CES in the Treatment of Depression

Part 1 of this two-part series reviews diagnoses, treatment modalities, and compares CES efficacy with that of the most popular pharmaceutical treatments for depression.

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According to NIH findings, one in 20 American adults experience major depression in a given year.[1] The Depression and Bipolar Support Alliance report that 16 million people suffer from depression annually, with twice as many women afflicted as men. They estimate that as many as 25% of women suffer from depression serious enough to require treatment at least once in their lifetime.[2] The National Alliance on Mental Illness indicates that "major depression is the leading cause of disability in the United States and many other developed countries, and affects 15 million American adults or about 5 to 8% of the adult population in a given year."[3]

Many other comorbid disabilities—such as cardiovascular events—can accompany depression. Depression may also result in chronically elevated levels of stress hormones, such as cortisol and epinephrine, and thus represents a condition that diverts metabolism away from tissue repair when needed for healing. Feelings of helplessness or of being out of control of one's life also impair the immune system, increasing susceptibility to a wide spectrum of pathologies from infections to cancer. The fact that women are twice as likely as men to develop depression is also in accord with the finding that, in U.S. society, it is more likely for women to feel out of control of their lives.[4]

Aside from the general population, chronic pain patients almost invariable suffer depression as a direct result of their pain and accompanying disability. Almost any chronic illness, especially ones with no clearly effective treatment, have a high incidence of comorbid depression. Based on these descriptions of the physical manifestations of depression, it is clear that it can have a devastating effect in the pain patient and others with chronic diseases.

While depression is a common term for describing how one feels, the technical psychiatric definition goes beyond just a feeling of sadness. For such a commonly-used term, it behooves us to scrutinize some technical definitions and terms. Depression is a "mental state characterized by feelings of sadness, loneliness, despair, low self-esteem, and self-reproach; accompanying signs include psychomotor retardation or, at times, agitation, withdrawal from interpersonal contact, and vegetative symptoms such as insomnia and anorexia. The term refers to either a mood that is so characterized or a mood disorder."[5]

Definitions

Mood disorder is now the preferred term in both the World Health Organization's (WHO) 10th revision of International Statistical Classification of Diseases and Related Health Problems (ICD-10) and the American Psychiatric Association's (APA) fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). Official mood disorder categories in current use include bipolar disorders (with manic or hypomanic, depressive, or mixed episodes) and major depressive disorders and their respective attenuated variants known as cyclothymic and dysthymic disorders.[6] Many of the older terms such as "atypical depression," "endogenous depression," and "involutional melancholia" are included within major depressive disorders. The older "depressive neurosis" has been replaced and absorbed by dysthymic disorder.

Table 1 summarizes the DSM-IV diagnoses that involve depression.[7] The specific psychiatric criteria for a Major Depressive Disorder, listed on pages 168-9 of the DSM-IV-TR, require that "five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning. At least one of the symptoms is either depressed mood or loss of interest or pleasure and the symptoms are not obviously secondary to a general medical condition or "mood-incongruent delusions or hallucinations." The symptoms are:

1. Depressed mood most of the day, nearly daily, and/or irritable mood in children and adolescents.
2. Markedly diminished interest or pleasure in most activities.
3. Significant weight loss when not dieting—or weight gain.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation.
6. Fatigue or loss of energy.
7. Feelings of worthlessness or excessive or inappropriate guilt.
8. Diminished ability to think or concentrate, or indecisiveness.
9. Recurrent thoughts of death beyond a fear of dying, recurrent suicidal ideation, or a suicide attempt or specific plan.

Treatment Protocols

The National Institutes of Health (NIH) describes depression as a serious medical condition that affects thoughts, feelings, and the ability to function.[1] Depression is labeled a treatable disorder of the brain, with 80% of patients responding to treatment. The NIH, as well as other researchers, declare depression to be mainly a biochemical problem and, therefore, the first line of

Table 1. DSM-IV-TR Diagnoses for Depression

Summary of Dsm-Iv-Tr Depressive Disorders	
296.xx	Major Depressive Disorder .2x Single Episode .3x Recurrent
300.4	Dysthymic Disorder
311	Depressive Disorder Not Otherwise Specified (NOS)
293.83	Mood Disorder Due to a General Medical Condition. Specify with Depressive Features/With Major Depressive-Like Episode/with Mixed Features.
___.__	Substance-Induced Mood Disorder Specify type as in 293.83 or With Onset During Intoxication/With Onset During Withdrawal
296.90	Mood Disorder Not Otherwise Specified
309.0	Adjustment Disorder With Depressed Mood
309.28	Adjustment Disorder With Mixed Anxiety and Depressed Mood

treatment should be psychopharmaceutical intervention, possibly accompanied by psychotherapy, counseling, exercise, or other wellness techniques. In the following sections, we will focus on three basic modalities in the treatment of depression: psychoanalysis-related, pharmaceutical, and micro-current cranial electrotherapy stimulation.

Psychoanalytic Foundations

The absolute foundation of all psychological treatments for depression comes from the principles of psychoanalysis, and this applies to all mental health professionals. By the 1960s, the basic precepts of psychoanalysis were so thoroughly inculcated into the fabric of Western society (at least with the upper middle and upper classes), that the notions of depression representing mental pain and possibly anger turned against the self were widely (mis)understood and used in treatment. In fact, there was even a somewhat popularized book published entitled, *Americanization of the Unconscious*.[8] However, the same decade saw the beginnings and popularization of various types of behavior therapies. With current managed care, psychoanalysis as a technique has become more of a foundation science of consciousness for less prolonged, behaviorally and cognitively-oriented systems of psychotherapy. Psychiatric residents are taught elements from much briefer techniques such as Albert Ellis's Rational Behavioral Therapy (RBT), Aaron Beck's Cognitive Behavioral Therapy (CBT), and Weissman and Klerman's Interpersonal Therapy (IPT).[9] Most of the methodologies used for depression in today's mental health teaching utilize psychodynamic principles but focus on briefer, time-limited, task- or sector-oriented psychotherapy systems as well as a large variety of group and peer-related interventions.

Rational Behavior Therapists recognize four specific steps required for depression to occur:

1. A disappointment occurs due to an unfortunate or unexpected event;
2. One experiences frustration at the disappointment and dwells on it at length;
3. When nothing can be done to change the situation, and one can not manage to let go of it, a feeling of hopelessness and helplessness ensues;
4. The final step is what cognitive therapists refer to as lying exaggerations. Typical of these are, "This is the story of my life. No one has ever loved me and no one ever will," or "Everyone has someone to love them except me. I am no good for anybody, not even myself. I would be better off dead."[10]

Rational Behavior Therapy (RBT) can treat depression by assisting the patient in examining any one of these steps, usually step one or step four, and the depression hopefully becomes manageable as the patient learns to better understand these feelings. The biggest problem the therapist has is in identifying the specific trauma that started the most recent depressive episode. That is because depressed people obsess and dwell on similar events in their history and run "reel after reel of mental depression tapes" that maintain the affliction. The strategy is to examine recent history to decipher what started the latest episode so that, once it is clear and exposed to rational thinking, the depression may be reduced.

Operationally, the difficulty with all the cognitive and behavioral approaches can be a lack of real communications about feelings on the part of both therapist and patient. There is the also the potential of mistaking depression as a singular issue or mainly a psychological problem that can be isolated from the physical body.

Pharmacological Mechanism of Action

The biochemical model recognizes levels of depression from mild, to moderate, to so severe that it affects every part of the person's life. The biomedical model maintains that all these levels require medication.[11] As a result, antidepressants are often prescribed and typically include one of the following pharmaceuticals: Prozac, Paxil, Zoloft, Effexor, and Serzone. One im-

portant issue not always addressed is how long treatment for depression should be continued, given that there are physiologic consequences to prolonged manipulation of neurotransmitters by such drugs.

Neurotransmitters tend to attain balance by mutual regulation activities. Once a person encounters a sympathetic dominant situation that can not be gotten out of by fleeing or fighting (e.g., bad job, worse marriage), the body adjusts to a new homeostatic stress level and this will affect the balance between neurotransmitters.[12] Psychological symptoms such as anxiety, depression, panic attacks and phobias are often the result.

Depression is thought to involve many neurotransmitters including dopamine, norepinephrine and serotonin, among others. Most physicians and researchers theorize the mechanism of depression in terms of the "hardwired" neurological system in which the axon terminals secrete neurotransmitters from the pre-synaptic membrane into the inter-synaptic space to bind to a post-synaptic membrane. The neurotransmitter that is not bound by the post synaptic membrane will either undergo reuptake by the pre-synaptic membrane or it can be metabolized by monoamine oxidase or catechol-o-methly transferase for elimination from the system.

The biochemical model views depression as being the byproduct of insufficient serotonin activity or inadequate serotonin level, and the neurotransmitter effects can be increased in several ways. A chemical can be added to the system to block the re-uptake into the pre-synaptic membrane, leaving more serotonin in the synaptic space. This is how the SSRI drugs work. Alternatively, a MAO inhibitor may be administered so that the serotonin in the synaptic space is not metabolized by monoamine oxidase and thereby remains available longer. A serotonin mimicking drug may stimulate the post synaptic membrane and serotonin activity.

This treatment approach comes from the theory of the hardwired (neuron-to-neuron), point-to-point hookup of traveling neuronal impulses, in which the synapses form the networks and define the neural circuits that, in turn, define and dictate performance.

It is now known that, in addition to the nervous system, cellular receptors throughout the body respond to ligands (molecules that bind to a receptor) such as serotonin flowing in the intercellular space outside the neural network. Manipulating levels of serotonin in the two percent of neuronal communications in the brain that are targeted in the treatment patterns as just described may actually influence the behavior of cells throughout all parts of the body in unknown ways. Depression is now often thought of as a mood produced by various neuropeptide ligands that activate cells simultaneously throughout the brain and the rest of the body.[13]

At all times, feedback mechanisms work to regulate mutual relationships between the individual neurotransmitters so that a higher or lower level of one neurotransmitter will be balanced or neutralized by a coupled feedback process on one or more corresponding neurotransmitters to reestablish physiological equilibrium. This is accomplished by the down-regulation by other neurotransmitters, when any one neurotransmitter is over-produced.[14,15]

When a reuptake inhibitor is added to the system, a temporary surplus of the targeted neurotransmitter occurs and neurons that control the production of other neurotransmitters react automatically to bring the surplus neurotransmitter back into homeostasis. Thus chemicals that mimic endorphins at the post synaptic receptors (e.g., alcohol and benzodiazepines) stimulate the feedback mechanisms to down-regulate endorphin production. The substance abstinence syndrome results when the alcoholic, the heroin addict, or the long term diazepam (Valium) user attempts to come off the endorphin mimicking drug because the newly down-regulated endorphin production can not balance the unchecked norepinephrine production causing the symptoms.[16]

It is for this reason that Birkmayer and other neuroscience researchers advise that medications, such as SSRIs, should only be used short term to manage an acute problem, theorizing that longer use may throw the system into imbalance and produce harmful and sometimes long lasting iatrogenicity.[17]

Cranial Electrotherapy Stimulation (CES)

Cranial electrotherapy stimulation is based on the concept that the biophysics underlying the body's biochemistry also plays a significant role in regulating brain processes. 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 generally experienced after three or more weeks of daily treatment.

The treatment is applied via clip-on electrodes that attach to the ear lobes. The only thing felt by the patient may be a slight tingling sensation at the site of the electrodes. The duration of application is 20 to 60 minutes every day, every other day, or on a prn basis. The treatment session may be in the office or performed by the patient at home with a small portable unit. In this regard, 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. CES still requires more education of clinicians and their patients about the modality.

CES can be utilized as an adjuvant treatment without fear of drug interaction. It's important to stress that add-on use of CES with one 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.

Cranial Electrotherapy Stimulation (CES) can occasionally be a single, time-limited treatment of many mild depressions with or without concomitant medication. Depressive disorders require competent medical evaluation to rule out a primary or comorbid substance-related effect or a primary or comorbid treatable medical illness. 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. The other crucial factor is patient compliance and acceptance of the modality. Neither CES nor antide-

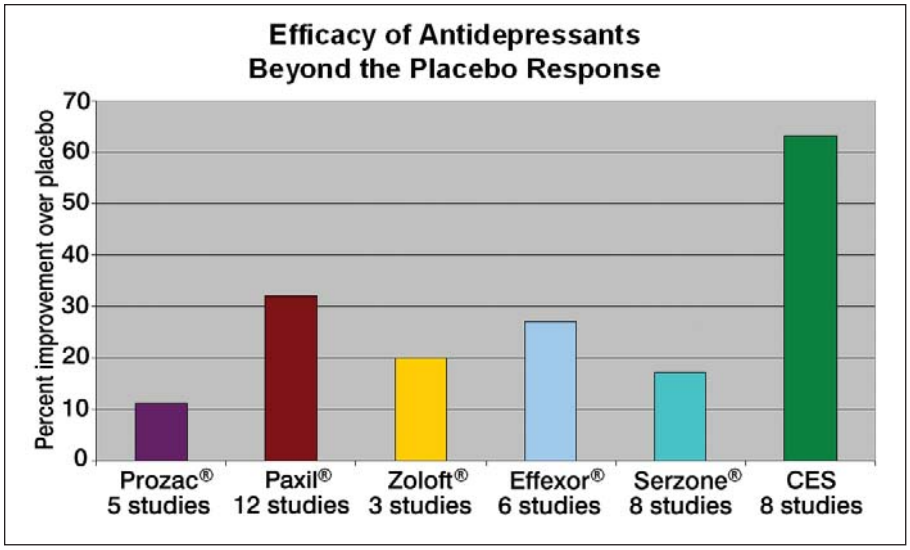

FIGURE 1. *Efficacy of Antidepressants and CES Beyond the Placebo Response*

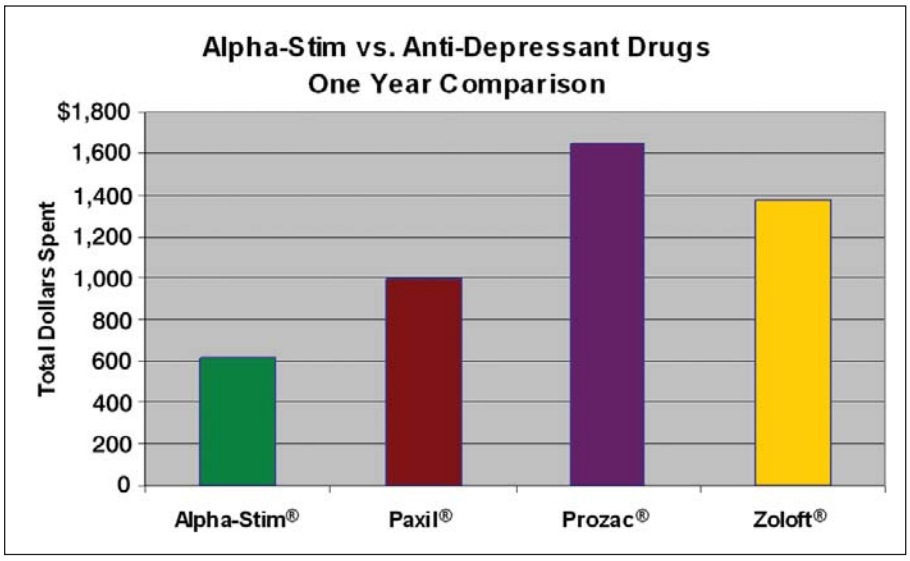

FIGURE 2. *Costs of Antidepressants and CES over a one year period.*

pressants 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), or even repetitive Transcranial Magnetic stimulation (rTMs) because CES is much cheaper and potentially as efficacious, with minimal side-effects.

Comparison of Pharmaceuticals versus CES

Statistical meta-analysis, conducted on five of the leading antidepressant medications and CES, allows a comparison of efficacy for these treatment protocols. As discussed in this department in the April issue, the statistical measure of efficacy is called the 'r effect size.' Simply stated, the r effect size represents the percentage improvement to be expected on a scale of 0 to 100. An r effect size of .15 means that there was an average of only 15% improvement among patients when measured across combined studies, while r=.60 means that there was an average of 60% improvement in patients found in the combined studies, etc. In this scale, an r effect size of .10 is small, while r of .30 is moderate, and r of .50 or above is considered to be high.

Kirsch has demonstrated that the studies submitted to the FDA for fluoxetine (Prozac®) had an effect size of r=.11, paroxetine (Paxil®) had an effect size of r=.32, sertraline (Zoloft®) had an effect size of r=.20, venlafaxine (Effexor®) had an effect size of r=.27, and nefazodone (Serzone®) had an effect size of r=.17%.[18] By comparison, the treatment effect size of CES (over and above that of placebo effect) was r=.60.[19] Figure 1 presents these results graphically.

While these results may seem astonishing, the results have been verified by others. Khan evaluated clinical trial data from the nine antidepressant medications approved by the FDA between 1985 and 2000.[20] These trials comprised 10,030 depressed patients in 52 studies evaluating 93 treatment arms. Fewer than half (48%, 45/93) of the antidepressant treatment arms showed superiority to placebo.

Based on these data, it might be concluded that antidepressant medications alone may be adequate when treating mild to moderate depression, if one can tolerate the negative side effects,[19] but that CES should always be considered a first line of treatment or, at least, an add-on to medication for the treatment of more difficult cases. It should certainly be given serious clinical consideration in patients before resorting to the electroconvulsive therapy that the NIH has suggested on their web site as appropriate for those 20% of patients who do not respond to the use of even combinations of antidepressant medications.

A more conservative—and the authors submit, wiser—approach to the treatment of depression (as with the treatment of anxiety disorders) would be to consider CES as a viable add-on or replacement for pharmacotherapy in milder depressions. For both moderately severe and severe depressions, CES should 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 known adverse metabolic interactions with the various hepatic isoenzymes responsible for metabolizing SSRI's, other antidepressants, or any other commonly prescribed medications.

Figure 2 presents cost comparisons between three of the leading antidepressant medications and a CES unit (Alpha-Stim CES Stress Control System by Electromedical Products International, Inc.,

www.alpha-stim.com) over the first year of use. CES will generally become more cost-effective after the first 4-6 months of use. The medication costs were obtained from a media article that investigated medication pricing but excludes the price of ongoing physician visits to change prescriptions, adjust dosages, or treat the side effects of the medications.[21]

While most patients and many physicians assume that the best selling medicine must be the best medication for the problem being treated, the reality is often otherwise. Three of the antidepressants listed above are in the top 15 of the 200 most often prescribed medications, but according to Kirsch's analysis, they appear in inverse order to their documented efficacy. It might also be of interest to note that one of the medications shown here, which was shown to be the least effective of the antidepressant drugs that have been approved by the FDA, far outsold all of the others and was number 10 on the list of the 200 most prescribed medications in 1999.[22]

Conclusion

Results of studies indicate that the effect sizes for antidepressant drugs are low to low moderate at best, and the adverse effects that those manufacturers report in the Physician's Desk Reference—such as hypertension, nervousness, insomnia, sexual incompetence, seizures, liver and kidney dysfunction, among others—are often prominent. Further, physicians are warned that the use of some of these medications in patients, treated concomitantly with MAO inhibitors, can prove fatal in some circumstances.[23] In fact, the FDA has required their most severe black box warnings on selective serotonin reuptake inhibitors (SSRI's) due to potentially adverse side-effects.[24]

In light of the low-to-moderate efficacy indicated by analysis of the manufacturers' own studies together with documented side-effects and potential for drug interactions—especially among pain patients already on potent drugs—the high efficacy of CES and lack of side effects make this an excellent option for the treatment of depression, alone or in combination with other antidepressants. ■

In The Next Issue

Part 2 of this series will present a detailed meta-analysis of all applicable studies of CES in the treatment of depression.

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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.

By Daniel L. Kirsch, PhD, DAAPM, FAIS and Marshall F. Gilula, MD

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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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