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A meta-analysis of cranial electrotherapy stimulation in the treatment of depression

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ABSTRACT

Background: Depression rates have reached historic highs, with 49% of Americans reporting unabating symptoms and signs of depression, representing a 12% increase compared to the same time in 2019. With depression as a moderating factor for suicide, the need for efficacious treatments for depression has never been more pronounced. Although the armamentarium of the psychiatrist seems impressive having multiple medications and psychotherapy options, with guidelines for combination and augmentation treatments; many patients do not improve or are not suitable candidates for the usual, customary and reasonable (UCR) depression treatments. The use of various forms of brain stimulation technology as a complementary or alternative treatment for depression is growing and is expected to be part of the armamentarium of most psychiatrists by 2030. One form of brain stimulation, available in a phone sized prescription device, is cranial electrical stimulation (CES) which has been used as a treatment for depression since the 1970s. We have conducted two meta-analyses of CES research for depression separating randomized controlled trials (N = 5) from non-randomized studies on interventions (N = 12). For the double-blind RCTs 100 μA was used for 1 hour per day as 100 μA is a subsensory level of current so identical sham treatment devices could be used.

Methods: Our literature review followed Cooper's Taxonomy of Literature Reviews that is appropriate for the behavioral and physical sciences and the PRISMA reporting guidelines. The evaluation of strengths and limitations of the research studies included in this report adheres to recommended published guidelines in the Cochrane Handbook for Systematic Reviews of Interventions, and in the Handbook of Research Synthesis and Meta-Analysis. We used the Cohen's *d* effect size summary metric in all analyses. Homogeneity of effect sizes within the fixed and random effects models are reported. Meta-analyses were performed using the Compressive Meta-Analysis, version 3 program.

Results: The 5 RCTs represent a combined N of 242 and the 12 NRSIs represent 16 data sets with a combined N of 1173 for total of 1415 subjects across 17 studies. There were male and female subjects, from adolescents to 60 years old. The average effect for the 5 RCTs was calculated as $d = -0.69$ (*i.e.,* the mean depression level at posttest for the active group was −0.69 standard deviations lower than the mean depression level for the sham group), a medium effect. The additional 12 NRSI studies analyzed show a small effect of $d = -0.43$ in favor of the active treatment group.

Conclusion: We conclude that CES has a small to medium significant effect in symptoms of depression across moderate to severe patients in civilian, military, veterans, advanced cancer and pediatric populations.

1. Introduction

Depression is a debilitating condition that decimates patients' quality of life, their relationships, ability to work and care for themselves. It is broadly defined to include both pure depression and mixed anxiety-depression. The National Institute of Mental Health (NIMH, 2018) rates depression as one of the most diagnosed mental disorders, with more than 300 million people worldwide suffering from this disorder (James et al., 2018; WHO, 2017a). Lifetime prevalence worldwide is estimated to be between 10% and 18% of adults and between 5% and

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10% of adolescents, while at any given moment, depression typically affects 7%–12% of the U.S. adult population (WHO, 2017b; Bromet et al., 2011; Lim et al., 2018; Wittchen et al., 2011). Lifetime risk of having at least one episode of major depression can be as high as 30% for males and 40% for females (Kruijshaar et al., 2005). Community survey data predict that a person with depression will average about eight episodes during their lifetime. Subclinical conditions that do not fit the diagnostic criteria of major depression are associated with some disability for 12–16 years of their life (Andrews et al., 2007). Epidemiologic studies have established that an anxiety disorder is present in 59% of patients with a history of major depression over their lifetime (Kessler et al., 2007). Despite known prevalence, depression is significantly underdiagnosed and undertreated, particularly in primary care, where most patients with depression seek care. Early detection, intervention, and appropriate treatment can promote remission, prevent relapse, and reduce the emotional and financial burden of the disease (Halfin, 2007).

The economic burden of the disease, which is a leading cause of disability worldwide, is significant and increasing (WHO, 2017b; Vos et al., 2017). It is estimated that major depression costs the USA over $210 billion each year (Greenberg et al., 2015).

The global coronavirus (COVID-19) pandemic of 2020 has resulted in depression prevalence rates in the U.S. reaching historic highs, with 49% of Americans reporting symptoms and signs of depression, as measured by the Patient Health Questionnaire (PHQ-4), a standardized measure of anxiety and depression. Symptoms that were sustained over several weeks show no signs of fading, representing a 12% increase compared to the same time period in 2019 (NIMH, 2018; Fitzpatrick et al., 2020). In a recent survey study that included 1441 respondents from during the COVID-19 pandemic and 5065 respondents from before the pandemic, depression symptom prevalence was more than 3-fold higher during the COVID-19 pandemic than before (Ettman et al., 2020).

No population group is immune to the spectrum of depressive disorders. Nor is there an objective pathognomonic test for depression, such as the use of a glucometer to diagnose and determine the severity of diabetes. Depression is diagnosed through structured questionnaires based on self-reported symptoms such as patient interviews or psychometric tests. Despite the valiant efforts of psychiatry to treat depression, patients continue to endure distressing and disabling symptoms, and suicide rates continue to rise. The impact of undiagnosed and untreated depression is monumental to patients, their families, and society (König et al., 2020); and the clinicians who report feeling demoralized and disheartened as their effort to treat patients is ineffective, and at times even counterproductive (Kalin, 2019).

Some clinicians argue that depression and anxiety are not discrete disease entities, but are changeable, fluctuating in time (Bowins, 2015). Composites of complex conditions and symptom clusters can wax and wane over time, varying from absent to severe (Cloninger, 2002; Maj, 2005) and exhibit multiple manifestations of a single clinical disorder (Prisciandaro and Roberts, 2005) instead of a group of diagnostic entities with defined boundaries (Parker et al., 1991; Kendler and Gardner, 1998; Benazzi, 2006; Kessing, 2007; Paykel, 2008; Rodríguez et al., 2012). Mild cases of depression at one moment in time also represent a substantial proportion of future severe cases (Kessler et al., 2003). The number, severity, and extent of depressive and anxiety symptoms may also differ across gender, genetics, developmental stage, and culture; and such differences cannot be examined by lumping symptoms into a single category like major depression (Stein, 2012).

1.1. Psychiatrists armamentarium

Although the tools available to psychiatrists and psychologists seem impressive, treatment for depression remains far from successful. Many patients are not suitable candidates for pharmacological or psychotherapeutic interventions - those with chronic illnesses, cognitive impairment, or treatment-resistant depression. Accordingly, the need for efficacious treatments has never been more pronounced. Decades-long research into depression and its underlying causes have resulted in a plethora of theories and models, yet a definitive explanation remains elusive. The ubiquitous chemical-imbalance disease-based drug model that led to the explosion of antidepressant drugs has not delivered on its promise of a 'silver-bullet' that would eradicate depression (Makovec, 2020).

1.2. Antidepressant efficacy

Several published systematic reviews comparing the effectiveness of antidepressants to placebo have shown a trend in favor or medication. A review of 14 studies comparing the efficacy of tricyclic antidepressants (TCA) on 1364 patients and 919 controls showed a RR of 1.24, (95% CI 1.11 to 1.38) in favor of TCAs against placebo and 1.28 (95% CI 1.15 to 1.43) for selective serotonin reuptake inhibitors (SSRI) (Arroll et al., 2009). These findings are consistent with a review of 6 FDA randomized placebo-controlled trials (N = 718) on the efficacy of antidepressants in the treatment of Major or Minor Depressive Disorder (Fournier et al., 2010). The authors reported significant medication vs placebo differences as a function of depression symptom severity. HAM-D scores below 23, the reported a small effect size in favor of medication (d = 0.20), with HAM-D scores above 25 meeting NICE (NICE, 2010) guidelines for a clinically significant difference from baseline and showing substantial benefit over placebo. The authors concluded that for mild to moderate depression, the magnitude of benefit from medication was minimal or non-existent.

A review of 522 trials, involving 116,477 participants, concluded that in adults with major depressive disorder antidepressants were more efficacious than placebo, with strong recommendation for their use as a first line treatment (Cipriani et al., 2018). A subsequent review of the same data using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the risk of bias and caliber of clinical evidence did not find any definitive support for the recommendation that antidepressants as more efficacious than placebo in the management of major depression (Munkholm et al., 2019). The authors proposed several reasons for what they believe inflated the true efficacy and acceptability of antidepressants for the treatment of major depression made in the prior review. Citing systemic bias toward publishing and reporting on antidepressant trials with higher effects ($p < 0.0001$), a conclusion consistent with others (Arroll et al., 2009; Fournier et al., 2010). One study reported that 94% of the published trials on antidepressants had yielded positive results, when those same studies were compared to the FDA's definition of a positive trial, the percentage dropped to 51% (Turner et al., 2008).

Munkholm et al. (2019) highlighted the methodological shortcomings of several studies included in the earlier favorable review of the efficacy of antidepressants by Cipriani et al. (2018), and inconsistencies in the reporting of the original findings in 12 of the 19 trials (63%). Significant differences in depression symptoms were noted in studies included in the review that had a 'placebo run-in' compared to those without a 'placebo run-in' ($p = 0.05$). The mean difference in the

Hamilton Depression Scale (HAM-D) between the antidepressant and placebo group was 1.97 points (95% CI 1.74 to 2.21), in a scale that ranges from 0 to 52, this equates to at best a marginal improvement to function and not commensurate with any substantive symptom relief. A difference of three points on the HAM-D or BDI is needed to be considered clinically significant in accordance with the British National Institute of Health and Clinical Excellence (NICE, 2004). These findings are consistent with Jakobsen et al. (2017), who compared 131 randomized placebo-controlled trials enrolling a total of 27,422 participants and reported a reduction in the HAM-D of −1.94 points (95% CI −2.50 to −1.37) below clinical significance. Jakobsen et al. concluded that SSRIs increase the risk of serious adverse events (OR 1.37; 95% CI 1.08 to 1.75; p = 0.009), corresponding to 31/1000 patients prescribed antidepressants that will experience serious adverse events compared to 22/1000 controls.

Those in favor of medication for depression often report that the HAM-D, typically under-reports the level of depression symptom relief that patients experience. Yet, a comparison of the sensitivity of the HAM-D with the Montgomery-Asberg Depression Rating-Scale (MADRS) did not find any evidence to support the theory that the HAM-D underreports the efficacy of antidepressants (Hengartner et al., 2020). The efficacy of antidepressants is often bolstered by baseline severity, and by decreased responsiveness of severely depressed patients in the placebo group (Kirsch et al., 2008).

The approach of using psychopharmacology as a first-line treatment for depression is inconsistent with an evidence-based approach to treatment, as antidepressants are ineffective for many patients (Cosgrove et al., 2019). A meta-analysis of 34 trials (N = 5260) utilizing 14 antidepressant medications reported that the risk:benefit of antidepressants in children and adolescents show no clear advantage (Cipriani et al., 2016). In addition to limited efficacy for depression, antidepressants include a range of adverse effects from mild (*e.g.*, weight gain, sexual dysfunction) to more severe (*e.g.*, anxiety, syndrome of inappropriate antidiuretic hormone (SIADH) (Nierenberg et al., 2008). Antidepressants may be contraindicated in some patients (*e.g.,* older adults) due to possible polypharmacy effects resulting in potentially dangerous medical conditions (*e.g.*, serotonin syndrome). The potential for toxicity with antidepressants is high, as they may be used in self-poisoning as part of a suicide plan, particularly in women (Hawton et al., 2010).

Depression is a significant risk factor for suicide (Thaipisuttikul et al., 2014; Gili et al., 2013; Suradom et al., 2019). The use of antidepressants has been shown to double the suicide risk compared to placebo, regardless of indication, particularly for young adults (Brent, 2016; Hammad et al., 2006; FDA, 2014). A systematic review and meta-analysis of the suicide risk of SSRIs and serotonergic-noradrenergic antidepressants (SNA) in observational studies of adults, that considered financial conflicts of interest (fCOI) and publication bias between 1990 and 2020, reported that in 27 original meta-analyses, 19 depression and anxiety studies, and 8 other non-specified studies, SSRIs and SNAs were associated with an increased risk of suicide (non-fatal suicide and completed suicides) with a reported relative risk estimate (RE) of RE = 1.29; 1.06–1.57 (Courtet and Lopez-Castroman, 2017).

An increase in completed suicide rates with OR = 2.83, 95% CI = 1.1.3–9.67 and non-fatal suicides of OR = 2.38 95% CI = 1.63–3.61 for antidepressant use was also established (Hengartner and Plöderl, 2019). A re-analysis of the same data reported lower OR of OR = 1.98, 95% CI = 0.71–5.50 for completed suicide and non-fatal suicides OR = 1.63 95% CI = 1.09–2.43 (Kaminski and Bschor, 2020).

A study of young women conducted between 1999 and 2013 found a covariance between increased prescription of antidepressants and suicide (Larsson, 2017). Toxicology reports showed antidepressant use in 23% of women who died by suicide between 1999 and 2003 and 39% between 2009 and 2013. An even greater risk of suicide has been reported in patients prescribed augmentation strategies in addition to antidepressants (Sung et al., 2019). The current COVID pandemic is expected to lead to increase the number of deaths by suicide (Moutier, 2020), as has been reported previously during other major health and economic crises (Gunnell et al., 2020; Sher, 2020; Cheung et al., 2008; Wasserman, 1992; Reger et al., 2020). Accordingly, the need for effective treatments for depression that will diminish the occurrence of suicide is imperative (Thakur and Jain, 2020).

1.3. Psychotherapy limits

Psychotherapy is an alternative to medication in the psychiatrist 'toolbox', with over 5000 Randomized Controlled Trials (RCT) to date. A meta-analysis of 173 RCTs reported that 7% (16 RCTs) showed evidence for the efficacy of psychotherapy, primarily attributable to cognitive behavioral therapy (CBT) (Dragioti et al., 2017). A second meta-analysis of 8 studies (2,402) on the effectiveness of individualized and computerized CBT programs (cCBT) for the treatment of depression, reported positive results (g = 0.54, 95% CI: 0.39–0.69). The authors concluded some cCBT programs in the meta-analyses showed greater efficacy than others, but with a positive medium effect size overall in favor of psychotherapy (Twomey et al., 2017).

Like medications, the underlying causal relationship between psychotherapy and the relief of depression symptoms is not well understood, and its efficacy is inconsistent (Kazdin, 2007; Parker et al., 2014). Patients that do garner benefit from SSRIs or prolonged exposure therapy (PET) do so in an unclear way. A causal relationship cannot be attributed - no different from the relationship between alcohol consumption and a *reduction* in shyness or sleep *relieving* symptoms of tiredness. Abstinence from alcohol does not *cause* shyness and tiredness may have another underlying cause (Jiménez-Fernández et al., 2015). In a meta-analysis of 84 trials and 214 study arms, psychotherapy per se did not lead to the overall improved functioning of patients with depression. The authors concluded that any improvement reported was primarily attributable to non-specific factors (*e.g.*, number of therapy sessions) (Palpacuer et al., 2017).

The scientific evidence in favor of psychotherapy for the treatment of depression is often questionable - a combination of methodological shortcomings and publication bias seem to be the main culprits (Høglend, 2018). Studies assessing the effectiveness of psychotherapy that do include robust designs, conclude that the majority of psychotherapies are ineffective, and studies showing symptom improvement are significantly biased (Ioannidis, 2016). A network meta-analysis of 49 RCTs, with 2730 participants, on the efficacy of psychotherapy trials in comparison to waitlist (WL), no treatment (NT), psychological placebo (PP), and CBT revealed efficacy varied greatly depending on the control group. With the NT over WL condition being statistically significant at 2.9 (95% CI: 1.3–5.7) in some comparisons. The authors concluded that the quality of the scientific evidence in favor of psychotherapy was questionable and that publication bias was evident (Furukawa et al., 2014), a conclusion that is not an isolated finding. A subsequent meta-analysis showed no reduction in depression symptoms for patients assigned to a WL compared to those in psychotherapy or treatment as usual (TAU). Suggesting that psychotherapy is no more effective than

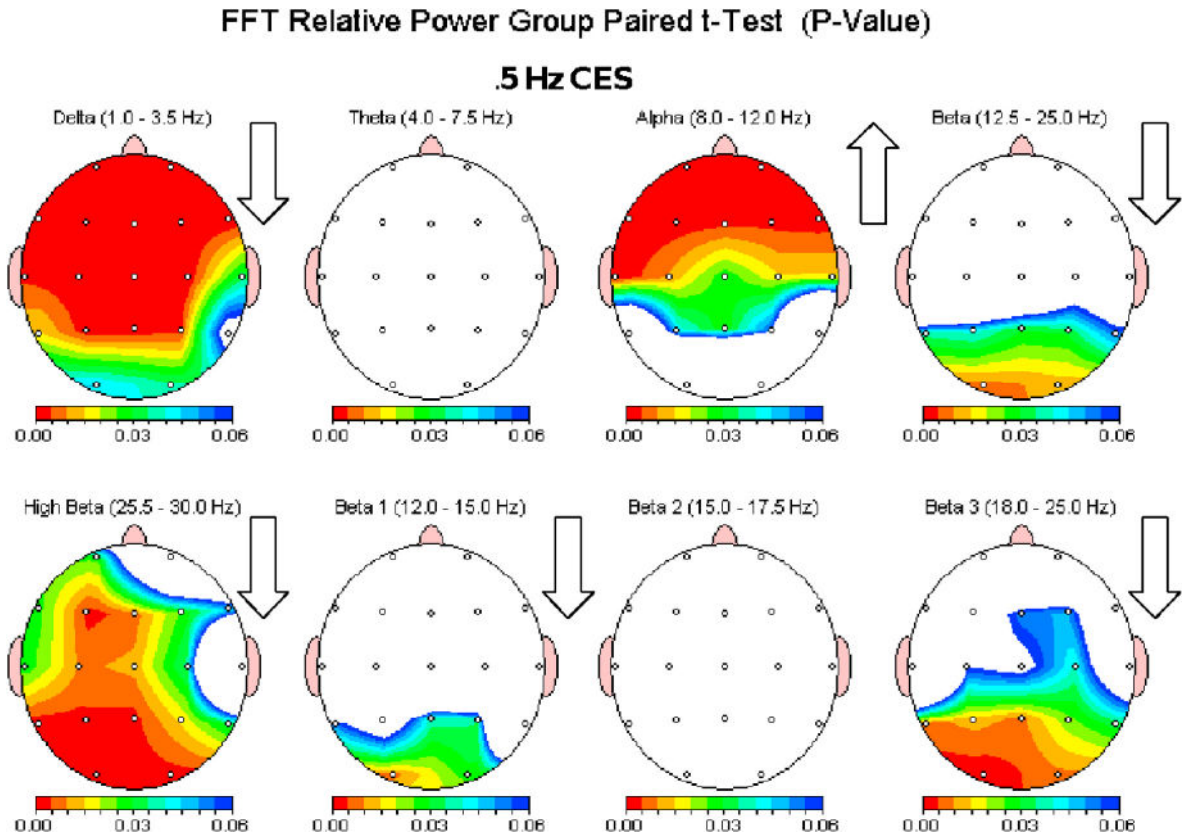

Fig. 1. CES induces changes to brain activity as measured by EEG.
Significant changes in the electroencephalogram (EEG) after a single CES treatment in 30 student volunteers organized by level of significance within frequency bands where red is the most significant ($p<.001$) and blue is the least significant ($p<.06$) (Kennerly, 2006). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article).

any other treatment or no treatment (Barth et al., 2013; Khan et al., 2012). A meta-analysis and meta-regression on seven different psychotherapies including CBT, Interpersonal Psychotherapy (IP), and problem-solving therapy (PST) in 21 trials, resulting in 25 comparisons, reported no significant benefit to psychotherapy compared to treatment as usual (TAU) for depression. The authors highlight PST, Behavioral Activation (BA), and IP as the least robust therapies.

Psychotherapeutic studies frequently fail to report or inconsistently define the level of impairment of patients receiving treatment, leading to subsequent inflated treatment effects (Krause, 2020). A systematic review of 26 studies on the relationship between functional improvement following psychotherapy and dose-response (*e.g.*, length and frequency of therapy) cautioned that the efficacy reported in many studies of psychotherapy were conducted in university counseling centers and outpatient psychotherapy clinics that are unlikely to translate to community samples (Robinson et al., 2020). A review of 16 RCTs on the efficacy of psychotherapy for patients with refractory unipolar depression reported no clinical response (Stimpson et al., 2002).

The shortcomings of the research on the effectiveness of psychotherapy is leading some to conclude that the effects of psychotherapy are small at best and inflated by the inclusion of non-adjusted meta-analyses (Cuijpers et al., 2019). Moreover, it results in an inability to adequately compare studies or to gain a cumulative understanding of the benefits of this tool in the psychiatrists' armamentarium.

1.4. Network activation via cranial electrotherapy stimulation

A review of research literature on pharmacological and psychotherapeutic intervention reveals a need for a paradigm shift in approaches to treating depression. New approaches to treatments are needed that can be used as stand-alone treatments or as augmentation strategies. The understanding of brain regions and their associated function(s) has grown substantially; and with it the realization that the brain is organized via networks that continually monitor and adapt to each other (Sung et al., 2020; Ramírez-Barrantes et al., 2019; Cabral et al., 2014). Like an electric orchestra that hums in unison relying heavily on rhythm and timing, governed by inter-regional functional connectivity (FC) that appears to modulate connectivity within and across brain networks (Feusner et al., 2012). Networks that are out of sync due to over or under activation results in structural alterations and emotional processing deficits (EPDs) (Gupta and Mittal, 2020) that present as heterogeneous symptoms such as disrupted sleep, low mood, changes in appetite, and suicidal ideation, are all labeled as depression (Scantamburlo and Salado, 2020; Beaulieu-Laroche et al., 2018). We

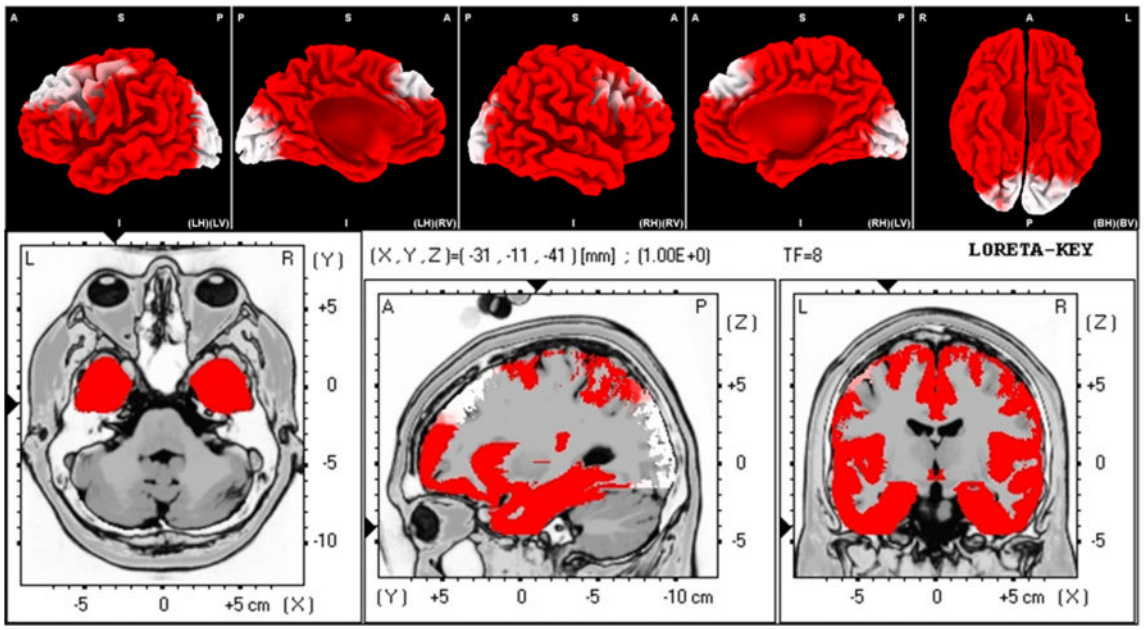

Fig. 2. Changes to brain wave activity at 8 Hz using Alpha-Stim CES (Kennerly, 2006).

support the idea of viewing depression from a network activation lens. Through the alteration of brain physics (brainwave electrical activities) and brain chemistry (neurotransmitters), research has shown that cranial electrotherapy stimulation (CES) can significantly decrease anxiety, insomnia, depression, and pain; while avoiding the serious risks and side effects (*e.g.,* cognitive and cardiovascular), of the relatively stronger current modalities such as electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) that are being used as adjuncts to pharmacological and psychotherapeutic treatment plans (van Rooij et al., 2020). 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 (George, 2019; Nasrallah, 2009).

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 (Jarzembski et al., 1970; Taylor et al., 2013). 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.) (Kirsch, 2002).

Fig. 1 depicts how CES induces changes in brain activity as measured by 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 (Kennerly, 2006). 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 and 30 Hz correlate with decreases in anxiety, ruminative thoughts, and obsessive/compulsive-like behaviors. A double-blind RCT of CES for generalized anxiety disorder and comorbid depression showed a highly significant reduction of 12 times the mean decrease in depression symptoms in the active treatment group compared to the sham treatment group (Barclay and Barclay, 2014).

Fig. 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 similar to those induced from medications (Feusner et al., 2012; Kennerly, 2006; Bonnet and Arand, 2010; Bystritsky et al., 2008). CES has also been shown to penetrate the hypothalamus resulting in secretion of neurotransmitters and neurohormones (Ferdjallah et al., 1996; Shealy et al., 1998; Liss and Liss, 1996).

1.5. *Rationale for meta-analyses*

CES is an FDA cleared, prescriptive, noninvasive electromedical treatment that has been shown to significantly decrease depression in multiple RCTs and Non-Randomized Studies on Interventions (NRSIs). A prior review on CES concluded that it is effective for the treatment of depression and has minimal side effects, which are mild and self-limiting (Kirsch and Nichols, 2013). To our knowledge, we believe this would be the first time that the body of evidence in favor of CES (RCTs and NRSIs) for the treatment of depression has been systematically investigated. We believe the novelty of the work adds value to the understanding of the other treatment approaches to depression.

Table 1
RCTs included in the meta-analysis.

Tillisch et al. (2020)	24	Males 18–40 Years with Mild to Moderate Anxiety and/or Depression	DB RCT	**Primary Outcome Measure: Hospital Anxiety and Depression Scale (HADS)**; Pretest to posttest change from baseline to 8 weeks, (t(23) = -2.32, p<.05). The active treatment group had a decrease in combined HAD score of 8.8 (20.5 pre to 11 posttreatment) and in the sham group (19.5 pre to 15.8 posttreatment) the decrease was 3.64 t = −2.32, p=.013. Secondary Outcome Measures: Mental health Continuum Short Form (MHC-SF); PROMIS-SF for sleep-related and pain; PCL-M for PTSD.
Barclay and Barclay (2014)	115	Males and Females, 18–65 years, with Anxiety and Comorbid Depression	RCT DB	**Hamilton Depression Rating Scale-17 (HAM-D_{17}):** Pretest to post-test change was measured at 1, 3, and 5 weeks. In the active treatment group, 82% had a decrease of ≥50% in scores from baseline to endpoint on the HAM-D_{17} ($p < 0.001$). There was a significant difference between groups ($p < 0.001$, $d = 0.78$) on the HAM-D_{17} from baseline to endpoint of study. The mean decrease on the HAM-D_{17} in the treatment group of 32.9% (9.64–6.47) was more than twelve (12) times the mean decrease on the HAM-D_{17} for the sham group of 2.6% (10.22–9.96) from baseline to endpoint of study.
Mellen and Mackey (2009)	21	Males and Females ≥ 21 Years Sheriff Officers with Depression	DB RCT	**Brief Symptom Inventory (BSI):** The pretest measures were taken 2 days before the onset of treatment, which took place for daily for 20 days (3 weeks); posttreatment measures were taken 1 week after the end of treatment. The active CES group had significantly lower depression scores on the BDI ($p < 0.05$) and the Brief Symptom Inventory (BSI-D) ($p < 0.01$) than the sham group.
Mellen and Mackey (2008)	22	Males and Females ≥ 21 Years Sheriff Officers with Depression	DB RCT	**Brief Symptom Inventory (BSI):** The pretest measures were taken before the onset of treatment, with a duration of 3 weeks (daily treatment for 20 days); posttreatment measures were taken 1 week after the end of treatment. The Beck Depression Inventory (BDI) pretreatment was 11.0 and post treatment 5.6. The 1. Somatization: measures bodily complaints (p<.008), 2. Obsessive/ Compulsive: repetitive thoughts and actions (p<.020), 3. Interpersonal Sensitivity: difficulties with interpersonal relationships (p<.077), 4. Depression: sad mood, loss of energy, difficulty sleeping or sleeping too much (p<.015), 5. Anxiety: excessive worry, (p<.015). Hostility: feelings of anger toward others and the world (p<.077), 7. Phobia: excessive fearful reactions toward objects, insects and such (p<.177), 8. Paranoia: excessive fears that are not supported by evidence (p<.066), 9. Psychoticism: these individuals can appear unusual and emotionally distant (p<.050).
Chen et al., 2007	60	Children 8–16 Years with Anxiety Depressive Disorder (MAD)	RCT IB	**Zung Depression Scale (SDS):** The treatment cycle lasted for 3 weeks, with each child receiving 3 courses of treatment, each lasting 5 days with 2 rest days between courses, with pretest measures before the start of the treatment and at the end. The ANOVA showed that the main effect between CES group and sham comparator group was significant ($F = 36.56$, $p < 0.01$). The mean depression score in the active condition was pretreatment was 49.6 and post treatment 34, in the sham condition the pretreatment 47.2 was and post treatment 46.8.

1.6. Meta-analysis of CES studies for depression

Alpha-Stim (Electromedical Products International, Inc., Mineral Wells, Texas, www.alpha-stim.com) is an original, patented CES technology on the market since 1981. To determine if Alpha-Stim CES is efficacious for depression, we conducted a systematic review and meta-analysis of the available studies on the efficacy of Alpha-Stim as a treatment for depression. 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 depression.

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. (2000), those in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019), and in the Handbook of Research Synthesis and Meta-Analysis (Cooper et al., 2019). We used the Cohen's *d* (Cohen, 1988) 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 (Borenstein et al., 2014).

The 5 RCTs included in this meta-analysis are shown in Table 1, where the total N = 242. All the RCTs found a significant reduction in depression and anxiety symptoms in adults with symptoms of depression and anxiety.

Table 2 provides a summary of the 12 (16 data sets) NRSIs. All studies were open-label with patients exhibiting symptoms of depression and/or anxiety and depression. A total of 1173 participants were included in this meta-analysis.

2. 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 depression disorders. The purpose of our meta-analyses is to summarize the scientific data on Alpha-Stim CES treatment of depression. In our literature review, we followed Cooper's Taxonomy of Literature Reviews (Cooper, 1988) that is appropriate for the behavioral and physical sciences and the PRISMA reporting guidelines (Liberati et al., 2009). Our literature review followed five guidelines from the Cochrane Black Group:

Table 2
NRSIs included in meta-analysis.

Royal et al. (2020)	47	Males and Females ≥ 18 Years with Mild to Moderate Anxiety and/or Depression	OL	**The Patient Health Questionnaire-9 (PHQ-9) for depression and The Generalized Anxiety Disorder Scale-7** (GAD-7) for anxiety. The pretest measures were taken before the start of the treatment and at the end of 8 weeks, with a treatment duration between 6 and 10 weeks. Also, a satisfaction survey providing responses in the experimental group with a selection of patients receiving usual care in an ad-hoc control group was employed. Results on the PHQ-9 yielded a reduction of 4.1 PHQ-9 points from baseline (15.34) to posttest (11.24), t(45) = -4.92, p<.001, representing an improvement that was significant at p < 0.05, and Cohen's d = .76 (large).
Morriss and Price (2020)	143	Males and Females 25–50 Years, with Anxiety and Comorbid Depression	OL	**This study was conducted by the NHS of the UK. Personal Health Questionnaire (PHQ-9) is a 9-item self-rated measure of the severity of depression symptoms. Remission is a total score of 9 or less at 12 or 24 weeks in those who had scored 10 or more at baseline.** After 6–12 weeks of treatment and a follow-up at 24 weeks, 72% of depressed patients achieved remission by week 12 and 80% by week 24. 51% of patients displayed a 5-point drop on PHQ-9 by week 12 (reliable improvement). There were 77 out of 143 (54%) patients exhibiting a 5-point drop on PHQ-9 by week 24 (reliable improvement). 58 out of 143 (41%) patients scored 9 points or below and exhibited a 5-point drop on PHQ-9 by week 12 (indicating recovery). There were 64 out of 143 patients (45%) scoring 9 points or below and exhibiting a 5-point drop on PHQ-9 by week 24 (44.8%), indicating recovery. All these changes were found to be significant (p<.001). The pretest PHQ-9 measure was 17.23 and the posttreatment was 8.77 at 12 weeks, and 9.90 at 24 weeks, with a large effect size. In order to address anxiety as a potential confounding variable related to depression, a latent variable cross-lagged panel analysis (LVCLPM) was conducted within a structural equation modelling (SEM) framework providing the authors a way to examine the parallel, simultaneous effects of anxiety and depression in a unified modelling framework. The LVCLPM analysis shows in patients with both moderate to severe GAD and depression, CES has effects that are important on both anxiety and depression and that the effects of CES on depression are not driven only by its effects on anxiety.
Platoni et al. (2019)	86	Male and Female First Responders ≥ 18 Years Reporting Depression	OL	**Monitoring Alpha-Stim CES treatment using a 0–11 Numerical rating scale (NRS) in a smartphone app. Outcome measures were anxiety, depression, insomnia and pain.** 86 police officers, sheriff's officers, and firefighters experienced a very significant decrease in anxiety, insomnia, depression, and pain by using Alpha-Stim CES. Measures were taken at baseline and 6 weeks post treatment. 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. The depression pretest mean was 3.95 on an 11-point scale and posttest mean of 2.83 for a reduction of 28%, p<.001 and effect size *d* = .81 (large).
Kirsch et al. (2019)	35	Male and Female Teachers Ages 22–60 Years Reporting Depression	OL	**Monitoring Alpha-Stim CES treatment using a 0–11 Numerical rating scale (NRS) in a smartphone app. Outcome measures were anxiety, depression, insomnia and pain.** Pretreatment measures were taken at baseline and following 6 weeks of treatment. Depression scores reduced from a mean of 6.5 (1.38) at baseline to 1.58 (0.79) at posttest (p < 0.001). Cohen's d values from a total of 237 treatments were greater than two standard deviations for all outcome measures indicating a high level of practical change from baseline to posttest supporting the capability of Alpha-Stim CES technology in reducing self-perceived symptoms and the ability to monitor progress on the Alpha-Stim app. 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.
Morrow et al. (2019)	91	Male and Female Veterans ≥ 18 Years, Reporting Depression	OL	**The Beck Depression Inventory (BDI), The Beck Anxiety Inventory (BAI), The Pain Catastrophizing Scale (PCS), The Subjective Units of Distress Scale (SUD), The Brief Pain Inventory (BPI).** Baseline measures were taken before the start of treatment and at the end of treatment, which occurred 5 days a week for 2 weeks. SUD score means decreased from 6.23

(*continued on next page*)

Table 2 (*continued*)

				(preintervention) to 3.51 (postintervention) ($p < 0.01$). Depression (as measured by the BDI) was significantly reduced from a preintervention mean of 24.62 to a postintervention mean of 14.38 ($p < 0.01$). The effect size was medium. In addition, veterans completing treatment showed a statistically significant improvement in self-reported relaxation scores.
Yennurajalingam et al. (2018)	36	Males and Females, 57–67 Years with Advanced Cancer	OL, IRBA	**Edmonton Symptom Assessment (ESAS), Hospital Anxiety and Depression Scale (HADS);** 33/36 (92%) completed the CES. The treatment plan was daily CES for 4 weeks with measures taken at baseline and posttreatment. 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, as measured by the HADS ($p = 0.024$) and the ESAS ($p = 0.025$) during 4 weeks of CES treatment. The baseline HADSs score was 6.36, with post treatment of 5.34, no effect size is reported.
Gong et al. (2016)	74	Males and Females $\geq$ 18 Yeas with Functional Constipation Secondary to Mental Illness	OL	**Self-Rating Depression Score (SDS):** After treatment, the participants in the experimental group had significantly lower scores of SAS, SDS, and the Wexner constipation score than the control group (all $p < 0.05$). The number of successful expulsions in the experiment group was larger than the control group ($p = 0.016$). The active group showed a pretreatment measure of SDS of 58.16 and a posttreatment measure of 43.08, no effect size is reported.
Rickabaugh et al. (2016)	49	Male and Female Service Members $\geq$ 18 Years with Mild TBI and Depression	Retrospective	**Self-report measure using 0–10 scale:** Treatments ranged from 5 to 10 depending on symptom severity over 5 weeks, with measures taken at baseline and posttreatment. Significant improvement ($p = 0.040$) found in depression before and after each treatment. There was also a trend toward overall decrease in depression post treatment across five sessions. Baseline measures for depression were 2.00 and posttreatment 2.46, no effect size is reported
Libretto et al., 2015	562	Male and Female Active Duty Service Members 22–62 Years with PTSD and Depression	Retro-spective	**Beck Depression Inventory.** This retrospective case series evaluated the efficacy of the Fort Hood Combat Stress Reset program. Depression was measured using the BDI at baseline before day 1 of treatment and at the end of treatment - 3 weeks. The Depression (BDI-II) baseline score was 30.3 and 21.5 posttreatment. From 2008 to 2013 the average initial score went from 30.3 to 21.5 (-9.0, $p < 0.0001$).
Amr et al. (2013)	7	Males and Females 35–50 Years with Bipolar Depression Patients	OL	**Clinical Global Impression:** Measures were taken at baseline and following 8 weeks of treatment. Patients reported 24.8% decrease ($p < 0.001$) on the CGI and a 34% decrease ($p = 0.122$) on the **Montgomery Asberg Depression Rating Scale** (MADRS). The baseline measure was 17.3 and the post treatment score was 11.5, with a small effect size.
Bystritsky et al. (2008)	12	Males and Females 18–64 Years with Anxiety and Comorbid Depression	OL	**Hamilton Depression Scale (HAM-D_{17}):** Scores were taken at baseline and 6 week post treatment. subjects had significantly lower scores from baseline to endpoint of study on the outcome depression measure, HAM-D_{17} ($p = 0.01$, $d = -.41$). The depression baseline measure was 10.5 and the posttreatment measure was 6. Due to small sample size no effect sizes are reported.
Lu et al., 2005	32	Children Aged 9 to 17 Yeats with Emotional Disorders (Depression)	OL	**Zung Depression Scale (SDS):** Measures were taken at baseline and 3 weeks post treatment. From baseline of 0.64 ± 0.08 to posttest 0.52 ± 0.10 ($p > 0.01$). 13 cases had significant effect (41%), 17 cases had effect (53%), and the effect was invalid in 2 cases (6%); the total effective rate was 94%. Skin temperature rose ($p < 0.01$); systolic blood pressure dropped, and the pulse slowed down after the treatment, and the differences were significant ($p < 0.05$). 26 cases followed up (81%), of which 24 cases had long lasting efficacy with relieved or eliminated symptoms, and 2 cases had relapse of symptom where drugs were needed to control their symptoms. The total effectiveness rate was 94%; Significantly effective – 40.62%, Effective – 53.12%, Ineffective – 0.062%. No formal effect size reported.

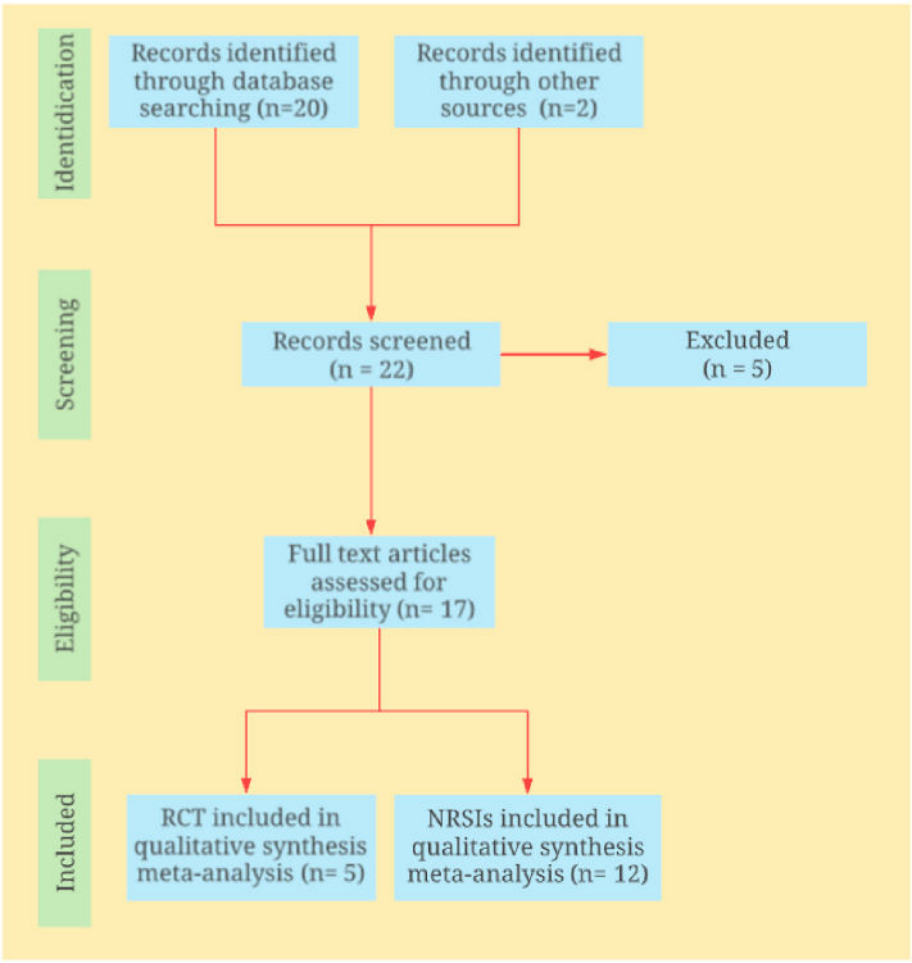

Fig. 3. PRISM flow diagram of inclusion criteria in CES research for depression meta-analysis.

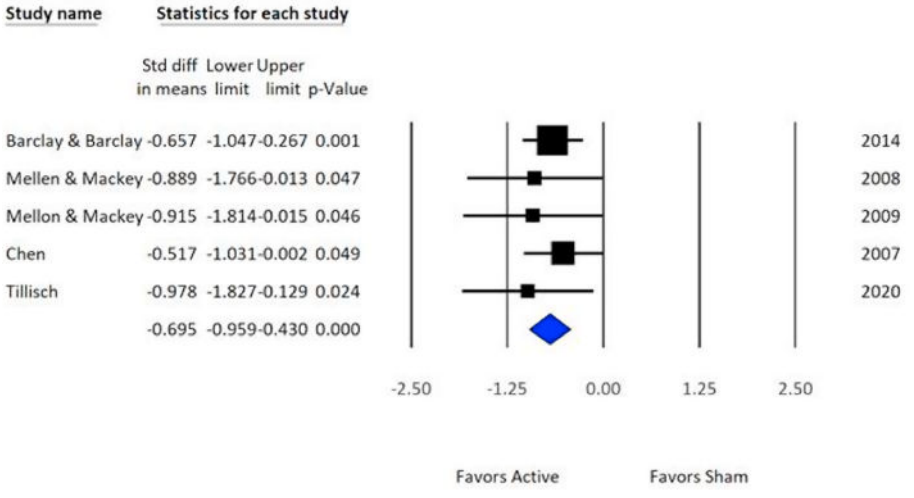

Fig. 4. Summary statistics of effect sizes and forest plot from Alpha-Stim®CES RCTs of depression (N = 5).

Table 3
Meta-analysis summary statistics – RCTs.

Model	N	Effect	S.E.	Variance	LL	UL	Z	P	Q	Df(Q)	P	I-squared	Tau-squared	S.E.	Variance.	Tau
Fixed	5	−0.69	0.14	0.018	-.0959	-.0430	−5.142	0.00	1.34	4	0.85	0.00	0.00	0.07	0.01	0.00
Random	5	−0.69	0.14	0.018	−0.959	−0.430	−5.142	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.

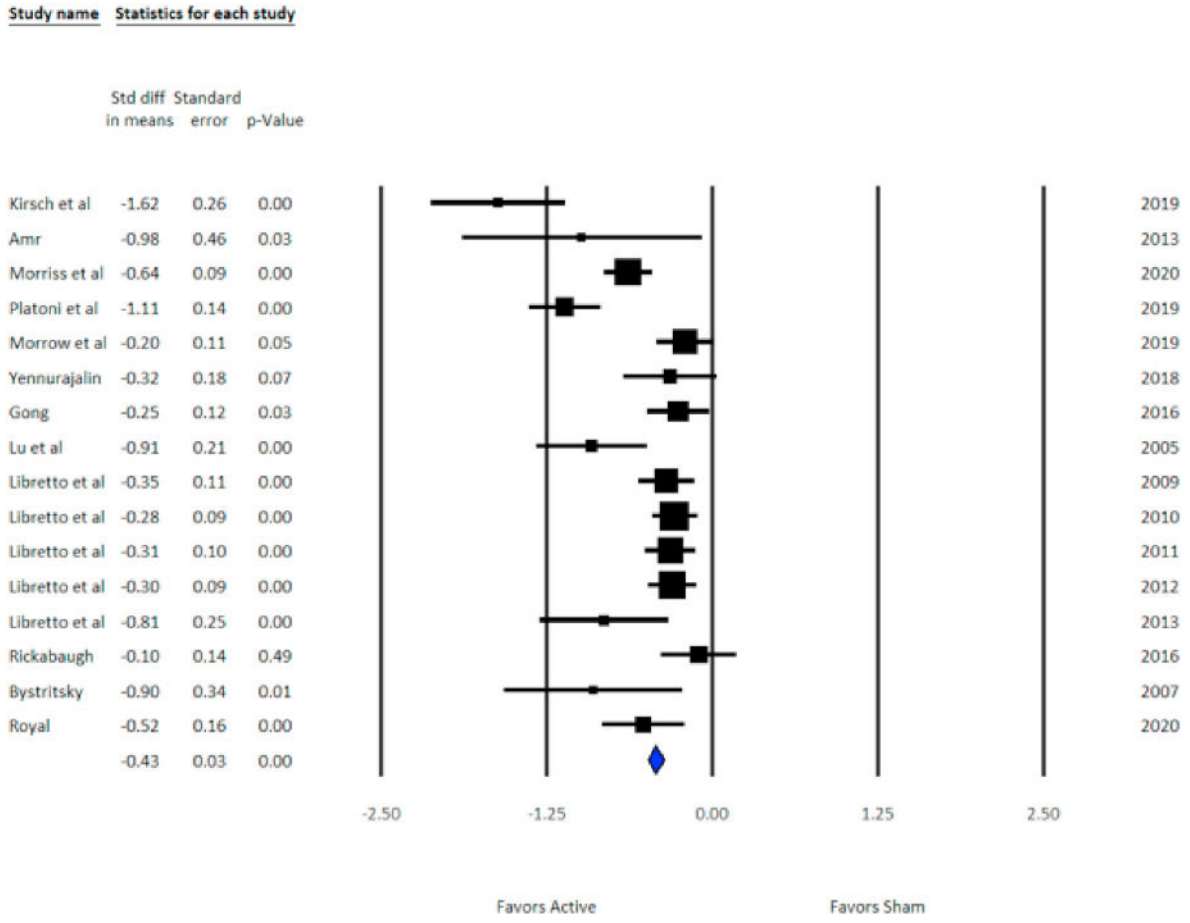

Fig. 5. Meta-analysis of non-randomized studies (N = 16).

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.
3. The search proceeded within abstract, subject terms, and titles of studies and reports published in peer-reviewed journals between January 1, 1981, and March 15, 2020. Keywords:
   a. Depression and Alpha-Stim and cranial electrotherapy stimulation and randomized control trial or non-randomized or open-label or case study.
   b. The search yielded 17 articles (5 RCTs and 12 NRSIs [16 effect sizes]) - see Fig. 4.
4. Screening references given in relevant systematic reviews and identified RCTs.
5. Personal communication with content experts in the field (adding one new 2020 RCT and one new 2020 NRSI).
6. 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. (2000) 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

Table 4
Meta-analysis summary statistics – NRSI.

Model	N	Effect	S.E.	Variance	LL	UL	Z	P	Q	Df(Q)	P	I-squared	Tau-squared	S.E.	Variance.	Tau
Fixed	16	−0.43	0.03	0.00	−0.49	−0.36	−13.38	0.00	81.82	15.00	0.00	81.66	0.08	0.04	0.00	0.28
Random	16	-.053	0.08	0.01	-.069	−0.37	−6.58	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.

studies in our meta-analysis on the efficacy of CES for depression. Additionally, we used the Revised Cochrane Risk-of-Bias Tool (Sterne et al., 2019) to inform our decision about including a study within a RCT design (Higgins et al., 2019). 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." Fig. 3 shows the PRISM flow diagram for selection of inclusion criteria into the meta-analysis yielding 5 RCTs and 12 NRSIs with 16 data sets (Liberati et al., 2009; Moher et al., 2009; McGrath et al., 2017).

3. Results

We used a complementary approach to synthesize the meta-analytic results from NRSIs with RCTs (Liberati et al., 2009). 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, NRSIs may provide valuable additional information regarding the efficacy of treatment outcomes.

3.1. Randomized controlled trials

Fig. 4 provides the meta-analytic results of the five (N = 5) studies on depression. The left side of Fig. 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 five studies, only the difference at posttest between groups was used in the calculation of the effect of Alpha-Stim CES on depression.

The forest plot provided in Fig. 4 reflects (a) the effect size *d*, (b) the variability of each study's effect via the 95% confidence interval, relative weight for each study's contribution, and (c) the average (*i.e.,* population estimate) effect size for all five studies (blue diamond). As is displayed, the average (population) effect for the five studies was observed as $d = -0.69$ (*i.e.,* the mean depression level at posttest for the active group was −0.69 standard deviations lower than the mean depression level for the sham group). An effect size of $d = -0.69$ is classified as a medium effect (Cooper et al., 2019; Schünemann et al., 2013; Card, 2015).

Table 3 displays a summary of the meta-analytic model for N = 5 studies. In meta-analytic studies, an important issue to evaluate is the heterogeneity of the studies. Heterogeneity in meta-analyses is defined and evaluated according to (a) clinical diversity, (b) methodological diversity, and (c) statistical heterogeneity (Deeks et al., 2019). For example, if the heterogeneity in the studies is statistically significant, including a moderator as part of the meta-analysis may be warranted to account for differential effects. 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 Cochran's Q-statistic is 1.34, p = 0.85, indicating that heterogeneity for the effect sizes is nonproblematic. 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 sizes in the N = 5 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 (*e.g.,* less than 20 subjects per group) and some clinical heterogeneity (diversity of subjects across studies), the impact of the small sample or diversity did not significantly influence the heterogeneity of effect sizes. The I-squared interpretative ranges as a magnitude of study heterogeneity are ~25% = small; ~50% = medium; ~75% = large (125).

In the Random-effects model, inferences are plausible 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 (−0.69) and the Random-effects model ($d = -0.69$) are the same, and tau-squared (*i.e.,* the population variance) is relatively close to zero. In summary, the studies included in this meta-analysis show a medium 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 also to state that the research shows a medium effect in favor of the active treatment group relative to reductions in depression.

3.2. 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. Fig. 5 displays a summary of the meta-analytic model for the twelve (12) studies. One U.S. Army study provided effect sizes for each year of the treatment program where different service members participated in each year of the studied program (Libretto et al., 2015). Therefore, separate effect sizes were more accurate for statistical analysis. Thus, there are 16 data points for this meta-analysis. For the Fixed-effect model, the average (population) effect was observed as $d = -0.43$ (small). As stated, in meta-analytic studies, an important issue is to evaluate the heterogeneity of the studies.

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 81.82, p = 0.00, indicating that 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 effect sizes in the N=16 NRSI meta-analysis, we turn to the I-squared value (81.66 or 82%) 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 81.66 (large) indicating the 16 NRSI studies display significant heterogeneity. I-squared interpretative ranges as a magnitude of study heterogeneity are: ~25% = small; ~50% = medium; ~75% = large. Based on these metrics, our analysis of the NRSIs yielded a large amount of between study statistical heterogeneity. The observed heterogeneity was likely due to clinical diversity in subjects across studies and different design components in the NRSIs. Although heterogeneity dictates cautious interpretation of the results, the consistency in the direction of the effects provides useful evidence regarding the effectiveness of Alpha-Stim.

A comparison of the point estimates between the Fixed-effect model (−0.43 - small) and the Random-effects model (−0.53 - medium) are different, and the population variance is relatively close is near zero (0.01). In summary, the studies included in this meta-analysis (N = 16) show a small effect in favor of the active treatment group.

4. Discussion

We examined the efficacy of CES for the treatment of depressive disorders in systematic meta-analyses of 5 RCTs, and 12 NRSIs with 16 data sets. Our results show that CES is an effective treatment for depression and a useful adjunctive to other ongoing treatments including pharmacotherapy and psychotherapy for depression. The findings from this systematic analysis are in line with a prior review of CES is an effective treatment for depression, showing a cumulative treatment effect with repeat use, and observable improvements following the first course of treatment (Kirsch and Nichols, 2013).

The studies used in our meta-analyses all had significant outcomes of $p < 0.05$ through $p < 0.001$ for depression and many also revealed equally good effects for the treatment of anxiety and insomnia. 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 is less than 0.15 (95% CI, 0.08 to 0.22) both qualifying as small (Cohen, 1988). When the side effect profile of medications vs CES is taken into account the supremacy of CES over antidepressants 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 depressed community patients was significantly more effective than wait-list controls. The studies included in the meta-analysis ranged from 2005 through 2020, 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 depression measures pre and post-treatment varied across the studies in the meta-analysis [RCTs: HAM-A and HAM-D (Barclay and Barclay, 2014); BSI (Tillisch et al., 2020; Mellen and Mackey, 2009); Zung Depression and Anxiety (Mellen and Mackey, 2008; Yennurajalingam et al., 2018); HADS (Tillisch et al., 2020)]; [NRSIs: PHQ (Royal et al., 2020); PHQ-9 and GAD-7 (Chen et al., 2007) BDI and BAI (Platoni et al., 2019; Kirsch et al., 2019; Rickabaugh et al., 2016); ESAS and HADS (Morrow et al., 2019); Child Zung Depression and Anxiety (Amr et al., 2013); MADRS (Rickabaugh et al., 2016); HAM-A and HAM-D (Bystritsky et al., 2008)] all the measurement scales incorporate depression, anxiety, somatization and indicate the severity of impairment and all have been extensively used as measures of efficacy for depression treatment.

CES is effective for depression in a range of community, veteran, and pediatric populations with a spectrum of depression severity as evidence by pre-and-post scores of the appropriate depression measures based on the sample population - civilian, military, and first responders, or pediatric. These studies report that patients receiving CES treatment have shown improvements in negative domains that typically cooccur with depression 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.

4.1. Limitations

Although our meta-analyses revealed CES is an effective treatment for depression, 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 that met DSM-V criteria for MDD. The RCT by Barclay & Barclay had 23 participants out of the 115 subjects diagnosed as having MDD although the total active CES group had significantly lower scores on the HAM-D17 from baseline to endpoint of study than the sham CES group ($p < 0.001$, $d = 0.78$) (Barclay and Barclay, 2014). The range for no depression of 0–7 on the HAM-D17 provided ample room for subjects in the active CES group to have lower scores on the HAM-D17 at the endpoint of the study from CES treatments and we hold forth that there is no reason to wait until a mild depression evolves into a major depression episode before treatment with CES given its safety profile as compared with psychopharmaceuticals.

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 depression and met the inclusion criteria for the studies so the effects can be considered over and above that of medication alone.

5. Conclusions

Our meta-analyses determined that Alpha-Stim cranial electrotherapy stimulation technology is an effective treatment in managing depression in community, active duty service members and veterans, first responders and pediatric populations with a spectrum of depression severity.

Author statement

This document serves to certify that all authors have reviewed and approved the final version of the manuscript being submitted. The manuscript reflects original work by the authors and is not submitted for publication elsewhere.

Declaration of competing interest

No conflict of interest

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