EFFICACY OF CRANIAL ELECTROTHERAPY STIMULATION IN THE TREATMENT OF DEPRESSION: A PILOT STUDY

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ABSTRACT

Efficacy of Cranial Electrotherapy Stimulation
in the Treatment of Depression: A Pilot Study

by

Marie D. Turner

This is a double-blind, placebo-controlled, exploratory study examining the efficacy of Cranial Electrotherapy Stimulation (CES) in the treatment of depression. Twenty participants who met criteria were selected from a rural community. Ten were randomly assigned to the active/experimental group, and 10 were randomly assigned to the placebo/sham group. A pre-test Beck Depression Inventory-II (BDI-II) was administered prior to administration of CES to measure baseline of depressive symptoms. The study protocol consisted of 21 consecutive days of treatment with the participants coming to the Research Center for administration of CES. The devices used in this study were supplied by Electromedical Products International, Inc. (EPI) and were locked at 0.002 amperes with the timer set at 60 minutes. The outcome measure for this study was the self-administered Beck Depression Inventory-II (BDI-II). Following the three-week protocol, the post-test scores on the BDI-II were significantly lower for the active/experimental group when compared to the pre-test scores. Likewise, the post-test scores on the BDI-II were significantly lower for the placebo/sham CES group compared to the pre-test scores. As there was no statistically significant difference between the post-test scores for the active/experimental group versus the placebo/sham CES group, the efficacy of CES cannot be confirmed by the present study. Limitations of the study were small sample

size and failure to include a second, untreated group which may have contributed to obscuring the effects of CES that may have been prevalent.

Keywords: cranial electrotherapy stimulation, CES, depression, medical device placebo effect

DEDICATION

With love and gratitude I dedicate my work to my Mother, who endured the pain of the disorder I have chosen to study, and to my Father, who staunchly stood by her side throughout her difficult journey. I am eternally grateful for their examples of courage, love, and inspiration.

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Chapter 1
Introduction

Purpose Statement

The purpose of this exploratory study was to evaluate the efficacy of cranial electrotherapy stimulation (CES) in reducing symptoms of depression. The independent variable was cranial electrotherapy stimulation (CES). This is a term designated by the FDA in 1978 for treatment involving microcurrent levels of electricity pulsed across the head (Gilula & Kirsch, 2005). The dependent variable was the level of depression as measured on the Beck Depression Inventory–II (BDI-II). Participants were selected for this study based on their scoring at or above 5 on the PHQ-9 and were randomly assigned to either an active experimental treatment group or a placebo treatment group. Baseline measure of intensity of symptomology was established on the first day of trials using the Beck Depression Inventory-II (BDI-II). Participants engaged in 21 consecutive days of CES treatment at the Research Center. Outcome of the exploratory study was measured using a post-treatment Beck Depression Inventory-II (BDI-II) (Beck, 1996).

Relevance of Topic for Clinical Psychology

This study was focused on the treatment of depression using Cranial Electrotherapy Stimulation. Advancing new treatments for depression is crucial since according to the National Institute of Health (2002), one in 20 American adults experience major depression in a given year. Approximately one in 50 depressed patients

diagnosed with depression is hospitalized (Seligman & Reichenberg, 2007). This number represents 75% of psychiatric hospitalizations (Seligman & Reichenberg, 2007). Thus, depression is considered a serious medical condition that affects thoughts, feelings, and the ability to function (Pratt, 2008).

Cranial electrotherapy stimulation (CES) is recognized by the Food and Drug Administration as a therapeutic treatment for depression, anxiety, and insomnia (Code of Federal Regulations, 2010). This treatment modality consists of applying clip-on electrodes attached to the earlobes. Using a low level of electrical current a biphasic pulse is applied across the head. It is believed that the effects of the microcurrent of electricity on the brain are primarily mediated through a direct action at the level of the limbic system, the reticular activating system (RAS), and the hypothalamus (Gilula & Kirsch, 2005).

Although CES may be shown to be cost effective in the treatment of depression and side effects may be shown to be minimal, acceptance of this treatment modality by mainstream professionals as well as the public has been slow. There are a number of hypotheses as to why this is the case. One hypothesis is the collective memory of the complications associated with ElectroConvulsive Therapy as administered in the 1960s and 1970s, resulting in the rejection of electricity as a therapeutic treatment modality (Shultz, 2009). Another popular hypothesis is the belief that powerful pharmaceutical companies block research and distribution of treatments other than pharmaceuticals (Strentzsch, 2008).

Lack of rigorous clinical research supporting the efficacy of this treatment modality appears to be the primary barrier to acceptance. It is hoped that this study will

add to the current body of knowledge leading to acceptance of this alternative treatment for this debilitating disorder.

Autobiographical Origins of Interest and Predisposition to the Topic

This topic carries a special interest for this researcher as my personal family has been affected by depression. My mother in her early 40s experienced a depressive episode that failed to respond to medication. The treatment modality in the 1960s for recalcitrant depression was a combination of pharmaceuticals and ElectroConvulsive Therapy (ECT). The side effects were horrific for both my mother and her loved ones.

When this episode occurred I was in my early 20s and, prior to my mother's illness, had no concept that mental disorders existed. Our family unit was run on the premise that what occurred within the family must stay within the family. Therefore, the depressive episode could not be discussed or shared with others outside the family unit. Our family was thrown into turmoil with few options. Our mother was suffering severely, and yet there was an element of shame. I was expecting my first child and was deeply concerned that I might be carrying a defective gene.

In the middle of this pain and confusion was an element of fear. There was no Internet to turn to for answers—no explanations whatsoever. Our family found itself at the mercy of doctors who refused to discuss mother's diagnosis or prognosis and how it would affect the family. In the 1960s the doctors did not consult with the family. Rather, they told the family what would be done, and their decision was ElectroConvulsive therapy. We had no understanding of what this encompassed and no understanding of what the outcome might be.

Following treatment mother came home; that is, a shadow of my former mother. A frail, fearful woman came home who now exhibited symptoms of severe anxiety. The effect on our family was devastating. Each member coped in his or her own way, but at that moment, I developed a determination to learn all that I could about mental disorders with a special focus on depression. I would seek explanations as to the causes and various modes of treatment. I would search for ways in which to help the individual who was suffering from the disorder as well as for means of supporting and educating their loved ones.

The journey has been long and arduous, as higher education for women was not acceptable, particularly within my family of origin and my community. Nevertheless, the pain that I carried in my heart at witnessing my mother's suffering propelled me in my quest to find an effective alternative treatment for others who suffer from this disorder.

Chapter 2
Literature Review

Depression

The medical model endorses the *DSM-IV*'s nosological categoralization of depression. However, debate continues as to whether Major Depressive Disorder should be conceptualized as a disease or as the extreme on a continuum of increasingly disturbed affective regulation (Fava, 2000). Some contend that depression is a heterogeneous syndrome comprised of numerous diseases of distinct causes and pathophysiologies (Nestler, 2002; Hasler, 2010; Albert, 2012). Kandel conceptualized unipolar depression as a group of disorders consisting of the subtypes melancholic depression, atypical depression, and dysthymia. Melancholic depression was formerly referred to as endogenous depression and accounts for 40 to 60% of treated unipolar depression. Syptoms of atypical depression are somewhat different than melancholic depression in that individuals do not experience loss of appetite but rather experience an increase of appetite and tend to sleep more rather than suffer from insomnia. In addition, they have prominent symptoms of anxiety. Dysthmia is experienced as a milder depression with symptoms persisting for at least two years (Kandel, 2002).

Epidemiology of depression. The World Health Organization (WHO) ranks depression as one of the most burdensome diseases in the world (World Health Organization, 2002). This disorder can result in the individual suffering in all domains of his or her life, including work, school, and interpersonal relationships. Evidence of social impairment may include deterioration of the family. This may include disharmony in the marriage, with increased likelihood of divorce. Further, there may be a disruption of the

family's social roles that include rearing of children and providing support in family members experiencing problems (Sartorius, 2001).

The American Psychological Association reported that 19 million Americans suffer from depression annually (Mazure, 2002). Women were found to be twice as likely as men to experience a major depressive episode. The report notes that an individual's social and physical functioning can be more severely impaired by depression than by medical conditions (Mazure, 2002).

In the results from the National Comorbidity Survey Replication, Kessler et al. report that the prevalence estimates for Major Depressive Disorder for lifetime is 16.2%. They found that 72.1% of these individuals also had comorbid *DSM-IV* disorders, with Major Depressive Disorders only rarely primary (Kessler, 2003). Of those with lifetime Major Depressive Disorders, 59.2% met criteria for an anxiety disorder, 24.0% met criteria for a substance use disorder, and 30% met criteria for an impulse control disorder (p. 3100).

Although depression has a high comorbidity with other psychiatric disorders, it is important to note that depression frequently occurs comorbidly with physical conditions such as diabetes, heart problems, backache, hypertension, and arthritis (Sartorius, 2001). This presentation of depression and physical condition results in a worse prognosis of both the depression and the physical illness (Sartorius, 2001).

A patient presenting with a chronic medical condition and depression may be less likely to receive effective interventions. In addition, there is an increased prevalence of unexplained somatic symptoms associated with depression that leads to unnecessary testing or therapeutic interventions (Simon, 2003). This combination of comorbid

medical condition and depression is associated with an overall increase in health services costs ranging from 50% to 70% after adjusting for comorbid chronic medical illness (Simon, 2003).

Katon (2003) confirmed this hypothesis of increased cost of medical services for patients presenting with comorbid anxiety and depressive disorders, noting that these patients had significantly more medically unexplained symptoms without identified pathology than did those with chronic medical illness alone (p. 219). He also addressed the adverse effect of major depression on health habits including sedentary lifestyle, diet, over-eating, smoking, and poor adherence to medical regimens (Katon, 2003).

Having identified behaviors and other health risks contributing to depression, the World Health Organization has implemented a plan to identify and reduce risk factors. According to this report, the preferable treatment options consist of psychosocial support combined with antidepressant medication or psychotherapy. Barriers to effective care include the lack of resources, lack of trained providers, and the social stigma associated with mental disorders (Mazure, 2002).

Pathophysiology of depression. In considering the current neurobiological theories as to the cause or etiology of depression, there are two prevailing hypotheses (Gunther, 2010). The first is a deficiency of norepinephrine, epinephrine, and dopamine. The second is a deficiency of serotonin (Gunther & Phillips, 2010). Approximately 60 years ago two classes of agents were discovered by accident to alleviate symptoms of depression. The tricyclic agents were developed while researching antihistamine, whereas the early monoamine oxidase inhibitors were derived from work on antitubercular drugs. With the discovery that these agents could be used to treat

depression came the first clues as to the types of chemical changes in the brain that regulate depression (Nestler, 2002).

Implicated in the more severe depressive disorders is the hypothalamic-pituitary-adrenal (HPA) axis (Nestler, 2002). This system manages the body's response to stress. When there is a perceived threat to the physical or psychological well-being, the hypothalamus increases output of corticotropin-releasing factor (CRF), which causes the pituitary to secrete ACTH. The secretion of ACTH results in the adrenal glands releasing cortisol. These changes put the body in a fight or flight mode. The appetite for food and sex is depressed while alertness is heightened. Chronic activation of the HPA axis is believed to lay the ground for depression (Nemeroff, 1998).

Pharmacotherapy for treatment of depression. Currently the predominant form of treatment for mental health disorders is psychotropic medication (Zuvekas, 2005). Depressed patients frequently receive these medications from their primary care physicians, with most never receiving treatment from a psychiatrist (Lieberman, 2003).

As noted above, there are two prevailing neurochemical hypotheses related to the etiology of depression. The first is a deficiency of norepinephrine, epinephrine, and dopamine. The second is a deficiency of serotonin (Gunther & Phillips, 2010). The above is consistent with there being tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAO) that were developed in the early phases of treatment. These developments profoundly changed how depression was viewed and how it was managed. However, there were significant safety and toxicity issues. In the 1970s, the selective serotonin reuptake inhibitors (SSRIs) were developed, which provided an improved safety and tolerability profile (Lieberman, 2003).

Lieberman (2003) noted that the underlying pathologic mechanisms linking depressive dysphoria, insomnia, and somatic complaints remain poorly understood and questioned the adequacy of the catecholamine hypothesis of depression. As depressive disorders appear to be a heterogeneous syndrome with distinct causes and pathophysiologies, treatment outcomes may vary. Complications affecting outcome may include negative side effects of medication, inadequate or excessive dosage of medication, failure to take medication as prescribed, and discontinuation of medication without prior consultation with prescriber. The present study is designed to explore an alternative treatment of depressive disorders using a natural supplement in the form of an electrical current rather than chemicals to treat depressive symptoms.

Cranial electrotherapy stimulation for treatment of depression. Cranial electrotherapy stimulation (CES) has been approved by the FDA for the treatment of depression, anxiety, and insomnia. It consists of applying microcurrents of electricity across the head using transcutaneous electrodes (Gilula & Kirsch, 2005). The use of electricity to treat these disorders has a long history dating back to the 1950s in Europe and the 1960s in the United States (Rosa & Lisanby, 2012). However, in 1978 the FDA began to control its applications mandating that medical devices emitting electrical currents across the skull be labeled *cranial electrotherapy stimulation* and placing the medical devices in Class III. This designation is used for those medical devices when the FDA's Neurological Devices Panel has determined that there is insufficient information available to assure safety and effectiveness of the devices solely through general or special controls. Despite numerous attempts to have the category changed, the FDA declined, citing lack of rigorous research confirming the efficacy of the medical devices

and insufficient evidence of safety. However, on June 13, 2014, the FDA announced its intent to move CES into Class II following receipt of sufficient documentation of safety. Endorsement of efficacy of this procedure was withheld.

In an effort to demonstrate efficacy, Smith (2006) published *Cranial Electrotherapy Stimulation: Its First Fifty Years, Plus Three: A Monograph,* in which he analyzed 67 studies involving 2,910 patients in five meta-analysis. He was careful to note that the studies and some of the participants were represented in more than one analysis if their symptoms were evaluated and tested separately. The studies were broken into the following syndromes: Insomnia, depression, anxiety, drug abstinence, and cognitive dysfunction. Within the Depression Syndrome, Smith considered 18 studies with 863 subjects.

This meta-analysis of 18 studies consisted of six studies that were double-blind, two studies that were single blind, three studies that were crossover, and seven studies that were open clinical trials. Smith failed to identify the different CES devices used in the studies, stating that they were all substantially equivalent, as they had all been grandfathered in by the FDA. Smith also failed to review the quality of the research designs and failed to control for medication.

In this meta-analysis, Smith considered three studies by Rosenthal, the first being a trial in 1970 consisting of nine subjects, six outpatients, and three inpatients. The duration of treatment was from seven to ten sessions for 10 to 30 minutes (Rosenthal, 1970). Inconsistent presentation of the independent variable prevented replication of the study and invalidated the results. Of greater concern, however, was the device used for the trials. It was an Electrosone 50 designed with four electrodes, two of which were

placed on the eyelids of the subject, which resulted in complaints of blurring of vision following treatment. In the study by Rosenthal published in 1972, Smith does not clarify that this was in fact a crossover design (Rosenthal, 1972). This is not an appropriate design for Cranial Electrotherapy Stimulation, as improvement that began following a week of CES treatment continues after the treatment stops. Therefore, results of this crossover design can be considered to be invalid.

Included in this meta-analysis by Smith (2006) was the clinical study by Feighner, et al., entitled Electrosleep therapy: A controlled double-blind study (Feighner, 1973). Although not clarified in the title, this study was in fact a crossover design, which calls into question the validity of the results. The device used by Feighner was the Electrosone 50, which required the placement of electrodes over the subjects' eyelids. A third crossover trial included in the meta-analysis was a study conducted by Moore (1975). The title of the study was *A double-blind study of electrosleep for anxiety and insomnia.* Smith failed to identify this as a crossover design, as did the title of the study. In fact, this was not a double-blind study, because even though the participants were blind to the treatment condition, the therapist/researcher was not (Moore, 1975). In addition, this study was for five treatment sessions at 30 minutes each, which might not be sufficient to elicit the effects under study and was not controlled for medication.

In his meta-analysis of the effectiveness of CES treatment on depressive symptoms, Smith (2006) also included a study by Hearst (1974). However, this study manipulated the current delivered by the device which was a Neurotone 101 eliminating the peripheral rhythmic electrical stimulation in order to independently evaluate the results of the current effect on the brain (Hearst, 1974). The protocol for this treatment

study was five treatments at 30 minutes each which is insufficient to demonstrate results for depression. Further, the researchers in this study failed to control for medication and psychotherapy treatment during trials.

A further issue in the Smith (2006) meta-analysis is that the study conducted by Levitt (1975) included in the meta-analysis did not have a sufficient sample size (11 participants), failed to control for medication, and failed to restrict the diagnosis to the syndrome under study (Levitt, 1975). Included were subjects diagnosed with schizophrenia, alcoholism, psychotic depression, mixed neurosis, and disorders of personality. The device used for this study was a Dormed, 100 Hz, which required electrodes to be attached to the eyelids with resultant side effects of blurring of vision being reported following treatments (Levitt, 1975).

With improved technology, the cranial electrotherapy stimulation devices were modified. One significant change was the reduction of four electrodes to two electrodes. This meant that the electrodes were no longer placed directly on the eyelids but rather were positioned on the earlobes or behind the ears depending upon the manufacturers' design of the CES devices.

A more recent study included in the Smith (2006) meta-analysis compared three cranial electrotherapy stimulation devices: Alpha-Stim CS, CES Labs, and Liss Stimulator in the treatment of stress related attention deficit disorder in 23 children and adults. All participants had been diagnosed with one or more of the following: generalized anxiety disorder (61%), depression (45%), or dysthymia (17%) with difficulty focusing when attempting cognitive tasks (Smith, 1999). Daily 45 minute treatments where given for 3 weeks. Smith reported that all three CES devices were

effective based on Duncan's Range test ($P = < .001$) and reduced depression as measured on the Institute for Personal and Ability Testing (IPAT) Depression Scale ($M = 19.38$ +/- 8.44 pretest to 13.19 +/- 7.00 post test (Smith, 1999). Although the protocol appears appropriate in terms of length of study and duration of sessions, there is some concern about mixing children and adults for the study. Further, including both diagnoses of dysthymia with major depressive disorder complicates the outcome measures, as there may be a restricted range of depression such that minimal to mild symptoms may not have registered changed on the outcome measures.

A second meta-analysis on the application of CES in the treatment of depression was published by Kirsch and Gilula (2007). Of the studies collected for the meta-analysis, 23 studies were identified as suitable for CES studies of depression. Seventeen of the 23 studies had been included in Smith's meta-analysis discussed above. That is, the meta-analysis conducted by Kirsch and Gilula included all the CES studies in Smith's meta-analysis except for one. This excluded study was a crossover design and the investigator did not report the treatment results prior to the crossover.

A second study that had been identified as suitable for CES studies of depression was excluded from the meta-analysis as the investigator also failed to report the treatment results prior to the crossover. However, a greater concern was the exclusion of two studies from the meta-analysis. One study was undertaken in 1974 and involved inpatients at a state hospital. Reportedly, the control group showed substantial improvement in their symptoms of depression during the course of the study, and therefore, the study was deemed invalid. A second study of inpatients conducted in 1976 also was deemed invalid as all participants in the study improved; that is, both the

participants in the active group and the participants in the sham group improved. Therefore, it was determined that no controls were present with which to measure treatment effects.

One study that was included in the meta-analysis conducted by Kirsch and Gilula was a postmarketing survey. This survey was completed by physicians who had treated 500 patients using CES. Of this number, 69 carried a primary diagnosis of depression, and the remainder had comorbid depression. Although the outcome indicated improvement, the courses of treatment varied, thereby preventing replication and generalizability.

The studies cited above were part of the meta-analysis of the effectiveness of CES in the treatment of depressive disorders. The first was conducted by Smith; the second by Kirsch and Gilula. These early studies under review clearly had defects. However, they laid the groundwork for future research. As noted by Gunther and Phillips (2010), research progressed with the early focus revolving around process issues such as wave forms, pulse rates, and current intensities. The focus of research then shifted to optimal length of treatment and measurement of outcomes. Studies meeting rigorous methodological standards must now be implemented in order to validate the efficacy of CES in the treatment of depression. Kavirajan (2014) attempted to conduct such a review of high quality clinical trials, and following an in-depth search reported that he was unable to find any methodologically rigorous RCTs in which patients/participants with acute depression were randomly assigned to either an active/experimental or a sham/placebo group to test the efficacy of CES. He suggested that this lack of trial data

may be a function of the regulatory system in place for oversight of medical device marketing (Kavirajana, 2014).

In their review of somatic treatments for management of mood disorders, Rosa and Lisanby noted the re-emergence of nonpharmacological somatic treatments suggesting that this may be due in part to the limitations of medications for a large percentage of individuals treated for mood disorders (Rosa & Lisanby, 2012). Under the category of Noninvasive Techniques, cranial electrotherapy stimulation was reviewed. Two commercial medical devices were considered, one of which was the Alpha-Stim manufactured by EPI and used in the present exploratory study. There are, in addition to these two commercial devices, several other CES devices available on the market. However, the lack of standardization in practice, including variability of placement of electrodes, the wide range of waveform parameters, and varying durations of application hampers the ability of researchers to draw conclusions regarding the clinical potential of CES in the management of mood disorders. Further, Rosa and Lisanby noted that no controlled trials have been conducted assessing the efficacy of CES on its use for major depression or other affective disorders (Rosa & Lisanby, 2012).

Notwithstanding the above, Barclay and Barclay recently published the results of their double-blind RCT entitled "A clinical trial of cranial electrotherapy stimulation for anxiety and comorbid depression" (Barclay & Barclay, 2014). The purpose of the study was to examine the effectiveness of CES as a treatment for anxiety and comorbid depression. A total of 125 participants were recruited for the study with 115 meeting criteria for inclusion in the RTC. The results indicated that the active group had significantly lower scores on the HAM-A than the sham CES group ($F = 43.404$, $df = 1$, p

= 0.001, *d* = 0.94). Further, results also indicated that the active CES group had significantly lower depression scores on the HAM-D than the sham CES group (*f* = 17.050, *df* = 1, p = 0.001, d = 0.78). In the active CES group, depression scores on the HAM-D from baseline to endpoint decreased ≥ 50%. The mean decrease in the active group was 32.9% (9.64 – 6.47) and 2.6% (10.22 – 9.96) from baseline to endpoint for the sham group. Barclay and Barclay noted that a limitation to their study was the small number of participants who had an anxiety disorder and comorbid depression. Although the total number of participants was 115, the number of participants presenting with an anxiety disorder and comorbid depression was 23. A further concern was the potential interaction between disorders that may confound the overall symptomology, thus clouding the contribution of each disorder to the other. These two issues would pose a barrier to generalizibility.

Purported mechanism of action of cranial electrotherapy stimulation. The exact mechanism by which cranial electrotherapy stimulation works is uncertain; however, the effects are generally believed to mediate on the brain through a direct action on the limbic system, the reticular activation system (RAS), and the hypothalamus (Gilula & Kirsch, 2005). Giordano (2006), the Director of Science for Electromedical Products International, hypothesized that the Alpha-Stim (the brand name of the Cranial Electrotherapy Stimulation device used in the present experiment) produces microcurrent waveforms that activate particular groups of nerve cells located in the brainstem. By a system known as modulation, the Alpha-Stim is believed to amplify activity in some neurological systems and diminish it in others; that is, it appears to change the electrical and chemical activity of certain nerve cells in the brainstem. This electrical activity

pattern can be measured on brain wave records and is known as an alpha state (Giordano, 2006).

Problems and Justification for the Study

Depression is a serious medical condition affecting one in 20 American adults in a given year (National Institute of Health, 2002). The condition affects thoughts, feelings, and the ability to function (American Psychiatric Association, 2000). Depression decreases the quality of life and is associated with an increase in health care costs (Pratt, 2008). Depression appears to be a heterogeneous syndrome comprised of numerous diseases of distinct causes and pathophysiologies (Nestler, 2002; Kandel, 2002; Hasler, 2010). It is suggested that treatment of this very complex disorder would best be approached in a wholistic manner (Nemade, 2007).

Currently the predominant form of treatment for mental health disorders is psychotropic medication (Zuvekas, 2005). However, it would appear that there is a re-emergence of nonpharmacological somatic treatments possibly due in part to the limitations of medications for a large percentage of individuals treated for mood disorders (Rosa & Lisanby, 2012). One noninvasive technique under the category of nonpharmacological somatic treatments is cranial electrotherapy stimulation (Rosa & Lisanby, 2012). Although it is approved by the FDA for treatment of depression, there is a dearth of evidence from rigorous clinical trials to support the use CES in the treatment of depression (Kavirajan, 2014).

This pilot study will lay the groundwork for a rigorous randomized control trial to be implemented to demonstrate the efficacy of cranial electrotherapy stimulation in the treatment of depression. Protocol will include 3 weeks of CES treatment, as this has been

established by earlier studies to be the minimum required to obtain an adequate assessment of treatment efficacy.

Research Questions

The present study is designed to investigate the effects of CES on Depression as measured by the Beck Depression Inventory-II.

Hypothesis I: After the completion of a 3-week protocol of 1-hour daily sessions of active CES at .002 amperes, 0.5 Hz, there will be no change in the post-treatment scores on the Beck Depression Inventory-II compared to baseline scores.

Hypothesis II: After the completion of a 3-week protocol of 1 hour daily sessions of active CES at .002 amperes, 0.5 Hz, there will be no significant difference in the post-test scores on the Beck Depression Inventory-II for the active/experimental CES group when compared with scores for the sham/placebo CES control group.

Definition of Terms

Depression. The phenomenon under examination for this study will be the range of depression consisting of the following symptoms and measured by the Beck Depression Inventory-II:

- Depressed mood
- Markedly diminished interest or pleasure in all or almost all activities
- Significant weight loss or gain, or increase or decrease in appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or inappropriate guilt

- Diminished concentration or indecisiveness
- Recurrent thoughts of death or suicide (American Psychiatric Association, 2000)

Cranial Electrotherapy Stimulation. The FDA requires that the application of electrical current across the forehead be termed *cranial electrotherapy stimulation*. Cranial electrotherapy stimulation is recognized by the Food and Drug Administration as a therapeutic treatment for depression, anxiety, and insomnia (Code of Federal Regulations, 2010). This treatment modality consists of applying clip-on electrodes attached to the earlobes. Using a low level of electrical current, a biphasic pulse is applied across the head. It is believed that the effects of this micro-current of electricity on the brain are primarily mediated through changes in the limbic system, reticular activating system (RAS), and the hypothamalus (Gilula & Kirsch, 2005).

Alpha-Stim. The Alpha-Stim is a cranial electrotherapy stimulation device developed by Electromedical Products International, Inc. (EPI) in Mineral Wells, Texas. According to the Owner's Manual, it generates a modified square, bipolar waveform of 0.5 pulses per second (Hz), 10 to 500 millionths of an ampere, at a 50% duty cycle (Owner's Manual: Alpha-Stim SCS, 2006).

The device is lightweight and simple to operate. It has an automated timer that assured the prescribed treatment time. It is operated by a 9-volt battery. The battery should last for over 50 treatments. The ear clip electrodes are attached to the earlobes. Depending upon the intensity, treatment for depression may last from 30 minutes to 1 hour. During a treatment, a mild tingling sensation may be experienced as a result of the stimulating current flow.

Active CES. Half of the devices supplied by the manufacturer were active; that is, the devices emitted a micro-current of electricity sufficient to theoretically induce therapeutic change via electrodes that were attached to the ear lobes. CES stimulation was administered for 60 minutes daily for 21 consecutive days. As the trials were double blind, neither the participants nor the investigators knew which devices were active.

Sham CES. Half of the devices supplied by EPI were CES sham devices; that is, the devices did not emit a micro-current of electricity. Participants who were randomly assigned to the sham/placebo group received 60 minutes daily treatment using the sham/placebo CES devices for 21 consecutive days. The participants were not able to distinguish the sham devices from the active devices as the devices were locked at a subsensory level by the manufacturer.

Beck Depression Inventory-II. The Beck Depression Inventory-II (BDI-II) is a self-report inventory consisting of 21 items used to measure the participants' level of depression. This instrument will be administered prior to treatment to obtain baseline measures of depression. Following 21 consecutive days of treatment, the Beck Depression Inventory-II will again be administered to measure any change in intensity of depression. The hypotheses will be evaluated by noting the BDI-II differences between the baseline and post-treatment scores for the active CES group as well as noting the difference between the active versus the sham/placebo CES group.

Chapter 3
Methodology

Research Design Summary

This exploratory study was a double-blinded, placebo-controlled investigation of the efficacy of cranial electrotherapy stimulation (CES) in the treatment of Depressive Disorders. The independent variable, CES, was administered using the Alpha-Stim. The dependent variable was the intensity of symptoms of depression. Participants selected for inclusion in this study were required to meet the criteria for Major Depressive Disorder as delineated in the *Diagnostic and Statistical Manual of the American Psychiatric Association-IV-TR* (American Psychiatric Association, 2000). Individuals diagnosed with dysthymia were not considered for this study as the range of intensity of their symptoms may not be sufficient to demonstrate treatment efficacy. Participants accepted for inclusion in the study were between the ages of 18 and 75 years of age. Baseline and outcome for this exploratory study were measured using the Beck Depression Inventory-II. Pre-test and post-test inventory scores were collected. *T*-tests were conducted to determine the statistical significance of the data. Clinical significance was determined using Cohen's *d*.

Participants

Participants for this exploratory study were self-referred, having responded to advertisements in the community newspaper or on the community Internet news, radio advertisements, or flyers posted on community bulleting boards. Both male and female candidates were considered for the study. Minimum age of the participants for this study was 18 years; maximum age was 75. A maximum age limit was set in an effort to avoid potential confounds of medical conditions often associated with geriatric populations.

Excluded from this study were individuals with psychotic symptoms, suicidal symptoms, or a history of suicide attempts, as these symptoms and current impulses may have introduced a safety factor that the researcher may have been unable to address. Candidates with a history of head injury or a history of epilepsy or convulsions, or those who use a pacemaker, were excluded from this study, as the manufacturer of the Alpha-Stim caution against using CES under these conditions.

The candidates for the study were administered a PHQ-9 by the principal investigator prior to the beginning of the trials to confirm diagnosis. On the first day of the study, the candidate was administered a BDI-II to measure the intensity of symptoms and to establish a baseline measure. All candidates were advised of the risks and benefits of cranial electrotherapy stimulation (CES). Those selected to participate were required to sign a statement of Informed Consent. Participants were encouraged to inform their medical providers of their participation in the exploratory study and to sign a release that would enable their health care providers to communicate with the researcher. They were encouraged to remain in contact with their medical providers throughout the term of the study in order that they could be provided appropriate care in the event that their symptoms of depression intensified to such a high level that the principal investigator was not able to manage their care appropriately. Participants were also provided the services of two counselors/therapists and a case manager should they require such services during the study. Furthermore, the principal investigator was available on site during the study and could also be reached by phone during other times throughout the study.

Materials

PHQ-9. PRIME-MD is an instrument that was developed for primary care practitioners to assist them in diagnosing mental health disorders. The instrument is based upon five types of *DSM-IV* disorders most commonly seen in medical patients. These disorders include mood, anxiety, somatoform, alcohol, and eating (Kroenke, 2002). A shortened version of this instrument is the patient health questionnaire (PHQ), which consists of three pages that are self-administered. The depression scale of this shortened version consists of nine questions and is referred to as the PHQ-9 (Kroenke, 2002).

The PHQ-9 is considered a dual-purpose instrument in that it can assist in identifying depressive disorders as well as determine the severity of depressive symptoms (Kroenke, 2001). The patient is instructed to assess his or her personal response to each of nine questions that are based on the *DSM-IV* criteria set for depression rating his or her response as follows: "Not at All," which is scored at -0-; "Several Days," which is scored at 1; "More Than Half the Days." which is scored at 2; or "Nearly Every Day," which is scored at 3. The healthcare professional then totals the scores, determines the severity of depression, and reviews the proposed treatment actions (Kroenke, 2002) as shown in Table 1, *PHQ-9 Scores of Depression Severity and Treatment Recommendations,* on page 24.

Table 1

PHQ-9 Scores of Depression Severity and Treatment Recommendations

PHQ-9 Scores	Severity Level	Treatment Recommendations
1 to 4	None	None
5 to 9	Mild	Watchful waiting; repeat PHQ-9 at follow-up
10 to 14	Moderate	Consider counseling, follow-up and pharmacotherapy
15 to 19	Moderately Severe	Immediate initiation of pharmacotherapy, consider psychotherapy
20 to 27	Severe	Immediate initiation of pharmacotherapy, consider expedited referral to a mental health specialist for psychotherapy and collaborative management

Research has shown internal consistency (Cronbach's a coefficient) of each item at 0.85 on the PHQ-9 and good test- retest reliability over one month interval (r + 0.894, P < 0.001) (Abiodun, 2006). Cameron (2006) found the Patient Health Questionnaire (PHQ-9) and the depression subscale for the Hospital Anxiety and Depression Scale (HADS-S) had reliabililty, convergent/discriminant validity, robustness of factor structure, and responsiveness to change in a sample of primary care patients referred to mental health workers. Cameron reported that both the PHQ-9 and the HADS-D demonstrated high internal consistency at baseline and at the end of treatment (PHQ-9 a = 0.83 and 0.92; HADS-D a = 0.84 and 0.89). He reported that one factor emerged each for the PHQ-9 (explaining 42% of variance) and HADS-D (explaining 62% variance). However, both scales converged more with each other than with the HADS anxiety (HADS-A) subscale at baseline (P < 0.001) and at the end of treatment (P = 0.01). Responsiveness to change was similar: effect size for PHQ-9 = 0.99 and for the HADS-D = 1. The HADS-D and PHQ-9 differed significantly in categorizing severity of depression, with the PHQ-9 categorizing a greater proportion of patients with moderate/severe depression (P < 0.001) (Cameron, 2006).

Although improving techniques to detect depression is important, Kroenke (2001) focused on the assessment of severity to assist in guiding treatment decisions. Researchers evaluated the PHQ-9 completed by 6,000 patients in eight primary care clinics and seven obstetrics-gynecology clinics. Construct validity was assessed using the 20-item Short-Form General Health Survey, self-reported sick days and clinic visits, and symptom-related difficulty. Criterion validity was assessed against an independent

structured mental health professional (MHP) interview in a sample of 580 patients. Data from the two studies provided strong evidence for the validity of the PHQ-9. Specifically, as PHQ-9 depression severity increased, there was a substantial decrease in functional status on all six SF-20 subscales. Also, symptom-related difficulty, sick days, and health care utililzation increased. Thus, construct validity was established by the strong associations noted above (Kroenke, 2001). Five hundred and eighty of the primary care patients underwent an independent reinterview by a mental health professional who confirmed the criterion validity of the PHQ-9. Using the MHP reinterview as the criterion standard, a PHQ-9 score > 10 had a sensitivity of 88% and a specificity of 88% for major depression. Validation of the external validity was established by replicating the findings from the 3,000 primary care patients in a second sample of 3,000 obstetrics-gynecology patients (Kroenke, 2001). Kroenke hypothesized that the similar results seen in different patient populations suggested that the PHQ-9 findings could be generalizable to outpatients seen in a variety of settings (Kroenke, 2001).

Beck Depression Inventory–II. The Beck Depression Inventory–II (Beck, 1996) was used to measure the level of depression during baseline (pre-test) and post-test phases of the study. The original instrument was introducted as the Beck Depression Inventory (BDI) in 1961 and reviewed in 1978. This version was known as the amended Beck Depression Inventory (BDI-IA). In 1996 the BDI-IA was again revised and published as the Beck Depression Inventory–II. This upgraded instrument was selected for the present study as it is more closely correlated with the diagnostic criteria for Major

Depressive Disorders that are described in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (Steer, 1999).

The BDI–II is a paper and pencil instrument consisting of 21 items with four response options to each item. The test taker must have a minimum 5th or 6th grade reading and comprehension level in order to complete the test. The BDI–II typically takes between 5 and 10 minutes to complte. The responder is asked to score each item on the instrument in a manner that would most closely reflect how he or she felt during the two weeks prior to completing the inventory questions. Each of the 21 items reflect the perceived level of intensity of the symptoms on a scale from -0- to 3. Total scores may be interpreted as follows:

-0- to 13	No or Minimal Depression
14 to 19	Mild Depression
20 to 26	Moderate Depression
29 to 63	Severe Depression
Below 4	Possible denial of depression; faking good; Lower than usual scores for individuals who do not manifest symptoms of depression (Groth-Marnat, 2009)

The Beck Depression Inventory–II is not a diagnostic tool but rather is used to measure the depth and nature of depression. The content validity is strong as the BDI items were constructed by consensus about the depressive symptoms exhibited by psychiatric patients (Groth-Marnat, 2009; Steer, 1999). Consideration was also given to the *DSM-IV* criteria set for depression. "Each item is representative of a particular symptom of depression and corresponds to the diagnostic criteria listed in the DSM-IV"

(Bedi, 2001; pp. 308). Beck reported that the convergent validity between the BDI-A and the BDI–II is robust (Beck, 1996). The concurrent validity evidence appears to be solid with the BDI–II demonstrating a moderately high correlation with the Hamilton Psychiatric rating Scale for Depression – Revised (r = .71) in psychiatric outpatients (Arbisi, 2001; Farmer, 2001) and with the Beck Hopelessness Scale (r = .58) (Farmer, 2001). In addition, Beck reported that the BDI–II was more positively correlated *(r* = .71) with the Hamilton Psychiatric Rating Scale for depression than it was with the Hamilton Rating Scale for Anxiety *(r* = .47) indicating a robust discriminant validity between depression and anxiety (Beck, 1996; Groth-Marnat, 2009).

Cranial electrothrapy stimulation device. The cranial electrotherapy stimulation (CES) devices used in this exploratory study were furnished by Electromedical Products International, Inc. (EPI) in Mineral Wells, Texas. Because this study was double blind, half of the 10 devices on loan administered treatment and half of the devices were sham devices. Electromedical Products International, Inc. coded the devices prior to shipment. Information as to which devices administered treatment and which were sham devices was not revealed to the participants nor to the principal researcher until all data had been collected.

Ear clips moistened with a conduction solution were attached to the earlobes of each participant. CES stimulation was administered for 60 minutes at an intensity of 2 volts, which produced 100 microampere at 0.5 hertz random biphasic square waveform. The placebo treatment ear clips did not pass current. Neither the participants receiving

active treatment nor the participants receiving placebo treatment felt any sensation at the attachment cite.

Procedure

Participants for the exploratory study were recruited through direct solicitation using local newspaper advertisements, Internet news advertisements, radio advertisements, and flyers posted on community bulletin boards. All forms of solicitation contained information regarding the study, inclusion/exclusion criteria, and a contact number for the principal investigator.

Candidates for the study contacted the principal investigator by phone. This initial telephone contact served as an early screening. If the candidate appeared to meet criteria for the study, an appointment was scheduled for enrollment. During the enrollment session, risks and benefits of the procedure under study were reviewed and any questions the candidates had regarding the study were addressed. The issue of commitment was also addressed in order that the candidates clearly understood that the protocol for the study required participation in the trials at the Research Center for 21 consecutive days. If the candidates were willing and able to agree to this condition, the PHQ-9 was administered. The candidates were then given a copy of the Informed Consent and encouraged to take it home with them for thorough review and, if desired, to discuss and review with their medical provider and family members. An initial date to begin the trials was then scheduled.

Half of the participants selected to participate in the study were randomly assigned to the active treatment group, and the remaining half of the participants were assigned to the placebo treatment group. Individuals selected to participate in the trials

selected a beginning date and were instructed to report to the Research Center on that date. On the initial day of the trials, each candidate was administered a Beck Depression Inventory–II to establish baseline. This same instrument was administered on the final day of the trials to measure outcome.

Participants were assigned a numbered CES device on the first day of the trials. This same numbered device was used by the participant throughout the 21 days of the trials. The principal researcher instructed the participants on how to use the device and how to attach the device to the ear lobes via clip-on electrodes. The duration of the application was 60 minutes at 0.5 Hz and delivered in the form of a biphasic pulse (Schroeder, 2001). Each participant was notified in advance that there may be up to a total of five participants in the treatment area at one time. The principal investigator remained at the Research Center throughout the treatment and was available to the participants as needed.

Ethical Concerns

Individuals who participated in this exporatory study were volunteers. They freely, without coercion, consented to participate in the study. The participants were assured of anonymity. Documents containing the participants' identification including Screening forms, Enrollment forms, Informed Consent documents, Release of Information for emergency contact, PHQ-9, and BDI–II were secured in a locked file cabinet. Access to this file cabinet was limited to the principal investigator.

Although providing safeguards for written documentation was a major concern, the participants' wellbeing was given equal or greater consideration and attention. It was noted that candidates for the study suffered from depressive disorders. Individuals

reporting suicidal ideation were excluded from the study as a safeguard. Candidates who were accepted were closely monitored by the principal investigator, who remained at the Research Center during the trials to observe participants for evidence of any change in symptoms. The names and contact numbers for two counselors were provided to the participants. In addition, participants were encouraged to remain in contact with their primary care provider.

Volunteers who were selected for the exploratory study were informed and clearly understood that half of the participants received active treatment and half received sham/placebo treatment. That is, active treatment was withheld from half of the participants. Upon completion of the study, participants who had been assigned a sham device were notified and offered an opportunity to use an active CES device for a period of 21 days.

The cranial electrotherapy stimulation devices used in this study were furnished by Electromedical Products International, Inc. in Mineral Wells, Texas. The company furnished 10 devices; five active and five sham. The principal investigator was not required to purchase the devices or any materials associated with the use of the devices. The company did not provide any financial incentives to the researcher nor attempt to influence the outcome or publication of results of the study.

Chapter 4
Results

A total of 27 participants provided informed consent to participate in the study. After screening, 25 of the 27 were found to meet the inclusion criteria. The two individuals excluded from the study scored below 14 on the BDI-II indicating no, or very mild, depressive symptoms. Of the five participants who did not complete the trials, one man withdrew after one day in the trials, stating he was not able to commit to 21 consecutive days of treatment. A second man withdrew after participating one day in the trials, stating he did not feel any different after the first treatment and, therefore, did not want to continue. One woman withdrew after one treatment session citing medical issues. Following three sessions, a female participant withdrew, informing the principal investigator that she had a conflict with her work schedule. A second female participant withdrew after three days of treatment. She did not notify the principal investigator of her intent to withdraw. The remaining 20 participants completed the study.

The age of the participants ranged from 35 to 72 ($M = 59.55$; $SD = 7.816$). Of these, 55% (11) were married or living with a partner and 45% (9) were living alone and were single, divorced, or widowed. Ten percent of the participants (2) were male, and 90% of the participants (18) were female. Fifty percent (10) of the participants were employed; 50% (10) were not working. Fifty-five percent (11) of the participants were not taking psychotropic medications. Forty-five percent (9) were stable on medication in that they had been taking psychotropic medication for a period of three months or longer prior to the investigation and continued on the same medication without any change in dosage throughout the trials. The following represented the educational level of the

participants: GED 5% (1); trade school 5% (1); high school 20% (4); college less than 1 year 30% (6); college 2 years 20% (4); college 3 years 5% (1); masters 10% (2); unknown 5% (1).

Of the 20 participants who completed the study, 10 were randomly assigned to the active CES group and 10 were randomly assigned to the sham/placebo CES group. Each group consisted of the following two levels: (1) participants who were not taking medication; and (2) participants who were stable on medication.

To obtain an effect size greater than 0.25 and to establish the sample requirements, a power analysis was conducted (Cohen, 1992; Ferguson, 2009) using the SAS System GLMPOWER Procedure. Results of the analysis for group indicated that in order to detect a difference for comparison of active devices and sham devices at a significance level of 0.05, a sample size of 92 would be required to achieve a power of 0.6. Likewise, if the power were increased to 0.8 at the same significance level of 0.05, the sample size required would be increased to 144. Results of the analysis for medication; that is, group not taking psychotropic medication versus group on active psychotropic medication, indicated that 24 participants would be required to achieve a power of 0.6 at a significance level of 0.05. If the power were increased to 0.8 at the same significance level of 0.05, the sample size required would be increased to 40.

As the present study was an exploratory study, the sample size was limited to $N = 20$. Based upon the power analysis, this sample size was underpowered and, therefore, not sufficient to detect significant differences (Oehlert, 2010). The effect size was calculated using Cohen's *d,* which evaluated the absolute size of the treatment effect and was not influenced at all by sample size (Gravetter & Wallnau, 2008). However, sample

size did affect the decision regarding the best procedure to use for data analysis. Although no model is perfect, it was determined that a *t*-test would be a good approach as it can be used with an extemely small sample size ($N \leq 5$) when the effect size is expected to be large (deWinter, 2013). As multiple comparisons were conducted, the Bonferroni Correction was used to control the overall error rate (Kazdin, 2003).

Because the present study was exploratory with a small sample size, and there was no difference between the pre-test and post-test change between the active group on medication and the active group not taking medication, the levels for the active group were collapsed and a paired *t*-test was conducted. The post-test score on the BDI-II was substracted from the pre-test score on the BDI-II. The results on the BDI-II scoring for active devices indicated an average reduction on the BDI-II ($M = 14.1$ with $SD = 9.96$). This represented a decrease in the BDI-II scoring following treatment that was significant, $t(9) = 4.48$, Bonferroni Corrected p level of 0.05/3 adjusted to $p < 0.0166667$, $r^2 = 0.084$, Cohen's $d = 1.69278$.

A paired *t*-test was then conducted on the sham/placebo group. As the sample size was small and there was no difference between the pre-test and post-test change between the sham/placebo group on medication and the sham/placebo group not taking medication, the levels for the sham/placebo group were combined into one group of participants on sham/placebo devices and a paired *t*-test was conducted. The post-test score on the BDI-II was substracted from the pre-test score on the BDI-II. The results on the BDI-II scoring for sham/placebo devices indicated a reduction on BDI-II scores ($M = 11.1$ with $SD = 7.84$). This represented a decrease in the BDI-II scoring following

treatment that was significant, $t(9) = 4.48$, Bonferroni Corrected p level of 0.05/3 adjusted to $p < 0.0166667$, $r^2 = 0.754$, Cohen's $d = 0.79831$.

A two-sample *t*-test was also conducted comparing the post-test mean BDI-II scores of the active CES group with the post-test mean BDI-II scores of the sham/placebo group. The above post-test mean score of the BDI-II was determined by substracting the post-test score of the BDI-II for each participant in the active group from the pre-test score of the BDI-II for each participant in the active group. The scores were summed and divided by the number of participants assigned to the active group to obtain the mean of the active group. The same procedure was used to obtain the post-test mean BDI-II scores of the sham/placebo group. That is, the post-test score of the BDI-II for each participant in the sham/placebo group was substracted from the pre-test score of the BDI-I for each participant in the sham/placebo group. The scores were summed and divided by the number of participants assigned to the sham/placebo group to obtain the mean of the sham/placebo group. The two-sample *t*-test was the conducted comparing the mean scores of the active versus the sham/placebo group. The results for the active group indicated *M* decrease = -14.10, *SD* 9.96. The results for the sham/placebo group indicated *M* decrease = -11.1, *SD* 7.84. Statistical analysis using the two-sample *t*-test indicated that the difference between the active and the sham groups was not statistically significant, $t(17) = 0.7485$, $p = 0.4644$.

Hypothesis I stated: After the completion of a 3-week protocol of 1-hour daily sessions of active CES at .002 amperes, 0.5 Hz, there will be no change in the post-treatment scores on the BDI-II compared to baseline scores. The null hypothesis was rejected based upon the results of the paired *t*-test which idicated a significant reduction

between post-treatment BDI-II scores as compared to the BDI-II baseline scores. This difference represented a significant improvement in depressive symptoms following the 3-week treatment protocol compared to depressive symptoms reported at baseline. It is further noted that Cohen's $d = 1.69278$ is a large effect size, which may indicate that future studies with greater power would continue to yield statistically significant results.

Hypothesis II stated: After the completion of a 3-week protocol of 1-hour daily sessions of active CES at .002 amperes, 0.5 Hz, there will be no difference in the post-test scores on the BDI-II for the active CES group when compared with scores for the sham/placebo CES control group. The null hypothesis was accepted based upon the results of the two-sample *t*-test indicating that the difference between the groups was not significant. This suggested that the reduction in BDI-II scores for the active CES group noted in Hypothesis I may be due to a placebo effect or a combindation of the treatment and the placebo effect rather than solely the therapeutic effect of CES itself. Further, the question of enhanced placebo effect is raised when comparing medical devices whether active or sham (Kaptchuk, 2000).

Chapter 5
Discussion

Introduction

The purpose of this study was to investigate the effects of Cranial Electrotherapy Stimulation (CES) on depression as measured by the Beck Depression Inventory–II (BDI-II). This was an exploratory study with a sample of 20 participants who were recruited from a rural community in Oregon. It was hypothesized that following 3 weeks of active CES treatment there would be no change in the post-test scores on the BDI-II compared to baseline scores. It was further hypothesized that following the 3-week protocol there would be no difference in the post-test scores on the BDI-II for the active CES treatment group compared to the post-test scores on the BDI-II for the participants in the placebo CES group.

Summary of Findings

Hypothesis I stated that there would be no significant difference in the post-test scores on the BDI-II compared to baseline for the treatment/experimental group following 3 weeks of CES at .002 amperes, 0.5 Hz for one hour daily. A paired *t*-test that included the 10 participants using active CES devices, whether medication free or stable on medication, was conducted which concluded that there was a decrease in the BDI-II scoring following treatment that was significantly more than would be expected by chance. Consequently, the null hypothesis was rejected.

Hypothesis II stated that there would be no significant difference in the post-test scores on the BDI-II for the active/experimental CES group following 3 weeks of CES treatment at .002 amperes, 0.5 Hz for one hour daily when compared with the post-test scores for the sham/placebo CES control group. A paired *t*-test that included all

participants using sham/placebo devices, whether medication free or stable on medication, was conducted which concluded that there was a significant decrease in BDI-II scores following the 3-week protocol. A two-sample *t*-test was then conducted to compare the outcome measures of the active/experimental versus the sham/placebo groups. It was determined that the difference between the active/experimental and the sham/placebo groups was not statistically significant thus confirming Hypothesis II. Consequently, the efficacy of CES in the treatment of depression was not supported.

Discussion

The results of this pilot study indicated that there was a significant decrease in depressive symptoms as measured by the self-report BDI-II following 3 weeks of active/experimental treatment. Data analysis also confirmed that there was a significant decrease in depressive symptoms as measured by the BDI-II following the 3 weeks of sham/placebo treatment. It is hypothesized that this decrease may be due to the placebo effect. The difference between the active/experimental group and the sham/placebo group was not statistically significant; consequently, the efficacy of CES in the treatment of depression was not supported.

The design of the present study may have contributed to the large placebo effect. The trials took place in an office labeled as the "Research Center." This gave an impression of expertise with the probability of a positive treatment outcome for the participant. A medical device was used in this pilot study that may have also contributed to an enhanced placebo effect. In addition, extensive daily rituals were followed and reflected that the participants were placing a good deal of effort into the procedure. The principal investigator also interviewed the candidates for the study, and this process

might have suggested to the participants that the treatment would be effective. Individual training in the use of the CES device was given by the principal investigator, who remained on the premises throughout the trials to ensure adherence to protocol and to respond to any questions from the participants. A rapport developed between the principal investigator and the participants. This relationship may have futher contributed to the placebo effect.

The use of a medical device, as discussed above, has been shown to impact the outcome of clinical trials. An enhanced placebo effect has been found to be present when comparing the active medical device to a sham medical device (Kaptchuk, 2000). An example of this was found in the studies using transcutaneous electrical nerve stimulation for controlling pain (TENS) that have found that the placebo response rates were inordinately high (Deyo, 1990; Oosterhof, 2012). This appears to have contributed to the problems of demonstrating the efficacy of TENS (McQuay, 1997). As Kaptchuk noted, whether a trial has a positive outcome or a negative outcome depends in part on the magnitude of the placebo response. A smaller placebo response favors a positive outcome, whereas a bigger placebo response favors a negative outcome (Kaptchuk, 2000). That is, a large placebo effect reduces the likelihood of demonstrating the efficacy of the experimental treatment, because the placebo outcome is likely to be as large as the experimental outcome. Thus, it is imperative when designing a study using a medical device such as TENS or CES to consider the potential for enhanced placebo effect with the understanding that the bigger the placebo response, the greater the probability that there would be no differences between the experimental versus the placebo device.

The use of healing rituals is also likely to have played a significant role in the present study. The contextual effects of the environment, the interactions between participants and researcher, and the actual ritual of preparing the device and using the device daily in accordance with the specified protocol contributed to a sense of purpose. With this creation of space and time for the ritual, the atmosphere was that of confidence with an expectation of healing (Foot, 2012).

Characteristics of the participants may have contributed to the outcome. Research has shown that expectations of the participants influence both the outcomes of the active treatment group and the placebo treatment group (Kaptchuk, 2002; Alladin, 2013). Not only an expectation of positive treatment outcome but also a willingness to adhere to the treatment protocol may contribute significantly to outcomes (Kaptchuk, 2002). In addition to positive expectancy contributing to the outcome, the role of cognitive dissonance must be considered (Festinger, 1985). This theory holds that when two cognitions are dissonant, that is, opposite of one another, the individual becomes psychologically uncomfortable and motivated to reduce the dissonance (Harmon-Jones, 1999). In the present study, participants freely chose to participate in the study, strongly believed in the outcome, underwent the inconvenience of the 3-week trial period, and endured 60-minute daily treatments. If the participant believed that the treatment was not effective, he or she may have experienced cognitive dissonance, given his or her level of commitment and belief in outcome. In order to avoid cognitive dissonance, the participant may judge the outcome more favorably on the outcome measure, the Beck Depression Inventory-II, which is a subjective self report measure. That is, the participant may have actually experienced little benefit from the treatment; however, in

order to reduce the conflict that would arise if the participant believed the treatment was of no avail, he or she may have reported false benefits in order to maintain cognitive consonance (Homer, 2000). Alternatively, the participant may have experienced an actual change in his or her level of depression as a function of reducing cognitive dissonance.

It would appear that the placebo effect accounted for a large portion of change in the present study for both the control as well as the experimental group. This is consistent with the findings of I. Kirsch, who sparked a large controversy with pharmaceutical companies dating back to 1998 with the publication of his meta-analysis "Listening to Prozac but Hearing Placebo: A Meta-analysis of Antidepressant Medication," which found that the response to inert placebos was approximately 75% of the response to active medication (Kirsch, I., & Sapirstein, 1998). Despite ongoing controversy, I. Kirsch continues to provide evidence to support his claim that "most of the response to antidepressant treatment can be obtained by placebo, and the difference between response to the drug and the response to any treatment is not clinically significant for most individuals diagnosed with major depressive disorder" (Kirsch I., & Low, 2013, pp. 221).

The inclusion criteria for the present study required that participants score 14 or above on the BDI-II in order to participate in the study. This resulted in concern that permitting individuals to participate in the trials with mild depression (14–19) might restrict the range for improvement, thus, making it difficult for a significant level of improvement to occur. However, in the present study this was not likely to have been an issue since only six participants scored in the mild range and these were in the upper mild

range (17, 17, 18, 18, 19, and 19). One participant scoring 17 was randomly assigned to the sham/placebo group of participants who were medication free. She subsequently scored 4 on her BDI-II post-test. The second individual scoring 17 on his BDI-II pre-test was randomly assigned to the active/experimental group of participants who were medication free. He subsequently scored 9 on his BDI-II post-test. The two participants scoring 18 on their BDI-II pre-tests were both randomly assigned to the active/experimental group of participants who were medication free. The BDI-II post-test scores for these two participants were 9 and 4 respectively. The two participants who scored 19 on their BDI-II pre-tests were both randomly assigned to the active/experimental group of participants who were stable on medication. The BDI-II post-test scores for these two participants were 9 and 10 respectively. This appears to represent scores that suggest clinically significant decreases in the participants' level of deperession. This is consistent with the summary of findings by Gunther and Phillips who stated that CES has been shown to be effective in the treatment of mild to moderate depression (Gunther & Phillips, 2010).

Although it is clear that the efficacy of CES in the treatment of depressive disorders was not supported in the present exploratory study, it must be noted that significant change did occur for both the participants in the active/experimental CES group as well as the participants in the sham/placebo CES group. However, were these results large enough not only to be statistically signnificant, but also clinically meaningful? In other words, did the effect of the intervention have any real or practical value in the everyday life of the participants (Kazdin, 2003)?

In order to determine the clinical significance of CES in the treatment of depressive disorders, the magnitude of the effect was measured using Cohen's *d*. Literally, Cohen's *d* is the difference between the means divided by the standard deviation. For the active CES group, Cohen's $d = 1.69278$ was much larger than typical (Kraemer, 2003). That is, the end point score was more than 1.69 standard deviations from the mean. For the sham/placebo CES group, Cohen's $d = 0.79831$ was a large effect size (Kraemer, 2003). Again, the end point score was more than 0.79 standard deviations from the mean. In summary, although the present exploratory study was underpowered and did not support findings of statistical significance, it did clearly demonstrate clinical significance of the CES treatment of depressive disorders among the small number of participants. With the principal investigator being physically present at the Research Center throughout the trials, direct clinical observation was also made of what appeared to be clinically significant changes in the participants. In addition, verbal reports were received regarding changes in motivation and behavior. The initial presentation of participants was flat affect with reported feelings of hopelessness and lack of motivation. As the trials progressed, affect appeared to change and participants frequently smiled. Gradually participants reported feeling some joy with a decrease in hopelessness. One male participant reported, at the end of the trials, that he was getting along better with his wife. Upon questioning, he reported that he was not as irritable, which he believed was part of his depression and which had been an issue in his relationship. Another woman reported that she was now able to enjoy her grandchildren. This participant explained that she had previously felt so sad and unmotivated that prior to the trials she could not participate in activities with her grandchildren. As the trials

were double blinded at the time of the observed and reported changes in mood, information regarding which participants were using the active versus which were using the sham devices was not available to the principal investigator. Therefore, it was not known which group the above qualitative observations referred to.

Upon completion of the trials, information regarding which devices were active and which were sham was disclosed to the principal investigator. Ten participants had been assigned active CES devices. Of these 10 participants, none scored in the Minimal Range of -0- to 13 on the pre-test of the Beck Depression Inventory-II. Five participants scored in the Mild Range of 14 to 19 with scores of 17, 18, 18, 19, and 19. All five of these participants scored within the Minimal Range on the post-test Beck Depression Inventory-II scoring: 9, 9, 4, 9, and 10 respectively. This would suggest a clinically significant change in depression for the participants. Two of the participants scored in the Moderate Range of 20 to 28 on the pre-test Beck Depression Inventory-II with scores of 23 and 27. The post-test score of the individual who scored 23 was 1, which may reflect possible denial of depression or faking good. That is, a score of 1 is lower than usual scores for individuals who do not manifest symptoms of depression (Groth-Marnat, 2009). The post-test score for the second individual was 16, which is in the Mild Range and reflected a clinically meaningful change in depression for this participant. Three of the participants scored within the Severe Range of depression on the Beck Depression Inventory-II pre-test, which is 29 to 63 with scores of 28, 33, and 39. The post-test score for the participants who scored 28 and 39 were 5 and 4, respectively, which placed them in the Mild Range. The one participant who scored 33 reported no change on the post-test score. With the exception of the one participant who reported no change, all

participants in the experimental/active CES group reported moving one or two levels on the Beck Depression Inventory-II following treatment which may be interpreted as clinically significant.

Ten participants were assigned a sham/placebo CES device for the trials. Of these 10 participants, none scored in the Minimal Range of -0- to 13 on the pre-test of the Beck Depression Inventory-II. One participant scored in the Mild Range of 14 to 19 on the pre-test with a score of 17. This individual scored within the Minimal Range on the post-test Beck Depression-Inventory-II with a score of 4. This would indicate a clinically significant change in depression for this participant. Four of the participants scored in the Moderate Range of 20 to 28 on the Beck Depression Inventory-II pre-test with scores of 20, 24, 24, and 27. Following the 3-week trials, these participants scored 5, 10, 18, and 13, respectively, on the post-test Beck Depression Inventory-II indicating a clinically significant decrease in depressive symptoms. Five of the paricipants assigned a sham/placebo CES device scored in the Severe Range of 29 to 63 on the pre-test of the Beck Depression Inventory-II with scores of 29, 41, 43, 49, and 49. The participants' post-test scores on the Beck Depression Inventory-II were 10, 47, 40, 35, and 30, respectively. It is noted that one participant scored 41 on the pre-test and subsequently scored 47 on the post-test. This is the only participant whose score increased during the trials. It is also noted that of the four remaining participants in the Severe Range, only one participant scored in the Minimal Range on the Beck Depression Inventory-II post-test. The remaining three participants scored in the Severe Range of depression on the post-test indicating no movement. This is consistent with the findings of Gunter and Phillips, who reported the CES was most effective for those reporting Mild to Moderate

symptoms of depression (Gunther & Phillips, 2010). It is further noted that those reporting the most severe symptoms of depression where randomly assigned to the sham/placebo group. Notwithstanding, although a decrease in depressive symptoms as reported on the subjective Beck Depression Inventory-II may be considered clinically significant, it is clearly a response to the placebo effect for this group.

One concern of note is the lack of rigorous published research on the efficacy of CES in the treatment of depression. For the present study, the meta-analysis published by Smith (2006) was reviewed. This work consisted of 18 studies with 863 subjects. There were a number of problems in this work including the inclusion of three studies that were crossover and seven studies that were open clinical trials. Further, the devices used were not clearly identified. Smith contended that it was not necessary to identify the devices as they were all substantially equivalent. He based his assessment of the devices on the fact that they had all been grandfathered in by the FDA. However, failure to identify the devices used in the studies prevents replication. Additional issues included duration of treatment both in number of treatment sessions and the length of each session within the trials. Medication was not controlled for, and studies failed to restrict participants to the disorder under study. A second meta-analysis was reviewed for the present study. This work was published by Gilula and Kirsch (2005), and consisted of 23 published studies identified by Gilula and Kirsch, as suitable for CES studies of depression. However, this work included all of the studies included in the meta-analysis by Smith except for one which was excluded as it was identified as a crossover design and the investigator did not report the treatment results prior to the crossover. Gilula and Kirsch, reported positive outcomes in 81% of the investigations and attributed the lack of

positive outcomes in the remaining 19% to the use of older primitive CES devices (Gilula & Kirsch, 2005). This second meta-analysis was actually flawed for the same reasons outlined above regarding the Smith meta-analysis. A further concern of the second meta-analysis was the exclusion of two studies as the control groups within the two studies showed improvement. As a consequence, these two studies were deemed invalid.

The World Federation of Societies of Biological Psychiatry (WFSBP) published guidelines on brain stimulation treatments in psychiatry (Schlaepfer, 2010). In their review of CES, they identified as troublesome the lack of negative studies reported in the literature. Further, the existing studies were identified as small and of poor quality. Consequently, they were not able to determine whether the treatment was truly effective. In their recommendations they called for rigorous academic studies. Others noting the lack of rigorous clincial reseach include Kavirajana (2014) who hypothesed that this lack of trial data may be a function of the regulatory system in place for oversight of medical device marketing (Kavirajan, 2014).

Notwithstanding the issues identified as problemic, the early clinical trials clearly laid the ground work for future studies. Focus must now be directed to establishing standards of CES treatment including most effective dosage and frequency of treatment. The present study used the established recommendation of 3 weeks daily use of CES for the treatment of depression. Use of proven outcome measures is imperative. Therefore, the present study employed the Beck Depression Inventory–II both for pre-test and post-test evaluation of intensity of symptoms. Although the present study failed to show a statistically significant difference between the active/experimental CES group and the sham/placebo CES group, a number of factors may have contributed to this outcome.

Inasmuch as the present study was a pilot study, it was clearly underpowered and this factor may have contributed to the outcome. Further, failure to use a second no-treatment/no-placebo control group to account for the natural course of the disease, may also have contributed to the outcome. These issues will be further explored in the Strengths and Limitations section below.

Strengths and Limitations

Participants for this study were recruited from the community through direct advertisements. One strength of the self-referred participant was that they were highly motivated to participate. This is not an uncommon characteristic of a relatively distressed individual who carries the belief that the intervention will alleviated their emotional distress. Motivation was demonstrated by individual commitment to participate in the trials that required that they come to the Research Center daily for 21 consecutive days. Of the 20 completers, one male missed one day due to a social commitment and one female missed one day due to illness. All other participants completed all 21 consecutive days of treatment and this clearly demonstrated high motivation. As a consequence of the participants full commitment, there was no missing data. This is important in that missing data can represent a serious threat to internal validity.

Another strength of the study was that the principal investigator was present at the Research Center daily and observed the participants using the Alpha-Stim device confirming that the research protocol was being followed. The devices used for this study were furnished by Electromedical Products International, Inc. (EPI) and were locked at a designated intensity that ensured that all participants who were assigned an

active device received the same current intensity. Another strength of this design was that the study was double blind removing any possibility for researcher bias.

A further strength of this study was that alcohol was controlled for. Participants were informed prior to beginning the study that use of alcohol may alter their perception of depressive symptoms and were requested not to use alcohol during the study. All participants agreed not to use alcohol during the 3-week trials. Periodically during the trials, the principal investigator checked in with participants to confirm that they were not using alcohol. However, confirmation of abstinence was verbal only; no objective tests were administered.

Inasmuch as the present study was an exploratory study, the sample size was limited to 20. This created a limitation for the study, as the small number of participants resulted in low statistical power decreasing the probability of detecting significant differences between the active/experimental CES group and the sham/placebo CES group. An increase in sample size would increase power and may result in the detection of significant difference between the active/experimental and the sham/placebo groups.

A possible flaw in the design of the present study that may have contributed to the outcome was the use of only two groups. The underlying assumption of the RCT is that the measureable outcome is the result of the action or influence of the independent variable on the dependent variable or the placebo effect. There has been a tendency to downplay the placebo effect, attributing it to the imagination or ignorance of the reporter of the effect. However, researchers are now recommending that a third group be added to the experimental research design when comparing the active intervention and the placebo. This third group would be a no-treatment no-placebo group and would be used

to help distinguish the placebo effect from the ordinary natural course of the disease, regression towards the mean, and other nonspecific effects (Kirsch, 2002; Kaptchuk, 1998; McDonald, 1983). Ernst, too, endorses the use of a second, untreated control group in placebo-controlled trials (Ernst, 1995). However, he has emphasized the need for researchers to clearly distinguish between placebo and untreated control groups when reporting their findings as failure to clearly distinguish between placebo and untreated control groups may be misleading and lead to misconceptions about the placebo effect (Ernst, 1995).

Another limitation of the research design was failure to consider the enhanced placebo effect of a medical device. As noted above, an enhanced placebo effect may result in a large placebo response increasing the probability that differences between the experimental and the control group would not be found.

A further limitation of the present study was the inclusion of individuals on psychotropic medication for depression as the use of psychotropic medication may be a confounding variable. Should the participant not be stable on the medication, it would be unclear whether any reductions in symptoms were due to the medication or to the independent variable. Therefore, the following guidelines were established:

1. Participants were required to be stable on their medication for a period of 3 months or longer prior to the beginning date of trials.
2. They were informed and agreed to notify the principal investigator should their medical provider recommend a change in their psychotropic medication.
3. In the event that medications were increased or decreased, or the type of

medication changed, the medicated participant understood that their data would not be considered for analysis.

No participant on medication reported any changes during the trials. Further, there were no differences in the pre-test BDI-II scores for participants on medication compared to participants who were medication free. As a result of the above guidelines, it was unlikely that medication represented a confounding factor.

Recommendations

Based upon the findings of the present study, several adjustments need to be made in the experimental design when considering a follow-up RCT. Perhaps the most important adjustment would be an increase in the sample size which would be required to detect a statistically significant difference between groups. Subjects in the present study were derived from a rural community. For a follow-up RCT, it may be necessary to expand the search for participants to a larger community with a greater number of potential participants.

The experimental design for a follow-up RCT also needs to be adjusted to include a second, no-treatment/no-placebo control group in order to account for the natural course of the disease, regression to the mean, and other nonspecific effects. This could be accomplished through the use of a Wait List Control Group. Active treatment would be offered to the Wait List Control Group following completion of the trials.

Conclusions

This exploratory study was a randomized, double-blind, clinical trial. The purpose was to determine the efficacy of CES in the treatment of depressive disorder as measured by the Beck Depression Inventory–II. Following the 3-week protocol, the post-

test scores on the BDI–II were significantly lower for the active/experimental CES group compared to the pre-test scores. Likewise, the post-test scores on the BDI–II were significantly lower for the sham/placebo CES group compared to the pre-test socres. As there was no statistically significant difference between the post-test scores for the active/experimental CES group versus the sham/placebo CES group, the efficacy of CES cannot be confirmed by the present study. Limitations to the present study, including small sample size and failure to include a second, untreated control group, may have contributed to obscuring the effects of CES that may have been prevalent. Future studies should adjust for these limitations.

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Appendix A

Screening Form

Date of Screening:_____

Name:_____

Address:_____

Male:_____Female:_____ Age:_____ Date of Birth:_____

Referral Source:_____

Health Care Provider:_____

Diagnosis:_____

Name and Credentials of Individual Making Diagnosis_____

Date of Diagnosis:_____

Presence of Psychotic Symptoms: _____Suicidal Ideation:_____

History of Suicide Attempt[s]:_____Parasuicidal BX:_____

Pacemaker:_____ History of Head Injury:_____

History of Epilepsy or Convulsions:_____

Currently [or within the past 6 months] using medications that effect the CNS:_____

Names of Medications:_____

Currently [or within the past 6 months] using marijuana_____

Currently [or within the past 6 months] participating in therapy:_____

Females Only: Pregnant or Nursing:_____

Willing and Able to Commit to 21 Consecutive Days of Trials at Research Center:_____

Date of Enrollment Interview:_____Rejected:_____

Reason for Rejection:_____

Marie D. Turner, Principal Researcher

Appendix B

Enrollment Form

Date of Enrollment:_____

Name:_____

Address:_____

Male:_____Female:_____Date of Birth:_____

Contact Number:_____

Emergency Contact Person: _____

Number for Contact Person: _____Release in File:_____

Criteria for Trials Met: _____

Inclusion Criteria Met:

Age: _____

Diagnosis: _____

PHQ-9 Score: _____BDI-II Score: _____

Willing to commit to 21 consecutive days of trial: _____

Exclusions Criteria Met:

Psychotic Symptoms: _____Suicidal Ideation: _____

HX of Suicide Attempt(s): _____

Current or History of Parasuicidal Behavior: _____

Taking medication that effects the CNS:

Currently: _____Within past 6 months: _____

Taking Illegal Substances including Cannabis:

Currently: _____Within past 6 months:_____

Currently participating in Psychotherapy: _____

HX of Head Injury and / or Traumatic Brain Injury:_____

HX of Epilepsy or Convulsions:_____

Pacemaker: _____

Women:

Pregnant:_____Nursing: _____

Informed Consent Signed:_____

Start Date of Trial: _____

_____ _____

Marie D. Turner, Principal Researcher Date

Appendix C

Patient Informed Consent

Study Title: Efficacy of Cranial Electrotherapy Stimulation in the Treatment of Depression: A Pilot Study

Principal Investigator: Marie D. Turner

Study Site: xxxxx N.E. Avery Street, Newport, Oregon 97365

Daytime Phone: 541-xxx-xxxx 24-Hour Emergency Phone: 541-xxx-xxxx

1. INTRODUCTION

This research study is a clinical trial. It will include only those people who choose to take part. Please read the following information and ask as many questions as you want. This document will describe what you can expect and what will be expected of you if you choose to take part in this study. It will also provide you with information regarding the risks and possible benefits of this treatment. Take your time to make your decision. You may wish to discuss this with your family and friends. You are encouraged to also discuss this with your doctor or health care provider.

This research study is under the direction and care of the principal investigator Marie D. Turner, PhD Candidate and is under the supervision of Dissertation Chair Dr. Gary Groth-Marnat of Pacifica Graduate Institute of Santa Barbara, CA. The results of this randomized control trial (RCT) will be published in a Dissertation which is a partial requirement for the degree of Doctor of Philosophy (PhD) and will be in the form of statistical analysis of the data collected. All information regarding individual

participants will be confidential.

2. WHY IS THIS STUDY BEING DONE?

The purpose of this study is to test the efficacy of cranial electrotherapy stimulation in the treatment of Depressive Disorders. This procedure will involve the application of microcurrents of electricity across the forehead. This microcurrent will be emitted by a handheld device that is known as an 'Alpha-Stim.' This device is manufactured by Electrical Products, Incorporated. Small ear clips will be attached to the earlobes from which microcurrents of electricity will be emitted in a biphasic pulse. At the present time this procedure may be prescribed for insomnia. Currently it is under study by this researcher and others in the field to measure the effectiveness of this treatment modality for Depressive Disorders.

3. WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

If you decide to take part in this research study, you will first contact the principal investigator, Marie D. Turner, for a telephone Screening Interview to determine if you meet criteria for the trails. If you appear to meet criteria, you will be scheduled for an Enrollment Interview with the principal investigator which will take place at the Research Center. At this initial meeting you will be asked to complete the Patient Health Questionnaire–9 (PHQ-9) which is a brief 9-question instrument that will be used to confirm your diagnosis of Major Depressive Disorder. The inclusion and exclusion criteria for the trials will be reviewed with you to confirm that you meet criteria. The

risks and benefits of participating in the study will be reviewed with you as will the Patient Informed Consent document which you will be asked to sign. You will then be asked to commit to participate in the trials for 21 consecutive days. If you agree to participate, you will be notified of the start date for your trials.

The trials will take place at the Research Center. On the first day of the trials, you will be asked to complete the BDI-II which will provide information regarding the level of intensity of your symptoms of depression. You will then be assigned a numbered cranial electrotherapy stimulation device. You will use this same numbered device that you are assigned throughout the trials. You will then be instructed on how to use the device. The treatment will last 60 minutes. You will be asked to return to the Research Center daily for 21 consecutive days for the 60 minute treatment. On the final day of the trials, you will again be asked to complete the BDI-II.

4. HOW LONG WILL I BE IN THE STUDY?

The study is designed for 3 weeks of treatment. Once you are assigned a beginning date for trials, you will meet with the principal investigator at the Research Center for 21 consecutive days of treatment.

5. CAN I STOP BEING IN THE STUDY?

You are encouraged to thoroughly consider what is involved in the trials prior to committing to participation. However, once trials have begun should you decide you do not want to continue for any reason whatsoever, you may notify the principal

investigator and you will be immediately terminated from the trials. There is no penalty for discontinuing the trials.

6. WHAT ARE THE RISKS OF THE STUDY?

While taking part in the study you are at risk for side effects. Adverse side effects of cranial electrotherapy stimulation are rare and may include:

- Dizziness
- Mild skin irritation or burn at the cite of the ear clips
- Minor headache
- Nausea

It is important to note that individuals with the following conditions will be excluded from the trials as the effects of cranial electrotherapy stimulation on these conditions is not known:

- Demand type pacemaker
- History of traumatic brain injury
- History of seizures
- Women who are pregnant or are nursing

7. ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

We do not know if you will benefit from being in the study. However, you may experience a decrease in your symptoms of depression following your participation in the 3-week trials.

It is hoped that the information gained from the current trials will add to the body of knowledge available regarding the effectiveness of cranial electrotherapy stimulation for the treatment of depression.

8. WHAT OTHER OPTIONS ARE THERE?

If you are suffering from Major Depressive Disorder, you are not required to participate in this research study. You may seek treatment or advise for the management of your symptoms from your health care provider. Traditional treatment modalities are available in the form of psychotropic medication and psychotherapy. There may be alternative treatment modalities that you health care provider could provide information about.

9. WHAT ARE THE COSTS?

There is no cost in terms of financial commitment for participating in the trials. However, as a participant you will be expected to arrange for transportation to the Research Center on a daily basis for a period of 21 consecutive days.

10. WILL I BE PAID FOR TAKING PART IN THIS STUDY?

I understand that I will not receive financial, or any other type of, compensation for my participation in this study.

11. WHAT ARE MY RIGHTS AS A PARTICIPANT?

As a participant in this research study, you have the right:

1. To have sufficient time to make your decision as to whether or not to be in the research study and to make this decision without any pressure from the individuals who are conducting the research.
2. To refuse to participate in the study; or to stop participating in the study at any time after beginning the study.
3. To be informed about what the study is trying to find out; to be informed about what will happen to you; and to be informed about what you will be asked to do if you decide to participate in the study.
4. To be informed about risks that may be reasonably foreseen if you decide to participate in the study.
5. To be informed about potential benefits if you decide to participate in the study.
6. To be informed about whether there will be any financial costs to you that are associated with being in the study and to be informed about whether you will be compensated for participating in the study.
7. To be informed about who will have access to information collected about you during the study; to be informed about how your confidentiality will be protected.
8. To be informed about whom to contact with questions or concerns about the research and about your rights as a research subject.
9. To be informed about the other non-research treatment modalities that may be available to you.

10. To be informed about any new information related to the research study that may affect your health, welfare, or may influence your willingness to participate in this research trial.

12. WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

All personal information disclosed to the Principal Investigator either during the Screening or Enrollment Interviews will be kept in a file in a locked cabinet. Access to this information will be limited to the principal investigator. Likewise, information disclosed on the PHQ-9 and BDI-II testing instruments will be secured in a locked cabinet with access being limited to the principal investigator. Results of the trials will be reported in terms of data analysis and individual information will not be disclosed.

13. WHO SHOULD I CONTACT IF I HAVE QUESTIONS OR PROBLEMS?

I understand that should I have questions or experience any type of a problem I should contact the principal investigator, Marie D. Turner at 541-xxx-xxxx. I understand that she will be present at the Research Center during the trials and, on an emergency basis may be reached at 541-xxx-xxxx.

I understand that if my symptoms increase in severity during the research trials:

- I should immediately notify the principal investigator, Marie D. Turner
- I should notify my health care provider
- I may consult with one of the following counselors without cost to me:

Barbara A., LPC

541-xxx-xxxx

Dennis B, MS

541-xxx-xxxx

- I may have access to a case manager to assist me in resolving unanticipated problems

  Dianne C.

  503-xxx-xxxx

14. RELEASING INFORMATION TO YOUR PRIMARY CARE PROVIDER

You may wish to inform your health care provider(s) that you are participating in a clinical research study. Please provide the following information if you would prefer that we notify your health care provider(s):

_____No. Do not notify my health care provider(s) that I am participating in this clinical trial. I will inform them myself.

_____Yes. Please notify my health care provider(s) that I am participating in this clinical trial.

Provider Name:_____

Address/City/State_____

Provider Name:_____

Address/City/State:_____

15. EMERGENCY CONTACT RELEASE

In the event of an emergency I give permission to the principal investigator, Marie D. Turner, to contact the following individual(s):

Name of Emergency Contact Person:_____

Address/City/State:_____

Emergency Phone Number:_____

Emergency Cell Phone Number:_____

Name of Emergency Contact Person:_____

Address/City/State:_____

Emergency Phone Number:_____

Emergency Cell Phone Number:_____

SIGNATURE

I have read and I understand the information on this Consent Form. By signing the form I am agreeing to volunteer to participate in this study. I have had a chance to discuss this with the principal investigator, Marie D. Turner. I understand the purpose of this research study and I understand what taking part in this study will involve. My questions have been answered to my full satisfaction and I understand that I can ask questions

while I am taking part in this study. I also understand that I can change my mind regarding participating at any time that I choose without any penalty.

I VOLUNTARILY AGREE TO TAKE PART IN THIS STUDY

_____ _____/_____/_____
Signature of Participant Date

_____ _____/_____/_____
Participant Printed Name Date

_____ _____/_____/_____
Signature of Person Obtaining Written Consent Date

_____ _____/_____ /_____
Person Obtaining Written Consent Printed Name Date

Copies to: Participant; Research Chart

Appendix D

Device Number and Record

Device Number: _____

Name: _____

Enrollment Date: _____

Date PHQ-9 Completed: _____ PHQ-9 Score_____

Date Initial BDI-II Completed:_____ BDI-II Score_____

Beginning Date of Trial: _____

Week 1 _____ _____ _____ _____ _____ _____ _____

Week 2 _____ _____ _____ _____ _____ _____ _____

Week 3 _____ _____ _____ _____ _____ _____ _____

Date Concluding BDI-II Completed:_____BDI-II Score: _____

Signature of Participant: _____

Date of Completion of Trials: _____