CES in the Treatment of Depression, Part 2

This second article, of a two-part series on the efficacy of Cranial Electrotherapy Stimulation (CES) in treating depression, reviews the results of meta-analysis conducted on CES studies.

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Cranial electrotherapy stimulation (CES) is the FDA recognized generic category for medical devices using microcurrent levels of electrical stimulation applied across the head via transcutaneous electrodes for the treatment of anxiety, insomnia and depression. CES treats depression by passing tiny electrical currents—similar to those found naturally in the body—imperceptibly through the brain. The microcurrent, delivered in a unique waveform, moves electrons through the brain at a variety of frequencies collectively known as harmonic resonance. This normalizes the electrical activity of the brain as measured by an electroencephalogram (EEG). The patient undergoing CES treatment will often report a pleasant, relaxed feeling of well-being. Improvement is usually experienced during treatment, but may be seen hours later, or even the day after treatment. Depression control is often experienced after two to three weeks of daily treatment. Ear clip electrodes, moistened with an appropriate conducting solution, are applied for 20 minutes to an hour or more on an initial daily basis for 3-6 weeks, followed by a reduced schedule of 2 or 3 treatments a week until the depression is resolved, and then further reduced to an as-needed (p.r.n.) basis.

This article focuses on the meta-analysis of CES studies of depression along with a discussion of individual study designs and outcomes. It is important to note that protocols for some CES studies were poorly designed; inconsistent patient selection and concurrent use of other pharmaceutical modalities rendered the results inconclusive with regard to CES efficacy in treating depression. The authors have carefully selected only valid studies to provide the most complete and accurate meta-analysis of CES depression treatment outcomes.

Early CES Studies In Treating Depression

Rosenthal conducted some of the earliest CES studies of depression when CES was first introduced in the U.S. His work was primarily with psychiatric outpatients, although he sometimes used medical staff as controls. He was basically trying to find out what, if anything, CES treatment would do for his patients, how many sessions it might require, and what level of current it took to get results.[1-4]

The early U.S protocols studied patients who had been refractive to previous antidepressant treatment, but only provided them with three, 30 minute CES sessions in an open clinical trial. This did not reduce depressive symptoms so stimulation was increased to a minimum of five, 30 minute sessions. At this level, measurable changes began to be seen. CES is now routinely prescribed for depression for a minimum of three weeks of daily treatment followed by a reduced schedule or for use on an as-needed basis for up to a year or more.

Some of the early studies are suited to meta-analysis in that scores on pre- and post-testing were given, using psychometric instruments such as the Zung Self Rating Depression Scale. Often other information was added such as the percent of patients who improved at least 50%, those who did not improve at all, and those who demonstrated signs of other responses. That form of data is a poor fit with meta-analysis.

Following the often dramatic results published by Rosenthal, other researchers began studying psychiatric inpatients. Such patients were all heavily medicated as well. Accordingly, CES would be required to demonstrate effects over and above the effects of medications, and that was usually found.

Complications in Some CES Test Protocols

Feighner was one of the early CES research pioneers working with psychiatric inpatients. He ran into two complications: patients were heavily medicated, and a crossover design was utilized. Adding to that, the patients were treated 30 minutes daily for only five days.[5] Only pre-crossover scores from that study are included in the meta-analysis since they are the only statistically legitimate data as explained in the discussion of meta-analysis in the previous issue of Practical Pain Management.[6]

Marshall subsequently studied inpatients in a state hospital by, once again, providing CES for 30 minutes a day for only five days. Here again, both the treatment and control subjects were heavily medicated. The study became invalid when the controls showed a substantial improvement in their depression during the course of the study, and there was no control group left against whom the treatment effect of CES could be measured.[7]

CES studies that were invalidated due to a loss of controls were often published, including the Marshall study and one by Passini, who repeated a similar protocol in 1976 with an inpatient sample that included a wide variety of diagnoses including addiction and psychosis. All patients also received psychotropic medication, and the study showed an improvement in depression following 14 days of daily CES for 30 minutes along with medications. This study had no controls with which to measure treatment effects and was thereby invalidated, but that did not prevent it from being

published. The authors concluded that since all of the sham treated patients improved, improvement from CES treatment could only be attributed to the placebo effect.[8]

Levitt studied six male and seven female psychiatric inpatients, divided into two groups, with diagnoses of schizophrenia, alcoholism, psychotic depression, mixed neurosis and personality disorders. Two of the CES devices malfunctioned, and this reduced his treated group to five who received treatment 30 minutes a day for ten sessions over a two week period. They were all on psychotropic and sleep medications. Some sham treated patients improved as did some CES patients, and some saw their conditions worsen. This was essentially a negative outcome from the point of view of CES treatment effectiveness. It should be noted however, that in addition to the medications, Levitt was using an early style of CES electrodes in which saline soaked gauze pads wrapped around thin steel plates were placed tightly over the closed eyes. This provided undesirable visual effects such as blurred vision.[9] Subjects in both groups reported the temporary visual disturbances which were later judged to be caused by mechanical pressure on the eyes, not the electrical intervention itself. This electrode method was abandoned over 30 years ago.

"…with an effect size of r =.50, CES is much more effective than any antidepressant medication, and, unlike them, lacks significant adverse effects."

Improved Study Methodology

In 1975, a depression study was conducted with 72 inpatient alcoholics who were provided 15 daily CES treatments, 40 minutes a day at a current level just below sensory threshold (sub-sensory). This length of treatment was chosen because of some of Rosenthal's earlier difficulties, and because most of the patients were also taking psychotropic medications. Their depression, as measured on the Profile of Mood States (POMS) improved 76% while the sham-treated patients continued to worsen.[10]

Krupitsky's group at Yale studied affective disturbance in 20 alcoholic patients in 1991, and found an average of 28% improvement on two depression measures. They concluded that CES was an effective non-pharmacological method to treat affective disturbances in alcoholic patients in remission.[11]

May also studied inpatient addicts and found that 60 minutes of CES for 25 days allowed the patients to attain an unprecedented recovery record, with the group of 14 patients improving 76% on the Multiple Affect Adjective Check List and improving 77% on the Beck Depression Inventory.[12] This was the longest treatment time studied to date. Although based on a successful pilot study, the U.S. government has now funded a six month CES treatment study for veterans with spinal cord injuries to be completed by 2008.

The final addiction study to date that included data on depression was a doctoral dissertation in 1994 by Bianco who studied 65 inpatient poly-substance abusers. He provided 45 minutes of CES daily from 6 to 14 days, and found their improvement on the Beck Depression Inventory to be 80%.[13]

Hearst studied 28 psychiatric outpatients who were on less medication than a typical inpatient sample. Because the study took place in 1974, the early protocol of five, 30 minute treatment or sham treatment sessions was followed. The patients were assessed on the National Institutes of Mental Health (NIMH) Self Rating Scale and obtained a 73% reduction in depression among the treated patients compared with a 21% improvement among sham treated controls.[14]

Shealy studied depression in chronic pain patients and controls. He found that CES therapy yielded a 60% improvement in their depression score and there was a significant elevation in serotonin (mean of 33.18 ± 9.33 pre-test to 44.64 ± 9.10 post test, $P<.0089$), and a significant decrease in cholinesterase (mean of 13.82 ± 2.86 pre-test to 10.45 ± 3.04 post test, $P<.0067$).[15]

Lichtbroun and, later, Tyers began a series of studies of depression in fibromyalgia patients.[16-18] They measured depression with the POMS test and found that as the patients' pain scores improved, so did their depression which showed between 26% to 35% improvement after three weeks of daily, 60 minute CES stimulation.

Two other groups of depressed subjects studied were graduate students in a business school suffering under the stress of completing an MBA program and patients suffering from lifetime disability due to closed head injuries.[19,20] Both were double-blind studies in which CES or sham CES was given for one hour daily, Monday through Thursday for three weeks in the closed head injured subjects and one hour daily for 21 days in the graduate students. The closed head injured subjects achieved a 30% improvement in their depression while the graduate students improved 34%.

A group of 28 children and adults with attention deficit disorder (ADD) were studied in an open clinical protocol that looked at various factors, including depression scales. They were given 45 minute daily CES treatments for three weeks. They were retested at 18 months follow up. Their depression improved by 32% at the conclusion of the study, and was maintained at that same level 18 months later.[21]

Physicians evaluated 500 patients who were treated with CES, 69 of whom carried a primary depression diagnosis with the balance having comorbid depression. The group improved an average of 71% over varying courses of treatment.[22] Another study examined patients' own self rating of improvement. This information was obtained from surveys of 318 patients who had been diagnosed with depression and who had used their Alpha-Stim CES device for at least three weeks prior to sending in the survey. They rated their improvement an average of 58% on a 100 point scale. While 12% rated their improvement less than 25%, more than twice as many (27%) rated their improvement between 75% and 100%.[23]

Two additional crossover studies were done, one in which sham treated patients were actually given CES at a low current while treated patients were provided CES at a higher current, after which they were crossed over.[24] No improvement was noted in the study, although there were protocol design flaws. Another double-blind crossover design, in which five 30 minute treatments were given, provided results in the patients prior to the crossover, allowing its use in meta-analysis.[25]

Studies Collected For Meta-Analysis

Table 1 presents all of the studies collected for meta-analysis. There were a total of 23 suitable CES studies of depression, representing some 1,075 subjects studied. It bears emphasis in this day of black box warnings on SSRI's that none of the CES studies found any significant negative side effects. CES is known to

Table 1. List and description of depression studies

		Blinding				
Author	**Primary Diagnosis**	**Subject**	**Therapist**	**Assessor**	**Study Design**	**OutcomeMeasure**
Bianco[13]	Alcoholism	Yes	Yes	Yes	Double Blind	Hamilton, Beck Depression Scales
Feighner[5]	Psychiatric Inpatients	Yes	Yes	Yes	Crossover	Zung[a]
Hearst[14]	Insomnia	Yes	Yes	Yes	Crossover	NIMH Self Rated Symptom Scale
Krupistsky[11]	Alcoholics	Yes	Yes	Yes	Double Blind	Zung, SRDS, MMPI Depression Scale
Levitt[9]	Psychiatric Inpatients	Yes	Yes	Yes	Double Blind	Clinical Rating Scale
Smith[20]	Closed Head Injured	Yes	Yes	Yes	Double Blind	POMS[b]
Marshall[7]	Psychiatric Inpatients	Yes	Yes	Yes	Double Blind	DES+D II
Matteson[19]	Graduate Students	No	No	No	Open Clinical	POMS
Tyers[17]	Fibromyalgia	No	No	No	Open Clinical	POMS
Tyers[18]	Fibromyalgia	No	No	No	Open Clinical	POMS
Lichtbroun[16]	Fibromyalgia	Yes	Yes	Yes	Double Blind	POMS
Kirsch[22]	Diagnosed Depression	No	No	No	Open Clinical	Physician's Rating
Smith[23]	Diagnosed Depression	No	No	No	Open Clinical	Patient's Self Rating
May[12]	Addiction	No	No	No	Open Clinical	Beck Depression Scale, MAACL[c]
Passini[8]	Psychiatric Inpatients	Yes	Yes	Yes	Double-Blind	MAACL
Rosenthal[4]	Psychiatric Outpatients	Yes	Yes	Yes	Double-blind Crossover	Clinical Ratings, Zung SRDS
Rosenthal[1]	Psychiatric Outpatients	No	No	No	Open Clinical	Zung, SRDS, Clinical Ratings
Rosenthal[2]	Psychiatric Outpatients	No	No	No	Open Clinical	Clinical Ratings, Zung SRDS
Rosenthal[3]	Psychiatric Outpatients	Yes	No	Yes	Single Blind, Crossover	Zung SRDS, Clinical Ratings
Shealy[15]	Chronic Pain, Depression	No	No	No	Open Clinical	Serum Neurochemicals
Smith[10]	Inpatient Alcoholics	Yes	No	Yes	Single Blind	POMS
Smith[21]	ADHD	No	No	No	Open Clinical	IPAT Depression Scale
Frankel[24]	Insomnia	Yes	Yes	Yes	Crossover	Zung SRDS
Moore[25]	Insomnia/Anxiety	Yes	Yes	Yes	Double-Blind Crossover	Beck Depression Inventory

[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

produce skin irritation at the electrode site in people with light skin and may cause an occasional headache. Such side effects are usually mild and self-limiting.

Table 2 presents the studies shown in Table 1, with three of the studies removed. In one, the study was invalidated when the sham treated patients also improved.[8] The other two studies had crossover designs, and the investigators did not report the treatment results prior to the crossover. The sham patients in a crossover design who had active CES during the initial arm of the study typically continue to improve, making them unfit subjects to use for subsequent crossover sham treatment. That leaves 20 studies involving 937 subjects that are considered valid for the purposes of meta-analysis.

Secondary Analysis of Studies

Some studies reported more than one measure of depression. Feighner reported two measures, as did Krupitsky, May and Rosenthal (in three different studies), while Moore reported three. In order to limit the input of error variance from any given study, each study was represented with only one score, and to be

Table 2. An Initial Analysis of studies shown in Table 1

	Number of Patients					
Author	**CES**	**Controls**	**Total**	**Statistic Reported**	**Results**	**Z_r Score[a]**
Bianco[13]	11	18	29	% Improvement	80%[b]	1.099
Feighner[5]	23	23	23	% Improvement Zung SRDS % Improvement, Clinical Rating Scale	17% 26%	.172 .266
Hearst[14]	14	14	28	% Improvement	73%	.929
Krupitsky[11]	110	10	20	% Improvement, Zung SRDS % Improvement, MMPI	23% 32%	.234 .332
Levitt[9]	5	6	11	% Improvement	25%	.255
Smith[20]	10	11	21	% Improvement	30%	.310
Matteson[19]	32	22	54	% Improvement	34%	.354
Tyers[17]	20		20	% Improvement	35%	.365
Tyers[18]	60		60	% Improvement	26%	.266
Lichtbroun[16]	40	20	60	% Improvement	31%	.321
Kirsch[22]	69		69	Average % Improvement	71%	.887
Smith[23]	318		318	Average % Improvement	58%	.662
May[12]	15		15	% Improvement, Beck DI % Improvement, MAACL	76% 77%	.996 1.02
Moore[25]	17	17	17	% Improvement, Clinical Assessment % Improvement, Self Rated % Improvement, Beck DI	59% 17% 5%	.678 .172 .050
Rosenthal[1]	11	11	22	% Improvement, Clinical Rating % Improvement, Zung SRDS	64% 21%	.758 .213
Rosenthal[2]	9		9	% Improvement, Clinical Rating % Improvement, Zung SRDS	38% 29%	.400 .299
Rosenthal[3]	12	6	18	% Improvement, Clinical Rating % Improvement, Zung SRDS	56% 37%	.633 .388
Shealy[15]	34	14	48	% Improvement	50%	.549
Smith[10]	36	36	72	% Improvement	67%	.881
Smith[21]	23		23	% Improvement	32%	.332

[a] From Fisher Tables of r to zr transformation[26]
[b] Percent change equals r, from the binomial effect size distribution. From Wolf[27]
[c] From Rosenthal[28]

equitable, means of all the scores given were computed and utilized. Since percentages can not be legitimately averaged, they were converted to Zr scores and then those scores were averaged. The mean Zr score was then converted back into a percent score. The results of this for CES in the treatment of depression are presented in Table 3.

The effect size from the 20 studies analyzed is r =.50, which is considered a strong effect size. While there was a wide disparity of number of subjects in the various studies, an N weighted effect size of r =.51 was obtained, showing that the number of people appearing in a given study was relatively unimportant. The effect size obtained is more than sufficient to show that CES is a very effective treatment for depression. In fact, with an effect size of r =.50, CES is much more effective than any antidepressant medication, and, unlike them, lacks significant adverse effects.[6,29]

To estimate the outer limits of the effect size to be expected in any future meta-analyses of studies of CES for depression, the confidence interval of the effect size needs to be derived. That is calculated from the standard deviation, divided by the square root of the number of studies in the analysis, yielding the standard error of the mean. The resulting score indicates that if 15 additional meta-analyses of 21 studies each is performed in the

Table 3. A Secondary Analysis of studies shown in Table 1

	Number of Patients					
Author	**CES**	**Controls**	**Total**	**Statistic Reported**	**Results**	**Z_r Score[a]**
Bianco[13]	11	18	29	% Improvement	80%[b]	1.099
Feighner[5]	23	23	23	% Improvement	22%	.219
Hearst[14]	14	14	28	% Improvement	73%	.929
Krupitsky[11]	110	10	20	% Improvement	28%	.283
Levitt[9]	5	6	11	% Improvement	25%	.255
Smith[20]	10	11	21	% Improvement	30%	.310
Matteson[19]	32	22	54	% Improvement	34%	.354
Tyers[17]	20		20	% Improvement	35%	.365
Tyers[18]	60		60	% Improvement	26%	.266
Lichtbroun[16]	40	20	60	% Improvement	31%	.321
Kirsch[22]	69		69	% Improvement	71%	.887
Smith[23]	318		318	% Improvement	58%	.662
May[12]	15		15	% Improvement	77%	1.008
Moore[25]	17	17	17	% Improvement	72%	.900
Rosenthal[1]	11	11	22	% Improvement	45%	.486
Rosenthal[2]	9		9	% Improvement	34%	.350
Rosenthal[3]	12	6	18	% Improvement	47%	.511
Shealy[15]	34	14	48	% Improvement	50%	.549
Smith[10]	36	36	72	% Improvement	67%	.881
Smith[21]	23		23	% Improvement	32%	.332
Total	869	190	937[d]	Mean .458 Mean Effect Size r = .50 Standard Deviation .29 Standard Error of the Mean .06 Effect Size Confidence Limits, p<.01=.32-.68		

[a] From Fisher Tables of r to zr transformation[26]
[b] Percent change equals r, from the binomial effect size distribution. From Wolf[27]
[c] From Rosenthal[28]
[d] The first two columns do not add to this figure due to subjects in the crossover studies appearing twice in the first two columns.

future (more than 300 additional studies), there is a 99% likelihood that the effect size obtained will fall within an effect size between r =.32 and r =.68.

Comparison To Efficacy of Antidepressant Fluoxetine

A different evaluation can be undertaken to determine how the effectiveness of CES compared with the current standard of care (i.e., antidepressant medications).

Under the Freedom of Information Act, Kirsch procured the studies submitted by Eli Lilly to the FDA for marketing approval of fluoxetine (Prozac).[30] Five studies were submitted, which Kirsch analyzed in terms of the degree of change in depression scores experienced by the treatment group over and above the change in depression scores of the controls in each study. Table 4 presents an abbreviated version of those results, from which the effect size for fluoxetine treatment of depression can be calculated.

In deriving the numbers, Kirsch divided the amount of change in the placebo group by the change in the treated group, then subtracted that score from 100 to get the percent effectiveness of fluoxetine over and above that of the placebo patients.

It can be seen from Table 4 that the effect of fluoxetine over and above that of the placebo patients in the five studies was only 8%. In study 25, the placebo group improved more than the fluoxetine treated patients. That figure rose to 11% when the studies were corrected (weighted) for sample size. Kirsch also evaluated other antidepressant drug studies that were sent to the FDA for marketing approval.

It should be noted that most researchers added subjects to their studies based on the Hamilton Depression Scale, a psychometric paper and pencil test that either the patient or the researcher can complete. Tests with similar validity and reliability were used in the CES studies. So from the standpoint of enlisting subjects, identical or similar diagnostic devices were used for both the pharmaceutical and CES research.

Patients suffering from depression would not be expected to improve as dramatically in the placebo condition as did the placebo patients in all the pharmaceutical studies reported to the FDA. Or to put it another way, one would not anticipate that 89% of placebo patients with any type of "deep-seated" depression would spontaneously improve in six weeks or less as they did in the fluoxetine studies. Most were recruited by advertisements in newspapers and other media. Most were outpatients, and many, like those in the CES studies, were on additional medications of one kind or another during the studies.

Certainly, the depressions studied in the CES research showed no such spontaneous remission, suggesting that they were either more serious cases of depression than those used in the pharmaceutical studies even though the pharmaceuticals were typically studied over a longer duration, or that placebo pills had a stronger placebo effect than sham CES treatment.

Summary of CES Modality For Depression

The following presents a brief synopsis of the discussion in parts 1 and 2 of this series.

- Cranial Electrotherapy Stimulation (CES) can occasionally be a single, time-limited treatment of many mild depressions with or without concomitant medication.
- Meta-Analysis is a valid way to assess the effect size of CES in the treatment of depression.
- Meta-Analysis of effect size has shown that CES, with and without concomitant medication, compares very favorably with the effect size of medication treatment.
- Although CES is nearly free of significant adverse effects, there is a spectrum of usually mild cutaneous irritative effects at the electrode site which can limit treatment compliance in depressed patients.
- Depressive disorders require competent medical evaluation to rule out a primary or comorbid substance-related effect or a primary or comorbid treatable medical illness.
- Neither CES nor antidepressants should be employed for treatment without continuing and competent healthcare supervision because of emerging suicidality as some depressions lift.
- CES should always be considered as an add-on to medications before considering the more invasive Vagal Nerve Stimulator (VNS) or Deep Brain Stimulation (DBS) because it is much cheaper and potentially as efficacious, or even more so.

Table 4. Effectiveness of fluoxetine over and above placebo effect in treating depression

	Fluoxetine	Placebo	Proportion of Placebo to Drug Effect	Z_r Score
Study #	Change	Change		
19	-12.50	-5.50	.44	.472
25	-7.20	-8.80	1.22	2.994
27	-11.00	-8.40	.76	.996
62 (mild)	-5.89	-5.82	.99	2.647
62 (moderate)	-8.82	-5.69	.65	.775
Average Relative Placebo Effect			92%	1.577
Average Drug Effect Above Placebo			8%	

Conclusion

Regardless of the manner in which one analyzes CES studies of depression, a moderate to strong effect size is revealed, which exceeds the results of antidepressant drug studies submitted to the FDA for marketing approval (see Table 4).

With moderately severe and severe depressions, CES should definitely be considered as an add-on modality because of the

potential for (a) synergizing the efficacy of the drug (s), and (b) reducing the overall adverse effects of psychopharmaceuticals in patients who can tolerate and be compliant with CES. CES has no adverse metabolic interactions with the various hepatic isoenzymes responsible for metabolizing SSRI's, other antidepressants, and various other commonly prescribed medications.

It's important to stress that adjunctive use of CES with a single antidepressant drug can often prevent the need for using multiple antidepressants, as is too frequently the case in the currently accepted clinical treatment of depression. CES can prove increasingly cost-effective compared to the long-term use of expensive SSRI's. CES can be an ideal treatment for enhancing a patient's sense of mastery over depression because CES also emphasizes having the patient take the initiative on a daily basis. This involves several behavioral steps beyond merely passively swallowing a pill. While CES requires more education of clinicians and their patients about the modality—especially due to an initial aversion to electric stimulation because of a mental association with "Electric Shock" (Electroconvulsive Therapy, ECT)—it is quite worthwhile especially because of the less onerous economics involved and the superior safety factors. It also should be obvious that CES should always be considered before the much more invasive electromedical options of the Vagal Nerve Stimulator (VNS) and Deep Brain Stimulation (DBS). ■

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