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Hypoglossal nerve stimulation: outcomes in veterans with obstructive sleep apnea and common comorbid post-traumatic stress disorder

Running Title: HNS in veterans with OSA and PTSD

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Abstract:

Objectives:

Veterans have an increasing prevalence of obstructive sleep apnea (OSA) and high levels of intolerance to positive airway pressure (PAP). The hypoglossal nerve stimulator (HNS) is a promising alternative surgical treatment for OSA in these patients, many of whom suffer from mental health conditions such as post-traumatic stress disorder (PTSD) that may negatively affect their ability to use PAP. Our aims were: 1) to assess postoperative changes in OSA severity and sleepiness in a veteran only population after HNS; 2) to compare postoperative changes in OSA severity, sleepiness and HNS adherence between veterans with and without PTSD; and 3) to compare HNS adherence in our population to HNS adherence in the current literature as well as published PAP adherence data.

Study Type:

Retrospective and prospective case series

Methods:

Clinical data on consecutive patients undergoing HNS in a Veterans Affairs hospital were examined for demographic data as well as medical, sleep and mental health comorbidities. The overall cohort as well as subsets of patients with and without PTSD were examined for postoperative changes in OSA severity (apnea hypopnea index [AHI], lowest oxygen saturation (LSAT]), and sleepiness (Epworth sleepiness scale [ESS]), as well as for device adherence. PTSD and depression symptomatology were measured using the PTSD Checklist 5 (PCL-5) and Patient Health Questionnaire 9 (PHQ-9).

Results:

Forty-six veterans were included. Forty-four patients were male (95.6%), 45 were white (97.8%) and the mean age was 61.3 years. Twenty-six patients met PCL-5 criteria for PTSD and 17 did not. OSA severity and sleepiness improved significantly in the overall cohort after HNS; median (IQR) AHI decreased from 39.2 (24.0, 63.0) to 7.4 (1.2, 20.8) events/hour (P<0.0001), mean LSAT increased from 81% to 88% (P<0.0001) and mean ESS decreased from 10.9 to 6.7 (P<0.0001). These improvements were similar between patients with and without PTSD (P=0.434-0.918). Overall device adherence was 6.1 hours/night for the overall cohort and was not significantly different between patients with and without PTSD (P=0.992).

Conclusions:

HNS is an efficacious therapy in a veteran population, providing patients with significant improvements in OSA severity and sleepiness. Veterans with and without PTSD benefited similarly from HNS when comparing improvements in sleep apnea severity and sleepiness as well as device usage. Adherence was similar to previously published HNS adherence data and better than PAP adherence reported in the literature.

Key words:

Obstructive sleep apnea, post-traumatic stress disorder, hypoglossal nerve stimulator, positive airway pressure intolerance

Level of Evidence: 4

Introduction:

Obstructive sleep apnea (OSA) was first described in the middle of the last century, but has only become recognized as a major contemporary health problem in the United States (U.S.) over the past 3-4 decades. The first major prevalence study of OSA, the Wisconsin Sleep Cohort Study, found OSA in 9% of women and 24% of men when assessed with polysomnography (PSG), with an estimated 2% and 4% of employed middle aged women and men noted to have abnormal PSG along with symptoms of OSA.[1] Several years later, the same authors examined a population seeking care in a sleep medicine clinic and estimated that 80% of moderate to severe OSA was clinically undiagnosed.[2] In light of these findings, the medical community has become increasingly aware of the social and economic impact of OSA and its related morbidity with respect to cardiovascular health, sleep related quality of life (QOL), mood disorders, automobile accidents and cognition; this has resulted in intensifying efforts to screen for and diagnose OSA.[3,4]

The nation's military and veterans have been identified as a group at high risk for OSA. In veterans this is related to their increasing age, predominantly male gender and high rate of obesity--all factors strongly associated with the presence of OSA.[3] The prevalence of OSA in the armed forces increased six-fold from 2000 to 2009 with a concomitant increase in obesity, particularly among personnel deployed to Iraq and Afghanistan.[5] More recent studies of active duty military seeking care for sleep complaints after deployment found that 51% to 77% of these patients were ultimately diagnosed with OSA by polysomnogram(PSG).[6–8] Many of these patients will go on to receive care in Veterans Affairs hospitals, the largest single health care system in the U.S., which served more than nine million veterans in 2018.

Veterans are also more likely to have mental health issues, which may be related to combat experience and socioeconomic challenges. One of these conditions is post-traumatic stress disorder (PTSD), which is defined by DSM-V as a specific cluster of symptoms after exposure to a traumatic event

that elicits a response of fear, helplessness and horror. The core diagnostic criteria for PTSD also encompasses disturbed sleep including insomnia and nightmares.[9] While the U.S. prevalence of PTSD is 3-4%,[10] the prevalence in military and veteran populations ranges from 5% to 30%.[11–14] The impact of PTSD in both the general and military/veteran populations is substantial, as these patients are reported to have high rates of health care utilization and lost productivity resulting in a significant economic cost to society.[15]

Both OSA and PTSD, as separate conditions, result in considerable patient burden; however, recent research suggests that there is a significant association between the two conditions. Multiple studies of diverse populations with PTSD all demonstrate subjective and objective associations with sleep disorders including OSA, upper airway resistance syndrome, insomnia and nightmares.[4,6,16] In studies of active military and veterans with PTSD who were referred to sleep disorder clinics, 57% to 79% were found to have OSA.[6,17,18] While not all data supports a clear association between comorbid OSA and PTSD,[8] the balance of evidence is in favor of a bidirectional relationship between OSA and PTSD rather than the two conditions occurring as epiphenomena.[19]

A number of recent studies supports concerns that comorbid PTSD and OSA negatively impact patients, particularly with regard to cognition, QOL and suicidality. For example, investigators found OSA severity in Vietnam veterans with PTSD and OSA was associated with poor memory and executive function.[4] In addition, military patients with PTSD and OSA experienced lower sleep related QOL and more somnolence than in those with OSA alone.[18] Most concerning is the dramatically higher rate of suicidal ideation noted in another study in patients with both PTSD and OSA (51%) compared to those with OSA alone (4%).[13] This suggests that accurate and timely diagnosis and management of concomitant sleep disorders is critical to optimize the physical, cognitive and emotional states in patients with PTSD symptomatology.

The gold standard for treatment of OSA remains positive airway pressure (PAP). A growing body of evidence has demonstrated that successful use of PAP improves PTSD symptomatology and nightmares [20–25] as well as self-reported sleepiness, energy and emotional well-being from SF-36 QOL

measures.[18,26] In addition, reductions in suicidal ideation (SI) and depression, mental health issues commonly comorbid with PTSD, were noted after three months of PAP.[27] Unfortunately, poor adherence to PAP is a well-documented problem in both civilian and veteran populations, with partial use of PAP more common in patients with a psychiatric comorbidity than among the general population.[28] Studies of regular PAP use in active duty military patients and veterans with OSA report that only 25% to 41% of patients with PTSD used PAP regularly compared to 58% to 70% of those without PTSD[21,26,29,30] with reported reasons for nonadherence including mask discomfort, claustrophobia and air hunger.[29] Additionally, comorbid insomnia with OSA (COMISA) has been shown to reduce PAP therapy's use and effectiveness due to problems with initiating and maintaining sleep.[23,31]

Given this high level of poor adherence or non-adherence to PAP, alternative treatments for OSA are often sought by both patients and providers. Sleep surgeries affecting the upper airway have been shown to improve quality of life at least as well as PAP.[32] Currently, no evidence of the efficacy of upper airway surgery and its potential benefits in the specific population of patients with PTSD and OSA is available. The hypoglossal nerve stimulator (HNS) was approved in the U.S. in 2014 for use in select patients with OSA who fail PAP. This fully implantable device produces contraction of the genioglossus muscle and tongue protrusion during inspiration to reduce upper airway collapse and improve airflow during sleep. It has been shown to improve OSA severity and daytime sleepiness in pre- and post-market studies.[33,34]

However, the HNS has not been widely studied in veterans. Our practice currently follows the largest number of veterans implanted with HNS in a single VA medical center in the U.S. We posited that while the overall group of patients may benefit from HNS therapy, those patients with PTSD might gain a lesser degree of benefit than those with without PTSD due to decreased adherence. In this study, our primary aims were to:

- Assess postoperative changes in OSA severity and sleepiness in a veteran only population after HNS

- Compare postoperative changes in OSA severity, sleepiness and HNS adherence between veterans with and without PTSD
- Compare HNS adherence in our population to HNS adherence in the current literature, as well as published PAP adherence data

We hypothesized that veterans undergoing HNS would significantly benefit from implantation when examining postoperative changes in OSA severity, regardless of PTSD status. We also hypothesized that veterans with PTSD would have greater sleepiness and lower adherence to the HNS device than those without PTSD. Finally, we hypothesized that our overall adherence data would be similar to published HNS adherence data and for those patients with OSA and PTSD, our HNS adherence would be improved compared to available PAP adherence data in the literature. Our secondary aim was to better understand the prevalence and severity of mental health disorders in our population and to gather preliminary information regarding the potential effect of successful treatment of OSA with HNS on PTSD symptomatology and depression.

Methods:

We included all consecutive patients who underwent HNS by a single surgeon (RDP) at the Cincinnati VA Medical Center. All patients were referred by regional VA sleep medicine providers for surgical evaluation due to patients' inability to tolerate PAP therapy. Patients were excluded if they had no follow-up after surgery, or no objective outcome data collected at the time of their follow-up. The study was approved by the University of Cincinnati Institutional Review Board as a retrospective review at the Cincinnati VA Medical Center.

Surgical Care:

The Inspire HNS system (Inspire Medical Systems, Minneapolis Minnesota) was implanted in all patients. Patients were evaluated for candidacy and underwent a drug-induced sleep endoscopy to determine the anatomic pattern of collapse. HNS implantation was performed according to standard

surgical techniques. All patients were discharged to home on the same day of surgery unless overnight observation was recommended for cardiopulmonary indications. Follow-up after surgery occurred at 1-2 weeks for a wound check, then one month postoperatively for device activation and initiation of therapy. Titration in-laboratory PSG occurred 2-3 months after surgery, except for two patients who underwent home sleep studies at a HNS level where they noted symptomatic improvement. After titration, patients were scheduled for follow-up with otolaryngology after approximately 6 and 12 months of use.

Data Collection:

Clinical records were reviewed to document age, sex, race, pre- and postoperative body mass index (BMI), history of prior OSA treatment including upper airway surgery (including uvulopalatopharyngoplasty (UPPP), tonsillectomy only and supraglottoplasty with hyoid suspension) and dental appliance, mental health history (anxiety, or depression), and sleep and medical comorbidities as reported in the VA medical record (Computerized Patient Record System). PTSD was defined as patients fulfilling Criterion A from the PTSD Checklist 5 (PCL-5) and not based on reporting in the problem list. Obesity was defined as a body mass index (BMI)>30 kg/m^2.

Subjective data consisted of pre- and postoperative Epworth Sleepiness Scale (ESS), PTSD Checklist 5 (PCL-5), and Patient Health Questionnaire 9 (PHQ-9) scores. These questionnaires were administered by a nurse in the Otolaryngology clinic who was not a part of the surgical or research team. The ESS data were obtained at the consultation or preoperative visit and again after the postoperative PSG. The PCL-5 and PHQ-9 data were obtained at approximately the 6 to 12-month period after surgery. A subgroup of 10 patients underwent this testing before and after surgery.

The presence of PTSD symptomatology was measured using Criterion A from the PCL-5, which provided evidence that a patient experienced a traumatic event that could have led to PTSD. If Criterion A was fulfilled, the patient went on to take the questionnaire, which was scored from 0 to 80 with a score $\geq$ 33 denoting probable PTSD.[35] The presence and severity of depressive symptoms was measured using the PHQ-9, a validated questionnaire scored from 0 to 27 with a score $\geq$ 10 indicating likely depression.[36]

Patients were asked to report any barriers they perceived that decreased device adherence as an open-ended question.

Adherence, measured as mean weekly hours of therapy use, was obtained through device interrogation during follow-up evaluations after postoperative PSG. This occurred in all except for three patients (one explanted, two lost to follow-up after postoperative PSG). Every patient's adherence obtained during 1 to 3 follow-up visits was included in the overall mean adherence and described at time since surgery in weeks. Best adherence was defined as the highest achieved adherence recorded for each patient, also reported at the number of weeks since surgery. Perioperative complications were documented and reviewed.

Sleep Study Data

Baseline PSGs were obtained from either our home institution or outside institutions and included full night or split night in-laboratory polysomnography, or home sleep apnea testing based on referring physician and/or patient preference. These reports were used to determine candidacy for HNS. If the patient demonstrated a change in weight of greater than 10% between otolaryngology consultation and baseline PSG, or if the PSG was more than 7 years old, a new diagnostic in-lab PSG was performed at our institution. Postoperatively, titration PSG was obtained approximately 8 weeks after surgery and consisted of a full night in-laboratory study at our institution to titrate optimum stimulation parameters. Three patients underwent home sleep testing due to referring physician and/or patient preference.

At our institution, in-laboratory studies followed the American Academy of Sleep Medicine (AASM) guidelines using an 18-channel inpatient PSG.[37] Review of all sleep studies ensured that scoring and reporting of hypopneas was based on AASM rule 1B: a peak signal excursion drop by ≥30% of pre-event baseline for ≥10 seconds with a 4% oxygen desaturation. Apneas were scored based on a 90% reduction in airflow for ≥10 seconds and were classified as obstructive, central, or mixed based on presence and duration of inspiratory effort.[37] Home sleep studies were performed using AccuSom (NovaSom, Inc., Glen Burnie Maryland) in two patients and Embletta MPR (Natus Neuro, Middletown

WI) in one patient. Both these systems reported the respiratory disturbance index (RDI) and LSAT according to AASM rules as an average over 3 nights.

Polysomnogram data collected included pre- and postoperative AHI and obstructive AHI (oAHI), lowest oxygen saturation (LSAT), percentage of total sleep time spent in Stage R sleep (%REM), sleep efficiency and arousal index. Postoperative treatment AHI and oAHI were calculated from the postoperative titration PSG according to the criteria for optimal titration AHI in Table 1. Oxyhemoglobin desaturation index is not reported on sleep reports at our institution and was not an outcome in this study. Surgical success was defined as a reduction in AHI> 50% and postoperative AHI<20 events/hour during optimal titration on PSG. Complete control of OSA was defined as an AHI< 5 events/hour.

Statistical Analysis

Descriptive statistics were calculated on all patient demographics and characteristics. For analysis of subjective and objective outcome measures, data distributions were reported as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables, and frequencies with percentages for categorical variables. Chi-square or Fisher exact tests were used to compare categorical variables between groups based on PTSD status. Independent t-tests or Wilcoxon Rank Sum tests were used to compare all continuous variables between groups defined as “with PTSD” and “without PTSD”. Paired t-tests were used to examine pre to post changes in continuous variables for the overall cohort and within groups. This study was powered based on the AHI reported by Strollo et al in which patients undergoing HNS reduced the mean (SD) AHI score from 32.0 (11.8) at baseline to 15.3 (16.1) after the intervention. Assuming a similar baseline score for our population using a paired t-test at 5% significance level and 80% power, the proposed 43 subjects would allow us to detect an effect size as small as 0.45. P values <0.05 were considered statistically significant. Analyses were performed using SAS version 9.4 (Statistical Analysis Software, Cary, NC). Finally, in terms of our power justification, we used data from the literature as an input for our effect size calculation.

Results:

Forty-six patients underwent HNS implantation between August 2015 and April 2019 for treatment of OSA due to PAP intolerance. Of these, one patient was lost to follow-up after surgery, and two patients had no objective outcomes data. Demographic and comorbidity data are described in Table 2. Of the forty-three patients who completed the PCL-5, twenty-six patients met PCL-5 Criterion A for PTSD, and seventeen patients did not.

The majority of patients were male (95.6%, n=44) and white (97.8%, n=45), with a mean (SD) age of 61.7 (10.7) years. The most common comorbidities included obesity (58.7%, n=27) with mean body mass index of 30.6 (3.5) kg/m2, insomnia (45.6%, n=21) and diabetes mellitus type II (34.8%, n=16). In addition to failure of PAP therapy, 14/46 (30.4%) patients underwent upper airway surgery (UPPP: 6/46; tonsillectomy only: 7/46; supraglottoplasty with hyoid suspension: 1/46) and 4/46 (8.7%) trialed dental appliance therapy prior to implantation. Patients with PTSD were significantly younger (mean (SD) age 59.3 (10.6) years vs 66.0 (8.0) years, P=0.031), and had less coronary disease (19.2% vs. 52.9%, P=0.021) than patients without PTSD. Otherwise, no statistically significant differences were found in demographic variables, comorbidities, or previous treatments for OSA between patients with and without PTSD (P>0.05, Table 2).

Baseline and postoperative outcome measures are shown in Table 3 for the 43 patients who underwent postoperative PSG. Median (IQR) baseline AHI was 39.2 (24.0, 63.0) events/hour, median (IQR) oAHI mean (SD) and lowest oxygen saturation (LSAT) was 81.1% (6.4). These and other baseline PSG values did not differ significantly between patients with and without PTSD (P>0.05, Table 3). Detailed information regarding preoperative and postoperative optimal titration AHI and oAHI is provided in the Appendix.

The mean (SD) AHI at optimal titration decreased significantly by 30.5 (23.4) events/hour (P<0.0001), while the mean (SD) oAHI decreased by 29.4 (22.2) events/hour (P<0.0001). The mean

reduction in AHI was similar between those with and without PTSD (P= 0.536). The overall mean (SD) LSAT significantly improved from 81.1% (6.4%) at baseline to 87.7% (4.2%) postoperatively (P<0.0001). This improvement was significant for both subgroups (with PTSD [P<0.001] and without PTSD [P<0.001]) and was also similar between groups (P=0.543). Tables 3 and 4 illustrate the primary outcome changes and comparisons between patients with and without PTSD.

Surgical success was attained in 71% (30/43) of patients. OSA was completely controlled (AHI<5 events/hour) at optimal HNS stimulation voltage in 45% (19/43) of patients. Surgical success and complete control of OSA were similar for patients with and without PTSD (P= 0.551 and 0.663, Table 3).

The overall mean (SD) ESS score improved post implantation with a mean decrease of 4.3 (4.4) (P<0.0001). ESS improved significantly for patients with and without PTSD (both P<0.001), and the results were similar between groups (P=0.338). Overall device usage was 6.1 +/- 2.1 hours/night with no significant difference between those with and without PTSD (P= 0.889). Overall mean best adherence was 6.6 (2.1) hours/night at median 37.2 [14.7, 61.8] weeks after surgery and this was similar between patients with and without PTSD (P=0.265). In a sub-analysis of patients with PTSD, there was a significant difference in overall adherence between patients with or without insomnia (mean (SD) 5.2 (2.3) hours/week vs. 7.0 (1.8) hours/week, P=0.046), but not for patients with or without depression (5.9 (2.3) hours/week vs. 6.6 (2.1) hours/week, P=0.512).

Twenty-five patients had at least one comorbid mental health condition, as shown in Table 5. These included PTSD (61%, 26/43) per PCL-5 results, depression (59%, 25/43) and anxiety (28%, 12/43) as determined by the problem list. Regarding the 26 patients with PTSD, 77% also had comorbid depression and 38.5% also had anxiety. The prevalence of depression in patients with PTSD was significantly higher than for those without PTSD (77% vs. 29% P=0.002). The mean (SD) active depression PHQ-9 score for the cohort was 9.5 (7.6); this was significantly higher in patients with PTSD compared to those without PTSD (P<0.001). The mean (SD) PCL-5 score for patients with PTSD was 40.2 (20.0). A subgroup of 12 patients underwent prospective screening with the PCL-5 and PHQ. Of those, 7 had PTSD and completed the PCL-5 questionnaire while all 12 completed the PHQ-9

questionnaire before and after surgery. The changes in PCL-5 and PHQ-9 scores for these patients are illustrated in Figures 1 and 2.

Barriers preventing all-night adherence were identified in 35% (15/43) of patients. Nine patients complained of insomnia, two patients cited chronic pain, and four patients had frequent nocturia.

Six patients (6/46, 13.0%) experienced an adverse event in the perioperative period. These included: (1) small intraoperative pneumothorax (requiring a pigtail catheter and 36-hour stay in the intensive care unit), (2) herpes zoster of the ipsilateral chest (starting on postoperative day 10), (3) methicillin-resistant *Staphylococcus aureus* infection of the sensing lead site requiring inpatient intravenous antibiotics and ultimate explant, (4) electrical leak to the sensing lead requiring replacement of the pulse generator, (5) wound infection of the neck incision that resolved after treatment with oral antibiotics and (6) displacement of the sensing lead from its position between the intercostal muscles requiring replacement.

Discussion:

Overall Clinical Outcomes:

This study is the first to report outcomes related to HNS implantation for OSA in a U.S. veteran-only, PAP-intolerant population with a high rate of comorbid PTSD. Our patients were primarily older (mean age 61.3 years), male and obese, with a high rate of OSA-associated comorbidities. Post-implantation, the majority of veterans in our cohort who underwent HNS had a significant reduction in AHI and an increase in the LSAT with resolution of OSA (AHI<5) seen in 45% of patients. Overall, the surgical success rate was 71% despite the fact that almost 20% of the cohort started with a preoperative AHI >65 and more than 40% had a preoperative BMI>32kg/m^2, both outside current Federal Drug Administration guidelines for HNS. Additionally, sleepiness improved significantly after surgery. These findings were true regardless of PTSD status, which is important as our veteran population had a high incidence of mental health disorders, with 60% suffering from PTSD, 58% with depression and 28% with anxiety. Moreover, patients with both OSA and PTSD suffered from higher rates of comorbid depression

(77%) and anxiety (39%) than our overall veteran cohort. Finally, mean adherence was high at 6.1 hours/night with no significant difference for those with or without PTSD.

Relationship between OSA and PTSD:

An understanding of the complex association between OSA and PTSD is essential for those practitioners treating patients who suffer from both disorders. In the late 1980's, researchers in psychiatric medicine first recognized the central relationship between sleep and PTSD, proposing that dysfunctional REM sleep mechanisms are responsible for distressing dreams common in patients with PTSD.[38] Subsequent studies supported this relationship with reports that frequent arousals and sleep fragmentation during REM sleep in patients with preexisting OSA can prevent recovery from exposure to traumatic events and lead to PTSD, for example, by impairing the extinction of learned fear.[39,40] Alternatively, others suggest that PTSD itself may contribute to the development of sleep disorders such as OSA.[39,40] For example, increased arousals and sleep fragmentation related to insomnia and frequent awakenings in PTSD have been shown to lead to a lower pharyngeal critical closing pressure, increasing the risk of upper airway collapsibility.[41] These data suggest that PTSD and OSA reinforce each other in a bidirectional manner.[16,25,40] This concept is increasingly supported by neurobiological data from studies of hippocampal neural damage and the hypothalamic-pituitary axis neurohormonal feedback loop that functions as part of the stress response system.[16]

Krakow et al has developed a comprehensive model proposing that patients who suffer from sleep disordered breathing (a broad category that includes OSA) prior to trauma may have stress-induced arousals and insomnia related to their trauma, further promoting sleep fragmentation. The cycle that follows subsequently worsens the preexisting sleep condition, as well as PTSD symptomatology.[25] This interaction between OSA and PTSD is especially relevant when applied to U.S. active military and veterans. In these populations, the number of patients receiving a diagnosis of PTSD and/or OSA has consistently risen over the past two decades.[4,6,17-19,38,42-44] A 2017 meta-analysis found the pooled prevalence rate of OSA was 76% in PTSD patients with AHI >5 and 44% with AHI>10. The study also

noted a significant difference in the prevalence of OSA in veterans with PTSD compared to a nonveteran sample (62.5% vs 7%), which persisted at AHI>10 (56% vs 7%).[19] Our findings in patients undergoing HNS are also consistent with a relationship between OSA and PTSD, with 60% of patients screening positive for PTSD symptomatology.

Treatment for Patients with OSA and PTSD:

Given the likely bidirectionality between OSA and PTSD, as well as their increasing prevalence in the military and veterans, the VA health care system and the medical community at large should be prepared to deliver innovative treatments for these disorders. While PAP is the gold standard for OSA treatment and is widely prescribed within the VA, it can be poorly tolerated in patients with comorbid PTSD. One author recently described PAP as a traumatizing experience with some patients experiencing a phobic response to the mask or pressurized air termed "fixed, pressure-induced expiratory pressure intolerance."[28] The mandibular advancement device (MAD) is another noninvasive therapy which is most effective for patients with mild to moderate OSA, but may not be a viable option for those with poor dentition and/or temporomandibular joint disease.[45] In a recent study performed in patients with both OSA and PTSD, use of the MAD reduced PTSD severity and improved QOL equally as well as CPAP. In addition, more than half of patients preferred MAD to CPAP. However, 71% of CPAP titrated participants had complete resolution of OSA with CPAP compared to only 14% with MAD.[24]

In our study, almost 10% of HNS patients were referred for MAD prior to surgery and had the device fitted and fabricated despite most patients having moderate to severe OSA. In these patients, the discomfort of the device in the mouth and failure to resolve OSA were the major barriers to successful usage of MAD; only one was using MAD at the time of surgery. Lastly, upper airway surgery (UAS) such as UPPP, tonsillectomy, supraglottoplasty and hyoid suspension are procedural alternatives to PAP that theoretically produce 100% compliance given the static nature of surgical changes within the airway once well healed. A 2008 review reported surgical success in 66% of patients undergoing multilevel UAS. However, pharyngeal surgery can involve significant discomfort and prolonged recovery periods,

whereas HNS is well tolerated in our experience.[32,46] Of the 30% of patients in our sample that previously underwent upper airway surgery, 2/14 reported temporary improvement that diminished over time, while the remaining twelve patients did not recall subjective benefit at any time after surgery. In this setting, our high rate of surgical success with HNS in patients with PTSD (68%) holds promise for veterans whose past combat experiences may sensitize them to PAP masks and who have had limited success with oral appliances and other surgical procedures for OSA.

Adherence to HNS:

Adherence to HNS in our study was high with mean use of 6.1 hours/night in the entire cohort and no significant difference between those with PTSD and without PTSD. When calculating the best adherence value, which often followed multiple return visits and counseling on optimal usage, we noted even higher mean adherence at 6.6, 6.7 and 6.5 hours/night for the entire cohort, patients with PTSD and patients without PTSD respectively. This speaks to the need for close follow-up of HNS patients to ensure optimal understanding of device usage. Our reported adherence was similar to several studies of HNS patients in the U.S, which noted use in the range of 5.4-7.5 hours/night.[33]

When comparing adherence between therapies such as PAP and HNS, however, it is difficult to compare these values given the lack of a consistent measure of success. With HNS, the goal is for use "all night, every night," and our adherence average in all groups of patients meets this goal. PAP, on the other hand, has traditionally defined successful adherence as at least 4 hours of PAP administered on 70% of days monitored. While most studies publishing results on adherence to PAP in patients with OSA and PTSD do not allow for a direct comparison between success with HNS versus PAP, one study did provide relatable results, finding that veterans with OSA and PTSD demonstrated significantly lower PAP adherence (an average of 3.4 hours/night) compared to patients with OSA alone (5.8 hours/night).[18] Our findings of adherence of 6.1 hours/night in veterans who underwent HNS with OSA and PTSD, as well as OSA alone, appears to be a clear improvement over those treated with PAP, at least when compared to this particular study. While we currently require that all veterans trial PAP as the initial "gold standard"

treatment of OSA prior to surgical referral, our results suggest that those with mental health comorbidities such as PTSD with PAP intolerance can significantly benefit from HNS with a reasonable expectation for successful usage. Our findings may spur future investigators to consider the usage of HNS as primary therapy in a carefully selected population unlikely to accept PAP.

Impact of Mental Health on Treatment of OSA:

When addressing OSA in patients with PTSD, it is important to consider how PTSD alone, as well as concomitant mental health disorders that often accompany it, may impact compliance and success with therapy. One study found that the relative odds of other lifetime mental health disorders were elevated among people with PTSD, and the overwhelming majority had another DSM-III disorder.[47] Similarly, a 2011 study of active military patients with both OSA and PTSD found them to have high levels of depression and anxiety.[6] We also found frequent depression and anxiety on our patients' problem lists, and many were in active treatment for these issues. In particular, the prevalence of depression was 79% for patients with PTSD. Previous reports have found that the presence of comorbid PTSD and depression negatively affects CPAP compliance,[48] however, patients with PTSD and depression in our study actually had similar adherence (5.9 hours/night) to patients with PTSD without depression (6.6 hours/night).

While these results are encouraging regarding the utility of HNS in this subgroup, several patients' experiences highlight the challenges that mental health disorders may pose to effective use of HNS. Three patients were entirely lost to follow-up after titration PSG despite repeated attempts to contact them. One patient with a low average adherence (3 hours/night) refused to attempt improved usage of the device despite multiple clinic appointments to optimize settings and provide teaching. The patient with lowest adherence (<1 hour/night) was intermittently lost to follow up due to very severe PTSD and depression; when he ultimately returned to our service we found that his mental health disease processes prevented sleep and consequently he was unable to use HNS effectively. All of the above patients suffered from moderate to severe depression, three had significant PTSD symptomatology and

two also had suicidal ideation, which we believe were direct barriers to regular use of HNS. Similar to PAP, HNS is a patient-controlled device. Despite good efficacy of HNS noted on titration PSG in all five patients, severe depression, sleep disturbances related to PTSD and apathy certainly contributed to their lack of adherence and poor follow-up.

Secondary aims in this study were to investigate the prevalence and severity of PTSD and depression in patients undergoing HNS, as well as prospective changes in symptomatology after surgery. Of the 43 patients who were administered the PCL-5 in our cohort, 60% fulfilled Criterion A as indicative of the presence of some degree of PTSD symptomatology within 12 months after surgery. The mean PCL-5 score was 40.2, with almost two-thirds (16/25) of these patients scoring greater than the cutoff score of 33/80 used by mental health providers to confirm the presence of probable PTSD. In patients administered the PCL-5 before and after surgery, scores remained essentially stable although five of seven patients showed a slight downward trend in scores. We consider this to be preliminary data given the small sample size, but worthy of continued investigation given that a previous study showed decreases in PCL scores after 6 months of CPAP treatment.[20]

With regard to depression, of the patients administered the PHQ-9 within 12 months after surgery, the mean score was 9.5 with 19/42 scoring 10 or above. These values indicate a high (45%) prevalence of active depressive symptoms amongst the cohort given that a score of 10/27 or higher is considered a positive screen for depression and corroborates the high level of reported depression in the patients' problem list within the medical record (58%). We collected the PHQ-9 prospectively on twelve patients, noting that scores also remained relatively stable after surgery, although half showed a downward trend. Further investigation is warranted to determine if alternative therapies for OSA such as HNS can substantially ameliorate depression, similar to improvements in depression noted after effective PAP treatment.[48]

Impact of Insomnia on Treatment of OSA and PTSD:

From our experience, another major factor that impacted the success of HNS in patients with

OSA and PTSD was the presence of insomnia. According to DSM-V, disturbed sleep is part of the diagnostic criteria for PTSD, with insomnia classified within the cluster of symptoms related to alterations in arousal and reactivity.[9] In patients with COMISA, sleep fragmentation can be exacerbated both by frequent arousals and the inability to maintain sleep. In this setting, the addition of the hyperarousal state of PTSD can act as a catalyst promoting reinforcement of somatic arousal from recurrent apneic events, resulting in even poorer sleep hygiene.[23] In a study of active military, patients with COMISA were significantly more likely to suffer from depression (71%) and PTSD (59.5%) compared to patients with OSA alone.[7] Patients with COMISA and PTSD also encounter barriers to effective PAP therapy.[23,30] In one study of patients with PTSD, the nightly CPAP usage for those with COMISA (2.2 hours/night) was significantly lower than for those with OSA alone.[23] In our study, we found that patients with PTSD and COMISA also had significantly lower adherence (5.2 hours/night) compared to those with PTSD and OSA alone (7.0 hours/night). We also noted that insomnia was the most frequently cited response when patients were questioned about barriers to usage of HNS. Our findings suggest that multidisciplinary treatment with the mental health and sleep medicine services for these patients will be critical to optimize adherence to patient-initiated treatments such as PAP and HNS.

Study Limitations/Future Research:

Our study was limited by several factors. The overall cohort size of 46 patients was small which limits the power for subgroup analysis. While power is limited for multiple comparisons, this analysis is hypothesis-driving for future studies. In order to increase our power for future studies, we continue to accrue new patients and plan to collaborate across VA hospitals to provide a larger sample size. A source of potential bias stems from the fact that all HNS procedures were performed by a single surgeon with follow-up in one VA Otolaryngology clinic. Our efforts to expand our cohort also intend to address this factor. In addition, 30% of patients underwent prior upper airway surgery, which introduces heterogeneity into our population given that these procedures were performed over a period of many years and across a variety of clinical settings with differing providers and surgical techniques. While it is important to note

that this heterogeneity with prior procedural therapy for OSA may have biased outcomes, our rate of UPPP prior to surgery (13%), in particular, was similar to that found in the STAR trial (17%) and all of our patients with OSA had tongue base collapse in common.[34] Moreover, we were not able to assess the impact of behavioral or pharmacologic therapy for co-existing mental health disorders or insomnia which may confound our results; we plan to investigate this in future studies.

Another limiting factor in this study is that the postoperative AHI in most patients was calculated from in-laboratory titration PSG, analogous to the AHI reported for optimal settings on a CPAP titration study. Full night PSG, possibly home sleep testing, at the optimal setting would likely be more representative of an entire night of sleep with the full cycle of sleep stages and range of body positions but was not available in our setting at the time of intervention.[49] To eliminate any concerns of "cherry-picking" AHI values on the titration PSG, we used a strict algorithm to determine the optimal AHI as delineated in Table 1. Lastly, our labeling of a patient as having PTSD in this study was based on usage of Criterion A of the PCL-5; however, this portion of the questionnaire simply confirms that a patient has PTSD symptomatology and qualifies the patient to take the remainder of the questionnaire. For mental health providers, the PCL-5 alone as a diagnostic tool may not be sufficient to warrant trauma psychotherapy, pharmacologic therapy and/or occasional inpatient care provided to patients considered to have PTSD by a "stricter definition" that also includes structured interviews and DSM-V criteria.[50] While screening for PTSD with the PCL-5 may overestimate its prevalence by equating the disorder with symptomatology, and by extension, overestimate the concomitant nature of PTSD with OSA in our population, we felt a wider clinical understanding of factors that might affect patients' acceptance of HNS justified the possibility of a greater false positive rate for PTSD.

Our intensive experiences with veterans undergoing HNS implantation highlight a number of areas for further research in patients with OSA and PTSD. In particular, a larger population of veterans being treated across a number of VA medical centers is needed to validate our findings and help us understand the impact of multidisciplinary teams (ideally including mental health and sleep medicine services) to improve treatment adherence for these patients. Another area that merits investigation is the

effect of insomnia on both efficacy and usage of HNS. Future research is also required to assess the impact of HNS on PCL-5 and PHQ-9 scores to determine if HNS can result in potential improvements in PTSD and depression as a result of successful treatment of OSA. Finally, current work focuses on the presumption that effective treatment of OSA improves PTSD given the centrality of sleep symptoms in PTSD. However, evidence pointing to the bidirectionality of PTSD and OSA suggests that early identification and aggressive treatment of PTSD is imperative as symptoms caused by a traumatic event may predispose patients to OSA. This relationship requires further study; early screening for both OSA and PTSD in active military and watchful care in veterans after return from service should be emphasized in an effort to prevent subsequent sleep disorders as well as other PTSD-related mental and physical health impairments.

Conclusion:

Our results provide evidence that HNS is an efficacious therapy in a veteran population, benefiting patients significantly with regard to OSA severity and sleepiness. Veterans with and without PTSD benefited equally from HNS when comparing improvements in sleep apnea severity and sleepiness, as well as device usage. Adherence was similar to previously published HNS adherence data and better than PAP adherence reported in the literature. A high rate of concomitant mental health disorders was noted in this cohort, especially PTSD and depression, when utilizing mental health questionnaires measuring active symptomatology. The presence of comorbid insomnia was a barrier to effective use of HNS in patients with PTSD and OSA, with decreased adherence compared to those without insomnia. Future studies should focus on providing further evidence of the benefit of HNS in a larger sample of veterans and the impact of effective OSA treatment on mental health disorders common in this population.

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Tables:

Table 1: Methodology used to determine treatment apnea-hypopnea index (AHI) using the postoperative titration polysomnography after hypoglossal nerve stimulator implantation

Treatment AHI is defined as the optimal titration AHI once therapeutic programming is established during titration polysomnography. Treatment AHI is calculated using the appropriate criterion using one of the three scenarios below:
i. When the therapeutic amplitude is achieved, and the AHI is consistent over the explored therapeutic range, then the treatment AHI is the AHI at therapeutic amplitude.
ii. When AHI is significantly variable after establishing therapeutic amplitude, the treatment AHI is the average AHI calculated across the therapeutic amplitude range.
iii. When there is no clear therapeutic effect, treatment AHI is considered to be the overall AHI for the entire study.

Table 2. Characteristics of veterans with obstructive sleep apnea and subgroups of patients with and without post-traumatic stress disorder (PTSD).

Characteristics	Cohort (N=46) †	With PTSD (N=26)	Without PTSD (N=17)	P- value
Age, years Mean (SD)	61.3 (10.7)	59.3 (10.6)	66.0 (8.0)	0.031
Sex, Male N (%)	44 (95.6)	25 (96.2)	16 (94.1)	1.0
Race				1.0
White, N (%)	45 (97.8)	25 (96.2)	17 (100.0)	
Black, N (%)	1 (2.2)	1 (3.8)	0 (0)	
Body Mass Index (BMI), kg/m^2, mean (SD)	30.6 (3.5)	31.1 (3.6)	30.4 (3.2)	0.525
Obese (BMI>30 kg/m^2), N (%)	27 (58.7)	18 (69.2)	9 (52.9)	0.280
Coronary artery disease, N (%)	14 (30.4)	5 (19.2)	9 (52.9)	0.021*
History of myocardial infarction, N (%)	8 (17.4)	4 (15.4)	4 (23.5)	0.502
Diabetes Mellitus II, N (%)	16 (34.8)	10 (38.5)	6 (35.3)	0.834
COPD, N (%)	6 (13.0)	2 (7.7)	4 (23.5)	0.143
Insomnia, N (%)	21 (45.6)	14 (53.8)	5 (29.4)	0.115
Asthma, N (%)	7 (15.2)	4 (15.4)	3 (17.7)	0.844
Stroke, N (%)	2 (4.3)	2 (7.7)	0 (0)	0.510
Previous treatment for sleep apnea				
Prior upper airway surgery, N (%)	14 (30.4)	10 (38.5)	4 (23.5)	0.307
Dental device, N (%)	4 (8.7)	4 (15.4)	0 (0.0)	0.095

P-value comparing veterans with PTSD to those with no history of PTSD.

*Indicates statistically significant value.

† Of the overall cohort of 46 patients, three were not administered PTSD Criterion A and are not included in the subgroups.

PTSD- post-traumatic stress disorder; COPD- chronic obstructive pulmonary disease; upper airway surgery- uvulopalatopharyngoplasty. tonsillectomy only or supraglottoplasty with hyoid suspension

Table 3. Baseline and postoperative data of veterans undergoing hypoglossal nerve stimulator surgery as well as subgroups of patients with and without post-traumatic stress disorder (PTSD).

	Cohort (N=43) †	With PTSD (N=26) †	Without PTSD (N=17) †	P- value
Preoperative ESS, Mean (SD)	10.9 (5.3)	10.5 (5.1)	11.8 (5.6)	0.434
Postoperative ESS, Mean (SD)	6.7 (3.9)	6.7 (3.9)	6.7 (4.2)	0.971
Preoperative AHI, Median [IQR]	39.2 [24.0, 63.0]	36.0 [24.0 44.4]	53.3 [25.2, 64.0]	0.449
Postoperative AHI, Median [IQR]	7.4 [1.2, 20.8]	5.3 [2.9, 20.8]	9.7 [0.60, 14.8]	0.898
Preoperative oAHI, Median [IQR]	31.9 [23.6, 54.2]	31.2 [22.7, 41.1]	44.1 [25.2, 58.0]	0.662
Postoperative oAHI, Median [IQR]	5.9 [1.1, 15.0]	4.1 [1.9, 15.3]	9.7 [0.6, 14.8]	0.837
Preoperative LSAT, Mean (SD)	81.1 (6.4)	81.0 (5.7)	80.9 (7.5)	0.918
Postoperative LSAT, Mean (SD)	87.7 (4.2)	88.0 (4.0)	87.2 (4.6)	0.539
Preoperative sleep efficiency, Mean (SD)	78.4 (12.0)	78.8 (11.9)	77.7 (12.6)	0.784
Postoperative sleep efficiency, Mean (SD)	75.1 (14.2)	73.0 (15.4)	78.1 (12.2)	0.278
Preoperative arousal index, Mean (SD)	42.1 (28.1)	41.3 (25.5)	43.3 (32.4)	0.832
Postoperative, arousal index, Mean (SD)	39.8 (21.6)	43.4 (21.1)	34.6 (22.0)	0.212
Preoperative %REM , Mean (SD)	13.8 (9.1)	12.0 (9.3)	16.4 (8.5)	0.152
Postoperative %REM , Mean (SD)	8.7 (7.0)	6.7 (7.2)	11.5 (5.8)	0.033
Surgical success, N (%)	30 (71.4)	17 (68.0)	13 (76.5)	0.551
Complete control, N (%)	19 (45.2)	12 (48.0)	7 (41.2)	0.663
Average adherence, hours/night,Mean(SD)	6.1 (2.1)	6.1 (2.2)	6.1 (1.8)	0.992
Best adherence, hours/night, Mean(SD)	6.6 (2.1)	6.7 (2.3)	6.5 (1.8)	0.747
# of weeks to average adherence, Median [IQR]	40.8 [23.4, 64.6]	39.9 [24.6, 61.9]	41.9 [23.4, 77.1]	0.758
# of weeks to best adherence, Median [IQR]	37.2 [14.7, 61.8]	37.0 [15.1, 48.1]	41.9 [14.0, 86.0]	0.265

Postoperative data represent optimal titration AHI from titration polysomnogram. Surgical success was defined as a >50% decrease in AHI and AHI<20. Complete control was defined as AHI<5 events/hour.

† the actual number used to calculate each variable was different: AHI, ESS: n=43; LSAT: n=42; oAHI: n=40; %REM, SE, AI: n=34

P-value compares veterans with PTSD to those without PTSD

PTSD- post-traumatic stress disorder; SD- standard deviation; IQR- interquartile range; BMI- body mass index kg/m^2; ESS- Epworth sleepiness scale; AHI- apnea hypopnea index events/hour; oAHI-obstructive apnea hypopnea index; LSAT- lowest oxygen saturation %; %REM- percentage of total sleep time spent in Stage R sleep

Table 4. Change between baseline and postoperative polysomnography measures in veterans undergoing hypoglossal nerve stimulation (HNS) as well as subgroups of patients with and without post-traumatic stress disorder (PTSD).

	Cohort			With PTSD			Without PTSD			
	N	Mean (SD)	P	N	Mean (SD)	P	N	Mean (SD)	P	P*
Change in AHI	43	-30.5 (23.4)	<.0001	26	-28.6 (24.4)	<.0001	17	-33.3 (22.3)	<.0001	0.536
Change in oAHI	40	-29.4 (22.2)	<.0001	23	-28.4 (23.0)	<.0001	17	-30.7 (21.8)	<.0001	0.750
Change in LSAT	42	6.9 (5.4)	<.0001	25	7.3 (5.2)	<.0001	17	6.2 (5.7)	0.0004	0.543
Change in ESS	43	-4.3 (4.4)	<.0001	26	-3.8 (4.3)	0.0001	17	-5.1 (4.7)	0.0004	0.338
Change in %REM	34	-5.18 (9.5)	0.003	20	-4.6 (11.3)	0.029	14	-6.0 (6.6)	0.004	0.682
Change in SE	34	-2.76 (15.2)	0.300	20	-3.60 (14.5)	0.281	14	-1.6 (16.7)	0.732	0.707
Change in AI	34	0.26 (24.9)	0.953	20	3.5 (29.3)	0.596	14	-4.43 (16.8)	0.342	0.323

Negative values indicate a decrease from **pre to post** measure

*P-value on far right compares the change between veterans with PTSD to those without PTSD. P-value to the right of each group is the p value for the change within the group.

PTSD- post-traumatic stress disorder; SD- standard deviation; AHI- apnea hypopnea index events/hour; LSAT- lowest oxygen saturation ESS- Epworth sleepiness scale; %REM- percentage of total sleep time spent in Stage R sleep; %; SE- sleep efficiency %; AI- arousal index=arousals/hour sleep;

Table 5: Mental health diagnoses within 12 months prior to or after hypoglossal nerve stimulator (HNS) placement.

	Cohort (N=43)	With PTSD (N=26)	Without PTSD (N=17)	P-value
Depression Diagnosis, N (%)	25 (58.1)	20 (76.9)	5 (29.4)	0.002
Anxiety Diagnosis, N (%)	12 (27.9)	10 (38.5)	2 (11.8)	0.084
Both depression and anxiety, N (%)	11 (25.6)	9 (34.6)	2 (11.8)	0.003
Mean PHQ-9, mean (SD)	9.5 (7.6) †	13.2 (7.4) ‡	4.2 (3.8) §	<0.0001
Mean PCL-5, mean (SD)	N/A	40.2 (20.0) ¶	N/A	

P-value comparing veterans with PTSD to those without PTSD

† N=42, ‡ N=25, § N=17; ¶ N=25.

Note that PHQ-9 and PCL-5 values listed are postoperative values

Figure Legends

Figure 1. PTSD Checklist 5 (PCL-5) questionnaire results for seven veterans undergoing hypoglossal nerve stimulator (HNS) implantation before and after surgery assessing for post-traumatic stress disorder (PTSD) symptomatology.

Figure 2. Patient Health Questionnaire 9 (PHQ-9) results for twelve veterans undergoing hypoglossal nerve stimulator (HNS) implantation before and after surgery assessing for symptoms of depression.

Appendix: Postoperative polysomnographic optimal titration data in consecutive patients undergoing hypoglossal nerve stimulator.

PSG=polysomnogram; AHI=apnea-hypopnea index; oAHI=obstructive apnea-hypopnea index; BMI=body mass index; min=minutes

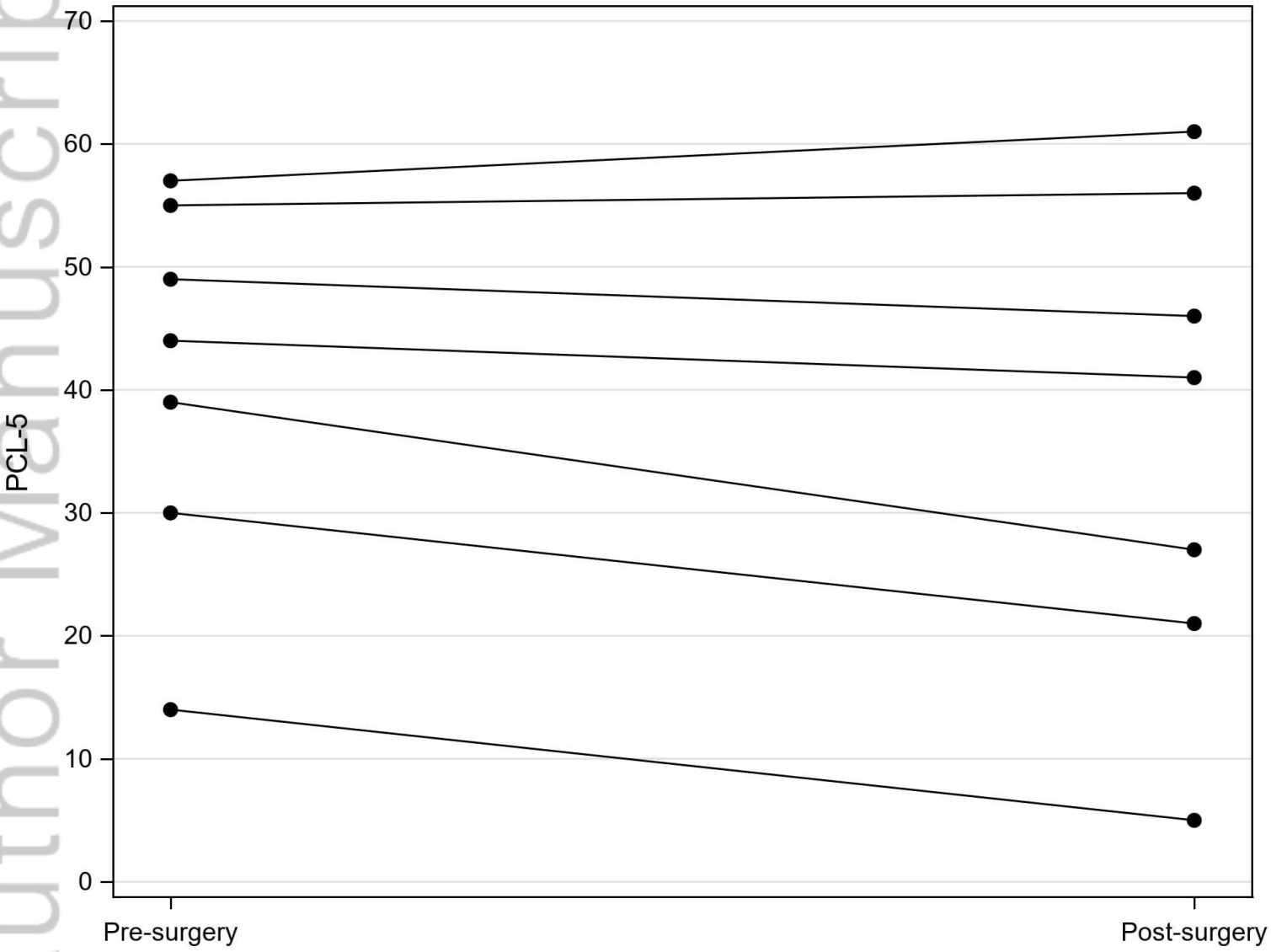
Appendix: Postoperative polysomnographic optimal titration data in consecutive patients undergoing hypoglossal nerve stimulator.

Patient #	Titration PSG Date	Pre-op BMI	Pre-op oAHI	Optimal Titration oAHI	Pre-op AHI	Optimal Titration AHI	Time at Optimal Titration Voltage (min)	Optimal Titration Voltage Range	Methodology (from Table 1)
1	11/5/15	25	38	0.0	38.0	3.7	32.44	2.7V	i
2	explanted	26.83			59.1				
3	8/30/16	33.63	8.8	0.0	9.5	0	38	1.8V to 2.1V	i
4	8/30/16	34.3	88	22.6	88.0	24.7	125.7	2.0V to 2.1V	i
5	9/7/16	27.7	27.5	1.2	27.5	1.2	51.7	2.4V to 2.5V	i
6	9/13/16	33.7	40.6	27.3	40.6	27.27	178	1.6V to 3.0V	iii
7	11/9/16	31.8	64	13.9	64.0	13.9	272.4	2.5V to 2.9V	ii
8	1/9/17	30.3	72	11.9	72.0	11.9	287	1.8V to 3.3V	iii
9	1/9/17	26.5	25.2	2.8	25.2	3.2	169	1.5V to 2.0V	ii
10	5/8/17	25.3	35	1.0	35.0	1	210.49	1.4V to 1.6V	i
11	6/26/17	30.5	41.2	3.5	41.2	3.5	34.64	1.8V	i
12	7/17/17	27.8	31.9	57.9	44.4	83.8	153.2	0.6V to 1.0V	iii
13	7/17/17	26.2	26.3	24.1	93.7	54.8	179.6	1.5V to 1.8V	iii
14	7/29/17	35.3	39.2	0.0	39.2	0	71.97	1.8V to 1.9V	ii
15	7/29/17	35.1	85.9	9.7	85.9	9.7	86.14	1.8V to 1.9V	ii
16	9/25/17	32.3	26.2	20.0	29.0	24.8	87.18	1.3V to 1.7V	ii
17	9/25/17	28.5	30.5	0.0	30.5	0	137.64	1.1V to 1.3V	ii
18	10/23/17	33.6	20.8	0.0	20.8	0	150.6	3.1V to 3.3V	ii
19	10/23/17	24.2	17	0.0	17.0	0	73.07	1.5V to 1.7V	ii
20	11/27/17	35.7	19.7	1.9	19.7	1.9	32.41	1.9V to 2.0V	ii
21	12/21/17	27	27.6	3.0	27.6	3	62.46	2.7V to 2.8V	ii

22	12/18/17	27.3	26.9	0.0	26.9	0	57.27	2.9V to 3.0V	ii
23	3/12/18	32.12	15.9	8.4	18.1	8.4	128.1	2.4V to 2.8V	ii
24	6/25/18	27.8	27.7	0.0	27.7	0	242.7	1.5V to 2.3V	ii
25	6/14/18	29.6	19.6	2.9	19.6	2.9	61.6	1.3V	i
26	5/7/18	25.04	8.3	0.6	8.3	0.6	158.6	1.3V to 1.9V	ii
27	7/30/18	34.1	30	4.1	30.0	4.1	131.5	2.4V to 2.6V	ii
28	6/27/18	32.1	52.8	0.0	53.2	0	37.5	2.6V to 2.8V	ii
29	8/27/18	33.5	52.1	11.9	53.3	14.3	399.4	2.1V to 4.5V	iii
30	8/20/18	34.6	21.8	8.7	21.8	9.1	164.9	3.1V to 3.5V	ii
31	8/8/18	30.4	57.1	14.5	63.4	14.5	205	2.5V to 3.3V	iii
32	3/6/19	32.3			40.7	24.6	494.5	home sleep test	iii
33	3/14/19	36.2			80.3	20.1	403	home sleep test	iii
34	11/19/18	32.4	81.2	29.4	83.1	29.9	111.9	1.2V to 1.6V	iii
35	4/22/19	23.7	28.7	15.3	34.8	20.8	172.7	1.2V to 1.5V	ii
36	12/17/18	30.4	23.6	6.5	23.6	6.5	55.6	2.6V to 2.7V	ii
37	2/27/19	35.45	83.7	4.0	83.7	4	277.9	3.8V	i
38	3/19/19	34	62.6	5.3	62.6	5.3	181.9	1.5V to 1.9V	ii
39	3/25/19	26.6	63	14.8	63.0	14.8	81.7	1.6V to 1.9V	ii
40	5/6/19	30.6	44.1	42.4	44.6	56.5	17	2.5V	i
41	4/8/19	31.4	54.2	23.1	67.1	24.9	333.4	1.5V to 2.6V	iii
42	no PSG available	30.9	13.4		13.4				
43	8/8/19	28.5	21.8	2.3	24.0	3.1	70.6	2.5V	i
44	6/27/19	33.3	58	0.0	58.0	0	59	2.1V	i
45	9/30/19	31.6	34.1	12.0	37.0	13.6	100.6	2.9V to 3.0V	ii
46	12/3/19	31.5	41	24.5	41.0	24.5	148.4	2.8V to 2.9V	ii

PSG=polysomnogram; AHI=apnea-hypopnea index; oAHI=obstructive apnea-hypopnea index;

BMI=body mass index; min=minutes



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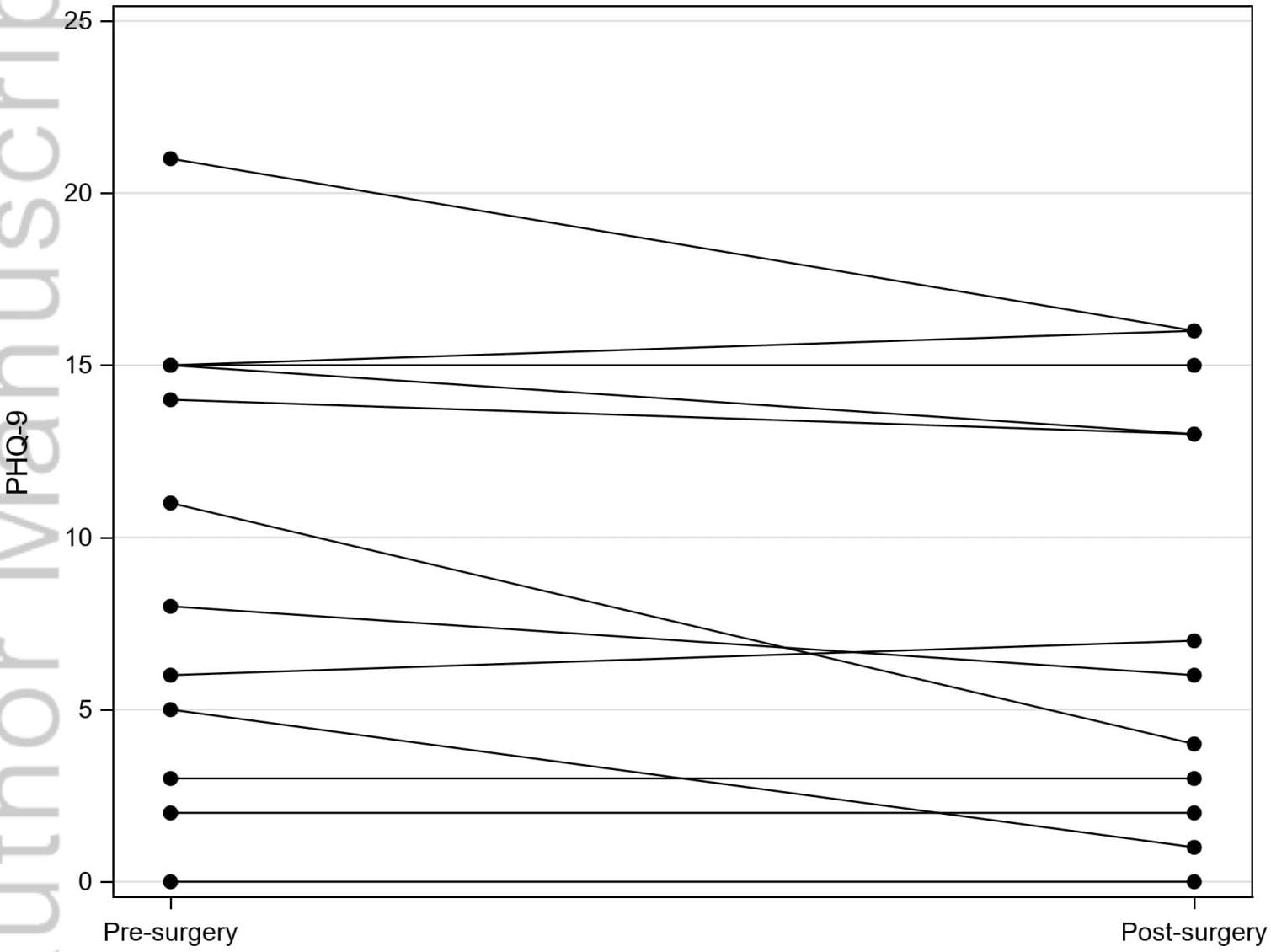

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