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REVIEW

Impact of Cranial Electrostimulation on Sleep: A Systematic Review

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Abstract

Purpose This paper aimed to systematically review the effectiveness of cranial electrostimulation (CES) to improve sleep.
Methods Electronic databases such as MEDLINE, CENTRAL and EMBASE were systematically searched from inception up to December 2018 to retrieve relevant literature. Randomized controlled trials (RCTs), crossover studies, quasi-experimental non-randomized controlled trials and pre–post-single-group experimental design investigating the effect of cranial electrostimulation on sleep assessed by either objective or subjective parameters were included in the present systematic review.
Result Twenty-three articles were found to be relevant and were then assessed for their characteristics. Out of the 23 studies, only 6 were RCTs. All the identified RCTs underwent quality assessment for their methodology using 11-point PEDro scale. Fifteen out of 23 studies (5 out of 6 RCTs) demonstrated that CES is beneficial to induce and improve sleep in various populations as assessed by both subjective and objective outcome measures.
Conclusion After critically analyzing the literature, it is concluded that cranial electrostimulation treatment leads to positive improvements in sleep parameters in various diseased and healthy population; however, further studies are needed to support the use of CES for sleep problems.

Keywords Sleep · Sleep disturbance · Insomnia · Cranial electrostimulation · CES · Electrosleep

1 Introduction

Sleep is a natural and reversible state of relative inactivity and reduced responsiveness to external stimuli, accompanied by a loss of consciousness, occurring at regular intervals [1]. As stated by pioneering researcher Allan Rechtschaffen, sleep is likely to support fundamental needs of the organism [2]. The primary function of sleep is to ensure adequate cortical function when awake [3]. Sleep disorders are a group of conditions that affect the ability to sleep well on a regular basis. Whether they are caused by a health problem or by too much stress, sleep disorders are becoming increasingly common [4]. In fact, a large proportion of population in modern era are reported to have sleeping difficulties fairly regularly [5]. Inadequate sleep leads to a plethora of problems including neurocognitive, metabolic, cardiovascular, systemic and immunological deteriorations [6]. With such high prevalence rates as well as well-established associations with various psychophysiological impairments, it is empirical to embark upon specific interventions which are lacking as per now, to manage sleep abnormalities.

Cranial electrical stimulation (CES) is a non-pharmacological and non-invasive method of applying low-intensity electrical current to the brain, indirectly [7]. It differs from other forms of transcranial stimulation including electroconvulsive therapy (ECT) and trans-magnetic stimulation [TMS; 8]. The different versions of transcranial electrical stimulation vary in the placement of electrodes, the intensity of the current, and the waveform of the current [9]. The use of CES dates back to 1960s, with a lot of researches being done during that time to prove its effectiveness in managing various psychophysiological conditions [10, 11]. But later, craze of studying CES went down due to the lack of quality researches backing its use with objective outcome measures to provide a quantitative evidence supporting the hypothesis that CES induces relaxation and initiates as well as maintains sleep [11, 12]. However, there is a revival of this technique nowadays, due to increasing statistics showing sleep irregularities which may be attributed to modern day lifestyle [13, 14].

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CES-induced sleep has been described as 'a state of consciousness grossly indistinguishable from ordinary sleep, produced by the direct action of a weak rhythmic current on the brain of a co-operating subject in a non-distracting environment' [7]. It is an FDA-approved intervention for conditions such as anxiety, depression and insomnia [15]. Despite the fact that CES modulates sleep behaviour, a limited published literature exists to evaluate its efficacy to improve sleep in various diseased and healthy populations. Considering the lacuna in existing literature, the present study sough to systematically review the evidence and to give a clear picture regarding the effectiveness of cranial electrostimulation to improve sleep.

2 Methods

2.1 Search Strategy

We developed a search strategy to identify studies that elucidated the effects of cranial electrotherapy stimulation on sleep. A systematic search was performed on the electronic databases MEDLINE (accessed via PubMed), CENTRAL (Cochrane Library Central Register of Controlled Trials) and EMBASE starting from the earliest records available till December 2018. Random Search items used were a combination of key words 'cranial electrotherapy stimulation, cranial electrostimulation, electrosleep, sleep, insomnia, sleep disturbance'. The keywords were combined with Boolean operators 'OR' and 'AND' to broaden or narrow the search. Furthermore, we reviewed reference lists of original and review articles to search for more studies on the same topic. Systematic search was carried out from September 2018 to December 2018.

2.2 Eligibility Criteria

Initially, the authors intended to include only randomized controlled trials (RCTs), however, due to unavailability of adequate number of RCTs, this review was expanded to include studies with quasi-experimental non-randomized controlled designs, pre–post-experimental designs and crossover study designs to clearly present the picture of existing literature.

Clinical trials investigating the effect of cranial electrotherapy stimulation with one or more treatment session on sleep assessed by either qualitative (clinical observation, questionnaires, self-report) or quantitative measures [polysomnography (PSG), nocturnal electroencephalography (EEG)] were included for the review. Studies examining the effect of cranial electrostimulation on other conditions such as pain, anxiety and depression were excluded. Furthermore, researches using other forms of neuro-modulation such as ECT and TMS were also excluded. No sample size restriction was applied. Studies in language other than English were excluded from this review.

2.3 Selection of Studies

Out of the total records (486) identified, 344 duplicates were removed, to retrieve records to be screened. 86 records underwent the screening process by reading titles and abstracts by one reviewer (AA). Seventeen articles (6 RCTs) were found to be relevant based on the pre designed eligibility criteria and were assessed by two independent reviewers (AA and EH) for the characteristics of study. All the 6 RCTs underwent quality assessment for their methodology by two independent reviewers (AA and EH), (Fig. 1).

2.4 Data Extraction

Data on the characteristics of the trial (author, year of trial conduction, design and duration), the participants (age and information on other medical comorbidities), intervention (device used, duration, dosimetry, safety and follow-up) were extracted by two of the authors (AA and EH). If the reported data were unclear, the authors of that study were contacted via email. The two reviewers worked independently and any conflicts were resolved through mutual consensus.

2.5 Measurement of the Treatment Effect

Effect size for the pre-decided outcome measures (qualitative-questionnaires as well as quantitative-PSG/nocturnal EEG) was calculated for the RCT reporting point measures and variability [13, 14, 19] using Cohen's *d* [20].

2.6 Quality Assessment of Included Trials

For assessing the methodological quality of all the retrieved RCT evidences, the authors used an 11-point PEDro scale having a set of generic core items for quality assessment of randomized clinical trials [RCTs, 21]. Trials were independently assessed for quality by the two authors (AA and EH). If there was any disagreement on any criterion, it was re-assessed by each reviewer independently. Unresolved disagreements were identified and discussed in a meeting to reach a final consensus.

Ten out of 11 criteria (criteria regarding the specification of eligibility criteria in the paper was not considered when assigning scores as all the included studies had mentioned their inclusions and exclusions) were used for quality assessment on PEDro and each criterion was rated either yes (score = 1) or no (score = 0) to minimize ambiguity in responses. The total score for the methodological quality

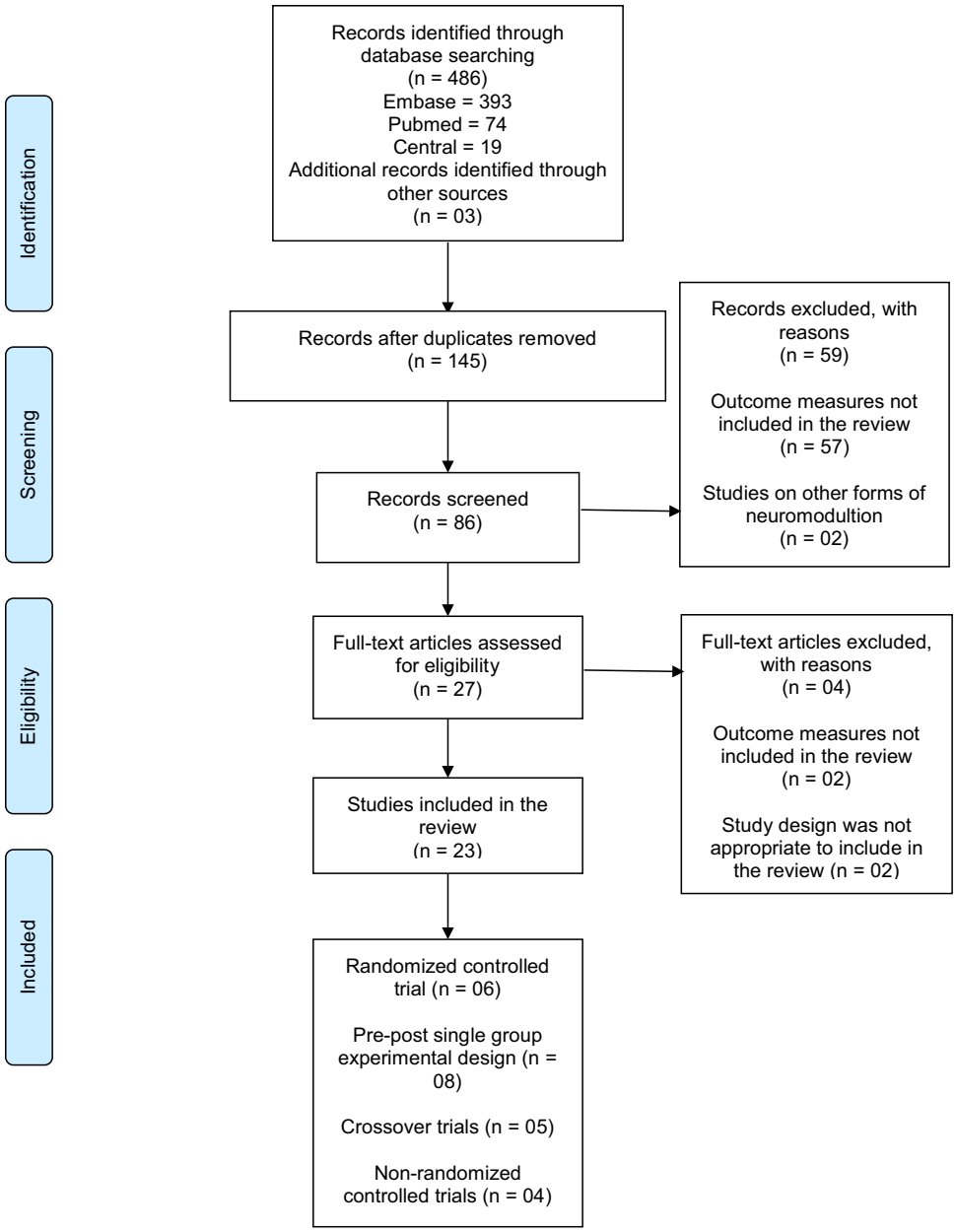

Fig. 1 PRISMA flowchart showing identification and selection of trials for the systematic review

of each included study was calculated by summing all the responses (maximum score = 10). Studies were then classified as poor (score of < 4), fair (score of 4 or 5), good (score of 6–8) and excellent quality (score of > 8) based on total scores obtained on PEDro scale [22].

3 Results

Only 6 relevant RCTs were retrieved which are discussed for their characteristics and quality in Sect. 3.1 and characteristics of non-RCT design trials are subsequently discussed in Sect. 3.2.

3.1 Section 1

3.1.1 Characteristics of Studies

3.1.1.1 Study Design Randomized controlled trial.

3.1.1.2 Participants Six included RCTs consisted of 222 participants with sample sizes ranging from 10 to 60 subjects. A common limitation in all the studies was lack of information on sample size and power calculation except one study [14]. The majority of subjects were adults including both the genders, with one study assessing only females [14] (Table 1).

Table 1 Characteristics of randomized controlled trials (RCTs), $n=6$

S. no.	Trial	Participants	Study design	Intervention	Control	Outcomes	Findings	Safety	Follow-up
1.	Weiss et al., 1973 [16]	10 subjects with insomnia	RCT	24 sessions for 15 min with Electroderm-1 device, I and ν not mentioned	Simulated electrosleep treatment	Nocturnal EEG for SOL, time to 1st spindle or K-complex, TST, time spent in sleep stages and the % of TBT subjects were awake	SOL decreased with CES and maintained over a no week treatment interval	Not reported	Follow-up after 14 days
2.	Gomez et al., 1978 [17]	28 methadone drug withdrawal patients with sleeping difficulty	RCT	CES for 2 weeks for 30 min, $\nu=100$ Hz, $I=0.4$–1.3 mA, pulse duration = 2 ms, device: not mentioned	Control group divided in 2 groups; Gp 1 = simulated CES, Gp2 = no sham CES	Self-reported subjective sleep	CES improved self-reported sleep	Reported	No follow-up
3.	Hozumi et al., 1996 [18]	27 dementia patients with irregular sleep–wake pattern	RCT	CES with HESS 100 device for 20 min for 2 weeks, $\nu=6$–8 Hz, $I=256$–560 µA	Placebo stimulation for 20 min for 2 weeks	Sleep diary, sleep–wake behaviour, clinical evaluation of sleep, wake EEG for α and θ wave ν	Improvement in sleep–wake behaviour with increase in α band ν	Not reported	No follow-up
4.	Lichtbroun et al., 2001 [19]	60 fibromyalgia patients with sleep dysfunction	RCT	CES with Alpha-Stim CES for 1 h for 3 weeks of $\nu=0.5$ Hz, $I=100$ µA	Sham and no treatment group	Self-rating for quality of sleep	Improvement in sleep quality in patients with fibromyalgia	Reported	No follow-up
5.	Lande et al., 2013 [13]	57 subjects with insomnia	RCT	CES with Alpha-Stim CES for 60 min for 5 days, $I=100$ µA and $\nu=0.5$ Hz	Sham for 60 min, for 5 days	Sleep log including SOL, TST and no. of awakenings	Significant increase in TTS post-CES treatment	Reported	No follow-up
6.	Wagenseil et al., 2018 [14]	40 females without sleep disorder	RCT	CES with Alpha-Stim 100 for 1 h during a night, $I=100$ µA and $\nu=0.5$ Hz	Sham device for same duration	PSG for SE, SOL, S1, S2, S3 and REM latency, duration of sleep stages	No change in sleep parameters as measured by PSG	Not reported	No follow-up

CES cranial electrostimulation, *I* current, ν frequency, *SOL* sleep-onset latency, *SE* sleep efficiency, *TST* total sleep time, *TBT* total bedtime, *EEG* electroencephalogram, *PSG* polysomnography, *REM* rapid eye movement, *S1* non-REM stage 1, *S2* non-REM stage, *S3* non-REM stage 3

3.1.1.3 Intervention All the studies investigated the effect of cranial electrostimulation using different commercially available devices like various derivative models of Alpha-Stim [13, 14, 17], Electroderm-1 [16] and Prototypic device HESS 100 [18], however, only some of them [13, 14, 19] reported if the device was FDA approved or not. Duration of CES treatment ranged from single session to 2 weeks. Duration of each session varied from 15 min to 1 h, frequency was between 0.5 and 8 Hz and intensity of current ranged from 100 µA to 1.3 mA. One study did not provide any information about the device used [17], whereas another study failed to give details of the frequency and intensity of current utilized during the experiment [16]. The placement of electrodes varied between the studies, however, majority of the studies used clip electrodes and attached them to earlobes [13, 14, 19]. Two of the studies reported on safety of the intervention [13, 17]; however, only one study took the follow-up of participants post-intervention [16].

3.1.1.4 Outcome Measures Two studies [14, 16] performed nocturnal EEG/PSG for assessing various parameters such as sleep efficiency, sleep-onset latency, latency and duration of different sleep stages. Two studies [13, 18] used sleep logs or sleep diary to quantify sleep–wake habits, total sleep time, number of awakenings in between sleep. Hozumi and colleagues [18] evaluated wake time EEG to assess the frequency of alpha and theta rhythms with respect to background activity in addition to sleep diary and clinical evaluation. Two studies [17, 19] examined self-reported sleep behaviour along with its quality. All the included studies used a variety of outcome measures making it difficult to perform meta-analysis/pooled quantification.

3.1.1.5 Quality of Trials Quality scoring was performed only for the RCTs included in the review. Average PEDro score for all the trials was 5/10 (fair quality). Two trials scored 5/10 [14, 16], one scored 8/10 [13], one scored 7/10 [19], one scored 3/10 [18] and one 2/10 [17]. All the studies randomly allocated the subjects into groups but only three maintained a concealed allotment. [13, 14, 19]. Three of the trials [14, 17, 18] did not blind either of the subject, the therapist or the assessor, however, two studies followed the double-blind procedure with one study [13] blinding the therapist and the assessor whereas the other [16] blinding the subject and the assessor. One study ([9] carried out triple blinding for the subjects, the therapist as well as the assessor in their carefully conducted trial. Three out of 6 RCTs reported very well about the between-group differences post-intervention with point estimates and measures of variability [13, 14, 18]. On the other hand, except one [13] no other study applied intention to treat analysis on drop-outs (Table 2).

Table 2 Quality scoring of randomized controlled trials (RCTs) using PEDro scale, $n = 6$

Trial	Eligibility criteria	Random allocation	Concealed allocation	Group similarity at baseline	Blinding of subjects	Blinding of therapist	Blinding of assessor	Drop-outs < 15%	Intention to treat analysis	Between-group differences reported	Point estimate and variability reported	Total score	Quality
Gomez et al., 1978 [17]	Yes	Yes	No	No	No	No	No	Yes	No	No	No	2/10	Poor
Hozumi et al., 1996 [18]	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes	3/10	Fair
Weiss et al., 1973 [16]	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	5/10	Good
Lichtbroun et al., 2001 [19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	7/10	Good
Lande et al., 2013 [13]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	8/10	Excellent
Wagenseil et al., 2018 [14]	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes	Yes	5/10	Good

3.1.1.6 Effect of CES Intervention on Sleep Majority of the studies [5 out of 6 RCTs; 13, 16–19] reported an improvement in sleep parameters after CES treatment. However, only three [14, 16, 18] out six studies included objective measures out of which, 2 reported in favor of CES [16, 18] to improve sleep and one study [14] demonstrated no change in sleep parameters after using CES. Some of the studies [13, 14, 16] reported changes using point estimates and measures of variability while some did not. Lande and colleagues [13] found positive improvement in hours of sleep (0.92) post-CES intervention for 5 days, while Wagenseil et al. [14] reported non-significant results after a single session of CES at night. Hozumi and colleagues [18] demonstrated significant improvement (0.32) in sleep followed by 2 weeks of CES therapy (Table 1). Most of the studies confirmed the efficacy of cranial electrostimulation to improve sleep.

3.1.1.7 Effect of CES Intervention on Sleep in Heathy and Diseased Population Five out of 6 RCTs [13, 16–19] were done on diseased population. Two studies included patients with insomnia [13, 16], one study included participants with sleep disturbance associated with drug withdrawal [17]. Hozumi et al. [18] conducted the study on dementia patients having irregular sleep–wake behaviour [18], while Lichtbroun et al. [19] included patients with fibromyalgia and assessed their sleep quality pre- and post-CES intervention. Only one study worked with normal population without any sleep dysfunction [14]. All of the RCTs conducted on the clinical population revealed improvement after CES [13, 16–19]; however, the result of the studies on healthy individuals [14] showed no change post-CES intervention.

3.2 Section 2

3.2.1 Characteristics of Studies

3.2.1.1 Study Design Eight trials [9, 10, 12, 23–25, 27, 32] out of 17 consisted of pre–post-single-group experimental design without control group. Five trials [28–30, 34, 35] followed a crossover design and 4 studies [26, 31, 33, 36] were non-randomized controlled trial (quasi-experimental design). None of the trials stated reason for non-randomizing participants into groups (Table 3).

3.2.1.2 Participants A total of 338 participants were included in these 17 studies. Sample size ranged from 8 to 40, though there was no information on sample size calculation and power analysis. Majority of the participants were middle-aged adults. Only one of the study [28] exclusively included male participants, while rest of the studies worked with both genders.

3.2.1.3 Interventions All the studies investigated the effect of cranial electrostimulation using different devices such as Electrosone-50 [24, 25, 28–30, 32], Somlec-3 [27], Dormed [33], Neurotone 101 [12, 31, 34, 35] and Diastym [36]. Two of the studies [10, 11] used self-made devices while two did not mention about the device [23, 26]. No study mentioned if the device they used were FDA approved or not. Duration of CES treatment ranged from single session to 1 month. Duration each session varied from 5 min to 2.30 h, frequency was between 20 and 350 Hz and intensity of current ranged from 0.02 to 12 mA. Location of electrodes varied in all the studies, however, majority used electrodes on orbits and mastoids [11, 24–26, 29, 30, 32, 36], others placed them over forehead and occiput [12, 23, 31, 35]. Twelve of the studies reported on safety of the intervention and found no ill effects [9, 10, 23–28, 31, 32, 34] while 5 studies took the follow-up of participants post-intervention [10, 12, 25, 30, 32, 35].

3.2.1.4 Outcome Measures The commonest outcome measure was questionnaires/self-rating scale used by 10 studies [24–26, 29, 31–36] to quantify changes in sleep parameters. Two studies relied only upon clinical observations for sleep outcomes such as eyelid movement, limb movement, and snoring [10, 12] while one study utilized clinical observations along with EEG recordings [9]. One study [30] utilized both night time EEG and questionnaire while three studies exclusively used nocturnal EEG [23, 27, 28] to quantify sleep parameters. All the included studies used a variety of outcome measures, making it difficult to perform a pooled analysis.

3.2.1.5 Effect of CES on Sleep Ten studies [9, 23–26, 28, 29, 31, 34, 36] found significant positive improvement in sleep after CES treatment and 4 studies reported no change [27, 30, 33, 35]. Three studies found variable results [10, 12, 32] with some of the patients showing improvement while some showing no change. Regarding the use of objective variables to quantify differences between pre- and post-CES, a very few studies [11, 23, 27, 28, 30] incorporated objective measurements, out of which three [11, 23, 28] reported improvement in sleep post-CES administration whereas, two studies [27, 30] reported no change.

3.2.1.6 Effect of CES Intervention on Sleep in Heathy and Diseased Population Majority of the studies were performed on diseased population [10, 12, 23–26, 29–36]. Eleven trials [10, 23–26, 29, 31–35] included patients showing symptoms of sleep dysfunction as a result of various psychiatric conditions such as anxiety, neurosis and depression. Only one study included patients with chronic primary insomnia [30], one study worked with hemiplegic patients [10] while Phillip et al. [36] dealt with patients showing

Table 3 Characteristics of non-randomized controlled trials (non-RCTs), $n = 17$

S. no.	Trial	Participants	Study design	Intervention	Control	Main outcome	Findings	Safety	Follow-up
1.	Forster et al., 1963 [10]	17 hemiplegic patients	Pre–post-single-group experimental design	CES with fabricated device, $\nu = 20$ Hz and $I = 0.5$–5 mA	No control group	Clinical observation	Inconclusive results, some patients going to sleep and some not	Reported	Follow-up after 1 year
2.	Magora et al., 1965 [11]	15 healthy subjects, 2 patients with Parkinson's disease and one with dystonia	Pre–post-single-group experimental design	CES with self-made device for 5–15 min, $\nu = 25$–100 Hz, $I = 5$–12 mA	No control group	Observation of eyelid and limb movt, snoring, reaction to auditory stimuli and EEG recordings during sleep	Sleep was induced and resembled physiological sleep on EEG	Reported	No follow-up
3.	Magora et al., 1967 [23]	20 patients with insomnia and other psychiatric problems	Pre–post-single-group experimental design	4 CES treatment session for 2–3 h a day, device: not reported	No control group	EEG recording for sleep rhythms	Restoration of sleep rhythms on EEG	Reported	No follow-up
4.	Rosenthal et al., 1970 [24]	40 patients with insomnia associate with chronic anxiety and depression	Pre–post-single-group experimental design	30 min CES with Electrosone-50 for 5–10 days, $I = 0.1$–0.2 mA and $\nu = 100$ Hz	No control group	Self-reported sleep	Improvement in self-reported night time insomnia	Reported	No follow-up
5.	Rosenthal et al., 1970 [25]	9 patients with insomnia associate with chronic anxiety and depression	Pre–post-single-group experimental design	CES with Electrosone-50 for 10 days, 30 min/day, $I = 0.1$–0.2 mA and $\nu = 100$ Hz	No control group	Self-reported rating of sleep disturbance	Improvement in self-reported symptoms of sleep disturbance	Reported	Follow-up after 2 and 4 weeks
6.	Rosenthal et al., 1972 [26]	22 neurotic patient with insomnia	Non-randomized controlled trial	Five, 30 min treatment with 100 Hz freq, and 0.5–1.3 mA, device: not reported	No control group	Clinical rating scale	Slight improvement in sleep disturbance	Reported	No follow-up
7.	Empson, 1973 [27]	8 healthy students	Pre–post-single-group experimental design	5 min single session with Somlec-3 device with 20 Hz ν	No control group	Nocturnal EEG	CES treatment didn't induce sleep as assessed by EEG	Reported	No follow-up
8.	Itil et al., 1973 [28]	10 male volunteers	Crossover design	2 days of CES with Electrosone-50 and 2 days of sham in a crossover manner	No control group	EEG	Slight improvement in sleep pattern on EEG with CES	Reported	No follow-up

Table 3 (continued)

S. no.	Trial	Participants	Study design	Intervention	Control	Main outcome	Findings	Safety	Follow-up
9.	Feighner et al., 1973 [29]	23 psychiatric patients	Crossover design	2 weeks of CES with Electrosone-50, 30 min daily for 5 days/week, 100 Hz ν and I 100–250 µA current Sham treatment for 2 weeks	No control group	Global rating of insomnia	CES active treatment improved sleep as compared to sham	Not reported	No follow-up
10.	Frankel et al., 1973 [30]	17 patients with chronic primary insomnia	Crossover design	30 days CES with Electrosone-50 at 2 different ν, ν = 100 Hz, I = 0.1–0.7 mA; ν = 15 Hz, I = 0.02–0.15 mA	No control group	Nocturnal EEG, EMG and EOG	No improvement in sleep parameters on EEG and questionnaire	Not reported	After 2 weeks follow-up
11.	Hearst et al., 1974 [31]	28 psychiatric patients	Non- randomized controlled trial	Five, 30 min CES with Neurotone-101, 100 Hz ν,	Five, 30 min session of sham	Physician and global rating for sleep	Difficulty to fall and stay asleep reduced	Reported	No follow-up
12.	Flemenbaum et al., 1974 [32]	28 patients with anxiety, depression and insomnia	Pre–post-single-group experimental design	5,1.5 h of CES with Electrosone-50, ν = 100 Hz, I = 0.1–0.3 mA	No control	Self-rating scale	Half of the patients improved and those who improved maintained it throughout 6 months	Reported	Follow-up taken 3 days after treatment, 6 weeks, 16 and 24 weeks after treatment
13.	Levit et al., 1975 [33]	13 psychiatric inpatients	Non-randomized controlled trial	Ten, 1.5 h session with Dormed machine for 2 weeks, ν = 100 Hz, I = 0.05–0.20 mA	Simulated treatment group, suboptimal current gradually turned down to zero	Subjective self-rating scale	No significant improvement in sleep as compared to placebo	Not reported	No follow-up
14.	Moore et al., 1975 [34]	17 patients with persistent insomnia and other psychiatric symptoms	Crossover design	Five, 30 min CES with Neurotone, 100 Hz freq, and 480 µA or simulated session	No control group	Subjective scale	Improvement in subjective insomnia	Reported	No follow-up
15.	Ryan et al., 1977 [12]	40 neurotic patients	Pre–post-single-group experimental design	Five, 30 min CES with Neurotone 101, 100 Hz ν	No control group	Clinical observation of sleep, snoring, breathing and difficulty in arousal	Variable results with some patients going to sleep and some not during the CES	Reported	No

Table 3 (continued)

S. no.	Trial	Participants	Study design	Intervention	Control	Main outcome	Findings	Safety	Follow-up
16.	Von Richthofen et al., 1980 [35]	10 subjects with anxiety neurosis	Crossover	5 consecutive days of active and 5 days of placebo CES with Neurotone 101 2 day rest in between; $\nu = 100$ Hz, $I = 1.5$ mA	No control group	Clinical rating for sleep duration and quality	No difference in sleep between active and placebo condition	Not reported	Follow-up taken at various time points; day 8 day 15, day 22 day 43
17.	Philip et al., 1991 [36]	21 patients with insomnia as a result of drug abstinence syndrome	Non-randomized controlled trial	30 min daily CES with Diastym, twice a day for 5 days $I = 1$–1.2 mA and $\nu = 350$ Hz	For 1 min, $I = 1$–1.2 mA and $\nu = 350$ Hz	Questionnaire for SOL, nocturnal arousals, SE, sleep duration and awakening time	Sleep duration improved in the active group as compared to control group	Not reported	No follow-up

CES cranial electrostimulation, *I* current, *ν* frequency, *movt* movement, *EEG* electroencephalogram, *SOL* sleep-onset latency, *SE* sleep efficiency

insomnia like symptoms as a result of drug abstinence. Three studies [9, 27, 28] worked with healthy volunteers, however, Magora et al. [9] in addition to healthy individuals involved 2 patients with Parkinson's disease and one with dystonia making his population heterogeneous. Most studies on the diseased individuals demonstrated that CES ameliorates sleep dysfunction [23–26, 29, 31, 34, 36], while some trials revealed inconclusive results [10, 12, 32] with most showing no change [30, 33, 35] post-CES. The results of the studies on healthy individuals were inconclusive with 2 studies showing improvement in sleep [9, 28] with CES while one [27] demonstrating no such effect.

4 Discussion

This is the first systematic review providing comprehensive information on the findings, characteristics and quality of clinical trials investigating the effect of CES on sleep in various diseased and healthy populations. Although the heterogeneity in the participants and the outcome measures restricted direct pooled analysis, the result derived from the existing evidence suggests engaging in CES treatment may have beneficial effect on sleep as indicated by various qualitative and quantitative methods.

4.1 Effect of CES on Sleep

Sleep disturbance is common in modern society. It often remains overlooked but can lead to severe deterioration of our physiological systems. Lack of restorative sleep during night is associated with decreased amounts of REM and slow wave activity [37] which in turn leads to excessive day-time sleepiness due to micro-sleep during day [38]. These micro-sleep phases contribute to slowing of cognitive processes during the day, which in turn hampers the daily functioning of poor sleepers [39]. Inadequate sleep is also considered to deteriorate complete physiology of human beings including the cardiorespiratory, neurological, and immunological systems [40]. Considering all these consequence of sleep disturbance, finding a safe and effective intervention to manage sleep problems is a major challenge for primary care clinicians. CES seems to be an easy, safe and time efficient intervention to improve sleep and relaxation. In the present review, most of the studies on healthy as well as on clinical population demonstrated positive change after CES therapy [9, 13, 16–19, 23–26, 28, 29, 31, 34, 36], while some of the studies showed no change [14, 27, 30, 33, 35]. A handful of studies also demonstrated variable results [10, 12, 32] with some subjects showing improvement and some not. It is shown previously that sleep abnormalities can be managed, and early management leads to better results [41]. Therefore, it becomes important to identify the problem, and implement

CES, a safe, user friendly and effective method to reverse sleep abnormalities.

4.2 Underlying Mechanism

Although, the underlying mechanism of how CES improves sleep is not clear, several theories can be used in an attempt to explain the empirical findings and clinical effectiveness of CES.

The brain functions electrochemically and, therefore, can be easily modulated by interventions using electric currents [15]. CES intervention, a type of energy medicine, stimulates the cortex using low level of AC currents. Several electromagnetic tomography and functional magnetic resonance imaging studies suggests that CES travels to all the cortical and sub-cortical structures including the thalamus [42]. Insomnia, and other sleep-related disorders, is thought to be exacerbated by excessive cortical activation [43]. A recent functional magnetic resonance imaging study showed that CES causes cortical brain deactivation in the midline frontal and parietal regions of the brain after treatment, thus facilitating sleep [44]. CES applications have been shown to modulate neurotransmitters and hormone production via the hypothalamic–pituitary axis [45]. Increase in the levels of melatonin, serotonin, norepinephrine and β-endorphin along with reductions in the concentration of cortisol may result in the alleviation of fatigue, drowsiness and sleep-related dysfunction [46]. CES treatments also significantly alters EEG activity such increasing alpha (8–12 Hz) relative power and decreasing relative power in the delta (0–4 Hz) and beta (12–30 Hz) frequencies [47]. Increased alpha is associated with improved relaxation, whereas decreased delta and beta correlates with reduction in anxiety and stress [48, 49]. Altogether, changes in neurochemicals, deactivation of certain cortical areas and modulation of brain rhythms may produce relaxation and facilitate sleep function. However, clinical trials included in the present review did not investigate these mechanisms associated with improvement of sleep post-CES. Therefore, studies in future should investigate these possible underlying mechanisms to support their findings.

Most studies included in this review showed positive improvements in sleep; however, there were many important methodological limitations in included clinical trials. There were only 6 RCTs with an average quality of fair [13, 14, 16–19]. Majority of the studies were either pre–post-experimental design without control group [9, 10, 12, 23–25, 27, 32] or quasi-experimental non-randomized controlled trials [26, 31, 33, 36]. Researches without control group are poorer designs, since they cannot control or trace the changes with time and can act as an important confounder to vary study results. Most of the studies lacked randomization while some of them did not blind the participants, therapists or assessors. Since blinding is an important component of clinical trials, these trials suffered from low scores on quality scoring. Despite these limitations, majority of the studies demonstrated improvement in sleep with CES. Therefore, it may be concluded that if CES is incorporated in the management of sleep problems, it may induce relaxation and lead to improvement in sleep, however, the results of this literature review should be interpreted with caution due to the presence of several limitations of the studies being reviewed.

4.3 Strength and Limitations

To date, this is the only systematic review which exclusively investigated the effect of CES on sleep. Due to availability of only 6 RCTs, this review provided information on studies with other designs also, however, randomization and control are extremely important components of clinical trials and they adequately control the effect of confounders on dependent variable. The authors included and discussed non-RCT trials to elucidate methodological limitations and flaws in existing clinical trials.

4.4 Implications and Future Recommendations

This systematic review indicates that there are several existing evidences pointing towards the efficacy of CES to improve sleep. However, due to paucity of RCTs, the strength of this evidence is fairly low. Inclusion of more objective outcome measures of sleep such as polysomnography which is a gold standard measure to quantify sleep may provide us with more high-level evidence regarding the efficacy of this treatment. In addition, more studies are required with optimal controls and randomization procedures to provide conclusive evidence for the same.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest.

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