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How Nexalin Therapy Works

Brain Stimulation Using Nexalin Technology: A Non-Invasive Method of Treating Anxiety, Depression, and Insomnia
SYNOPSIS

The human brain is the most complex organ in the body and is constantly changing, making it difficult for science to know exactly how it works. Although we have very strong opinions about it, the exact mechanism by which Nexalin® Advanced Therapy produces such positive results is not fully understood. However, laboratory and clinical evidence suggest that Nexalin’s patented electrical stimulation affects the hypothalamus and related brain structures to adapt and change the levels of neurochemicals including neuropeptides, neurotransmitters and neuromodulators. The data support that the Nexalin electrical stimulation results in the endocrine outputs moving toward “normalization,” specifically those coming from the hypothalamic nuclei and associated brain structures. A key indicator of this is a significant clinical change in levels of enkephalins and beta-endorphins in the cerebral spinal fluid of Nexalin treated subjects, as well as other neurochemicals like serotonin. The change in these neurochemicals is also apparent based on the responses noted by the patients after they receive Nexalin Advanced Therapy.

The hypothalamus’ main function is to maintain homeostasis (state of equilibrium) of the body. In order to perform this function, it is constantly sensing and adapting to information received by the brain. So, by nature the hypothalamus is sensitive and responsive to stimuli. Many disorders including depression, anxiety, and insomnia are believed to be a result of a decrease in the production of specific neurochemicals. Pharmaceutical therapies act by replacing these neurochemicals with a drug; Nexalin Therapy works by permitting your body to manage the production of these neurochemicals on its own. With its regimen of consecutive treatment sessions, Nexalin Therapy utilizes the hypothalamus’ adaptive ability resulting in changes in the production of these neurochemicals to more normalized levels. The clinical effect is a decrease in the symptoms. Clinical trial results confirm these results, as illustrated in Figures 3 & 4, where the clinical effect maintains its statistical significance through the 12-week follow up period.

The Nexalin device has extensive clinical experience; the clinical trials have studies more than 700 subjects and provided more than 10,000 therapies. Nexalin Therapy has been and continues to be used in clinical studies involving a number of additional symptoms that arise from an imbalance in neurochemicals. The symptoms include those in patients with Parkinson’s disease, chronic osteoarthritis pain, and post surgical pain. Although the numbers of therapy sessions differ, the Nexalin electrical stimulation has consistently shown positive results and statistically significant results in most cases. Furthermore, the improvements are clinically significant and lasting, typically for months, with no statistically significant drop off. We believe that this provides strong support for Nexalin Therapy’s positive and durable effects on the hypothalamus and associated brain structures.

Attachment A is included to provide more detailed information on the function of key brain structures.

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1 U.S. Patent #6904322B2
Brain Stimulation using Nexalin Technology:
A Non-Invasive Method of Treating Anxiety, Depression and Insomnia
HOW DOES NEXALIN ADVANCED THERAPY WORK?

As stated earlier, the brain is the most complex organ of the human body, thus the exact mechanism by which Nexalin Advanced Therapy produces such dramatic results is not fully understood. However, data suggest that the patented waveform delivered during the Nexalin Therapy effects the hypothalamus and associated brain structures. A key indicator of this effect is a significant change in levels of enkephalins and beta-endorphins in the cerebral spinal fluid and brain structures, as well as other neurochemicals including serotonin and substance P.

A major function of the hypothalamus is to maintain homeostasis by constantly sensing and adapting to information received by the brain. When the body is faced with a degenerative or chronic process the hypothalamus appears unable to maintain normal levels of serotonin, beta-endorphins and other neuropeptides, neurotransmitters and neuromodulators. The result of reduced levels of these important neurochemicals can be anxiety, depression, and insomnia; which can increase in frequency and severity if not treated.

Nexalin Therapy consists of consecutive, daily treatment sessions. Through this repetitive stimulation of the hypothalamus, Nexalin Therapy can trigger significant changes in the levels of important neurochemicals within the brain. Since the hypothalamus’ primary job is maintaining the body in a stable, constant condition (homeostasis), changes in the normalized levels of neurochemicals including serotonin, beta-endorphins, and substance P may then be used within the brain to effect a response, i.e., “stop the degenerative or chronic process” – to restore, rebalance, and renew the homeostasis. We believe that Nexalin Therapy assists the hypothalamus to re-establish and sustain these neurochemicals at the brain’s healthy, normalized levels, resulting in prolonged improvement, as observed in recent clinical studies.

SCIENTIFIC EVIDENCE

Nexalin’s Patented Waveform

The Nexalin device produces a patented waveform that provides transcranial electrical stimulation (TES) delivered at a frequency of 77.5 Hz. This unique frequency results in the greatest increase in beta-endorphins as illustrated in Figures 1 and 2. The study resulted in an average of 580% increase (p<0.001) in beta-endorphins in the cerebral spinal fluid measured in patients with chronic spinal pain and 350% increase (p<0.001) in normal patients with no chronic pain symptoms.

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2 U.S. Patent #6904322B2
3 CHANGE IN THE BETA-ENDORPHIN LEVELS IN BRAIN AND CEREBROSPINAL FLUID IN TRANSCRANIAL ELECTROANALGESIA, L. N. Airapetov, A. M. Zaitchik, M. S. Trukhmanov, V. P. Lebedev, V. A. Sorokoumov, Ya.S. Katsnelson, V. G. Abisogomian, and Yu. K. Kodzaev, Pavlov Institute of Physiology of the USSR Academy of Sciences, Pediatric Medical Institute, Leningrad, USSR
5 CHANGE IN THE BETA-ENDORPHIN LEVELS IN BRAIN AND CEREBROSPINAL FLUID IN TRANSCRANIAL ELECTROANALGESIA, L. N. Airapetov, A. M. Zaitchik, M. S. Trukhmanov, V. P. Lebedev, V. A. Sorokoumov, Ya.S. Katsnelson, V. G. Abisogomian, and Yu. K. Kodzaev, Pavlov Institute of Physiology of the USSR Academy of Sciences, Pediatric Medical Institute, Leningrad, USSR
Figure 1 – Amount of Beta-Endorphin in the Cerebral Spinal Fluid (CSF) in Chronic Spine pain patients when stimulated using TES at 77 Hz. In patients with chronic pain, beta-endorphin concentration was 1.5-times lower than that in normal subjects and had average value of 11.9+0.8-pmole/l. After 30-min. electrostimulation, average CSF beta-endorphin concentrations to increase 580% to reach the level of 69.9+7.5-pmole/l (p <0.001).

Figure 2 – Amount of Beta-Endorphin in the Cerebral Spinal Fluid (CSF) in normal patients when stimulated using TES at 77 Hz. Average beta-endorphin concentration in CSF of normal individuals was 19.1+0.9-pmole/l. Transcranial electro analgesia caused average beta-endorphin concentrations to increase 350% (p <0.001) and to reach the level of 67.6+7.6-pmole/l. 15 minutes after the end of electrostimulation, no significant increase in the beta-endorphin levels were observed (p <0.05).
THE CLINICAL RESULTS

The results of a double-blind-placebo controlled Phase II Study, Using Nexalin Advanced Therapy to Treat Symptoms Associated with Mild to Moderate Depression Episodes, showed a statistically significant reduction in symptoms for those patients treated with “active Nexalin devices + placebo drugs” (Figures 3 and 4). These results indicate that Nexalin Therapy continues to show improvement during the 12 weeks after therapy. Patients treated with Nexalin Therapy reported normal behavioral responses (measured using the Hamilton Depression Rating Scale (HAM-D21) and the Hamilton Anxiety Rating Scale (HAM-A21)) that lasted the entire 12-week follow up period6.

![Graph of HAM Depression](image)

**Figure 3** - HAM-D21 by Device and Time Interval (p < 0.001)

**Graph of HAM Anxiety**

**Figure 4** - HAM-A21 by Device and Time Interval (p < 0.001)

6 Phase II Study, Using Nexalin Advanced Therapy to Treat Symptoms Associated with Mild to Moderate Depression Episodes

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In addition to the Hamilton scales, the clinical study also used the BDI (Beck) Scale, the MADRS, the HADS<sub>D</sub> and HADS<sub>A</sub> Scales. The different methods produced results that correlated in all cases as can be seen in the Table 1 below.

### Outcome of Study Measures

<table>
<thead>
<tr>
<th>Control Variable – treatment day</th>
<th>HAM_D</th>
<th>HAM_A</th>
<th>MADRS</th>
<th>BDI</th>
<th>HADS_A</th>
<th>HADS_D</th>
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<tr>
<td>N</td>
<td>825</td>
<td>825</td>
<td>825</td>
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<td>HAM_D Correlation</td>
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<td>.979</td>
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<td>.001</td>
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<td>.929</td>
<td>.849</td>
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<td>.783</td>
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<tr>
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<td>MADRS Correlation</td>
<td>.925</td>
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<td>BDI Correlation</td>
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<td>HADS_A Correlation</td>
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<td>.001</td>
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<td>.001</td>
</tr>
<tr>
<td>HADS_D Correlation</td>
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<td>.783</td>
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<td>.001</td>
<td>.001</td>
<td>.001</td>
<td>.001</td>
<td>.</td>
</tr>
</tbody>
</table>

Table 1 - Correlations of Different Scales - all depression and anxiety scales had high and very significant bivariate correlations with the Correlation Coefficient > 0.75

**DEMONSTRATED CLINICAL SAFETY**

The Nexalin device has undergone extensive safety analysis with the results clearly indicating that the device is safe for its intended use. Additionally, the classification of the device places it into a non-significant risk (low risk device) category.

A review of Phase III Pivotal Clinical Trials (with a follow up period of one year) demonstrates that Nexalin Therapy does not result in any significant untoward responses. In fact, there was no significant difference between reported events in the placebo group and reported events in the active treatment group (Figure 5).
**HOW IS THE THERAPY ADMINISTERED?**

The patented waveform of Nexalin Advanced Therapy is administered through medical grade conductive pads that are produced specifically for the Nexalin technology. The pads are placed on the forehead and behind each ear, and are connected to the Nexalin device with thin cables.

Nexalin Advanced Therapy is a highly effective, yet soothing treatment. Most patients feel nothing during Nexalin Therapy. At Nexalin Advanced Therapy Centers, patients are treated to a quiet, 45-minute session where many actually relax to the point of sleep during a session.

Relief starts as early as the first therapy and most by the third.

**CONCLUSION**

The brain is the most complex and least understood organ of the human body. Nexalin Therapy appears to provide stimulation that affects the hypothalamus and associated brain structures to adapt and alter the levels of neuropeptides, neurotransmitters and neuromodulators critical to maintaining normal mood behavior. This effect is long lasting. It is hypothesized that with a maintenance program normalization can be maintained for prolonged periods.

The other important factor is that at the completion of the Nexalin Therapy the hypothalamus has either adapted to a new level and stabilized or is in the process of stabilizing, resulting in the long lasting benefit.
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2. CHANGE IN THE BETA-ENDORPHIN LEVELS IN BRAIN AND CEREBROSPINAL FLUID IN TRANSCRANIAL ELECTROANALGESIA


4. Robust and tissue-specific expression of TPH2 versus TPH1 in rat raphe and pineal gland
   Paresh D. Patel, Crystal Pontrello and Sharon Burke

5. Brain Basics: Know Your Brain, National Institute of Neurological Disorders and Stroke
   (part of the National Institutes of Health), NIH Publication No.01-3440a, last updated May 01, 2007

6. Neuroscience Tutorial, created by Diana Weedman Molavi, PhD at the Washington University School of Medicine; Washington University Program in Neuroscience, copyright 1997


8. Excerpts from KidsHealth website, created by The Nemours Foundation's Center for Children's Health Media; updated and reviewed by: Steven Dowshen, MD; July 2007
ATTACHMENT A

FUNCTION OF KEY BRAIN STRUCTURES

An overview of the endocrine system, and more specifically the hypothalamus, is provided below to help you better understand the impact of Nexalin® Advanced Therapy's stimulation on these vital areas of the brain.

The Hypothalamus

Within the body’s endocrine system, the hypothalamus a collection of specialized cells located in the lower central part of the brain. This vital area is the control center of all autonomic regulatory activities of the body. It has been said that the hypothalamus is the “brain of the brain.” It is also:

• An important emotional center, controlling the molecules that make you feel exhilarated, angry, or unhappy.\(^7\)
• The hub for automatic (or subconscious) and endocrine homeostatic systems such as cardiovascular, temperature, and abdominal visceral regulation.
• Management system for all endocrine hormonal levels, sensory processing, and organizing body metabolism, as well as ingestive behaviors.

The hypothalamus is the primary link between the endocrine and nervous systems; it appears that almost everything the hypothalamus does is related in some way to the management of the brain and body connection. Nerve cells in the hypothalamus control the pituitary gland by producing chemicals that either stimulate or suppress hormone secretions from the pituitary.

The hypothalamus is responsible for maintaining homeostasis, the body’s regulation of its internal environment so as to maintain a stable, constant condition. To maintain homeostasis, the hypothalamus is constantly adapting to stimuli from the five senses (sight, hearing, touch, taste, smell) as well as feedback from the nervous and endocrine systems.

“Once the hypothalamus is aware of a problem, how does it fix it? Essentially, there are two main outputs: neural signals to the autonomic system and endocrine signals to/through the pituitary.”\(^8\)

The hypothalamus controls pituitary output by secreting specific chemicals to the pituitary's front lobe. If the hypothalamus is the “command center,” the pituitary gland is the “first lieutenant.” “The pituitary gland is often portrayed as the ‘master gland’ of the body. Such praise is justified

\(^7\) Brain Basics: Know Your Brain, National Institute of Neurological Disorders and Stroke (part of the National Institutes of Health), NIH Publication No.01-3440a, last updated May 01, 2007

\(^8\) Neuroscience Tutorial, created by Diana Weedman Molavi, PhD at the Washington University School of Medicine; Washington University Program in Neuroscience, copyright 1997
in the sense that the anterior and posterior pituitary secretes a battery of hormones that collectively influence all cells and affect virtually all physiologic processes. The pituitary gland may be king, but the power behind the throne is clearly the hypothalamus.9

The paraventricular nucleus (PVN) is an aggregation of neurons in the hypothalamus, which produces many hormones. It is adjacent to the third ventricle (hence the name of the nucleus.) Although it is in the periventricular zone, it is not to be confused with the periventricular nucleus that occupies a more medial, subjacent position to the third ventricle. The PVN is highly vascularised and is within the blood-brain barrier, although the neuroendocrine neurons in this nucleus project to sites (the median eminence and the posterior pituitary) that lack a blood-brain barrier.10

**Neurochemicals**

The brain produces more than 50 identified active drugs. Some of these are associated with memory, others with intelligence, still others are sedatives. Some of the neurochemicals believed to be affected by Nexalin Therapy are:

- **Endorphin** – Called the brain's painkiller, it is 3 times more potent than morphine.
- **Serotonin** – An opiate-like chemical that helps maintain a "happy feeling," and seems to help keep our moods under control.
- **Melatonin** – Produced by the pineal gland, regulates behavioral and physiological circadian rhythms. Levels of melatonin in the blood are highest prior to bedtime.
- **Dopamine** – Similar to adrenaline; it affects brain processes that control movement, emotional response, and ability to experience pleasure and pain. The brains of people with Parkinson's disease contain almost no dopamine.
- **Substance P** – In the central nervous system, is associated with the regulation of mood disorders, anxiety, stress, reinforcement, neurogenesis, neurotoxicity and pain.
- **Acetylcholine** – The first neurotransmitter ever identified, it is particularly important in the stimulation of muscle tissue. In high doses, it can cause convulsions and tremors. In deficient levels, it can contribute to motor dysfunction.

Neurologists have long been aware of four classical neurotransmitters: epinephrine, norepinephrine, serotonin, and acetylcholine; but recently there have emerged a large number of additional neurotransmitters, of which an important group is the neuropeptides. While neuropeptides function as neurotransmitters, some of them also perform the role of neuromodulators; they do not act directly as neurotransmitters but rather as inhibitors or stimulators of neurotransmission. Opiates are a group of neuropeptides that act as both neurotransmitters and neuromodulators. Opiates' are so named because they are the naturally occurring neuropeptides with a strong affinity to the receptors that bind opiate drugs such as morphine and heroin. In effect, they are the body's opiates.

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10 Paraventricular nucleus of hypothalamus - Wikipedia

Brain Stimulation using Nexalin Technology: A Non-Invasive Method of Treating Anxiety, Depression and Insomnia
The Endocrine System

“Although we rarely think about them, the glands of the endocrine system and the hormones they release influence almost every cell, organ, and function of our bodies. The endocrine system is instrumental in regulating mood, growth and development, tissue function, and metabolism, as well as sexual function and reproductive processes. Even though the nervous system and endocrine system are separate systems, they often work together to help the body function properly.

The foundations of the endocrine system are the hormones and glands. As the body's chemical messengers, hormones transfer information and instructions from one set of cells to another. Hormone levels can be influenced by factors such as stress, infection, and changes in the balance of fluid and minerals in blood.

A gland is a group of cells that produces and secretes, or gives off, chemicals. Some types of glands release their secretions in specific areas. Endocrine glands release more than 20 major hormones directly into the bloodstream where they can be transported to cells in other parts of the body.

The major glands that make up the human endocrine system are the hypothalamus, pituitary, thyroid, parathyroids, adrenals, pineal body, and the reproductive glands.

The Pituitary Gland

The pituitary gland is located at the base of the brain just beneath the hypothalamus and is considered the most important part of the endocrine system. It's often called the "master gland" because it receives instructions from the hypothalamus and then releases hormones that control the thyroid and adrenal glands. The production and secretion of pituitary hormones can be influenced by factors such as emotions and seasonal changes. To accomplish this, the hypothalamus relays information sensed by the brain (such as environmental temperature, light exposure patterns, and feelings) to the pituitary. One of the hormones secreted by the pituitary is endorphins, chemicals that act on the nervous system to reduce sensitivity to pain.”

The Pineal Gland

The pineal body, also called the pineal gland. The pineal gland is a small organ shaped like a pine cone (hence its name) located in the middle of the brain. The pineal gland synthesizes and secretes melatonin, a structurally simple hormone that communicates information about

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11 Excerpts from KidsHealth website, created by The Nemours Foundation's Center for Children's Health Media; updated and reviewed by: Steven Dowshen, MD; July 2007
environmental lighting to various parts of the body. The duration of melatonin secretion each day is directly proportional to the length of the night. The light-transducing ability of the pineal gland has led some to call the pineal the "third eye".  

The Limbic System

The limbic system wraps around the brain stem and is beneath the cerebral cortex. It is a major center for emotion formation, behavior, learning, and memory. The limbic structures are also connected with other major structures such as the cortex, hypothalamus, thalamus, and basal ganglia.

The structures of the limbic system are highly interconnected with the rest of the brain, and they likely form a gateway for communication between the cerebral cortex and the hypothalamus. This gateway allows for cognitive processes to modify the affect of the limbic system on hypothalamic functions, which provides a more extensive adaptive mechanism in an effort to normalize.
ABSTRACT

The number of people in this country exhibiting symptoms of depression and anxiety continues to grow and is projected to continue growing through the next decade at least. The symptoms of these disorders cause substantial distress for the sufferers and their families and cost society dearly each year in lost time and suboptimal job performance. Recent research has raised questions about the effectiveness of medications long considered a standard of care in the treatment of these conditions. In light of this information it seems appropriate to explore alternative therapies that demonstrate a high level of effectiveness in mediating anxiety and depression without serious side effects.

This presentation reviews and evaluates the outcomes of a clinical study involving anxious and/or depressed patients who were treated in a clinical setting using a specific form of transcranial electrical stimulation (TES) that lightly stimulates the hypothalamus and associated brain structures at a frequency shown to encourage the normalization of neurochemistry. The purpose of the present study has been to replicate the effectiveness of this TES protocol in the everyday clinical setting using as measurement standards the quantitative EEG (QEEG) and a multifaceted battery of pre- and post-tests and scans readily available in the clinical setting.

The value of targeting the hypothalamus is discussed, rationalizing that approach as a key to highly effective outcomes. Then, the treatment outcomes of a population undergoing TES in the clinical setting are summarized and several case studies presented to illustrate more specifically the potential of TES as a therapeutic treatment and what may be its implications for treating the symptoms of aging.

Keywords: TES, transcranial electrical stimulation, depression, bipolar, anxiety, hypothalamus, neurochemistry.

INTRODUCTION

In an average year in the U.S. some 40 million people suffer from anxiety and another 20 million become clinically depressed. The symptoms of these disorders cause substantial distress for the sufferers and their families and cost society dearly each year in lost time and suboptimal job performance. Moreover, the number of people exhibiting symptoms of depression and anxiety continues to grow and is projected to continue growing through 2020. Persons who cannot find an effective solution to their depression or anxiety tend to get worse and develop dysfunctional behaviors and habits as they seek to compensate, making treatment even more complex. These behaviors and habits not only complicate treatment, but can speed the progress of degenerative diseases and advance the aging process.

Medication has been considered a primary course of treatment for mood disorders in conventional medicine and its use continues to increase. For instance, the number of Americans taking antidepressants alone has doubled in the last decade. Now recent research has raised questions about their actual effectiveness.

A recently published study submitted to the FDA examined the current status of research on antidepressant drugs’ effectiveness. The study, involving four meta-analyses of antidepressant efficacy, suggested that antidepressants may be only marginally efficacious compared with placebos. Further, the authors document profound publication bias that apparently inflates efficacy figures. Considering this information in light of the drugs’ side effects – including death via suicide or uncontrolled behavior – it may make sense to explore therapies shown to be highly effective for anxiety and depression without serious side effects.

One such path leads to forms of brain electrical stimulation amenable to administration in the office setting. The first experiments with low intensity electrical stimulation of the brain were conducted by Drs. Leduc and Roux in 1902. As the field has progressed several technologically advanced methods of brain electrical stimulation have found their way into current practice: Transcranial electrical stimulation
European and U.S. methods, cranial electrical stimulation (CES), and transcranial magnetic stimulation (TMS). Table 1 outlines the characteristics, treatment focus, applications, contraindications and reported effectiveness levels of each.

### Technology Evaluation

<table>
<thead>
<tr>
<th>Type of Brain Stimulation</th>
<th>Treatment Protocol/Duration</th>
<th>Treatment Focus</th>
<th>Applications</th>
<th>Contraindications</th>
<th>Effectiveness</th>
<th>Duration and Cost of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TES (Transcranial Electrical Stimulation)</td>
<td>Rectangular Pulse of 1.0-5.0 mA administered via pads on forehead and each mastoid; 5-20 sessions lasting 30-45 min, depending on condition</td>
<td>Psycho-Physiological effects of stimulating endorphinergic and antinoceptive structures (medial brainstem)</td>
<td>Stress, Depression; alcohol/drug withdrawal; pain syndromes; migraine; hypertension; speeding up wound healing; immune stimulation; endometriosis; sports injuries</td>
<td>Seizures, Epilepsy; acute brain injury/infection, brain tumors; Hydrocephaly; hypertensive crisis; acute psychiatric disorders; implanted electronic stimulators; under 5 y</td>
<td>Not approved by FDA</td>
<td>20-30% acceleration of wound healing; 81% long-term remission in gastric ulcers/pain. Persistence varies</td>
</tr>
<tr>
<td>TES - U.S. Method (Device approved by FDA)</td>
<td>Rectangular AC pulse administered via pads on forehead and each mastoid; 10-15 treatments of 40 min, duration in groups of five consecutive sessions. Additional sessions if indicated.</td>
<td>Psycho-physiological effects of balancing neurochemistry through benign stimulation of the hypothalamus</td>
<td>Treatment of Depression, Anxiety and insomnia. Studies underway for Parkinsons, Osteoarthritis, other studies in prospect</td>
<td>Seizures, Epilepsy; acute brain injury/infection, brain tumors; Hydrocephaly; hypertensive crisis; acute psychiatric disorders, implanted electronic stimulators; under 13 y</td>
<td>Avg. Improvement after 2-3 wks: Anxiety = 77%; Depression = 74%; Insomnia = 84%. Persistence = &gt;1 yr.</td>
<td>Two to three weeks $4,500 - $6,750</td>
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<tr>
<td>CES (Cranial Electrical Stimulation)</td>
<td>Bipolar asymmetrical Rectangular wave 10-600 mA, adjustable. Administered via earlobe electrode on each earlobe @ mastoid. Used in office or at home 20-40 min. daily or as needed.</td>
<td>Moves to normalize electrical activity of the brain and nervous system</td>
<td>Stress reduction; improvement of anxiety, depression and insomnia symptoms</td>
<td>Pregnancy, significant hypotension, implanted electronic stimulators. Use only @ mastoid.</td>
<td>Anxiety: 67% had improvement of 50%; Depression: avg. 50% reduction; weeks or more studies = significant pain reduction. Persistence low</td>
<td></td>
</tr>
<tr>
<td>TMS (Transcranial Magnetic Stimulation) (Device approved by FDA – must have failed two attempts at antidepressants)</td>
<td>Focused pulsed magnetic field (electromagnetic induction) administered via magnetic coil (several types) placed next to the head; 15-30 treatments of 40 min. duration.</td>
<td>Stimulation of the areas of the brain thought to control mood</td>
<td>Treatment of depression, including severe depression. Research underway for tinnitus, Parkinsons, schizophrenia.</td>
<td>History of seizures, epilepsy; cerebrovascular disease; implanted electrical stimulators; metal implants in or near head; efficacy not established &lt;22 y or &gt;70 y.</td>
<td>(1)Avg. improvement in depression after 4-6 wks = 22.1%. (2) Recovery rate after 3 wks = 14%. Persistence = 6 mo. +</td>
<td>Four to six weeks $8,000 - $12,000</td>
</tr>
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### TRANSCRANIAL ELECTRICAL STIMULATION – US METHOD

The U.S. method of TES was selected for use in programs of treatment for functional brain problems, mood disorders, and emotional trauma. The FDA approved device delivering this form of TES works to normalize neurochemistry by benignly stimulating the hypothalamus and associated brain structures using a specific, patented waveform and frequency. No serious side effects have been reported and it appears to provide a high level of positive outcomes.

The hypothalamus, often called “the brain’s brain” or “the seat of emotion”, attracts attention as an appropriate target for this TES approach to mediating mood disorders because of its wide role in maintaining homeostasis in the brain-body system, including the use of various neurotransmitters, distributed among its nuclei, in its control of the pituitary or which it releases into the bloodstream in the pituitary. Electrical stimulation studies reveal pleasure centers in the hypothalamus (ventral and lateral) as well as centers for anger and rage (anterior and dorsal), pain (central and posterior), and fear (dorsal and posterior). These and other centers in the hypothalamus release chemical messengers designed to mediate conditions pertaining to them. The U.S. method of TES is designed to directly direct the hypothalamus to rebalance neuropeptides, neurotransmitters, and neuromodulators that are critical to maintaining normal mood and behavior.

The hypothalamus also connects with the amygdala and higher parts of the cerebral cortex, including the orbitofrontal cortex, either by direct projections or through the thalamus, facilitating interaction between physical and mental processes, including those interactions affecting mental and emotional states.
In particular, the hypothalamic-pituitary-adrenal (HPA) axis assumes considerable importance in depression. Pariente notes that depression is characterized by an overactivity of the HPA axis that resembles the neuroendocrine response to stress and that these HPA axis abnormalities participate in the development of depressive symptoms.\textsuperscript{12} While the exact mechanism by which this occurs is unknown, an increasing number of researchers believe that stress-induced HPA axis activation directly causes depressive symptoms by interacting with the brain neurotransmitter systems regulating these behavioral changes. The influence of TES on hypothalamic control of the HPA axis, by quieting the HPA circuit so to speak, may account for many of the positive neurobehavioral and physiological effects arising from this treatment.

Clinical Methods Used to Treat and Monitor Patient Progress

1. Quantitative EEG\textsuperscript{13} – A quantitative EEG (eyes closed) was performed both before and after the ten or fifteen sessions of TES. Quantitative EEG (QEEG or Brain Mapping) is the measurement, using digital technology, of electrical patterns at the surface of the scalp which primarily reflect cortical electrical activity or “brainwaves.” The QEEG is the analysis of the digitized EEG and involves comparison of the electrical activity generated from the patient’s brain with a database of normal individuals. The QEEG is interpreted and used as a clinical tool to evaluate brain function and to track changes in brain function due to the intervention of the TES therapy.

2. 3D body scan\textsuperscript{14} – As part of the pre-post measurement for the patients undergoing treatment, the EIS system, a bio-impedance medical device, was chosen. This device measures the effect of the DC current in interstitial fluid of twenty two segments of the body. It is non-invasive, quick and low cost, and offers an understanding and measurement of the pre-conditions of the patient and the post-effect of the treatment with the TES. The body scan Wellness aspect of this device offered suggestions for good nutrition for each individual and this was deemed of value for the long-term support for the health and balance of the treated patient. The chiropractor indicators offered information as to the electrical flow of energy up the spine. A blockage could indicate that the brain was not receiving the energetic information for good function and perhaps not getting the full effect of the TES treatment. If an electrical block was seen a referral to a chiropractor for adjustments was indicated. Most importantly, for the purpose of this treatment, the brain analysis aspect of the EIS system allowed the monitoring of cerebral dopamine, cerebral serotonin, cerebral adrenaline and noradrenaline, and estimated acetylcholine. Neuronal excitability was monitored along with the tissue oxygen pressure and conductivity of the right and left frontal lobe and right and left limbic system.

3. A “0-10” scale for rating patient’s conditions on a daily basis pre- and post-treatment are used; “0” representing “symptom free” and “10” representing “very severe”. For consistency these same scales are used to rate anxiety, depression, and insomnia.

4. A clinical assessment of the patient’s condition is made by both therapist and doctor as the patient progresses through the treatment.

5. Additional testing is added based on the environmental history and factors experienced by the patient to prevent outlining factors from affecting the long-term effectiveness of our work. These tests include food sensitivity, micronutrients, metal toxicity, and neurotransmitter balance.

Therapy

The estimated time for the therapy session will be approximately 60 to 75 minutes per session. The patient will be seated comfortably in a reclining chair as most patients sleep through the treatment period. The forehead and mastoid areas (behind the ears) will be wiped down to remove oils and dirt that may be present in preparation for the application of the electrodes. Specifically designed single use electrode pads are then placed at each of these locations. To prevent miss connections a small cable with one snap and two connecting clips is used to connect the three pads to the TES Device. The device is then switched on to begin the treatment. Upon completion of the therapy the technician removes and discards the pads, interviews the patient, and escorts them out. On a selective basis, the medical director may also spend additional time with the patient. Patient follow-up may be for up to a year.
Measured Results

Traditional treatment might result in 25% of patients having >30% improvement. TES therapy has resulted in ninety percent (90%) of patients treated having > 50% improvement in their diagnosed condition, with the average improvement just under 80%. This coincides with the clinically observed improvements in the patients.

Case Study #1

Case study #1 is a high-functioning 50-year-old medical doctor who wanted to experience the TES therapy before she began referring patients. Prior to therapy she was described as distractible. After 10 sessions of the TES therapy her dominant brain wave frequencies (Hz) increased significantly, which is generally considered desirable for an awake, alert, and high-functioning adult (See Figure 1). Moreover, her brain wave amplitudes (power) moved toward a more optimal balance; slow wave power decreased significantly (36%-51%; [p< 0.000]) while the power of the frequency bands supporting concentration and on-task behavior (“alpha,” particularly high-alpha, and “beta,” particularly low-beta) increased significantly (78%-87%; [p<0.000]), (See Figure 2).

She is now even more functional and more highly productive than before, evidenced not only by her writing four training manuals in a short period without effort, but by significant strides she has made – and is making – to enhance her medical practice. She reports being more organized and functional. She feels great and thinks the planet could benefit from having everyone do this treatment.

![Figure 1. Case 1: QEEG, before and after TES treatment.](image-url)
**Case Study #2**

TP had been a typical healthy and functional 17-year-old male, well-liked by most who knew him. He had a recreational marijuana habit and had been offered some “pot” which apparently had been laced with a powerful foreign narcotic. Within 36 hours he was in complete psychosis. He spent two weeks locked up in the psychiatric department of a major hospital from which he emerged no better. He then spent four weeks in the psychiatric unit of another major hospital where he was diagnosed as bipolar and given a list of medications that his father said made him a “zombie.” He was sent to a third hospital where doctors told his father and his grandparents that they could do no more for him and that he would have to be cared for the rest of his life. He was then sent home with four medications.

Of necessity, he had dropped out of school during his senior year when his psychosis began and was subsequently unable to return to classes. Once home, this previously popular teenager became a recluse with extreme social anxiety and psychotic episodes (hearing voices, etc.). At one point he was found walking down the street in the middle of the night. He didn’t know his name or where he was.

At the suggestion of his best friend’s mother, who had begun investigating treatments that could be helpful to him, his father and grandparents called the Enhancement Institute to investigate the possibility that TES could provide hope for the young man’s recovery. His family drove him 80 miles each way for extensive testing and evaluation, then later on for the three week period of five consecutive treatments each.

Initially he was severely depressed, highly anxious, and heavily affected by prescription drugs. He threw up prior to the first and second days’ treatments and barely spoke during the first week. After the first week it was like working with a completely different person than that who initially came for therapy. Our medical director was reducing his meds as fast as was safe. He had become friendlier, had gained near-normal affect and carried on effortless conversations with staff, but still reported extreme social anxiety. For instance, he refused to go into public places, such as a restaurant; rather, he would sit in the car while his grandparents got food to take with them. By the last day of his treatment he was willing to go into a restaurant to eat. There was no further socially anxious behavior a month after the therapy ended and a six month follow-up confirmed that there have been no repeat episodes of psychotic behavior or hearing voices.

A remarkable feature of the young man’s post-treatment QEEG compared with his pre-treatment readings was the reduction in left frontal alpha (8-9 Hz)(Figure 3). A pattern of left frontal hypoactivation,
particularly in the alpha range, is a pattern found by Davidson’s research to be indicative of possible depression.\textsuperscript{15} Measured improvements ranged from 54\% - 67\% \(p<0.000\) (Figure 4).

![Figure 3. Case 2: QEEG, before and after TES treatment.](image)

![Figure 4. Case 2: QEEG, percent difference and paired t-test.](image)

Figure 5 illustrates differences in the pre- and post-analysis of the 3D body scan. Right and left frontal lobe conductivity, right and left frontal lobe tissue oxygen pressure, neuronal excitability, estimated cerebral serotonin, estimated cerebral dopamine, estimated cerebral adrenaline/noradrenaline and estimated acetylcholine are measured. Initially there is a predominance of out-of-range readings. After 15 sessions of the TES all the identical readings are in range except left frontal tissue oxygen pressure and
estimated acetylcholine. Actually, left frontal tissue oxygen pressure is barely low, with a measurement score of 43 – the norm being 44 to 46, leaving only estimated acetylcholine clearly out of range with a measurement of 50 versus a normal range of 22-34 (Figure 5).

Figure 6 offers a graphic of estimated cerebral serotonin, estimated cerebral adrenaline/noradrenaline and estimated cerebral dopamine. The green bar represents normal range. The first measurements were well out of range, while all three neurochemicals normalized post-treatment, measuring in the center of the normal range.

His family is thrilled to have their son and grandson back and functioning normally. In the five month follow-up, he has had no more episodes of psychosis and is quite normal with no medication and has overcome his social anxiety. He took his GED and passed it and has now entered college successfully.

Figure 5. Case 2: 3D body scan, before and after 15 TES treatments.

Figure 6. Case 2: 3D body scan, 3 week chart of progress viewing the neurochemistry.
Case Study #3

Case Study #3 involves a 19 year-old college student diagnosed with depression, traumatic brain injury (TBI), and bipolar disorder. He had been referred based on a prior evaluation using the 3D body scan. He arrived with his mother with whom he was quite angry. He wouldn’t look at anyone and exhibited an inability to talk. Although he had been a jogger in the past his body was so out of balance that he was unable to run at the time he came for therapy. He was hearing voices and exhibiting bipolar tendencies, evidenced by the first three data points on the charts in Figures 10 and 11 and the “before” chart in Figure 7.

![Figure 7. Case: 3D body scan, before and after 3 TES treatments.](image)

His pre-treatment scan and those taken during the first week of treatment showed unstable neurochemistry, conductivity, and neuronal excitability, suggesting a basis for his bipolar disorder (in Figures 10 and 11 the green band represents normal range). This instability continues through the first week of treatment even though the neurochemistry was beginning to normalize as evidenced by charts in Figures 7 and 8. Beginning with the second week of treatment his measurements of neuronal excitability moved to the center of normal range as measured in Figure 8. Estimated cerebral serotonin, dopamine, and adrenaline/noradrenaline, which exhibited pretreatment instability similar to that of neuronal excitability, showed similar improvement at the beginning of the second week. The conductivity measure in Figure 11 also showed initial instability, visible in the right frontal lobe, left frontal lobe and the left limbic region, and these began to normalize in the second week of treatment. The right limbic system remained normal pre and post-treatment. The normality seen in the measures at the beginning of the second week persisted through the remainder of treatment and 3 months of follow-up as evidenced in Figure 9. Although not contained in the measures shown, normal measures had maintained in a five month follow-up.

After the end of the first week the patient became more communicative and his activities were returning to normal. He returned to jogging in the mornings, as had been his pre-illness routine, even though he was in a strange city. No further bipolar behavior was observed and this has been consistent through the five months of follow-up.

In his post treatment interview, the patient reported that when he first arrived he was unable to find words, which created his inability to talk. He reported that during the first few days of treatment he had been unable to think of words. He then progressed to finding the words but was unable to form them or speak them. Toward the end of the first week he began speaking fluently and then told us that he could now find words, form words, and then speak the words. His depression was also resolved and upon returning home he began living a more normal life and was better able to interact with his friends.
Figure 8. Case 3: 3D body scan, after the 6th and 10th TES treatment.

Figure 9. Case 3: 3D body scan, three month follow-up after the end of the TES treatment
Figure 10. Case 3: 3D body scan, 4 month chart of progress viewing changes in neuronal excitability.

Figure 11. Case 3: 3D body scan, 4 month chart of progress viewing changes in neurochemistry and brain conductivity
CONCLUSIONS

Results from the review of clinical case studies show that the QEEGs and scans were effective tools for monitoring pre- and post-TES therapy, clearly showing the improvements achieved. The TES therapy was shown to be highly effective (>90% of cases), resulting in normalized brain neurochemistry and activity within two to three weeks. This was consistent with the original clinical results, in that the patients in these case studies achieved normal levels of behavior post therapy. Other therapies were used on a case-by-case basis to resolve additional patient issues identified by the scans.

REFERENCES


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