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Does Transcutaneous Vagal Nerve Stimulation (t-VNS) Reduce Seizure Frequency in Adult Patients with Pharmacoresistant Epilepsy?

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Does transcutaneous vagal nerve stimulation (t-VNS) reduce seizure frequency in adult patients with pharmacoresistant epilepsy?

Scott Poirier, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 14, 2018
Abstract

Objective
The objective of this selective EBM review is to determine whether or not transcutaneous vagal nerve stimulation is an effective measure in reducing seizure frequency in adult patients with pharmacoresistant epilepsy.

Study Design
This systematic review comprises a randomized controlled trial and an observational pilot study, both published in 2014, as well as a double-blind randomized control trial published in 2016.

Data Sources
All articles were published and displayed in English. The articles were obtained via the PubMed database.

Outcomes Measured
Reductions in average seizure frequency were analyzed based on data from patient seizure diaries.\textsuperscript{6,7,8} Secondary outcomes, including quality of life and seizure severity, were measured through the Quality of Life in Epilepsy-31 (QoLIE-31) and Liverpool Seizure Severity Scale (LSSS), respectively.\textsuperscript{6,7,8}

Results
Aihua et al. and Peijing et al. demonstrated a significant reduction in seizure frequency, as well as significant improvements in QoLIE-31 and LSSS scores.\textsuperscript{6,8} Bauer et al. did not achieve statistically significant reductions in seizure frequency compared to the control, nor did they demonstrate significant improvements in the QoLIE-31 or LSSS scores.\textsuperscript{7}

Conclusion
The results evaluated in this systematic review showed promise for the use of tVNS in the treatment of pharmacoresistant epilepsy. However, due to conflicting data and study design limitations, no definitive conclusion could be achieved at this time. Further study is required to better characterize the efficacy of tVNS in reducing seizure burden.

Key Words
Epilepsy, Seizures, Transcutaneous Vagal Nerve Stimulation
Introduction

Seizures are a condition of aberrant electrical activity in the brain which disrupt normal physiologic processes. A person is considered to have epilepsy when multiple seizures occur without an identified and reversible cause, such as alcohol withdrawal. While 5-10% of the population will experience a seizure in their lifetime, only about 0.3-0.5% are affected by epilepsy. Not only is this disease fairly common, it also carries a significant financial burden. A 2015 systematic review found annual per-patient epilepsy costs ranged from $1,022-19,749. Those with refractory disease are affected to an even greater degree, with costs over twice as high as those with controlled epilepsy. Refractory patients also average 3.6 annual visits for their epilepsy, compared to 2.2 for controlled, and are hospitalized roughly twice as often.

The etiology of seizures is diverse and largely varies by age. Febrile seizures are most common among young children and epilepsy in older children is often due to anatomical abnormalities or developmental disorders. In adults and the elderly, head trauma and stroke are the most common causes, respectively. Other causes include neoplasms, infections, metabolic disturbances and autoimmune disorders. Only 10% of epileptics have generalized tonic-clonic seizures as their main presentation. Others with generalized seizures present with brief impairment of consciousness, as seen in absence seizures, or may have myoclonic or atonic episodes. Seizures may also have a focal onset, which may cause motor symptoms or sensory abnormalities and may or may not impair consciousness. Focal seizures also possess the potential to disseminate from the affected area to both cerebral hemispheres, producing a generalized seizure.

The cornerstone of epilepsy treatment is prophylactic antiepileptic medications. While indications for medications vary by seizure classification, common medications include valproate and lamotrigine. Surgical resection of the problematic areas of the brain remains an
option for those who have failed at least two medications. For those without well-defined seizure foci, or that are poor surgical candidates, surgically implanted vagal nerve stimulation (iVNS) exists. iVNS was approved by the FDA in 1997 and has been demonstrated to be a safe and effective treatment, though is not without adverse reactions. The most common reactions include cough and voice hoarseness, but vocal cord paralysis and device infection remain rare complications. Transcutaneous VNS (tVNS) circumvents these adverse reactions by stimulating the somatic branch of the vagus nerve via the Ramsay-Hunt zone of the ear. tVNS also avoids the need for invasive surgical implantation and periodic battery replacements.

**Objective**

The objective of this selective EBM review is to determine whether or not transcutaneous vagal nerve stimulation is an effective measure in reducing seizure frequency in adult patients with pharmacoresistant epilepsy.

**Methods**

The population of interest consists of men and women of at least 18 years of age with pharmacoresistant epilepsy. This review compares tVNS to either stimulation of a non-therapeutic zone of the ear or to stimulation at a sub-therapeutic frequency. The efficacy of tVNS was primarily evaluated via reduction in seizure frequency and secondarily through quality of life improvement and reduction in symptom severity.

The Cochrane and Medline database searches were used to find articles relevant to the clinical question that contained patient-oriented outcomes. Keywords used in searching included epilepsy, seizures, transcutaneous electric nerve stimulation and vagus nerve stimulation. This
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># Pts</th>
<th>Age (yrs)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aihua, 2014&lt;sup&gt;6&lt;/sup&gt;</td>
<td>RCT</td>
<td>60</td>
<td>Treatment group mean: 34.5 (IQR 26.5, 41.3) Control group mean: 29.0 (IQR 24.5, 42.0)</td>
<td>&gt; 4 years of age &gt; 4 seizures per month Taking ≥ 2 AEDs over 2 years with ineffective seizure control Unable or unwilling to complete surgical treatment</td>
<td>Pregnant Lactating Serious heart, liver or kidney disease Implanted medical devices Could not tolerate t-VNS for more than 6 months</td>
<td>13</td>
<td>Bilateral Ramsey-Hunt zone tVNS vs Bilateral earlobe tVNS</td>
</tr>
<tr>
<td>Bauer, 2016&lt;sup&gt;7&lt;/sup&gt;</td>
<td>RCT, double-blind</td>
<td>76</td>
<td>18-65, mean 38.8 ± 12.5</td>
<td>Age 18-65 years Have epilepsy with focal and/or generalized seizures ≥ 3 seizures per month Stable regimen of ≤ 3 AEDs for ≥ 5 weeks</td>
<td>≤ 21 consecutive seizure-free days &gt; 1 episode of status epilepticus within 6 months Current or prior treatment with tVNS or DBS Ablative epilepsy surgery History of non-epileptic seizures Major Psychiatric disorders Deteriorating neurological or medical conditions and/or relevant cardiovascular disease</td>
<td>18</td>
<td>Therapeutic unilateral tVNS at 25 Hz vs Subtherapeutic unilateral tVNS at 1 Hz (active control)</td>
</tr>
<tr>
<td>Peijing, 2014&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Observational Pilot Study</td>
<td>50</td>
<td>25.2 ± 13.1</td>
<td>Age 12-65 years Frequent disabling seizures, intractable to treatment with ≥ 1 AEDs for ≥ 1 year Bilateral and/or non-localized findings, not candidates for surgical treatment Valid record of the patient’s daily frequency of seizures</td>
<td>Tumors, progressive encephalopathy, progressive neurodegenerative disorders and serious pulmonary and heart disease Patients treated concomitantly with corticosteroids, anxiolytics or antidepressants</td>
<td>3</td>
<td>Triangular fossa of the auricle Transcutaneous electrical nerve stimulation (TENS) (no comparison, observational study)</td>
</tr>
</tbody>
</table>
systematic review is comprised of a randomized controlled trial, a randomized double-blind controlled trial and an observational pilot study. All evaluated articles were displayed in English and contained published data. Inclusion criteria in the search included randomized controlled trials or observational studies published between 2007 and the time of writing. Exclusion criteria included studies with fewer than 50 participants. Reported statistics used include P-values, CIs and mean change from baseline.

**Outcomes Measured**

The primary outcome measured in all articles was reduction in seizure frequency.\textsuperscript{6,7,8} This was evaluated through seizure diaries kept by the patients and reported through surveys\textsuperscript{8} or follow-up telephone correspondence\textsuperscript{6}. Changes in quality of life were monitored through the Quality of Life in Epilepsy-31 (QoLIE-31). This questionnaire utilizes a health-focused perspective, with scores ranging from 0% to maximal quality of life at 100%.\textsuperscript{7} Changes in symptom severity were monitored through the Liverpool Seizure Severity Scale (LSSS). As the name suggests, this 20-question survey assesses seizure symptoms, with maximal symptoms given a score of 80.\textsuperscript{7}

**Results**

Aihua et al. published a randomized controlled trial in 2014 in which 81 patients with pharmacoresistant seizures were selected from Xuanwu Hospital in China. Patients were required to have taken at least 2 antiepileptic drugs (AEDs) for at least 2 years with poor results and in which surgery was not an option.\textsuperscript{6} Patients excluded from the study totaled 21, another 5 were lost to follow up and an additional 8 discontinued due to adverse reactions.\textsuperscript{6} Of the 47 that completed the study, 25 were female and 22 were male.\textsuperscript{6} Full inclusion and exclusion criteria may be found in Table 1. The average age of the treatment and control groups were 34.5 (IQR:
26.5 - 41.3) and 29.0 (IQR: 24.5 - 42.0), respectively. The most common seizure type was simple partial at 68.1% of the study population. Complex partial seizures accounted for another 12.8%, and 19.1% had generalized seizures. The average length of epilepsy diagnosis, in years, was 19.7 ± 11.1 in the treatment group and 17.6 ± 9.6 in the control group. Baseline seizure frequency was 6.0 (IQR: 4.8 - 25.0) for the treatment group and 7.0 (IQR: 4.0 - 11.5) in the control group. Each group was randomly assigned 30 patients. Those receiving treatment underwent bilateral stimulation of the Ramsay Hunt zone of the ear at a frequency of 20 Hz with a 0.2 s pulse width. Current was titrated up from 2 mA, as dictated by patient tolerance. Stimulation was continuous for 20 minutes, three times daily for 12 months. Control group patients received the same stimulation, but of the earlobe. All patients were maintained on their baseline antiepileptic regimen.

The researchers found a significant reduction in seizure frequency, with median values at 5.5 (IQR: 3.0 - 12.0) at 6 months and 4.0 (IQR: 2.8 - 8.3) at 12 months. Despite these results, a significant difference between the treatment and control groups was not observed until 12 months, where median seizure frequency was 4.0 (IQR: 2.8 - 8.3) and 8.0 (IQR: 4.5 - 12.0), respectively. Results are summarized in Table 2. Significant improvements were also observed in QoLIE-31 and LSSS scores after 12 months of treatment (P < 0.001, P = 0.001), though the data were not published.

### Table 2: Reduction in Seizure Frequency in the Aihua Study

<table>
<thead>
<tr>
<th>Duration of Therapy</th>
<th>Median Seizure Frequency</th>
<th>Percent Reduction from Baseline</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Months</td>
<td>5.5 (IQR 3.0 - 12.0)</td>
<td>8.3%</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>12 Months</td>
<td>4.0 (IQR 2.8 - 8.3)</td>
<td>33%</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>
In 2016, Bauer published a double-blind randomized controlled trial that included 87 patients from Germany and Austria. Selected patients had to have at least 3 monthly seizures and no seizure-free period of greater than 21 days. Screening parameters deselected 11 patients and an additional 18 discontinued the study due to non-compliance, withdrawal of consent, patient risk, death or various other reasons. Full inclusion and exclusion criteria may be found in Table 1.

The mean age in years of the treatment group was 40.1 ± 12.7, compared to 37.5 ± 12.2 for the control group. Partial seizures accounted for 71.1% of the patients. The average length of epilepsy diagnosis was 23 years for the treatment group and 24.2 years for the control group. Of those initially enrolled in the study, 45 were female and 31 were male. Patients were randomly selected into the treatment and control groups, which initially contained 37 and 39 patients, respectively. Those enrolled in the treatment group were subjected to unilateral stimulation at 25 Hz with a 0.25 s pulse width at cycles of 30 seconds on and 30 seconds off. Stimulation was continued as described above for 4 hours daily for 20 weeks. Patients enrolled in the control group received equivalent stimulation, but at a sub-therapeutic frequency of 1 Hz. Current was titrated between perception of the stimulation and painful stimulation to an average of 1.02 ± 0.83 mA in the control group and 0.50 ± 0.47 mA in the treatment group. The antiepileptic regimen of the patients remained constant throughout the study. Statistics were analyzed using the ANCOVA model. Median compliance was found to be 93.3% for the control group and 96.7% for the treatment group.

The study found LS-mean reductions in seizure frequency of approximately -2.9% (95% CI: [-26.4%; 21.5%], p = 0.842) in the control group and 22.9% (95% CI: [-1.7%; 47.5%], P = 0.067) in the treatment group. Neither of these values demonstrated clinical significance. However, a significant reduction of 34.2% (P = 0.034) was observed in the 26 patients who
completed the 20 weeks of stimulation. A 25.3% (95% CI; [-9.0%; 59.7%], P = 0.146) difference in LS-mean was observed between the control and treatment groups at end of treatment, though this value was also found to be insignificant. Results are summarized in Table 3. Average LSSS scores increased by 0.83 in the control group and 1.56 in the treatment group, though only the change in the treatment group was found to be significant. No significant difference was found between the groups. The QoLIE-31 values were also found to have increased throughout the study by 4.65 and 2.68 in the control and treatment groups, respectively. Only the control group difference was found to be significant. Again, no difference was found between the groups. Results are summarized in Table 4.

Table 3: Reduction in Seizure Frequency in the Bauer Study

<table>
<thead>
<tr>
<th>Group</th>
<th>LS-Mean Reduction in Seizure Frequency at 20 Weeks</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>-2.9%</td>
<td>[-26.4%; 21.5%]</td>
<td>P = 0.842</td>
</tr>
<tr>
<td>Treatment</td>
<td>22.9%</td>
<td>[-1.7%; 47.5%]</td>
<td>P = 0.067</td>
</tr>
</tbody>
</table>

Table 4: Change in LSSS and QOLIE-31 Scores at End of Treatment in the Bauer Study

<table>
<thead>
<tr>
<th>Group</th>
<th>Change in LSSS Score at End of Treatment</th>
<th>P Value</th>
<th>Change in QoLIE-31 Score at End of Treatment</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.83</td>
<td>P = 0.194</td>
<td>4.65</td>
<td>P = 0.01</td>
</tr>
<tr>
<td>Treatment</td>
<td>1.56</td>
<td>P = 0.017</td>
<td>2.68</td>
<td>P = 0.077</td>
</tr>
</tbody>
</table>

Published in 2014, Peijing et al. conducted an observational pilot study with 50 patients from three Chinese hospitals. Patients included in the study had to have pharmacoresistant seizures while taking at least 2 AEDs for at least 1 year. Full inclusion and exclusion criteria may be found in Table 1. Over the course of the study, 3 discontinued due to adverse reactions. Of the 47 that completed the study, 28 were male and 19 were female.
participating in the study was 25.2 ± 13.1 years.\textsuperscript{8} 84% of the participants suffered from complex partial seizures, with the remaining 16% suffering from generalized seizures.\textsuperscript{8} The average length of diagnosis of epilepsy was 12.0 ± 8.1 years and the average monthly seizure frequency was 85.2 ± 14.4.\textsuperscript{8} All patients underwent unilateral stimulation of the triangular fossa of the auricle for 30 minutes, twice daily, for a total of 24 weeks.\textsuperscript{8} Stimulation was accomplished at a frequency of 20-30 Hz with a ≤ 1 ms pulse width and at 1 mA of current.\textsuperscript{8} Patients were maintained on their baseline AED treatment for the duration of the study.\textsuperscript{8}

The authors found a significant decrease in average seizure frequency of 51.3\% (P < 0.01) after 24 weeks of treatment.\textsuperscript{8} This was improved from 46.6\% (P < 0.01) at 16 weeks and 34.3\% (P < 0.05) at 8 weeks of treatment.\textsuperscript{8} Significant improvement was also observed in the QOLIE-31 scores, with an increase of 4.4 (P < 0.001) at the end of treatment.\textsuperscript{8} Similarly, significant improvements were seen in LSSS scores (P < 0.017), though the data were not reported.\textsuperscript{8}

Table 5: Reduction in Seizure Frequency in the Peijing Study\textsuperscript{8}

<table>
<thead>
<tr>
<th>Duration of Therapy</th>
<th>Reduction in Seizure Frequency from Baseline</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 Weeks</td>
<td>34.3%</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>16 Weeks</td>
<td>46.6%</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>24 Weeks</td>
<td>51.3%</td>
<td>P &lt; 0.01</td>
</tr>
</tbody>
</table>

Overall, tVNS was well tolerated over all three studies. Aihua et al. had 1 patient discontinue due to dizziness and had 3 experience daytime drowsiness.\textsuperscript{6} Bauer et al. found headache to be the most common treatment emergent adverse reaction.\textsuperscript{7} Other common reactions included ear pain, erythema, fatigue, vertigo and nausea.\textsuperscript{7} A summary of all adverse reactions from this study is detailed in Table 6. A total of 4 control group participants discontinued due to syncope, palpitations, erythema and exacerbation of seizures.\textsuperscript{7} Another 3 treatment group participants
discontinued due to vestibular neuronitis, basal cell carcinoma and headache/exhaustion/nausea.\textsuperscript{7}

One patient passed away after a sudden unexplained death in epilepsy (SUDEP), which was considered to be unrelated to tVNS treatment.\textsuperscript{7} Peijing et al. found similar results, with one patient discontinuing due to dizziness.\textsuperscript{8} Another two patients reported having erythema and edema.\textsuperscript{8}

Table 6: Treatment Emergent Adverse Reactions in the Bauer Study\textsuperscript{7}

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Control Group (n = 39) N (%)</th>
<th>Treatment Group (n = 37) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>2 (5.1)</td>
<td>7 (18.9)</td>
</tr>
<tr>
<td>Ear Pain</td>
<td>2 (5.1)</td>
<td>6 (16.2)</td>
</tr>
<tr>
<td>Erythema</td>
<td>1 (2.6)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>1 (2.6)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (5.1)</td>
<td>1 (2.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (2.6)</td>
<td>2 (5.4)</td>
</tr>
</tbody>
</table>

Discussion

In this systematic review, the efficacy of transcutaneous vagal nerve stimulation (tVNS) was evaluated in the reduction of seizure frequency and improvement of quality of life in patients suffering from pharmacoresistant epilepsy. One of the randomized controlled trials and the observational pilot study found statistically significant reduction in the average seizure frequency of those enrolled.\textsuperscript{6,8} The double-blind RCT did not find statistically significant reductions in seizure frequency overall but did find significant improvements in the subset of participants that completed the full study period.\textsuperscript{7} Similarly, the former two studies found statistically significant improvements in QoLIE-31 and LSSS scores.\textsuperscript{6,8} The later study demonstrated conflicting
evidence, finding significant improvement of the QoLIE-31 scores only in the control group and statistically worse LSSS scores in the treatment group.\textsuperscript{7}

Comparing the three trials, efficacy was directly related to treatment duration.\textsuperscript{6,7,8} This suggests a greater benefit may be observed in patients over time as they continue with therapy. Interestingly, efficacy was found to be inversely related to both length of diagnosis and to average age of participant when comparing results to population demographics between the three studies.\textsuperscript{6,7,8} This may suggest tVNS therapy is more effective when started earlier in the disease process, when patients are younger.

The most significant limitation of all three studies was the subjectivity of patient-recorded seizure diaries and surveys. The utilization of objective measures, such as ambulatory EEG monitoring, may yield more conclusive results in future studies. In addition, the Aihua study utilized bilateral stimulation, which may have magnified efficacy relative to the other studies, which used unilateral stimulation.\textsuperscript{6,7,8} The authors also noted the study population contained a sample size too small to be able to compare efficacy against various AEDs.\textsuperscript{6} The study also had a fairly high dropout rate at 22\%, which may have impacted the end results.\textsuperscript{6} While this study demonstrated high precision in terms of statistical significance, the IQRs reported were wide, indicating substantial variability among the subjects.\textsuperscript{6} In the Bauer study, the researchers had to utilize higher current in the control stimulation to ensure blinding, which may have artificially reduced the observed difference between treatment and control groups.\textsuperscript{7} They also noted that while medication regimens were maintained, approximately 33\% of those enrolled were not on an AED throughout the study, limiting the comparability to the other studies included.\textsuperscript{7} This study also had a high dropout rate at 24\%.\textsuperscript{7} In the Peijing study, the major limitations were that the study was not blinded or controlled.\textsuperscript{8}
Currently, there are no tVNS devices that are FDA approved for the treatment of seizures. This is reflected in the paucity of research available from the US, which was a major factor in the selection of studies with mainly Chinese\textsuperscript{6,8} and German\textsuperscript{7} populations. However, the gammaCore tVNS system was FDA approved in 2017 for cluster headaches and in 2018 for migraine headaches.\textsuperscript{9} The tVNS device is also currently being researched for other diagnoses, including heart failure\textsuperscript{10}, depression\textsuperscript{11} and autism\textsuperscript{12}. Alternative methods of neurostimulation are also under investigation, including trigeminal nerve stimulation (TNS), deep brain stimulation (DBS) and the responsive neurostimulation system (RNS).\textsuperscript{5}

**Conclusion**

The evidence appears inconclusive as to whether tVNS is effective in reducing seizure burden in those with pharmacoresistant epilepsy. The Peijing and Aihua studies found significant reductions in average seizure frequency at end of treatment ranging from 33-51\%.\textsuperscript{6,8} However, the Peijing study was not a randomized controlled trial\textsuperscript{8} and Bauer et al. did not observe a significant reduction in seizure frequency\textsuperscript{7}. Nevertheless, the results are promising, and the Bauer study did find a significant reduction among the participants that were able to complete the trial.\textsuperscript{7} Due to these results and the relatively benign side effect profile, further research is warranted to better characterize the effectiveness of tVNS in reducing seizure burden. Future studies will benefit from increased sample sizes and greater diversity of geographical regions. Furthermore, as a direct relationship was observed between length of treatment and efficacy, longer trials may be necessary to observe maximal efficacy. Finally, greater standardization of patient demographics, study design and treatment modality may help to confirm the efficacy of tVNS and determine which patient populations are of greatest benefit.
References


