Upper Airway Stimulation for Obstructive Sleep Apnea: Self-Reported Outcomes at 24 Months

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Objectives: To evaluate the long-term (24-mo) effect of cranial nerve upper airway stimulation (UAS) therapy on patient-centered obstructive sleep apnea (OSA) outcome measures.

Methods: Prospective, multicenter, cohort study of 126 patients with moderate to severe OSA who had difficulty adhering to positive pressure therapy and received the surgically implanted UAS system. Outcomes were measured at baseline and postoperatively at 12 mo and 24 mo, and included self- and bedpartner-report of snoring intensity, Epworth Sleepiness Scale (ESS), and Functional Outcomes of Sleep Questionnaire (FOSQ). Additional analysis included FOSQ subscales, FOSQ-10, and treatment effect size.

Results: Significant improvement in mean FOSQ score was observed from baseline (14.3) to 12 mo (17.3), and the effect was maintained at 24 mo (17.2). Similar improvements and maintenance of effect were seen with all FOSQ subscales and FOSQ-10. Subjective daytime sleepiness, as measured by mean ESS, improved significantly from baseline (11.6) to 12 mo (7.0) and 24 mo (7.1). Self-reported snoring severity showed increased percentage of “no” or “soft” snoring from 22% at baseline to 88% at 12 mo and 91% at 24 mo. UAS demonstrated large effect size (> 0.8) at 12 and 24 mo for overall ESS and FOSQ measures, and the effect size compared favorably to previously published effect size with other sleep apnea treatments.

Conclusions: In a selected group of patients with moderate to severe OSA and body mass index ≤ 32 kg/m2, hypoglossal cranial nerve stimulation therapy can provide significant improvement in important sleep related quality-of-life outcome measures and the effect is maintained across a 2-y follow-up period.

Keywords: sleep apnea, surgery, neurostimulation, hypoglossal nerve, cranial nerve stimulation


INTRODUCTION

Patients suffering from moderate to severe obstructive sleep apnea (OSA) commonly report symptoms consistent with excessive daytime sleepiness, neurocognitive dysfunction, and impaired quality of life.1 Although the underlying pathophysiologic mechanisms of OSA are complex, multifactorial, and variable among patients, the goals of any longitudinal care model are generally consistent across all patients and fall into two categories: (1) to improve sleep related symptoms and quality-of-life measures, and (2) to reduce cardiovascular and related health risks.

Continuous positive airway pressure (CPAP) therapy has a wealth of data on safely and effectively accomplishing these goals and remains the standard first-line therapy.2,3 Despite the low morbidity and high effectiveness of CPAP, long-term adherence and acceptance rates are suboptimal and necessitate consideration of alternative treatment options in many patients.4–6 A variety of interface-related or pressure-related side effects as well as psychosocial barriers frequently preclude adequate use. Recent multicenter trials reported 6-mo adherence rates of only 39% to 50%.3,6 A universally accepted second-line therapy does not exist; however, oral appliance

BRIEF SUMMARY

Current Knowledge/Study Rationale: Hypoglossal cranial nerve stimulation therapy consists of a surgically implantable and medically titratable second-line treatment option for obstructive sleep apnea (OSA), and was previously shown to provide safe and effective short-term management for patients who meet specific clinical and anatomical inclusion criteria. Since OSA represents a chronic condition requiring longitudinal care, this study was undertaken to examine the durability of effect of the therapy on patient-centered outcome measures at 24 months after implantation.

Study Impact: This study demonstrates long-term clinically meaningful improvement in snoring, daytime alertness, and sleep-related quality of life with hypoglossal cranial nerve stimulation therapy. The treatment effect size is large and is maintained across a 2 year follow-up period, providing support for consideration of this therapeutic option in selected patients who are unable to adhere to positive pressure therapy.
therapy, upper airway reconstructive surgery, weight loss, positional therapy, and more recently, hypoglossal cranial nerve upper airway stimulation (UAS) therapy can provide effective management in patients with OSA who have certain clinical, polysomnographic, and anatomical characteristics.

In a prospective multicenter trial, UAS therapy has been shown to provide safe and effective short-term management in a cohort of patients with moderate to severe OSA who were unable to achieve benefit with positive pressure therapy. The randomized withdrawal portion of the study demonstrated that withdrawal of therapy leads to recurrence of OSA and that resumption of nightly therapy restores subjective and objective benefits. These observations emphasize the need to monitor durability of effect over time, particularly because OSA is most commonly a chronic long-term condition that requires effective management throughout the lifespan.

The subjective sleep-related symptoms and quality-of-life effects of OSA constitute the patient-centered experience of disease presentation, cost-benefit assessment, and treatment outcomes. Excessive daytime sleepiness and impairment of daytime functioning, for example, are consequences of the disease that prompt patients to seek care and are associated with an increased motor vehicle accident risk and increased health care utilization. These important outcome measures are not adequately represented on objective sleep laboratory testing. As previously stated by Flemons, for the majority of patients without significant medical comorbidities, “the primary reason to test for and treat sleep apnea is the potential to improve the quality of life. Clinicians do not make decisions about treatment on the basis of the apnea–hypopnea index alone because it correlates poorly with the quality of life and the severity of symptoms.”

The aim of this study was to evaluate the long-term (24-mo) effect of UAS therapy on (1) intrusive snoring as measured by self- and bedpartner-report, (2) the propensity for waketime sleepiness as measured by the Epworth Sleepiness Scale (ESS), and (3) daytime functioning as measured by the Functional Outcomes of Sleep Questionnaire (FOSQ) including subscale analysis.

**METHODS**

**Study Design**

The Stimulation Treatment for Apnea Reduction (STAR) trial was a multicenter, prospective trial with 126 participants serving as their own control. The primary assessments were safety and effectiveness of UAS therapy at 12 mo. Long-term follow-up visits were performed every 6 mo, including report of adverse events, and assessment of quality of life using standardized questionnaires. The current report aims to summarize the patient-centered outcomes of UAS therapy at 24 mo postimplantation. Key selection criteria of the STAR trial included a history of moderate to severe OSA, nonadherence to CPAP, BMI equal to or less than 32 kg/m², and absence of complete concentric collapse at the level of the soft palate during sedated endoscopy. Qualified participants received an implanted device that consists of three parts: a stimulation lead that was placed on the distal medial branch of the right hypoglossal nerve to recruit protrusor muscles of the tongue; a pressure sensing lead placed within the intercostal muscles; and an implantable pulse generator placed in the midinfraclavicular region that delivers electrical stimulation to the twelfth cranial nerve, synchronous with the respiratory cycle.

**RESULTS**

**Demographics**

The study cohort consisted of 126 participants—mostly Caucasian (97%), male (83%), middle aged (54.5 ± 10.2 y, ranged from 31 to 80 y), and overweight (BMI of 28.4 ± 2.6 kg/m², ranged from 18.4 to 32.5 kg/m²). A total of 124 participants completed follow-up at 12 mo (one participant died due to an unrelated cardiac cause, and one participant requested elective explantation due to lack of satisfaction with therapy response). A total of 111 participants (88% of 126) completed all follow-up questionnaires at 24 mo. Three participants were lost to long-term follow up and 10 participants missed the data collection during the 24-mo visit window. The mean BMI was 28.5 ± 2.7 at 12 mo and 28.5 ± 3.2 at 24 mo, both unchanged from baseline.

**Epworth Sleepiness Scale**

There was a significant decrease in self-reported daytime sleepiness measured by the mean ESS score from baseline to 12 mo (p < 0.01), as well as at 24 mo (p < 0.01). Mean ESS...
remained unchanged from 12 to 24 mo (Table 1). The report of ESS score < 10, often considered acceptable daytime alertness, increased from 32.5% at baseline, to 74.8% at 12 mo, and 77.5% at 24 mo among all participants. Compared to baseline, the percentage of participants with a significant reduction (change of 2 or more) in ESS score was 72% at 12 mo and 70% at 24 mo. The percentage of participants with an increase in ESS score (change of 2 or more) was 7% at 12 mo and 9% at 24 mo.

**Table 1—ESS and FOSQ.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline mean (SE)</th>
<th>12-mo mean (SE)</th>
<th>24-mo mean (SE)</th>
<th>Mean Baseline – 12-mo difference (95% CI)</th>
<th>Mean Baseline – 24-mo difference (95% CI)</th>
<th>Mean 12 mo – 24-mo difference (95% CI)</th>
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<tr>
<td>ESS</td>
<td>11.6 (0.4)</td>
<td>7.0 (0.4)</td>
<td>7.1 (0.4)</td>
<td>4.7 (3.8 to 5.6)*</td>
<td>4.4 (3.4 to 5.4)*</td>
<td>0.0 (−0.6 to 0.6)</td>
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<td>FOSQ</td>
<td>14.3 (0.3)</td>
<td>17.3 (0.3)</td>
<td>17.2 (0.3)</td>
<td>−2.9 (−3.5 to −2.4)*</td>
<td>−3.0 (−3.5 to −2.4)*</td>
<td>−0.1 (−0.5 to 0.02)</td>
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<td>Activity</td>
<td>2.7 (0.1)</td>
<td>3.4 (0.1)</td>
<td>3.4 (0.1)</td>
<td>−0.7 (−0.8 to −0.5)*</td>
<td>−0.7 (−0.9 to −0.6)*</td>
<td>−0.0 (−0.1, 0.02)</td>
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<tr>
<td>Productivity</td>
<td>3.0 (0.1)</td>
<td>3.3 (0.1)</td>
<td>3.6 (0.1)</td>
<td>−0.5 (−0.6 to −0.4)*</td>
<td>−0.5 (−0.6 to −0.4)*</td>
<td>−0.0 (−0.1, −0.04)</td>
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<tr>
<td>Social</td>
<td>3.1 (0.1)</td>
<td>3.6 (0.1)</td>
<td>3.7 (0.1)</td>
<td>−0.5 (−0.7 to −0.3)*</td>
<td>−0.5 (−0.7 to −0.4)*</td>
<td>−0.0 (−0.2, 0.03)</td>
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<tr>
<td>Intimacy</td>
<td>2.7 (0.1)</td>
<td>3.3 (0.1)</td>
<td>3.3 (0.1)</td>
<td>−0.6 (−0.8 to −0.4)*</td>
<td>−0.6 (−0.8 to −0.4)*</td>
<td>0.0 (−0.3, 0.07)</td>
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<tr>
<td>Vigilance</td>
<td>2.7 (0.1)</td>
<td>3.4 (0.1)</td>
<td>3.3 (0.1)</td>
<td>−0.7 (−0.8 to −0.5)*</td>
<td>−0.7 (−0.8 to −0.5)*</td>
<td>0.1 (−0.12, 0.04)</td>
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*P < 0.01. ESS, Epworth sleepiness scale; FOSQ, Functional Outcomes of Sleep Questionnaire; SE, standard error.

**Figure 1**—Significant improvement in short version Functional Outcomes of Sleep Questionnaire (FOSQ-10) at 12 months is maintained at 24 months after implant.

![Figure 1](image)

Reported as mean and standard deviation in error bar.

**Table 2—Effect size of upper airway stimulation on ESS FOSQ, and FOSQ subscales.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Effect Size at 12 mo</th>
<th>Effect Size at 24 mo</th>
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<tbody>
<tr>
<td>ESS</td>
<td>0.94</td>
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<td>FOSQ</td>
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<tr>
<td>Intimacy</td>
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<td>0.66</td>
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<tr>
<td>Vigilance</td>
<td>0.88</td>
<td>0.95</td>
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ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire.

of effect was seen in the shorter version FOSQ-10 (Figure 1). Compared to baseline, the percentage of participants reporting a clinically significant improvement (increase ≥ 2) in FOSQ was 53% at 12 mo and 59% at 24 mo. The percentage of participants reporting a significant reduction (decrease ≥ 2) in FOSQ was 3.3% at 12 mo and 5.4% at 24 mo.

**Effect Size**

UAS showed large effect size (> 0.8) at 12 and 24 mo for overall ESS and FOSQ measures. Moderate (≥ 0.5) to large effect size was also observed among all individual subscales of FOSQ measures (Table 2).

**Self-reported Snoring**

Snoring severity based on participant self-report showed increased percentage of “no” or “soft” snoring from baseline of 22% to 88% at 12 and 91% at 24 mo. Reports collected from bed partners supported participant self-report with overall reduced snoring level with therapy use. The percent of “bed partner leaves room” reduced from 30% at baseline to 3% at 12 and 24 mo (Figure 2).

**DISCUSSION**

The goal of this study was to examine the durability of treatment effect of upper airway cranial nerve stimulation therapy...
over a 2-y period using validated questionnaires of patient-centered outcome measures that reflect the sleep related symptoms and quality-of-life components of the disease. The major findings of the study were: (1) UAS therapy provides clinically meaningful and statistically significant improvements in key patient-centered OSA outcome measures, including snoring, daytime sleepiness, and sleep related quality of life, and (2) the beneficial effect on subjective sleep outcomes is maintained through the first 2 y of treatment. This sustainability is critical in a chronic condition such as OSA that requires long-term management and has not been previously demonstrated in other surgical studies.

The detrimental effect of OSA on activities of daily living and quality-of-life measures contributes significantly to the disease morbidity as well as the financial burden of patients with OSA on the health care system. Untreated moderate-severe OSA has been associated with increased health care costs and physician visits, increased motor vehicle accidents, increased workplace errors, and loss of work productivity.16,17 Although CPAP, the standard first-line therapy, is highly effective, suboptimal patient acceptance and adherence frequently limit long-term results.18–20 As such, alternative medical or surgical therapies are required to effectively manage a large portion of the OSA population.

Numerous upper airway reconstructive surgical procedures have been described to reduce OSA severity by improving the anatomical and structural vulnerability of the upper airway. The routine use of many upper airway surgical procedures is limited by increased risk and morbidity as well as a relative lack of high-quality data on the consistency of results. Most surgical studies are also limited by a lack of long-term follow-up and sustainability of effect, which is important because OSA is chronic condition requiring ongoing reevaluation and management as part of a longitudinal care model.

UAS therapy differs markedly from traditional OSA surgery in many respects. In patients with moderate to severe OSA and specific clinical and anatomical characteristics, UAS therapy has previously been shown to provide multilevel (retropalatal and retrolingual) improvement in airway dimension and airflow by augmenting neuromuscular function of specific upper airway muscles while avoiding anatomy-altering surgery – dramatically reducing side effects, recovery, and risk.21–23 Prior reports have also demonstrated significant and sustained reductions in polysomnographic measures of OSA severity over a 12- to 18-mo follow-up period.24 At 18 mo, the median apnea-hypopnea index (AHI) was reduced by 67.4% from the baseline of 29.3 to 9.7/h, and the median 4% oxygen desaturation index (ODI) was reduced by 67.5% from 25.4 to 8.6/h. A treatment AHI of less than 15/h was achieved in 69% of participants at 18 mo.

Although patient-reported outcome measures are subjective, multifaceted, and variable among certain subpopulations, it is precisely these self-reported symptoms that often drive patients to seek care from health care professionals. Polysomnography measures alone do not capture important aspects of OSA disease burden and treatment outcomes.24,25 Subjective measures of patients’ daytime sleepiness state, and how the sleepiness affects daily function and quality of life, are likely to contribute significantly to the long-term disease morbidity as well as direct and indirect health care costs. A large retrospective OSA cohort rated snoring as the OSA symptom of highest importance and magnitude from the patient’s perspective.26 With increasing emphasis on quality outcomes relative to health care cost, the long-term quality-of-life outcome measures for OSA treatment have clinical and economic relevance.

This study demonstrated that UAS therapy provides clinically and statistically significant improvements in self-reported quality of life, daytime alertness, and snoring; and the treatment effect was maintained over the first 2 y of treatment. Improvement in the FOSQ-30 and subscale analysis was similar to improvement observed in the FOSQ-10 supporting the notion that the shorter FOSQ-10 accurately reflects the original longer version and may be easier to implement in the clinical setting and in future studies. Although the reliability of self-report and bed partner-report of snoring intensity may be questioned, there is currently no accepted standard objective measure of snoring, and it is precisely this subjective report that often drives evaluation and management. The majority of participants in this cohort achieved successful reduction...
in their snoring from loud or disruptive levels to soft or no snoring.

In this study, UAS therapy demonstrated large effect size (> 0.8) in quality-of-life measures as assessed by ESS and FOSQ. Cohort studies have been previously shown to provide reliable data with a large effect size (i.e., > 0.5). When effect sizes are small (i.e., < 0.3), the amount of uncontrolled data and uncontrollable confounding inherent to such designs is as large as the postulated effect size.\(^\text{27}\) In a comparison between multilevel temperature-controlled radiofrequency tissue ablation and CPAP for treatment of mild to moderate OSA, the effect size of ESS was 0.5 for ablation and 0.4 for CPAP, and the effect size of FOSQ was 0.66 for ablation and 0.6 for CPAP.\(^\text{28}\) Thus, the effect size results suggest that, in the setting of an uncontrolled prospective cohort study, UAS therapy convincingly provides strong improvement in daytime sleepiness and sleep related quality of life, and the effect compares favorably to CPAP as well as other second-line therapies.

To our knowledge, this is the first study of a surgical intervention for OSA that evaluated quality of life outcomes 2 y postoperatively. The strengths of this study include the large prospective cohort and high percentage of available long-term follow-up data. Limitations relate to the lack of a control group and the highly selected patient population based on clinical, polysomnographic, and endoscopic/anatomical screening criteria, which may limit generalizability of these findings to other OSA populations. Such limitations of the current uncontrolled study design may also introduce the possibility that a placebo effect could have contributed, at least in part, to the study findings. To corroborate these improvements in quality-of-life measures, long-term sleep laboratory data and other objective outcome measures, in conjunction with responder versus nonresponder analysis, are also needed to further demonstrate therapy effectiveness across a longitudinal care model.

## CONCLUSIONS

In a selected group of patients with moderate to severe OSA and BMI ≤ 32 kg/m\(^2\) who are unable to achieve benefit with CPAP, hypoglossal cranial nerve stimulation therapy can provide significant improvement in important sleep related quality of life outcome measures and the effect is maintained across a 2-y follow-up period.

## ABBREVIATIONS

AHI, apnea-hypopnea index  
BMI, body mass index  
CPAP, continuous positive airway pressure  
ESS, Epworth Sleepiness Scale  
FOSQ, Functional Outcomes of Sleep Questionnaire (30-item)  
FOSQ-10, Functional Outcomes of Sleep Questionnaire (10-item)  
OSA, obstructive sleep apnea  
SD, standard deviation

## STAR TRIAL INVESTIGATORS

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Submitted for publication December, 2014
Submitted in final revised form July, 2015
Accepted for publication July, 2015
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DISCLOSURE STATEMENT

Funding source for this study was Inspire Medical Systems. Dr. Soose: Inspire Medical Systems–study investigator, consultant; Philips Respironics–consultant. Dr. Woodson: Inspire Medical Systems–study investigator, consultant; Medtronic–consultant, royalty; Siesta Medical–consultant. Dr. Gillespie: Inspire Medical Systems–study investigator, consultant, research support; Medtronic, Olympus, Arthrocare–consultant; Surgical Specialties–consultant, research support. Dr. Maurer: Inspire Medical Systems–study investigator, consultant, personal fees from GlaxoSmithKline, Weinmann, Olympus, RespMed, Neurwith, Medtronic, and Heinen & Lo wenstein, outside the submitted work. Dr. de Vries: Inspire Medical Systems–study investigator, consultant; Philips, Olympus–consultant; Night Balance/ReVent–medical advisor, shareholder, funding from company. Dr. Steward: Inspire Medical Systems–study investigator, consultant. Dr. Strollo: Inspire Medical Systems–study investigator (site principal investigator for Phase III study), consultant. Dr. Baskin: Inspire Medical Systems–study investigator, consultant, grant funding; Dr. Badr: Inspire Medical Systems–study investigator, consultant. Dr. Lin: Inspire Medical Systems–study investigator, consultant; Intuitive Surgical–proctor. Dr. Vandervenne: Inspire Medical Systems–study investigator; SonnoMed–research grant. Dr. Mickelson: Inspire Medical Systems–study investigator, consultant. Dr. Strollo Jr.: Inspire Medical Systems–study investigator, consultant, research grant; RespMed–scientific advisory board, research grant; Philips Respironics–research grant. Dr. Chasens has indicated no financial conflicts of interest.