors. Acute insomnia is a brief episode of difficulty falling or staying asleep, frequently associated with life stressors, self-limiting medical conditions,

pain or physical discomfort, unfamiliar surroundings, jet lag, or certain medications or stimulants.

Conversely, chronic insomnia is associated with a long period of difficulty falling or staying asleep and is associated with several comorbid factors, resulting in it often being labeled as 'comorbid insomnia.' A range of conditions co-occurs in chronic insomnia including medical, neurological, and psychiatric disorders, especially anxiety and depression [10]. In addition to occupational and health-care costs, it is a risk factor for cardiovascular disease, cognitive decline, and psychiatric disorders, including suicide [12-16]. A meta-analysis of 21 studies on insomnia by Baglioni et al. [17], indicated a two-fold increase in de novo depression [odds ratio of 2.10 (CI: 1.86–2.38)] compared to people without insomnia, with estimates of 40% to 60% of those with insomnia having a comorbid anxiety or mood disorder [18].

Treatment for acute insomnia is seldom needed as the condition typically resolves within a few days. Chronic insomnia that results in significant impairment has been treated with medications such as non-benzodiazepine hypnotics, benzodiazepines, benzodiazepine-receptor agonists, antidepressants, antihistamines off label, and antipsychotics. Complementary treatments such as melatonin, Cognitive Behavioral Therapy for Insomnia (CBT-I), exercise, yoga, and medication have been shown to be helpful [19-21]. Cranial electrotherapy stimulation (CES) and Transcranial Magnetic Stimulation (rTMS) have also been shown to be efficacious in reducing the frequency and latency of chronic insomnia [10,22-32].

RISK FACTOR

Sleep disturbance is ubiquitous in every psychiatric disorder and a principal feature of anxiety and depression [33]. Disordered sleep may predispose and precede a psychiatric disorder or occur as part of the illness [34]. It is considered to have a directional relationship - with the strongest causal pathway being disrupted sleep preceding psychiatric illness [35]. Disordered sleep is also a risk factor for psychiatric relapse [36,37].

Treatment of disordered sleep lessens all psychiatric problems and may function as a preventative approach for the onset of psychiatric disorders [38]. DSM-V diagnostic criteria for GAD include experiencing sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep). Anxiety, depression, and reports on insufficient sleep are strongly correlated. A diagnosis of anxiety or depression increases the odds of a comorbid sleep disorder [39]. Moreover, psychiatric medications such as Tricyclic Antidepressants (TCAs), Selective Serotonin Reuptake Inhibitors (SSRIs), and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), can cause disordered as these drugs are known to exacerbate or lead to the onset of restless leg syndrome, a common underlying cause of disordered sleep [34].

In addition to other psychiatric disorders – disrupted sleep is a risk factor for suicide across the lifespan [40]. In a 3 year follow up study, Geoffroy et al. [41], reported that difficulty falling asleep, early morning awakening, and hypersomnia were risk factors for suicidal behavior independent of psychopathology [41]. The relationship between suicidal behavior and disordered sleep has been reported in adolescents as well [42-44].

The prevalence of anxiety and insomnia disorders continues to increase, yet the treatment approaches have changed little in the last 30 years [45]. The shortcomings in the current treatment approaches for insomnia warrant the utilization of other effective modalities such as Alpha-Stim® cranial electrotherapy stimulation for this drug-treatment resistant population who suffer from mixed anxiety, insomnia and depression.

NETWORK ACTIVATION

We support the idea of viewing insomnia from a network activation lens. Through the alteration of brain physics (brainwave electrical activities) and brain chemistry (neurotransmitters), research has shown that CES can significantly decrease anxiety, insomnia, depression, and pain; while avoiding the serious risks and side effects (e.g., cognitive and cardiovascular), of medications. CES is also neurostimulation for normalizing brain activity, and in contrast, is a more cost-effective, non-invasive type of device that can be safely used by patients at home. It is being used as an adjunct to medication or psychotherapy or as a stand-alone treatment. Based on an increasing body of evidence, brain stimulation that is available now is expected to be part of the armamentarium of most psychiatrists by 2030 [46,47].

CES now has a foundation of more than 50 years of research and clinical use in the USA from which proof of safety and effectiveness has been well established. The mechanisms of action of externally applied CES has been observed in the limbic system associated with emotional regulation and memory and the cingulate gyrus, insula and prefrontal cortex associated with the processing of pain [48,49]. Early research into the use of CES as a treatment for insomnia subsequently revealed it was an effective treatment for mood-related symptoms as well, as determined using various psychological assessment scales of anxiety and depression (e.g., Hamilton Anxiety Scale, State/Trait Anxiety Inventory, Zung Depression Scale, Profile of Mood States, etc.) [50]. Figure 1 depicts how CES induces changes in brain activity as measured by Electroencephalogram (EEG), increasing alpha (8-12 Hz), relative power, and decreasing relative power in the delta (0–3.5 Hz), and beta (12.5-30 Hz), frequencies [51]. Increased alpha correlates with improved relaxation and increased mental alertness or clarity. Decreased delta waves indicate a reduction in fatigue. Beta wave reductions between 20-30 Hz correlate with decreases in anxiety, ruminative thoughts, and obsessive/compulsive-like behaviors.

Figure 2 shows via low-resolution electromagnetic tomography (LORETA) that CES currents have an effect on the entire brain within the alpha band frequency of 8 Hz. Functional MRI studies showed that CES reached all cortical and subcortical areas of the brain, producing changes like those induced from medications [51, 55, 56, 57, 58]. CES has also been shown to penetrate the hypothalamus resulting in secretion of neurotransmitters and neurohormones [32, 53, 54].

RATIONALE FOR META-ANALYSES

CES is an FDA cleared, prescriptive, noninvasive electromedical treatment that has been shown to significantly decrease insomnia in multiple RCTs and Non-Randomized Scientific Investigations (NRSIs). To our knowledge, this would be the first time that the body of evidence examining CES (RCTs

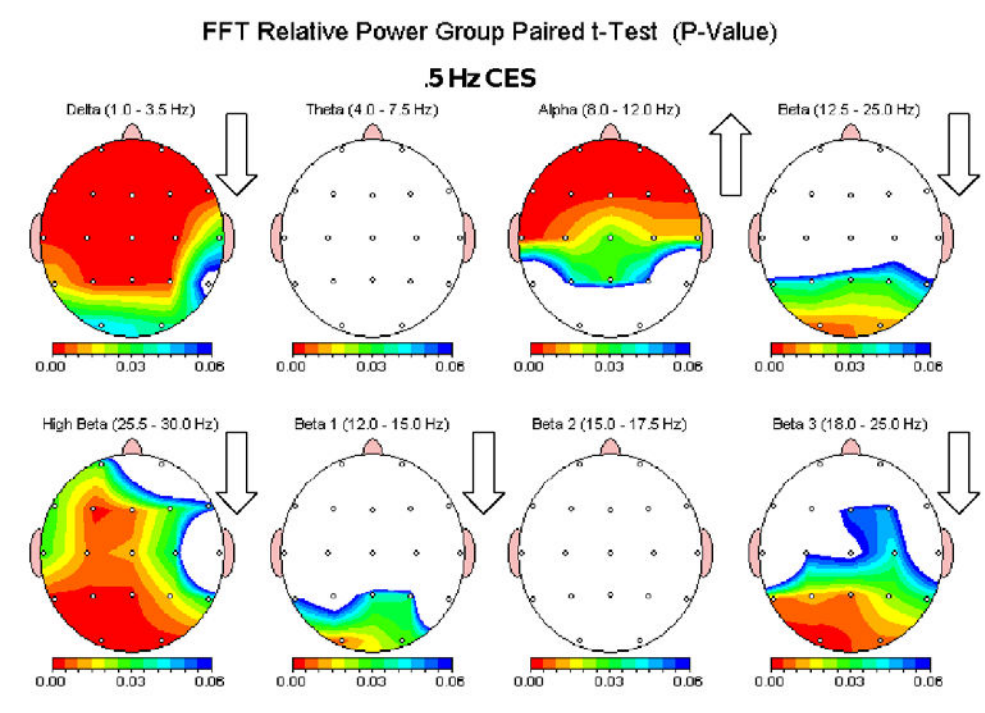

Figure 1 Significant changes in the electroencephalogram (EEG) after a single CES treatment in 30 student volunteers organized by level of significance within frequency bands where red is the most significant (p<.001) and blue is the least significant (p<.06) [51].

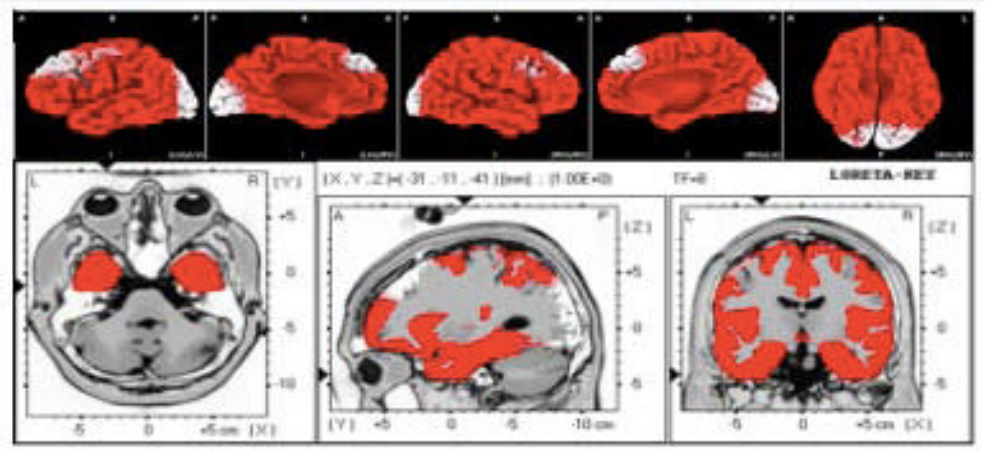

Figure 2 CES has also been shown to penetrate the hypothalamus resulting in secretion of neurotransmitters and neurohormones [32, 53, 54].

and NRSIs), for the treatment of insomnia has been systematically investigated. We believe the novelty of the work adds value to the understanding of the other treatment approaches to insomnia.

META-ANALYSIS OF CES STUDIES FOR INSOMNIA

Alpha-Stim® (Electromedical Products International, Inc., Mineral Wells, Texas, www.alpha-stim.com) is an original, patented CES technology on the market since 1981 and the only CES device approved for the Federal Supply Schedule (FFS) for purchases by the Department of Defense and Veterans Affair's Medical Centers. To determine if Alpha-Stim® CES is efficacious for insomnia, we conducted a systematic review and meta-analyses of the available studies on the efficacy of Alpha-Stim® as a treatment for insomnia. We included both Randomized Controlled Trials (RCTs), and Non-Randomized Studies on Interventions (NRSIs). As CES devices differ significantly in their electrical outputs and usage, individual assessment is warranted. Accordingly, we limited our meta-analysis to one CES device for the treatment of insomnia.

The Alpha-Stim® device design has changed incrementally over 39 years consistent with the evolution of technology, but the waveform and output parameters have remained the same; thus facilitating comparisons across time. Research performed using previous models of Alpha-Stim® CES during the 1980s and 1990s are still replicable today using the current 7th and 8th generation

models, the Alpha-Stim® AID and Alpha-Stim® M. The evaluation of strengths and limitations of the research studies included in this report adheres to guidelines published by Zaza et al. [59], those in the *Cochrane Handbook for Systematic Reviews of Interventions* [60], and in the *Handbook of Research Synthesis and Meta-Analysis* [61]. We used the Cohen's *d* [62], effect size summary metric in all analyses. Homogeneity of effect sizes within the fixed and random effects models are also reported. Meta-analyses were performed using the Comprehensive Meta-Analysis, version 3 program [63]. The 3 RCTs [49,64,65], included in this meta-analysis are shown in Table 1, where the total N=163. All the RCTs found a significant improvement in insomnia following treatment with CES.

Table 2 provides a summary of the 5 NRSIs [66-70]. All studies were open-label with patients exhibiting symptoms of insomnia. A total of 376 participants were included in this meta-analysis.

MATERIALS AND METHODS

Our systematic review involved locating relevant scientific literature, including RCTs and NRSIs, for the use, effectiveness, and the risk/benefit of Alpha-Stim® CES in the treatment of insomnia disorders. The purpose of our meta-analyses is to summarize the scientific data on Alpha-Stim® CES treatment of insomnia. In our literature review, we followed Cooper's Taxonomy of Literature Reviews [61,71,72] that is appropriate for the behavioral and physical sciences (Cooper, Hedges, and Valentine, 2009). and the PRISMA reporting guidelines [72]. Our literature review followed five guidelines from the Cochrane Black Group:

1. A computer-based search of MEDLINE and EMBASE databases since their beginning.
2. A search of the Cochrane Central Register of Controlled Trials (CENTRAL) included in the Cochrane Library.

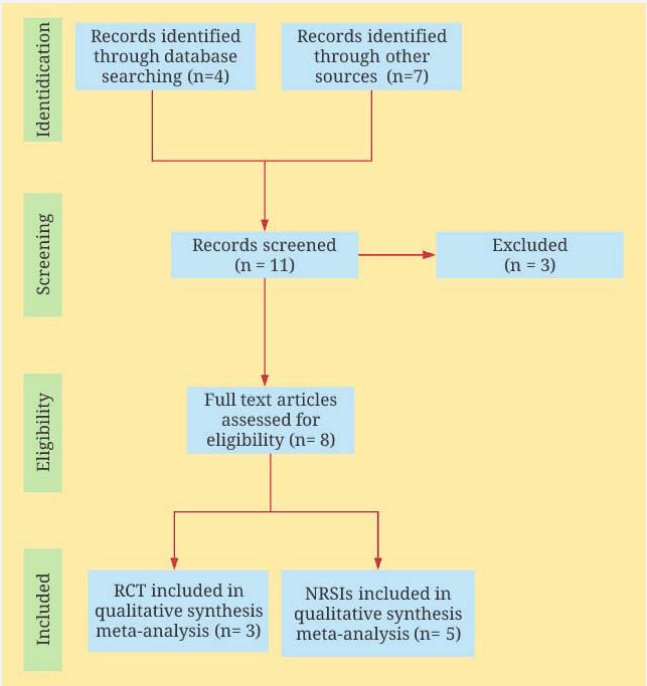

Figure 3 PRISM flow diagram of inclusion criteria in CES research for insomnia meta-analyses.

3. The search proceeded within abstract, subject terms, and titles of studies and reports published in peer-reviewed journals between January 1, 1981, and August 26, 2020. Keywords:
   a. Insomnia **and** Alpha-Stim **and** cranial electrotherapy stimulation **and** randomized control trial **or** non-randomized **or** open-label **or** case study.
   b. The search yielded 8 articles (3 RCTs and 5 NRSIs) - see Figure 3.
4. Screening references given in relevant systematic reviews and identified RCTs.
5. Citation tracking of identified RCTs using the Science Citation Index through the Web of Science.

Any meta-analysis includes a range of research studies with varying degrees of scientific rigor directly impacting the validity of conclusions arising from the synthesis, and ours is no different. We followed the scoring rubric of Zaza et al. [59], with scoring categories of 0-1 limitations (rating = good); 2-4 limitations (rating = fair); 5-9 limitations (rating = limited) which we have used in the selection of the research studies in our meta-analysis on the efficacy of CES for insomnia. Additionally, we used the Revised Cochrane Risk-of-Bias Tool [73], to inform our decision about including a study within an RCT design [60]. To be included in this meta-analysis, studies were RCTs - inclusive of subjects blinding (with a description of how blinding was implemented), a sham versus active condition, use of valid and reliable measurement instruments, at a minimum, a pretest-posttest design (additional repeated measures were acceptable), and rated as "good" or "fair." Figure 3 shows the PRISM flow diagram for selection of inclusion criteria into the meta-analysis yielding 3 RCTs and 5 NRSIs [72,74, 75].

RESULTS AND DISCUSSION

We used a complementary approach to synthesize the meta-analytic results from NRSIs with RCTs [72]. One goal of complementary non-randomized studies is to provide additional information about interventions that were evaluated in RCTs. For example, the information in some RCTs may be incomplete or too narrow. In this case, NRSI's may provide valuable additional information regarding the efficacy of treatment outcomes.

RANDOMIZED CONTROLLED TRIALS

Figure 4 provides the meta-analytic results of the three (N=3) RCT studies on insomnia. The left side of Figure 4 provides a statistical summary of the studies, each represented by the standardized mean difference (i.e., d) between study groups at posttest. Due to variation in reporting of results across the 3 studies, only the difference at posttest between groups was used in calculation of the effect of Alpha-Stim® CES on insomnia. To examine the magnitude of change within study groups from baseline to posttest (and other measurement points captured.

The forest plot provided in Figure 4 reflects (a) the effect size d, (b) the variability of each study's effect via the 95% confidence interval, and (c) the average (i.e., population estimate) effect size for all 3 studies (blue diamond). As is displayed, the average (population) effect for the 3 studies was observed as d = -0.83

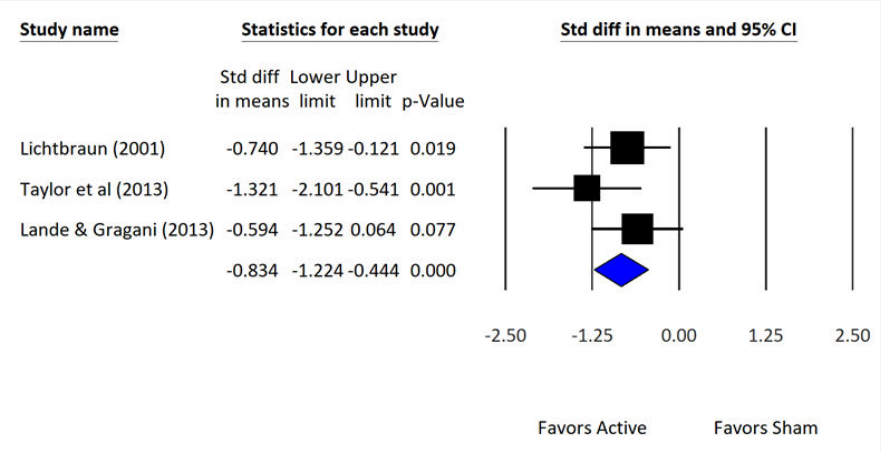

Figure 4 Summary Statistics of Effect Sizes and Forest Plot from Alpha-Stim CES RCTs of Insomnia (N=3).

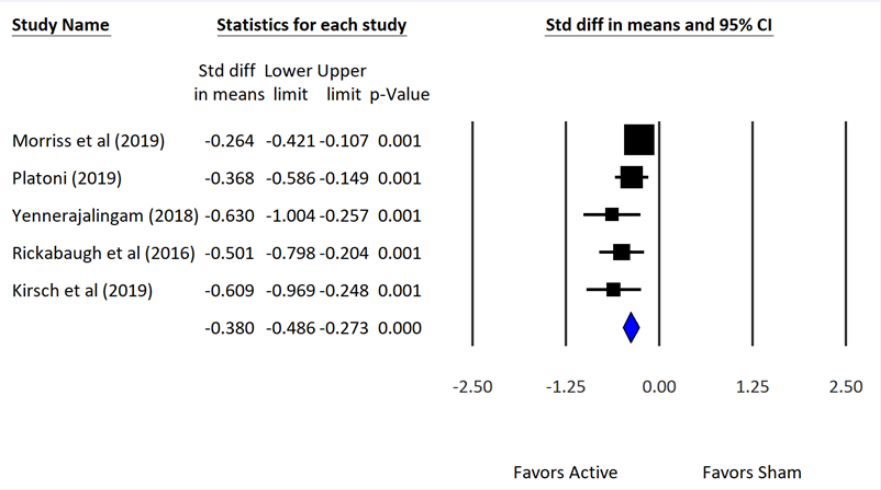

Figure 5 Summary Statistics of Effect Sizes and Forest Plot from Alpha-Stim CES NRSIs of Insomnia (N=5).

(i.e., the mean insomnia level at posttest for the active group was -0.83 standard deviations lower than the mean insomnia level of quality sleep for the sham group). An effect size of -0.83 is classified as large [61,76].

Finally, the symbols in the forest plot in Figure 4 depict the relative weight for each of the 3 studies (e.g., the larger the symbol the greater the relative contribution each study makes to the final result). Also informative is the width of the confidence interval. For example, the larger the sample size of an individual study, the smaller the width of the interval and the greater the precision of the effect size.

Table 3 displays a summary of the meta-analytic model for the N=3 studies. In meta-analytic studies, an important issue to evaluate is the heterogeneity of the studies. For example, if the heterogeneity in the studies is statistically significant, including a moderator as part of the meta-analysis may be warranted. The Q-statistic is used to test for significant heterogeneity in the effect sizes used in the analysis (i.e., that the effect sizes are more heterogeneous than expected by sampling variability alone). In Table 3, the Q-statistic is 2.06, p=.35, indicating that heterogeneity for the effect sizes is nonproblematic (although this analysis includes only 3 studies). However, the Q-test does not provide information regarding the magnitude of the heterogeneity of the effect sizes – a critical issue. To evaluate the magnitude (practical) effect of the effect sizes in the N=3 meta-analysis, we turn to the I-squared value (0.000 or 0%) in Table 3. The I-squared statistic is derived as the ratio of between study variance to within study variance. Studies with small sample sizes inflate the I-squared statistic. In the present meta-analysis, although some of the studies included small sample sizes, the impact of the small sample did not significantly influence the heterogeneity of effect sizes. Card (2012, p. 189) states that I-squared interpretative ranges as a magnitude of study heterogeneity are ~25% = small; ~50% = medium; ~75% = large.

In the Random-effects model, inferences are justified beyond a certain set of studies included in a specific meta-analysis to a population of potential studies of which those are representative. A comparison of the point estimates between the Fixed-effect model (-0.83), and Random-effects model (-0.84), are nearly the same and tau-squared (i.e., the population variance) is

Table 1: Randomized Control Trials (RCTs) included in the insomnia meta-analysis.

Taylor, et al., [49]	46	Males & Females >18 Years with Insomnia & Comorbid Fatigue	RCT	**Primary Outcome Measure: GSDS Score.** The primary effectiveness endpoint was the change from baseline in the last post-treatment scores on the outcomes measures for sleep disturbance, pain, fatigue and functional status compared to the sham treatment group at the endpoint of the 8 week study. CES group had significantly lower scores on GSDS (indicating less sleep disturbance) than sham from baseline to the end point of study (p=0.001, d=-0.30) and completed the study with scores below the range of insomnia. While all 3 groups reported scores that were in the insomnia range at baseline, the active CES group was the only group that reported decreased scores over the course of the study and completed the study with scores below the range of insomnia. Baseline GSDS score was 3.75 in the Active group, 4.01 in the Sham condition, and 3.6 in the TAU group. At the end of treatment, the Active group scores had lowered to 3.7, with the Sham and TAU condition at 3.8. No effect size is reported.
Lande & Gragnani [64]	57	Males & Females 21-40 Years with Insomnia, Severe Trauma & Mild Depression	RCT	**Primary Outcome Measure: PIRS Score.** The active CES group had a longer total time slept (43 minutes) from baseline than the sham CES group who averaged 19 minutes less total time slept. Men who completed 5 sessions of CES had significant improvement in total time slept after the first CES treatment (p=0.04, d=0.41) and on day 4 (p=0.03, d=0.49). The difference between the active CES and Sham CES groups approached significance on day 5 (p=0.079). Men in the active CES group slept an average of 53 minutes more after the first CES treatment and an average of 61 minutes more on day 4 compared to the sham CES group. There were no significant changes in total time slept among the females in this short, 5-day study.
Lichtbroun et al., [65]	60	Males & Females >18 Years with Insomnia	RCT	**Primary Outcome Measures: NRS & POMS Score.** Measures of overall pain, quality of sleep, feelings of well-being and quality of life. Measures were taken at baseline and at the end of week 3 of the study. The active CES group had significant findings on 8 of the 11 variables compared to the sham group: significantly lower anxiety scores (p=0.04, d=-.60), higher quality of sleep scores (p=0.02, d=.45), lower pain scores (p=.004, d=.65), higher feelings of well-being scores (p=.007, d=.73), higher quality of life scores (p=.001, d=.97), lower fatigue scores (p=0.03, d=.72 and lower anger scores (p=0.04, d=.60) compared to sham group.

Abbreviations: Randomized Control Trials (RCTs), Standard Deviation (SD) General Sleep Disturbance Scale (GSDS), Numerical Ratings Scale (NRS), Treatment as Usual (TAU), Profile of Mood States (POMS), Pittsburgh Insomnia Rating Scale (PIRS).

Table 2: Non-Randomized Studies on Interventions (NRSIs) included in the insomnia meta-analyses.

Kirsch et al., [66]	44	Males & Females >18 Years with Insomnia, Anxiety, Depression & Pain	NRSI	**Primary Outcome Measure: NRS Score.** Measure of sleep on a scale of 0-10 as an indicator of sleep using a smartphone app. Outcome measures were insomnia, anxiety, depression, and pain. Measures were taken at baseline and after 6 weeks of treatment. Insomnia scores reduced from a mean of 6.03 (1.55) at baseline to 1.18 (0.45) at posttest (p<0.001, d=4.9). This treatment effect with Alpha-Stim CES on anxiety, insomnia, depression, and pain was consistent with prior surveys and confirmed the precision of the new app in determining progress from a single treatment and a series of treatments. The study design included a single subject convenience sample design using one pretest posttest trial with teachers choosing to participate.
Morriss et al., [67]	161	Males & Females 25-50 Years with Insomnia, Anxiety & Depression	NRSI	**Primary Outcome Measure: AIS Score.** Measure of sleep taken at baseline, 12, and 24 weeks. A quarter of participants achieved remission on the Athens Insomnia scale at 12 and 24 weeks. There was a statistically significant within subjects decrease in insomnia over the 24-week period (F=42.69, p<0.001) and the effect size was medium (partial Eta square=0.21). AIS score at baseline significantly improved from 13.02 (4.88) to 8.64 (5.43) and 8.05 (4.83) at 12 and 24 weeks respectively (p<0.001) **Secondary Outcome Measures: PHQ-9, GAD-7, WSAS, EQ5D-5L Scores.** Measures of depression, anxiety, work and social function, and health utility and quality of life. The within subjects effect was significant (F = 42.89, dfl = 3. 9/df = 559.01, p < 0.001) with the mean PHQ-9 score dropping from the moderately severe range to the mild range but the effect size was small (partial Eta square = 0.21). A total of 72 (44.7%) and 77 (47.8%) achieved remission on the GAD-7 at 12 and 24 weeks respectively with 122 (75.8%) receiving at least 6 weeks CES. Mean (SD) GAD-7 score at baseline significantly improved from 15.77 (3.21) to 8.92 (5.42) and 8.99 (6.18) at 12 and 24 weeks respectively (p<0.001). 80 (49.7%) participants required further individual CBT. The proportions of participants achieving reliable improvement on the GAD-7 were 102 (63.4%) and 105 (65.2%) at 12 and 24 weeks respectively. Just over a quarter of participants made a functional recovery on the WASA at 12 and 24 weeks with CES. There is a significant within-subjects effect of Alpha-Stirn CES over the 24 weeks (F = 17.35, dfl = 3.5/ df = 557.45, p < 0.001) but the effect size is small (partial Eta square = 0.10). The effects of Alpha-Stirn CES on the EQ-5D-5L were very similar to the WASA with a significant within subjects effect over 24 weeks (F = 13.94, dfl = 4.1/df2=651.3,p < 0.0001) but the effect size is also small (partial Eta square = 0.08).

Platoni et al., [68]	86	Males & Females >18 Years with Insomnia, Anxiety, Pain & Depression	NRSI	**Primary Outcome Measure: NRS.** Outcome measures of insomnia, anxiety, depression, and pain taken using a smartphone app at baseline and 6 weeks post treatment. Results were seen in insomnia with a pretest mean of 5.70 and posttest mean of 3.80 for a reduction of 33% with p<.001 (two-tailed), and effect size d=1.18 (large). The anxiety pretest mean was 4.18 and posttest mean of 1.93 for a reduction of 54% (p<.001), and the effect size was d=1.21 (large). These 86 police officers, sheriff's officers, and firefighters experienced a very significant decrease in insomnia, anxiety, depression, and pain by using Alpha-Stim CES. The statistical analyses revealed highly significant values of p<.001 for anxiety, depression, insomnia, and pain. The effect size Cohen's d values were large for all outcome measures indicating a high level of practical change from baseline to posttest, which supports the capability of Alpha-Stim CES technology in reducing anxiety, insomnia, depression and pain symptoms and the ability to monitor progress on the Alpha-Stim app.
Yennurajalin-gam et al., [69]	36	Males & Females, 57-67 Years with Insomnia, Anxiety, Pain & Depression	NRSI	**Primary Outcome Measure: PSQI Score.** Measures were taken baseline and after 4 weeks treatment. A total of 33 out of 36 (92%) completed CES. Median (IQR) adherence CES use and satisfaction scores were 93% (89-100) and 10 (9-10) respectively and the adherence criteria was met in the study. CES use was safe (no grade 3 or higher adverse events). The baseline PSQI score was 10.23 at the start of treatment and to 8.4 at the end. PSQI daytime dysfunction (p=0.002), and Medication use (p=0.006) scores improved after 4 week CES treatment. **Secondary Outcome Measures: ESAS and HADS Scores.** Participants demonstrated significant improvement in anxiety and depression as measure ay baseline and post treatment. HADS anxiety (p<0.001), HADS depression (p=0.024), ESAS anxiety (p=0.001), depression (p=0.025), BPI pain (p=0.013), and Medication use (p=0.006) scores improved after 4 weeks of CES treatment. There were no significant differences in salivary cortisol, alpha-amylase, CRP, IL-1β, or IL-6 levels in this 4-week study. The median (IQR) adherence CES use and satisfaction scores were 93% (89-100) and 10 (9-10) respectively and the adherence criteria was met in the study. Terminal cancer patients demonstrated significant improvement in depression symptoms and severity. The baseline HADSs anxiety score was 8.81 at the start of treatment and to 6.16 at the end. HADSs depression score was 6.36 at baseline, and 5.34 at the end of treatment. No effect size is reported.
Rickabaugh et al, [70]	49	Males & Females >18 Years with Insomnia, TBI, Anxiety, Pain & Depression	NRSI	**Primary Outcome Measure: NRS Score.** Hours slept and self-report measure using a 0-10 scale on functional improvement with regards to anxiety, depression, headache, tinnitus, and pain. Significant improvement (p=0.001) found in hours slept over five treatments. 4.88 to 5.42 hours after 5 treatments No effect size is reported.

Table 2 Abbreviations: Non-Randomized Studies on Interventions (NRSIs), Standard Deviation (SD), Numerical Ratings Scale (NRS), Traumatic Brain Injury (TBI), Athens Insomnia Scale (AIS), Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder Scale-7 (GAD-7), Work and Social Adjustment Scale (WSAS), EuroQol (EQ5D-5L, Pittsburgh Sleep Quality Index, Edmonton Symptom Assessment (ESAS), Hospital Anxiety and Depression Scale (HADS).

Model	N	Effect	S.E.	Variance	LL	UL	Z	P	Q	df (Q)	P	I-squared	Tau Squared	S.E.	Variance	Tau
Fixed	3	-0.834	0.20	0.04	-1.224	-0.289	-0.444	0.00	2.10	2	0.35	4.55	0.01	0.13	0.02	0.08
Random	3	-0.836	0.20	0.04	-1.236	-0.341	-0.436	0.00								

Note. N=number of studies. Effect=average d across studies. LL=lower limit of 95% confidence interval, UL=upper limit of 95% confidence interval. Z= test statistic based on the Z distribution. S.E. = standard error. P= probability value.

Table 3 Meta-Analyses Summary Statistics – Insomnia RCTs.
Point estimate = average standard effect, d, over 3 studies. Q-value = test of study heterogeneity (i.e., are the set of effect sizes homogeneous). I-squared = magnitude of study heterogeneity (~25% = small; ~50% = medium; ~75% = large).

relatively close to zero. In summary, the studies included in this meta-analysis (N=3), show a large effect in favor of the active treatment group. Given the congruency (i.e., closeness), between the summary statistics of Fixed- and Random-effects models in Table 3, it is reasonable to also state that the research shows a large effect in favor of the active treatment group relative to reductions in insomnia.

NON-RANDOMIZED STUDIES OF INTERVENTIONS

The use of Non-Randomized Studies on Interventions (NRSIs), in the field of psychiatry and psychology is vital to building the evidence base and developing best practices for patient care. Often research in psychiatric or psychological care involves challenges that make use of the gold standard research design, the randomized controlled trial (RCT), inappropriate or not possible. Challenges to the RCT include patient recruitment, gatekeeping by physicians, crossover contamination, high attrition rates, and small sample sizes. Other challenges include variation in access to psychiatric care and disparities in the use and provision of care that are unable to be answered without NRSI-based research methods. Well-designed NRSIs or observational studies are described in Reeves et al. [77], and Shadish et, al. [78]. Meta-analyses of NRSIs present challenges due to inherent (uncontrolled) biases and differences in study design. However, they also provide an important way to quantify sources of variability in results across studies. Here we follow

Model	N	Effect	S.E.	Variance	LL	UL	Z	P	Q	df (Q)	P	I-squared	Tau Squared	S.E.	Variance	Tau
Fixed	5	-0.380	0.05	0.003	-0.486	-0.273	-6.967	0.00	6.00	4	0.20	33.38	0.01	0.02	0.00	0.09
Random	5	-0.414	0.07	0.005	-0.555	-0.272	-5.736	0.00								

Note. N=number of studies. Effect=average d across studies. LL=lower limit of 95% confidence interval, UL=upper limit of 95% confidence interval. Z= test statistic based on the Z distribution. S.E. = standard error. P= probability value.

Table 4 Meta-Analysis Summary Statistics – Insomnia NRSI.
Point estimate = average standard effect, d, over 5 studies. Q-value = test of study heterogeneity (i.e., are the set of effect sizes homogeneous). I-squared = magnitude of study heterogeneity (~25% = small; ~50% = medium; ~75% = large).

recommendations from Reeves, et al. [77], Schünemann et al. [79], Stroup et al. [80], and Haidich [81], for ensuring the quality and consistency in the meta-analysis of NRSIs. Based on our review of the literature we identified 5 NRSIs that exhibited a quality of "Good" or "Fair" according to Zaza [59], and Reeves et al. [77], criteria (see Figure 5).

Table 4 displays a summary of the meta-analytic model for the 5 studies. For the Fixed-effect model, the average (population) effect was observed as -0.38 (small), and for the Random-effects model, the average effect was -0.41 (medium). In meta-analytic studies, an important issue to evaluate is the heterogeneity of the studies. For example, if the heterogeneity in the studies is statistically significant, including a moderator as part of the meta-analysis may be warranted. The Q-statistic is used to test for significant heterogeneity in the effect sizes used in the analysis (i.e., that the effect sizes are more heterogeneous than expected by sampling variability alone).

In Table 4, the Q-statistic is 6.00, p=0.20, indicating that non-significant heterogeneity for the effect sizes exists. However, the Q-test does not provide information regarding the magnitude of the heterogeneity of the effect sizes – a critical issue. To evaluate the magnitude (practical) effect of the 5 data sets included in the meta-analysis, we turn to the I-squared value (33.38 or 33%), in Table 4. The I-squared statistic is derived as the ratio of between study variance to within study variance. Studies with small sample sizes inflate the I-squared statistic. In the present meta-analysis, the I-squared statistic is 33.38 (small) indicating the data displays a minimal amount of heterogeneity. Card (2012, p. 189) states that I-squared interpretative ranges as a magnitude of study heterogeneity are: ~25% = small; ~50% = medium; ~75% = large.

In the Random-effects model, inferences are justified beyond a certain set of studies included in a specific meta-analysis to a population of potential studies of which those are representative. A comparison of the point estimates between the Fixed-effect model (-0.38 - small), and Random-effects model (-0.41 - medium), are different and the population variance is relatively close to zero (0.003). In summary, the 5 studies included in this meta-analysis show a small effect in favor of the active treatment group.

DISCUSSION

We examined the efficacy of CES for the treatment of insomnia disorders in systematic meta-analyses of 3 RCTs, and 5 NRSIs. Our results show that CES is an effective treatment for insomnia and a useful adjunctive to other ongoing treatments including pharmacotherapy and psychotherapy for insomnia.

The studies used in our meta-analyses all had significant outcomes of $p<0.05$ through $p<0.001$ for insomnia and many also revealed equally good effects for the treatment of anxiety and depression. The effect sizes and Cohen's d values were medium for the RCTs and small for the NRSIs. In comparison, the effect sizes typically associated with antidepressant medication for published studies is 0.37 (95% CI, 0.33 to 0.41), and for unpublished studies it's less than 0.15 (95% CI, 0.08 to 0.22), both qualifying as small [62]. When the side effect profile of medications vs CES is considered, the supremacy of CES over medications is even more notable. The risk profile for CES was virtually negligible, with mild and self-limiting vertigo or cervicogenic headaches when the current is too high, and skin irritation at the electrode site reported in less than 1% of patients.

CES in community dwelling adults with insomnia was significantly more effective than wait-list controls. The studies included in the meta-analysis ranged from 2001 through 2013, and although the Alpha-Stim® devices used in all the RCTs and NRSIs have changed during that time, the waveform and output parameters have remained the same facilitating comparisons across time just as pills and capsules of the same drug delivered in the same dosages are expected to have the same effects regardless of the packaging.

The insomnia measures pre and post-treatment varied across the studies in the meta-analysis (RCTs: GSDS [49], NRS [65], PIRS [64]); (NRSIs: NRS [67,68,70], AIS [67], PSQI [69]).

CES is effective for insomnia in a range of populations with a spectrum of insomnia severity, as evidenced by pre-and-post scores of the appropriate insomnia measures based on the sample population - civilian, military, and first responders. These studies report that patients receiving CES treatment have shown improvements in negative domains that typically cooccur with insomnia such as somatization, interpersonal sensitivity, obsessive or compulsive thoughts, excessive worry, hostility, fearfulness, alcohol and substance use, and paranoia. Concurrently patients report improvement in symptoms associated with CES treatment as measured by the Global Assessment of Function (GAF), a measure incorporated in some of the studies in our meta-analyses and by clinicians using the Clinical Global Impression (CGI), scale to report on patient improvement.

Although our meta-analyses revealed CES is an effective treatment for insomnia, the RCTs and NRSIs had limitations. In these, as in most studies, participants were self-selected with the likely consequence of selection bias. The RCTs were double-blinded and inclusive of sham control but the studies had a limited number of patients with significant symptoms for a diagnosis of disordered sleep. The NRSIs lacked randomization

and a control group and many of the patients were continuing to receive other treatments (e.g., pharmacotherapy), although all patients reported continued insomnia and met the inclusion criteria for the studies so the effects can be considered over and above that of medication alone [82].

CONCLUSION

Our meta-analyses examined CES for the treatment of insomnia - 3 RCTs and 5 NRSIs incorporating 8 data sets. CES for insomnia was significantly more effective than wait-list and sham-treated comparator groups. The effectiveness of CES as an adjunctive treatment is yet to be systematically explored. Since the clinical benefit that might arise from the combination of CES with other interventions could be a step forward in insomnia treatment, further investigation is pressing. Our meta-analyses determined that Alpha-Stim® CES technology is an effective treatment in managing insomnia in community, active duty service members and veterans, and first responders with a spectrum of insomnia severity. In addition, we conclude that CES is an effective tool for the treatment of insomnia and may be a useful adjunctive to other ongoing treatments including pharmacotherapy and psychotherapy for insomnia.

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CONFLICT OF INTEREST

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