Protocol Title:	Adherence to Electrical Glossal In Situ Stimulation for Sleep Apnea
Protocol Number	20210068
Protocol Version:	2.0
NCT Identifier	NCT04974515
PI Name:	Naresh Punjabi. MD.
Target Population:	Mild Obstructive Sleep Apnea (OSA)
Study/Trial Design:	Prospective randomized parallel-group trial comparing high versus low intensity eXciteOSA device
Primary Objective:	To assess whether adherence to the eXciteOSA® device varies as a function of level of stimulation in patient with mild OSA.
Secondary Objectives:	To assess whether the level of adherence to the eXciteOSA® is associated with improvements in respiratory event index (REI), daytime sleepiness as assessed with the Epworth Sleepiness Scale, snoring intensity as assessed by bed partner reports using a visual analog scale, and quality of life.
Endpoints	Primary: • Adherence to the eXciteOSA® device defined as the number of days device used and the number of sessions over the 6-week period. Secondary. • Respiratory event index (REI) • Epworth Sleepiness Scale (ESS) score • Snoring visual analog scored assessed by partner • SF-20 • EQ-5D-5L • Pittsburgh Sleep Quality Index (PSQI) • Work Productivity and Activity Impairment Questionnaire • Acceptance of long-term treatment
Sample Size:	40 (20 per arm)

1. **Protocol Title**
   Adherence to **E**lectrical **G**lossal **I**n Situ **S**timulation for Sleep Apnea (The **AEGIS** study)

2. **IRB Review History***
   Not applicable

3. **Objectives***

   Aim 1: To assess whether adherence to the eXciteOSA® device varies as a function of level of stimulation in patients with mild OSA.

   Aim 2: To assess whether the level of adherence to the eXciteOA® is associated with improvements in respiratory event index (REI), daytime sleepiness as assessed with the Epworth Sleepiness Scale, snoring intensity as assessed by bed partner reports using a visual analog scale, and quality of life.

4. **Background***

   Obstructive sleep apnea (OSA) is a common, chronic, sleep disorder characterized by recurrent collapse and obstruction of the pharyngeal airway during sleep. Untreated OSA is associated with long-term health consequences including hypertension, prevalent cardiovascular disease, type 2 diabetes, cognitive impairment, and depression. Common symptoms include excessive daytime sleepiness, fatigue, non-refreshing sleep, nocturia, morning headache, irritability, and memory loss. Untreated OSA is also associated with lost productivity and workplace and motor vehicle accidents resulting in injury and fatality. The costs of untreated OSA and sleep loss are substantial. Treatment can relieve symptoms and reduce some of the associated sequelae. However, many people with OSA struggle with the first-line therapy, positive airway pressure CPAP), for which adherence rates remain unacceptably low. Non-PAP therapies (e.g., oral appliance therapy) are beneficial in many cases but have variable and unpredictable efficacy. Thus, new approaches to treat OSA are required. The problem of adherence to PAP therapy for OSA is particularly problematic for patients with mild OSA. Although the clinical consequences of mild obstructive sleep apnea are poorly defined, patients with mild disease might present with debilitating symptoms that warrant treatment. Although alternative options, such as oral appliance therapy, are available for the management of mild sleep apnea and have comparable efficacy to PAP therapy in sleepiness and disease-specific quality of life, it is not without its drawbacks including discomfort and pain particularly with the temporomandibular join, the need for custom fitting, excessive salivation, dental misalignment, tooth movement, and gum irritation. Thus, alternative therapeutic approaches are needed to treat mild and moderate sleep apnea. The eXciteOSA® device is a possible alternative that uses electrical stimulation of the tongue during the day for one 20-minute session. The device is based on the premise that improving muscle endurance and responsiveness will lead to a decrease in collapsibility of the upper airway during sleep. In fact, studies that used other means for training the upper airway during sleep have shown that OSA severity can, in fact, be decreased. Preliminary work on the eXcite device has shown that there is improvement in snoring intensity, reduction in the AHI, and resolution of daytime sleepiness as assessed by the Epworth Sleepiness Scale. While the simplicity and potential efficacy of the eXciteOSA® device provide a promising venue for treatment of snoring, mild sleep apnea, questions remain as to the potential adherence to the use of the device. Foremost is the question of whether adherence is a function of the intensity of stimulation. Thus, the current study was designed to examine adherence levels to the eXcite device in patients with mild OSA.

Utilizing a randomized design, we will examine whether adherence differs between high vs. low intensity.

5. Inclusion and Exclusion Criteria*

Inclusion Criteria

a) Age ≥ 18 years
b) Ability to consent
c) In-lab or home sleep apnea test demonstrating mild obstructive sleep apnea.
d) Smartphone or tablet that can run the eXciteOSA app

Exclusion criteria:

a) Current pacemaker, defibrillator, or neurostimulation device
b) No prior oropharyngeal surgery for OSA
c) No implants, metal prostheses, dental braces, or soft tissue/bony ulcerations in the oral cavity
d) No prior use of mandibular advancement device (MAD) or continuous positive airway pressure (CPAP)
e) Heart failure – New York Heart Association Class 3 or 4; or ejection fraction < 45%
f) Active coronary disease defined as an intervention (e.g., angioplasty, coronary artery bypass surgery) in the prior 6 months
g) Uncontrolled HTN - BP 160/100
h) Clinician diagnosis of any chronic lung disease except asthma
i) Chronic fatigue syndrome or fibromyalgia
j) Self-reported current illicit drug use in the past 30 days
k) Self-reported use of marijuana or opiates in the past 30 days
l) Use of supplemental oxygen
m) Self-reported use of prescribed or over the counter sleeping medications in the past 30 days
n) Current pregnancy or intention of becoming pregnant
o) Oropharyngeal abnormalities (class 2 or class 3 malocclusion)
p) Periodic breathing (Cheyne Stoke respiration)
q) Central sleep apnea (central apnea index [CAI] < 5/h)
r) Investigator discretion
s) Prisoners

6. Number of Subjects*

We propose to recruit a sample size of 40 patients with mild sleep apnea for this study.

7. Study-Wide Recruitment Methods*

Recruitment for potential participants will be based on clinical and community efforts. Patients with mild sleep apnea, as determined by a home sleep apnea test or an in-lab study conducted as part of routine clinical care, will be recruited from the patient panel of the study investigators. In addition, referrals from other physicians who become aware of the study will be screened for participation. In addition, volunteers responding to study flyers or advertisements will be interviewed on the telephone by the study staff using a screening questionnaire in RedCap to assess eligibility. Subjects whose questionnaire responses meet eligibility will be scheduled for an in person or a telehealth/video visit. At the first visit, the protocol will be explained in detail and written informed consent obtained. Study flyers will be posted at: (a) U-Miami sleep clinic (b) grocery stores; and (c) community centers. In addition, we will also use social media posts to recruit for the study. There will be no effort made to otherwise review medical records to identify or recruit other patients.

8. Study Timelines*

a) Participant eligibility: Eligibility (via phone) of study participants will be assessed either by telephone, a video visit, or if needed an in-person visit. Based on whether the participant meets initial study criteria, a visit will be scheduled for informed consent before any study procedures.

b) Screening (1-2 visits): If a participant does not have any exclusion criteria based on the preliminary screen, they will be invited for a visit to complete the consent process and assess remaining eligibility criteria before any study procedures. Assessment of remaining eligibility criteria will include: (a) urine pregnancy test in women; (b) oral exam assessment to assess for oropharyngeal abnormalities, and (c) blood pressure. Individuals who consent to participate in the study will be provided a self-applied monitor (Nox A1, Nox Medical) to record three nights of sleep in the home setting (research procedure). The Nox A1 monitor allows for an assessment of breathing abnormalities during sleep using self-applied electrodes that collect the necessary physiologic signals (e.g., oxygen saturation, respiratory effort). Analysis of the acquired physiological signals will be used to the Respiratory event index ([REI] = Number of respiratory events per hour based on a 3% desaturation threshold). Only those participants with a REI of 5.0-14.9 events/hr (i.e., mild OSA) will be considered for continued screening. We will aim to collect three nights of data using the Nox A1 and use a minimum window of 2 weeks to complete all sleep testing if any particular night attempt fails. A study with less than 3h recording time will be considered a failure and repeat attempt will be made.

c) Baseline Assessments: Participants will complete the following baseline assessments: (a) a questionnaire packet including the ESS, the Medical Outcomes Study Short Form Survey-20 (SF-20), snoring visual analog scale (VAS) completed by the partner, EuroQOL EQ-5D-5L, Pittsburgh Sleep Quality Index (PSQI), Work Productivity and Activity Impairment Questionnaire, and global assessment survey, (b) physical exam including body mass index (BMI), anthropometry (waist and neck circumference), an upper airway assessment for Friedman and tonsillar score, oropharyngeal abnormalities, blood pressure, and (c) an assessment of prevalent medical comorbidity and current medication use. Participants will be provided with instructions on use of the eXciteOSA® device and the associated smartphone app. After the baseline assessment, participants will be randomized to either the high intensity versus low intensity stimulation arm. Within each arm, the participant will be further able to further adjust the degree of stimulation level on a range of 1-15.

   Study investigators, staff, and the participants will be blinded to the treatment assignment. Allocation to a specific arm will be based using a computer/digital randomization scheme using blocks of four to keep the sizes of treatment groups similar. The assignment table will be used the manufacturer to tag the devices in the sequence of use prior to shipment. The allocation table will be shared with the investigators and all involved in the study including the patients after the study is completed.

d) Follow-up Assessments: After a 6-week period of use of the eXciteOSA® device, all of the baseline assessments will be repeated including (a) 3 nights of Nox A1 monitoring within a 2-week period), (b) a questionnaire packet as before, (c) physical exam including body mass index (BMI), anthropometry (waist and neck circumference), an upper airway assessment, blood pressure, and (d) ongoing medication use.

It is anticipated that the study duration for a participant will be about 3 months. The number of study visits required are as follows:

- Consent visit (setup with 20-minute run-in period with eXcite device)
- Baseline assessments (questionnaires, BMI, neck circumference, Mallampati score, history/medication inventory) (can be completed within 1 or 2 visits).
- Follow-up assessments (after 6-weeks of use) [Can be completed within 1 or 2 visits].

Thus, we expect a up to five visits over an approximate 3 month period.

Post Study Follow-up: At the end of the study, the participant will be transitioned to a sleep clinic and physician of his / her choice. Continued therapy with the eXcite OSA device after the study period will be determined by the participant and the treating sleep physician. Therapy can continue if the primary sleep physician deems it to be clinically appropriate and the participant agrees to continue. We propose to follow-up the adherence to therapy for 12 month period.

9. Study Endpoints*

a. Primary outcome variable.
Adherence to the eXciteOSA® device defined as the number of days device used and the number of sessions over the 6-week period. The device usage data are stored in the device that can be used to assess overall use.

b. Secondary outcome variables.
- Respiratory event index (REI)
- Epworth Sleepiness Scale (ESS) score
- Snoring visual analog scored assessed by partner
- SF-20
- EQ-5D-5L
- Pittsburgh Sleep Quality Index (PSQI)
- Work Productivity and Activity Impairment Questionnaire
- Acceptance of treatment at 6 weeks

10. Procedures Involved*

Home sleep study: Recording methods for sleep will include continuous monitoring of EEG, EOG (electrooculogram), oronasal airflow (by a pressure sensitive nasal cannula), pulse oximetry, and thoracic and abdominal movements. There are no risks related to routine monitoring of sleep. Electrode placement may lead to a minor skin reaction in rare situations that is most often self-limited.

Home treatment with eXciteOSA® device: This is an FDA approved treatment for snoring and mild obstructive sleep apnea in patient who are 18 years or older. The device works by delivering electrical muscle stimulation through a mouthpiece that sits around the tongue. The eXciteOSA mouthpiece has four electrodes, two located above the tongue and two located below the tongue. The device provides electrical muscle stimulation action in sessions that consist of a series of electrical pulses with rest periods in between. It is used for 20 minutes a day during a wakeful state.

Stimulation Level: With each arm, participants will have the ability to increase the stimulation level which has a scale of 1-15. Instructions will be provided to participants to advance the stimulation level as tolerated based on the experience from a prior session. If at any level, the participant feels that the stimulation is excessive, the participant can adjust the level down even during a session. At

the highest setting of 15 in either arm, the maximum voltage (current) levels for the low and high intensity arms are 6.7 V (11.1 milliamps) and 29.8 V (58.6 milliamps), respectively. Physicians involved in the study will guide the participant on the use of varying levels of stimulation intensity as will be any study staff who are added to the investigative team.

11. Data and Specimen Banking

There are no specimens that will be banked for future use.

12. Data Management*

Statistical analyses for the primary evaluation of adherence will follow the intention-to-treat paradigm, which means that all randomized patients will be included in the treatment group to which they were assigned. Participants who do not have the requisite data for our primary outcomes will be accounted for and compared by assigned group. Participants not able to be included in the intention-to-treat analyses will be compared to those who are included with respect to demographic and other characteristics.

The primary outcome for the study is the overall adherence to the eXciteOSA® device as determined by the number of days the device was used out of 42 days (6 weeks) as instructed. Initial analyses will tabulate demographic and baseline characteristics of the participants by randomization group. χ^2-tests and one-way ANOVA will be used to compare groups on these characteristics. If differences in some characteristics are observed, even though not statistically significant, these variables will be considered for inclusion in regression models assessing our outcomes. The analytical approach will consist of using mixed model linear regression of adherence with an indicator variable for the fixed effect for treatment group and baseline value of the measure. Additional covariates (e.g., age, sex, BMI) will be included in the model particularly if the randomization results in imbalances in a covariate across treatment groups.

The secondary outcomes include change in: (1) REI (2) ESS score, (3) snoring assessment from the bed partner using a visual analog score, (6) SF-20 and EQ-5D-5L quality of life scores; (7) PSQI score, (8) Work Productivity and Activity Impairment Questionnaire, and (8) acceptance of long-term treatment. All analyses for our secondary outcomes will be done under the intention to treat principle. Initial analyses will tabulate baseline characteristics of participants by randomization group. For our continuous outcomes, we will use multivariable regression and mixed model repeated measures analyses as done for the primary outcomes.

13. Provisions to Monitor the Data to Ensure the Safety of Subjects*

The principal investigator will have the responsibility for monitoring and oversight of any study related events or problems. No interim analysis or interpretation of data for a safety signal are included as the eXciteOSA® therapy will be used for its approved indication. Any adverse event will be notable during the visit itself and any unexpected untoward event will be reported to the IRB by the PI within 48 hours of occurrence. Performance of sleep testing and other assessments planned are all part of the routine clinical practice and the procedures for these are well established.

14. Withdrawal of Subjects*

A subject will be withdrawn from the study if he/she does not wish to complete the testing as specified by the study protocol.

15. Risks to Subjects*

Questionnaires: There are no risks to completing the study questionnaires.

Overnight sleep study: There are no major risks with a sleep study. Rarely, some individuals may experience minor redness or irritation at the site of the monitoring electrodes from the sleep study.

Anthropometry: There are no risks with anthropometric measurements.

eXciteOSA® Device: There are no major side effects of using the eXciteOSA® device. Expected minor side effects from using the eXciteOSA® device include pooling of saliva, tooth sensitivity during use and tingling of the tongue that can continue after use. All of these side effects are transient and resolve shortly after use of the device stops.