



Research Paper

OSA treatment history in an upper airway stimulation trial cohort



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KEYWORDS

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Abstract *Objectives:* Analyze the obstructive sleep apnea (OSA) treatment history in a group of participants who enrolled in a hypoglossal nerve stimulation trial.

Methods: Moderate-severe OSA patients with difficulty adhering to CPAP presented for enrollment in a multicenter trial. Self-reported history on prior OSA medical therapy was collected at enrollment, including OSA diagnosis date, CPAP start and stop dates, oral appliance trial, and reasons for discontinuation or non-adherence.

Results: The cohort consisted of 929 participants, 83% male, with a mean age (53.9 ± 10.5) years. Ninety percent ($n = 835$) had complete CPAP information including 47% ($n = 435$) who discontinued therapy prior to enrollment and 43% ($n = 400$) who were still attempting CPAP but had inadequate adherence. Abandonment rates were 60% at 1-year, 73% at 3-years, and 86% at 5-years. Oral appliance therapy was attempted by 171 patients for mean (1.8 ± 2.3) years, with 81% abandonment at 1 year, 89% at 3-years, and 94% at 5-years.

Conclusions: In this CPAP-refractory cohort, high rates of CPAP abandonment were reported in the first several years with approximately half of the participants not receiving any treatment despite being diagnosed for >5 years. Close clinical follow-up and consideration of alternative

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treatment options is indicated in all OSA patients in order to ensure adequate longitudinal care.

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Introduction

Moderate-to-severe obstructive sleep apnea (OSA) has been associated with increased vascular and metabolic health risks as well as patient reported symptoms that include excessive daytime sleepiness, neurocognitive dysfunction, and impaired quality of life.¹ Continuous positive airway pressure (CPAP) therapy is the most thoroughly studied therapy with data supporting its safety and effectiveness in accomplishing treatment goals including reduction of cardiovascular risk and improvement in alertness, cognitive function, and quality of life measures.^{2,3} CPAP therefore remains the standard first-line therapy for moderate to severe OSA.

Despite the low morbidity and high effectiveness of CPAP, long-term adherence and acceptance rates are sub-optimal 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-month adherence rates of only 39%–50%.^{5,6} A universally accepted second-line therapy does not exist; however, oral appliance 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 OSA patients with 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 moderate-to-severe OSA patients who were unable to achieve benefit with positive pressure therapy.⁷

Since OSA is most commonly a chronic long-term condition that requires effective management throughout the lifespan, the treatment or combination of treatments that are likely to be effective and accepted by the patient may vary depending on the patient's age and other clinical and personal factors. This longitudinal model of care emphasizes the need to monitor durability of treatment effect over time, both with proper adherence monitoring and outcome measures with medical device treatments and with proper clinical follow-up and outcome assessments after surgical therapy or weight loss. The aim of this study was to examine the prior medical and surgical treatment history in a large group of participants enrolling in a multicenter trial for a newly available alternative treatment option – hypoglossal cranial nerve UAS therapy. In order to qualify for the study, patients had to have attempted CPAP as a first-line therapy. Therefore this cohort provides unique insight into the clinical history of patients who found CPAP unacceptable and had to seek out alternative therapy.

Methods

Study design

The Stimulation Treatment for Apnea Reduction (STAR) trial is a multi-center, prospective trial studying the effectiveness of upper airway stimulation (UAS) therapy via the hypoglossal cranial nerve. The trial protocol was approved by the institutional review board (in the United States) or medical ethics committee (in Europe) at each participating center. All the participants provided written informed consent before enrollment. Enrollment in the STAR trial was available November 2010 to March 2012 at 22 sites across the United States and Europe. Candidates were recruited from sleep medicine and otolaryngology practice populations as well as newspaper and radio advertisement to the general public. Potential participants were required to have a preexisting diagnosis of moderate to severe obstructive sleep apnea and were unable to adhere to or achieve adequate benefit with CPAP.

A total of 929 participants presented for enrollment and underwent screening history and physical examination. Data collected at baseline screening included 1) date of original OSA diagnosis, 2) whether participant discontinued CPAP or still attempting to use, and, if discontinued, 3) reasons for CPAP discontinuation, and 4) time of CPAP discontinuation. In addition to CPAP treatment history, data was collected on prior oral appliance treatment or prior uvulopalatopharyngoplasty or other surgery for OSA.

The group of participants still attempting CPAP with inadequate adherence was compared to the group of participants who had discontinued CPAP altogether. Data collected included age, gender, body mass index (BMI), CPAP pressure, Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ), apnea-hypopnea index (AHI), and 4% oxygen desaturation index (ODI).

Participants meeting the initial clinical inclusion criteria underwent a screening evaluation process that included in-lab diagnostic polysomnography (PSG), surgical consultation, and drug-induced sedated endoscopy. The first 126 participants meeting the clinical, BMI, polysomnographic, and anatomical inclusion criteria received the implantable hypoglossal nerve stimulation system. Primary outcome assessments were safety and effectiveness of UAS at 12 months. Primary outcome data as well as reports on the randomized therapy withdrawal, 18 and 36 month PSG outcomes, and 24 and 48 month patient-centered outcomes have been previously published.^{7–9} The present report analyzed the prior medical and surgical OSA treatment history in the original baseline cohort including the timing of and reasons for CPAP discontinuation.

Table 1 Baseline demographics of study subjects ($n = 929$).

Characteristics	Mean \pm SD	Range (min, max)
Age	53.9 \pm 10.5	23–88
Sex (number of female)	151	
Body mass index (kg/m ²)	28.3 \pm 3.0	14.2–48.8
Number of years on CPAP	3.4 \pm 3.7	Less than a year – 17 years
ESS	11.3 \pm 5.2	0–24
FOSQ	14.7 \pm 3.4	5.0–20.0
AHI (events/h)	25.6 \pm 19.7	0–120
ODI	22.1 \pm 18.6	0–120

Statistical analysis

All results of continuous variables are expressed as mean \pm standard deviation (SD). A logistic regression analysis with a single variate model was used to examine the association between baseline characteristics of the CPAP groups.

Results

Demographics

The study cohort consisted of 929 participants – mostly Caucasian (97%), male (83%), middle aged [mean age (53.9 \pm 10.5) years, ranged from 23 to 88 years], and overweight [mean BMI of (28.3 \pm 3.0) kg/m², ranged from 14.2 to 48.8 kg/m²] (Table 1). All participants had tried CPAP therapy in the past and reported attempting CPAP for mean (3.4 \pm 3.7) years. Ninety percent ($n = 835$) had complete CPAP information available including 47% ($n = 435$) who discontinued therapy prior to enrollment and 43% ($n = 400$) who were still attempting CPAP but had inadequate adherence as defined as less than 4 h per night

and less than 70% of nights used (Fig. 1). The three most commonly cited categories for struggling with CPAP were mask discomfort, pressure- or equipment-related side effects, and persistent OSA symptoms despite use. In the CPAP discontinuation group ($n = 435$), 60% (263/435) reported abandoning CPAP within the first year, 73% (318/435) within the first 3 years, and 86% (375/435) within 5 years.

The baseline characteristics and sleep apnea outcome measures of the group that completely abandoned CPAP were compared to the group that reported still attempting CPAP (Table 2). There was no difference in age, gender, BMI, or reported CPAP pressures between the two groups. Polysomnographic measures of OSA were also similar between the groups with mean AHI and ODI levels in the moderate range. A total of 347 (37%) of participants were screened out due to an AHI < 20 events/h. This group of participants with a screening AHI too low represented the largest subset of participants excluded from the trial.

There was also no difference in self-reported daytime sleepiness or sleep-related quality of life measures, with both groups in the abnormal range for the Epworth Sleepiness Scale (ESS) and Functional Outcomes of Sleep Questionnaire (FOSQ).^{10,11} Mean ESS was 11.2 \pm 5.1 in the CPAP abandonment group and 11.5 \pm 5.2 in the group still attempting CPAP ($P = 0.33$). Mean FOSQ was 14.6 \pm 3.4 in the CPAP abandonment group and 14.7 \pm 3.3 in the group still attempting CPAP ($P = 0.57$).

171 (18%) participants also reported attempting oral appliance (OA) therapy. Mean duration of OA treatment period was (1.8 \pm 2.3) years per self-report. 63% (108/171) had discontinued OA therapy at the time of enrollment whereas 37% (63/171) reporting still attempting to use but struggling with side effects, inadequate adherence, or persistent sleep apnea (Fig. 2). Of the 108 participants who completely discontinued oral appliance use, 81% (88/108) abandoned therapy by the end of the first year, 89% (96/108) within the first 3 years, and 94% (101/108) within 5 years.

A total of 162 (17%) participants reported prior upper airway surgical therapy for the indication of obstructive sleep apnea including palatal surgery, genioglossus

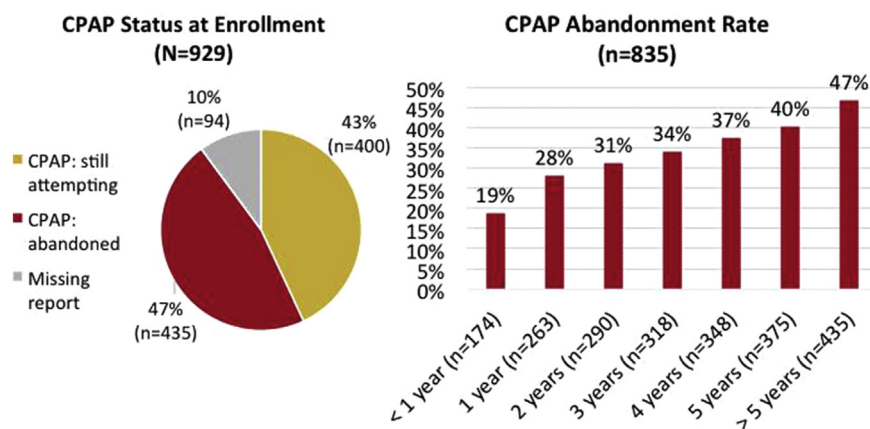


Fig. 1 Forty-seven percent discontinued CPAP prior to enrollment and 43% were still attempting CPAP but struggling with inadequate adherence. Of the 835 participants with complete CPAP data available, 28% abandoned therapy within a year of starting it.

Table 2 Comparison between subjects who abandoned and those still attempting CPAP usage.

Characteristics	CPAP: abandoned (n = 435)	CPAP: still attempting (n = 400)	P value
Age	53.9 ± 10.5	53.9 ± 10.4	0.96
BMI (kg/m ²)	28.2 ± 2.9	28.4 ± 3.2	0.32
Sex (% female)	15%	18%	0.35
CPAP pressure (cm H ₂ O)	9.5 ± 3.3	10.0 ± 2.9	0.17
ESS	11.2 ± 5.1	11.5 ± 5.2	0.33
FOSQ	14.6 ± 3.4	14.7 ± 3.3	0.57
AHI (events/h)	24.7 ± 18.3	26.7 ± 21.3	0.19
ODI	21.2 ± 17.4	23.3 ± 20.0	0.14

advancement, tongue base reduction procedures, and hyoid suspension, with either recurrence or persistence of OSA at the time of presentation. 54 (6%) participants reported unsuccessfully attempting all three treatment modalities: CPAP, OA, and upper airway surgery (Table 3).

Discussion

The goal of this study was to examine the prior OSA treatment history in a group of almost a thousand participants who voluntarily presented to a multicenter trial with interest in an implantable hypoglossal nerve stimulation device as an alternative OSA treatment option. According to the study eligibility criteria, all participants had to document prior diagnosis of moderate-to-severe OSA and treatment with CPAP. One interesting finding was the overstated presenting diagnosis with over one third (37%) of participants demonstrating a screening AHI in the milder range (AHI < 20 events/h). Although this may represent the strict 4% hypopnea scoring criteria of the blinded study core lab, these findings may also suggest that many of these participants may have been a candidate for more conservative medical or surgical treatment options. It likewise stresses the need for re-evaluation of patients over the course of care in order to ensure that the treatment plan matches the severity of the disorder.

The primary result of this study was that almost half of the participants in this large cohort had discontinued CPAP prior to presentation and were completely untreated.

Furthermore, in the group that had discontinued CPAP and was no longer attempting any treatment, 60% of that group reported abandoning CPAP within the first year of use. Although CPAP, the standard first-line therapy, is highly effective when used, suboptimal patient acceptance and adherence has been shown to limit long-term results in many patients.^{12,13}

These findings are important as untreated moderate-severe OSA has been correlated with increased health care costs and physician visits, increased motor vehicle accidents, increased workplace errors, and loss of work productivity.^{14–15} The detrimental effect of OSA on activities of daily living and quality of life measures also contributes significantly to the disease morbidity as well as the financial burden of OSA patients on the health care system. These findings emphasize the need for close clinical follow-up as the participants were still searching for effective

Table 3 OSA treatment history of study subjects.

Treatment history	Number of participants	Percent of study participants
CPAP	929	100%
Oral appliance (OA)	167	18%
Airway surgery	162	17%
All three (CPAP, OA, and surgery)	54	6%

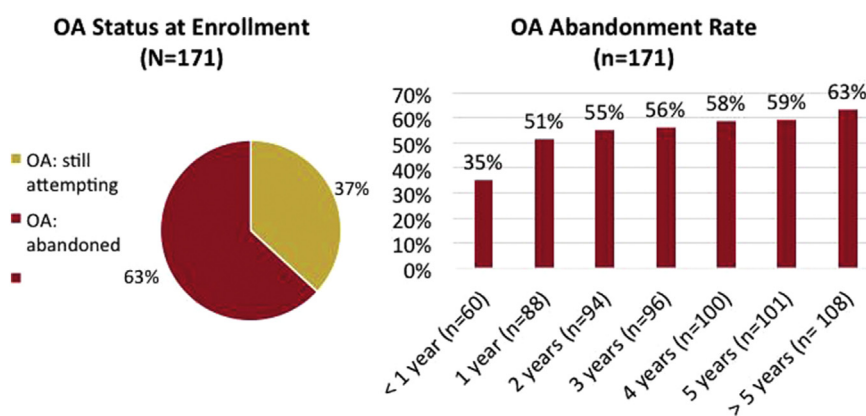


Fig. 2 Of the 171 participants who attempted oral appliance (OA) therapy, 63% discontinued OA prior to enrollment whereas 37% were still attempting it with inadequate adherence or effectiveness. Abandonment rates were highest in the first year.

treatment an average of 5 years after their original diagnosis.

Prompt identification of patients who discontinue therapy and consideration of alternative treatment strategies such as oral appliance therapy, weight loss, positional therapy, upper airway reconstructive surgery, or, in the case of this trial, hypoglossal nerve stimulation therapy may reduce the delay in treatment and the incidence of diagnosed but untreated OSA. Of the 126 participants who met all of the study inclusion criteria to qualify for the implant procedure, 66% (84/126) achieved successful control of OSA based on objective outcome measures at 12 months.⁷ These results suggest that at least a subset of patients who are unable to achieve benefit with CPAP could be successfully managed with UAS therapy. Although the precise degree of AHI reduction needed to mitigate health risks is not known, and likely varies between patients, even alternative treatments that provide only partial OSA control may be better than no treatment at all.

The corollary to this finding is that 43% of participants struggling with CPAP and exploring alternative treatment options were still attempting to use their CPAP. Although this group reported actively attempting CPAP, they did not meet previously published standards for minimum use.¹⁶ A number of common mask-related, pressure-related, and psychosocial side effects have been shown to limit CPAP adherence and were reiterated by the participants here.¹⁷ Interestingly, comparison of the two CPAP groups showed that both reported excessive daytime sleepiness and impaired sleep-related quality of life. The group still attempting CPAP had the same abnormal ESS and FOSQ scores as the group without any treatment at all emphasizing the need for ongoing monitoring of patient symptoms over time.

Patients' ongoing attempts to use CPAP in the setting of adverse side effects, however, suggests that either the therapy is providing at least partial symptomatic benefit or that the patient is still motivated to make the therapy more successful. Identification and troubleshooting of CPAP side effects and inadequate therapy results (through close clinical follow-up, patient education, data download monitoring software, mask refits, and pressure/mode adjustments) may convert a portion of these patients into CPAP successes and obviate the need to consider alternative options.

The often termed *CPAP-intolerant* patients comprise a large portion of the practice of many medical, dental, and surgical sleep specialists. Although this term is used routinely to categorize patients in research studies and clinical practice, our experience with the STAR trial participants emphasizes that this is a heterogeneous population and a vague term that requires further clarification and investigation. Distinguishing those CPAP intolerant patients who are struggling with modifiable side effects from those who have completely abandoned or refused therapy, likely has treatment implications and provides an opportunity for intervention.

This may be particularly important when considering upper airway reconstructive surgical procedures which have at least some degree of inherent risk compared to medical device treatments. In our cohort of 929 participants, 17% had undergone prior uvulopalatopharyngoplasty

(traditional or related modifications) or hypopharyngeal surgical procedures. Such data also emphasizes the need for proper subjective and objective outcome measures after surgical therapy. Six percent of participants had even failed to achieve benefit with all three of the most common treatment modalities—CPAP, OA, and upper airway surgery — and were still in need of an effective solution, underscoring the need for the development of new therapeutic options.

Finally, we think the data here further puts into perspective the need for longitudinal care and likely need for multimodality therapy across the lifespan. Self-reported discontinuation of CPAP and oral appliance therapy increased steadily in our cohort in the first 5 years after treatment initiation. In the oral appliance abandonment group, more than half reported discontinuation of therapy by the end of the first year and almost 90% had discontinued therapy by the three year mark. These results are consistent with previously published reports that also demonstrate diminishing oral appliance adherence rates over time with prior reviews reporting median self-reported adherence of 77% at one year and 56%–68% by year three.^{18,19} Objective adherence monitoring for UAS therapy and for oral appliance therapy is now available and needs to be incorporated into routine clinical practice to assist in the assessment of long-term management.

To our knowledge, this is the first study examining the prior OSA treatment history of a population presenting for a surgical intervention for OSA. The strengths of this study include the large prospective cohort and high percentage of available long-term follow-up data. Limitations include the lack of objective CPAP adherence monitoring information, the lack of a control group, and the highly motivated group of study participants potentially biased by their interest in being a subject in a new OSA treatment trial.

Conclusions

In this CPAP-refractory cohort, high rates of CPAP abandonment were reported in the first several years with more than half of the subjects left completely untreated despite being diagnosed for >5 years. Close clinical follow-up and consideration of alternative treatment options should be considered to ensure adequate longitudinal care.

Disclosure statement

Funding source for this study was Inspire Medical Systems.

Conflicts of interest

Ryan J. Soose, Inspire Medical Systems—study investigator, consultant; Philips Respironics—consultant.

Tapan A. Padhya, Inspire Medical Systems—study investigator, consultant, grant funding.

M. Boyd Gillespie, Inspire Medical Systems—study investigator, consultant, research support; Cook Medical, Omniguide—consultant.

Ho-sheng Lin, Inspire Medical Systems—study investigator, consultant; Intuitive Surgical—proctor.

Oleg Froymovich, Medtronic – consultant.

B. Tucker Woodson, Inspire Medical Systems—study investigator, consultant; Medtronic—consultant, royalty; Siesta Medical—consultant.

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