From the book
Bioelectromagnetic Medicine
Paul J. Rosch, M.D. and Marko S. Markov, Ph.D., Editors
Marcel Dekker, Inc.
2004

Chapter 44

Cranial Electrotherapy Stimulation for Anxiety, Depression, Insomnia, Cognitive Dysfunction, and Pain: A Review and Meta-Analyses

Unabridged Version

By

Daniel L. Kirsch, PhD, DAAPM
Fellow of The American Institute of Stress
Diplomate, American Academy of Pain Management
Chairman, Electromedical Products International, Inc.
2201 Garrett Morris Parkway
Mineral Wells, TX 76067 USA
(940) 328-0788
Email: dan@epii.com

and

Ray B. Smith, Ph.D.
Former Vice President of Science
Electromedical Products International, Inc.

Bioelectromagnetic Medicine

Edited by: Paul J. Rosch, M.D. *The American Institute of Stress, Yonkers, New York, U.S.A., and New York Medical College, Valhalla, New York, U.S.A.*
and Marko S. Markov, Ph.D. *Research International, Buffalo, New York, U.S.A.*

Published: April, 2004 by Marcel Dekker, Inc., New York
ISBN: 0-8247-4700-3; 850 pages; $195.00

Over the last two decades, progress in MRI, PET, SQUID, and other sophisticated imaging techniques have revolutionized medical diagnosis. Similar advances in bioelectromagnetic therapy now promise to replace drugs and surgery for many disorders. The sudden surge of interest in this rapidly emerging modality has produced a plethora of spurious products making worthless claims that make it difficult to distinguish between true and false claims of efficacy. ***Bioelectromagnetic Medicine*** provides the tools and skills to make such evaluations and distinctions by:

- thoroughly explaining the biologic effects of magnetic and electromagnetic fields and the importance of dosimetry in determining clinical efficacy and safety
- presenting examples of cutting edge breakthroughs supported not only by rigid clinical trials but also by solid basic science research
- tracing the origin and evolution of transcutaneous electrical nerve stimulation (TENS), cranial electrotherapy stimulation (CES), vagal nerve stimulation, (VNS), repetitive transcranial magnetic stimulation (rTMS) and other proven therapies by pioneers and authorities responsible for their discovery and development
- identifying promising new approaches based on research advances in the U.S., Europe, Eastern Europe, Russia, and Pacific Rim countries

The 86 internationally recognized contributors to ***Bioelectromagnetic Medicine*** have strived to insure that it will remain the gold standard in the field for many years. Its 50 chapters and thousands of references dealing with every aspect of this topic make it an essential guide for physicians and all health care professionals, biophysicists, physiologists, biochemists and other basic scientists, as well as students and anyone interested in non-invasive and authoritative alternative medicine approaches.

The cranial electrotherapy stimulation (CES) chapter (Section VI, Chapter 44) was written by Dr. Daniel L. Kirsch and Dr. Ray B. Smith (during the term of his employment at Electromedical Products International, Inc.). Due to space limitations, the published book edited the tables and other data from the chapter. The original, unabridged version of the chapter is available free online at www.alpha-stim.com.

Bioelectromagnetic Medicine – Chapter 44 Unabridged Version

Cranial Electrotherapy Stimulation for Anxiety, Depression, Insomnia, Cognitive Dysfunction, and Pain: A Review and Meta-Analyses

Daniel L. Kirsch, Ph.D., D.A.A.P.M., F.A.I.S. and Ray B. Smith, Ph.D.

I. Introduction and History of CES

While the use of electric currents in medical practice dates back more than 2,000 years, today's interest in cranial electrotherapy stimulation (CES) probably had its beginnings in the research thrusts that began in France in 1903 by Leduc and Rouxeau. Leduc's student, Robinovitch, made the first claim for inducing sleep from electrical treatment in 1914. (1)

Subsequent research interest revolved around electronarcosis and then electroconvulsive shock treatments through the late 1930s. Interest in the smaller amounts of electric current involved in CES did not begin in earnest until work by Anan'ev and his group, in 1957, and in 1958 when Gilyarovski published a book entitled: Electrosleep. (2) That work initiated the interest in CES that has lead linearly to the present research and clinical use of CES in America and elsewhere.

The term "cranial electrotherapy stimulation" is used in the U.S.A. for what in much of the rest of the world is still called "electrosleep." The treatment arrived in America as "electrosleep," but American researchers soon found that it did not necessarily induce sleep during treatment, and that its clinical effects were obtained whether or not sleep occurred. (3,4) Today, any small electrical current that is passed across the head for therapeutic purposes is called cranial electrotherapy stimulation, officially, though many related terms such as "transcranial electrical stimulation," "cerebral electrostimulation," "alpha induction therapy," "neuro-modulation," "neuroelectric therapy," can be found in the titles of many research articles, making it difficult to find and index CES studies in the literature. (5,6) A recently revised annotated bibliography of CES research summarized 126 human studies, 29 animal studies, and 31 review articles. (7)

Another cause of confusion was the great number of stimulus parameters that fell under the CES rubric. An earlier report found that frequencies used in CES treatment ranged from 1 to 15,000 Hz, the pulse width varied from 0.1 to 20 millisecond, and the maximum peak pulse amplitude varied from 0 to 20 milliampere (mA), while the output potential ranged up to 50 volts, and the supply voltage ranged from a 3.6 volt battery source to line voltage of 120 volts AC. (8)

The United States is the only country in the world that requires a prescription from a licensed health care practitioner to dispense a CES device, and the Food and Drug Administration's (FDA) officially accepted marketing claims for its use are for the treatment of anxiety, depression and insomnia. Other clinical disorders have been found to be positively affected by CES, however, including several types of cognitive dysfunction, the substance abstinence syndrome, and more recently such widely disparate areas as reflex sympathetic dystrophy, multiple sclerosis and fibromyalgia. Each of these will be discussed in turn.

One of the major problems CES has had in entering mainstream medicine – and staying there – is that since the dawn of electromedicine, everything imaginable has been claimed to be successfully treated by medicinal applications of electricity at one time or another. Possibly underlying the large variety of claims for CES effectiveness were the early findings of Jarzembski and his research group at the University of Wisconsin. When CES was applied to the head of primates in whose brains sensors had been implanted, they found that 42% of the current applied externally actually penetrated through every region of the brain, though it canalized especially along the limbic system. (9) More recent research conducted by Ferdjallah at the Biomedical Engineering Department of the University of Texas at Austin has shown that from 1 mA of current, about 5 $\mu A/cm^2$ of CES reaches the thalamic area at a radius of 13.30 mm which is sufficient to affect the manufacture and release of neurotransmitters. (10)

Accordingly, CES stimulates regions of the brain responsible for pain messages, neurotransmitter genesis, and the hypothalamic-pituitary axis which controls hormone production and control throughout much of the body. If one assumes that such stimulation, even at the microampere level, is sufficient over time to generate activity in each of those areas of the brain, then one has cause to suspect symptom reduction in a multiplicity of areas of the body.

This chapter will focus on the scientific clinical studies of CES and will report primarily on the three treatment claims for CES presently permitted by the FDA: anxiety, depression and insomnia. We will then report on promising emerging clinical uses of CES that have been scientifically demonstrated, as published in the peer-reviewed scientific literature.

II. Summaries of the Scientific Studies

A. Depression

Many studies of depression have appeared in the American literature. While some studies found a remission of depression serendipitously while researching other symptoms (11), others, while researching depression specifically, did so with varying protocols which ranged from open clinical designs with no controls (12), to single blind with sham treated controls (13), to double blind with placebo controls. (14)

Measuring strategies have also ranged widely from clinical estimates of no known reliability or validity (15) to measurement with standardized tests of known reliability and validity. (16)

While the typical study reported significant changes at the 0.05 or 0.01 level or above, some reported the percent of patients showing clinical improvement of various degrees instead. (12) More recently, in the era of competing pharmaceuticals in medical treatment, American medicine has become less interested in statistically significant results and more interested in comparative effectiveness and safety of one treatment as opposed to another.

Two problems have developed from that interest; the term “significant” still often refers to the confidence limits of 0.05 or 0.01 found when comparing the mean differences between treated and control subjects, but in pharmaceutical studies it now often refers also to the number of patients improving at a level of 25% or more above their initial score, which is also termed “significant improvement.” On the other hand, while the number or percent of patients in a study experiencing sometimes very difficult negative side effects are usually published in the report, that number is not factored into the “significant” findings of the study, regardless of which of the two meanings is intended. The reader of such studies is left on his own to determine what the outcome means in his overall appreciation of the clinical importance, in terms of safety and effectiveness, of any new treatment.

CES studies have been guilty of the “significance” trap also, in that most have reported out only the significance of the confidence limits of the mean changes among patients in the studies, and have not concentrated on the actual amount of change effected by CES treatment. That is known as the “effect size” and will certainly become more commonly reported in future scientific studies, where “percent improvement” is now reported at best. The two terms are statistically synonymous. For now, effect size is the basic unit reported in the increasing number of meta-analytic studies appearing in the literature in which a reviewer statistically combines a large number of studies, the outcomes of which can vary widely, to learn what improvement a new group of patients should experience from a given treatment on average, and what the upper and lower limits of the mean of that expected outcome would ordinarily be 95% (or 99%) of the time when the treatment is applied. Those numbers are reported in meta-analyses as the effect size, usually including the standard error of the mean effect size obtained from the studies included in a given meta-analysis. That is, giving a new group of patients a range within which the expected effect size might reasonably be seen to vary.

What can a practitioner expect for his depressed patients when he recommends CES treatment after more than 30 years of CES studies and clinical application in the U.S.A.? Tables 1 and 2 give a meta-analytical summary of 25 studies of depression over the past 32 years dating from 1970 through 2002.

Table 1. List and description of CES studies of depression

Author	Treatment Parameters	Primary Diagnosis	Blinding			Study Design	Outcome Measure
			Subject	Therapist	Assessor		
Bianco (14)	45 min Daily, 6-14 Days	Alcoholism	Yes	Yes	Yes	Double Blind	Hamilton, and Beck Depression Scales
Feighner (82)	30 min Daily, M-F, 14 Days	Psychiatric Inpatients	Yes	Yes	Yes	Crossover	Zung SRDS (a)
Frankel (17)	45 min Daily, M-F, 15 Days, 15 Hz & 100 Hz Groups Combined	Insomnia	Yes	Yes	Yes	Crossover, 100Hz/15 Hz	Zung SRDS
Hearst (83)	30 min Daily, 5 Days	Insomnia	Yes	Yes	Yes	Crossover	NIMH Self Rated Symptom Scale
Krupistsky (84)	30 min Daily, M-F, 20 Days	Alcoholics	Yes	Yes	Yes	Double Blind	Zung, SRDS, MMPI Depression Scale
Levitt (85)	30 min Daily, M-F, 10 Days	Psychiatric Inpatients	Yes	Yes	Yes	Double Blind	Clinical Rating Scale
Smith (86)	45 min Daily, M-Th, 12 Days	Closed Head Injured	Yes	Yes	Yes	Double Blind	POMS (b)
Marshall (24)	30 min Daily, M-F, 5 Days	Psychiatric Inpatients	Yes	Yes	Yes	Double Blind	DES+D II
Matteson (16)	30-40 min Daily, 14 Days	Graduate Students	No	No	No	Open Clinical	POMS
Tyers (64)	60 min Daily, 21 Days	Fibromyalgia	No	No	No	Open Clinical	POMS
Tyers (65)	60 min Daily, 21 Days	Fibromylagia	No	No	No	Open Clinical	POMS
Lichtbroun (43)	60 min Daily, 21 Days	Fibromyalgia	Yes	Yes	Yes	Double Blind	POMS
Kirsch (7)	Various, Home Use	Diagnosed Depression	No	No	No	Open Clinical	Physician's Rating
May (87)	60 min Daily, 25 Days	Addiction	No	No	No	Open Clinical	Beck Depression Scale, MAACL (c)
Moore (42)	30 min Daily, 5 Days	Anxiety, Insomnia, Depression	Yes	Yes	Yes	Double Blind, Crossover	Beck's Depression Scale, Clinical Ratings
Passini (25)	30 min Daily, M-F, 10 Days	Psychiatric Inpatients	Yes	Yes	Yes	Double-Blind	MAACL
Phillip (26)	30 min, 2x Day, 5 Days	Psychiatric Inpatient Addicts	Yes	Yes	Yes	Double-Blind	MADRS (d)
Rosenthal (88)	30 min Daily, 5 Days	Psychiatric Outpatients	Yes	Yes	Yes	Double-blind Crossover	Clinical Ratings, Zung SRDS
Rosenthal (12)	30 min Daily, M-F, 5 to 8 Days	Psychiatric Outpatients	No	No	No	Open Clinical	Zung SRDS, Clinical Ratings
Rosenthal (18)	30 min Daily, M-F, 5 to 10 Days	Psychiatric Outpatients	No	No	No	Open Clinical	Clinical Ratings, Zung SRDS
Shealy (89)	20 min Daily, 14 days	Chronic Pain, Depression	No	No	No	Open Clinical	Serum Neurochemicals

Smith (13)	40 min Daily, M-F, 15 Days	Inpatient Alcoholics	Yes	No	Yes	Single Blind	POMS
Smith (11)	45 min Daily, 21 Days	ADHD	No	No	No	Open Clinical	IPAT Depression Scale

(a) Zung's Self Rating Depression Scale
(b) Profile of Mood States
(c) Multiple Affect Adjective Check List
(d) Montgomery and Asberg Depression Rating Scale

Table 2. Analysis of studies shown in Table 1

Author	Number of Patients			Statistic Reported	Results	Z_r Score (a)
	CES	Controls	Total			
Bianco (14)	11	18	29	% Improvement	80% (b)	1.099
Feighner (82)	23	23	23	% Improvement Zung SRDS	17%	.172
				% Improvement, Clinical Rating Scale	26%	.266
Frankel (17)	17	17	17	% Improvement	0%	.000
Hearst (83)	14	14	28	% Improvement	73%	.929
Krupitsky (84)	10	10	20	% Improvement, Zung SRDS	23%	.234
				% Improvement, MMPI	32%	.332
Levitt (85)	5	6	11	% Improvement	25%	.255
Smith (86)	10	11	21	% Improvement	30%	.310
Marshall (24)	20	20	40	% Improvement	0%	.000
Matteson (16)	32	22	54	% Improvement	34%	.354
Tyers (64)	20		20	% Improvement	35%	.365
Tyers (65)	60		60	% Improvement	26%	.266
Lichtbroun (43)	40	20	60	% Improvement	31%	.321
Kirsch (7)	69		69	Average % Improvement	71%	.887
May (87)	15		15	% Improvement, Beck DI	76%	.996
				% Improvement, MAACL	77%	1.02
Moore (42)	17	17	17	% Improvement, Clinical Ass.	59%	.678
				% Improvement, Self Rated	17%	.172
				% Improvement, Beck DI	5%	.050
Passini (25)	30	30	60	% Improvement	24%	.245
Phillip (26)	10	11	21	% Improvement	0%	.000
Rosenthal (88)	11	11	22	% Improvement, Clin Rating	64%	.758
				% Improvement, Zung SRDS	21%	.213
Rosenthal (12)	9		9	% Improvement, Clin Rating	38%	.400
				% Improvement, Zung SRDS	29%	.299
Rosenthal (18)	12	6	18	% Improvement, Clin Rating	56%	.633
				% Improvement, Zung SRDS	37%	.388
Shealy (89)	34	14	48	% Improvement	50%	.549
Smith (13)	36	36	72	% Improvement	67%	..881
Smith (11)	23		23	% Improvement	32%	.332
Total	826	306	1075	Mean Mean Effect Size N Weighted Effect Size Heterogeneity X^2 = 3.11, Df= 31. Standard Error of the Mean = 0.31	38%	.437 r = .41 r = .53 n.s.

(a) From Fisher Tables of r to z_r transformation (Edwards, 1964)
(b) Percent change equals r, from the binomial effect size distribution From Wolf, 1986, p33.

While all studies that could be easily found are included in the analysis above, some comments on specific studies are indicated. For example, Frankel's study, which found no positive effect from CES treatment, virtually stands alone in the CES literature and has been puzzling reviewers for three decades as of this writing. (17) His was basically a sleep study in which he included the Zung Self Rated Depression Scale to measure depression, and found no changes whereas Rosenthal routinely did find changes on that scale in his CES studies. (18) Frankel used the Taylor Manifest Anxiety Scale to measure anxiety, and found no changes among his patients whereas other CES researchers did. (19) He also measured 24 hour urinary ketosteroids and found no changes among his CES treated patients whereas Briones did. (20) He utilized overnight EEG measures in his sleep laboratory to measure sleep and found no changes, whereas Weiss obtained very good sleep changes on every EEG area measured. (21)

There were a couple of notable methodological issues in Frankel's design and analysis. First, while others had studied CES at a single frequency, usually 100 Hz, Frankel stated in his methods section that he studied both 100 Hz and 15 Hz, "…in order to study any differences in effects between these two types of CES treatments." He then proceeded to use a crossover design in which half of his 17 patients received 100 Hz while the other half received 15 Hz for 15 days. Then he crossed them over so that the patients who had received 100 Hz now received 15 Hz for the next 15 days, and vice versa. Obrasov, whom he quoted in his discussion, but not on this topic, and the present authors, have warned researchers against crossover studies due to the tendency of CES patients to continue to improve following treatment, thus muddling study results in crossed over controls. (22) But Frankel did do a crossover design, and in his statistical analysis did one of the strangest things to be found in the CES literature to date: He combined scores from both the 100 Hz group and the 15 Hz group in his pre study to post 15 day study analysis, then combined them again in his post 30 day study analysis. That is, he did not analyze his data "in order to study any differences in effects between these two types of CES treatments," rather he combined two different treatment parameters as if making the assumption that they had similar effects, and found no effect at all.

Perhaps most important to understanding what happened in his study is his CES treatment procedure in which, "the operator slowly increased the current to the maximum level compatible with the subjective comfort." One of the present authors did a study in which he turned the current up high to the maximum level of patient comfort in one group, very low (below 20 microamperes) in another group, or allowed the patients to set the current level to their sensation level, then back it down to just below the sensation level. It was noted that when the patients who chose their own intensity setting were matched with the high intensity pre-set group the results were striking. Marked improvement occurred in the first group of patients in every category of measurement, while the high setting patients remained about the same throughout. The conclusion was that while a high intensity setting might be beneficial to some patients, it may be detrimental to approximately the same number of other patients, so the best strategy apparently is to let the patient determine his own current setting at the beginning of each session. (23) That is, the high intensity group responded exactly like Frankel's group and also did not replicate any other CES findings in the literature.

Marshall lost control of his study in which both the controls and the CES treated patients improved significantly, most likely because they were inpatients all of whom where on psychoactive medication. (24) Passini had the identical problem with his VA hospital inpatients, and while he reported treatment effects for his CES treated subjects, the controls can be seen to have improved to a similar extent. (25)

Phillip was studying the drug abstinence syndrome in depressed patients in whom he abruptly discontinued all psychoactive medications to prepare the patients for electroshock therapy. (26) They were still depressed after 5 days of 30 minute treatments. This was similar to findings in other addiction literature in which 14 to 21 days are generally required to relieve post substance withdrawal depression.

If the effect sizes from all of the studies less the four noted above, are combined, the non-weighted effect size becomes .45, the effect size weighted for number of subjects in each study becomes .57 and the standard error of the mean effect size drops to 0.06. Keep in mind that these are r calculated effect sizes in which .50 is considered high.

Another source of information that has not appeared in the literature is that gained by an analysis of self reported improvement by patients when submitting their warranty card. On the warranty cards supplied with the purchase of Alpha-Stim CES technology (Electromedical Products International, Inc, Mineral Wells,

Texas 76067, USA; www.alpha-stim.com), there is a survey form in which the patient can volunteer information regarding the treatment diagnosis, the length of time the device has been used to date, and the treatment results. While most patients don't send in warranty cards, the company has a return for credit policy for patients buying the device and not receiving benefit. Since the cost is not always covered by insurance, and fewer than 1% of the units are returned for refund, it is assumed that the vast majority of purchasers feel they are receiving benefit from the treatment, even though they do not remit their warranty card. Three hundred warranty cards of depressed patients have been received since initializing the survey. When these were analyzed, it was found that the average age of the respondent was 47 years, 62% were females, and they reported an average improvement of 58%, which can be translated directly from the binomial effect size distribution as an effect size of .58 This is very much in line with the overall .57 effect size of the research (excluding the four questionable studies discussed above) and would seem to add additional confirming value to the CES literature.

As noted above, the study designs have varied widely in terms of the scientific controls employed, and many modern day reviewers tend to ignore less well controlled studies, scrutinizing more closely the results only of those that employ a double blinded protocol. After many years of evaluating multiple studies, Glass and his colleagues are reported to have presented convincing evidence that in the typical meta-analysis there is no strong relation between the quality of the study and the average size of the effect obtained. If anything, the effect sizes tend to be higher in both the less well controlled and the most strongly controlled, with other effect sizes falling toward the middle. (27)

Another question often arises regarding the type of depression that responds to CES treatment. Most readers will recall the internecine struggles that have gone on regarding the diagnosis of depression in its various forms over the past 30 plus years that CES has been in clinical use in America. The various forms of depression that may be present have often centered diagnostic attention, as has the various levels of depression that may be involved in a given group of patients. Clearly there is some distinction between a patient who "feels blue" and a patient experiencing psychotic depression, though whether that distinction is of a physiological nature or whether the two are only at different points along a continuum is sometimes still debated.

Since no type of deliberate selection factor was reported to be at work in any of the above studies, it may reasonably be assumed that CES was an effective treatment regardless if it was used as a treatment of addicts undergoing the depression of the substance abstinence syndrome, or in those patients who were hospitalized for inpatient treatment of their depression; from the depression that accompanies the difficult stressful studies of graduate students, to that accompanying the often times debilitating attention deficit hyperactivity disorder (ADHD) syndrome (see primary diagnosis of patients given in Table 1).

Another consistent finding is that in none of the studies reported above was there any significant negative side effects reported from the use of CES in the treatment of depression. The clinical staff of at least one addiction treatment center are known to have followed up CES treated inpatients for from 12 to 14 months, and none of them reported an addicting or habit forming response to the use of CES in this strongly addictive population. (28) Similarly an 18 month follow up of ADHD patients who had been treated with CES and who still owned and could use their CES device during that period, showed both no apparent continuing dependence on the devices or any sign of negative effect from having used them over that period of time. (11)

B. Anxiety

This section presents a review of more than 40 published studies of anxiety, plus the results of a survey of 47 physicians who evaluated its effectiveness as a treatment for anxiety and stress in 500 of their patients. An analysis is also given of perceived treatment effects from surveys on warranty cards submitted by 500 patients who had been prescribed CES units for the treatment of their anxiety, and/or anxiety related disorders.

The recommended research protocol for the treatment of anxiety with the various CES devices is typically to apply CES for one hour each day for two to three weeks, with the patient determining the comfortable stimulation intensity. By the end of the first week or two presenting symptoms have usually subsided

significantly or resolved completely in the vast majority. Four studies (all using Alpha-Stim CES) support the effectiveness of managing anxiety during a single treatment session making it an efficient anxiolytic therapy in dentistry and other procedures. (5, 29-31)

Among the more than 40 CES studies of anxiety published in the U.S.A., few reported the required means and standard error of the means that were required in the early days of meta-analyses for such studies. Meta-analyses were performed, however, at the University of Tulsa by O'Connor, and by Klawansky at the Department of Health Policy and Management, Harvard School of Public Health. (32,33) Both concluded that CES was unquestionably effective for the treatment of anxiety.

In the very early days of CES treatment in the U.S.A., it began to be used for treating the substance abstinence syndrome in which patients suffering from various addictive substances suffered intensively from anxiety, depression and sleep disturbance. Because that group has proven susceptible to cross addiction to psychoactive medications, and because they are also more resistant to the effects of such medications than are non addicted patients, CES soon became a treatment of choice in both inpatient and outpatient treatment programs for this group of patients. (13,14,19,28,34)

In 1976, the United States Congress passed the Medical Device Amendments Act, giving FDA control over medical devices. Subsequently, the FDA called CES manufacturers before its Neurology Panel in 1978, and the Panel recommended that CES be approved immediately for the treatment of anxiety in addiction patients. They recommended that it be called back later to assess the several other uses that had become apparent in the published literature. The FDA decided to leave CES on the open market in its grandfathered status, for the treatment of anxiety, depression and insomnia, the continuing approved treatment labels for CES as of this writing.

In the mid-1990s, a researcher polled 47 physicians to ascertain treatment results of 500 patients for whom the physicians had prescribed Alpha-Stim CES treatment. The physicians reported that among 349 previously treatment resistant anxiety patients, 94% had achieved significant improvement in their anxiety symptoms with the use of CES. (7)

Recently, self report records of 500 patients suffering from various anxiety states were analyzed to see how they rated the effects of CES treatment on their symptoms. As noted above, patients whose physicians prescribe the Alpha-Stim CES device are provided survey forms on warranty cards in which they can volunteer information regarding their diagnosis, the length of treatment prior to submitting the card, and their self evaluation of the treatment results.

From more than 3,000 warranty cards most recently submitted, as of the Spring of 2002, the cards of 500 anxiety patients were selected for evaluation, in the order they were received. Of the 500 cards selected, 311 (62%) were submitted by female patients. The ages ranged from 3 years to 89 years of age with the breakdown as shown in Table 3, where it can be seen that patients were prescribed treatment with CES throughout the life span, with the majority falling between the ages of 40 and 59. Patients rated their improvement in each of the improvement categories provided, as shown in Table 4.

Table 3. Age range of patients using Alpha-Stim CES, reported on warranty cards

Age Range	3-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89
Number	13	37	69	159	119	62	33	8
Percent	2.6%	7.4%	13.8%	31.8%	23.8%	12.4%	6.5%	1.7%

Table 4. Treatment outcome following Alpha-Stim CES treatment of anxiety

Improvement	None	1 - 24%	25 - 49%	50 - 74%	75 - 100%	Significant (25%+)
N Reporting	24	63	110	156	147	413
% Reporting	5%	13%	22%	31%	29%	82%

Many of the cards were sent in following one or two days of treatment, but several were sent in following 12 months of treatment and two were sent in following 156 weeks of treatment. When a correlation was run between the length of treatment and the results of treatment, it was found that while some patients

responded at the 100% improvement level within the first week, and at least two patients had received no treatment benefit from three months of treatment, there was an overall correlation of .63 between the length of CES use and improvement in anxiety, which had strong statistical significance ($p<0.001$).

While 473 of the cards analyzed listed anxiety as the primary diagnostic factor, 27 listed stress, but did not name anxiety as such. Another 27 listed both stress and anxiety. For purposes of this evaluation, stress and anxiety were combined. Only 175 (35%) listed anxiety alone, while 100 (20%) listed anxiety and depression, 195 (39%) listed anxiety and pain, and 30 (6%) listed anxiety and sleep problems. In addition, many listed other anxiety related states and those, along with their self rated treatment results are shown in Table 5.

Table 5. Analysis of treatment outcome for treatment of anxiety related states

Anxiety Related State	Number Responding	Age Range	% Females	Weeks Treated	Mean Improvement	Significant Improvement
Panic Disorder	14	30-69, Mean = 49	50%	0.14 – 52, Mean = 9	45%	42%
OCD	5	13-41, Mean = 27	60%	1 – 16, Mean = 6.25	68%	100%
Bi-Polar	9	33-61, Mean = 49	89%	3 – 24, Mean = 10	71%	88%
PTSD	8	39-58, Mean = 51	63%	Mean = 9	55%	71%
Cognitive Problems (ADHD)	23	7-65, Mean = 37	61%	.14-52, Mean = 9	62%	81%
Phobias	9	31-72, Mean = 52	78%	.29 – 24, Mean = 8	49%	60%
Total	54	7-72, Mean = 37	63%	.14-52, Mean = 9	64%	73%

The figures shown in Table 5 include many patients who had their CES device for a week or less. On further inspection of the data for the group reporting panic disorder, it was found that those who had used CES for three weeks or less reported insignificant treatment results, while those using it ten weeks or more reported a 99% remission of symptoms. When the treatment times for the combined group shown in Table 5 were examined, it was found that those using CES one week or less prior to submitting their warranty card reported an average 49% improvement, while those using CES from two to three weeks reported a 62% gain, and those using it four weeks or more reported 64% improvement. Among the last group of patients who had their CES device for four weeks or more, 81% claimed significant treatment response of 25% or greater, the outcome standard commonly used in medication studies.

The treatment effect size, evaluated as the binomial effect size, is equal to the percent improvement claimed, and as shown in Tables 4 and 5, the mean effect size for all 500 patients reporting was .62. When the smaller groups of patients with special types of anxiety related disorders was broken out, the effect size among those suffering from panic disorder was .45, that of obsessive compulsive disorder (OCD) patients was .68, those with bi-polar disorder .71, and for post traumatic stress disorder (PTSD) .55, ADHD .62, and phobias .49. The overall mean effect size for the combined smaller groups was .64. Those can be compared with the standard r rated effect size ratings of .10 for small, .30 for medium and .50 for large. (27)

In summary, there has now been four decades of experience with CES in the U.S.A. as a non medication treatment for anxiety, yet it has never reached mainstream status as the treatment modality of choice by members of the medical and allied professions. That is most likely due to the fact that no U.S. medical school teaches CES treatment as part of its curriculum, and none of the seven or eight CES companies in the U.S.A. has had sufficient staff to visit physicians' offices in the ubiquitous manner of pharmaceutical representatives. Therefore, there has been no post graduate inservice or updating of physicians regarding the literature on CES as a treatment modality except via the rare lecture at continuing medical education conferences.

Nonetheless, when physicians who had prescribed CES were asked, those responding were enthusiastic about its effectiveness, as are the great majority of CES experienced patients themselves, as reported on their warranty card survey forms.

Also noteworthy is that among the more than 4,541 patients who have been involved in CES studies in the U.S.A., and among the 500 patients who submitted the warranty cards reported here, there has been no significant, negative side effect reported from the use of CES. Or as the National Research Council reported to the FDA when asked to evaluate the safety of CES, "Review of these reports reveals that significant side effects or complications attributable to the procedure are virtually nonexistent." (35) Rosenthal agreed, stating that, "As a substitute for medication, CES has several advantages. It is possibly more effective. It avoids the common medication side effects as well as problems of medication abuse, incorrect dosage, and suicidal and accidental overdoses. (36)

C. Insomnia

This section presents the results of published insomnia data, plus data derived from patient self reports. Twenty-one insomnia studies in which CES was used as the treatment variable were meta-analyzed. While a diversity of research protocols, numbers of patients studied, and measurement strategies employed were found among the studies, an analysis of heterogeneity indicated that those factors did not significantly contaminate the results, which found a mean effect size of r = .62 and a combined probability estimate of significance of the changes in pre treatment to post treatment mean = .0018.

Employing electrical stimulation to improve sleep began some years ago when Christian Gottlieb Kratzenstein, a 20 year old student attending Krueger's medical lectures in Halle, Germany in 1743 was so impressed by Krueger's lectures on electrical therapy that he wrote a report on it. (37) He had decided to try this new electrotherapy on himself, and was astonished when it permitted him to sleep better.

While electricity has been used off and on to treat insomnia since then, the treatment attracted substantial enthusiasm beginning in 1954 when Russians, then other Europeans began to explore it scientifically. They examined the possibility of turning down the electrical stimulation level from that used in electroanesthesia, which had, earlier, been reduced from that used in electroconvulsive shock therapy, to a level that would induce natural sleep in their patients. Their new technique was named electrosleep, and was intended to replace sleep medications and their numerous negative side effects, not the least of which was the addictive properties of many of them. (38) Electrosleep treatment quickly spread around the world, arriving in the U.S.A. in the early 1960s.

The clinical intent was that electrosleep treatment should induce sleep immediately when the current was applied to the patient's head, and that the patient should remain asleep naturally, once the induced sleep was begun. That did not appear to be happening, however, so many of the earliest clinical studies of electrosleep in the U.S.A. were concerned with discovering the stimulus parameters that would induce sleep in patients. The pulse rates were varied from less than one per second to thousands per second, while the pulse duration was varied from microseconds to continuous. The stimulus intensity was varied from just a few microamperes to several milliamperes, while the shape of the pulse wave was varied from sinusoidal to modified square to a modified sawtooth wave, and so forth. (39-41)

As the treatment arrived in the U.S.A. from Europe, the electrodes were placed over each closed eyelid in front of the head and the mastoids in back of the head. (38) Later, because of the discomfort from the pressure on the eyelids and the temporarily distorted vision patients typically experienced immediately following their removal, researchers began to place the frontal electrodes just above each eyebrow while the rear electrodes remained on the mastoids. (42) Still later, the electrodes were placed on the mastoid process just behind each ear only, so that the stimulus current now went from side to side across the head instead of from front to back. (28) That placement is still used in the U.S.A., but the most recent placement to enhance efficacy and convenience is on each ear lobe via ear clip electrodes. (43)

EEG studies soon followed, when no treatment strategy could be found that would reliably induce sleep in the patients. The EEG studies were to see what, if anything, happened when electrosleep current was applied across a patient's head. The first study was designed to see if there were any sleep changes in the

EEG. There were none. Some patients slept when in the treatment condition and some slept when in the control condition, while the rest never slept during any phase of the study. (3)

Another EEG study found that one 30 minute electrosleep treatment per day for five days yielded slower EEG frequencies with increase amplitude in the fronto-temporal areas in all of the patients. Most also showed increased quality and quantity of alpha with increased amplitude in the occipital-parietal leads. (44)

Itil and his colleagues gave 10 volunteers two days of CES and two days of sham CES in a crossover design. They found that the patients who exhibited no decrease of vigilance when CES was off also showed no significant changes in vigilance when CES was on. Those who showed a slight-to-moderate drowsiness during the off recording did show a slight-to-moderate sleep pattern when the CES was on. (45)

What the researchers did find was that while they could not induce sleep in the laboratory, with one exception they all found that CES was associated with patient reports of better sleep at night. One EEG study that was deliberately done during evening hours in a sleep laboratory, simply allowed patients who had been diagnosed with insomnia to sleep in their usual way in the university sleep laboratory while having their EEG monitored. Five patients were given actual subsensation CES treatments 30 minutes a day for 10 days, and five were given sham treatments. On subsequent monitoring of their EEG pattern it was found that patients receiving actual treatment went to sleep faster when "their head hit the pillow," spent more time in stage IV sleep during the night, had fewer awakenings during the night, went back to sleep sooner when they did awaken in the night, and reported a significantly more restful and restoring sleep upon awakening the next morning than did the sham treated subjects. (21) That study and others found that those results still held up and in some areas even improved somewhat following a two year follow up period. (46)

Soon a growing number of researchers discovered that electrosleep not only ensured sound, restful sleep for patients suffering from insomnia, but effectively treated stress in the process, as measured by various psychological measuring scales of depression and anxiety. Importantly, it was found that the stress measures, including the patients' sleep patterns, improved whether or not the patient slept during the treatment. (4)

In addition to more than 20 studies, all of which were published in peer reviewed science journals, in the mid 1990s, a physician's survey was conducted in which physicians were asked to rate the sleep response of their insomnia patients from Alpha-Stim CES treatment. The physicians rated overall sleep improvement in 135 patients as 79%. Only 12% were rated as not improved, and 9% as insignificant improvement. (7)

More recently, as part of a larger study, 140 CES warranty cards that had been sent in by insomnia patients following a minimum of three weeks of treatment were analyzed to assess their perception of its effectiveness in the treatment of their sleep disorder. (47) As noted above, patients who submit warranty cards can volunteer information regarding their medical diagnosis. Among the persons who listed insomnia as a major diagnosis were those who also included other areas of stress such as anxiety or depression, while still others also listed pain as a major accompanying symptom. The results were broken down into several sub categories and are shown in Table 6.

Table 6. Patient's self reported results from using CES for insomnia

Diagnosis	N	% Females	Age	Weeks Used	Improvement
Insomnia only Range Average	32	59%	3 – 81 yrs 47.86 yrs	0 – 52 wks 6.79 wks	0 – 99% 75 - 99%
Insomnia + Anxiety and/or Depression Range Average	41	59%	24 – 86 yrs 49.37 yrs	1 – 28 wks 5.71 wks	0 – 100% 75 - 99%
Insomnia + Pain Range Average	67	78%	21 – 85 yrs 50.66 yrs	0 – 78 wks 9.68 wks	1% - 99% 75 - 99%
Total Insomnia Range Average	140	68%	3 – 86 yrs 49.66 yrs	0 – 78 wks 7.95 wks	0 – 100% 75 - 99%
Mean Effect Size					R = .87

It can be seen that fewer than a fourth (23%) of the patients listed insomnia as their only symptom. A slightly larger group (29%) listed insomnia in combination with anxiety and/or depression as accompanying symptoms, while the largest group (48%) listed pain as their most severe accompanying symptom.

It is of interest that while the second, more stressed group used their CES device almost six weeks before reporting, the pain group used theirs 10 weeks on average before sending in their cards. While one might assume that the longer the patient used the unit, the better the response they would have, that does not appear to be the case. The majority of patients, no matter what category the fell into, claimed 75 to 99% improvement, and this improvement did not appear to be correlated with the length of time used.

The effect size, in this case, is a measure of the percent improvement in their sleeping pattern reported by this group of patients suffering from insomnia. The average r effect size from this sample was .87. As stated earlier, that compares quite favorably with Cohen's guidelines for small (r=.10), medium (r=.30) and large (r=.50) treatment effect sizes. (27)

A word should be said about warranty cards. As with most things one buys, most people, including patients suffering from insomnia, do not send in warranty cards. Among those who do, the vast majority do not volunteer information about their diagnosis and treatment outcome. So this can not be construed to be a random sample of the population of insomnia patients who use CES devices to treat their disorder.

On the other hand, as noted above, in the majority of cases if a patient uses a CES device and does not get substantial relief from symptoms within 30 days, the unit can be returned for a refund. Since prices for CES units can vary up to nearly $1,000, there would be a strong incentive for patients to return their units if they found them to be ineffective, and yet fewer than 1% of all Alpha-Stim CES devices sold are returned by the purchaser. That lends credibility to the idea that the summary found in Table 6 is a fairly accurate reflection of patients' perception of the results of CES treatment of insomnia.

Table 7 gives a synopsis of 21 studies that have been published in the peer reviewed scientific literature (one in an edited book), plus the analysis reported just above. The studies were completed over a 30 year period and involve a total of 940 patients. None reported significant negative side effects during or following any study.

Table 7. List and description of CES studies of insomnia

	Number Patients				Blinding				
Author	CES	Sham	Total Analyzed	Primary Diagnosis	Patient	Therapist	Assessor	Study Design	Outcome Measure
Feighner (82)	10	9	19	Insomniacs	Yes	No	Yes	Crossover 2 wks/2 wks	Global Rating Scale
Flemen-baum (90)	28	None	28	Insomniacs	No	No	No	Open Clinical	Clinical Rating Scale
Frankel (17)	17	17	17	Insomniacs	No	No	No	Crossover 3 wks/3 wks	Psychology Tests/ Biochem.
Gomez (19)	14	14	28	Drug Abstinence Syndrome	Yes	No	No	Single Blind	PRN Medication
Hearst (83)	14	14	28	Insomniacs	Yes	No	No	Single Blind	Clinical Rating Scale
Hozumi (91)	14	13	27	Multi-Infarct Dementia	Yes	?	?	Double Blind	EEG/ Clinical Rating Scale
Kirsch (7)	135	None	135	Insomniacs	No	No	No	Post Treatment Physician Survey	Physician's Rating

Lichtbroun (66)	10	20	30	Fibromyalgia	Yes	Yes	Yes	Double Blind Placebo Controlled	Self Rating Scale
Lichtbroun (43)	20	40	60	Fibromyalgia	Yes	Yes	Yes	Double Blind Placebo Controlled	Self Rating Scale
Moore (42)	17	17	17	Insomniacs	Yes	No	Yes	Crossover 1 wk/1wk	Self Rating Scale
Patterson (49)	186	None	186	Drug Abstinence Syndrome	No	No	Yes	Post Rx Physician Survey	Clinical & Self Rating Scales
Patterson (92)	8	10	18	Drug Abstinence Syndrome	Yes	Yes	Yes	Double Blind	Clinical Rating Scale
Philip (26)	10	11	21	Drug Abstinence Syndrome	Yes	Yes	No	Double Blind	Self Rating Scale
Rosenthal (18)	9	None	9	Insomniacs	No	No	No	Open Clinical	Clinical Rating Scale
Rosenthal (93)	12	6	18	Insomniacs	Yes	No	No	Single Blind	Clinical Rating Scale
Rosenthal (88)	11	11	22	Insomniacs	Yes	No	Yes	Double Blind	Clinical Rating Scale
Smith*	140	None	140	Insomniacs	No	No	No	Patient Self Report Survey	Self Rating Scales
Straus (40)	17	17	34	Insomniacs	Yes	No	Yes	Crossover 2wk/2wk	Clinical Rating Scale
Tyres (64)	20	None	20	Fibromyalgia	No	No	No	Open Clinical	Self Rating Scale
Tyres (65)	60	None	60	Fibromyalgia	No	No	No	Open Clinical	Self Rating Scale
Weiss (21)	5	5	10	Insomniacs	Yes	Yes	No	Double Blind	EEG/Self Rating Scale

*From Table 6

Table 8. Analysis studies shown in Table 7

	Number of Patients						
Author	CES	Controls	Total Analyzed	Statistic Reported	Result	Z Score	Effect Size (r)
Feighner (82)	10	9	19	Global Rating Scale	.0002[a,b]	3.719	.85
Flemenbaum (90)	28	None	28	Global Rating Scale	.01[a]	2.576	.49
Frankel (17)	17	17	17	EEG Sleep fficiency	.003[c,d]	0.00	0.00
Gomez (19)	14	14	28	PRN Medication	.93[c]	3.719[e,f]	.70
Hearst (83)	14	14	28	Self Rating Scale	.42[c]	2.216	.42
Hozumi (91)	14	13	27	EEG/Clinical Rating Scale	.05[a]	1.96	.38
Kirsch (7)	135	None	135	Physician's Ratings	.89[c]	3.719	.32
Lichtbroun (66)	10	20	30	Self Rating Scale	.72[c]	3.719	.68
Lichtbroun (43)	20	40	60	Self Rating Scale	.82[c]	3.719	.48

Moore (42)	17	17	34	Self Rating Scale	.76[b,c]	3.719	.64
Patterson (49)	186	None	186	Self Rating Scale	.56[c]	3.719	.27
Patterson (92)	8	10	18	Clinical Rating Scale	.02[a]	2.326	.55
Philip (26)	10	11	21	Sleep Diary	.38[c]	1.699	.37
Rosenthal (18)	9	None	9	Clinical Rating Scale	.50[c]	1.373	.46
Rosenthal (93)	12	6	18	Clinical Rating Scale	.60[c]	2.636	.62
Rosenthal (88)	11	11	22	Clinical rating Scale	.81[c]	3.919	.84
Smith*	140	None	140	Patient Self Report	.67[c]	3.719	.31
Straus (40)	17	17	34	Clinical & Self Rating Scales	.05[a,b]	1.96	.34
Tyres (64)	20	None	20	Self Rating Scale	.79[c]	3.719	.83
Tyres (65)	60	None	56	Self Rating Scale	.53[c]	3.719	.50
Weiss (21)	5	5	10	EEG Sleep Efficiency	.00077[a]	3.363	1.00
Total	757	204	940			61.218	
Mean						2.915	Mean Z_r =.716[g]
Mean Probability						<.0018	Mean Effect Size =.62
Heterogeneity						P<.30[h]	

* From Table 6

[a]Probability test of mean differences, two tailed

[b]Score taken from the initial treatment period only. Crossover has been shown to wash out due to continuing patient improvement post CES treatment

[c]Percent improvement over controls, or over own pretreatment score

[d]Only the combined crossover score was available from the Frankel study

[e]Z scores obtained from % improvement = r scores, and t=r/square root of 1-r^2 x square root of n-2, with Z score derived from the probability associated with the t score

[f] Z scores were artificially cut off at this level due to limitations of the conversion tables used

[g]r scores were converted to z_r from Fisher's r to z_r transformation tables

[h]Due to the wide discrepancy of research strategies and numbers of subjects reported, the test of heterogeneity is a test to determine if the variety of methods made a significant difference. The formula is: sum(each Z minus the Mean Z)squared, gives a X^2 distribution with df = 20

As can be seen, the number of patients in each study varies widely, as does the amount of scientific control measures applied and the measurement strategies employed. While all studies involved patients suffering from insomnia, several studied the sleep disorder of patients withdrawing from addicting substances, while others looked at the sleep problems accompanying difficult pain syndromes such as fibromyalgia.

Whether this variety of approaches to studying CES has a significant effect in understanding the role of CES in the treatment of insomnia can be ascertained from the last line in Table 8 where the heterogeneity of studies failed the significance test. The probability obtained of p <0.30 indicates that the studies included in Table 7 can be safely combined without prejudice to our understanding of the overall role of CES in the treatment of insomnia.

In Table 8, the results reported by the authors of the various studies were converted into Z scores to make them comparable, and an effect size for each study, based on that Z score, is given in the final right hand column. Two summary findings from Table 8 are that the average r effect size from all the studies combined is .62, while the average probability of type I error among the studies is less than 2 in 1,000 such studies.

Conclusions

This section has been a review of 20 previously published studies of the use of CES in the treatment of insomnia, and an update analysis of 140 patient self reports as found on CES warranty cards. While the mean effect size from patient self reports on their warranty cards was .67, the overall effect size from the meta-analysis of 21 studies was .62, both very high and both quite similar.

It can be concluded that CES, while remarkably underutilized as compared to pharmaceuticals, is a safe, and very effective, non drug treatment for insomnia of various etiologies. The fact that no significant negative side effects were reported in any of the studies analyzed is equally important. Also, once a CES device is prescribed for a patient there are no major costs associated with its use except the occasional replacement of batteries, electrodes and conducting solution. This may turn out to be the deciding factor for CES in an age of rapidly expanding medical costs.

D. Cognitive Dysfunction

Early in the history of CES in the U.S.A., controlled scientific studies began of the substance abstinence syndrome, with its major symptoms of anxiety, depression and sleeplessness in withdrawing addicts. Those studies involved patients withdrawing from illegal and/or pharmaceutical drugs, alcohol and nicotine. (13,14,19,34,48,49)

Up until that time in the early to mid 1970s it was taught that with each shot of alcohol that one drank, thousands of brain cells were destroyed, and that these would never return. By the time an alcoholic person entered one of the many inpatient treatment centers he or she was assumed to be significantly advanced down the road toward irreversible Korsakoff psychosis. Among the chief signs of the Korsakoff psychosis syndrome were various cognitive problems, including short term memory loss, cognitive confusion, the inability to store new information reliably, and mental problems such as confabulation. (50-52)

It therefore came as an unexpected surprise to practitioners of CES when they discovered that in the process of successfully treating the depression, anxiety and insomnia in withdrawing patients, they also totally reversed the Korsakoff's psychosis syndrome present in the large majority. These studies will be shown in the analysis below.

In neuropsychology, Korsakoff type degeneration was often measured with the Benton Visual Retention Scale in which patients were shown a drawing with circles, squares, triangles and the like, then given a clean piece of paper and asked to reproduce it. (53) Also used were the so-called Organic Brain Syndrome subscales of the Weschler Adult Intelligence Scale (or the Weschler Intelligence Scale for Children). Those subscales are the Digit Span, the Digit Symbol and the Object Assembly subscales, and these three subscales were known to fall significantly below the functional level of the other subscales on those tests in Korsakoff patients. Other researchers in the addiction field used the Maize and Form Design subtests on the nonverbal Revised Beta I.Q. examination comparing them with the remaining three subscales on that test in the same way. (54-56)

It was serendipitously found that in every case where patients experienced an improvement in stress level from CES, they also experienced a dramatic improvement in cognitive function, with an average gain of 12 to 18 points on standardized I.Q. tests administered previous to and following three weeks of daily CES treatment, one hour of treatment per day. (28) It was in this manner that researchers found that so-called permanent brain damage in drug and alcohol addiction was not permanent at all. (57)

We now know that while the cognitive abilities of most such patients will approach normal following two years of total abstinence, (57-59) they will return to normal with just three weeks of daily CES treatment. (23,28,57)

By the mid 1970s researchers found that the Confusion/Bewilderment factor on the widely used Profile of Mood States (POMS) correlated strongly with these other measures of cognitive dysfunction. (13) and began to use it as a cognitive function measuring device. According to the test manual, it is thought to measure

“bewilderment and muddleheadedness, and may represent a state of cognitive inefficiency, a mood state, or both. It may also be related to the classical organized-disorganized dimension of emotion, possibly a by-product of anxiety or related states.” (60) It was not thought to be a measurement of brain damage when that edition of the manual was written.

Following close on the heels of studies of the substance abstinence syndrome, another study looked at the stress related cognitive problems of graduate students in a business management training program, and found CES offered significant improvement as measured by the POMS. (16)

Research attention also turned to patients with acquired closed head injuries, resulting from such things as motorcycle accidents, falls from high elevations on construction projects, inoperable brain tumors and so forth. That group drew special attention because the majority of them were known seizure patients and little was known of the effects of CES on seizure patients. Under the supervision of a research physician, 21 closed head injured patients who were living in a supervised care home were selected for a double blind study. (61)

It was found that along with their anxiety and depression scores, following one hour treatments daily, four days a week for three weeks the cognitive function score improved significantly in the treatment group, as measured on the POMS. During the study one of the subjects who had brain cancer had a seizure and was immediately removed from the study by the study physician. Following the study, the 11 patients in the two control groups were also given CES for three weeks. It had been learned that the patient who had the seizure during the double blind phase of the study was receiving sham CES treatment. Upon the insistence of his parents, he also received actual CES treatment for three weeks following the study. Neither he nor any of the other subjects in the study experienced a seizure while receiving actual treatment, and their seizure experience in the weeks following the study was unremarkable, according to house attendants.

Another report of the effectiveness of CES in post-traumatic amnesia cited two cases, in which the first was a 21 year old male who was comatose for weeks following a motorcycle accident recovered much of his tested memory recall functions following three weeks of one hour daily CES treatments. The other patient was a 58 year old orthopedic surgeon who suffered head injury in a motor vehicle accident. He was diagnosed with diencephalic amnesia secondary to trauma. He had difficulty distinguishing between fantasy and reality, and experienced overwhelming anxiety during periods of disorientation. His amnesia improved by 28% on immediate recall and 39% on delayed recall after only one week of daily CES treatments. These were accompanied by numerous other behavioral improvements. (62)

Some researchers have theorized that the present mass epidemic of fibromyalgia patients is due to brain dysfunction following whiplash injury or similar traumas to the brain. (63) That concept is still under investigation, but meanwhile several recent published studies have shown CES to be a very effective treatment for fibromyalgia. (43,47,64-66)

Perhaps due to its hypothesized ability to functionally stabilize a traumatized brain and return it toward a condition of pre injury homeostatic functioning, CES has proven to be an effective treatment for patients with acquired brain injury. It has also proved to be a significantly beneficial adjunct to other forms of physical and psychological therapies.

Table 9. List and description of cognitive function studies

Author	Number of Subjects			Primary Diagnosis	Blinding			Study Design	Outcome Measure
	CES	Sham	Total Analyzed		Subject	Therapist	Assesor		
Smith (13)	36	36	72	Alcoholism	Yes	No	Yes	Single Blind	POMS
Smith (23)	116	111	227	Alcoholism	Yes	No	Yes	Single Blind	BRT/ RBII
Weingarten (94)	12	12	24	Alcoholism	Yes	No	Yes	Single Blind	POMS
Smith (57)	50	50	100	Addiction	Yes	No	Yes	Single Blind	RBII
Schmitt (28)	30	30	60	Addiction	Yes	Yes	Yes	Double Blind	POMS
Schmitt (48)	27	33	60	Addiction	Yes	Yes	Yes	Double Blind	WAIS/ RBII
Matteson (16)	32	22	54	Graduate Student Stress	No	No	No	Open Clinical	POMS
Childs (62)	2		2	Post Traumatic Brain Injury	No	No	No	Open Clinical	Neuro-psychiatric Tests
Braverman (71)	13	2	15	Addiction	No	No	No	Open Clinical	EEG/ P300 TxA
Smith (11)	23		23	ADHD	No	No	No	Open Clinical	WAIS/ WISC
Tyers (64)	20		20	Fibromyalgia	No	No	No	Open Clinical	POMS
Tyers (65)	60		60	Fibromyalgia	No	No	No	Open Clinical	POMS
Lichtbroun (43)	40	20	60	Fibromyalgia	Yes	Yes	Yes	Double Blind	POMS

Table 10. Analysis of studies shown in Table 9

Author	Number of Patients			Statistic Reported	Results	Z_r Score (a)
	CES	Controls	Total			
Smith (13)	36	36	72	% Improvement	54%	.604
Smith (23)	116	111	227	% Improvement	86%	1.293
Weingarten (94)	12	12	24	% Improvement	37%	.388
Smith (57)	50	50	100	Probability	.0025	.234
Schmitt (28)	30	30	60	% Improvement	77%	1.020
Schmitt (48)	27	33	60	% Improvement	68%	.829
Matteson (16)	32	22	54	% Improvement	17%	.172
Childs (62)	2		2	% Improvement	39%	.412
Braverman (71)	13	2	15	% Improvement	46%	.497
Smith (11)	23		23	% Improvement	20%	.203
Tyers (64)	20		20	% Improvement	18%	.182
Tyers (65)	60		60	% Improvement	18%	.182
Lichtbroun (43)	40	20	60	% Improvement	15%	.151
Total	461	316	777	Mean Mean Effect Size N Weighted Effect Size	40	.47 .44 .62

(a) From Fisher Tables of r to z_r transformation (Edwards, 1964)

A meta-analysis of 13 CES studies, shown in Table 9, in which cognitive function was measured, reveals the following, as shown in Table 10:

The overall treatment effect size for the combined studies, when corrected for the size of each study (N), is r=.62.

Since there were a variety of study designs utilized, and possibly a range of etiologies of the cognitive functioning problems represented, a test for homogeneity was run, using the formula: $\text{Sum}(N_j - 3)(z_{rj} - \text{mean } z_r)^2 = X^2$ with a df of 12, where N_j is the N of any given study, and z_{rj} is the z_r of any given study. Degrees of freedom is the number of studies–1.

Among the combined studies, the non-weighted X^2 was equal to more than 96, indicating a very heterogeneous group of studies.

When the addiction studies and the traumatic brain injury study were separated out from the others, on the assumption that a more physiological or biochemical, as opposed to a psychological stress force might have been at work in this group, the X^2 was 45, with a df of 7, indicating, still, a significant heterogeneity. Upon inspection, the two double blind studies by Schmitt, and the one study by Smith which contained the largest N studied, had the strongest effect sizes. (23,28,48) Since heterogeneity can be the result of effect size differences or sample size differences, (67) the study with the largest N was set apart, and the remaining addiction study results achieved homogeneity, with the X^2 dropping to an insignificant 13, (df = 6).

Turning to the other, non addiction studies which included perhaps only stress related cognitive dysfunction accompanying fibromyalgia, ADHD, and stress in graduate students, all of whom also had high measured stress levels going into the study, it was found that they comprised a highly homogeneous grouping with a X^2 of .04 and df of 4.

The effect size of the group of 7 addiction and one brain trauma studies, when separated out and corrected for effect of study sample size was now increased to r = .71, the effect size of the remaining group of studies dropped to only r = .18, and remained at that level when corrected for sample size. This indicated that these two groupings in the overall meta-analysis were not only significantly different, but, while still responding well, responded much differently to CES treatment in terms of the amount of treatment effect recorded in effect size.

The use of CES in the treatment of patients addicted to various substances was not planned originally when “electrosleep” came into America. It just happened that these devices were made available for the treatment of large groups of addicts who had to go through the difficult substance abstinence syndrome (withdrawal) as part of their treatment. Because of the earlier fear of the Korsakoff brain syndrome in these patients, they were routinely measured for cognitive loss when they came into inpatient addiction treatment facilities.

It was the striking finding that the so-called permanent brain damage was cleared up by three weeks of daily CES treatment that led to the several follow-on addiction studies.

More recently, there have been an increasing number of CES research protocols in which the impact of high levels of stress on cognitive functioning is being evaluated. Measures of cognitive functioning are now often included in present and ongoing CES studies of fibromyalgia patients (68), and have been added to an upcoming study of pain in spinal cord injured veterans. (69)

It is possible to conclude from the foregoing analysis that there may be at least two, if not more, distinctly different etiologies of cognitive dysfunction in the studies cited, but that whatever their nature, CES has been shown to be significantly effective in treating each of them.

III. Mechanisms of Action

Scientists at the University of Tennessee Medical Center completed a series of five different studies in which various drugs were used to deliberately upset the homeostatic balance of the brains in canine subjects and thereby give them Parkinson like symptoms. They found that once the homeostasis was thrown into disarray, the application of CES could bring them back into apparent neurochemical homeostasis within three to seven hours. Left to their normal care, but without CES, the animals required four to seven days to return to normal behavior once the drugs had been removed. (70) The postulated mechanism of action, in the neurotransmitter system studied, was that CES stimulated the areas of the brain that were responsible for catecholamine and dopamine production, bringing the experimentally imbalanced neurotransmitter homeostasis back to its original homeostatic condition.

Over the years a number of EEG studies have been done pre and post CES treatments, as noted above in the sleep sections. In addition, a study of the P300 wave of outpatients who were addicted to various substances found that the P300 wave anomaly earlier found to be diagnostic of this group returned to normal following CES treatment. (71)

In another study presynaptic membranes were analyzed before, during and following CES stimulation of four squirrel monkeys. It was found that the number of vesicles in the presynaptic membrane declined when stimulation first began, that a greater than normal number of vesicles were found in the presynaptic membrane after five minutes of stimulation, and that the number of vesicles in the presynaptic membrane returned toward normal shortly after cessation of stimulation. The authors concluded that CES induces firing of neurotransmitter substances from presynaptic membrane vesicles into the synaptic space, while stimulating the increased manufacture of replacement neurotransmitter substances at the presynaptic membrane. (72)

The last two studies above suggest that CES is quite possibly re-establishing neurotransmitter homeostasis by inducing maximal production of each given neurotransmitter allowing each to reestablish homeostatic balance with others by means of the known ability of neurons to induce inhibitory effects in each other.

There is a growing body of evidence indicating the ability of stress of various kinds to throw the natural neurotransmitter balance out of control. It is also thought that some stressful life experiences may elevate the serum cortisol level to such an extent that neurons are actually debilitated or killed. It is known now that small electrical pulses can stimulate neuron regeneration and repair, and this will likely be the thrust of our next research efforts.

IV. Fibromyalgia Syndrome

Among the most recent Alpha-Stim CES studies published are those by Lichtbroun, and Tyers on fibromyalgia. In the Lichtbroun study, a very tight, three group protocol was used, one to receive treatment, one to receive sham treatment and a third wait-in-line group to measure the amount of any placebo effect in the sham treated group. The clinical evaluations were also done in a blind manner as was the statistical analysis. (43) When Lichtbroun's study did not find a placebo effect in the fibromyalgia patients studied, Tyers followed with two CES studies of fibromyalgia patients, deleting sham treated controls for an open clinical trial of CES alone in one study (64), and compared the effects of CES alone and CES plus physical manipulation treatments. (65) Both studies had 30 patients in the first trial and 60 patients in the second trial, and both found CES as effective or more effective than findings from multiple drug studies in terms of the reduction of pain at tender point sites, plus self ratings of over all pain. Unlike the typical medication study in which as many as 20% of patients suffer significant negative side effects, the CES studies have yet to find any significant negative side effect.

In addition, in CES studies of fibromyalgia, not only is the pain significantly reduced, but sleep returns to normal in the vast majority of the patients studied, as does their feelings of well being and the quality of life experienced. As if that were not enough, the fatigue problems that plague fibromyalgia patients were significantly alleviated, as was the stress related cognitive confusion that haunts many such patients.

Louisiana State University Health Science Center at Shreveport is also conducting a one hundred patient double blind Alpha-Stim CES study of fibromyalgia. (68)

V. Reflex Sympathetic Dystrophy

While double blinded studies have not yet been done in this area, a clinical report has been published which detailed the remarkable improvement and recovery of many functions of an advanced reflex sympathetic dystrophy (RSD) patient. (73) In addition, 55 RSD patient self reports, obtained from completing surveys on their warranty cards to the manufacturer has been published, in which 83% of them had significant improvement of at least 25%, and 53% reported at least a 50% reduction in their symptoms. (47)

VI. Multiple Sclerosis

As this chapter was being written, we were in the midst of a one hundred patient, double blind study on multiple sclerosis (MS). An earlier five patient pilot study in which patients used CES for one hour a day for one month yielded remarkable improvement ranging in effect size (percent of improvement) from 7% to a very respectable 37%. That pilot study came after several MS patients had written in to tell us how well they were progressing with CES treatment, and a number of warranty card submissions tended to verify those reports.

VII. Addiction

Following the earlier addiction studies which began in 1972, the use of CES continued in the District of Columbia's Rehabilitation Center for Alcoholics, but was not being utilized in the quickly burgeoning inpatient addiction treatment chains. That changed in the 1980s, as Comprehensive Care Corporation, possibly the largest in the world with over 120 facilities, completed two double blind placebo controlled studies which replicated earlier findings of the reduction of anxiety, depression and cognitive dysfunction, and in addition, reduced their recidivism rate in half over a 14 month follow up period which gave them competitive bragging rights when compared with other addiction treatment chains. CES also reduced the rate by which patient's left early against medical advice following the first, most medically intensive treatment period of their stay, and gave them more opportunity to recover their costs prior to the end of the patient's usual 21 to 28 day treatment stay. They put CES in nine of their facilities to evaluate the treatment clinically for a year, and then decided to include CES in the core program which would have required 5,000 CES units every quarter.

Meanwhile the Shick Shadel Corporation did a study, comparing their Santa Barbara patients on CES treatment with patients from their Seattle facility. They then placed CES units in all of their facilities. In addition, Charter Hospital Corporation put CES devices in several of their facilities prior to beginning their own double blind study.

Presumably all of this activity by addiction treatment centers would have mainstreamed CES into the medical addiction treatment milieu, and quite possibly from this clinical group to others suffering from many of the same, though non addiction related symptoms, had not two important things happened.

First, there was only one CES manufacturer in the U.S.A. at the time, and they could make only about eight devices a day. Secondly, inpatient treatment of addiction was becoming increasingly unpopular with insurance companies who were beginning to opt for short term outpatient treatment alone. Their thought was that if the nation's state hospitals for the insane could fill their patients' pockets full of Thorazine and put them back out on the street, addicts could be given the increasingly available psychoactive drugs and be treated with a couple of three hour visits to an outpatient clinic each week. Unfortunately, Librium, the new miracle drug most often used with outpatient addicts was said to be non addictive at the time.

The use of CES in addiction treatment never made the change into outpatient programs, since addicts were extremely unreliable risks to be sent home with devices that could be sold for alcohol or drugs. Too, there is something of a universal tendency of persons owning CES devices to loan them to other family members or friends who are in emotional straits, and they might or might not be able to access the unit again when needed.

Alcoholism was said by NIH to be a problem of 10 to 14 million Americans in 1970. That figure still holds in the year 2002. Since NIH also considers alcoholism to be an incurable disease, it would appear that the 10 to 14 million alcoholic persons from 1970 are dying off and being replaced by new ones coming on stream annually as the deaths occur. Or it could be that NIH is parroting figures necessary for funding and that ballpark figure is doing a good job of generating funds in the halls of Congress?

In any event, many former alcoholic patients are now addicted to other things, while a few have learned to use CES successfully to withdraw from the prior drugs used for their treatment. We have no science on that other than one successful study conducted at the Chicago VA Hospital in which methadone users were allowed to use CES to self withdraw from methadone over a two week period. (19) As of this writing, after

decades of positive research outcomes, only a few addiction treatment programs in the U.S.A. are taking advantage of the CES in addiction treatment.

VIII. Summary

Cranial electrotherapy stimulation treatments result in a relaxed body with an alert mind. The quality of life of those who use it is substantially improved. When all the research is viewed in aggregate, and without bias against non drug interventions, CES has already been proven to be the safest, and perhaps most effective treatment for a wide range of centrally mediated disorders. There is now enough evidence to establish it as a first line of treatment. Also, CES is so cost effective that it alone could relieve such a substantial burden from limited health care funds that enough money would be freed up to find more effective treatments for the disorders CES does not address. At the very least, the concomitant use of CES reduces the usage of pharmaceuticals by at least one-third, and with that alone comes billions of dollars in savings. (31,73-81) The day is rapidly approaching when CES will no longer be the best kept secret in American medicine.

References

1. Appel CP. Effect of electrosleep: review of research. *Goteborg Psychol Rep* 1972; 2:1-24.

2. Brown CC. Electroanesthesia and Electrosleep. *Am Psychol* 1975; 30:402-425.

3. Taaks H, Kugler J. Electrosleep and brain function. *Electroenceph Clin Neurophysiology* 1968; 24:62-94.

4. Ryan JJ, Souheaver GT. The role of sleep in electrosleep therapy for anxiety. *Dis Nerv Syst* 1977; 38:515-517.

5. Gibson, TH, O'Hair DE. Cranial application of low level transcranial electrotherapy vs. relaxation instruction in anxious patients. *Am J of Electromedicine* 1987; 4:18-21.

6. England RR. Treatment of migraine headache utilizing cerebral electrostimulation. M.S. thesis, North Texas State University, Denton, Texas, 1976.

7. Kirsch DL. The science behind cranial electrotherapy stimulation (2nd Ed). Edmonton, Alberta: Medical Scope Publishing, 2002.

8. Smith RB. Cranial electrotherapy stimulation. In: Myklebust JB, Cusick JF, Sances A Jr, Larson SF, (eds). Neural Stimulation, Vol II. Boca Raton: CRC Press, 1985:130.

9. Jarzembski WB, Laarson SJ, Sances A Jr. Evaluation of specific cerebral impedance and cerebral current density. *Annals of the New York Academy of Sciences* 1970; 170:476-490.

10. Ferdjallah M, Bostick FX. Jr., Barr RE. Potential and current density distributions of cranial electrotherapy stimulation (CES) in a four-concentric-spheres model. *IEEE Transactions on Biomedical Engineering* 1996; 43(9):939-943.

11. Smith RB. Cranial electrotherapy stimulation in the treatment of stress related cognitive dysfunction, with an eighteen month follow up. *Journal of Cognitive Rehabilitation* 1999; 17:14-18.

12. Rosenthal SH, Wulfson NL. Electrosleep: a clinical trial. *American Journal of Psychiatry* 1970; 127:175-176.

13. Smith RB, O'Neill L. Electrosleep in the management of alcoholism. *Biological Psychiatry* 1975; 10:675-680.

14. Bianco F Jr. The efficacy of cranial electrotherapy stimulation (CES) for the relief of anxiety and depression among polysubstance abusers in chemical dependency treatment. Ph.D. dissertation, The University of Tulsa, Oklahoma, 1994.

15. Tomosovic M, Edwards RV. Cerebral electrotherapy for tension-related symptoms in alcoholics. *Quarterly Journal of Studies on Alcohol* 1973; 34:1352-1355.

16. Matteson MT, Ivancevich JM. An exploratory investigation of CES as an employee stress management technique. *Journal of Health and Human Resource Administration* 1986; 9:93-109.

17. Frankel BL, Buchbinder R, Snyder F. Ineffectiveness of electrosleep in chronic primary insomnia. *Arch Gen Psychiatry* 1973; 29:563-368.

18. Rosenthal SH, Wulfsohn NL. Electrosleep: A preliminary communication. *Journal of Nervous and Mental Disease*1970; 151:146-151.

19. Gomez E, Mikhail AR. Treatment of methadone withdrawal with cerebral electrotherapy (electrosleep). *British Journal of Psychiatry* 1978; 134:111-113.

20. Briones DF, Rosenthal SH. Changes in urinary free catecholamine and 17-ketosteroids with cerebral electrotherapy (electrosleep). *Diseases of the Nervous System* 1973; 34:57-58.

21. Weiss, MF. The treatment of insomnia through use of electrosleep: an EEG study. *Journal of Nervous and Mental Disease* 1973; 157:108-120.

22. Smith RB. The use of cerebral electrostimulation in the treatment of alcohol addiction. Winter Conference of Brain Research, Keystone, Colorado, January, 1977.

23. Smith RB, Day E. The effects of cerebral electrotherapy on short-term memory impairment in alcoholic patients. *The International Journal of the Addictions* 1977; 12:575-582.

24. Marshall, AG, Izard CE. Cerebral electrotherapeutic treatment of depressions. *Journal of Consulting and Clinical Psychology* 1974; 42(1):93-97.

25. Passini FG, Watson, CG, Herder, J. The effects of cerebral electric therapy (electrosleep) on anxiety, depression, and hostility in psychiatric patients. *Journal of Nervous and Mental Disease* 1976; 163(4):263-266.

26. Philip P, Demotes-Mainard J, Bourgeois M, Vincent JD. Efficiency of transcranial electrostimulation on anxiety and insomnia symptoms during a washout periods in depressed patients; a double blind study. *Biological Psychiatry* 1991; 29:451-456.

27. Wolf FM. Meta-analysis; quantitative methods for research synthesis. Newbury Park: Sage Publications, 1986; p. 51.

28. Schmitt R, Capo T, Frazier H, Boren D. Cranial electrotherapy stimulation treatment of cognitive brain dysfunction in chemical dependence. *Journal of Clinical Psychiatry* 1984; 45:60-63.

29. Heffernan M. The effect of a single cranial electrotherapy stimulation on multiple stress measures. The *Townsend Letter for Doctors* 1995; 147:60-64.

30. Voris MD. An investigation of the effectiveness of cranial electrotherapy stimulation in the treatment of anxiety disorders among outpatient psychiatric patients, impulse control parolees and pedophiles. *Delos Mind/Body Institute*, Dallas and Corpus Christi, Texas, 1995.

31. Winick, R. Cranial electrotherapy stimulation (CES): a safe and effective low cost means of anxiety control in a dental practice. *General Dentistry* 1999; 47(1):50-55.

32. O'Connor ME, Bianco F, Nicholson R. Meta-analysis of cranial electrostimulation in relation to the primary and secondary symptoms of substance withdrawal. 12th Annual Meeting of the Bioelectromagnetics Society, June 14, 1991.

33. Klawansky S, Yeung A, Berkey C, Shah N, Phan H, Chalmers TC. Meta-analysis of randomized controlled trials of cranial electrotherapy stimulation: efficacy in treating selected psychological and physiological conditions. *Journal of Nervous and Mental Diseases* 1995; 183(7):478-485.

34. Gold, M, Pottash, ALC, Sternbach H, Barbaban J, Annitto W. Anti-withdrawal effects of alpha methyl dopa and cranial electrotherapy. 12th Annual Meeting of the Society for Neuroscience, 1982.

35. National Research Council, Division of Medical Sciences. An evaluation of electroanesthesia and electrosleep. FDA Contract 70-22, Task Order No. 20 (NTIS PB 241305), 1974; 1-54.

36. Rosenthal, SH. Electrosleep therapy. *Current Psychiatric Therapies* 1972; 12:104-107.

37. Kratzenstein CG. Schreiben von dem Nutzen der Electricitaet in der Arzneiwissenshaft. Halle, 1745.

38. Wageneder FM, Iwanovsky A, Dodge CH. Electrosleep (cerebral electrotherapy) and electroanesthesia-the international effort at evaluation. *Foreign Science Bulletin* 1969; 5(4):1-104.

39. Forster S, Bernard S, Bendon JG. Preliminary observations on electrosleep. *Arch Phys Med Rehabil* 1963; 44:481-489.

40. Straus B, Elkind A, Bodian CA. Electrical induction of sleep. *Am J Med Sci* 1964; 248:514-520.

41. Magora F, Beller A, Assael MI, Askenazi A. Some aspects of electrical sleep and its therapeutic value. In: Wageneder FM, St. Schuy, eds. Electrotherapeutic Sleep and Electroanaesthesia. Excerpta Medica Foundation, International Congress Series No. 136. Amsterdam, 1967:129-1354.

42. Moore JA, Mellor CS, Standage KF, Strong H. A double-blind study of electrosleep for anxiety and insomnia. *Biol Psychiatry* 1975; 10(1):59-63.

43. Lichtbroun AS, Raicer MC, Smith RB. The treatment of fibromyalgia with cranial electrotherapy stimulation. *Journal of Clinical Rheumatology* 2001; 7:72-78.

44. McKenzie RE, Rosenthal SH, Driessner JS. Some psychophysiologic effects of electrical transcranial stimulation (electrosleep). In: Wulfsohn NL, Sances A. eds. The Nervous System and Electric Currents. New York: Plenum, 1976:163-167.

45. Itil T, Gannon P, Akpinar S, Hsu W. Quantitative EEG analysis of electrosleep using frequency analyzer and digital computer methods. *Electroencephalography and Clinical Neurophysiology* 1971; 31:294.

46. Cartwright RD, Weiss MF. The effects of electrosleep on insomnia revisited. *J Nerv Ment Dis* 1975; 161(2):134-137.

47. Smith RB. Is microcurrent stimulation effective in pain management? An additional perspective. *Am J Pain Management* 2001; 11(2):64-68.

48. Schmitt R, Capo T, Boyd E. Cranial electrotherapy stimulation as a treatment for anxiety in chemically dependent persons. Alcoholism: *Clinical and Experimental Research* 1986; 10:158-160.

49. Patterson MA, Firth J, Gardiner R. Treatment of drug, alcohol and nicotine addiction by neuroelectric therapy: Analysis of results over 7 years. *J Bioelectricity* 1984; 3(1,2):193-221.

50. Mellow NK, Mendelson JH. Alterations in states of consciousness associated with chronic ingestion of alcohol. In Zubin, J. & Shagass, C. (Eds.) Neurobiological aspects of psychopathology. 58th Annual Meeting of the American Psychopathological Association, 1969.

51. Clarke JG. Some aspects of intellectual deficit and depression in heavy drinkers. *Journal Irish Medical Association* 1976; 69:29-32.

52. Ornstein P. Cognitive deficits in chronic alcoholics. *Psychological Reports* 1977; 40:719-724.

53. Kapur N, Butters, N. Visuoperceptive deficits in long-term alcoholics and alcoholics with Korsakoff's psychosis. *Journal of Studies in Alcohol* 1977; 38:2025-2035.

54. Sivan AB. Benton visual retention test, 5th ed. San Antonio, Texas: Psychological Corporation, 1991.

55. Wechsler D. Statistical properties of the scale. In Manual for the Wechsler Adult Intelligence Scale-Revised. New York: Psychological Corporation, 1981.

56. Kellogg CE, Morton NW. Revised beta examination, second edition (beta-II). San Antonio, Texas: The Psychological Corporation, 1978.

57. Smith RB. Confirming evidence of an effective treatment for brain dysfunction in alcoholic patients. *Journal of Nervous and Mental Disease* 1982; 170:275-278.

58. Sharp, JR, Rosenbaum G, Goldman MS, Whitman RD. Recoverability of psychological functioning following alcohol abuse; acquisition of meaningful synonyms. *Journal of Consulting and Clinical Psychology* 1977; 45:1023-1028.

59. O'Leary MR, Radford LM, Chaney EF, Schau, EJ. Assessment of cognitive recovery in alcoholics by use of the Trail Making Test. *Journal of Clinical Psychology* 1977; 33:579-582.

60. McNair DM, Lorr M, Droppleman LF. Edits manual for the profile of mood states. San Diego, California: Educational and Industrial Testing Service, 1992.

61. Smith RB, Tiberi A, Marshall J. The use of cranial electrotherapy stimulation in the treatment of closed-head-injured patients. *Brain Injury* 1994; 8:357-361.

62. Childs A, Crismon ML. The use of cranial electrotherapy stimulation in post-traumatic amnesia: a report of two cases. *Brain Injury* 1988; 2:243-47.

63. Bennett RM, Cook DM, Clark SR, et al. Hypothalamic-pituitary-insulin-like growth factor-1 axis dysfunction in patients with fibromyalgia. *Journal of Rheumatology* 1997; 24:384-389.

64. Tyres S, Smith RB. Treatment of fibromyalgia with cranial electrotherapy stimulation. *Original Internist* 2001; 8(3):15-17.

65. Tyers S, Smith RB. A comparison of cranial electrotherapy stimulation alone or with chiropractic therapies in the treatment of fibromyalgia. *The American Chiropractor* 2001; 23(2):39-41.

66. Lichtbroun AS, Raicer MC, Smith RB. The use of Alpha-Stim cranial electrotherapy stimulation in the treatment of fibromyalgia. 15th Annual International Symposium on Acupuncture and Electro-Therapeutics, Columbia University, New York City, October 21-24, 1999.

67. Rosenthal R. Meta-analytic procedures for social research. Newbury Park: Sage Publications, 1991; 74-87.

68. Cork RC. Alpha-Stim CES for fibromyalgia. Study in progress: Louisiana State University Medical Center, Shreveport, 2002.

69. Tan, G., Rintala, D., Herrington, R., Yang, J., Wade, W., Vasilev, C. and Shanti, B.F. Treating spinal cord injury pain with cranial electrotherapy stimulation (abstract). *Journal of Spinal Cord Medicine* 2003; 26(3).

70. Pozos RS, Strack LE, White RK, Richardson AW. Electrosleep versus electroconvulsive therapy. In DV Reynolds & AE Sjoberg (Eds.). Neuroelectric Research. Springfield: Charles Thomas, 1971; 23:221-225.

71. Braverman E, Smith RB, Smayda R, Blum K. Modification of P300 amplitude and other electrophysiological parameters of drug abuse by cranial electrical stimulation. *Current Therapeutic Research* 1990; 48:586-596.

72. Siegesmund KA, Sances A Jr., Larson SJ. The effects of electrical currents on synaptic vesicles in monkey cortex. In Wageneder FM, St. Schuy eds. Electrotherapeutic Sleep and Electroanaesthesia. Internaliton Congress series No. 136. Amsterdam: Excerpta Medica Foundation, 1967:31-33.

73. Alpher EJ, Kirsch DL. A patient with traumatic brain injury and full body reflex sympathetic dystrophy treated with cranial electrotherapy stimulation. *American Journal of Pain Management* 1998; 8:124-128.

74. Champagne C, Papiernik E, Thierry JP, Noviant, Y. Transcutaneous cerebral electric stimulation by Limoge current during labor. *Ann Fr Anesth Reanim* 1984; 3:405-13.

75. Childs A. Droperidol and CES in Organic Agitation. Clinical Newsletter of the Austin Rehabilitation Hospital, 1995.

76. Naveau S, Barritault L, Zourabichvili O, Champagne C, Prieur G, Limoge A, Poynard T, Chaput JC. Analgesic effect of transcutaneous cranial electrostimulation in patients treated by Nd:YAG laser for cancer of the rectum. A double-blind randomized trial. *Gastroenterol Clin Biol*. 1992; 16:8-11, 1992.

77. Stanley, TH, Cazalaa JA, Atinault A, Coeytaux R, Limoge A, Louville Y. Transcutaneous cranial electrical stimulation decreases narcotic requirements during neurolept anesthesia and operation in man. *Anesthesia and Analgesia* 1982; 61(10):863-866.

78. Stanley TH, Cazalaa JA, Limoge A, Louville, Y. Transcutaneous cranial electrical stimulation increases the potency of nitrous oxide in humans. *Anesthesiology* 1982; 57:293-297.

79. Mantz J, Azerad J, Limoge A, Desmonts JM. Transcranial electrical stimulation with Limoge's currents decreases halothane requirements in rats. Evidence for the involvement of endogenous opioids. *Anesthesiology* 1992; 76:253-60.

80. Stinus L, Auriacombe M, Tignol J, Limoge, A, Le Moal, M. Transcranial electrical stimulation with high frequency intermittent current (Limoge's) potentiates opiate-induced analgesia: blind studies. *Pain* 1990; 42(3):351-363.

81. Warner R, Hudson-Howard L, Johnston C, Skolnick M. Serotonin involvement in analgesia induced by transcranial electrostimulation. *Life Sciences* 1990; 46:1131-1138.

82. Feighner JP, Brown SL, Olivier JE. Electrosleep therapy: A controlled double-blind study. *J Nerv Ment Dis* 1973; 157(2):121-128.

83. Hearst ED, Cloninger CR, Crews EL, Cadoret RJ. Electrosleep therapy: A double-blind trial. *Arch Gen Psychiatry* 1974; 30(4):463-466.

84. Krupitsky EM, Burakov AM, Karandashova GF, Katsnelson J, Lebedev VP, Grinenko AJ, Borodkin JS. The administration of transcranial electrical treatment for affective disturbances therapy in alcoholic patients. *Drug and Alcohol Dependence* 1991; 27:1-6.

85. Levitt EA, James NM, Flavell P. A clinical trial of electrosleep therapy with a psychiatric inpatient sample. *Australian and New Zealand Journal of Psychiatry* 1975; 9(4):287-290.

86. Smith RB, Tiberi A, Marshall J. The use of cranial electrotherapy stimulation in the treatment of closed-head-injured patients. *Brain Injury* 1994; 8:357-361.

87. May B, May C. Pilot project using the Alpha-Stim 100 for drug and alcohol abuse. In-house publication: 1993.

88. Rosenthal SH. Electrosleep: A double-blind clinical study. *Biological Psychiatry* 1972; 49(2):179-185.

89. Shealy CN, Cady RK, Wilke RG, Cox R, Liss, S, Clossen, W. Depression: a diagnostic, neurochemical profile and therapy with cranial electrical stimulation (CES). *Journal of Neurological and Orthopaedic Medicine and Surgery* 1989; 10(4):319-321.

90. Flemenbaum A. Cerebral electrotherapy (Electrosleep): an open clinical study with a six month follow-up. *Psychosomatics* 1974; 15(1):20-24.

91. Hozumi S, Hori H, Okawa M, Hishikawa Y, Sato K. Favorable effect of transcranial electrostimulation on behavior disorders in elderly patients with dementia: a double-blind study. *Int J Neuroscience* 1996; 88:1-10.

92. Patterson M, Flood NV, Patterson L. Neuroelectric therapy (NET) in addiction detoxification. *Subtle Energies* 1992; 3(3):1-22.

93. Rosenthal SH, Wulfsohn NL. Studies of electrosleep with active and simulated treatment. *Current Therapeutic Research* 1970; 12(3):126-130.

94. Weingarten E. The effect of cerebral electrostimulation on the frontalis electromyogram. *Biological Psychiatry* 1981; 16(1):61-63.