Vagus Nerve Stimulation in the Treatment of Treatment Resistant Depression

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VAGUS NERVE STIMULATION IN THE TREATMENT OF TREATMENT RESISTANT DEPRESSION

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Rachel A. Keller-Kaplan

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Abstract

Initially used to treat epilepsy, vagus nerves stimulation (VNS) was approved by the FDA in 2005 for long-term use in treating chronic treatment resistant depression. Cyberonics, the manufacturer of the VNS device, commissioned a pilot study to investigate vagus nerve stimulation's effects as a treatment for depression due to reports of improved mood in some epilepsy patients who received VNS. Although the exact mode of action is unknown it is believed that the use of VNS increases blood flow to areas of the brain, such as the limbic region, that are responsible for regulating mood and anxiety and increases production of Serotonin and Norepinephrine. Since the completion of the first study in 1999 additional studies have been done to examine the long term benefits of VNS for the treatment of treatment resistant depression. Results of these studies suggest that VNS is both efficacious and durable when used for this purpose.

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CHAPTER 1
INTRODUCTION

Second only to anxiety disorders, depressive disorders are the most prevalent psychiatric condition in the world affecting approximately 19 million American adults and 121 million people worldwide (Marangell, Martinez, Martinez, George & Sackeim, 2005). Measured by years lived with disability, depression is considered to be the leading cause of disability worldwide by the World Health Organization (Rado & Janicak, 2007). Although myriad treatments exist 30% of those affected do not respond to these treatments resulting in a chronic and reoccurring condition referred to as Treatment-resistant depression or TRD (Thase, 2005). Keller et al. (as cited in Schlaepfer et al., 2008) tracked depression treatment over a five-year period and found that the recovery rate actually decreased over time. Although there are many different definitions of treatment resistance the non-response to two treatments is generally used as the most comprehensive definition (Thase, 2005). The economic impact of TRD is huge, costing billions of dollars each year due to absenteeism, disability and premature death. Additionally, this chronic and long-term depression uses a disproportionately large share of healthcare resources due to increased depression-related and general medical-related costs. As such TRD is ripe for continued therapeutic research (Rado & Janicak, 2007; Thase, 2005).

Due to the need for new and different treatment options, the Food and Drug Administration (FDA) approved vagus nerve stimulation (VNS) in July 2005 for use as an adjunctive treatment for patients with chronic or recurrent depression and who had failed to benefit from at least four other treatments (Marangell, Martinez, Jurdi & Zboyan, 2007; Rado & Janicak, 2007). Initially approved in 1997 for use in controlling seizures in patients with epilepsy VNS came to be used for depression after epilepsy patients implanted with the device reported increased good mood (Rado & Janicak, 2007). However, as reported in the New York Times,

approval of the device was not without controversy. As was reported, Dr. Daniel G. Schultz, director of the Center for Devices and Radiological Health for the Food and Drug Administration, decided to approve the use of the VNS device for treatment-resistant depression in spite of the unanimous opinion of his scientific staff against it. In its only clinical trial the device had not shown that it was effective in treating depression. As a result, scientists at the FDA unanimously recommended rejecting its application for use due to the lack of adequate data to support its approval especially in light of the failed study. However, Dr. Schultz continued to push the application forward and ultimately approved it (Harris, 2006).

Since that failed study, additional studies have been done including one and two year extensions of the failed clinical study. These studies suggest that VNS is both efficacious and durable when used for the treatment of treatment resistant depression. This paper will provide an overview of VNS including implantation, parameters, side effects and clinical trial data.

Statement of the Problem

In July 2005 the U.S. Food and Drug Administration (FDA) approved vagus nerve stimulation (VNS) as an adjunctive long-term treatment for treatment-resistant depression. Initial research showed that not only was VNS effective during short-term and mid-term studies but that the benefits appeared to increase over time. If so, to what extent does the effectiveness of VNS increase over time? Additionally are the benefits maintained?

Delimitations of the Research

The research was conducted through the Karmann Library (University of Wisconsin-Platteville) over a period of one hundred and four (104) days. Primary searches were conducted by way of the Internet through EBSCO Host. Additional publications were identified from reference lists of retrieved articles. Due to the limited number of studies done on vagus nerve stimulation many of the resources make reference to the same study criteria, outcomes and device specifications. To avoid lengthy citations either the most inclusive/original article (when used) or the most recent article is cited. Key search topics included “vagus nerve stimulation,” “vagus nerve stimulation,” “depression,” “treatment resistant depression,” “electroconvulsive therapy,” “neurofeedback,” “serotonin,” “norepinephrine” and “transcranial magnetic stimulation.”

CHAPTER II

REVIEW OF THE LITERATURE

Biochemical Cause of Depression

Depression is a serious medical condition affecting 9.5 % of the population in the United States each year (Marangell et al., 2005). It is a persistent condition which can have a significant impact on one's ability to function in everyday life. Although it affects all ages, races and socio-economic classes it may be triggered by stress, difficult life events or other environmental factors. Two neurotransmitters, serotonin and norepinephrine, have been found to play a significant role in depression. Serotonin is a hormone found in the brain and digestive tract and acts as chemical messenger that transmits signals between nerve cells. It plays a fundamental role in sleep, appetite, mood, memory and sexual behavior. Defects in serotonin have been implicated in eating disorders, migraines, personality disorders and depression. Possible malfunctions include low brain cell production of serotonin, lack of receptor sites which receive serotonin, inability of serotonin to reach the receptor sites, or a shortage in tryptophan, the chemical from which serotonin is made. Although serotonin levels cannot be measured in the living brain, serotonin levels are measureable in the blood stream and have been found to be lower in depression sufferers (Schloss & Williams, 1998). Norepinephrine, another neurotransmitter in the central nervous system, is released in times of stress. When stimulated it triggers the physiological changes associated with a stressful event such as increased heart rate. Similar to serotonin, when norepinephrine and its pathways malfunction it can result in a number of disorders including attention disorders and depression (Nutt, 2006). Medication which affects the amount, duration and action of these neurotransmitters, have largely been used to treat

depression. Initially, monoamine oxidase inhibitors (MAOIs) and tricyclics (TCAs) were used. The MAOIs mode of action is to block the metabolism of norepinephrine and serotonin while tricyclic antidepressants block the uptake of norepinephirine and serotonin. Norepinephrine uptake was discovered in the 1960s when researchers learned that the brain takes neurotransmitters back into its cells and terminals. It was then learned that TCAs blocked both norepinephrine and serotonin uptake. This led to the development of selective serotonin reuptake inhibitors (SSRIs), which are commonly prescribed for depression. SSRIs block serotonin uptake and have been found to be more effective and tolerable than TCAs. Most recently, serotonin-norepinephrine reuptake inhibitors (SNRIs), which block both norepinephrine and serotonin, have been used (Nutt, 2006). Unfortunately, not all depression sufferers benefit from medication. Depression that fails to improve with a sufficient dose of at least two different approved medications administered for at least four to six weeks is generally considered to be treatment resistant (Thase, 2005).

Treatment Alternatives

Therapeutic alternatives for patients who do not respond to the more commonly used options include ECT, rTMS and VNS. (George et al., 2007)

Electroconvulsive Therapy (ECT)

Electroconvulsive Therapy (ECT), also known as shock therapy, was established in the 1930s (Burke & Husain, 2006). Approximately 100,000 people per year receive a course of electroconvulsive therapy. It is most often used to treat severe depression which has not responded to multiple courses of antidepressants (Rush et al., 2000). ECT is administered via electrodes positioned on the head either bilaterally or unilaterally (Burke & Husain, 2006). An electric current passes through the brain inducing a grand mal seizure similar to an epileptic

event. In turn, the seizure alters the chemical features of the brain. Treatment consists of six to twelve sessions over a period of two to four weeks. ECT has improved a lot since its inception in the 1930's. The amount of electricity has been decreased, muscle relaxants are given to prevent muscle convulsions and patients are anesthetized prior to treatment (Donovan, 2006). ECT has been the standard of efficacy for decades; however, there are no up-to-date randomized, controlled trials. Studies from the 60's & 70's document that ECT is an effective treatment for difficult to treat forms depression and that these patients have at least a 50% of responding (George et al., 2007).Due to its rapid effect, ECT is the best intervention for patients experiencing an acute, major depressive episode for which an immediate response is required (Burke & Husain, 2006) however, it does not have a sustained response. Approximately 60-70% of patients who have not responded to one or more medication trials relapse in the 12 months following treatment. The relapse rate is estimated to be twice that for patients who have not received an adequate medication trial in the current episode (Sackeim et al., 2000, 2007). Risks associated with ECT are prolonged seizure, complications of anesthesia, including death, increased blood pressure and pulse and irregular heart beat. Short-term memory loss and impaired ability to retain new information have also been associated with ECT. Generally, the cognitive side effects usually end a few weeks after the treatment ends, however, in some cases long-term memory loss can occur (Donovan, 2006).

Transcranial Magnetic Stimulation (TMS)

Transcranial magnetic stimulation (TMS) was introduced in 1985 as a new form of noninvasive brain stimulation. TMS uses an intense magnetic field to generate pulses of electrical activity and depolarize neurons. The magnetic field is generated when a rapidly alternating current passes through a specially designed coil located in a hand held device which

is placed over the scalp. The hand-held device is connected to a console which, similar to VNS, is used to adjust stimulus parameters. Adjusting these parameters modifies treatment effects. Treatments can occur daily and last up to 45 minutes. Patients are awake during treatment and TMS is generally well tolerated with the most common adverse effect being headaches. No significant adverse cognitive effects have been reported as a result of TMS. A shortfall of TMS is that treatment is spread out over several weeks and the therapeutic effects appear to be short-lived. (Marangell et al., 2007).

Neurofeedback

Another treatment that is gaining popularity is neurofeedback. According to Hammond (2006), "EEG biofeedback (neurofeedback) originated in the late 1960's as a method for retraining brainwave patterns through operant conditioning" (p. 25). Researchers discovered in the late 1960s and 1970s, that it was possible to retrain or learn different brainwave patterns. Brain waves occur at a range of frequencies; some are small and fast while others are slow and large. Different brainwaves are more dominant under different circumstances. Without training, a person cannot generally change their brainwave patterns because they are not aware of them. When a person sees their brainwaves on a computer screen, it gives a person the ability to recondition and retrain the brain through operant conditioning. Although the changes are short-lived initially, ongoing feedback, coaching and practice can typically retrain unhealthy brainwave patterns and these changes are gradually maintained (Hammond, 2006).

Prior to treatment, an assessment is needed so that treatment goals can be established and neurofeedback treatment can be individualized to the specific brainwave patterns of the patient. The initial assessment consists of a clinical history, examination of existing brainwave patterns and possibly neuropsychological or psychological testing. Treatment occurs in the practitioner's

office with the client comfortably seated in a chair. Two electrodes, which measure the electrical patterns in the brain, are placed on the scalp and one or two are placed on the earlobes. The electrodes then transmit these patterns to a computer providing instantaneous audio and visual feedback. The patient then watches the brainwaves displayed on the computer screen and focus on retraining their brainwave pattern. Some people may need to work on decreasing the speed and size of their brainwaves while others may need to learn how to increase the speed and amplitude. Each session generally lasts 40-60 minutes and a person may need anywhere between 15 and 50 sessions depending on their condition. Mild side effects as a result of treatment such as headache, anxiety, irritability, difficulty falling asleep or sleepiness may occur. Many of these feelings pass within a short time after a training session or can be easily remedied with adjustments in treatment. Treatment can be ineffective or more adverse effects can occur if treatment is not being conducted by a knowledgeable, certified professional and if treatment is not customized to the patient (Hammond, 2006).

Davidson (as cited in Hammond, 2005) has summarized a body of research documenting that an activation disparity between the right and left prefrontal cortex is associated with depression. EEG studies summed up by Davidson (as cited in Hammond, 2005) have shown that the left frontal area is linked to a more positive affect and memories while the right hemisphere is associated with negative emotional. The left frontal area of those people with a biological predisposition to depression have been shown to have less activated left frontal areas resulting in a lack of awareness of positive emotions. Uncontrolled case studies have shown that neurofeedback has produced significant, enduring improvements approximately 80% of the time in patients who are shown to have a biological predisposition to depression. Generally, patients

report feeling a difference after three to six sessions, very significant improvement after 10-12 sessions, and conclude treatment within 20-22 sessions (Hammond, 2005).

One to five year follow-ups of depression sufferers treated with neurofeedback conducted by Baeher et al (as cited in Hammond, 2004) documented that not only had the frontal alpha asymmetry changed at the end of treatment but that these changes endured on long-term follow-ups.

Vagus Nerve

The vagus nerve, sometimes referred to as the "wandering" nerve (Nemeroff et al., 2006), is the longest of the cranial nerves and runs distally from the brain stem through organs in the neck, thorax and abdomen. The vagus nerve is responsible for both efferent functions such as heart rate, gastrointestinal peristalsis, sweating and keeping the larynx open for breathings, and afferent functions such as bringing sensory information back from the ear, tongue and larynx (Rado & Janicak, 2007). The vagus nerve also helps regulate the body's autonomic functions, which are important in a variety of emotional tasks (George, Rush, Sackeim & Marangell, 2003). Although the exact means of therapeutic action is unknown it is believed that the electrical impulses transmitted to the brain via the vagus nerve affect the neurotransmitters, serotonin and norepinephrine (Marangell et al., 2007; Rado & Janicak, 2007) and PET scans done on epilepsy patients during vagus nerve stimulation (VNS) therapy have shown changes in blood flow and metabolic activity in the limbic areas of the brain affecting mood regulation (Rado & Janicak, 2007). Further, studies have shown that VNS causes both immediate and long term effects and that the long term effects of VNS are different than the immediate effects and are maintained over time (Burke & Husain, 2006; Labiner & Ahern, 2006).

Vagus Nerve Stimulation Device

The vagus nerve stimulation device is a small, multi-programmable, pacemaker-like pulse generator that sends pulsed electrical signals to the vagus nerve by way of an implanted lead system. The generator weighs 25 g and is 6.9 mm thick (Rado & Janicak, 2007). The procedure takes one to two hours and is done as an outpatient procedure under general anesthesia usually by a neurosurgeon (Marangell et al., 2005). During implantation two incisions are made; the first is made in the upper left chest where the generator is placed and the second is made in the neck allowing access to the vagus nerve. The leads are then wrapped around the left branch of the vagus nerve and connected to the generator. After implantation, the generator transmits electrical signals to the vagus nerve at programmed intervals. The cost of implantation is approximately $25,000 (Rado & Janicak, 2007)

Complications can occur as a result of both the surgery and the device itself. Known complications due to implantation are pain at incision site (30%), infection (1%) and nerve damage (1%). There are also risks associated with the use of anesthesia during surgery (Rado & Janicak, 2007). Potential side effects during stimulation include alteration in voice quality, tingling in the neck (paresthesia), tightening in the throat, shortness of breath (dyspnea), hoarseness and increased cough. The most common side effects seen resulting from stimulation are voice alteration (55%), cough (24%), dyspnea (19%), neck pain (16%), laryngisimus (11%) and paresthesia (10%) (Marangell et al., 2007).

The pulse generator's adjustable parameters include signal-on and signal-off time (duty cycle), signal frequency, pulse width and output current. Programming is done in the office using a computer and telemetric wand. Parameters are adjusted for each patient to maximize efficacy, minimize side effects and preserve battery life. Signal-on time ranges from seven to sixty

seconds with signal-off time ranging from 0.2 to 180 minutes. This duty cycle is commonly set to alternate between 30 seconds of stimulation and 5 minutes without. Patients are also given a magnet that is used to turn the VNS system off if necessary. Output current is set at .025 milliamperes (mA) at the onset of treatment and increased in increments of 0.25 - .05 mA every two to four weeks depending on patient tolerability. The output current has a range of 0 to 3.5 mA. Frequency ranges from 1 to 30 Hz with optimum frequency being between 20 and 30 Hz. The pulse width has a range of 130 – 1000 microseconds with a typical setting being 250 or 500 microseconds (Labiner & Ahern, 2006).

Pilot (D01) Study

In June 1998, the first patient was implanted with the VNS device for the purpose of treating depression. This launched the pilot study (D01) of VNS for the treatment of treatment resistant depression. The study initially involved 30 patients but later included an additional 30 patients to clarify the effect size and look for response indicators (George et al., 2003). Admission criteria for this open-label study was to have a diagnosis of either treatment resistant or chronic, non-psychotic unipolar or bipolar depression (as defined by the DSM-IV), be in their current episode for at least two years or have had at least four major depressive episodes (MDE) in their lifetime and have failed at least two medication trials. Participants ranged in age from 18 to 70, had an average length of depression of ten years and had not responded to an average of 16 different types of therapies. All participants scored $\geq$ 20 on the $HDRS_{28}$ prior to implantation with a mean baseline of 36.8 ($\pm$ 5.8). Participants were maintained on their current medication regimen, however doses could not be increased and patients had to be stable on their current regimen for four weeks prior to implantation (Rado & Janicak, 2007). Patients were not given any stimulation for two weeks post-surgery, creating a single-blind placebo phase and allowing

for surgical recovery (George et al., 2003) After two weeks the device was turned on and stimulation was adjusted to the maximum tolerable dose during weekly visits over the following two weeks. The dose then remained fixed for the following eight weeks resulting in ten weeks of treatment. After ten weeks of treatment the response rate was 30.5% as indicated by $\geq$ 50% improvement over baseline on $HDRS_{28}$ and 15.3% achieved remission defined by a score $\leq$ 10 on $HDRS_{28}$ (Rado & Janicak, 2007).

All patients from the D01 study were then followed for a total of two years, however, after the initial 12 week study, VNS dosing as well as medication regimens could be adjusted. Response was defined as $\geq$ 50 reduction on the $HDRS_{28}$ and remission was defined as a $\leq$ 10 on the $HDRS_{28}$. Sustained response was defined as those participants who had at least a 40% improvement in their $HDRS_{28}$ score relative to baseline at the next follow-up. During this two-year follow-up improvement was seen between the 3 and 12 month marks with the percent of responders increasing from 30.5% to 44.1% and the percent of remitters increasing from 15.3% to 27.1%. Forty-eight patients were still receiving VNS at the two-year point and study results reflected non-significant decreases in both the responder rate (42.4%) and remitter rate (22%) from the 12 to 24 months point. Although the greatest antidepressant response was seen at three months, additional benefit was seen at 12 months with those benefits mostly being sustained at 24 months (Nahas et al., 2005).

Pivotal (D02) Study

The D01 study was followed by a larger, 21 site, double-blind, randomized sham-controlled study (D02). This 235 participant study used similar inclusion criteria to the D01 study (diagnosis, length of current MDE/number of lifetime MDEs, number of failed medication trials & $\geq$ 20 baseline $HDRS_{24}$). The mean baseline $HDRS_{24}$ was 29.3 ($\pm$ 5.3). Participants

ranged in age from 18 to 80 and were allowed to maintain their current medication regimen as long as the dose had been stable for four weeks prior to the onset of the study. As in the D01 study, there was a two week post-surgery single blind recovery period after implantation of the device before stimulation was turned on (participants were told stimulation may or may not be turned on). Patients were then assigned with 1:1 randomization to either the active treatment (device turned on) group or the sham (device left off) group. Only the programmer knew which treatment group the patient was assigned to. Device settings were adjusted over the following two weeks in the active group and remained fixed for the next eight weeks. During the ten-week study period the device remained off for the sham group. To preserve the blind, the programmer turned off the stimulation in the active group at all clinic appointments to eliminate the possibility of tell-tale side effects such as voice alteration**.** After the ten-week trial no significant difference was shown between the active and sham groups. Response rates defined as $\geq$50% reduction in baseline $HDRS_{24}$ were 15.2% for the active group and 10.0% for the sham group (Rush et al., 2005a).

After the ten week trial the study was extended to allow for two years of observation. Patients in the active group were given an additional nine months of treatment while patients initially in the sham group were switched to active treatment. Similar to the D01 group medications and device settings could be adjusted after the initial ten-week study. The primary measure of outcome was change over time in the $HDRS_{24}$ ratings. Again response was defined as $\geq$ 50% over baseline on the $HDRS_{24}$ and remission was defined as $\leq$ 9 on the HDRS24. At the 12 month point the remaining 181 evaluable patients (both initial active and sham crossovers) showed an increase of 12.8% (14.4% to 27.2%) in responders and an increase of 8.5% (7.3% to 15.8%) in remitters (Rush et al., 2005b). These results were maintained at two years as shown by

a response rate of 32% and remission rate of 17%. These results demonstrated not only an increase in benefit over the two year trial period but also durability of the benefit with 70% of the patients who responded during the ten week trial maintaining that benefit at the two year mark (Marangell et al., 2007).

TAU vs. VNS + TAU Study

A parallel 124 patient study was conducted and used as a long term naturalistic comparison group to the open-label (D02) extension phase patients. Admission criteria for this non-randomized comparison group was similar to that of the D02 (current MDE of $\geq$ 2 years or $\geq$ 4 lifetime episodes, resistance to $\geq$ 2 but $\leq$ 6 antidepressant trials and were taking $\leq$ 5 medications at entry) but were receiving treatment as usual (TAU) without VNS. After the 12 month trial period the results of the TAU group were compared with the 205 patients from the D02 extension phase patients who were receiving vagus nerve stimulation plus treatment as usual (VNS + TAU). Response rates for the VNS + TAU group were significantly higher than for the TAU only group. Response rates according to the $HDRS_{24}$, which was the secondary method of measure, were 27% for the VNS+TAU group compared to 12.5% for the TAU group at 12 months. Remission rates were 15.6% for the VNS + TAU group and 6.7% for the TAU group (George et al., 2005). "This comparison of two similar but non-randomized TRD groups showed that VNS plus TAU was associated with a greater antidepressant benefit over 12 months" (George et al., 2007, P.252). These data showed the use of VNS to be advantageous and served as the basis for FDA approval of VNS for the treatment of chronic TRD (George et al., 2007).

A European (D03) Study

Schlaepfer et al. (2008) conducted a similar study of VNS for TRD to see if the results obtained in the United States' studies could be replicated. This European (D03) study utilized a different patient population with different severity in a different health care environment. Participants for this study were signed up between 2001 and 2005 in six European countries. Study protocol was similar to that of the D01 study except that at age of entry participants ranged in age from 18 to 80 years of age, the number of failed medication trials was $\geq$ 2 but < 6 and study inclusion required a $\geq$ 20 on the $HDRS_{24.}$ Patients in this study were diagnosed based on DSM-IV diagnosis with either non-psychotic major depressive disorder or bipolar disorder I or II. Participants' current major depressive episode (MDE) had lasted more than two year or the patient had term suffered from more than four MDEs in their lifetime. Participants could be on medication at the time of entry as long as treatment had been stable for four weeks prior (Schlaepfer et al., 2008).

The D03 study was a multicenter, open, unblended, non-sham controlled study. There was a two week post-surgical recovery period in which patients were told that stimulation may or may not be turned on resulting in a single-blind period. At the end of the recovery period stimulation was turned on in patients with a score of $\geq$ 18 on the $HDRS_{24}$. Stimulation was then adjusted as to the maximum tolerable level over the following two weeks. Stimulation parameters were then held constant for the next eight weeks. After the three month acute study period patients were extended for 12 month follow-up period. Both changes in medication and stimulation parameters were allowed during this period (Schlaepfer et al., 2008).

Response and remission were defined as $\geq$ 50% reduction in $HDRS_{24}$ and $\leq$ 10 on $HDRS_{24}$ respectively. Response and remissions rates demonstrated a decrease in the severity of

depression at each interval. Thirty-six percent of participants had reached the response criterion at three months. This increased to 44% at nine months and 55% after one year of VNS. Remission rates were 17% at three months and reached 33% after one year of treatment. Although results of the D03 study were similar to the D01study in that response and remission rates increased steadily over time the reduction in severity of depression was greater in this study. The authors speculated that the higher level of effectiveness was attributed to the lower level of baseline depressivity at the time entry. Regardless these results suggest that VNS is efficacious for treatment resistant depression (Schlaepfer et al., 2008).

Summary of the Studies

Participant response and remission rates were recorded at three and 12 months intervals in each of the three trials (D01, D02 and D03) and at 24 months for both the D01 and D02 studies. Inclusion criteria was the same for all three studies except that the upper age limit for the D01 study was 70 years old versus 80 years for the D02 and D03 study. Participants were assessed using the 28 item HDRS for the D01 study and the 24 item HDRS for the D02 and D03 studies. Mean baselines were 36.8, 29.3 and 34 respectively (Rado & Janicak, 2007; Rush et al., 2005a; Schlaepfer et al., 2008). Both the D01 and D03 studies were both non-sham controlled open-label studies with the D02 being a sham-controlled double-blind study. While both the D01 and D03 studies showed clinically significant improvements after three months there was no significant difference between the active and sham groups in the D02 study (Rush et al., 2005a). All three studies showed improvement between the three and 12 month time periods with both the D01 and D02 studies also indicating sustained results at 24 months.

CHAPTER III

CONCLUSIONS & RECOMMENDATIONS

Although medication is the most commonly used treatment for depression, it does not work for everyone. In the past, when medication failed and alternative treatment was needed, depression sufferers would turn to ECT. ECT has been shown to be extremely effective; however, it does not have a sustained response and is primarily used for acute treatment of depressive episodes. Although the procedure has improved from what it once was, there continues to be a stigma attached to ECT which deters some people from utilizing it in addition to the cognitive side effects, such as short and long-term memory loss, which are common with its use. TMS has also been found to be an effective treatment for depression; however, similar to ECT it is considered an acute treatment unlike VNS which is considered long-term. TMS has virtually no side-effects and patients do not need to be anesthetized during treatment eliminating any anesthesia related concerns. TMS is less convenient than VNS as the patient must go to the practitioner several times a week, if not daily, for four to six weeks for treatment, increasing the chances the patient may not follow through. Like TMS, neurofeedback involves a time commitment, requiring 10-12 sessions before any significant improvement is seen (Hammond, 2005). However, the improvement, once made, is long-term so clients may not need future treatment. Side-effects associated with neurofeedback are minimal and are not a deterrent to its use. Although case studies have found neurofeedback to be an effective treatment, there have been no controlled studies and future studies may be needed before it gains approval by the Food and Drug Administration (FDA). Like ECT and TMS, VNS is FDA approved increasing the likelihood that insurance will cover the cost, otherwise the cost would be prohibitive.

While VNS is not an acute treatment option, 12 and 24 month study results suggest that not only do the benefits of VNS increase over time but that the benefits are maintained as well making it an effective long-term treatment option when medication trials fail. VNS is implanted surgically so there are risks associated with anesthesia however, after implantation no serious side-effects have been reported. The main side-effect associated with VNS is hoarseness which has been found to diminish over time and can be stopped temporarily if needed. A downfall to VNS is that the generator battery will need to be replaced over time requiring at least one, if not more additional surgeries. Aside from its effectiveness, a big benefit of VNS is that there is virtually no time commitment. After implantation device settings may need to be readjusted initially, but then VNS delivers constant treatment guaranteeing patient compliance.

In comparison to the other treatment alternatives, VNS seems to fare will. This is largely due to its long-term benefits unlike ECT and TMS which do not have a sustained response. Conversely, VNS is not an acute, short-term treatment option due to the time it takes to take effect and would not be useful in treating an acute major depressive episode. Compared to the other long-term option, neurofeedback, VNS does not require a time commitment therefore compliance with treatment is virtually compared. VNS is also FDA approved improving the likelihood that insurance will cover the cost of treatment. However, there are more side effects associated with VNS than with neurofeedback including the risks associated which anesthesia which may deter some people from pursuing it. Although there are some downsides, overall VNS appears to be a good treatment alternative for those people who are looking for an effective, long-term treatment option for treatment resistant depression.

Since chronic treatment-resistant depression can be a life-long problem for many sufferers, additional studies are clearly warranted to assess the benefits and potential

complications associated with the use of VNS (and alternate treatments) over the span of many years. Research should also be done to examine whether or not adjusting device settings can achieve short-term benefits. Additionally, studies are also needed to establish whether or not the benefits derived from the use of VNS are the result of treatment or natural remission.

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