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Results of the ADHERE upper airway stimulation registry and predictors of therapy efficacy.

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Results of the ADHERE Upper Airway Stimulation Registry and Predictors of Therapy Efficacy

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Objective/Hypothesis: The ADHERE Registry is a multicenter prospective observational study following outcomes of upper airway stimulation (UAS) therapy in patients who have failed continuous positive airway pressure therapy for obstructive sleep apnea (OSA). The aim of this registry and purpose of this article were to examine the outcomes of patients receiving UAS for treatment of OSA.

Study Design: Cohort Study.

Methods: Demographic and sleep study data collection occurred at baseline, implantation visit, post-titration (6 months), and final visit (12 months). Patient and physician reported outcomes were also collected. Post hoc univariate and multivariate analysis was used to identify predictors of therapy response, defined as ≥50% decrease in Apnea-Hypopnea Index (AHI) and AHI ≤20 at the 12-month visit.

Results: The registry has enrolled 1,017 patients from October 2016 through February 2019. Thus far, 640 patients have completed their 6-month follow-up and 382 have completed the 12-month follow-up. After 12 months, median AHI was reduced from 32.8 (interquartile range [IQR], 23.6–45.0) to 9.5 (IQR, 4.0–18.5); mean, 35.8 ± 15.4 to 14.2 ± 15.0, $P < .0001$. Epworth Sleepiness Scale was similarly improved from 11.0 (IQR, 7–16) to 7.0 (IQR, 4–11); mean, 11.4 ± 5.6 to 7.2 ± 4.8, $P < .0001$. Therapy usage was 5.6 ± 2.1 hours per night after 12 months. In a multivariate model, only female sex and lower baseline body mass index remained as significant predictors of therapy response.

Conclusions: Across a multi-institutional study, UAS therapy continues to show significant improvement in subjective and objective OSA outcomes. This analysis shows that the therapy effect is durable and adherence is high.

Key Words: Obstructive sleep apnea, surgery, upper airway stimulation, drug-induced sleep endoscopy.

Level of Evidence: 2

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INTRODUCTION

Obstructive sleep apnea (OSA) is a disorder characterized by repetitive collapse of the upper airway during sleep with consequences of nocturnal hypoxemia and recurrent arousals from sleep.[1] There is increasing evidence that those with moderate to severe sleep apnea, as defined by an Apnea-Hypopnea Index (AHI) value >15 events per hour of sleep, more often experience sequelae of sleep apnea, including daytime sleepiness and cardiovascular morbidity and mortality.[2] The gold standard for treatment of OSA is considered to be continuous positive airway pressure (CPAP).[3] However, approximately one-third of patients have such difficulty with its chronic use that they seek other options or choose to remain untreated. Upper airway

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stimulation (UAS) with electrical activation of the hypoglossal nerve has been shown to be a safe and effective treatment option in controlled studies[4,5] and post-approval studies[6,7] in clinical practices. This report details the results of an international registry designed to evaluate efficacy of UAS in patients with moderate to severe OSA and those who could not or would not use CPAP as a primary therapy. A second goal was to identify patients who might be more likely to benefit from UAS.

METHODS

The ADHERE registry is an ongoing international, multicenter prospective observational study. The registry collects patient and physician reported outcomes after UAS implantation. The registry was approved by ethics committees or institutional review boards at every implantation center. The study was registered with ClinicalTrials.gov (http://www.clinicaltrials.gov, NCT02907398).

Upper Airway Stimulation System

The UAS system (Inspire Medical Systems Inc., Maple Grove, MN) consists of a respiration sensor, programmable implanted pulse generator (IPG), and stimulating electrodes. The sensor detects respiratory efforts from the chest that are analyzed by the IPG. The IPG delivers stimulation synchronized with each respiratory cycle to the anterior branches of the hypoglossal nerve. Upon stimulation, these nerves cause forward protrusion of the tongue, which in turn increases the size of the oropharyngeal airway. Anterior palate movement is commonly coupled with tongue movement.

Device Implantation Procedure

Details of device implantation and activation are described in detail in prior publications.[8] Figure 1 is an updated illustration emphasizing several of the most important proper steps for identification of anterior branching of the hypoglossal nerve. The posterior edge of the anterior belly of the digastric muscle and then the posterior edge of the mylohyoid muscle are retracted anteriorly. Just underneath this, and at the anterior edge of the submandibular gland, is the hypoglossal nerve as it begins to divide. The cuff electrode is placed on the genioglossus branches of the hypoglossal nerve.

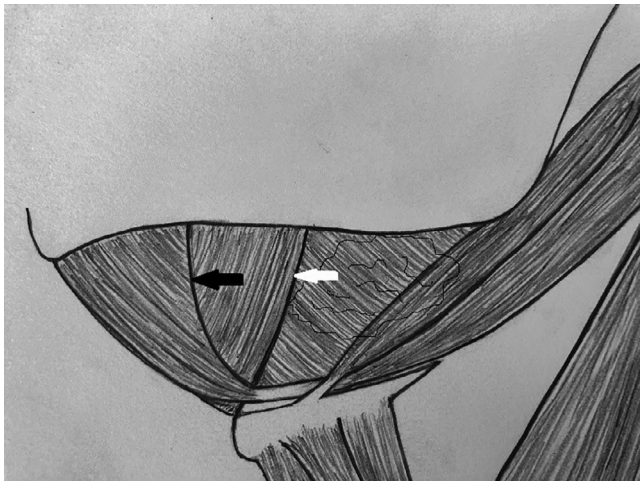

Fig. 1. Approach to the anterior branches of the hypoglossal nerve. The first step is to identify and retract the posterior edge of the anterior belly of the digastric muscle (black arrow). The second step is to identify and anteriorly retract the posterior edge of the mylohyoid muscle. Just underneath this and at the anterior border of the submandibular gland is the hypoglossal nerve as it begins to branch. Genioglossus branches are identified with nerve stimulation and a neuromonitor.

Data Collection

The registry enrolls adult participants who meet the approved indications of UAS including AHI between 15 to 65 events per hour inclusive, who are intolerant to CPAP, and who are free of complete concentric collapse during sedated endoscopy. Following baseline and implant data collection, the registry collects information from two clinical visits during post-implantation follow-up: the post-titration visit, approximately 6 months post-implantation, and the final visit, approximately 12 months post-implantation.

During the post-implantation visits, study investigators determine OSA severity by AHI via either an in-lab attended polysomnography or a type 3 home sleep apnea test, daytime sleepiness as reported by participants using the Epworth Sleepiness Scale (ESS), and objective therapy use of hours per night from data stored in the IPG.

Data Analysis

The AHI and ESS distributions were tested for normality using the Shapiro-Wilk test, with a significance level of 0.05. We compared outcome measures of AHI and ESS from the final visit with the baseline using the Wilcoxon signed-rank test with continuity correction, with a type I error rate of >0.05. Results are presented as median and mean $\pm$ standard deviation. Post hoc logistic regression analyses included a model of all potential predictors of treatment success using Sher criteria,[9] defined as ≥50% reduction to AHI ≤ 20. Sensitivity analysis to two other definitions of AHI therapy success, defined ≥50% reduction to AHI < 10, and AHI < 10, was performed to confirm the robustness of the predictor findings. Age, sex, baseline body mass index (BMI), baseline AHI, therapy usage per week per week at 6 and 12 months, binary therapy use (<28 hours vs. ≥28 hours) at 6 and 12 months, and tongue-motion phenotype at implantation were entered into the model as potential predictors. An additional multivariate model with stepwise selection was used to reduce the model to retain only significant parameters to assess for predictors of the therapy. Sex, baseline BMI, and binary therapy use (<28 hours vs ≥28 hours) at final follow-up were entered into the model in the first, second, and third step. No other variable met the χ^2 score of 0.2 significance level for entry into the model. The significance level of the Wald χ^2 for an effect to stay in the model is 0.05. An odds ratio (OR) <1 indicates success is less likely, whereas an OR > 1 indicates success is more likely. A P value <.05 is considered statistically significant.

RESULTS

Participants

The registry has enrolled 1,017 participants from October 2016 through February 2019. Thus far, 640 participants have completed their 6-month post-titration follow-up and 382 have completed the 12-month final follow-up. Average age was 60 $\pm$ 11 years, BMI of 29.3 $\pm$ 3.9 kg/m^2, 74% male, and 96% Caucasian. Participants were generally healthy; the most common baseline comorbidity was hypertension (48%). Prior to implantation, 97% of participants

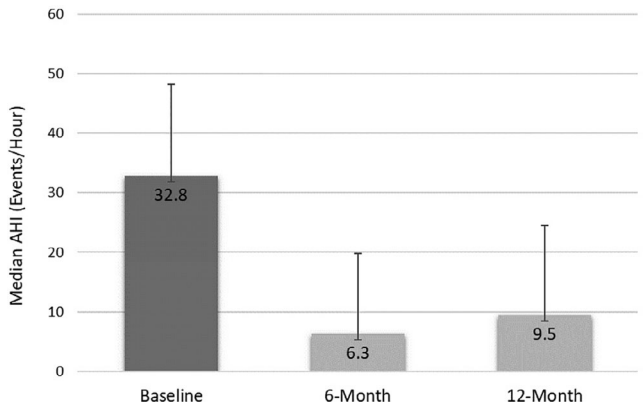

Fig. 2. Median AHI measurements at baseline and at 6 and 12 months postoperatively. Error bars in SD. AHI = Apnea-Hypopnea Index; SD = standard deviation.

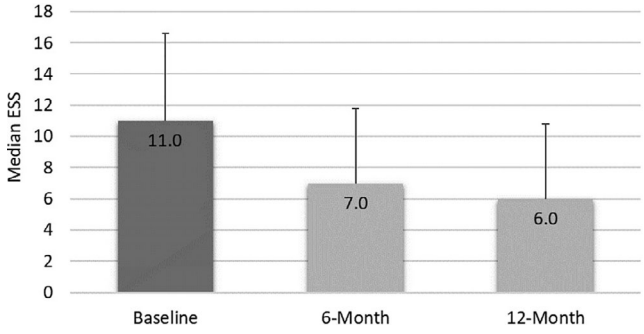

Fig. 3. ESS measurements at baseline and at 6 and 12 months postoperatively. Error bars in SD. ESS = Epworth Sleepiness Scale; SD = standard deviation.

reported history of positive airway pressure use for treatment of OSA: 20% with oral appliances, 22% with nasal procedures, 29% with palatal procedures, and 5% with tongue-base procedures.

Treatment Effects

After receiving the implant, AHI was reduced from 32.8 (interquartile range [IQR], 23.6–45.0) at baseline to 6.3 (IQR, 2–14.8) at 6 months, and 9.5 (IQR, 4.0–18.5) at 12 months (mean, 35.8 ± 15.4 at baseline to 11.0 ± 13.5 at 6 months and 14.2 ± 15.0 at 12 months, $P < .001$; Fig. 2). Using Sher criteria[9] on patients with baseline and follow-up AHI data, 83% (n = 485/582) and 69% (n = 265/381) participants met treatment success after 6 and 12 months, respectively.

Similarly, participants reported reduced daytime sleepiness with ESS of 11.0 (IQR, 7.0–16.0) at baseline to 7.0 (IQR, 4.0–11.0) at 6 months and 6.0 (IQR, 3.0–10.0) at 12 months (mean, 11.4 ± 5.6 at baseline to 7.7 ± 4.8 at 6 months and 7.2 ± 4.8 at 12 months, $P < .0001$ comparing with baseline; Fig. 3). Using the normalizing threshold of ESS < 10,[10] 37%, 67%, and 74% had normal daytime sleepiness at baseline, 6 months, and 12 months post-implantation.

After 12 months, the median device report of objective therapy use was 5.7 (IQR, 4.1–7.1; mean, 5.6 ± 2.1) hours per night; 92% of investigators reported improvement with treatment after participant receiving implantation; 93% of participants reported overall satisfaction with UAS treatment, 95% preferred UAS over positive airway pressure, 94% would choose UAS again if asked, and 96% would recommend UAS to family and friends.

Predictors of Therapy Response

Using logistic regression models, we examined predictors of treatment success based on Sher criteria. In the univariate analysis, female sex has 90% increased odds of having a more favorable AHI response compared with male sex. Each unit decrease of BMI is associated with 8.5% increased odds of having a more favorable AHI response. Other baseline characteristics of age and baseline AHI did not predict AHI response. Tongue motion reported from the implantation procedure did not predict

TABLE I.
Predictors of Therapy Response.

	Univariate Results		Multivariate Results, Full Model		Multivariate Results, Reduced Model	
Parameter	OR (*P* Value)	95% CI for OR	OR (*P* Value)	95% CI for OR	OR (*P* Value)	95% CI for OR
Sex, F vs. M	1.943 (.0457)	1.013-3.729	3.634 (.0041)	1.505-8.772	3.413 (.0049)	1.452-8.019
Age at consent	1.014 (.1862)	0.993-1.034	1.000 (.9998)	0.976-1.025		
BMI at baseline	0.915 (.0028)	0.863-0.970	0.913 (.0108)	0.851-0.979	0.909 (.0050)	0.851-0.972
Baseline AHI	0.993 (.2914)	0.979-1.006	1.006 (.5198)	0.988-1.024		
Tongue motion	(.6414)	—	(.3795)	—		
Bilateral protrusion vs. right protrusion	1.312 (.3488)	0.743-2.318	1.554 (.1645)	0.835-2.894		
Bilateral or right protrusion vs. other	0.963 (.9244)	0.442-2.100	—	—		
Other vs. right protrusion	1.284 (.5843)	0.525-3.141	1.339 (.6320)	0.406-4.415		
Therapy hr/wk at 6 mo	1.011 (.2457)	0.993-1.029	1.004 (.8103)	0.971-1.038		
<28 hr vs. ≥28 hr	0.726 (.3864)	0.352-1.498	1.130 (.8362)	0.355-3.592		
Therapy hr/wk at 12 mo	1.017 (.0390)	1.001-1.033	1.001 (.9668)	0.969-1.034		
<28 hr vs. ≥28 hr	0.622 (.0769)	0.367-1.053	0.651 (.3732)	0.254-1.673		

AHI = Apnea-Hypopnea Index; BMI = body mass index; CI = confidence interval; F = female; M = male; OR = odds ratio.

TABLE II.
Predictors of Therapy Success, Defined as 50% Reduction in AHI From Baseline and AHI < 10.

	Univariate Results		Multivariate Results, Full Model		Multivariate Results, Reduced Model	
Parameter	OR (*P* Value)	95% CI for OR	OR (*P* Value)	95% CI for OR	OR (*P* Value)	95% CI for OR
Sex, F vs. M	2.123 (.0083)	1.213-3.713	3.363 (.0008)	1.651-6.848	2.926 (.0017)	1.494-5.728
Age at consent	1.010 (.3023)	0.991-1.029	0.985 (.2104)	0.963-1.008		
BMI at baseline	0.910 (.0008)	0.861-0.961	0.936 (.0466)	0.877-0.999	0.926 (.0153)	0.869-0.985
Baseline AHI	0.974 (.0002)	0.960-0.987	0.981 (.0246)	0.964-0.998	0.980 (.0168)	0.964-0.996
Tongue motion	*P* = .1628	—	*P* = .1839	—		—
Bilateral protrusion vs. right protrusion	1.606 (.0902)	0.928-2.778	1.731 (.0765)	0.943-3.176		
Bilateral or right protrusion vs. other	0.723 (.3803)	0.350-1.492	—	—	—	—
Other vs. right protrusion	2.011 (.1054)	0.863-4.683	1.994 (.2275)	0.650-6.114		
Therapy hr/wk at 6 mo	1.012 (.1569)	0.995-1.029	0.993 (.6620)	0.962-1.025		
<28 hr vs. ≥28 hr	0.607 (.1670)	0.299-1.232	0.792 (.6829)	0.258-2.430		
Therapy hr/wk at 12 mo	1.018 (.0211)	1.003-1.033	1.023 (.1456)	0.992-1.055		
<28 hr vs. ≥28 hr	0.744 (.2494)	0.450-1.230	1.254 (.6228)	0.509-3.086		

AHI = Apnea-Hypopnea Index; BMI = body mass index; CI = confidence interval; F = female; M = male; OR = odds ratio.

AHI outcome. In multivariate analysis with only baseline sex and BMI included, both parameters remain significantly associated with the AHI outcome (Table I).

To test the robustness of these predictors, we performed sensitivity analysis by repeating the univariate and multivariate analysis to two other definitions of therapy success besides the Sher criteria (e.g., AHI < 10, or 50% reduction of AHI and AHI < 10; Tables II and III). Using both definitions, female sex and lower BMI remained as positive predictors of AHI response. Higher baseline AHI emerged as a new additional negative predictor of success.

In further comparing female versus male participants, female patients had a statistically significant lower AHI after 12 months of therapy than did male patients. Female participants were of older age and lower BMI at

TABLE IV.
Comparing Baseline and OSA Characteristics Between Sexes and Their UAS Response.

	Sex = F	Sex = M	*P* Value
Age, yr	62.9 ± 9.9	59.5 ± 11.5	<.0001
BMI, kg/m^2, baseline	28.9 ± 4.5	29.4 ± 3.6	0.04
AHI, events/hr, baseline	34.4 ± 15.6	36.2 ± 15.3	0.11
ESS, baseline	11.4 ± 5.3	11.4 ± 5.7	0.92
AHI, events/hr, 12 mo	10.3 ± 11.0	15.0 ± 15.6	0.02
ESS, 12 mo	7.1 ± 4.3	7.2 ± 4.9	0.88
Therapy use, hr/night, 12 mo	5.9 ± 2.1	5.5 ± 2.1	0.18

AHI = Apnea-Hypopnea Index; ESS = Epworth Sleepiness Scale; F = female; M = male; OSA = obstructive sleep apnea; UAS = upper airway stimulation.

TABLE III.
Predictors of Therapy Success, Defined as AHI < 10.

	Univariate Results		Multivariate Results, Full Model		Multivariate Results, Reduced Model	
Parameter	OR (*P* Value)	95% CI for OR	OR (*P* Value)	95% CI for OR	OR (*P* Value)	95% CI for OR
Sex, F vs. M	2.145 (.0073)	1.228-3.745	3.240 (.0012)	1.592-6.592	2.875 (.0021)	1.467-5.634
Age at consent	1.011 (.2272)	0.993-1.030	0.988 (.3089)	0.966-1.011		
BMI at baseline	0.911 (.0010)	0.863-0.963	0.939 (.0571)	0.879-1.002	0.929 (.0201)	0.872-0.988
Baseline AHI	0.972 (<.0001)	0.959-0.986	0.979 (.0126)	0.962-0.995	0.978 (.0085)	0.962-0.994
Tongue motion	*P* = .1466	—	*P* = .1705	—		—
Bilateral protrusion vs. right protrusion	1.645 (.0751)	0.951-2.845	1.759 (.0681)	0.959-3.226		
Bilateral or right protrusion vs. other	0.737 (.4089)	0.357-1.521	—	—	—	—
Other vs. right protrusion	2.011 (.1054)	0.863-4.683	1.975 (.2336)	0.644-6.054		
Therapy hr/wk at 6 mo	1.013 (.1443)	0.996-1.030	0.994 (.7086)	0.963-1.026		
<28 hr vs. ≥28 hr	0.595 (.1506)	0.293-1.208	0.805 (.7042)	0.262-2.469		
Therapy hr/wk at 12 mo	1.017 (.0225)	1.002-1.032	1.020 (.2033)	0.989-1.052		
<28 hr vs. ≥28 hr	0.728 (.2167)	0.441-1.204	1.168 (.7348)	0.475-2.875		

AHI = Apnea-Hypopnea Index; BMI = body mass index; CI = confidence interval; F = female; M = male; OR = odds ratio.

TABLE V.
Summary of Postoperative Adverse Events.

Type	Post-Titration		Final Visit	
	No. of Events	% of Patients	No. of Events	% of Patients
Tongue weakness	3	<1	0	0
Swallowing or speech related	4	1	1	<1
Discomfort, incision/scar	14	4	8	2
Discomfort, device	10	3	5	1
Infection	2	<1	0	0
Postoperative other*	14	4	6	2
Stimulation-related discomfort	41	12	28	8
Tongue abrasion	12	3	14	4
Insomnia/arousal	10	3	17	5
Revision interventions, including explantation	1	<1	2	<1
Other discomfort	12	3	8	2
Activation, other	37	3	23	7
Total	161	46	113	32

*Postoperative other includes shortness of breath, seroma, numbness of the throat, hoarseness during the day, and a mild tongue-base and epiglottic obstruction. A total of 71 patients reported adverse events at the post-titration visit and 49 at the final visit (not mutually exclusive). Some patients reported multiple adverse events. Percentage of patients was calculated based on the number of patients at each visit who completed the visit form, which contains adverse event information.

baseline. Female participants showed a trend of higher therapy use after 12 months (Table IV).

Adverse Events

Adverse events are reported in Table V. Stimulation-related discomfort was the most common complaint reported by participants, reported by 12% of participants at 6 months and 8% of participants at 12 months post-implantation. Surgical intervention was required for device revision in three cases: in one participant due to stimulation electrode dislodgement within 6 months and in another two participants with stimulation electrode repositioning within 12 months.

DISCUSSION

UAS therapy shows durable response in this large cohort of patients followed for 12 months post-implantation. The ADHERE study group continues to demonstrate limited adverse events and overall excellent outcomes both in term of success rates and device utilization. In addition, patients' reported reduction in symptomatology and satisfaction with UAS treatment are significant and durable measures of success.

Although the study cohort's average age of 60 years might appear high, age as an independent variable did not predict response. This finding contrasts with prior reporting of the ADHERE registry.[8] There may be some self-selection of patients that skews the population older. Perhaps older patients are less inclined to pursue ablative procedures. Also, with age, perhaps the presence of an implanted device in the chest wall is less concerning than it might be in a younger age cohort. It should be emphasized that this procedure is not precluded by the presence of a pacemaker or automated implantable cardioverter-defibrillator. At this juncture, the authors do not find that age should be a significant selection criterion either in favor of or against implantation.

When using the Sher criterion (≥50% reduction in AHI and ≤ 20) as the basis of therapy response, baseline AHI did not predict response. However, when using other definitions of therapy response, namely AHI < 10, or 50% reduction in AHI and < 10, baseline AHI did predict response, as did sex and BMI. This is most likely due to the varying definitions of AHI response. Thus, the usefulness of baseline AHI as a response predictor will depend on the criterion chosen to define therapy response. We chose to use the Sher criterion as it is the most commonly used metric in the surgical sleep apnea literature. When using this definition of response, increasing severity of apnea (within the range enrolled in this registry) should not preclude the decision for implantation or lessen a patient's potential for excellent response. Treatment success at AHI values higher than the range stipulated by the Stimulation Therapy for Apnea Reduction (STAR) trial criteria have been reported.[11]

Not surprisingly, improved outcomes are associated with a lower BMI. This has been shown to be true for other OSA surgical procedures,[12] and UAS implantation does not appear to be an exception, despite some prior evidence to the contrary.[13] Although surgical success has been reported at higher BMIs, the BMI cutoff of 32 by STAR criteria remains a useful guide for surgical decision-making until there are better preoperative assessment tools available to screen out those patients who would not succeed with UAS therapy. The drug-induced sleep endoscopy criteria for UAS implantation that excludes circumferential collapse is helpful in screening out only some patients whose fat distribution contributes to upper airway collapse. Surgeons should be mindful that when considering patients with higher BMI, careful attention to fat distribution may enhance success.

The statistically significant improved success rate with female patients bears further investigation. Unsurprisingly due to the demographics of OSA, this cohort was a small percentage of the overall group studied. There is no anatomic explanation for this finding and no distinguishing features in the demographics of the female patients in this study to suggest causality. The small, but statistically significant, difference in BMI at baseline might account for improved success, in keeping with the overall incremental improvement in AHI reduction with lower BMI. It is important to note the trend toward higher use in female patients, which may also account for at least some of the improvement in AHI reduction.

The greatest strength of this study is that the ADHERE registry has a large sample size and is an ongoing effort. Its greatest limitation is that both home and in-laboratory studies were used in the analysis, with attendant lack of uniformity of AHI recording. Furthermore, sensitivity analysis using other metrics of outcome success showed that sex and BMI remained as predictors of success. Baseline AHI as an outcome predictor depends on the definition of outcome success. Home sleep studies may underestimate AHI—this may have affected both the pre- and post-implantation studies, though not the titration studies, which were all done in laboratory.

CONCLUSION

Across a multi-institutional registry, UAS therapy shows significant improvement in subjective and objective OSA outcomes. This analysis shows that the therapy effect is durable and adherence is high. When using the Sher definition of surgical outcome, female sex and lower baseline BMI are positive predictors of therapy.

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