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-

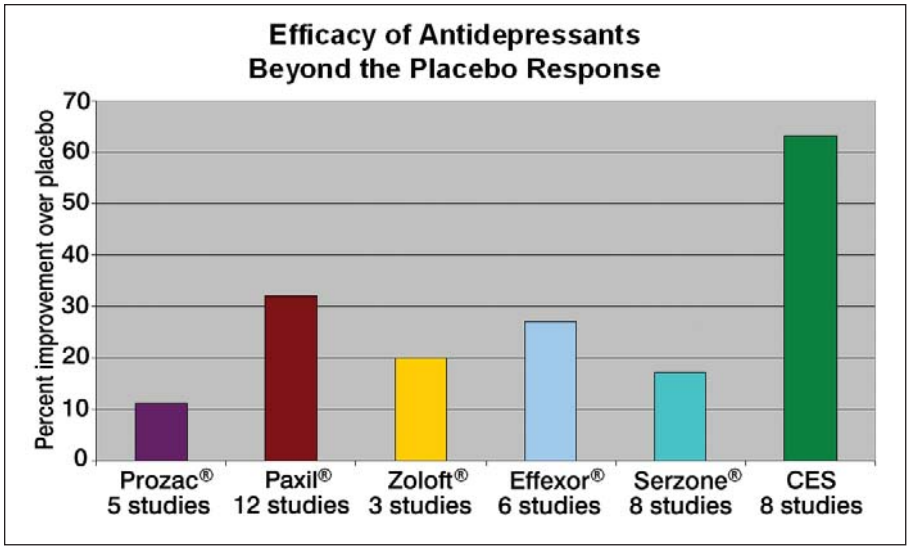

FIGURE 1. *Efficacy of Antidepressants and CES Beyond the Placebo Response*

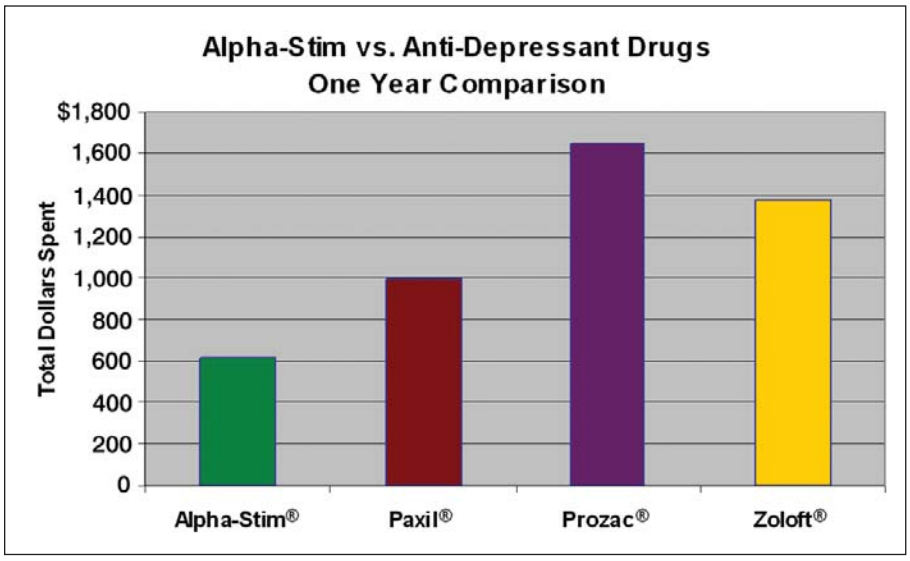

FIGURE 2. *Costs of Antidepressants and CES over a one year period.*

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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