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Review Article

Review of Alpha-Stim and Cranial Electro Stimulation in the Treatment of Psychiatric Disorders

Hani Raoul Khouzam MD;MPH[1,2]*, Sarah Jackson MFT;PhD[3], Jacob J Mathew PhD[4] and Nestor Manzano MD[5,6]

[1]*Psychiatrist, Rural Mental Health Clinic -VA Central California Health Care System (VACCHCS), Fresno, California, USA*

[2]*Health Sciences Clinical Professor of Psychiatry, UCSF- Fresno Medical Education Program, Fresno, California, USA*

[3]*Associate Professor ,Clinical Psychologist ,Department of Psychiatry and Behavioral Sciences, University of Texas Health, McGovern medical School, Texas, USA*

[4]*Psychologist-VACCHCS, Fresno, California, USA*

[5]*Chief of Mental Health, VACCHCS, Fresno, California, USA*

[6]*Health Sciences Clinical Associate Professor of Psychiatry, UCSF- Fresno Medical Education Program, Fresno, California, USA.*

***Corresponding Author:** Hani Raoul Khouzam, Psychiatrist, Mental Health Clinic -VA Central California Health Care System (VACCHCS), USA.

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Abstract

Cranial electrotherapy stimulation (CES) used in an Alpha -Stim device is a neuromodulation intervention utilized to treat specific psychiatric disorders. This review describes the historical background of CES and the application of the alpha-stim device to regions of the face and scalp with its proposed mechanism of action. The effectiveness of CES in the treatment of insomnia, anxiety, and depression is summarized along with its possible adverse effects. Although plausible, the use of CES for the treatment of posttraumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), and substance use disorders has not yet been determined. The strength of evidence for CES effectiveness and Alpha-Stim application safety is considered low and based on few randomized clinical trials (RCTs). Clinicians advocating CES need to exercise caution in recommending it as an alternative intervention until more RCTs are conducted to validate its efficacy as an evidence-based clinical practice.

Keywords: *Cranial Electrotherapy Stimulation; Alpha-Stim; Psychiatric Disorders; Alternative Psychiatric Treatments*

Historical Background

Cranial electrical stimulation (CES) is a non-invasive intervention that applies low intensity electrical current to the head. Although distinct in its use of high-definition stimulation, CES is related to other transcranial electrical stimulation therapy because it uses an electrical current, such as electrosleep [1], electroconvulsive therapy (ECT) [2], transcranial magnetic stimulation (TMS) [3], transcranial direct current stimulation (tDCS) [4] and deep brain stimulation (DBS) [5,6]. Electrosleep consists of transcerebral stimulation with low intensity direct current, however the word 'electrosleep' could be a misnomer since most individuals undergoing this procedure do not sleep during the treatment, and if they fall asleep, the sleep is unrelated to any treatment outcome [7]. ECT is performed under anesthesia and involves using small electric currents to trigger a brief, controlled seizure [2]. Although ECT is considered an effective and relatively safe treatment, it is not widely used as a desirable intervention, possibly due to social stigma, media misinformation and scarcity. Treatment with ECT occurs in a series, usually twice weekly. Some patients may require maintenance ECT treatments following the completion of the initial series. TMS is a non-invasive treatment that uses magnetic fields to stimulate nerve cells in the brain [3]. During TMS, an electromagnetic coil is placed on a person's scalp near their forehead lateral parietal site. Short magnetic pulses are painlessly directed into areas of the brain that are associated with mood and cognition [3]. The amount of magnetic energy needed during the first treatment session is determined based on the motor threshold. TMS treatments usually last between 40 - 60 minutes. TMS does not require the use

of anesthesia and like ECT, it includes several sessions that occur over a period of weeks. Rapidly administered pulses repetitive TMS (rTMS) provide longer lasting changes in brain activity and in current clinical practices TMS is usually used for diagnostic purposes while rTMS in used for its therapeutic effectiveness [3]. In tDCS one or more tiny wires, or electrodes, are surgically inserted in brain regions and connected to a very small pulse generator that is placed in the chest [4]. The device settings may require adjustments, which may take weeks to few months, to determine the stimulation level that would lead to the relief of symptoms, and for reducing any side effects that are experienced. The different versions of transcranial electrical stimulation vary in the placement of electrodes, as well as the intensity and waveform of the electrical current [4]. The clinical indications for DBS are targeted toward advanced treatment options for a variety of neurologic and neuropsychiatric conditions and could hold the potential for further clinical improvement [5,6]. The method of CES evolved from the concept of "electro sleep" first investigated in Russia at the beginning of the 20th century [7]. Beginning in the 1960s, "electrosleep" began gaining popularity in the USA. Once it was believed that the electrical stimulation did not actually induce sleep per se, but rather the byproduct of its relaxing effect on the brain, the name was changed from "electro sleep" to "cranial electrical stimulation" [7].

The alpha-stim device

Alpha-Stim device combines two protocols: Cranial Electrotherapy Stimulation (CES) and Microcurrent Electrical Therapy (MET). CES uses high-frequency pulsed waves (15,000 Hz) at a low-intensity electrical current (50 μA to 4 mA) to affect the brain's neurotransmitter levels and functioning. It delivers a patterned, subsensory (cannot be felt or detected), electrical waveform and has been associated with a reduction in delta (0 - 3.5 Hz) and beta (12.5 - 30 Hz) frequency brainstem and cortical electroencephalography (EEG) activity and an increase in alpha (8 - 12 Hz) activity (associated with states of relaxation) [7] CES differs from traditional transcutaneous electrical nerve stimulation (TENS) which uses low-frequency pulsed waves (200 Hz) and high-intensity electrical currents (hundreds of mA). CES uses a special form of wavelength to adjust and interfere with brain signals without blocking these signals like the TENS. As illustrated in figure 1, the Alpha stim deice delivers a low-intensity of electrical current via clips applied to the head around the eyelids, earlobes, mastoid bones, or the temples.

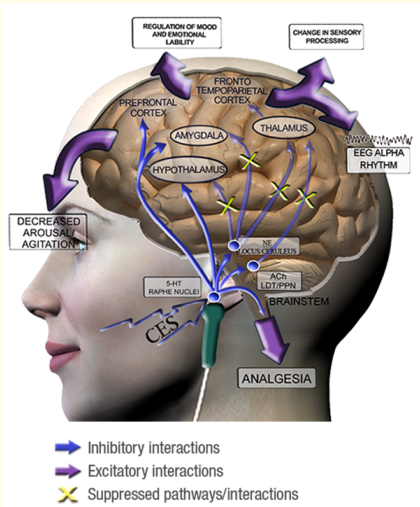

Figure 1: *Areas where the alpha-stim devise are positioned*.*

**The blue dots on the figure indicate the locations for the device positioning on the lobule of the ear auricle.*

Efficacy of cranial electrotherapy stimulation for neuropathic pain following spinal cord injury and in treating various spinal cord conditions is beyond the scope of this review [8].

Cranial electrostimulation (CES) low-level electrical current interacts with cell membranes to produce modifications in information transduction associated with classical second messenger pathways, calcium channels and cyclic adenosine monophosphate (cAMP). It is hypnotized that the pulsed electrical currents emitted by CES affect changes in the limbic system, the reticular activating system and/or the hypothalamus that result in neurotransmitter secretion and downstream hormone production [9]. A decrease in the latency of alpha-rhythm appearance at sleep onset has also been recorded with CES use showing reduced rigidity in the central nervous system (CNS) stimulation process and enhanced activity of the alpha-rhythm generating systems.

Mechanism of action

The exact mechanism by which alpha-stim produces its therapeutic effects is not fully known. The application of alpha-stim appears to amplify activity in some neurological systems and diminishes activity in others leading to modulation of chemical and electrical activity patterns in the brain known as an alpha state, which is measurable with electroencephalogram recordings (EEG). In one study EEG changes were realized and correlated with beneficial effects of CES therapy [10]. And in another study quantitative EEG data were obtained before and after a 20-minute session of CES and showed a significant and strong effect in the beta region, suggesting an increase in mental alertness, focus and concentration [11]. In addition, it is hypothesized that alpha-stim stimulates the serotonergic (5-HT) raphe nuclei in the brainstem leading to the inhibition brainstem cholinergic acetylcholine (Ach) and the noradrenergic (NE) systems. This subsequently suppresses thalamo-cortical activity, arousal, agitation, alters sensory processing and induces alpha rhythm commonly associated with reducing stress and increasing relaxation. Following single or repeated Alpha-Stim applications, patients often experience feelings of calmness, decreased agitation, mood stabilization, and regulation of the sensations and perceptions associated with certain types of centrally-mediated pain syndromes, such as fibromyalgia, multiple sclerosis, spinal cord injuries, and global reflex sympathetic dystrophy [12]. Some individuals have experienced permanent relief of symptoms suggesting that the electrical and chemical changes evoked by Alpha-Stim have led to a durable modulation and restoration of normal 5-HT, Ach, and NE neurotransmission.

The most important feature in any CES device is to assure its FDA clearance. All CES devices perform the same action of sending slight electrical pulse to the brain. The various available CES devices may perform their actions differently than others and some include some extra features. The currently available CES devices include The CES Ultra, The Alpha Stim, The Fisher Wallace Stimulator, StimTens 1100 and the MyoCalme. The Alpha Stim, MyoCalme, StimTens 1100 Pro and CES Ultra work with ear clip electrodes. They are convenient and comfortable to use. The MyoCalme, StimTens 1100 and CES Ultra can also be used with cloth electrodes that can be placed as an alternative behind the ear. An illustration of an Alpha-Stim device and its accessories is shown in figure 2. The Atang, Lastek and a few other CES devices, despite their availability they have not been cleared by the FDA.

Approved indications

The US Food and Drug Administration (FDA) approved and classified CES devices to treat anxiety or insomnia as Class II medical devices [13]. Devices classified into Class II are those for which special controls, combined with general controls, are necessary to provide reasonable assurance of safety and effectiveness. The FDA gives a Class III designation for devices for which general controls are insufficient to provide reasonable assurance of the safety and effectiveness of the device. The FDA determined that CES devices for the treatment of depression will be slotted as class III requiring its administration or its order by a licensed healthcare practitioner, due its potential for unreasonable risk of illness or injury [13] and confirmed that the evidence supporting its effectiveness for treating depression was the weakest.

Figure 2: *The alpha-stem monitoring device and its accessories.*

Clinical usefulness

In clinical practice the CES, alpha-stim device in addition to its use for the treatment of anxiety, insomnia and depression; has been explored as an alternative intervention for treating posttraumatic stress disorder, obsessive compulsive disorder, and substance use disorders.

Anxiety

Anxiety disorders rank among the most frequent psychiatric disorders. Although many psychotherapeutic and psychopharmacological interventions effectively treat anxiety disorders, many patients do not respond to these interventions. Few RTCs and meta-analysis describe CES as a safe and effective treatment for anxiety [14,15]. Sham-controlled studies and meta-analyses have shown that CES could be a safe and effective treatment of generalized anxiety disorder [14,15]. A relatively large study has also shown compelling results for CES effectiveness in anxiety and co-morbid depression [14]. In this study, 115 participants with a diagnosed anxiety disorder received either sham or active (100 μA, 0.5 Hz) CES for 5 weeks (60-min/day) using the Alpha-Stim 100 device with bilateral earlobe electrodes. The sham condition used inactive devices provided by the manufacturer, and no assessment of vestibular or cutaneous sensation was reported. By week 5, results demonstrated an ~32% reduction in anxiety symptoms measured using the Hamilton Rating Scale for anxiety (HAM-A-17) [15]. Despite these results, the evidence for the effectiveness and safety of CES for the treatment of anxiety remains sparse.

Insomnia

According to The International Classification of Sleep Disorders, primary insomnia is associated with difficulty initiating sleep or sleep onset insomnia, difficulty maintaining sleep or mid-sleep awakening, and early morning awakening. It could be described as "chronic non-restorative sleep", which persists longer than three weeks despite having an adequate opportunity for sleep and result in impaired daytime functioning [16]. Primary insomnia is not a consequence of existing and ongoing psychiatric disorders, medical conditions, or substance use disorders [6]. In primary insomnia, the sleep difficulties are not related to any underlying medical conditions or other sleep-wake disorders and persist despite the adequate opportunity and circumstances for sleep. It is estimated that about one-third of the population would experience insomnia symptoms, with 10% - 15% recording daytime impairments [16]. Between 6% and 10% of

individuals with sleep difficulties would meet the criteria for a primary insomnia disorder, making it the most common sleep disorder among other sleep-wake disorders [16]. Insomnia is a disorder that is quite different from a brief period of poor sleep and it can take its toll on both physical and mental health. It is a persistent condition with a negative impact on many aspects of daily life and could seriously affect interpersonal, vocational, academic, and social functioning. The goal of treating insomnia is to improve sleep quality and quantity, as well as daytime functioning, while avoiding adverse events and next-morning residual effects. The prevalence of insomnia is considerably higher in patients with chronic medical disorders and comorbid psychiatric conditions, especially mood, anxiety, substance use, and stress- and trauma-related disorders. Despite the availability of various pharmacological and nonpharmacological treatments for primary insomnia, many individuals do not respond to these treatment modalities, and some develop problematic side effects to treatment [18]. Studies have demonstrated that CES could be beneficial for inducing, improving, and maintaining sleep in various populations [19]. Alpha-Stim application is flexible and can be used at bedtime and when awakened during the night. Some patients would apply 20 - 60-minute of Alpha-Stim treatment at least 3 hours before bedtime to prevent interference with sleep onset. Some individuals use it in the morning to promote better nighttime sleep. Following treatment, no physical limitations are imposed, and most users can immediately resume normal daily activities. Some users may have a response that may affect their ability to perform potentially hazardous tasks, such as operating a motor vehicle or heavy machinery for several hours after treatment. Clinicians treating primary insomnia using Alpha-Stim need to be mindful that the currently available RCTs do not provide solid evidence supporting the efficacy of CES for decreasing the symptoms of insomnia compared to the usual conventional available therapeutic interventions.

Anxiety and comorbid insomnia

Patients with persistent anxiety and insomnia who have not responded to currently available treatment interventions could be evaluated for possible CES. However, this assumption was based on a single 40 years old RCT study [14]. Since then, the treatment of these conditions has undergone numerous changes with more evidence-based interventions. No recent RCTs confirm the value of CES compared to the currently available contemporary usual care for anxiety and comorbid insomnia.

Depression

Major depressive disorder [MDD] is a severe and complex mental disorder, with a prevalence of approximately 1% to 3% worldwide, representing the fourth leading cause of disease burden globally [20]. The combination of psychotherapy and antidepressant medications is considered first-line treatment for adults with moderate to severe major depression. Many patients do not respond to treatment and are categorized as having treatment resistant depression (TRD). Alpha-Stim application could be an alternative treatment for TRD and for patients who opt out of psychotherapy and psychopharmacology. The impaired neurotransmission and disrupted pathways affecting neuroplasticity have been postulated as an underlining brain dysfunction in depression [21]. The primary hypothesis for CES use in depression is that reactivating 5HT and NA neurotransmission would reset the brain neuroplasticity [22]. There is a lack of scrupulous RTCs confirming the enduring effects of CES in the management of major depressive disorder [23]. A review of CES applications for depression revealed a severe lack of rigorous RCTs and a tendency to use non-standard instruments for diagnosing and monitoring depression symptoms with a high risk for bias [23]. In December 2019, the FDA announced that there is no valid evidence for CES as a treatment for depression and request new trials to be made. FDA concluded that the four studies published after January 1, 2016, through November 1, 2019, did not contribute sufficient information in the form of valid scientific evidence to demonstrate that the subjects met the criteria for any recognized depressive disorder.

Anxiety and comorbid depression

The co-occurrence of anxiety and depression is considered a complex clinical entity that impacts patients' prognosis and treatment outcomes. When anxiety disorders are accompanied by comorbid depression, this further complicates the treatment process. Adherence to pharmacological agents is usually difficult due to medications' potential adverse and side effects, thus requiring alternative treatments

such as CES. The use of CES as an effective alternative treatment for anxiety and comorbid depression has only been explored in one RCT study [23]. Until further studies are conducted, clinicians recommending CES as an effective treatment modality should convey to their patients that the low strength evidence of its efficacy suggests a modest benefit in treating anxiety and depression.

Posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) is a complex, heterogeneous disorder that develops following trauma and often includes perceptual, cognitive, affective, physiological and psychological features. It is characterized by hyperarousal, intrusive thoughts, exaggerated startle response, flashbacks, nightmares, sleep disturbances, emotional numbness and persistent avoidance of trauma-associated stimuli. The efficacy of available treatments for PTSD may result in part from the relief of associated depressive and anxiety-related symptoms and treatment of core symptoms that derive from re-experiencing, numbing, and hyperarousal [24]. The treatment of PTSD combines several types of evidence-based psychotherapies, such as prolonged exposure or cognitive processing therapy, with psychopharmacology for symptomatic relief of its disabling symptoms [24,25]. Reviews of RCTs for military-related PTSD demonstrated that although these therapies result in meaningful improvement in patients with PTSD, approximately two-thirds of patients do not experience remission of symptoms and endure ongoing suffering and disability [25,26]. Thus, alternative treatment approaches such as CES are critically needed to improve PTSD treatment outcomes. However, limited data are currently available on the effectiveness of this treatment intervention in PTSD [27].

Obsessive compulsive disorder

Obsessive compulsive disorder (OCD)is characterized by repetitive thoughts (obsessions) and behaviors (compulsions) in which the afflicted individuals feel compelled to complete these behaviors despite their insight into the irrationality of practicing these behaviors [28]. The obsessive thoughts revolve around fears, unwanted thoughts, or extreme preoccupation with cleanliness, or order. The compulsions are usually manifested by excessive cleaning, counting, checking, and organizing endless tasks. Several anatomical and neuroimaging studies have suggested a possible relation between obsessive compulsive disorders (OCD) and frontotemporal and brainstem dysfunction, a probable involvement of serotoninergic central pathways, with a significant impairment of pontine segment and the mesencephalic region brain regions [28]. Neuromodulation techniques for treatment resistant OCD have included ECT, TMS, tDCS, and DBS. It has been postulated that patients with OCD who do not respond to neuromodulation techniques could benefit from Alpha-Stim and CES treatment, however, there are no RCTs trials to confirm this option. To date, there is no evidence-based research that supports this treatment modality for treatment resistant OCD.

Substance use disorders

Specific investigations have shown that CES effectively relieve stress that accompanies withdrawal from substance use and decrease cravings. There is a dearth of research on noninvasive brain stimulation for substance use disorders, and CES could be considered a novel treatment modality that should be further investigated [29]. However, there is still a general reluctance to use this modality in the clinical treatment of substance use disorders due to the lack of evidence-based research confirming its effectiveness as an alternative for substance use and addictive disorders [30].

Adverse effects

Alpha-Stim has been associated with some side effects such as skin irritation, headaches, and dizziness [1,13]. It is not recommended for use during pregnancy or the lactation period and in patients with cardiac pacemakers and other implanted bioelectric equipment. It is difficult to differentiate these side effects from the pre-existing symptoms of the disorder being treated [13]. The potential for emerging versus preexisting adverse effects needs to be seriously addressed by clinicians administering the treatment [1,31].

Cost effectiveness?

The delivery of Alpha-Stim CES may be a feasible, acceptable and less expensive intervention of providing treatment for some patients, who are reluctant to receive pharmacological treatment for their new presentations of symptoms of anxiety, insomnia and depression [32].

Comparison between alpha-stim and medications?

The evidence for the effectiveness and safety of CES is sparse. There is low strength evidence of a modest benefit in patients who used it. CES is probably safe, but the strength of evidence is low since few RCTs report adverse events. It is necessary to confirm its evidence based efficacy by conducting series of RCTs with adequate blinding to confirm the relative effectiveness and safety of this non-pharmacological treatment intervention.

Summary

Alpha-Stim is a prescriptive medical device that delivers CES with possible clinical utility in treating anxiety, insomnia and depression [1,13]. Its adverse effects are usually rare, mild, and reversible, consisting mainly of skin irritation under the electrodes, headaches, and dizziness [1,13]. It is often used as a sole intervention, or as an adjunctive therapy. The FDA has approved it to treat anxiety, and insomnia with its weakest evidence for depression. A review of the literature suggests that the effectiveness and safety of this treatment modality are still sparse, with low strength evidence of a modest benefit in patients with anxiety, insomnia and depression. The assumption of its efficacy and safety are based on limited numbers of RCTs. Although it is probably a safe intervention, the strength of evidence of its safety is low since only few RCTs report adverse effects. Clinicians advocating its use need to exercise caution and prudeness in recommending it as an alternative intervention until more RCTs are conducted to validate its efficacy as an evidence-based clinical practice.

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Conflict of Interest Statement

The materials described in this manuscript are those of the author and do not reflect the views of the Department of Veterans Affairs, the VA Central California Health Care System , the Department of Psychiatry of UCSF-Fresno Medical Education Program or the Department of Psychiatry and Behavioral Sciences, University of Texas Health, McGovern medical School.

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