BIOELECTROMAGNETIC AND SUBTLE ENERGY MEDICINE

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19 The Evolution of Cranial Electrotherapy Stimulation for Anxiety, Insomnia, Depression, and Pain and Its Potential for Other Indications

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NATURAL ELECTRICITY: THE DISCOVERY OF A PECULIAR PROPERTY OF FISH

Ancient writings on papyri inform us that electric catfish in the Nile River were used to relieve pain by the Egyptians 4700 years ago. The ancient Greeks used them to numb the pain of childbirth and surgical procedures.[1] In his 380 B.C. dialogue *Meno*, Plato accused Socrates of "stunning people" with his puzzling questions in a manner similar to the way the torpedo fish stuns or numbs.[2] In fact, the word "narcotic" stems from narke, which is the Greek word for these types of electric ray fish.

Perhaps the first known use of what is now referred to as cranial electrotherapy stimulation (CES) was when electrical fish were applied to the skull to relieve headache by the Greek physician Claudius Galen, who had more of an influence on Western and Arabic Medicine than any other individual. Galen was called "The Medical Pope of the Middle Ages" as his word was considered gospel and his humoral theory of disease lasted well into the nineteenth century. He

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was the first to describe migraine, which is derived from the Greek word hēmikrania (half the head). After investigating the ancient treatment of headache with torpedo fish, Galen wrote:

> The whole torpedo, and I mean the sea-torpedo, is said by some to cure headache and prolapsus ani when applied. I indeed tried both of these things and found neither to be true. Therefore, I thought the torpedo should be applied alive to the person who has the headache, and it could be that this remedy is anodyne and could free the patient from pain as other remedies which numb the senses: This I found to be so. And I think that he who first tried this did so for the above-mentioned reason.[3]

Galen's endorsement made this the treatment of choice for headache and other pains. Books and poems were written about it, and some who used a trident (a three pronged metal spear) for fishing claimed that the shock that traveled up the metal spear relieved their arthritic pains. Recommendations for applying live torpedo fish for headache and joint pain persisted throughout medieval Europe and were advocated by leading Muslim physicians such as Avicenna (Ibn Sina) and Averoës in the tenth and eleventh centuries.[4] In the 1500s, Dawud al-Antaki, the famous Syrian physician and philosopher declared it to be effective in "relieving chronic headache, unilateral headache (migraine), and vertigo, even in desperate cases."[5]

The most powerful source of electricity came from the huge South American eel (*Electrophorus electricus*) which, despite its name, is more closely related to a giant catfish. Adults are typically 6 or 7 feet long and can generate electric shocks of up to 600 volts through 24 feet of water, which allows them to feed on other fish and small mammals. When they were brought to Europe in 1750, people flocked to be treated with its "natural electricity," especially those suffering from arthritis.

THE MODERN ERA

The practice of using electrical fish eventually diminished following the advent of the Leyden jar and Volta's primitive battery. These were much more accessible sources of electricity in dosages that could be controlled.[6]

At the turn of the last century, Edison and Tesla's electrification of New York and beyond replaced candles and gas lighting, ushering in the modern era and bringing previously unimaginable technologies to the patent office and then the market. During this time, many physicians and scientists experimented with a multitude of electromedical devices and their applications. These included the many variations of transcutaneous electrical nerve stimulators (TENS) that continues to evolve today for numerous pain and non-pain related conditions, along with the putative mechanisms to explain such phenomena.

While electricity has historically been used therapeutically on all areas of the body, cranial electrotherapy stimulation, or CES, is a specific term denoting electrical stimulation to the brain. CES involves devices that deliver electrical currents transcranially through electrodes. The brain functions electrochemically and it can readily be modulated by electrical intervention. Unlike peripheral electromedicine, CES has been less frequently cited in older, historic literature. Krueger is perhaps the first person to mention this use, noting in 1743 that the experimental self-application of electric current allowed him to sleep better.[7] Aldini wrote in depth about its use in mental disease in 1802.[8] Marat described the application of strong currents across the head that produced convulsions.[9] These latter studies were a precursor to the development of electroconvulsive shock treatment (ECT) in the 1930s.[10]

Originally referred to as "electrosleep," the intended purpose of early CES devices had been to induce sleep through the application of small amounts of electrical stimulation to the brain as a primary or adjunctive modality of the "sleep cure" widely employed in psychiatry throughout the early part of the twentieth century.

In 1902, the French physiologist Stephen Leduc produced sleep in rabbits by the transcranial delivery of 35 volts, at 110 Hz. He attempted to extend his successes to himself with 100 Hz direct currents (DC) of 3–12 milliamperes (mA) of a 10% duration. While he remained conscious, he could not move or speak, and experienced blunted sensations of pain.

Using himself as a test subject, Leduc attached an electrode to his forehead and another electrode near the base of his spine. His sensations after administering a series of 50-volt pulses in the milliampere range were similar to "...a dream but I was conscious of the absence of power to move and an inability to communicate with my colleagues; I felt the contact, the pinches, striking of pins in my forearm, but the sensations were dulled."[11,12] Despite Leduc's reported success with electroanalgesia, these findings failed to arouse significant interest among clinical practitioners outside of the former Soviet Union and France.

In 1914, Louise Robinovitch distinguished between electrically induced sleep and analgesia, producing electric sleep in patients suffering from insomnia by applying a negative electrode to the forehead and a positive electrode to the hand. She reported that patients fell asleep within the 1 h treatment period and continued to sleep after the current was discontinued.[13]

The work of Gilyarovsky and associates in the former USSR were responsible for advancing the use of electrosleep in clinical settings during the decades of the Cold War. According to declassified government documents containing English translations of the authors' observations:

> In hospitals the procedure is performed in bed. The patient undresses and lies down as though for his night's sleep. Usually electric sleep is administered simultaneously to a group of patients in a separate half-darkened ward. Gradually the sensation of heaviness of the lids, ideas of 'going off' appear, sometimes a mild dizziness occurs, and a drowsy state supervenes, which gradually deepens to the degree of physiological sleep. The patient is in a calm relaxed position, usually on his side; the respiration becomes deeper, slower and more regular; the pulse slows up by several beats a minute.[14]

In its contemporary form, CES is a descendant of the aforementioned investigations. In the electroconvulsive shock paradigm, 120 volts at 60 Hz and 500 mA was applied in 0.2 s bursts. From this electroanesthesia was derived, which used a reduced current level of 2 volts at 700 Hz and 30 mA given for the duration of major surgery. A final derivation to electrosleep was produced by 700 Hz at 1 volt and 5 mA. Today's CES devices typically deliver a range from 0.5 to 15,000 Hz from a 9 volt or 1.5 volt AA or AAA battery source supplying from 50 microamperes (μA) to 4 mA.

CES COMES TO AMERICA

The attention of psychiatrists and experimental psychologists in the United States was heightened by clinical research conducted in Europe involving electrosleep that appeared in English language journals during the late 1960s.[15,16] Professional interest coupled with popular notions of "instant sleep" achieved through techno-wizardry prompted independent consultant and businessman, Arsen Iwanovsky, to market a device he named the Electrosone 50, as America's first portable, battery-operated cranioelectrical sleep generator around 1973.[17] Prior to the device's debut, Iwanovsky published the basic circuit schematics of the unit for the benefit of biomedical researchers and experimenters.[18]

According to promotional materials that accompanied the device,[19] the Electrosone 50 was used for "Assisting in the fields of relaxation and sleep... [A] very weak, pulsating electrical current produced and controlled in this instrument passes through the patient's brain by means of four electrodes: two are placed on the closed eyelids and in the back of the neck (occipital area)." The sleek and compact Electrosone represented a considerable improvement over the bulkiness of Gilyarovsky's original design due to the unit's dependence on vacuum tube technology from the 1950s.[20]

When CES was first utilized in the USA, psychopharmaceutical treatments were less well known than they are today so intense interest was generated by the possibilities that this new method offered for treating difficult psychiatric cases. Studies were conducted in university laboratories to identify the mechanisms of action that putatively were responsible for the clinical responses beginning to be observed. More devices came on the market with names such as Anesthelec, Diastim, Electrodorn, Electroson, Neurometer, Neurotone, Neurotransmitter Modulator, RelaxPak, and Somlec, among others.[15]

The clinical intent was that electrosleep treatment should induce sleep immediately when the current was applied to the patient's head, and that the patient should remain asleep naturally, once the sleep was induced. That did not occur, however, even though many of the earliest clinical studies in the USA focused on discovering the waveform that would successfully induce sleep.[17] Researchers used a variety of frequencies, current levels, and waveforms as well as electrode configurations. Unfortunately, not all reports of CES use included descriptions of the waveform used, and these varied widely. Older devices utilized frequencies ranging from 100 to 4000 hertz (Hz) and current intensity up to 8 milliamperes (mA), while more recent devices utilize frequencies as low as 0.5 Hz and current intensity as low as 100 microamperes (μA).[15] Of course, all these variables meant that the results from different CES devices varied as well, and this remains true with the devices commercially available today.

The evolution of electrode placements was particularly notable. As the treatment arrived in the U.S. from Europe, devices such as the Electrosone used saline saturated gauze pads wrapped around metal plates placed over each closed eyelid connected to electrodes placed over the mastoids. At the time it was thought that the eyes were the best, if not the only, place where electricity could enter the brain. Later, because of the discomfort from the pressure on the eyelids and the side effect of blurred vision lasting approximately 15–45 min immediately following treatment, researchers began to place the frontal electrodes just above each eyebrow while the rear electrodes remained over the mastoids. Subsequently, the frontal electrodes were no longer used, with electrodes only placed on the mastoid processes just behind each ear, so that the current went laterally across the head instead of anterior-posteriorly. This caused vertigo; therefore, the electrodes were next moved to the temples. The typical electrode placement used today employs ear clip electrodes clipped to each ear lobe, although some devices still direct the current across the temples.[15]

EARLY ELECTROENCEPHALOGRAPHY RESEARCH AND THE SUBSEQUENT EXPANSION INTO THE TREATMENT OF MOOD DISORDERS

When a treatment strategy that would reliably induce sleep could not be found, electroencephalography (EEG) studies were initiated to examine the possible neurophysiologic events that occurred when current was applied across the head. The first study was designed to see if there were any changes in the EEG relevant to sleep. The findings were inconclusive as some patients slept when in the treatment condition, some slept in the control condition, while others never slept during any phase of the study.[20]

Another EEG study found that one 30 min electrosleep treatment per day for 5 days produced slower EEG frequencies with increased amplitude in the fronto-temporal areas in all of the patients. Most patients also showed increased quality and quantity of the EEG alpha rhythm with increased amplitude in the occipital-parietal leads.[21]

Weiss conducted an early EEG study in a sleep laboratory, in which patients who had been diagnosed with insomnia were allowed to sleep in their usual way in the university laboratory while having their EEG monitored. Five patients were given subsensory electrosleep treatments 30 min daily for 10 days, and five were given sham treatments. Subsequent monitoring of their EEG sleep patterns showed that patients receiving actual treatment went to sleep faster, spent more time in stage IV sleep during the night, had fewer nocturnal awakenings, went back to sleep sooner when they did

awaken in the night, and reported significantly more restful and restorative sleep upon awakening the next morning than did the sham group.[22] All these changes were maintained at a 2-year follow-up.[23]

Soon thereafter, a growing number of researchers demonstrated that CES not only ensured sound, restful sleep for patients suffering from insomnia, but was an effective treatment for stress-related symptoms as well, as determined through the use of various psychological assessment scales of anxiety and depression (e.g., Hamilton Anxiety Scale, State/Trait Anxiety Inventory, Zung Depression Scale, Profile of Mood States, etc.). More importantly, it was confirmed that numerous psychophysiologic measures, including sleep patterns, improved regardless of whether the patient slept during the treatment or not.[11,20]

As a result, the term "electrosleep" was dropped in the USA although it remains in use in parts of Europe. Instead, American researchers called it by several names, including "transcranial electrostimulation." In 1978, the Neurology Panel of the Food and Drug Administration (FDA) suggested that it be called "cranial electrotherapy." The FDA agreed, but added the word "stimulation" to the phrase, as they were not yet convinced that it was therapeutic. The FDA also determined that CES would be only available by prescription, making the USA the only country in the world in which an order from a licensed health care practitioner must be obtained for its use, a restriction continued through today.

CES now has a foundation of more than 50 years of research and clinical use in the USA from which proof of safety and effectiveness have been well established for the nonbiased reviewer.

Nasrallah commented on psychiatry's future, predicting that "neurostimulation for brain repair" was one of the top six trends in clinical practice.[24] He cited repetitive transcranial magnetic stimulation (rTMS), vagal nerve stimulation (VNS) and deep brain stimulation (DBS), all of which are invasive and costly medical procedures. CES is also neurostimulation for brain repair and in contrast is a more cost-effective, noninvasive type of device that can be safely used by patients at home. It can be used as an adjunct to medication or psychotherapy or as a stand-alone treatment. The only contraindications to CES are pregnancy and having a pacemaker or other implanted electrical device, and even those are dubious.

The FDA recognizes CES devices for the treatment of anxiety, insomnia and depression.[25] Off-label use in chronic pain is increasing, particularly in the treatment of such difficult management problems as fibromyalgia and spinal cord injuries in war veterans where double-blind studies with significant outcomes have been conducted and replicated.[26–28] There is also increased interest in its use in the treatment of cognitive dysfunctions, such as attention deficit disorder (ADD).[29] Future research on central nervous system mechanisms of CES may well demonstrate its potential utility in a widespread range of neurological and psychological disorders. What is currently known, however, is that CES has been proven to be a safe, efficacious, and inexpensive intervention for a wide variety of disorders of the nervous system.

MECHANISMS OF ACTION

The mechanisms of action of CES have not been clearly identified; however, several mechanisms have been postulated. Most commonly, CES is thought to be derived from a direct mode of action, and thus, under the current paradigm of thought, CES has been described largely from a neurobiological standpoint regarding its effect on electrical brain activity, neurotransmitters, and hormones.

Animal studies indicated that CES might have one of two possible effects: postsynaptic hyperpolarization or alterations in neurotransmitters. In either case, early research revealed a resultant increase in the degree of inhibitory processes resulting in analgesia and sleep.[30,31] Subsequent research in CES focused on the changes in neurotransmitter concentrations. In an early study, psychiatric patients and controls that received 5 days of CES showed increased urinary free catecholamines but no change in 17-ketosteroids.[32] Normal and depressed subjects receiving CES had increased blood concentrations of serotonin and cholinesterase after one 20 min session and following 2 weeks of daily 20 min sessions.[33] Additionally, substance abuse subjects receiving 30 min sessions of CES for 4 weeks had increased blood concentrations of monoamine oxidase-B and gamma amino butyric acid (GABA) that also corresponded with an improvement in symptoms in contrast to the control group. However, no changes were noted in concentrations of serotonin, dopamine, or beta-endorphin in that study.[34]

A small study of volunteers revealed an increase in cerebral spinal fluid concentrations of serotonin and beta-endorphin following 20 min of CES. The average increase for beta-endorphin was 50% from baseline although one subject had a 219% increase.[35] These data should be viewed with caution as the small sample size included executives of a CES manufacturer. However, those possible chemical changes are consistent with clinical findings suggesting that increased neurotransmitter concentrations may be involved in the sedative effects of CES with regard to GABA and beta-endorphins at the GABA and mu opioid receptor sites.[36] Because GABA serves as a major inhibitory neurotransmitter, increased concentrations of GABA may result in anxiolysis. Likewise, sedation is one result of mu opioid receptor stimulation. Several studies report decreased opioid requirements and increased potency of nitrous oxide in surgical patients receiving CES for which increases in beta-endorphin were postulated as the likely mechanism.[37–39] Patients experiencing anxiety from alcohol withdrawal were found to have a concentration of beta-endorphin that was inversely correlated to anxiety.[40]

In a series of five canine studies, Pozos and his group at the University of Tennessee Medical Center examined the effects of CES on central neurotransmitters.[41] Characteristically, most neurons regulate the production, intracellular transport and release of neurotransmitters through a multi-component feedback system. This maintains a relative equilibrium of neurotransmitters produced, released, and reuptake into the presynaptic cell, postsynaptic action. The amount of

neurotransmitter released and available within a synapse also affects the activity and chemistry of proximate neurons in the local environment. As a variety of drugs can affect these mechanisms, they can also be used as research tools that alter brain chemistry and thus behaviors and other psychiatric effects.

Pozos' group increased the amount of dopamine in the brains of experimental dogs by administering the drug reserpine, which induces a robust release of dopamine throughout the brain. Dopamine controls a variety of behaviors, most notably movement and emotional status. Pozos' reserpine-treated dogs developed mild movement abnormalities (e.g., tremor) as a result of dopamine depletion and loss of neural circuits in the motor areas in the brain that are stimulated by the neurotransmitter acetylcholine. The decreased dopamine in the reserpine-treated dogs led to an imbalance of acetylcholine-induced motor stimulation. Interestingly, CES produced the same effect as reserpine, so it was hypothesized that electrical stimulation of the brain was capable of altering the release of neurotransmitters.

To examine further the role of CES on neurotransmitter systems, the researchers discontinued the administration of all drugs and let half of the dogs rest with their usual allotment of food and water. They found that these animals returned to an apparently normal state within 3–5 days. Another group had the drugs discontinued but were given CES treatment. The theory was that if CES stimulated the down-regulated dopamine system, the animals would return to normal more quickly. The dogs given CES returned to normal within 3–7 h, which was comparable to recovery seen following the administration of the dopamine precursor L-dopa. This suggests that CES appears to stimulate the dopamine system, although it is not known if this effect is direct or indirect.

Pozos also studied the biochemical effects of ECT and found them to be similar to CES. He surmised that treatment with CES would accomplish the same effects as ECT, but over the course of several weeks instead of milliseconds. Conversely, none of the negative side effects from ECT should be encountered in the process.

In an attempt to determine a possible cellular mechanism of CES, Siegesmund and his coworkers examined whether electrical stimulation affected the quantity or quality of neurotransmitter release.[42] Neurotransmitters are stored in vesicles, packets of chemicals that upon stimulation are released into synaptic space to exert an action. Sigismund's group found that electrical stimulation of the brain tended to force the pre-synaptic vesicles present to release their contents into the synaptic space, while at the same time causing the development of many more pre-synaptic vesicles. Once the stimulus was terminated, the system tended to return toward normal.

Taken together, these findings strongly suggest that CES is capable of producing both neurotransmitter release and resynthesis, a process known as "turnover." The next step was to find a clinical connection to these studies.

Following Pozos' studies, a human double-blind study was conducted in which narcotic addicts were withdrawn from opiate use and given either alpha methyl dopa (a dopamine and norepinephrine reuptake blocker) or CES.[43] Heroin acts on endogenous opioid receptors in the brain, down-regulating the production of endorphin, and thus, disturbing norepinephrine production in the locus ceruleus. When heroin is discontinued sensitized opioid receptors on norepinephrine neurons evoke an uninhibited release of norepinephrine, which acts at adrenergic receptors of the central and peripheral nervous systems to produce characteristic withdrawal signs and symptoms.

In the study, half the patients received CES while the other half were given alpha methyl dopa to block the postsynaptic norepinephrine receptors. Those patients that had been treated with the norepinephrine reuptake blocker did not show profound withdrawal effects but they all experienced rebound depression. In contrast, CES treatment resulted in patients becoming heroin abstinent without any withdrawal or depressive signs or symptoms. Many more studies were conducted on substance abuse populations and then mood disorders became the focus of modern research.[15]

MORE ELECTROENCEPHALOGRAPHIC STUDIES

About 20 EEG studies have appeared in the CES literature beginning shortly after CES achieved popularity in Eastern Europe during the late early 1960s. Using enhanced EEG technology, U.S. researchers continue this type of investigation to this day.

Research to date has shown that CES treatment evokes a change in the EEG pattern of every person to whom it is applied. CES induces significant changes in the EEG as shown in the brain map in Figure 19.1. It increases alpha (8–12 Hz) relative power, and decreases relative power in the delta (0–3.5 Hz) and beta (12.5–30 Hz) frequencies.[44] Increased alpha correlates with improved relaxation and increased mental alertness or clarity. Decreased delta waves indicate a reduction in fatigue. Beta wave reductions from 20–30 Hz correlate with decreases in anxiety, ruminative thoughts, and obsessive/compulsive-like behaviors.

Low resolution electromagnetic tomography (LORETA) and functional magnetic resonance imaging (fMRI) studies showed that CES reached all cortical and subcortical areas of the brain, producing changes similar to those induced by anxiolytic medications.[45,46] Many symptoms seen in psychiatric conditions, such as anxiety, insomnia, and attention deficit disorders are thought to be exacerbated by excess cortical activation.[47,48] An fMRI study in an anxiety population showed that CES causes cortical brain deactivation in the midline frontal and parietal regions of the brain after just one 20 min treatment.[45] Another fMRI study was conducted as part of a randomly controlled double-blind trial (RCT) in a pain population that revealed greater decreases in average pain levels ($p = 0.023$) than those using a sham device or receiving usual care without CES.[49] The active CES device was shown to decrease activation of pain processing regions of the brain, such as the cingulate gyrus, insula and prefrontal cortex, compared to the sham device.

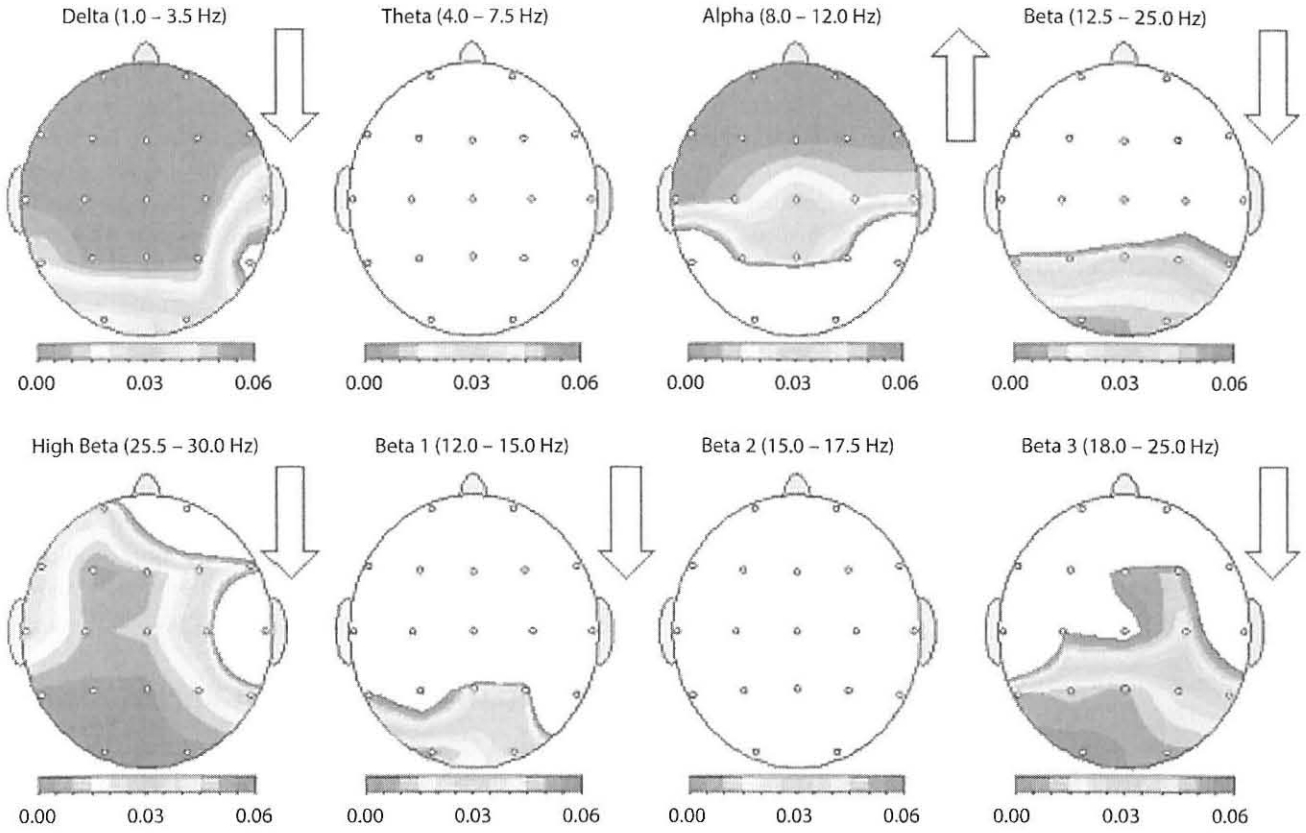

FIGURE 19.1 (See color insert.) Relative power p-value topographical map for 0.5 Hz cranial electrotherapy stimulation (CES). Statistically significant changes ($p < 0.05$ or better) after a single 0.5 Hz CES session are indicated by color; white indicates no significant change. The arrows indicate the direction of change. Statistically significant decreases were seen in delta and beta with statistically significant increases in alpha.

The above mechanisms provide evidence that CES changes the brain in a way that reduces anxiety, depression, and pain. It also helps people fall asleep by inducing relaxation while decreasing compulsive thoughts.

THE CLINICAL ROLE OF CES

CES may be seen, then, not as a treatment for a specific disorder, but as a bioelectrical intervention that acts through mechanisms known to be consistent with the functions of various physiological functions and the effects of drugs that are frequently prescribed for the same indications.

While the exact mechanism of CES remains unclear, the same is true for pharmacological interventions used to treat mood disorders, and it seems likely that both have similar effects on neurotransmitters or other relevant mechanisms.

Most practitioners in the fast growing fields of complementary, integrative, and alternative medicine assume that the body will heal itself if it has the necessary building blocks (e.g., proper nutrition and sufficient exercise). Reparative processes require energy from ATP, which is produced by oxidative phosphorylation in the electron transport chain. It seems plausible that an electrical boost, whether it be from electroacupuncture, electrical or electromagnetic stimulation from CES, may also fuel or enhance this process. Conscious direction, intentionality, or mindfulness shown to alter EEG patterns could provide similar benefits to restore normal function when homeostasis is threatened.

There are individuals without any obvious significant physical, mental, or emotional problems but many are not functioning or performing optimally. In addition, the numerous psychosocial pressures of modern life place an increasing allostatic load that can contribute to a variety of stress related complaints and disorders. CES may help to prevent, lessen, or alleviate these in an extremely safe and very cost effective fashion.

CLINICAL STUDIES

At present, there is a wealth of data on CES from over 50 years of research. As with the chemical composition of drugs, each CES device has a different waveform so clinicians should not generalize the research to a generic category of CES as results from the various technologies differ widely. In the 1970s when CES was new to the U.S., most of the research was done with the Neurotone device, which used 100 Hz in a 20% duty cycle with a maximum current level of 1.5 milliamperes. The research methodology used

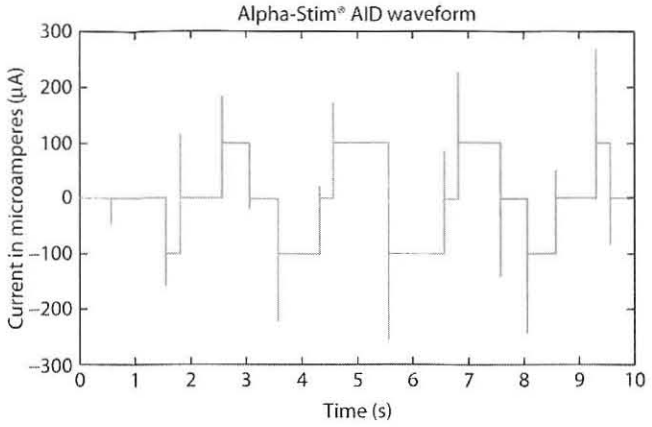

FIGURE 19.2 The Alpha-Stim waveform shown over a 10 s period.

was consistent with the standards of the day, but fall well below modern standards. Depending on the device, the quality of the research protocol, including the blinding method, in those early studies exhibited mixed results.[15] While there are copies of the Neurotone waveform sold under the brand names of CES Ultra and HealthPax, several other private labeled versions of these that are still on the market are produced by small companies with no research studies to support their claims.

Most recent CES studies use reliable and valid outcome measurement scales. The majority of these have been conducted with the Alpha-Stim CES device, which has been progressively refined over the past three decades. It uses a complex and patented bipolar asymmetric waveform consisting of multiple frequencies at a 50% duty cycle having a variable pulse width with a maximum duration of 0.5 Hz (2 s) provided over a 10 s time frame with random factors to avoid habituation by the nervous system. The maximum current level of the device is 600 microamperes. The impedance range within which the waveform parameters remain valid is from 100 Ω to 10 KΩ. The waveform is balanced to achieve 0 net current in either direction as shown in Figure 19.2.

Randomly controlled double-blind trials of CES can be accomplished today in the same manner used to evaluate pharmaceuticals. As dosage can be portrayed as current indirectly proportional to time, double-blinding is achieved by reducing the current to a subsensory 100 microamperes while increasing the usual 20 min treatment time to a full hour. The following is a summary of this modern level of RCT studies, open clinical trials, and scientifically conducted surveys.

SUMMARY OF THREE SURVEYS (N = 5917)

Peer-reviewed outcomes conducted on the Alpha-Stim brand of CES for FDA from 2500 patient surveys published in 2001 correlated well with 47 physicians' reports on 500 patients. This data revealed that a significant effect of at least 25% improvement was reported by nine out of ten in a group of 3000 patients.[15,50] In another survey of 152 Service Members and veterans conducted for FDA in 2011 the outcomes, while still significant, were not quite as robust as prior surveys of civilians.[51] However, a third survey conducted in 2013 of 2861 Service Members, veterans, and civilians was closer to the original survey of civilians. This confirms the observation that Service Members and veterans who use CES most likely suffer from more extreme trauma, and, therefore, experience slightly less efficacy than a civilian-only cohort. Nevertheless, the results remain significant (≥50%) and they should be considered as clinically relevant. Figure 19.3 provides a detailed summary of all three of the post marketing surveys conducted for FDA totaling nearly 6000 Service Members, veteran, and civilian self-reports.

MODERN RESEARCH

As CES has been cleared by the FDA for the treatment of anxiety, insomnia, and depression since 1978, it is used primarily for these indications. As a result, there are numerous supportive studies and publications but only recent ones that comply with the more rigid current standards will be described in this section.

ANXIETY DISORDERS

Anxiety disorders are characterized by anticipation of a future threat, excessive fear, and related behavioral disturbances. Fear is associated with the stress response, or surges of sympathetic arousal seen in fight or flight responses, thoughts of immediate danger, and escape behaviors. Anxiety is also often associated with increased muscle tension and vigilance in preparation for future danger along with cautious or avoidant behaviors. Anxiety patients typically overestimate the danger in situations they fear or avoid. Anxiety is about twice as prevalent in women.[52]

The key features of general anxiety disorder or GAD are persistent and excessive anxiety and worry, which impairs work or school performance that the individual finds difficult to control. In addition, affected patients experience physical symptoms, including restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbances.[52]

Anxiety disorders affect 40 million American adults aged 18 and older, or about 18.1% of the population. Anxiety disorders frequently co-occur with depressive disorders or substance abuse and most people who are diagnosed with one type of anxiety disorder often develop others.[53]

Table 19.1 lists nine randomized controlled trials (RCT), eight of which are double-blind and one that is investigator-blind with summaries of the research outcomes based on the measurement scales used. Table 19.2 shows four open-label studies and four user surveys investigating the efficacy or treating anxiety with CES. Table 19.3 summarizes the findings of two meta-analyses of CES studies of anxiety. The

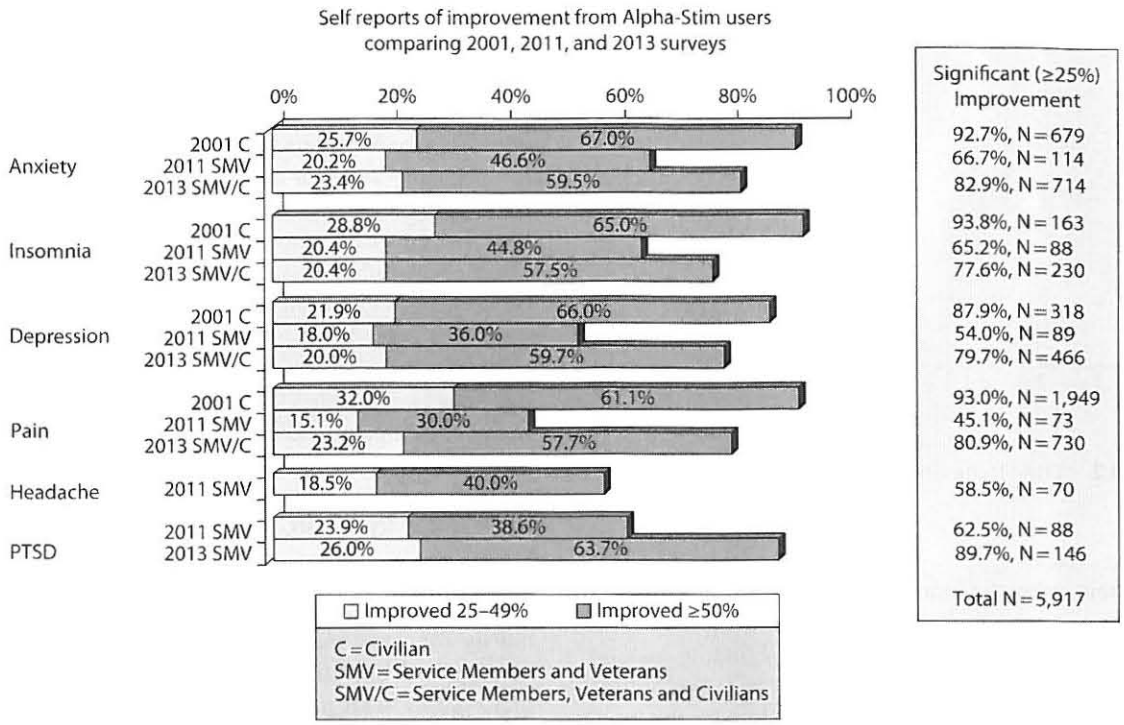

FIGURE 19.3 Summary of three surveys of cranial electrotherapy stimulation users (n = 5917).

TABLE 19.1
Cranial Electrotherapy Stimulation (CES) Randomized Controlled Study (RCT) Anxiety Studies

Principal Investigator	Total n	Subjects	Study Type	Measurement Scales/Outcomes
Barclay et al.[54]	115	Anxiety Patients	RCT, DB	Hamilton Anxiety Rating Scale (HAM-A): In the active treatment group, 83% had a decrease of ≥50% in scores from baseline to endpoint on the HAM-A ($p < 0.001$). There was a significant difference between groups ($p < 0.001$, $d = 0.94$) from baseline to endpoint of study. The mean decrease on the HAM-A in the treatment group of 32.8% (19.89 to 13.37) was more than three (3) times the mean decrease on the HAM-A for the sham group of 9.1% (21.98 to 19.98) from baseline to endpoint of the study.
Lee[55]	50	Preoperative Patients	RCT	Likert Anxiety Scale: CES group had significantly lower scores from baseline on Likert anxiety scale that the control group, which got the usual care ($p = 0.016$). There was also reduction in withdrawal scores for patients during injections ($p = 0.049$).
Kim et al.[56]	60	Preoperative Patients	RCT, IB	Likert Anxiety Scale: CES group had significantly lower scores from baseline on Likert anxiety scale than control group at end point of study ($p < 0.05$, $d = -0.88$).
Strentzsch[57]	38	Chronically Mentally Ill Patients	RCT, DB	Spielberger State Trait Anxiety Inventory (STAI): CES group had significantly lower scores from baseline on SAI (indicating less state anxiety) than sham group at endpoint of study ($p = 0.02$, $d = -0.41$).
Chen et al. [58]	60	Children with Mixed Anxiety and Depressive Disorder (MAD)	RCT, IB	Zung Anxiety Scale (SAS): The ANOVA showed that on SAS, the main effect between CES group and sham comparator group was significant ($F = 83.21$ $p < 0.01$). Changes in EEG of Occipital Lobes via brain electrical activity mapping (BEAM): on left and right $\alpha 1$ revealed the main effect of group was significant ($F = 5.98$, $p < 0.05$; $F = 6.39$, $p < 0.05$); on left and right $\alpha 2$, the main effect of group was also significant ($F = 7.54$, $p < 0.01$; $F = 6.72$, $p < 0.05$).
Cork et al. [27]	74	Fibromyalgia Patients	RCT, DB, OL	Profile of Mood States (POMS) for anxiety: CES group had significantly lower scores from baseline on POMS (indicating less anxiety) than sham group at end point of study ($p < 0.01$). Open label CES group had significantly lower scores on POMS at post-test from baseline scores ($p < 0.001$).

TABLE 19.1 (continued)
Cranial Electrotherapy Stimulation (CES) Randomized Controlled Study (RCT) Anxiety Studies

Principal Investigator	Total n	Subjects	Study Type	Measurement Scales/Outcomes
Lichtbroun[26]	60	Fibromyalgia Patients	RCT, DB, OL	Profile of Mood States Anxiety Subscale (POMS-A): CES group had significantly lower scores on POMS-A (indicating less anxiety) from baseline than sham group at end point of study ($p = 0.02$, $d = -0.60$). There was no significant difference in Open Label crossover group from pretest to post-test on POMS-A ($p > 0.05$).
Winick[59]	33	Dental Patients	RCT, DB	Visual Analog Scale (VAS), Inverse Likert Scale: CES group had significantly lower scores from baseline, indicating less anxiety, on the VAS ($p < 0.02$, $d = -0.61$) and higher scores on Likert Scale, indicating less anxiety ($p < 0.01$) than sham group at end point of study.
Voris[59]	105	Psychiatric Patients with Anxiety	RCT, DB	State Anxiety Inventory (SAI): CES group had significantly lower scores (indicating less anxiety) on SAI than the sham and control groups at end point of study ($p = 0.0001$, $d = -1.60$). CES group had significantly higher finger temperature scores ($p = 0.001$, $d = 0.50$) and significantly lower EMG scores ($p = 0.0001$, $d = -1.08$), indicating less anxiety, than sham CES and control groups.

IB: investigator blind; DB: double blind; OL: open label; n = 595 for anxiety RCT Studies.

TABLE 19.2
CES Open Label and Survey Anxiety Studies

Principal Investigator	Total n	Subjects	Study Type	Measurement Scales/Outcomes
Price[61]	146	Service Members and Veterans with PTSD	Survey	7-point Likert scale. Of the total group, 63.7% reported fewer PTSD symptoms and clinical improvement of ≥50% (improvement of substantial clinical importance category, Dworkin et al.[68]), while 26.0% reported clinical improvement of PTSD symptoms between 25% and 49% (improvement of moderate clinical importance). In the total group, 89.7% of respondents reported ≥25% fewer PTSD symptoms and clinical improvement with the majority of these respondents reporting ≥50% improvement in PTSD.
Price[61]	714	Civilians, Service Members and Veterans with anxiety	Survey	7-point Likert scale. Of the total group, 59.5% reported less anxiety and clinical improvement of ≥50% (improvement of substantial clinical importance category, Dworkin et al.[68]), while 23.4% reported clinical improvement of anxiety between 25% and 49% (improvement of moderate clinical importance). In the total group, 82.9% of respondents reported ≥25% less anxiety and clinical improvement with the majority of these respondents reporting ≥50% improvement.
Bracciano[62]	2	Veterans with PTSD	OL	Daily Symptom Severity Ratings—Treatment Log (0–10) decreased from a baseline mean of 6 to a post-test mean of 2 ($p < 0.05$, $d = 1.61$). PTSD Symptom Scale Interview (PSS-I) was reduced from 34 to 13 and 29 to 10 in the respective patients and re-experiencing decreased from 7 to 2 and 9 to 2. Avoidance decreased from 15 to 7 and 9 to 5, and Increased arousal decreased from 12 to 4 and 11 to 3.
Bystritsky[63]	12	General Anxiety Disorder Patients	OL	Hamilton Rating Scale for Anxiety (HAM-A), Four Dimensional Anxiety and Depression Scale (FDADS): Anxiety scores decreased significantly on HAM-A from baseline to endpoint of study ($p = 0.01$, $d = -1.52$). Anxiety scores were significantly lower on FDADS at end point of study from baseline ($p < 0.039$, $d = -0.75$).
Lu et al.[64]	32	Children with Emotional Disorders (Anxiety)	OL	Zung Anxiety Scale (SAS): From baseline of 58.30 ± 11.50 to post-test 45.91 ± 10.36 ($p > 0.01$); 13 cases had significant effect (41%), 17 cases had effect (53%), and the effect was invalid in two cases (6%); the total effective rate was 94%. Skin temperature rose ($p < 0.01$); systolic blood pressure dropped and the pulse slowed down after the treatment, and the differences were significant ($p < 0.05$). 26 cases followed up (81%), of which 24 cases had long lasting efficacy with relieved or eliminated symptoms, and 2 cases had relapse of symptom where drugs were needed to control their symptoms.
Overcash[65]	197	Anxiety Disorder Patients	OL	0–100 Numerical Rating Scale (NRS): Subjects rating of anxiety was significantly less from baseline to post-test ($p < 0.05$). Subjects' physiological measures of anxiety—EMG, EDR and Temp—changed significantly from baseline to post-test indicating less anxiety ($p < 0.05$).

(continued)

TABLE 19.2 (continued)
CES Open Label and Survey Anxiety Studies

Principal Investigator	Total n	Subjects	Study Type	Measurement Scales/Outcomes
Kirsch et al.[51]	202	Service Members and Veterans with anxiety (includes PTSD)	Survey	7-point Likert scale: Anxiety (n=114). Of the total group, 46.5% reported less anxiety and clinical improvement of ≥50% while 20.2% reported clinical improvement of anxiety between 25% and 49%. In the total group, 66.7% respondents reported ≥25% improvement in anxiety. In the CES only group (no medications), 57.7% reported decreased anxiety and clinical improvement of ≥50% while 15.4% reported clinical improvement of anxiety between 25% and 49%. In the total group, 66.7% respondents reported ≥25% improvement in anxiety. In the CES only group (no medications), 57.7% reported decreased anxiety and clinical improvement of ≥50% while 15.4% reported clinical improvement of anxiety between 25% and 49% for a total of 73.1% of respondents who reported less anxiety and clinical improvement ≥25%. In the CES and medications group, 43.2% of respondents reported decreased anxiety and clinical improvement ≥50% while 21.6% reported decreased anxiety 25%–49% improvement for a total of 64.8% of respondents who reported decreased anxiety and clinical improvement ≥25%. PTSD (n = 88). Of the total group, 38.6% reported less anxiety and clinical improvement of ≥50% while 23.9% reported clinical improvement of anxiety between 25% and 49%. In the total group, 62.5% respondents reported ≥25% improvement in anxiety. In the CES only group (no medications), 50.0% reported decreased anxiety and clinical improvement of ≥50% while 22.2% reported clinical improvement of anxiety between 25% and 49% for a total of 72.2% of respondents who reported less anxiety and clinical improvement ≥25%. In the CES and medications group, 35.7% of respondents reported decreased anxiety and clinical improvement ≥50% while 24.3% reported decreased anxiety 25%–49% improvement for a total of 60.0% of respondents who reported decreased anxiety and clinical improvement ≥25%.
Alpha-Stim User Survey, 1995–1998[15]	679	Patients with anxiety	Survey	4-point Likert Scale: Anxiety (alone), n = 128. Of this group, 67.19% reported less anxiety and clinical improvement of ≥50% after using Alpha-Stim, while 22.66% reported less anxiety and improvement between 25% and 49%. A total of 89.84% of these respondents reported ≥25% improvement in anxiety. Anxiety (with other condition), n = 370. Of this group, 68.11% reported less anxiety and clinical improvement of ≥50% after using Alpha-Stim, while 22.97% reported less anxiety and improvement between 25% and– 49%. A total of 91.08% of these respondents reported ≥25% improvement in anxiety. Anxiety (with depression), n = 58. Of this group, 62.07% reported less anxiety and clinical improvement of ≥50% after using Alpha-Stim, while 32.76% reported less anxiety and improvement between 25% and –49%. A total of 94.83% of these respondents reported ≥25% improvement in anxiety. Stress, N = 123. Of this group, 70.73% reported less anxiety and clinical improvement of ≥50% after using Alpha-Stim, while 24.39% reported less anxiety and improvement between 25% and –49%. A total of 95.12% of these respondents reported ≥25% improvement in anxiety.

OL: open label; PTSD: posttraumatic stress disorder; PSS-I: PTSD symptom scale interview; n = 1984 for anxiety open label and survey studies. Total n = 2579 for all CES anxiety studies.

total number of subjects (n) for all anxiety studies was 4819 with 595 from RCTs.

There are nine RCTs showing that CES has proven to be a safe and effective treatment for anxiety with effect sizes ranging from medium ($d = -0.41$) to very large ($d = -1.60$).[57,60] Three of the studies looked at acute anxiety, such as preoperative anxiety ($p < 0.05$, $d = -0.88$), including anxiety prior to dental procedures ($p = 0.02$, $p = -0.61$). Another that monitored changes in EEG mapping revealed significant changes due to CES on the left and right side of the brain in the $\alpha 1$ and $\alpha 2$ regions.[56,58,59]

There have been two surveys and one open label case series to evaluate the effects of treating posttraumatic stress disorder (PTSD) with CES. The case series lasted for 4 weeks and provided a very large effect size ($d = 1.61$) with statistical significance ($p < 0.05$).[62] Two patients reported a 38% and 34% reduction, respectively, in the PTSD Symptom Scale Interview. The case series results were further supported by the survey data that showed 64% and 39% of respondents reporting clinical improvement of ≥50%.[61] When looking at clinical improvement, the highest category is "substantial clinical importance" which is defined as ≥50%.[68]

TABLE 19.3
Meta-Analyses of CES Studies of Anxiety

Principal Investigator	Total n	Subjects	Study Type	Findings
Kirsch and Gilula[66]	2049	41 studies examined the effect of CES on anxiety	Meta-analysis	The analysis of reordered data on the effect of CES on anxiety yielded an effect size of r = 0.57; a large effect size is ≥0.50.[99] Analysis of the studies that used only a double-bind method produced an effect size for CES on anxiety of r = 0.53. Studies that used extraneous measures of anxiety were removed and only studies for state or trait anxiety that used the Spielberger State/Trait Inventory were analyzed. The effect of CES on state anxiety was r = 0.60 and trait anxiety was r = 0.68. When the results of analysis was corrected for the number of subjects in each study, state anxiety was r = 0.59 and trait anxiety was r = 0.60. The effect sizes for the 41 studies in this meta-analysis ranged from high 50s to low 60s.
Klawansky et al.[67]	241	8 RCT, DB, CES studies that examined the effect of CES on anxiety	Meta-analysis	The pooled result for the eight studies, including 241 subjects, analyzing the effect of CES treatment on anxiety was in favor of CES over sham at a statistically significant level (effect size estimate r = −0.5883, $p < 0.05$). When three studies were dropped because they provided no convincing sensation to their sham protocol, the result in favor of CES remained significant.

The three anxiety specific surveys reported substantial clinical importance in 47%, 60%, and 67% of respondents, as shown in Figure 19.3. In the two anxiety meta-analyses, one combining the results of 41 anxiety studies and the other using eight selected RCTs, both confirmed the effectiveness of CES in treating anxiety with consistently large effect sizes ($d = 0.57$, $d = 0.59$).[66,67]

DEPRESSIVE DISORDERS

The common feature of all depressive disorders is the presence of sad, empty, or irritable mood accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function. Major depressive disorder represents the classic condition in this group of disorders since it requires clear-cut changes in affect, cognition, and neurovegetative functions. Diagnostic criteria include five or more of the following symptoms present in a 2-week period with at least one being either depressed mood or loss of interest or pleasure.[52]

- Depressed mood
- Diminished interest
- Significant weight loss
- Insomnia or hypersomnia
- Psychomotor agitation
- Fatigue
- Feelings of worthlessness
- Diminished ability to think or concentrate
- Recurrent thoughts of death

The above symptoms must cause distress in normal social, occupational, or other important areas of functioning.

Major depressive disorder is the leading cause of disability in the U.S. for ages 15–44, affecting approximately 14.8 million American adults or about 6.7% of the population in a given year. The mean age at onset for depressive disorders is 32 and these are seen more frequently in women than men.[53]

Table 19.4 includes eight human studies investigating the effects of CES for the treatment of depression. The table includes three RCTs (two double-blind), two open label trials, and three user surveys. In addition, there is a meta-analysis of 20 CES studies of depression summarized in Table 19.5. The total n for the eight studies was 1113 with 196 from RCTs.

The three RCTs showed significantly decreased depression scores ($p < 0.001$, $p < 0.01$, and $p < 0.01$) using three different scales to measure depression (HAM-D17, Beck Depression Inventory and Zung Depression Scale).[54,58,69]

The two open label trials showed significant improvements as well, with one study reporting a medium effect size ($d = -0.41$) and the other a total effective rate of 94%.[63,64] Upon follow-up of 26 cases, 24 had long lasting efficacy of relieved or eliminated symptoms. Lu also measured physiological changes during and after treatment with significant changes seen in skin temperature, systolic blood pressure and pulse ($p < 0.05$).[64]

The three separate user surveys reached substantial clinical importance in 66%, 58%, and 36% of depression patients, with the lowest score reported by Service Members and veterans. The meta-analysis for depression included 937 patients across 20 separate studies and reported a large effect size of 0.050 (Table 19.5).[70]

In a double-blind RCT, 82% of the active treatment group reported ≥50% reduction in depression scores. These active treatment group results were 12 times higher than the sham treatment group. There was some initial transient improvement in the anxiety scores among the sham group but no change in their depression scores.[54]

INSOMNIA

Insomnia is considered a sleep-wake disorder. Its diagnostic criteria is a predominant complaint of dissatisfaction with

TABLE 19.4
Cranial Electrotherapy Stimulation (CES) Depression Studies

Principal Investigator	n	Subjects	Study Type	Measurement Scales/Outcomes
Barclay et al.[64]	115	Anxiety Patients	RCT, DB	Hamilton Depression Rating Scale17 (HAM-D17): In the active treatment group, 82% had a decrease of ≥50% in scores from baseline to endpoint on the HAM-D ($p < 0.001$). There was a significant difference between groups ($p < 0.001$, $d = 0.78$) on the HAM-D17 from baseline to endpoint of study. The mean decrease on the HAM-D17 in the treatment group of 32.9% (9.64 to 6.47) was more than twelve (12) times the mean decrease on the HAM-D17 for the sham group of 2.6% (10.22–9.96) from baseline to endpoint of study.
Price[61]	466	Civilians, Service Members and Veterans with depression	Survey	7-point Likert scale. Of the total group, 59.7% reported less depression and clinical improvement of ≥50% (improvement of substantial clinical importance category, Dworkin et al.[68]), while 20.0% reported clinical improvement of depression between 25% and 49% (improvement of moderate clinical importance). In the total group, 79.7% of respondents reported ≥25% less depression and clinical improvement with the majority of these respondents reporting ≥50% improvement in depression.
Kirsch et al.[51]	89	Service Members and Veterans with Depression	Survey	7-point Likert scale: 36% of the total group reported decreased depression and clinical improvement of ≥50% while 18% reported clinical improvement of depression between 25% and 49%. 54.0% of the total group reported ≥25% improvement in depression. In the CES only group (no medications), 38.5% reported decreased depression and clinical improvement of ≥50% while 23.1% reported clinical improvement of depression between 25% and 49% for a total of 61.6% of respondents who reported decreased depression and clinical improvement ≥25%. In the CES and medications group, 35.5% of respondents reported decreased depression and clinical improvement ≥50% while 17.1% reported decreased depression between 25% and 49% improvement for a total of 52.6% of respondents who reported decreased depression and clinical improvement ≥25%.
Mellon[69]	21	Depressed Jail Security and Patrol Officers	RCT, DB	Beck Depression Inventory (BDI), Brief Symptom Inventory Depression Subscale (BSI-D): The CES group had significantly less depression from baseline than sham group at end point of study on BDI ($p < 0.01$) and on BSI-D ($p < 0.05$).
Bystritsky et al.[63]	12	Generalized Anxiety Disorder Patients with Depression	OL	Hamilton Depression Scale 17. Depression scores were significantly less on HAM-D_{17} at end point of study from baseline ($p = 0.01$, $d = -0.41$).
Chen et al.[58]	60	Children with Mixed Anxiety Depressive Disorder (MAD)	RCT, IB	Zung Depression Scale (SDS): The ANOVA showed that on SDS, the main effect between CES group and sham comparator group was significant ($F = 36.56$, $p < 0.01$).
Lu et al.[64]	32	Children with Emotional Disorders (Depression)	OL	Zung Depression Scale (SDS): From baseline of 0.64 ± 0.08 to post-test 0.52 ± 0.10 ($p > 0.01$); 13 cases had significant effect (41%), 17 cases had effect (53%), and the effect was invalid in two cases (6%); the total effective rate was 94%. Skin temperature rose ($p < 0.01$); systolic blood pressure dropped and the pulse slowed down after the treatment, and the differences were significant ($p < 0.05$). 26 cases followed up (81%), of which 24 cases had long lasting efficacy with relieved or eliminated symptoms, and two cases had relapse of symptom where drugs were needed to control their symptoms.
Alpha-Stim User Survey, 1995–1998	318	Depressed Patients	Survey	Four point Likert Scale: Depression (alone), n = 53. Of this group, 66.04% reported less depression and clinical improvement of ≥50%, while 20.75% reported less depression and improvement between 25% and 49%. A total of 86.79% of these respondents reported ≥25% improvement in depression. Depression (with other condition), n = 265. Of this group, 66.03% reported less depression and clinical improvement of ≥50%, while 23.02% reported less depression and improvement between 25%and 49%. A total of 89.06% of these respondents reported ≥25% improvement in depression.

RCT: randomized controlled trial; DB: double blind; IB: investigator blind; OL: open label. Total n = 1113 for all CES depression studies.

TABLE 19.5
Meta-Analysis of CES Studies of Depression

Principal Investigator	Total n	Subjects	Study Type	Findings
Kirsch and Gilula[70]	937	20 Studies that included depressed patients and investigated the effectiveness of CES on depression	Meta-analysis	20 studies which included 937 patients with depression were analyzed to determine the effect of CES on depression and produced an effect size of r = 0.50 defined as a large effect size (p.115).[99] Note: A Cochrane Systematic Review by Moncrieff and colleagues (2004)[100] on the effect of antidepressants on depression that included nine studies involving 751 participants produced a pooled estimate of effect of r = 0.39 standard deviations (0.24 to 0.54) in favor of the antidepressant measured by improvement in mood. One study was then removed as it was a strongly positive trial. Sensitivity analysis after omitting this trial reduced the pooled effect to r = 0.17 (0.00 to 0.34).

sleep quantity, associated with one (or more) of the following symptoms:

- Difficulty initiating sleep
- Difficulty maintaining sleep
- Early-morning awakening with inability to return to sleep

Sleep disturbances cause clinically significant distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning. The sleep difficulty must occur at least three nights a week for at least 3 months despite adequate opportunity for sleep.[52]

A study done by the National Institutes of Health in 2005 estimated that approximately 10% of Americans suffer from insomnia.[53]

Tables 19.6–19.8 include six human studies and one equine study investigating the effects of CES for the treatment of insomnia. The tables include three RCTs (all double-blind), three user surveys, and a meta-analysis. The n for the six human studies totaled 654, with 163 from RCTs.

When comparing data from the three RCT studies, we have one small effect size ($d = -0.03$, $p = 0.001$) and one medium effect size ($d = 0.54$, $p = 0.02$).[72,26] The third RCT did not report effect sizes but did see significant improvement at day 1 ($p = 0.04$) and day 4 ($p = 0.03$) during the study. The study design called for 5 consecutive days of CES treatment in an attempt to improve sleep among active duty Service Members. After 5 days of treatment, the subjects in the active group saw an average of 43 more minutes of sleep per night compared to 19 min less sleep over those 5 days in the sham treated group.[71]

The three separate user surveys reached substantial clinical importance in 65%, 58%, and 45% of insomnia patients. The lower score of 45% is from a survey given to Service Members and veterans, which are typically a more difficult population to treat. The meta-analysis grouped the results from 20 insomnia studies, encompassing 1087 patients and reported a large effect size of 0.64.[66]

A RCT focusing on the sleeping habits of fibromyalgia patients showed significant clinical improvement during the rigid double-blind portion of the study, then even better results coming in the open label phase when patients were allowed to control the current, duration, and time of day the treatment took place.[26]

The Service Member and veteran survey divided the patients up into sub groups depending on medication use; 40.3% of patients using CES in combination with sleeping medications reported ≥50% improvement, while 65.2% of patients using CES *without* medications reported ≥50% improvement. This trend was consistent among each category that was studied (anxiety, PTSD, insomnia, depression, pain, and headache) as seen in Figure 19.9.[51]

PAIN

Chronic pain affects almost 100 million Americans with a total annual cost to health care ranging from $560 billion to $635 billion in 2010. Chronic pain also has the greatest economic impact due to disability days and lost wages and productivity.

An estimated 20% of American adults (42 million people) report that pain disrupts their sleep at least a few nights a week. Even with the options we have available for pain management now, more than half of all hospitalized patients experienced pain in the last days of their lives with 50%–75% of patients dying of cancer reporting moderate to severe pain.[74]

Table 19.9 includes seven double-blind RCTs, one open-label, and two user surveys investigating the efficacy of treating chronic pain with CES. The total n from this pain research is 1712 with 366 from double-blind RCTs.

The RCTs included patients suffering with fibromyalgia, Parkinson's, and spinal cord injuries. All reported effect sizes were measured as large with p-values ranging from $p = 0.03$ to $p < 0.001$. Most of the double-blind studies added an open-label arm at the end of the double-blind portion in sham treated subjects so that all participants had an opportunity to receive treatment. In each case, subjects in the open-label phase also achieved significant pain relief (see Table 19.9).

The results from two different surveys included substantial clinical importance (≥50% improvement) in patients with pain (30%), headaches (40%), reflex sympathetic dystrophy (53%), fibromyalgia (54%), and migraine headaches (57%).[15] As with

TABLE 19.6
Cranial Electrotherapy Stimulation (CES) Insomnia Studies

Principal Investigator	n	Subjects	Study Type	Measurement Scales/Outcomes
Price[61]	230	Civilians, Service Members and Veterans with insomnia	Survey	7-point Likert scale. Of the total group, 57.5% reported less insomnia and clinical improvement of ≥50% (improvement of substantial clinical importance category, Dworkin et al.[68]), while 20.4% reported clinical improvement of insomnia between 25% and 49% (improvement of moderate clinical importance). In the total group, 77.6% of respondents reported ≥25% less insomnia and clinical improvement with the majority of these respondents reporting ≥50% improvement in insomnia.
Lande and Gragnani[71]	57	Active Duty Service Members with Insomnia	RCT, DB	Pittsburg Insomnia Rating Scale: The active CES group had a longer total time slept (43 min) from baseline than the sham CES group who average 19 min less total time slept. The difference between the active CES and Sham CES groups approached significance ($p = 0.079$). A gender difference was noted. Men who completed five sessions of CES had significant improvement in total time slept after the first CES treatment ($p = 0.04$) and on day 4 ($p = 0.03$). Men in the active CES group slept an average of 53 min more total time slept after the first CES treatment and an average 61 min more total time slept on day 4 compared to the sham CES group. There were no significant changes in total time slept among the females in the study.
Taylor et al.[72]	46	Fibromyalgia Patients	RCT, DB	General Sleep Disturbance Scale (GSDS): CES group had significantly lower scores on GSDS (indicating less sleep disturbance) than sham from baseline at end point of study ($p = 0.001$, $d = -0.30$) and completed the study with scores below the range of insomnia.
Lichtbroun et al.[26]	60	Fibromyalgia Patients	RCT, DB, OL	0–10 Numerical Rating Scale (NRS): CES group had significantly higher scores on the quality of sleep outcome measure than the sham and control groups at end point of study ($p = 0.02$, $d = 0.54$).
Kirsch et al. [51]	98	Service Members and Veterans with Insomnia	Survey	7-point Likert scale: of the total group, 44.8% reported less insomnia and clinical improvement of ≥50% while 20.4% reported clinical improvement of insomnia between 25% and 49%. In the total group, 65.2% of respondents reported ≥25% improvement in insomnia. In the CES only group (no medications), 62% reported decreased insomnia and clinical improvement of ≥50% while 23.8% reported clinical improvement of insomnia between 25% and 49% for a total of 85.8% of respondents who reported less insomnia and clinical improvement ≥25%. In the CES and medications group, 40.3% of respondents reported decreased insomnia and clinical improvement ≥50% while 19.5% reported decreased insomnia 25%–49% improvement for a total of 59.8% of respondents who reported decreased insomnia and clinical improvement ≥25%.
Alpha-Stim User Survey, 1995–1998	163	Insomnia Patients	Survey	4-point Likert Scale: of this group, 65.03% reported less insomnia and clinical improvement of ≥50%, while 28.83% reported less insomnia and improvement between 25% and 49%. A total of 93.87% of these respondents reported ≥25% improvement in insomnia.

RCT: randomized controlled study; DB: double blind; OL: open label; n = 654 for all insomnia studies.

TABLE 19.7
Meta-Analysis of CES Studies of Insomnia

Principal Investigator	n	Subjects	Study Type	Measurement Scales/Findings
Kirsch and Gilula[66]	1087	20 Studies that examined the effect of CES on insomnia	Meta-analysis	Twenty (20) studies, which included 1087 patients, were analyzed to determine the effect of CES on insomnia produced an effect size of r = 0.64 defined as a large effect size (p.115).[99] Note: A meta-analysis by Huedo-Medina and colleagues (2012) on the effect of non-benzodiazepine hypnotics that included 13 studies involving 4378 subjects produced a "significant, but small to medium difference" on subjective sleep latency (−0.33) and polysomnographic sleep latency effect (−0.36) in favor of the treatment versus the control group.

TABLE 19.8
CES Study of Insomnia in Horses

Principal Investigator	n	Subjects	Study Type	Measurement Scales/Outcomes
Clarke et al.[73]	8	6 Horses, 1 Mare, and 5 Geldings	OL	The proportion of time spent standing dozing throughout the four trial phases was analyzed. In phase three, values are higher or equal to the values in phase one. A paired t-test comparing the mean values during these phases one and three suggests the difference is significant ($t = -2.44$, $p < 0.05$). In phase four, the same trend is seen with each horse's value higher ($n = 6$) or equal ($n = 2$) to that in phase one. A paired t-test confirms the significance of this difference ($t = -3.29$, $p < 0.05$). The proportion of time spent standing dozing across the phases was also found to have positive correlation with trial phase ($r = 0.220$, $p = 0.013$), time spent with lower lip relaxed ($r = 0.620$, $p < 0.001$), time spent with lower lip quivering ($r = 0.484$, $p < 0.001$), the time spent with the left ear back ($r = 0.265$, $p = 0.002$) time spent with the right ear back ($r = 0.268$, $p = 0.002$), and head wobbling ($r = 0.353$, $p < 0.001$). Time spent standing dozing across the trial phases was also found to have a negative correlation with time spent standing alert ($r = -0.945$, $p < 0.001$), time spent eating bedding ($r = -0.205$, $p = 0.05$), and time spent eating forage ($r = -0.331$, $p < 0.001$).

the anxiety, insomnia and depression surveys conducted with Service Members and Veterans achieved less pain relief.[51] This is believed to be the result of the type of injury and associated pain incurred by Service Members in theaters of war.

The most recent fibromyalgia RCT used functional MRI studies to determine the areas of the brain that are responsible for processing pain during a fibromyalgia flare-up. Once these key areas had been identified, patients using active CES and sham CES were examined, revealing that consistent with all other factors measured, only the active CES treatment group was experiencing less pain.[49] Heffernan was able to measure and identify EEG patterns of patients with pain and was then able to normalize the pattern exclusively with the use of the Alpha-Stim CES device, but not the other devices he tested.[78]

Unfortunately, the FDA is arbitrary and capricious in performing its duties in regulating medical devices. In fact, they have authorized the marketing of CES devices with no research at all by allowing them to use studies conducted on other devices with widely differing waveform characteristics

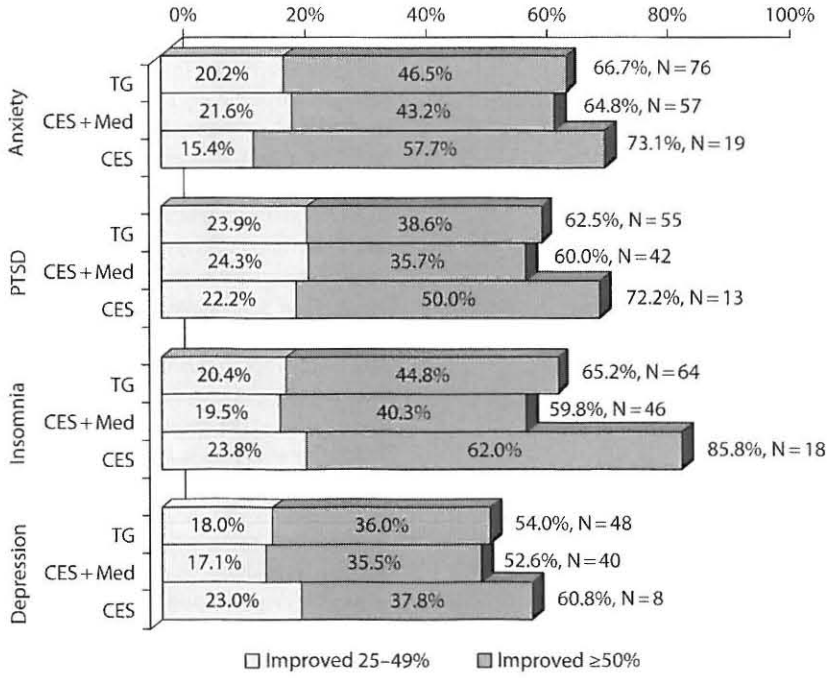

FIGURE 19.4 Service Member and Veteran survey comparing the use of cranial electrotherapy stimulation (CES) as a stand-alone treatment to CES with medications.

TABLE 19.9
Cranial Electrotherapy Stimulation (CES) Randomized Controlled Study (RCT), Surveys and Open-Label Studies of Pain

Principal Investigator	n	Subjects	Design	Measurement Scales/Outcomes
Taylor et al.[49]	46	Fibromyalgia Patients	RCT, DB	0–10 NRS: Those individuals using the active CES device had a significant decrease in average pain ($p = 0.023$) when compared to those individuals using the sham device or those receiving usual care alone over time.
Tan et al.[28]	105	Military, Spinal Cord Injury	RCT, DB, OL	0–10 NRS: Pain Intensity and Pain Interference Subscales of the BPI: The active CES group reported a significantly greater average decrease in pain pre to post daily treatments than the sham group ($p < 0.05$). The active CES group showed larger pre- to post-treatment decreases in pain interference than the sham group did ($p < 0.01$, $d = 0.59$). The active CES group had a significant mean pain intensity decrease of 0.60 points on the 0–10 scale ($p < 0.001$, $d = 0.73$).
Rintala et al.[75]	13	Veterans, Parkinson's Disease	RCT, DB	0–10 NRS: Subjects receiving active CES had, on average, a 1.14-point decrease in pain compared with a 0.23-point decrease for those receiving sham CES ($p = 0.028$).
Tan et al.[76]	38	Military, Spinal Cord Injury	RCT, DB, OL	0–10 NRS: Active CES group had significantly less pain intensity, pre to post CES session, compared to sham group ($p = 0.03$, $d = 0.76$). Active CES group reported significantly decreased pain interference ($p = 0.004$, $d = 0.50$), pre versus post intervention, while there was a nonsignificant decrease in pain interference in the sham CES group, (pre versus post-intervention. Open Label group had significantly less pain intensity from baseline to endpoint of study ($p = 0.03$).
Cork[27]	74	Fibromyalgia Patients	RCT, DB, OL	0–5 NRS: Active CES group had significantly less pain intensity compared to sham group at endpoint of study ($p < 0.01$). NRS, 0–10: Active CES group has lower tender point scores compared to sham group ($p = 0.01$). McGill: No significant difference in pain scores between Active CES and Sham groups. 0–5 NRS: Open Label group had significantly decrease pain from baseline to end point of study ($p < 0.001$). McGill: Open Label group had significantly decreased pain from baseline to end point of study ($p < 0.001$).
Lichtbroun[26]	60	Fibromyalgia Patients	RCT, DB, OL	0–10 NRS: The active CES group had significantly lower pain scores ($p = 0.002$, $d = -0.65$), lower tender point scores ($p = 0.01$, $d = 0.36$), higher quality of sleep scores ($p = 0.02$, $d = 0.45$), higher feelings of well-being scores ($p = 0.005$, $d = 0.73$), higher quality of life scores ($p = 0.03$, $d = 0.97$), lower fatigue scores ($p = 0.03$, $d = -0.72$) and lower anger scores ($p = 0.04$, $d = -0.60$) than the sham and control groups. The open label group had significant gains on tender point scores ($p < 0.001$) and decreased pain ($p < 0.005$) from baseline to endpoint of study. The active CES group and open clinical CES group had a 27% reduction in self-rated pain scores and a 28% decrease in tender point scores.
Alpha-Stim User Survey, 1995–1998[15]	678	RSD, Fibromyalgia and Migraine patients	Survey	5-point Likert Scale: Reflex Sympathetic Dystrophy (RSD), n = 55. Respondents reported improvement of pain as follows: 52.73% reported pain relief of ≥50%, 29.09% reported pain relief between 25% and 49%. A total of 81.82% of respondents reported pain relief as ≥25%. Fibromyalgia (alone), n = 142. Respondents reported improvement of pain as follows: 53.52% reported pain relief of ≥50%, 37.32% reported pain relief between 25% and 49%. A total of 90.85% of respondents reported pain relief as ≥25%. Fibromyalgia (with other condition), n = 363. Respondents reported improvement of pain as follows: 54.82% reported pain relief of ≥50%, 36.09% reported pain relief between 25% and 49%. A total of 90.91% of respondents reported pain relief as ≥25%. Migraine (n = 118), respondents reported improvement of pain as follows: 56.78% reported pain relief of ≥50%, 41.53% reported pain relief between 25% and 49%. A total of 98.31% of respondents reported pain relief as ≥25%.

TABLE 19.9 (continued)
Cranial Electrotherapy Stimulation (CES) Randomized Controlled Study (RCT), Surveys and Open-Label Studies of Pain

Principal Investigator	n	Subjects	Design	Measurement Scales/Outcomes
Kirsch et al.[51]	143	Pain Patients, Service Members and Veterans	Survey	7-point Likert scale: Pain (n = 73): 30% of the total group reported decreased pain and clinical improvement of ≥50% while 15.1% reported clinical improvement between 25% and 49%. A total of 45.1% of total group participants using CES reported ≥25% clinical improvement. In the CES only group (no medications), 61.6% of respondents reported decreased pain and clinical improvement ≥25% (46.2% ≥50%, 15.4% between 25% and 49% improvement) while 41.7% of the CES and medications group reported decrease pain and clinical improvement ≥25% (26.74% ≥50%, 15% between 25% and 49% improvement. Headache (n = 70): 40% of the total group reported decreased pain and clinical improvement of ≥50% while 18.6% reported clinical improvement between 25% and 49%. Of the total group, 58.6% of participants reported ≥25% clinical improvement. In the CES only group (no medications), 100% of respondents reported decreased pain and clinical improvement ≥25% (64.7% ≥ 50%, 35.3% between 25% and 49% improvement) while 45.3% of the CES and medications group reported decrease pain and clinical improvement ≥25% (32.1% ≥50% pain relief and 13.2% reported between 25% and 49% improvement.
Holubec[77]	525	Pain Patients	OL	1–10 NRS: 525 consecutive pain patients in a pain management clinic were administered 20 min of CES treatment. Of those, 261 were given a second treatment at their next visit, 160 were given three treatments, 57 were given four treatments, and 26 were given five treatments. The 79.81% who responded to the first treatment experienced a 42.40% reduction in self-rated pain, with 5.14% of the patients declaring they were pain free. Cumulative results were seen among those subsequently treated. There was a 70.64% reduction in pain after five treatments, including 15.38% of the remaining patients reporting no pain.
Heffernan[78]	30	Chronic Pain Patients	RCT, DB	5-point Likert Pain Scale: The active Alpha-Stim CES group's brain wave pattern changed from an uneven, jaw-tooth pattern consistent with pain to a smooth spectral pattern consistent with a pain-free pattern. The active CES group had significantly less pain as measured by the five point Likert pain scale than the Liss CES and control device groups ($p < 0.01$).

RCT: randomized control trial; DB: double blind; OL: open label; NRS: numerical rating scale; n = 366 for RCTs; n = 1346 OL and survey studies; total n = 1712 for all CES pain studies.

while also allowing spurious "CES devices" that never registered with FDA to be sold openly through magazine ads and websites. Conversely, FDA applies adverse events, however minor, equally to all CES devices that comply with the FDA definition, and limits what device manufacturers and distributors may say about effects from their legally marketed devices, even when such statements are accurate and truthful rather than misleading. These and other problems with the Center for Devices and Radiological Health (CDRH) approval process is discussed in Chapter 49.

OTHER POTENTIAL APPLICATIONS

Tinnitus

As indicated in the first edition of *Bioelectromagnetic Medicine*, various forms of cranial electrical stimulation have been used to treat tinnitus for over 200 years.[79]

Over the past decade, there has been increased interest and numerous advances in the use of this approach, not only with respect to rTMS but also vagal nerve stimulation.[80–83] Pulsed signal therapy (PST), widely used for the treatment of osteoarthritis in Europe, has also been found to be effective, and, although available in 20 other countries, it is only approved in the USA for veterinary use.[84]

At the Veterans Administration Medical Center in Cleveland, OH, USA, the use of Alpha-Stim technology to treat tinnitus was evaluated in a two arm experimental study.[85] The first arm consisted of seven males and three females from 23 to 69 years old (mean of 43 years) having tinnitus in a total of 18 ears. Otological and audiological evaluations revealed all subjects except one had varying degrees of sensory hearing loss. Between one and 17 treatments of 50 μA Alpha-Stim stimulation was given at 13 sites around the ear for 24 s to 2 min. The tinnitus was matched after each treatment with simulated sounds from a Norwest

SG-1 Tinnitus Synthesizer using an ascending procedure. Six of the ten subjects reported at least a 60% improvement in eight of the 18 ears, confirmed by tinnitus matching. Three additional subjects were undecided whether improvement had occurred. The permanence of improvement lasted from 8 h to 2 months (last contact with the experimenter).

In the second arm, 20 subjects were divided into two groups, an active and a control group, in a single blind protocol. All subjects were male, with either normal hearing or sensory hearing loss, most having idiopathic or noise exposure tinnitus. Each subject received a baseline audiological evaluation utilizing standard equipment referenced to ANSI standards of air conduction, speech reception threshold, most comfortable loudness level, speech discrimination (W-22 word lists), and when indicated, bone conduction, impedance battery, and tone decay. The treatment was identical to the first arm except the current was at 50 or 100 μA, and the stimulus duration was either 12 or 24 s at the 13 sites. After each treatment, the tinnitus was again analyzed using the same protocol. The control group had the identical procedure repeated twice, the first time without stimulation, followed by actual stimulation. Of 17 ears treated in the experimental group, only one subject (both ears) were perceived as not having improved by stimulation. Thus, nine of ten subjects (90%) corresponding to 15 of 17 ears (88%) reported improvement in their tinnitus. The decrease in tinnitus frequency for the subjective improvement ranged from 48% in one subject to complete remission (none) in the six ears combined for four subjects. One subject did not perceive a 19% decrease as being significant. In the control group of 15 ears, in only one ear did a subject believe there had been any change, and measurements indicated a 13% decrease in frequency. The range of change for the 15 ears was from +16 (after sham stimulation, frequency was measured as higher) to –22%. Once the control group had actual stimulation, 80% reported improvement in at least one ear. The measured decrease in tinnitus frequency ranged from 28% to complete remission (none) in four subjects.

Because both groups in the second arm had actual stimulation, the data was pooled. Overall improvement was 82% as reported by 20 subjects (27 of 33 ears). In ten cases, there was complete remission. In the remaining 17 ears, the range of frequency decrease was from 28% to 92%. The permanence of the improvement ranged from 20 min to at least 6 months (last contact with investigators). Most of the subjects had either one or two treatment sessions; however, one subject who had seven sessions found that each session tended to increase the duration of improvement and he concluded that he could live with his tinnitus after the seventh session and requested to be discharged from the program. Age, duration of tinnitus prior to stimulation, and frequency of the tinnitus did not appear to be a determinant to the success of treatment. Some subjects reported the current of 100 μA felt like "pin pricking" but were able to tolerate that level of current. Others could not tolerate greater than 50 μA because of marked sensitivity. There were no other adverse effects reported either during or immediately following CES stimulation.

A significant number of subjects reported improvement in hearing activity but this could not be verified by objective evaluation. The authors concluded that the 82% success rate in improvement in tinnitus implies a feasible treatment procedure in this often devastating disorder that can predispose to suicidality.

In another small pilot study of five patients treated with Alpha-Stim in a university-based neurotherapy clinic, tinnitus handicap and tinnitus severity, as well as EEG pre and post measures, were used for baseline and treatment outcomes. The researchers reported that 40% of the participants (those with unilateral tinnitus fluctuating in intensity) evidenced appreciable improvements in their tinnitus symptoms and that responsiveness to treatment in this subgroup may occur as early as the first treatment session.[86]

A cochlear implant that can be activated with "low rate electric stimulation" was attempted and appeared to be very effective for deaf patients with tinnitus but is presently contraindicated in others because of associated nerve damage.[87]

Cancer

Therabionic noninvasive low energy emission therapy (LEET), another form of cranial electrotherapy stimulation, has been found to be the most effective treatment for hepatocellular carcinoma and has shown promising results in certain metastatic malignancies. There are no adverse side effects, and the daily three 1 h sessions can be self-administered at home while the patient is reading or watching television.[88–91]

Novocure tumor treating fields (TTF) has been approved by the FDA for treating glioblastoma multiforme and clinical trials are in progress to extend this to lung cancer and metastatic brain lesions.[92] TTF therapy is delivered using noninvasive, insulated transducer arrays placed directly on the skin area surrounding the tumor in a manner that allows patients to maintain their normal daily activities while treating their disease. While it has been referred to as "24/7 CES," TTF therapy does not deliver any electric current to the tissue, stimulate nerves, or heat tissue. Rather, it creates an alternating electric field that interferes with mitosis and cell division within the tumor. The only side effects are occasional skin irritation at the transducer array sites.

Whether FDA cleared CES devices may have antitumor effects is not yet known, although anecdotal reports, such as one published in the form of a book by Margaret Waddington, MD, a retired neurologist with lymphatic leukemia, suggest this possibility. Her oncologist gave her a maximum 2-year prognosis if she refused chemotherapy. As this book goes to print it has been over 20 years since Dr. Waddington refused chemotherapy and relied on electrical therapy for her apoptosis treatment. Yet she is still able to live alone and continue having a productive life while running a 105-acre maple tree farm in Vermont.[93]

Preliminary studies also support the use of CES in cancer patients to reduce the sequelae of radiation therapy for

cancer. In one study, the authors concluded that the clinical impression at M.D. Anderson Cancer Center is that Alpha-Stim therapy is similar to hyperbaric oxygen and both of these modalities are achieving a degree of tissue repair and revascularization of the irradiated field. Although it is still unclear what is specifically occurring physiologically and histologically, the irradiated soft tissues appear to become revascularized. It is apparent that these modalities have relieved discomfort, enhanced healing of irradiated hard and soft tissues, and improved the quality of the irradiated soft tissues.[94]

A 61-year-old male veteran receiving 6000 rads of radiation therapy by a megavolt cobalt linear accelerator for T2N1M0 squamous cell carcinoma of the right tonsilar area at the Cleveland VA Medical Center was given a maximum of 30 min of Alpha-Stim therapy of 50–500 μA at 0.5 Hz, immediately following each radiation treatment. The following adverse reactions to radiation were expected: irreversible xerostomia because all the salivary glands were included in the radiation field, temporary dysgeusia, throat pain, possible mucositis, and radiation dermatitis. Following the CES treatments, all adverse reactions were reduced drastically and xerostomia and dysgeusia were eliminated. The patient required no regimen of pain medication because CES reduced the level of pain each day following radiation; he showed no signs of mucositis or radiation dermatitis at any time which is highly unusual as some degree of xerostomia and mucositis is anticipated in all such irradiated patients. The author added that several patients have been seen at the Cleveland VA Medical Center for Alpha-Stim treatment for postradiation dryness, with equally good results.[95]

ALZHEIMER'S DISEASE, PARKINSON'S DISEASE, AUTISM, PTSD

Transcranial magnetic stimulation uses a magnetic field to create electrical changes in the brain. As such, it can be considered an indirect form of CES. Brainsway's patented DEEP TMS technology differs from other transcranial magnetic stimulation approaches by using several Deep TMS coils (termed H coils) rather than a single focal stimulation. This is designed to stimulate deeper brain lesions without increasing the electrical field intensity of superficial cortical regions or excessively stimulating facial nerves. Typical treatment protocol consists of 15–20 sessions, each lasting 15–20 min, over a course of 3–4 weeks. DEEP TMS was approved by the FDA in 2013 for the treatment of major depressive disorder or in patients who did not respond to antidepressant drugs. In the European Economic Area, it also has CE marking for Alzheimer's disease, autism, bipolar disorder, chronic pain, Parkinson's disease, and PTSD; approval for some of these in the USA are planned.

CLINICAL CONSIDERATIONS AND GUIDELINES

To integrate CES into clinical practice we recommend a trial series of treatments in a clinic or office to evaluate responses in each individual. After the initial trial, patients can be prescribed a CES device to use at home giving them increased control over the management of their symptoms. In addition to a regular 20–60 min treatment daily or every other day, patients can add treatments as needed. Some clinicians find it useful to set up a CES lounge where patients can come in for unattended low cost treatments whenever they feel stressed. This concept was studied at the Michael E. DeBakey Veterans Affairs Medical Center in Houston, TX, USA. After being trained to use five different types of stress relieving devices at a walk-in pain clinic, veterans preferred Alpha-Stim CES 73% of the time. The benefits observed included improved attendance and veterans' involvement in group-based therapies, reductions in reported pain and anxiety, improved sleep, and an increased sense of emotional well-being in the participants. Decreases on the 0–10 Numerical Rating Scale of pain intensity during the study period were statistically significant at $p < 0.001$, and represented a large effect size of 0.93.[96]

DURING PSYCHOTHERAPY SESSIONS

CES may also be used during psychotherapy sessions. Using CES during a talk therapy session decreases anxiety and usually improves the patient's desire and ability to share problems, concerns and worries with the therapist, as well as to respond to the therapist's questions more effectively. Anecdotal reports from psychiatrists, psychologists and other mental health professionals on the use of CES during therapy are consistently enthusiastic. CES induces a prehypnotic relaxed state of mind and body that is complementary with talk, biofeedback, eye movement desensitization and reprocessing (EMDR), hypnotherapy, and many other interventions.

CONCURRENT PHARMACOTHERAPY

CES can be used with pharmacologic therapy without concern about potential polypharmacy interactions. However, it is important to inform the patient that CES may decrease the need for medication. As the patient improves, both the clinician and patient should be alert for symptoms that may indicate a need for a dosage adjustment.

SELF-DIRECTED HOME TREATMENT

Most individuals are capable of doing self-directed CES therapy at home. The USA is the only country in the world that requires CES devices to be sold only by, or on the order of, a licensed healthcare practitioner. Treatments may need to be done daily during the first 1 to 3 or 4 weeks, then two to three times per week during a maintenance phase. The individual can also use CES as often as needed, as there are no side effects from extended use. This is especially beneficial for those individuals diagnosed with PTSD and others who experience panic attacks.[97]

EVALUATING IMMEDIATE AND LONG-TERM EFFECTS

Feelings experienced during a CES treatment are shown in Figure 19.5. If the patient feels heavy, groggy, or euphoric at the end of the allotted time, it is important to continue the treatment session until the patient feels "light." At the end of a CES session, the majority of patients will feel more relaxed while remaining alert, and have an increased sense of well-being. CES is demonstrably effective by both the patient receiving treatment and those observing its relaxation and other benefits, which are sometimes evident after the first treatment.

Accordingly, evaluating a single 20–40 min trial of CES in a clinic or office will help identify those individuals who are likely to respond rapidly to treatment. However, CES effects are cumulative so those who do not respond initially may benefit when given daily treatments (20–60 min) for 1 month or longer.[28,77] This is particularly true in depression and fibromyalgia which may take several treatments to induce a preliminary effect.

A clinician who would like to document treatment progress in CES patients may choose to use the Hamilton Anxiety Rating Scale (HARS), State-Trait Anxiety Index (STAI), Hamilton Depression Rating Scale (HAM-D17) and/or Beck Depression Inventory, the Pittsburg Sleep Quality Index (PSQI), Numerical Rating (NRS), Visual Analog Scale (VAS), or Likert Scale, all of which have proven useful in evaluating CES outcomes. The anxiety testing should be administered before and immediately after the first treatment, and after 3 weeks and 6 weeks of daily use. For depression and insomnia, which typically respond more slowly, patients should be tested before, but not immediately after the first treatment. Measurements at 3–4 weeks and then again at 6–8 weeks provide useful assessments of patient progress.

CONTRAINDICATIONS, PRECAUTIONS AND ADVERSE EFFECTS

There are no known contraindications to the use of CES. The only precaution is regarding use during pregnancy. A study of potential teratogenic effects from CES was conducted on 844 Spraque-Dawley fetal rats.[98] The treated rats were divided into three groups and given CES 1 h daily throughout their pregnancy at either 10, 100, or 1000 Hz, while the parameters of 1 volt, 0.125 milliampere, at a 0.22 microseconds pulse width remained constant. On day 18 of pregnancy, the dams were killed and cesarean section was performed immediately. After thorough external examination, autopsies evaluated the palate, heart, major vessels, lungs, liver, kidneys, ureters, and bladder. Examinations under light microscopy revealed no neural tube defects, limb reduction deformities, or anterior abdominal wall abnormalities in the controls, or in any of the treatment groups. Skeletal surveys of the fetal rats found no vertebral column, rib, or long bone deformities. Comparison between groups revealed more pregnancy resorptions and fewer offspring in all treatment groups compared to the control group, with the difference only reaching significance in the 1000 Hz treatment group. Average fetal weights were inversely proportional to frequency and were significantly different among groups. Fetal brain weight followed a similar pattern of reduction, except that weights were not significantly different between the medium and highest frequency treatment groups.

In their discussion, the researchers stated that while the incidence of congenital anomalies was zero, the reason pregnancy resorptions were increased may be due to the CES treated rats being more complacent. Their behavior resembled the calming effects of CES in humans. The treated rats were not as active as the controls. Accordingly, it is possible that

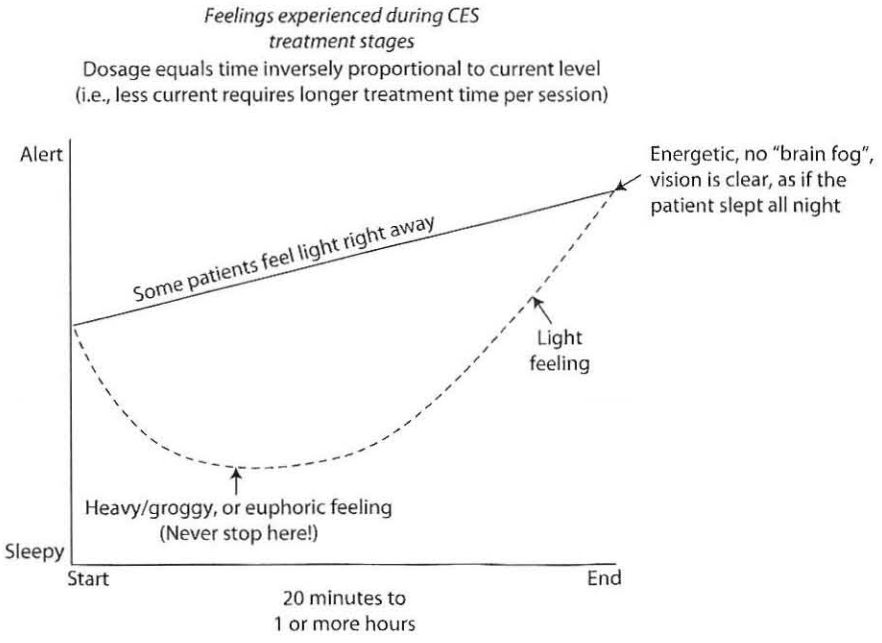

FIGURE 19.5 Cranial electrotherapy stimulation dose response curve.

food intake was lowered in the treatment group, a reasonable implication given the reduction in fetal weights. They concluded that CES may be embryolethal in the very early stages of pregnancy in the rat and might cause some miscarriages, especially at 1000 Hz, but there is no evidence of fetotoxic effects. The relevance of these findings to humans is unknown.

Adverse effects of CES in humans occur in less than 1% of cases and they are mild and self-limiting. These include vertigo, skin irritation at electrode sites, and headaches. Headaches and vertigo are usually experienced when the current is set too high for a particular individual. These effects resolve when the current is reduced or within minutes to hours following treatment. Irritation at the electrode site can be avoided by moving electrodes around slightly during treatments. No serious adverse effects have ever been reported from using CES.[15]

CONCLUSION

CES can improve the safety and effectiveness of treatment for anxiety, insomnia, and depression as well as contribute to the management of pain and other disorders. When prescribed for home use, patients are empowered to regulate their own moods, to overcome their sleep problems, and manage their own pain, thus enhancing outcomes. Compared to other neuerostimulation techniques for brain repair, CES is noninvasive, less expensive, and can be used safely and conveniently by patients at home. It is useful both as an adjunct to medication or psychotherapy or as a stand-alone treatment. While the efficacy of CES in cancer and other serious diseases with poor responses to conventional treatment is currently supported only by anecdotal reports, such patients can certainly benefit from its ability to improve mood and sleep as well as relieving pain.

Historically CES has been used as a last resort when medications and other interventions fail or are not well tolerated because of adverse side effects. CES often provides benefits in such "treatment-resistant" patients, and, because it is so safe and cost effective, should be considered a first line treatment for anxiety, insomnia, depression, pain, and possibly some of the other disorders noted above.

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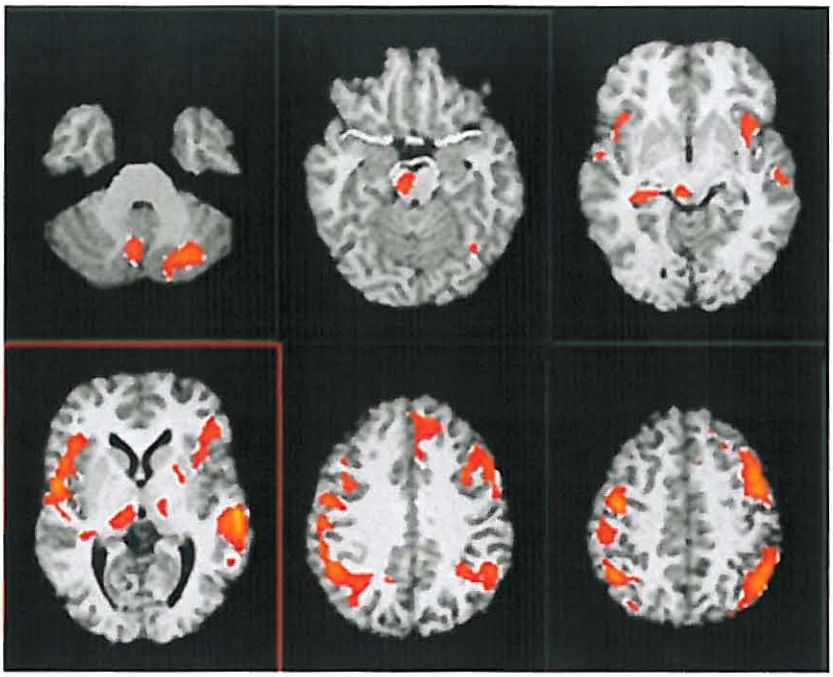

FIGURE 18.2 fMRI demonstrates the secondary brain effects of prefrontal transcranial magnetic stimulation (TMS). Shown in color are the brain regions that are significantly activated compared to rest ($p < 0.01$, extent $p < 0.05$) in six adults with clinical depression during left prefrontal TMS at 1 s. The differences are projected on a common brain (Talairach). The arrow depicts the TMS coil position, which follows the algorithm developed in 1994 for probabilistically finding the prefrontal cortex based on relative distance from the motor cortex. TMS was originally used over the prefrontal cortex to treat depression because of the potential for activating cortical-limbic loops. Imaging studies such as this one show that this assumption was likely correct and that the prefrontal cortex is a window to stimulating subcortical and limbic sites. Future work is needed to determine the optimum cortical sites for maximal clinical effectiveness, and whether there are general rules for finding this across individuals or should be individually guided based on structural or functional imaging.[2(9)] (From MUSC Brain Stimulation Laboratory and Center for Advanced Imaging Research, Dr. Li.)

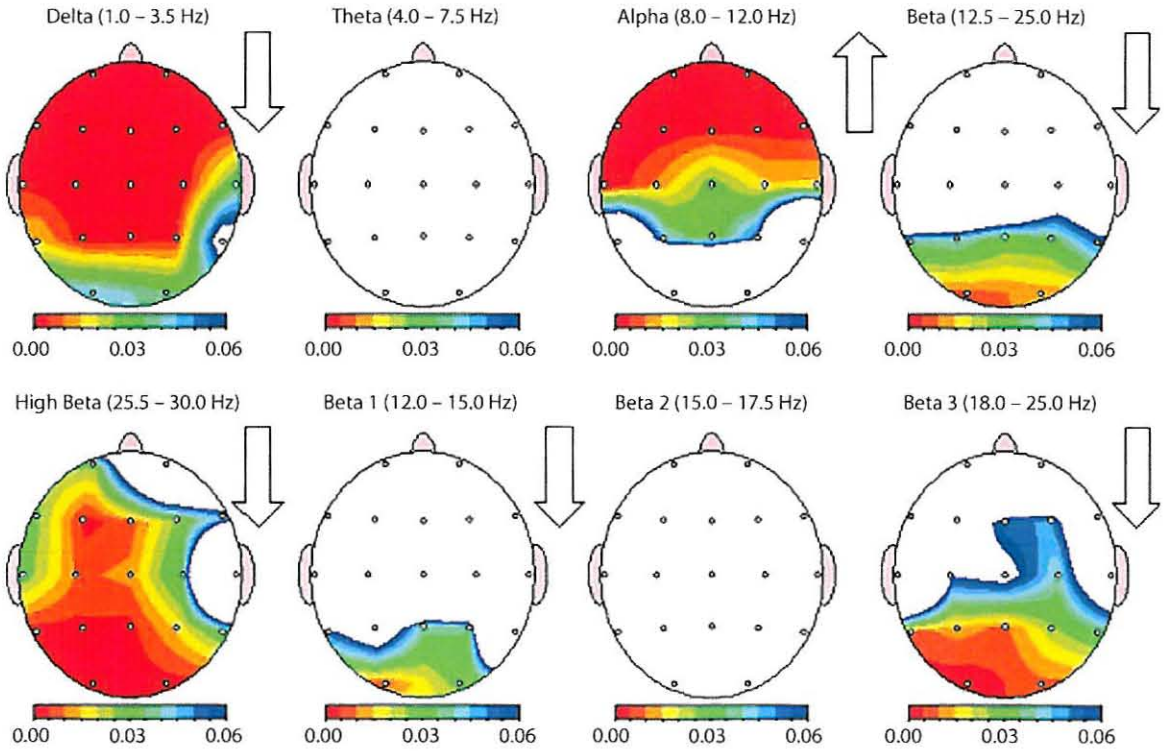

FIGURE 19.1 Relative power p-value topographical map for 0.5 Hz cranial electrotherapy stimulation (CES). Statistically significant changes ($p < 0.05$ or better) after a single 0.5 Hz CES session are indicated by color; white indicates no significant change. The arrows indicate the direction of change. Statistically significant decreases were seen in delta and beta with statistically significant increases in alpha.