Pilot Study: Evaluation of Changes in Depressive Symptoms After One Year in Patients with Refractory Epilepsy Treated with Vagus Nerve Stimulation

Leah Enright
Sarah McGinn
Alya Reeve

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Pilot Study:
Evaluation of Changes in Depressive Symptoms After One Year in Patients with Refractory Epilepsy Treated with Vagus Nerve Stimulation

Primary Researchers: Leah Enright and Sarah McGinn
Research Mentor: Dr. Reeve - Department of Psychiatry
Abstract

Depression is a major co-morbid condition with epilepsy, and has been found to be the single largest determinant of health-related quality of life in patients with epilepsy, even greater than seizure frequency and severity. Several studies have looked at the changes in symptoms of depression in patient treated with Vagus Nerve Stimulation for epilepsy. However, these studies have had some major limitations, including that they relied on scales designed to measure severity of depression in a population of clinically depressed patients instead of a scale that measures depressive symptoms in a community population, and that they measured changes in symptoms after only six months of VNS, even though research suggest that the benefit of VNS, in terms of reducing both seizure frequency and depression, strengths over a longer time period than six months.

Our study aims to demonstrate an improvement in depression symptoms measured by the Center for Epidemiologic Study of Depression scale (CES-D) after one year or more of VNS. Methods: Seven adults with epilepsy treated with VNS were asked to fill out two sets of scales, one in reference to how they felt the month prior to VNS implantation and the other for how they felt after at least one year of VNS. Results: Scores on the CES-D improved from an average of 24.3 before VNS to an average of 19.8 at least one year after insertion, however, this change was not statistically significant (p=0.327). Overall functioning, as measured by the Dartmouth COOP scale, improved from an average score of 29 before VNS to an average of 2.2 at least one year after VNS (lower score indicates higher functioning), which was statistically significant (p=0.012). Seizure severity, as determined by a continuous 0-10 scale, improved from an average of
6.64 prior to VNS insertion to 2.98 after at least one year of VNS, which approached statistical significance (p=0.06). Conclusion: Our results suggest that there is an improvement in symptoms of depression and overall functioning in patient with epilepsy after one year or more of VNS, and that the change in functioning is directly related to a reduction in seizure severity.

Introduction

Vagus Nerve Stimulation and Epilepsy

In 1985, Dr. Jacob Zabara first proposed Vagus Nerve Stimulation, or VNS, as a potential treatment for seizures due to its potential ability to desynchronize electrocerebral activities. Observations from animal studies indicated that VNS can affect seizure activity and could be a potential treatment for epilepsy in humans.

Two randomized clinical trials were conducted in the 1990’s by the Vagus Nerve Stimulation Group and Handforth et al. in patients with localized epilepsy to evaluate VNS as a treatment for epilepsy. These two studies used an “active placebo” design with low and high intensity stimulation to measure the percent change in seizure frequency compared with baseline seizure rates. The Vagus Nerve Stimulation Group analyzed 114 patients and found that there was a 24.5% reduction in seizures in the high stimulation group vs. a 6.1% reduction in the low. The Handforth et al. study analyzed 196 patients and found a 28% reduction in seizure frequency in the high stimulation group and a 15% reduction in the low stimulation group. These results along with a long term follow up study by DeGiorgio et. al demonstrated the efficacy of VNS in treatment
for epilepsy, and proved that this efficacy was maintained and actually increased over time.

On the basis of these findings VNS was approved by the FDA in 1997 “for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset of seizures which are refractory to antiepileptic medications.” Despite its approval by the FDA the exact mechanisms of action of VNS is still under investigation. The current putative mechanisms for VNS in epilepsy are that the antiseizure effects are mediated through: 1) increased synaptic activities of the thalamus and its projections leading to increased arousal and decreased synchrony of activities in the cortex which may influence the generation of generalized seizures and secondary generalization of focal seizures; 2) increased activity in the insula, hypothalamus and autonomic system; 3) decreased synaptic activity in the amygdala, hippocampus and limbic system; 4) increase in norepinephrine and perhaps serotonin exerting inhibitory influences on postsynaptic neurons.

VNS is currently used as one of three treatments for pharmaco-resistant seizures or for those patients who have unacceptable side effects for anti-epileptic drugs. VNS has been shown to be efficacious in short term treatment of epilepsy, and in the longer term maintenance of seizure reduction. The antiseizure effects of VNS also appear to increase with time, beginning with a 34% reduction after 3 months and increasing to a 45% reduction after 12 months, with 20% of patients having a seizure frequency reduction of over 75%. The incidence of adverse events with VNS is very low, and complications of surgery to place the VNS device such as wound infection or vocal chord paralysis occurs in only about 0.1% of cases. VNS has an advantage over most
AEDs in that its efficacy does not depend on patient compliance, and has emerged as an important adjunctive therapy for patients with refractory seizures.\textsuperscript{13}

**VNS for the Treatment of Major Depression**

With the increased use of VNS for refractory depression, patients began to report improvements in mood associated with the use of VNS. These self-reports, along with the history of successful use of many other anti-epileptic therapies for the treatment of psychiatric disorders, created an impetus to investigate the use of VNS for treatment of mood disorders. In 2000, Rush et al. published the first report in of VNS for use in adult outpatients with severe, treatment-resistant major depressive episodes.\textsuperscript{14} The study demonstrated that the positive treatment response rate was sustained starting at 40\% at 3 months and rising to 46\% at 12 months. Also of significance, three non-responders after 3 months (characterized by less than 50\% reduction in depression symptoms) became responders at the 12 month follow up, demonstrating that VNS effects on depression improve with time.\textsuperscript{15}

A study by George et al. subsequently compared the use of VNS and usual therapies for treatment-resistant depression and found that VNS was associated with greater antidepressant benefits over 12 months than typical treatment.\textsuperscript{16} The use of trial periods of 12 months in the above two studies is important, as other studies have failed to show evidence of short-term efficacy of VNS for treatment-resistant depression. For example, one randomized, controlled trial comparing adjunctive VNS with sham treatment in 235 outpatients with non-psychotic major depressive disorder found no significant difference in response rates to VNS in the treatment vs. sham group after 10
weeks. Such studies suggest that a longer term treatment period is necessary to produce results with VNS.\textsuperscript{17}

In 2005, the results of studies such as those above prompted the FDA to approve VNS “for the \textit{adjunctive long-term treatment} of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.”\textsuperscript{18}

\textbf{Depression and Epilepsy}

Epilepsy affects 6 to 7 people per 1,000 in the United States, with 40 to 50 new cases developing per 100,000 each year.\textsuperscript{19} Depression is highly prevalent in this population and is the most frequent co-morbid psychiatric disorder in patients with epilepsy.\textsuperscript{20,21} Overall, the rate of depression in patients with epilepsy is significantly higher than that of the general population; it is also higher than rates of depression in patients with other chronic diseases such as diabetes or asthma.\textsuperscript{22,23} The lifetime prevalence of depression in patients with epilepsy is estimated to be between 6\% and 30\%, and up to 50\% in patients followed in tertiary care centers.\textsuperscript{20} In patients with medically intractable, or only partially controlled epilepsy, rates of depression range from 20\% to 55\%, while in patients with controlled epilepsy, rates range from 3\% to 9\%.\textsuperscript{24,25}

While the increased rate of depression in those with intractable epilepsy suggests a direct association between seizure frequency and severity with depressive symptoms, the relationship is actually more complex. In fact, some patients have noted a decrease in seizure frequency prior to onset of depressive episodes.\textsuperscript{26} Furthermore, studies examining mood improvement in patients with epilepsy treated with VNS, have found no
direct association between seizure reduction and mood improvement. Further complicating the issue is the concept of “forced normalization”, which suggests eliminating/suppressing seizure may actually prompt psychiatric disorders, such as depression. This concept is based on the idea that seizures produce alterations in brain chemistry that reduce/prevent depression. It is further supported by the efficacy of electroconvulsive therapy, in which seizures are induced in non-epileptic patients for the treatment of depression. “Forced normalization” has been reported to occur in patients whose seizures have been suppressed with VNS, anti-epileptic drugs, and epilepsy surgery.

Although it is unclear exactly how seizure frequency and severity contribute to the increased rate of depression in patients with epilepsy, there are many factors which have been suggested to play a role. The most common include: psychosocial factors, side effects of anti-epileptic drugs (AEDs), and a common pathogenic mechanism for epilepsy and depression. Psychosocial factors experienced as a direct result of having epilepsy such as perceived stigma, fear of seizures, discrimination, joblessness, lack of social support, and lifestyle changes imposed by increased seizure severity/frequency (giving up driving privileges, changing jobs, etc.), have all been theorized to contribute to depression. Furthermore, many of the drugs used to treat epilepsy are known to have negative effects on mood. Phenobarbital has been reported to cause depressive disorder, while primidone, tigabine, vigabatrin, felbamate, and topiramate can frequently cause symptoms of depression.

The impact of depression in the epileptic population is substantial. People with epilepsy are four times more likely to be hospitalized for depression than those without
epilepsy and the risk of suicide has been estimated to be 10 times higher in those with epilepsy than in the general population. Furthermore, depression has been found to be the single strongest predictor of health-related quality of life in patients with epilepsy. In a survey of the concerns of people with epilepsy, approximately 30% of people spontaneously reported depressed mood as a significant problem in living and dealing with epilepsy. Despite the obvious impact of depression in patients with epilepsy, it often remains unrecognized and untreated. Reasons cited for this include the incorrect assumption on the part of clinicians and patients that mood disorders are to be expected with chronic health conditions, and the false beliefs that antidepressants are either ineffective or will exacerbate seizures in patients with epilepsy.

While the clinical presentation of depression in epilepsy can be identical to that of patients without epilepsy, it can also differ considerably. Depression in patients with epilepsy can present as and major depression, bipolar disorder, dysthymic disorder, and minor depression; a considerable number of cases fail to meet the clinical criteria of the DSM-IV Axis I categories. This is primarily due to the intermittent course of interictal depression, with symptomatic periods ranging from hours to days interrupted by symptom-free periods of similar duration. This discrepancy has recently lead Blumer et al to introduce the term “interictal depressive disorder” to describe the syndrome seen specifically in patients with epilepsy. The existence of a depressive disorder exclusive to patients with epilepsy, however, remains controversial. It is still uncertain whether it represents a unique clinical syndrome or a simply a cluster of symptoms failing to fully meet the DSM-IV criteria for a depressive disorder. This diagnostic labeling variability
is part of the problem with using a categorical classification system such as the DSM-IV to identify depression in patients with epilepsy.\textsuperscript{38}

In addition to the above factors, some theorize that a common neuropathogenic mechanism for both depression and epilepsy is the reason for their high rates of co-morbidity. Not only is the prevalence of depression high in patients with epilepsy, but a study in Sweden found that a history of depression was associated with a 4- to 6-fold greater risk of developing epilepsy.\textsuperscript{39} This has led to the suggestion that decreased serotonergic and noradrenergic function may be a common pathogenic mechanism for both depression and epilepsy.\textsuperscript{20}

**Depression in Patients with Epilepsy Treated with VNS**

To our knowledge only three studies (Harden et al.\textsuperscript{40}, Elger et al.\textsuperscript{41} and Hoppe et al.\textsuperscript{42}) have looked into the effects of VNS on the treatment of depressive symptoms in patients with epilepsy. In 2000, Harden et al. used the Cornell Dysthymia Rating Scale, the Hamilton Depression Scale (HAM-D), the Hamilton Rating Scale for Anxiety and the Beck Depression Inventory (BDI) to assess changes in symptoms of depression in 20 patients with epilepsy after 3 months of treatment with VNS as compared to a control group of 20 patients with epilepsy not treated with VNS. They found a significant decrease in depression scale scores after three months the VNS group, however the scores at three months in the VNS group were not significantly different from those in the control group. Interestingly, the study found no correlation between seizure frequency reduction and mood change.\textsuperscript{40}
The Elger et al. study used the Rating Scales for Psychiatry, the Brief Psychiatric Rating Scale, the Montgomery Asberg Depression Rating Scale, the Scale for the Assessment of Negative Symptoms and the Hypomania Scale to measure symptoms of depression at baseline, 4 weeks before VNS implantation, and 3-6 months after implantation in patients with epilepsy randomly assigned to either high- or low-stimulation VNS. In both groups they found significant improvement in scores on most scales (including the Brief Psychiatric Rating Scale, the Montgomery Asberg Depression rating scale, and the flattened affect, alogia, and abulia subsets of the Scale for the Assessment of Negative Symptoms), at 3 and 6 months as compared to baseline, with improvement being more pronounced in the high-stimulation group at the end of the study. Again, this study found no correlation between seizure activity and mood changes.

The study by Hoppe, et al. measured changes in symptoms of depression in 28 patients with epilepsy treated with VNS for at least 6 months, using the Befindlichkeits-Skala (a German mood adjective list), the Beck Depression Inventory, the Self-Rating on Anxiety Scale, and the Behavioral Psychosocial Scales on Epilepsy. They found improvement in symptoms of tension and dysphoria, but not in symptoms of depression, level of activity, or health-related quality of life.

The above studies have two major areas of concern. First, all three measured changes in symptoms of depression after 3-6 months of VNS therapy, despite the fact that the literature shows that the efficacy of VNS in treating depression and epilepsy improves with longer duration of treatment. Furthermore, these studies assessed changes in symptoms of depression with scales designed to gauge symptom severity in patients who
have already received a clinical diagnosis of depression. The Beck Depression Inventory is of primary clinical use, according to the American Pyschiatric Association, to “assess severity of depressive symptoms in patients with previously diagnosed depressive illness.” Similarly, the Hamilton Depression Scale has its main clinical utility as a “useful gauge of the degree of symptom severity in depressed cohorts.” Finally, the Montogmery-Asberg Depression Rating scale is best used to “gauge the degree of symptom severity in depressed patients.”

The CES-D is the only scale that “measures the degree of depressive symptoms in a community sample”, and has also been shown to be effective at identifying depression when compared to the “gold standard” of structured psychiatric interviews such as the Mini International Neuropsychiatric Interview (MINI) and the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Thus, the CES-D seems to be a more appropriate scale for patients with epilepsy, as it may be better at identifying depressive symptoms consistent with the so-called interictal dysphoric/depressive disorder, but which fail to meet the criteria of Major Depressive Disorder.

**Methods**

*Design* – This study was an un-blinded survey study of self-reported effects of VNS on symptoms of depression in patients with epilepsy. Effects were assessed retrospectively, with a group of patients who have had VNS for 1 to 3 years rating their depressive symptoms before VNS and 1 year after.

*Inclusion Criteria* - Participants had to 18 years of age or older and have epilepsy treated with VNS for one year or more. Participants also had a level of cognition, as assessed by
clinician who knew them well, that would allow them to complete self-survey forms independently or with slight assistance.

*Patients* – Patients were recruited from the epilepsy clinic at UNM as well as from the Epilepsy Support Group.

*Measures* – Patients were asked to complete two different self-report surveys, the Center for Epidemiology Studies – Depression Scale (CES-D) and the Dartmouth Primary Care Cooperative Information Functional Health Assessment Charts (COOP). The COOP Charts was designed for everyday use in the clinical setting to quickly determine information about a patient’s health status. It consists of 9 charts, each with a single question that refers to the status of health in the last 4 weeks. All of the charts have a descriptive title, a single question, and 5-point response scale (1 represents no limitations and 5 represents severe limitation), with an illustration for each response. Each chart assesses a different concept and is scored individually. Overall the COOP Charts assess physical activity, emotional status, daily and social activities, pain, emotional support, and general health. The charts were used in our subjects to evaluate their functioning and see if it correlated with their depression scores. This gave us another tool with which to further assess the validity of our retrospective method.

The CES-D is a 20-item checklist that assesses the severity of depressive symptoms over a period of 4 weeks. It is scored by summing items which are rated on a four-point scale corresponding to four different response phrases: “rarely or none of the time”, “some”, “occasionally”, or “most or all of the time”. Depressed subjects are defined as those who score 15 points or higher.
In addition to these two scales, subjects were asked a series of questions about their epilepsy. All subjects were asked what medications they are currently taking, the cause of their seizures (if known), how long they have had seizures, whether they have any past or present history of substance abuse, and if they have ever been hospitalized for seizures or drug toxicity. Subjects were asked to determine their seizure frequency (defined as number per month) and to rate the severity of their seizures on a line scale (see attached). Finally, subjects were asked why they got the implant, the date of implantation, and the “dose” of VNS (estimated by multiplying the percentage of VNS stimulation “on” time by the output current in mA).46

Time points for the measures - The retrospective group was asked to respond to one set of these scales and questions in reference to their memory of their mood and functioning for the month before they started VNS and to respond to another set of these scales and questions in regard to their mood and functioning after 1 year of VNS treatment.

Statistical Analysis - A paired t-test was used to calculate the statistical significance of VNS at baseline and one year after treatment in our retrospective group. The rationale for the use of the paired t-test was the desire to compare the mean before and after treatment of the same patients, and to look for a significant difference. All statistical calculations were performed using Excel.

Results

After one year of recruitment at the VNS clinic and epilepsy support group we were able to recruit 7 patients in to our retrospective group, and were unable to recruit any patients in to our prospective group.

Study Subject Demographics
Six out of seven subjects listed uncontrollable seizures as the reason they were being treated with VNS. One participant listed “depression from seizures” as their reason for getting the implant. Duration of treatment with VNS ranged from 9-5 years, with an average of 5.75 year. Two participants were actually on their second implant. The doses of VNS (defined as the product of the percent of VNS “on” time and the output current in milliamps) ranged from 0.05 to 0.25, with the average being 0.16. The average number of seizures per month reported by participants ranged from <1 to 30, with an average of 8.1 seizures/month. Participants reported taking 1 to 3 antiepileptic medications, with an average of 1.8. The most common medications were Keppra (3 participants) and Lamictal (2 participants). The number of years participants have had seizures ranged from 5 to 41 years, with an average of 19.3 seizures years. Participants listed a variety of etiologies for their epilepsy including: unknown, hereditary, history of high fever, and traumatic brain injury.

**CES-D**

The main scale that was used to evaluate depressive symptoms in our patient population was the Center for Epidemiologic Study of Depression scale. The scoring system defines scores of 0 to 14 points as not depressed, 15 to 21 points as mild to moderate depression, and 22 or above as severe depression. Depressed subjects are defined as those who score 15 points or higher. The results are listed in table 1-1.

*Table 1-1, CES-D scores 1 month prior to VNS and at least 1 year after VNS insertion*

<table>
<thead>
<tr>
<th>Subject #</th>
<th>1 mo prior to VNS insertion</th>
<th>1 year post VNS insertion</th>
</tr>
</thead>
<tbody>
<tr>
<td>845</td>
<td>12 (not depressed)</td>
<td>14 (not depressed)</td>
</tr>
<tr>
<td>471</td>
<td>44 (severe depression)</td>
<td>19 (mild depression)</td>
</tr>
<tr>
<td>248</td>
<td>38 (severe depression)</td>
<td>39 (severe depression)</td>
</tr>
</tbody>
</table>
Three of the seven subjects (43%) showed a drop in their CES-D score after one year of VNS insertion, and two of these subjects changed from a classification of severely depressed to mild to moderately depressed. Three subjects (43%) actually showed an increase, one changing from a classification of not depressed, to a classification of mildly depressed. One subject showed no change. These results are shown in table 1-2.

Table 1-2, Total change in CES-D score after 1 year of VNS

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Change after 1 year VNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>845</td>
<td>+2 (none to none)</td>
</tr>
<tr>
<td>471</td>
<td>-25 (severe to mild)</td>
</tr>
<tr>
<td>248</td>
<td>+1 (severe to severe)</td>
</tr>
<tr>
<td>463</td>
<td>0 (severe to severe)</td>
</tr>
<tr>
<td>542</td>
<td>-14 (severe to mild)</td>
</tr>
<tr>
<td>20</td>
<td>-1 (none to none)</td>
</tr>
<tr>
<td>827</td>
<td>+6 (none to mild)</td>
</tr>
</tbody>
</table>

The overall mean change was from a CES-D initial score of 24.3, one month prior to VNS insertion, to a final score of 19.8, at least one year after insertion. This represents a total change of 4.42 points for the group as a whole. After performing a paired T test on the group, the t value was determined to be 1.065, correlating to a p value of 0.327, indicating that these results are not significant. Therefore, despite an average overall decrease in CES-D scores observed with our seven subjects, the group results remain insignificant. For the individuals who had a 14 and 25 point changes (subjects 471, 542), the differences were clinically significant.
COOP

The Cooperative Information Functional Health Assessment Charts (COOP) was designed for everyday use in the clinical setting to quickly determine information about a patient’s health status. Overall the COOP Charts assess physical activity, emotional status, daily and social activities, pain, emotional support, and general health. Although the CES-D was the main scale for measurement, we also chose to include the COOP, to try and determine if the VNS was actually acting just on depression, or if by improving functioning and quality of life, depressive symptoms would improve. Table 2-1 shows the results of the COOP survey one month prior to VNS insertion, and at least one year after insertion.

Table 2-1, COOP results

<table>
<thead>
<tr>
<th>Subject #</th>
<th>1 mo prior to VNS insertion</th>
<th>1 year post VNS insertion</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>248</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>463</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>542</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>471</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>827</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>845</td>
<td>23</td>
<td>16</td>
</tr>
</tbody>
</table>

Six out of the seven subjects (86%) showed improvement, after VNS insertion, as demonstrated by a decrease in total score. These results are listed in Table 2-2.

Table 2-2, Total change in COOP scale after at least one year of VNS treatment

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Total Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>-5</td>
</tr>
<tr>
<td>248</td>
<td>+1</td>
</tr>
<tr>
<td>463</td>
<td>-2</td>
</tr>
<tr>
<td>542</td>
<td>-10</td>
</tr>
<tr>
<td>471</td>
<td>-13</td>
</tr>
<tr>
<td>827</td>
<td>-10</td>
</tr>
<tr>
<td>845</td>
<td>-7</td>
</tr>
</tbody>
</table>
The average COOP score for the group one month before VNS implant was 29, dropping to 22.2 at least one year after VNS. The change of 6.8, was significant, yielding a t value of 3.528, correlating to a p=0.012.

**Seizure Frequency Scale**

In addition to the CES-D and COOP, we also had participants rate their seizure severity during the one month prior to VNS insertion, and at least one year after insertion. The scale was a line scale ranging from “no seizures” to “worst seizures you’ve ever had”. The scale measured 10 cm in length, so that participant’s marks could be easily converted to a numerical value, ranging from 0-10. Table 3-1 lists the results.

*Table 3-1, Seizure Severity Scale Results*

<table>
<thead>
<tr>
<th>Subject #</th>
<th>1 mo prior to VNS</th>
<th>1 year after VNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>845</td>
<td>Omitted</td>
<td>omitted</td>
</tr>
<tr>
<td>248</td>
<td>Omitted</td>
<td>omitted</td>
</tr>
<tr>
<td>471</td>
<td>6.7</td>
<td>2.5</td>
</tr>
<tr>
<td>463</td>
<td>5</td>
<td>3.3</td>
</tr>
<tr>
<td>542</td>
<td>8.4</td>
<td>4.7</td>
</tr>
<tr>
<td>20</td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td>827</td>
<td>10</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Four out of the seven subjects (57%) showed decrease in seizure severity after at least one year of VNS, while one showed no change. Two subjects did not fill out the scale. The total change is reported in Table, 3-2.

*Table 3-2, Total change in seizure severity after at least one year of VNS insertion*

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Change in seizure severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>845</td>
<td>Omitted</td>
</tr>
<tr>
<td>248</td>
<td>Omitted</td>
</tr>
<tr>
<td>471</td>
<td>-4.2</td>
</tr>
</tbody>
</table>
The average seizure severity among the group was 6.64 prior to VNS insertion, dropping to 2.98 after at least one year of VNS. The represents a total change of 3.66, correlating to a p value of 0.06, which is approaching statistical significance.

General Trends between Seizure Severity, Mood and Functioning

Although the number of subjects in our study was small, there did appear to be a few general trends observed among the group.

Depression and Seizure Severity

Five out of seven subjects filled out scales on both depression (CES-D) and seizure severity after at least one year of VNS treatment. Of those, two out of five (40%), had improvement of both mood and seizures. One out of five, (20%), showed improvement in depression alone, with no change in seizure severity. Another participant, (20%), showed improvement in seizures alone, with no change in symptoms of depression. Lastly, one out of five, (20%), showed improvement in seizures with worsening depression.

Table 4-1-Relationship between depression and seizure severity at least one year after VNS insertion

<table>
<thead>
<tr>
<th>Depression</th>
<th>Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.7</td>
<td>463</td>
</tr>
<tr>
<td>-3.7</td>
<td>542</td>
</tr>
<tr>
<td>-8.7</td>
<td>827</td>
</tr>
<tr>
<td>0</td>
<td>020</td>
</tr>
</tbody>
</table>

-negative values=improvement  -positive values=worsening
Functioning and Seizure Severity

Five out of seven individuals reported results on seizure severity and functioning (COOP). In this case, four out of five (80%), showed an improvement in both seizure severity and functioning after at least one year of VNS treatment. One subject had improvement in functioning only.

Table 4-2, Relationship between functioning and seizure severity after at least one year of VNS treatment

Changes in functioning and seizure severity at least one year after VNS
Functioning and Depression

On the topic of the relationship of functioning and depression after one year of VNS treatment, four out of seven (57%), had a correlation between the two factors. Three of those four had improvement in both, and one individual had worsening of both. Two had improvement in functioning with no change in depression, and one had a worsening of depression despite improvement in functioning.

Table 4-3, Relationship between functioning and depression after at least one year of VNS treatment

Discussion

Our study sought to provide further understanding on how treatment with VNS alters symptoms of depression in patients with epilepsy. We hoped to expand upon the current research in this area by using a different scale, one that may be appropriate than those used in previous studies for assessing symptoms of depression in patients with epilepsy. Furthermore, we sought to assess changes in symptoms of depression after a
longer period of treatment with VNS (1 year), as research suggests the efficacy of VNS in treating both seizures and depression improves over time periods of 1 year or more.

Although our main scale for determining depressive symptoms in our population did show a small decrease of 4.42, this decrease did not have statistical significance. This is likely due to the very small number of individuals we were able to recruit into our study. The two subjects that showed a clinically significant improvement in depression with changes of 14 and 25 on the CES-D, suggest that there may be a subset of strong responders to VNS as a treatment for depression. Our results also suggest that if the study size could be larger, perhaps a more significant difference could be seen. 49

Of interest is that the COOP showed statistically significant improvement after at least one year of VNS treatment. It is hard to determine if these results suggest that the VNS is acting mainly on seizure control, thereby improving the quality of life, and in turn depressive symptoms, or if it is actually improving all three. In our limited population we found more of a correlation between improvement in functioning and depression (57%), and functioning and seizure severity (80%), than depression and seizure severity (40%). This would suggest, as studies by Harden40 and Elger41 have found, that a decrease in seizure severity is not directly related to the change in depression observed in patients treated with VNS. Our results seem to indicate that a decrease in seizure severity relates more with an improvement in functioning, and thereby an improvement in depression.

Change in seizure severity after one year of VNS approached statistical significance, with 4 out of the 5 participants who filled out the scales reporting a decrease in severity and the fifth reporting no change. While this finding is encouraging in terms
of the effectiveness of VNS, it makes it difficult to determine if the improvements in symptoms of depression and overall functioning were due to decreased seizures severity alone.

As we had anticipated, we had difficulty in obtaining the number of individuals necessary to power our study. The duration of one year for recruitment does not appear to be long enough, and the VNS clinic and epilepsy support group did not provide enough subjects. Besides the fact that there are simply a limited number of patients with epilepsy treated with VNS, this population contains a significant portion of people with congenital neurological disorders. Many of these disorders are associated with limited cognitive function, which may preclude participation in survey study such as this, which requires skills in reading comprehension and ability for personal insight.

We had also intended to have a second group of individuals, with whom we could measure depressive symptoms using the CES-D scale before implant and then one year after, but were unable to recruit any subjects for this group. This group would have provided valuable information about the reliability of our retrospective collection method.

The design of the study was problematic in several ways. The process of simply handing out packets of surveys in clinic and having the participants fill them out and return them in their own time likely limited the number of participants who completed the study. Furthermore, the somewhat complicated nature of the survey packets, with two sets of surveys for before VNS and after, required detailed labeling of each page, which made it impossible to blind the scorers as to which scales were filled in reference to before and after VNS.
Although this pilot study had areas that need improvement, our results do suggest that one year of treatment with VNS is improving symptoms of depression, and that the CES-D is a useful scale for measuring depressive symptoms in individuals with epilepsy. This study also seems to suggest that there may be a group of strong responders to VNS as a treatment for depression. The initial aim of this study was to look mainly for changes in depressive symptoms, but this study also showed significant changes in overall functioning. These changes in overall functioning appear to be strongly correlated with reduction in seizures and improvement in depression.

We hope this project will be continued in the future, with a longer collection time and more expansive recruitment sites. It would likely greatly improve patient willingness to participate and full completion of scales if they were filled out during an office visit with the help of a research assistant who would not be involved in the scoring process. This would also help with obtaining patients for a truly prospective arm of the study. Scales could be filled out during an intake process before implantation and repeated one year after implantation. For all of these reasons, continuation of this project would be best implemented in a VNS clinic, with the completion of scales integrated into office visits.

Acknowledgments

We would like to thank Dr. Vickers and Mona Chaney for allowing us to recruit individuals from their VNS clinic. We would also like to thank Audrey Autry for allowing us to come participate in the epilepsy support group, and for all her help in recruiting subjects for our study.
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