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CRANIAL ELECTROTHERAPY STIMULATION (CES) IN THE TREATMENT OF ANXIETY AND OTHER STRESS-RELATED DISORDERS: A REVIEW OF CONTROLLED CLINICAL TRIALS

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SUMMARY

This CES review covers published and to be published clinical trials in the English language and reported to be controlled in some fashion and completed from January 1963 to January 1996. Cranial electrotherapy stimulation (CES) is defined as the application of low-level pulsed electrical current through skin surface electrodes on the head for the treatment of anxiety and other stress-related disorders. A total of 34 controlled clinical trials concerning the efficacy of CES in the treatment of anxiety and other stress-related disorders were evaluated. Overall the results suggest that CES may be capable of producing significant ($p < 0.05$) benefit in the short-term symptomatic relief of anxiety and other stress-related disorders. CES may be effective alone and as an adjunct to other conservative measures of treatment. The primary mechanism of action of CES appears to be a direct effect on the brain followed by secondary responses. While adverse effects were reported to occur in less than 3 per cent of patients, it is believed they are substantially underreported. The short- and long-term efficacy, adverse effects, safety and mechanism of action of CES remain to be established in rigorous, well-controlled clinical trials. Results reported in this review suggest that CES warrants further study.

KEY WORDS — electric stimulation therapy; brain; controlled clinical trials; anxiety; stress (psychological); safety

This review covers published and to be published clinical trials in the English language and reported to be controlled in some fashion and completed from January 1963 through January 1996.

Cranial electrotherapy stimulation (CES) is defined as the application of low-level pulsed electrical current through skin surface electrodes on the head for the treatment of anxiety and other stress-related disorders for the purpose of this review.

CES has been known by a number of other names such as transcranial electrotherapy (TCET), transcranial stimulation (TCS), cranial stimulation (CS), neuroelectric therapy (NET) and the 'original' electrosleep (ES), to name a few. It differs from electroacupuncture (EA), which involves applying small amounts of electricity to needles or staples which penetrate the skin at traditional Chinese acupuncture points, or transcutaneous electrical nerve stimulation (TENS), which refers to the use of electrical current of a much higher level than CES to surface electrodes placed over specific peripheral nerve route sites. TENS devices are reported to be approved by the FDA for the relief of pain via attachment to the body below the head but not on it.[1] CES apparently requires further evaluation by the FDA before formal approval can be granted for anxiety and other stress-related indications.

HISTORY

The Russian scientist Rabinovich is credited with coining the term 'electrosleep' around 1914.[2] The rationale for electrosleep was based originally on Pavlov's observation that dogs required to make difficult conditional discriminations fell asleep during the conditioning stimulus. This phenomenon was attributed to the spread of inhibition over the cortex from a specific locus to a generalized condition.[3] By electrosleep, the Russians did

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not mean a deep narcosis-like, or even hypnotic-like sleep but rather a sort of sedation during which the patient was more relaxed and less anxious and stressed. Unfortunately, most of the early American researchers appeared to have misunderstood CES and tried to actually induce sleep, with variable results.

The present form of CES in the United States is based chiefly on the systematic studies by Gilyarovsky and his collaborators.[2,4] Obrosow published the first American review paper on CES in 1959.[5] By the early 1980s, the use of CES for the treatment of anxiety and other stress-related disorders became commonplace in the United States.

CES LITERATURE REVIEWS/ META-ANALYSES

Several authors reviewed the development of CES up to the mid-1980s.[1,2,4–12] Bianco[13] recently published a meta-analysis of controlled trials pertaining to the use of CES in the treatment of anxiety and withdrawal symptoms in narcotic addicts. He concluded that CES produced significant ($p < 0.05$) reduction of anxiety in patients suffering from drug withdrawal. Klawansky[14] published a meta-analysis of several randomized control trials of patients suffering primarily from neurotic anxiety. He found that CES was significantly more effective ($p < 0.05$) than sham treatment in controlling anxiety. Kirsch[15] also found CES to be effective in producing significant ($p < 0.05$) reduction in anxiety.

CES CONTROLLED CLINICAL TRIALS

A total of 34 controlled trials were evaluated for efficacy, adverse effects and safety in this review. They involve a total of 767 patients receiving CES and an additional 867 serving as controls. It should be noted that few of these trials can be considered to be rigorous and well-controlled according either to the criteria used by Klawansky *et al.*[14] or by the US Food and Drug Administration. Results are summarized in Table 1.

These controlled clinical trials employed CES devices which differed in electrical current design and output as well as frequencies, types of electrodes and placements used. In two of the studies[38,39] (including reference 58) a CES device with a carrier frequency of 15,000 Hz and a modulating frequency of 15 Hz was used. It remains to be established in rigorous, well-controlled clinical trials whether or not any of these device differences plays a significant role in CES efficacy, adverse effects, safety or mechanism of action. In addition, since there is no well-accepted statistical approach that allows one to combine studies of varying quality and methodology (using different CES devices) in any convincing manner,[16] only clinical judgement was used in determining the clinical significance of results of the controlled clinical trials covered in this review.

Twenty-six of these 34 (76.5 per cent) controlled clinical trials are reported to be positive ($p < 0.05$), and eight (23.5 per cent) negative. The average length of treatment was around 2 weeks (range 1–42 days). In 13 of the 34 trials, the duration of treatment ranged from 3 to 6 weeks. Treatment sessions generally were 20–60 minutes in length. Electrode placement varied. Placement of electrodes over the eyes (closed eyelids), employed in some of the earlier studies, is no longer used in the United States because of adverse effects produced. Current used was 1.5 mA or less and frequency pulse repetition rate was 100 Hz or less in most trials.

Bianco[13] evaluated CES in 65 polysubstance abusers with anxiety/depression in a double-blind, randomized, parallel group design comprising CES-treated, sham and control groups. He reported a statistically significant improvement ($p < 0.05$) of anxiety and depression in the active CES group over the sham and no-treatment control groups. No CES adverse effects were reported.

Costain[17] conducted a randomized double-blind crossover study of CES in 24 patients with anxiety/depression. Anxiety, agitation and somatic symptoms were significantly ($p < 0.05$) improved by CES versus sham CES. Slight skin sensitivity to sticking-plaster or irritation under the electrodes, often due to drying out of electrodes with diminished area of contact, sometimes necessitated a change of the electrode placement. Instances of mild headache occurred in both the CES and control group. There were no other CES adverse effects reported.

England[18] studied CES in a controlled trial of 18 patients with stress-related migraine headache. CES produced a significant ($p < 0.05$) reduction in headache duration and intensity. One patient in the study developed mild skin irritation at the location of the electrode. No other CES adverse effects were reported.

Feighner[19] conducted a randomized, double-blind, controlled, crossover trial of CES in 23 chronically ill patients with anxiety, insomnia and depressive symptoms. Active CES treatment significantly ($p < 0.05$) improved anxiety, depression and insomnia. No CES adverse effects were reported.

Gibson[20] carried out a randomly assigned, single-blind trial of CES in 64 patients with significant levels of anxiety as measured by STAI (State/Trait Anxiety Inventory). CES was reported to be significantly ($p < 0.05$) more effective than placebo in reducing state anxiety and EMG readings of muscle tension. No CES adverse effects were reported.

Gomez[21] studied CES in 28 patients randomly divided into three groups undergoing methadone detoxification. CES was reported to reduce anxiety significantly ($p < 0.05$). Nine of the patients receiving active CES were drug-free by the end of 8–10 days of treatment, and all experienced a marked reduction of their symptoms. No CES adverse effects were reported.

Hearst[22] evaluated CES in 28 psychiatric outpatients with anxiety/depression in a randomized controlled trial. By day 5, patients receiving active treatment appeared to be less depressed ($p < 0.1$) than those receiving simulated treatment (79 per cent vs 21 per cent). After 19 days of treatment there was no significant difference between the active CES-treated versus sham-treated patients regarding anxiety or depression. No CES adverse effects were reported.

Heffernan[23] evaluated the ability of CES to block the acute stress response in 20 patients selected from a clinical treatment population of people seeking help for stress-related problems. Ten patients received active and 10 sham CES under double-blind conditions. CES produced a significant reduction in stress response ($p < 0.05$). No CES adverse effects were reported.

Krupitsky[24] conducted a randomized, double-blind controlled trial of CES in 20 alcoholic patients with anxiety/depression. CES produced significant ($p < 0.05$) improvement on the MMPI depression and Zung scales as well as the Taylor Manifest Anxiety Scale. No CES adverse effects were reported.

Levitt[25] carried out a double-blind crossover evaluation of CES in 11 psychiatric inpatients suffering from anxiety, depression and sleep disturbance. CES was reported to be no better than placebo in improving anxiety, depression or sleep disorders. No CES adverse effects were reported.

Matteson[26] evaluated CES in stress management in 32 members of an executive MBA program. Twenty-two similar subjects served as controls. CES was reported to produce significant ($p < 0.05$) reduction in frequency of health complaints, tension discharge, anxiety, depression and anger/hostility. Four subjects reported headache during CES treatment but none left the study for this reason. No other CES adverse effects were reported.

Moore[27] studied CES in a randomized, double-blind crossover study in 17 patients suffering from anxiety, depression and insomnia. There were no significant differences between the two groups at the conclusion of treatment. No CES adverse effects were reported.

Overcash[28] studied CES in a randomly assigned controlled trial involving 32 marijuana abusers. The CES-treated group was reported as significantly ($p < 0.05$) better able to reduce their frontalis EMG than the control group. In addition, the CES-treated group was able to reach the same level of relaxation after eight sessions that it took the control group to reach in 10 sessions. The CES-treated group also became significantly ($p > 0.05\%$) more planful, self-sufficient, assertive, ego-strengthened and more decisive in handling their interactions with others. No CES adverse effects were reported.

Passini[29] carried out a randomly assigned controlled trial in 60 anxious, depressed inpatients. Significant ($p < 0.05$) post- versus pre-treatment differences occurred in both groups; however, none of the between-group effects approached significance. No CES adverse effects were reported.

Philip[30] conducted a randomized, double-blind study of CES in 21 anxious/depressed inpatients undergoing drug withdrawal in a hospital psychiatric department. During benzodiazepine withdrawal, epileptic seizures occurred in two patients with no history of epilepsy in the simulated CES group. However, no benzodiazepine withdrawal seizures occurred in the active CES group. Anxiety was exacerbated in the placebo group (simulated CES) and significantly ($p < 0.05$) reduced in the active CES treatment group. No CES adverse effects were reported.

Rosenthal[31] evaluated CES in 22 mostly outpatients suffering from anxiety, depression and insomnia in a double-blind crossover experimental design. Of the 11 patients receiving active CES

Table 1. — Summary of 34 controlled clinical trials of CES in the treatment of anxiety, mixed anxiety/depression and other stress-related disorders

Study	Indication	No. patients		Duration treatment	Electrode placement	Current		Adverse effects	Significance of results
		CES	Contr.			mA	Hz		
Bianco[13]	Anxiety/ depression	21	44	Up to 42 days	Both mastoids	< 1.5	100	None reported	Anxiety/depression reduced, $p < 0.05$
Costain[17]	Anxiety/ depression	12	12	2 weeks	Over eyes & leg	0.1–0.25	NA	Occasional headache	Anxiety/depression reduced, $p < 0.05$
England[18]	Stress-related migraine	6	12	3 weeks	Both mastoids	NA	100	Skin irritation	Headache intensity/ duration reduced, $p < 0.05$
Feighner[19]	Anxiety/ depression	23	23	4 weeks	Over eyes & mastoid	0.1–0.25	50–100	None reported	Anxiety/depression/ insomnia reduced, $p < 0.05$
Gibson[20]	Anxiety	32	32	1 day	Ear lobes	0.05	0.5	None reported	Anxiety reduced, $p < 0.05$
Gomez[21]	Anxiety	14	14	10 days	Over eyes & mastoid	0.4–1.3	100	None reported	Anxiety reduced, $p < 0.05$
Hearst[22]	Anxiety/ depression	14	14	19 days	Over eyes & mastoid	< 1.1	100	None reported	Anxiety/depression, NS
Heffernan[23]	Stress response	10	10	1 day	Ear lobes	0.1	0.5	None reported	Stress reduced, $p < 0.05$
Krupitsky[24]	Anxiety/ depression	10	10	4 weeks	Forehead & mastoid	4–7	70–80	None reported	Anxiety/depression reduced, $p < 0.05$
Levitt[25]	Anxiety/ depression	5	6	2 weeks	Over orbits & mastoid	0.05–0.20	100	None reported	Anxiety/depression, NS
Matteson[26]	Stress/anxiety/ depression	32	22	14 days	Both mastoids	< 1.0	100	Headache 4 patients	Anxiety/depression/stress reduced, $p < 0.05$
Moore[27]	Anxiety/ depression	17	17	5 days	NA	0.2–0.7	100	None reported	Anxiety/depression, NS, subjective insomnia reduced, $p < 0.05$
Overcash[28]	Stress/anxiety	16	16	10 weeks	Ear lobes	0.5	0.5	None reported	Stress/anxiety reduced, $p < 0.05$, self- sufficiency increased, $p < 0.05$
Passini[29]	Anxiety/ depression	30	30	2 weeks	Over eyes & mastoids	NA	100	None reported	Anxiety/depression, NS
Philip[30]	Anxiety/ insomnia	10	11	5 days	Over eyes & mastoids	1.0–1.2	350	None reported	Anxiety/insomnia reduced, $p < 0.05$
Rosenthal[31]	Anxiety/ insomnia	22	22	5 days	Over orbits & mastoids	0.5–1.2	100	None reported	Anxiety/insomnia reduced, $p < 0.05$
Ryan[32]	Anxiety	12	12	5 days	Forehead & mastoid	NA	100	None reported	Anxiety reduced, $p < 0.05$

Scallet[33]	Anxiety	5	5	3 weeks	Over eyes & mastoid	< 1.5	100	None reported	Anxiety, NS
Schmidt[34]	Anxiety	30	10	3 weeks	Over eyes & mastoid	< 1	100	None reported	Anxiety reduced, $p < 0.05$
Smith[35]	Anxiety/ depression	36	36	3 weeks	Occiput/mastoids	1.5	100	None reported	Anxiety reduced & mood improved, $p < 0.05$
Smith[36]	Anxiety/ depression	10	11	3 weeks	Ear lobes	up to 1.5	100	None reported	Anxiety/depression reduced, $p < 0.05$
Smith[37]	Anxiety/ depression	23	80	3 weeks	NA	NA	NA	None reported	Anxiety and depression reduced, $p < 0.05$
Solomon[38]	Tension headache	57	55	6 weeks	Head/temples	up to 4	*	Skin irritation	Tension/mixed headache improved, $p < 0.05$
Solomon[39]	Tension/vascular headache	21	41	NA	Scalp & occiput	up to 4	*	None reported	Tension/mixed headache improved, $p < 0.05$
Sousa[40]	Anxiety	80	80	3 weeks	NA	16V	NA	None reported	Anxiety reduced, $p < 0.05$
Taylor[41]	Stress/anxiety	10	20	1 day	Ear lobes	0.24	100	None reported	Stress & anxiety reduced, $p < 0.05$
		54	18	1 day	Ear lobes	0.24	5–2K		
		30	60	1 day	Ear lobes	0.24	100		
Tomsovic[42]	Anxiety	43	47	5 days	Orbits & mastoids	0.5	100	None reported	Anxiety, NS
Von Richthofen[43]	Anxiety	10	10	5 days	Forehead & mastoid	1.5	100	None reported	Anxiety, NS
Voris[44]	Anxiety/stress	38	54	10 days	Ear lobes	0.3	0.5	None	Anxiety/stress, $p < 0.05$
Weingarten[45]	Stress/anxiety/ depression	12	12	3 weeks	NA	NA	NA	None reported	Anxiety and depression reduced, $p < 0.05$
Weiss[46]	Anxiety/ insomnia	5	5	24 days	Over eyes & nape of neck	0.1	100	Minor complaints of warm skin prickling	Insomnia improved, $p < 0.05$, anxiety 51–110% higher in controls, NS
Winick[47]	Anxiety	17	16	1 day	Ear lobes	0.2	0.5	None	Anxiety reduced, $p < 0.05$
Totals									
Controlled trials		34							
CES patients		767							
Control patients		867							

Contr., controls; NA, not available; over eyes, over closed eyelids; NS, not significant; mA, milliamps; Hz, Hertz; V, volts.
*15 Hz modulating a carrier of 15,000 Hz.

treatment eight were markedly and two partially improved and one showed no change. Only one showed marked and two partial improvement in the 11-patient placebo group. Average total clinical ratings on anxiety, sleep disturbance and depression fell from 11.3 before treatment to 3.2 following treatment. For the patients receiving sham CES, total clinical ratings fell from 12.2 to 9.5. The average anxiety rating fell from 4.3 prior to treatment to 1.4 following treatment. In contrast, for patients receiving sham CES, anxiety scores fell from 4.4 prior to treatment to 3.2 following treatment. Sleep disturbance scores of the patients receiving active CES fell from 4.2 prior to treatment to 0.8 following treatment whereas those receiving inactive treatment fell from 4.2 to 3.6. Between-group differences were reported to be significant ($p < 0.05$) in favor of active CES. No CES adverse effects were reported.

Ryan[32] conducted a randomly assigned control trial of CES in 24 psychiatric inpatients with neurotic anxiety. CES produced significant ($p < 0.05$) reduction in anxiety. No CES side-effects were reported.

Scallet[33] evaluated CES in a randomized controlled trial in 20 outpatients suffering from hysterical anxiety. Anxiety diminished throughout treatment and increased again when treatments were completed. Between-group differences were not significant. CES was reported to have no specific benefit for patients with hysterical anxiety. No CES adverse effects were reported.

Schmidt[34] studied the effects of CES in a double-blind controlled trial in chemically dependent patients. Twenty others served as waiting-in-line patients. CES-treated patients showed significantly ($p < 0.05$) greater improvement on all anxiety measures than did either control groups. No CES adverse effects were reported.

Smith[35] evaluated CES in 72 male alcoholics in two separate studies. Thirty-six (36) patients were randomly assigned to simulated and 36 to active CES. CES-treated patients were reported to be significantly ($p < 0.05$) improved on every scale of the profile of mood states as well as on the total mood disturbance score. No CES adverse effects were reported.

Smith[36] conducted a randomized, double-blind trial of CES in 21 patients living in a sheltered living facility and suffering from closed head injury, anxiety, depression and insomnia. CES-treated patients responded significantly ($p < 0.05$) on all negative mood factors of the profile of mood states. No CES adverse effects were reported.

Smith[37] carried out a CES study in patients who were in various stages of a 28-day inpatient treatment regimen for cocaine and/or polysubstance withdrawal. The first 39 patients admitted to the facility had CES added to their regimen. One hundred and seven such patients served as controls. Anxiety and depression were significantly ($p < 0.05$) reduced by CES therapy as compared with controls. No CES adverse effects were reported.

Solomon[38] conducted a multicenter, parallel group, double-blind clinical trial of CES in 100 outpatients with tension headache occurring alone or as part of migraine (mixed headache). Sixty-three per cent of the simulated CES patients rated the treatment as not effective compared with 38 per cent of the active CES group ($p < 0.05$). Six of 57 patients reported adverse events in the active CES group compared to seven of 55 in the simulated CES (placebo) group. Irritation at the electrode sites occurred in two of 57 (3.5 per cent) of the active CES group. The overall incidence of adverse events was not significantly different between active and placebo groups.

Solomon[39] evaluated active CES versus sham CES in 62 outpatients attending a hospital headache clinic with stress-related migraine or muscle contraction (tension) headache. Active CES-treated patients had significant ($p < 0.05$) improvement in their headaches compared to controls. No CES adverse effects were reported.

Sousa[40] conducted a randomized control trial of CES in 160 patients with anxiety. Patients were divided into four groups, 40 patients in each: group 1, simulated CES; group 2, auditory stimulus; group 3, active CES; and group 4, active CES plus auditory stimulus. CES produced a 35 per cent improvement on the Hamilton Anxiety Scale score (HAS). In the auditory plus CES group, the improvement was 80 per cent on the HAS and 60 per cent on the Taylor Manifest Anxiety Scale (TMAS). There was only minimal improvement in the simulated CES group. Differences between groups were considered to be statistically significant ($p < 0.05$). No CES adverse effects were reported.

Taylor[41] conducted three CES controlled trials in healthy volunteers subjected to mild psychological stress sufficient to elevate the level of anxiety. A standardized stress test was used in all three studies.

The first Taylor double-blind trial involved 30 health volunteers randomly assigned to three

groups. Significant ($p < 0.05$) reductions in stress (systolic and diastolic blood pressure and anxiety, but not pulse rate, peripheral vascular tension or muscle activity) were found in treatment-blind subjects after CES. No CES adverse effects were reported.

The second Taylor double-blind study involved 90 healthy volunteers randomly assigned to five different treatment groups, 16 subjects in each. CES significantly ($p < 0.05$) reduced systolic and diastolic blood pressure and pulse rate, but not peripheral vascular tension or anxiety at 100 Hz but not after 5 or 2000 Hz as compared to the no-treatment control group. No CES adverse effects were reported.

In the third Taylor double-blind study, 90 healthy volunteers were evaluated. Thirty received active CES, 30 simulated and 30 no treatment for 30 minutes immediately followed by 3 minutes of the standardized stress test. Significant ($p < 0.05$) reductions in systolic blood pressure, pulse rate and anxiety, but not diastolic blood pressure or peripheral vascular tension were observed subsequent to 30 minutes of 100 Hz, 0.24 mA CES as compared to the no-treatment control group. Significant reductions in diastolic blood pressure were also observed after simulated CES. No significant antianxiety effect was observed with simulated CES. No CES adverse effects were reported.

Tomosovic[42] conducted a randomized, double-blind CES study in 90 alcoholic rehabilitation center inpatients suffering from anxiety and sleep disorders. The authors concluded that the negative findings of their study questioned the assumption that CES is beneficial in reducing anxiety/tension-related neurotic symptoms in alcoholics after alcohol withdrawal. However, the marked placebo effect observed in the simulated CES group may have obscured the beneficial effect of active CES. Mild tingling under the electrodes occurred. No CES adverse effects were reported.

Von Richthofen[43] evaluated CES in 10 patients suffering from anxiety in a randomized crossover experimental design. Spearman rank-order correlation of 0.71 was found to be significant ($p < 0.05$), indicating an association between extraversion and the response to the procedure of active CES. There was a statistically significant ($p < 0.05$) overall improvement in the levels of anxiety, but no significant difference between active and simulated CES. No CES adverse effects were reported.

Voris[44] carried out a randomized controlled trial in 60 psychiatric outpatients suffering from anxiety disorder. CES produced significant ($p < 0.05$) reduction in anxiety as compared with sham CES or no-treatment controls. No CES adverse effects were reported.

Weingarten[45] studied CES in 24 stressed, anxious/depressed inpatients in an alcoholic rehabilitation center, randomly assigned into active and simulated CES. CES produced significant ($p < 0.05$) improvement on the profile of mood states (POMS), tension/anxiety, depression/rejection and fatigue/inertia scales. The beneficial effect of CES on anxiety/depression did not appear to be associated with reduction of arousal as measured by frontalis EMG. No CES adverse effects were reported.

Weiss[46] evaluated CES in a randomized, double-blind study in 10 outpatients suffering from anxiety/insomnia. Electroencephalographic (EEG) results revealed that the CES produced a significant ($p < 0.05$) decline in latency of sleep onset, percentage of bed time awake and percentage of total sleep in stage I, as well as an increase in total sleep in stage 4 and total delta sleep. There were no statistically significant differences at the end of treatment between groups on anxiety. However, MMPI anxiety index mean score at the end of treatment was 64.52 for simulated and 42.60 for active CES (51 per cent higher for placebo versus active CES). The Taylor manifest anxiety score for the simulated treatment group was 24.4 compared with 11.6 for the active CES group (110 per cent higher for placebo). The small sample size used in this study may account for the failure of active CES to achieve the desired level of statistical significance regarding reduction of anxiety. Some patients reported warmth and prickling sensations over the eyes and some prickling/tingling under electrodes on the neck. No CES adverse effects were reported.

Winick[47] conducted a randomly assigned, double-blind study in 33 anxious dental patients undergoing a variety of procedures. The results indicate that CES produced significant ($p < 0.05$) reduction in anxiety compared with controls. No CES adverse effects were reported.

NEGATIVE CONTROLLED CLINICAL TRIALS

Eight controlled clinical trials (23.5 per cent) were considered to be negative. The reasons for these eight negative trials are not entirely clear.

Hearst[22] studied a small sample of diverse psychiatric diagnoses which did not appear to be randomly distributed between the active and control groups. Small group sizes and non-comparable groups may have contributed to the failure to demonstrate significant differences between groups.

Levitt[22] also employed a very small sample of patients, which not uncommonly lacks the statistical power to discriminate between groups unless very large differences are observed. In addition, not all patients selected for study appeared to be suitable candidates for CES therapy: four were schizophrenic, two chronic alcoholics, two psychotically depressed and five suffered from mixed neuroses and disorders of personality. Also, no attempt appears to have been made to control concomitant antidepressant and/or tranquilizing medications. Each of these factors may have contributed to the negative results found in this study.

Moore[27] used a crossover design, which not uncommonly fails to demonstrate significant differences in psychiatric studies. Current used was somewhat lower than other studies and this also may have played a role. The small sample size employed may also have been a factor as well as the diverse psychiatric diagnoses evaluated. Interestingly, subjective insomnia did improve significantly, and several patients had a remarkable improvement in their symptoms some 2–3 weeks after CES therapy was concluded.

Passini[29] used patients with nine different diverse psychiatric disorders in a study with too few patients. This, together with the marked 'placebo' effect observed in the control group, most likely precluded finding significant differences between CES and controls.

Scallet[33] used a small group of hysterics in his study. This, together with the marked placebo effect in the control group, presented difficulties in finding statistically significant differences. Patients suffering from hysteria are generally considered to be very suggestible and this may account for the marked 'placebo' effect seen.

Tomosovic[42] also found a marked 'placebo' response in the control group, precluding demonstrating significant differences between CES and controls.

Von Richthofen,[43] like Moore previously, also employed a crossover design, which not uncommonly fails to demonstrate significant differences in psychiatric studies. As such, a crossover design may not have been appropriate.

The small sample size used in the Weiss[46] study may account for the failure to achieve statistical significance in spite of the far greater reduction of anxiety in the active CES group versus controls.

ADVERSE EFFECTS

Adverse effects were reported in five of 34 controlled trials (14.7 per cent). Less than 20 of 767 CES-treated patients (2.6 per cent) were reported to have had mild to moderate adverse effects due to CES. Complaints of self-limiting headache, discomfort or skin irritation under the electrodes and lightheadedness were reported. Aching/pain in the eyes and blurring of vision reported in a few patients are considered to be due to electrode placement over the eyes, a procedure which is no longer used or recommended in the United States. No cases of CES-induced seizures, skin burns or any other evidence of serious toxicity were reported to have occurred in any of the patients treated with CES. While adverse effects were reported in less than 3 per cent of patients treated, it is believed that they are substantially underreported.

The National Research Council concluded, after a review of the preclinical and clinical literature prior to 1974, that there apparently are few complications attributable to CES.[48] The results of other reviews also appear to support this conclusion.[1,2,4–12,15] Follow-up of a small number of patients (6 months–2 years) receiving CES therapy is reported to reveal no clinically significant evidence of CES toxicity.[15]

The nature and true incidence of adverse effects of CES remain to be established in short- and long-term rigorous and well-controlled clinical trials.

OPEN CLINICAL TRIALS

Open CES clinical trials are not included in this review because information on such studies may be found in the paper by Kirsch.[15]

ANIMAL STUDIES

Jarzembski[49] reported CES studies in monkeys which showed that thalamic current density was slightly higher than the cortical current density, and that from 40–50 per cent of the total applied current entered the brain substance.

Pozos[50] provided evidence in dogs that CES electroshock and lithium all produce a Parkinson-like state when combined with reserpine. Thus, all three have some effect on catechoamines. Since reserpinized adrenergic neurons release their neurotransmitters in proportion to the amount of stimulus, it is assumed that electrical current causes a selective depletion of dopamine. Also, Pozos points out that the net effects of CES and electroshock therapy seem quite similar. It is hypothesized that CES given in a low current over a longer period of time, and electroconvulsive stimulation given at much higher current and a shortened time-frame, might accomplish similar effects on the brain.

Reigal[51] showed in monkeys that 1-hour treatment with CES markedly reduced gastric acid secretion (volume reduced 28 per cent and acid production reduced 60 per cent) and these changes returned to pretreatment levels within 1–2 hours after stimulation. CES effects on gastric secretions were found to be similar to those obtained with stimulation of the limbic structures in the brain.

Richter,[52] using electron microscopy, found no evidence of injury from electric currents applied to the brain of monkeys. Currents studied were up to 50 mA sine wave and 13 mA square wave.

Titaeva[53] found that the major CES effect in rabbits was a change from desynchronization to slow, high-voltage waves and later to a faster rhythm. These principal changes in the EEG from CES were attributed to a direct action of CES on the brain. The very rapid appearance of synchronized activity was observed chiefly in the subcortex and brainstem, in the region of the thalamus and the reticular formation of the mesencephalon.

Wilson[54] studied the effects of CES on gastric acid secretion in six monkeys. CES was reported to produce a marked decrease (50 per cent) in gastric secretions with a current of 0.1 mA and 15 Hz in monkeys with hypersecretion due to shock avoidance behavior. The author concluded that the results most likely were due to decreased parasympathetic output from the brain centers. The author also pointed out that various types of stress in humans are associated with gastric hypersecretion.

Wulfsohn[55] found from studies in cats that the application of CES in the form of trains, or short bursts, seems more readily to shift the mental and physical functions from wakefulness to sleep. Whether this shift is due to a neural mechanism or a neurohumoral modality remains to be clarified. EEG-modulated trains were reported to produce better sleep effects than non-modulated trains and were better than EEG-modulated current without trains. Wulfsohn appears to be the first to introduce a new element into CES, namely, that of administering pulses periodically and not intermittently as had been done previously. Apparently, a certain adaptation takes place in the nervous system with the use of intermittent pulses, but with periodic pulses this adaptation may be overcome.

Zuperku[56] evaluated the effects of CES in monkeys. Visual and somatosensory evoked potentials were found not to be altered by currents of 0.2–1.5 mA and 2.5–80 Hz as measured from electrodes implanted in various areas of the brain. The currents used were found to produce slower frequency and higher voltage brain waves. EMG amplitude was reduced. Respiration and EKGs were not affected.

Animal studies support the view that approximately 40–50 per cent of the CES pulsed current applied to the head enters the brain and affects subcortical structures, and produces a rapid, synchronized slowing of the EEG and a neurohumoral response. This appears to be accomplished without significant adverse effects or evidence of toxicity.

MECHANISM OF ACTION

Electrical current is reported to pass from the skin surface electrodes over the surface of the cranium into the brain. It then is reported to spread from the cortex to subcortical structures producing various secondary effects. Studies in animals[49] and man[57] have shown that approximately 40–50 per cent of the total current applied enters the brain.

The primary effect of CES appears to be due to a direct effect on the brain producing cortical and subcortical inhibition. It is not clear how this direct effect and other secondary effects reported may be related to the action of CES itself and/or the particular devices used, electrical current design and output, or the frequencies and type of electrodes and placement used.[1,2,17,24,30,41,49,50,58]

CES also may produce cortical and subcortical inhibition by way of the Melzack-Wall gate control mechanism.[20] Evidence for inhibition of synaptic transmission at CES currents used is not considered to be convincing since this could only be demonstrated at significantly higher currents (7 mA) than CES.[3]

The effects of CES have also been ascribed to the work of Pavlov, who showed in dogs that prolonged monotonous stimuli can lead to an inhibitory condition of the cortex, referred to as 'protective inhibition', which encompasses the cerebral hemispheres and descends to the lower brain centers. The concept that a pulsating current produces a type of Pavlovian conditioned response in the brain may account, at least in part, for the effects of CES[2,3–5,55,59]

'Alpha state conditioning' has also been put forth as a possible mechanism recently.[60] Brainwave frequencies are viewed as conditioned reflexes, and high amounts of EEG beta frequencies are seen not only as maladaptive but also responsible in a significant way for subjective feelings of general anxiety. In the non-anxious state, individuals usually demonstrate a mixture of alpha and beta frequencies in the EEG. As one closes the eyes and relaxes, beta frequencies tend to fade and alpha frequencies predominate in the EEG. Individuals with significant clinical anxiety usually are unable to evoke very much alpha or lower frequencies during waking periods. Low CES current/frequency is believed to produce a 'pacemaking' effect which is adapted by the brain so that neuronal firing simulates essentially the same tempo and becomes synchronized. This assists one in attaining the 'alpha state', a decrease in muscular tension and stress and a more conscious control over anxiety. This is supported by studies which show that CES leads to a significant increase in EEG slowing, synchronization of brain waves over the hemispheres, cortical inhibition and a state of relaxation.[3,23,24,41,46,53,55,56,60]

Milieu and suggestion also appear to play a role in the mechanism of action of CES, as can be the case with other therapeutic modalities. When administering CES, the patient usually is asked to lie or sit down in a comfortable, quiet, semi-dark room and accept a new type of treatment recommended by the doctor and perceived by the patient to be beneficial. Such factors obviously play a role in the overall efficacy of CES. However, it is recognized that while such factors may produce some beneficial results, and may even predominate in some cases, in the vast majority of studies CES was demonstrated to be superior to placebo (suggestion and milieu factors). Thus, suggestion and milieu, while clinically important, usually appear to play a minor role in the efficacy of CES.

The mechanism of action of CES in the treatment of anxiety and other stress-related disorders needs further clarification.

DISCUSSION AND CONCLUSION

The efficacy, adverse effects and safety of CES in the treatment of anxiety and other stress-related disorders were evaluated in a total of 34 controlled trials. Twenty-six (76.5 per cent) of the controlled trials presented in this review were reported to be positive ($p < 0.05$) and eight (23.5 per cent) negative. However, few of these studies can be considered to be rigorous, well-controlled clinical trials per criteria employed by Klawansky *et al.*[14] or the U.S. Food and Drug Administration. Possible reasons for the negative controlled trials were discussed previously.

Adverse effects were reported to be self-limiting and to occur in less than 3 per cent of patients receiving CES, and consisted chiefly of mild to moderate headache, discomfort or skin irritation under the electrodes and lightheadedness. It is believed that adverse effects may be significantly underreported in the controlled trials reviewed. Complaints of aching/pain in the eyes and blurring of vision were found only in those patients who had electrodes placed over the eyes, a procedure which is no longer recommended or used in the United States. Electrode placement on the ear lobes or over the mastoid area is preferred. No seizures or toxicity due to CES were reported.

The published data support the view that CES may be effective for the symptomatic relief of mild to moderate anxiety and other stress-related disorders at currents up to 1.5 mA. CES is reported to be effective alone as well as an adjunct to acceptable conservative measures of treatment.

Additional well-controlled clinical trials are needed to confirm and establish the efficacy, adverse effects, safety and mechanism of action as well as the value of CES in comparison with other therapeutic approaches used in the management of anxiety and other stress-related disorders.

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