2-month transcutaneous auricular Vagus Nerve Stimulation (taVNS) in PTSD Pilot Study: Significant Reduction in CAPS-5 and Quality of Life Scores

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BACKGROUND

The lifetime prevalence of Post-Traumatic Stress Disorder (PTSD) in the United States is estimated at 7.8%. The clinical, societal, and financial burdens of PTSD are enormous. In the VA alone, in 2017, more than 900,000 veterans were receiving disability compensation for PTSD, at a cost of $15B.

PTSD is a complex mental disorder caused by trauma and resulting in dysfunctional memory processes that trigger an inappropriate fear response. It is associated with severe impairment in Quality of Life, including bad life circumstances, poor role functioning, poor subjective life satisfaction, increased drug abuse rates, and greatly increased suicide risk.

The nervous system continuously monitors and evaluates risk in the environment; patients with PTSD are more likely to move from a neutral state to a hyper-aroused state, or, in other words, move from a parasympathetic state (rest and recuperate) to a sympathetic state (fight or flight). A person with PTSD may consciously understand that a situation is safe but may be unable to shift to the appropriate physiological state because there is a disconnect between their conscious appraisal and their neurophysiological reaction.

The vagus nerve directly affects how the parasympathetic nervous system operates, so vagus nerve stimulation can improve the parasympathetic response.

taVNS stimulates the auricular branch of the vagus nerve through the ear. The auricular branch of the vagus nerve allows stimulation of afferent vagus nerve fibers, sending signals directly to the brain and permitting a non-invasive treatment with no known serious adverse or off-target side effects. A systematic review of safety and tolerability of transcutaneous VNS showed that the technology was safe and well-tolerated.

OBJECTIVES

This pilot study was conducted to assess the feasibility, usability, and adherence of a novel take home (taVNS) device. This single arm unblinded study was also used to collect PTSD CAPS-5 symptom severity scores and PROMIS-29 Quality of Life results from extended (2 month) use of twice per day taVNS.

METHODS

- Enrollment included a confirmed PTSD diagnosis by the PTSD Checklist (PCL-5) and confirmation via a clinical interview
- Weekly check-in meetings were conducted during the study and a verbal PCL-5 was administered to track symptom changes
- A one-month baseline observation period was followed by 2 months of at home taVNS device use. The device was used 30min 2x per day, preferably AM and PM
- The CAPS-5 assessment and PROMIS-29 were conducted at baseline, one month, and two months
- Participants were asked to maintain all medications and treatments for the duration of the study to the best of their ability

Endpoints

- Primary endpoint – Reduction in CAPS-5 Score after 2 months of device use (figure 1)
- Secondary endpoint – Improvement in PROMIS-29 Quality of Life measurement (figure 2)

STUDY POPULATION AND COMPLIANCE

- 12 subjects recruited; all completed the study. No adverse events were reported during the study
- 7 male, 5 female, average age 44 (range 21-61), average duration of PTSD 18.8 years (range 1.5-53)
- 8 participants were military veterans with all of them attributing PTSD to events occurring during active service, 4 were combat related
- Only 1 subject was noncompliant with the study procedure (<50% device use) and 1 subject was a non-responder (CAPS-5 reduction < 6pts)

RESULTS

Primary Outcome – CAPS-5 Scores

The Clinician-Administered PTSD Scale (CAPS-5) is a widely considered the gold standard scale for symptom severity measurement. This 30 question assessment measures symptoms over 1 month and is scored between 0 and 80 points.

- Overall study participants demonstrated a 10.9-point reduction at month 1 (paired t-test P=0.0206 95%CI 2.0 – 19.8) and an 18.8-point reduction at month 2 (paired t-test P=0.0013 95% CI 9.2 – 28.5)
- 3 subjects achieved full remission levels (CAPS-5 Score <12) and 7 no longer met the full CAPS-5 diagnostic criteria for PTSD at 2 months

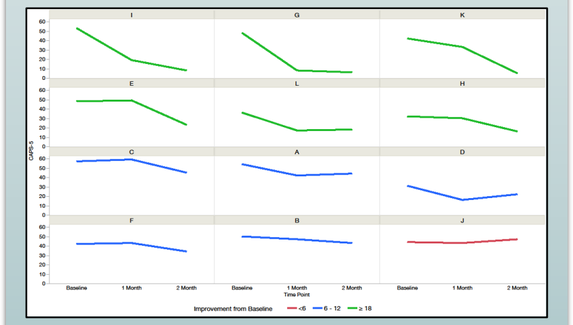

Figure 1 – The average CAPS-5 scores at baseline, 1 month, and 2 months for the 12 study participants charted individually and sorted from largest response (top left) to lowest response (bottom right). Red indicates a treatment non-responder, blue represents a clinically meaningful 6-12 point reduction response, and green is a larger greater than 18 point response to treatment.

Discussion

- All study participants enjoyed using the device, felt that it positively impacted their symptoms, and would continue using the device if able after the end of the study, including the one non-responder
- It is interesting to note that the individual responses to the treatment demonstrated large variation month 1 to month 2 and clearly fell into 2 distinct response categories
  - Blue lines - small but clinically meaningful responses
  - Green lines - very large (> 18 point) response

Secondary Outcome - Quality of Life

The PROMIS-29 is a self-report questionnaire that assesses Quality of Life (QOL) over 7 domains. The results are T-scored as compared to the general US population.

- Change from baseline to two months showed statistically significant improvement in 5 of the 7 domains (paired t-tests) Anxiety/Fear -9.1, 0.0021; Depression/Sadness -5.9, 0.0294; Fatigue -7.6, 0.0036 Sleep Disturbance -9.23, 0.0038; Ability to Participate in Social Roles/Activities +5.6, 0.0257
- Small improvements were seen in both pain interference and physical

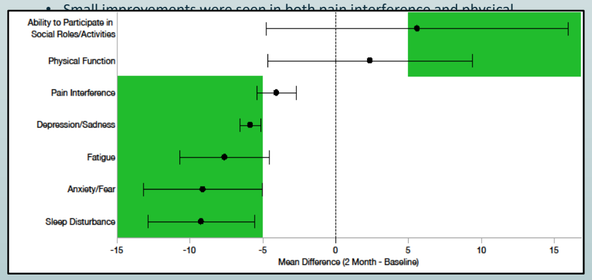

Figure 2 – The PROMIS-29 assessment is t-scored against the standard US population with a score of 50 indicating the average and a standard deviation of 10 points. The figure above displays the average change (2 months-baseline) and confidence interval for the point change for each domain.

A shift of ½ standard deviation is generally considered meaningful (5 points). Ability to Participate in Social Roles and Physical Function are positively scored with a green box representing a meaningful change, the other 5 clusters are negative symptoms therefore a reduction in score is considered a positive change.

Discussion

- The improvements in QOL are complex and may not be solely explained by a reduction in CAPS-5 symptoms. Some PTSD treatments have demonstrated symptom reduction without QOL improvement while others have demonstrated a direct relationship
- We expect increased parasympathetic activity induced by VNS to exhibit an independent positive effect on Social Activates, Depression, Fatigue, Anxiety, and Sleep Disturbance. This is an area that should be investigated in future studies
- Based on other research we expect VNS to have a positive effect on pain interference and the lack of statistical significance may be due to the relatively low baseline level of pain interference in this population

Moderate to Severe Comorbid TBI: Subgroup

Traumatic Brain Injury is a potential target for taVNS therapy due to the increased inflammation and autonomic dysregulation seen after acute brain injury.

Although our study was not designed to look at comorbid TBI we did see a drastic change in this population.

- 4 study subjects had a moderate to severe TBI. Even with these very small numbers, the CAPS-5 score improvement compared to the non TBI subjects was marginally significant at month 1 (t-test p=0.06) and month 2 (p=0.07)
- 3 of the 4 TBI subjects achieved full remission (figure 1: G, I, K) levels during the study and the 4th had a greater response at 1 month than at month 2 (figure 1, D). They reported such dramatically reduced symptoms that protocol adherence decreased for the second month of the study.

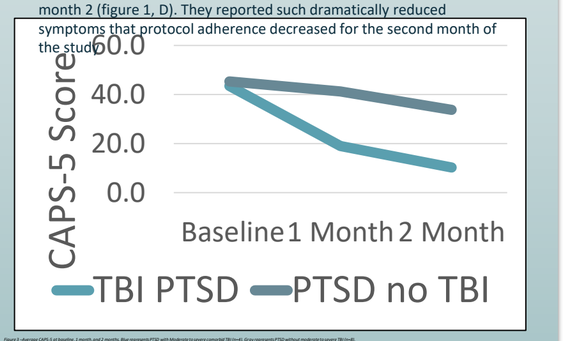

Figure 3 –Average CAPS-5 at baseline, 1 month, and 2 months. Blue represents PTSD with Moderate to severe comorbid TBI (n=4). Gray represents PTSD without moderate to severe TBI (n=8).

Discussion

- Mild TBI and mild TBI with comorbid PTSD are active areas of research for taVNS and few completed studies are currently available
- We believe that the increased inflammation, decreased neuroplasticity, and profound autonomic dysregulation associated with a moderate TBI may be significantly by taVNS treatment. This could help to explain the precipitous drop in PTSD-like symptoms compared to the other study subjects

CONCLUSIONS

- All subjects were able to use the device at home without any major issues and 92% of the subjects were compliant with the protocol for the full 2 months. This is very promising given the low adherence rates typically found in PTSD populations
- The results demonstrate significant reductions in PTSD symptoms with minimal side effects and a low dropout rate
- Many PTSD treatments only address symptoms and fail to improve overall functioning. Our quality-of-life results may indicate broader functional improvements
- The dramatic difference between the moderate to severe TBI group may be explained by overlapping mechanisms of action. taVNS could address inflammation, autonomic dysregulation, and decreased neuroplasticity and cognitive functioning that can be associated with both PTSD and with TBI

FUTURE

Partner with Evren

- Seeking Cooperative Research and Development Agreements (CRADAs)
- Pursuing funding through CDMRP/DoD grants

Potential topics:

- PTSD Treatment
- TBI with or without comorbid PTSD
  - Improved outcomes in the acute phase of TBI
  - Improved treatment or reduced recovery time
  - CTE or Persistent Post-Concussion Syndrome
- Acute Stress / COSRs / PTSD prevention / Sleep

Suggested strategic locations:

- Military Operational Medicine Research Program
- Congressional Directed Medical Research Program
- Walter Reed Army Institute of Research
- Psychological Health Center of Excellence
- Naval Health Research Center

Army STTR Recipient July 2022

17th Annual Amygdala, Stress, and PTSD Conference, April 23, 2024