Obstructive Sleep Apnea: Alternative Therapies for PAP-Intolerant Patients

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GBMC Health Partners

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Disclosures

- In the past 24 months I have attended several education programs and/or conferences sponsored by:
  - Inspire Medical
  - ZOLL Respicardia
  - Avadel Pharmaceuticals

Learning Objectives

Understand the pathophysiology of obstructive sleep apnea

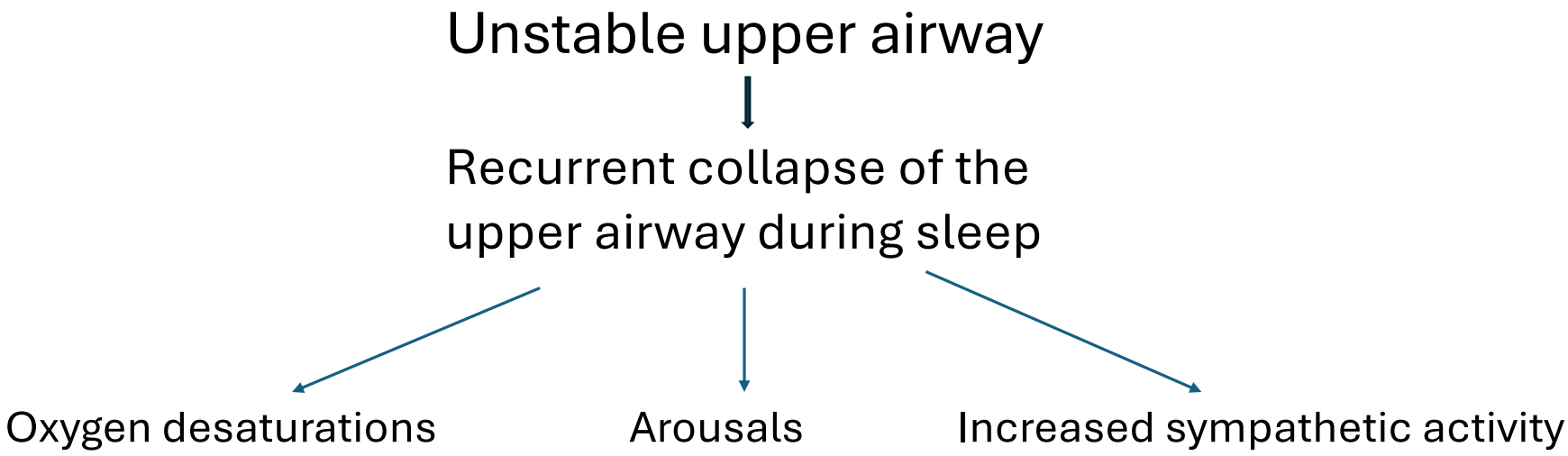
Understand goals of OSA treatment

Identify potential reasons for PAP non-adherence or intolerance and ways to troubleshoot

Become familiar with alternative OSA therapies

Pathophysiology of Obstructive Sleep Apnea

Pathophysiology of Obstructive Sleep Apnea



Obstructive Apnea

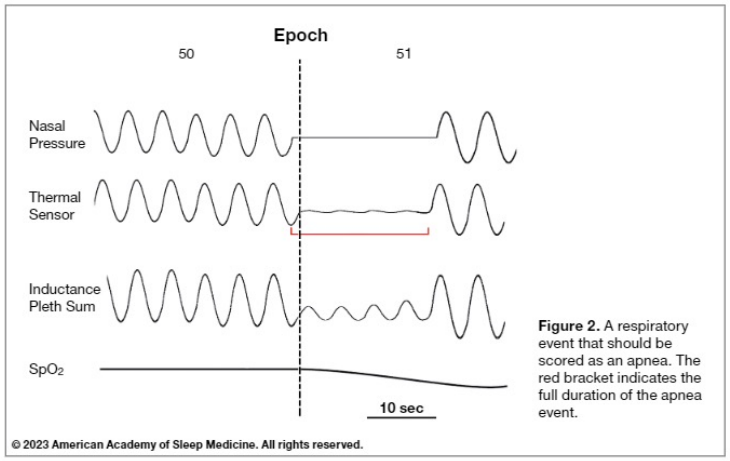


Figure 2. A respiratory event that should be scored as an apnea. The red bracket indicates the full duration of the apnea event.

Obstructive Hypopnea

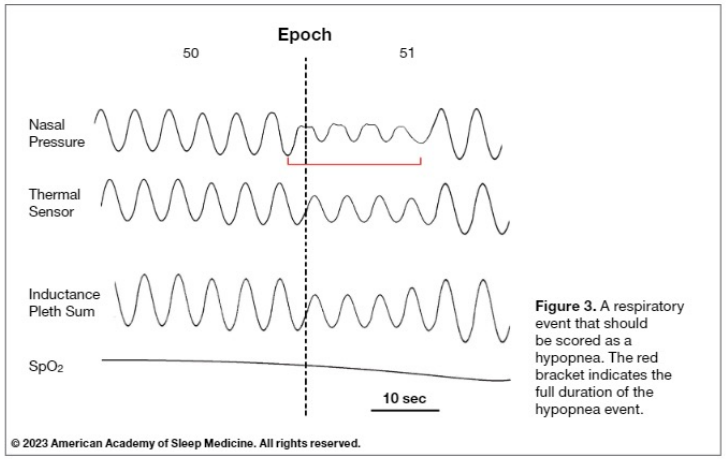


Figure 3. A respiratory event that should be scored as a hypopnea. The red bracket indicates the full duration of the hypopnea event.

Rule 1A: >=3% oxygen desaturation or associated with arousal (RECOMMENDED)

Rule 1B: >=4% oxygen desaturation (OPTIONAL)

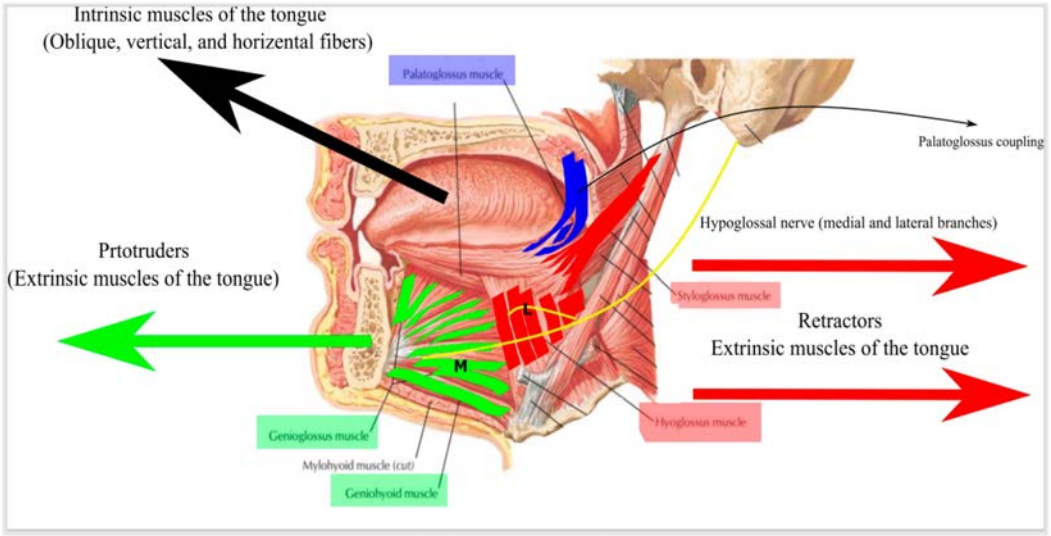
Diagnostic Criteria for OSA: AHI >=5 on PSG or HSAT

Mild OSA:	$5 \leq AHI < 15$ with symptoms*
Moderate OSA:	$15 \leq AHI < 30$
Severe OSA:	$AHI \geq 30$

AASM Manual for the Scoring of Sleep and Associated Events 2023
AASM ICSD-3-TR (Text Revision) 2023

Upper Airway Anatomy

- Tongue is a muscular hydrostat
- Muscle contraction *changes shape/position*
- Hypoglossal nerve controls <u>all</u> tongue muscles
  - Protrusion (*Genioglossus)*
  - Retraction (*Hyoglossus)*
- Airway shape/size very different awake vs asleep



OSA is NOT a “One-size-fits-all” Disease

- Structural Endotypes
  - Obesity (increased tongue fat)
  - Craniofacial abnormality
- Physiologic Endotypes
  - High loop gain
  - Low arousal threshold
  - Poor upper airway dilator response to collapse
  - Variable ventilatory response to arousal
- Phenotypes
  - Disturbed sleep
  - Excessive sleepiness
  - Moderate sleepiness
  - Minimally symptomatic

Eckert et al AJRCCM 2013
Mazzotti et al AJRCCM 2019
Edwards et al AJRCCM 2019

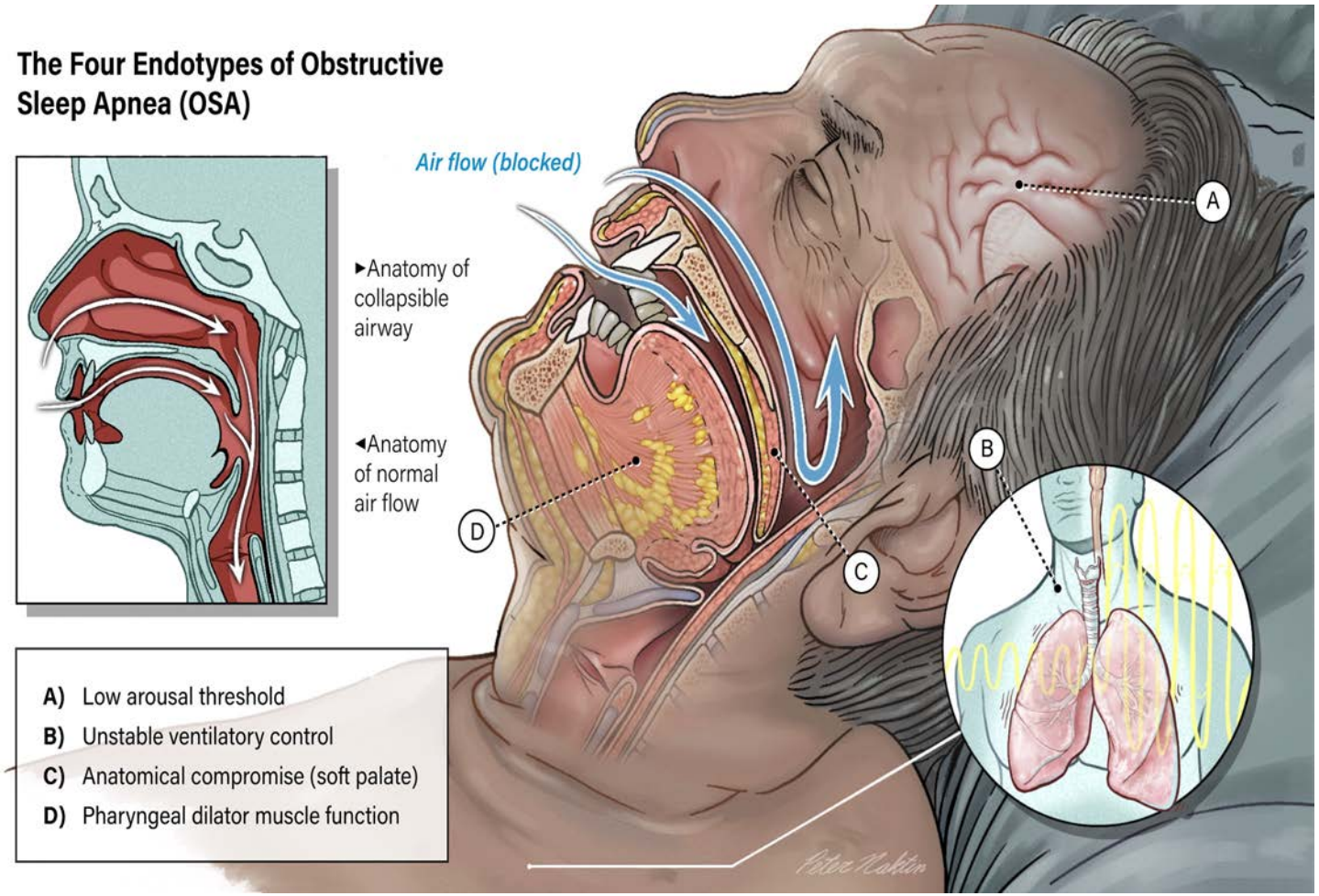


Figure 1. The four currently identified obstructive sleep apnea endotypes. Reprinted by permission from © 2023 Augusta University and Peter Naktin.
https://www.atsjournals.org/doi/abs/10.34197/ats-scholar.2023-0022OT
Published in: Ana Sanchez-Azofra; Atul Malhotra; Robert L. Owens; William J. Healy; *ATS Scholar* Ahead of Print. DOI: 10.34197/ats-scholar.2023-0022OT

Excessive sleepiness phenotype associated with increased risk of CVD

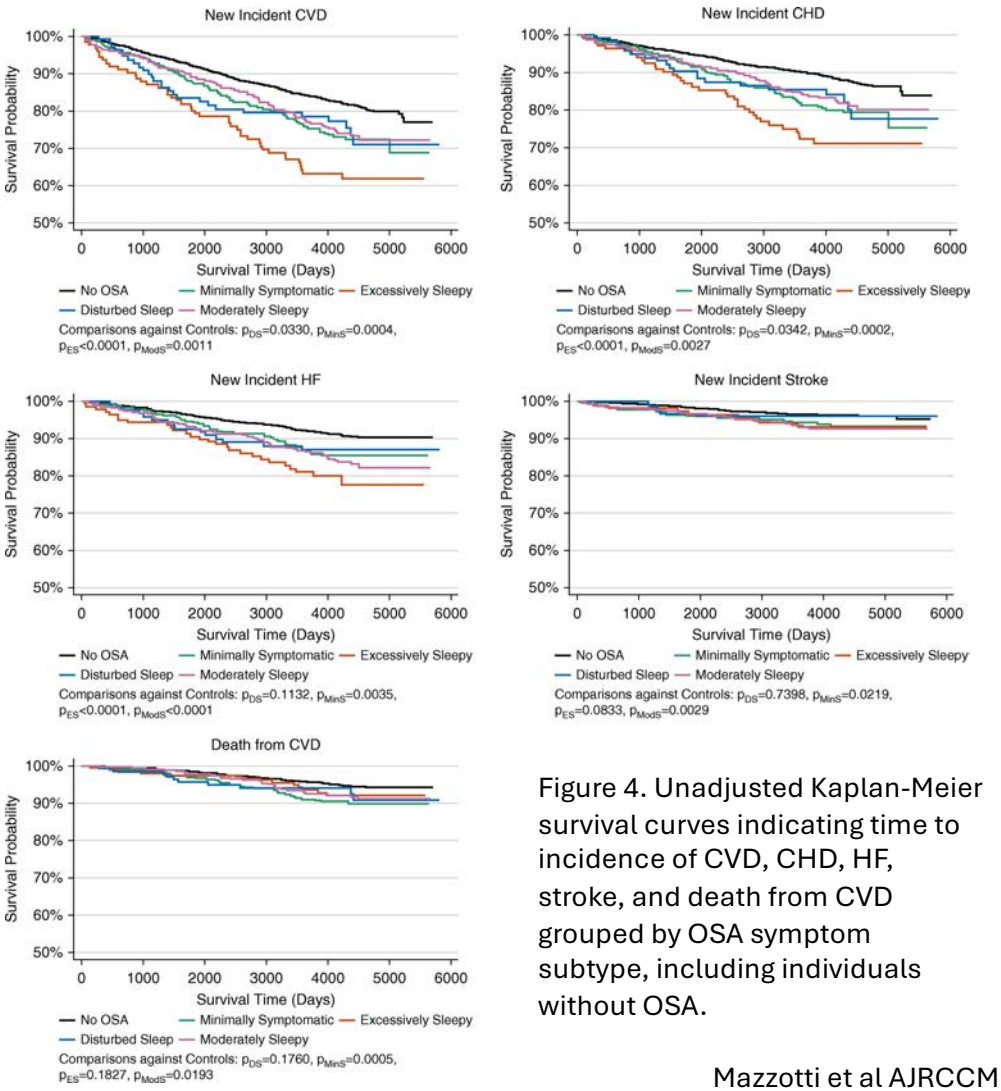


Figure 4. Unadjusted Kaplan-Meier survival curves indicating time to incidence of CVD, CHD, HF, stroke, and death from CVD grouped by OSA symptom subtype, including individuals without OSA.

Mazzotti et al AJRCCM 2019

The Problem of Obstructive Sleep Apnea

- Increased
  - All cause mortality
  - Stroke (CVA) risk
  - Hypertension
  - Atrial fibrillation
  - Cancer risk
  - Diabetes
  - Accidents
- Decreased
  - Cognitive function
  - Mood
  - Quality of life
  - Work productivity

Patients Report Benefits from OSA Treatment

Improved blood pressure: 41%
(reported improvement)

Less medication for HTN: 17%

Improved A1c: 31%

Improved sleep quality *7x increase in "good quality sleep"*

Improved mental health: 49%

Less substance use (cigarettes, alcohol)

Lowered CV risk: 56%

Improved respiratory function: 54%

AASM 2016 survey by Frost & Sullivan

Goals of OSA Treatment

Goals of OSA Treatment

Adherence

“Compliance” defined as usage for >=4 hours for >=70% of days

Objective benefit:

AHI reduction

Decreased hypoxia (ODI, SASHB)

Conversion of apneas to hypopneas?

Improved sleep architecture, less arousals

Subjective benefit (symptom improvement)

Reasons for PAP Non-adherence or Intolerance and Ways to Troubleshoot

Continuous Positive Airway Pressure (CPAP) is gold standard treatment for OSA

- Very effective (average AHI reduction of 80%) but…
- Adherence is poor (29-83% non-adherence)
- Predictive factors of CPAP adherence:
  - Subjective daytime sleepiness
  - Improvement in daytime sleepiness @ 1 month
  - Early adherence to CPAP
- Factors associated with poor PAP adherence:
  - Spouse referral
  - Poor early adherence
  - High nasal resistance
  - High mask leak

Mask selection

Positional component

Comorbid insomnia

Central sleep apnea

“Comfort” features on CPAP

In-lab PAP titration

Education and close follow up

Troubleshooting PAP non-adherence and/or Intolerance

TECA's caused by CPAP

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Treatment-emergent central sleep apnea resolves with lower inspiratory pressure

William H. Noah, MD[1]; Ludovico Messineo, MD, PhD[2]; Bernard Hete, PhD[1]; Evelyn Thompson, RPSGT[1]; David P. White, MD[2]; Robert J. Farney, MD[3]; Krishna M. Sundar, MD[3]

[1]*Sleep Centers of Middle Tennessee, Murfreesboro, Tennessee;* [2]*Division of Sleep and Circadian Medicine, Harvard Medical School, Brigham & Women's Hospital, Boston, Massachusetts;* [3]*Division of Pulmonary and Critical Care Medicine, University of Utah, Salt Lake City, Utah*

Study Objectives: Treatment-emergent central sleep apnea (TECSA) is an important problem during therapy with continuous positive airway pressure (CPAP) in patients with obstructive sleep apnea. We tested a device designed to improve CPAP comfort through reducing inspiratory positive airway pressure (IPAP; V̇-Com) to determine whether such a reduction in IPAP could eliminate central apneas in patients with TECSA. Because increasing tidal volume (potentially via IPAP increments) has been suggested as a possible mechanism contributing to TECSA onset, our hypothesis was that reducing IPAP would yield a drop in the central apnea index.

Methods: The addition of a known resistance (V̇-Com device) that reduces IPAP was implemented into the CPAP circuit during the second half of CPAP titrations in a cohort of community-dwelling patients who developed TECSA during a split-night CPAP titration. Central apnea index was quantified from the sleep periods without and with V̇-Com in place.

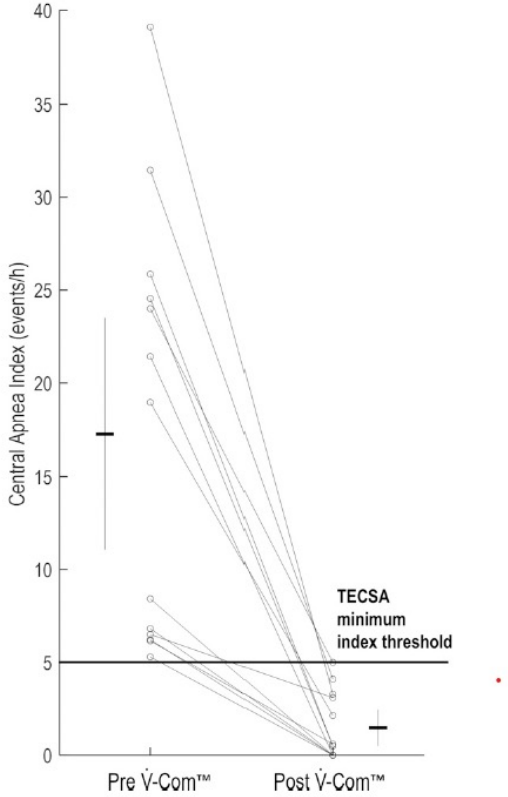
Results: A total of 1,613 patients underwent CPAP titration, with 19 of them developing TECSA during the titration. The addition of V̇-Com resulted in complete resolution of TECSA in all patients with adequate sleep data under all conditions (n = 13), yielding a significant reduction in the central apnea index (17.3 ± 11.0 vs 1.5 ± 1.7 events/h without and with V̇-Com, respectively; $P < .001$).

Conclusions: V̇-Com virtually resolved all instances of TECSA, suggesting that reducing IPAP could be an effective strategy for managing the occurrence of central respiratory events in patients with obstructive sleep apnea using CPAP.

Keywords: central sleep apneas, continuous positive airway pressure, biphasic intermittent positive airway pressure

Citation: Noah WH, Messineo L, Hete B, et al. Treatment-emergent central sleep apnea resolves with lower inspiratory pressure. *J Clin Sleep Med.* 2025;21(3):559–564.

Figure 2—Central apnea index before and after the placement of the V̇-Com device.



The 2 treatment conditions were significantly different ($P < .001$ per Student's *t* test). Lateral bars are mean ± 95% confidence interval. TECSA = treatment-emergent central sleep apnea.

Noah et al JCSM 2025

Comorbid Insomnia and Sleep Apnea (COMISA)

Lower rates of PAP adherence

Cognitive behavioral therapy for insomnia (CBT-I) may help

No evidence supporting efficacy of sedative hypnotics in improving PAP adherence

Alternative OSA Therapies

PAP Alternatives for OSA

Positional Therapy

- Positional OSA: supine AHI > 2x non-supine AHI
- At least 50% of patients with OSA may be positional
- Positional OSA patients tend to be younger, lower BMI, less severe disease
- Vibratory positional therapy similar efficacy to CPAP in terms of AHI reduction, more comfortable than CPAP, but CPAP perceived as more effective

Oksenberg et al CHEST 1997

Mandibular Advancement Devices

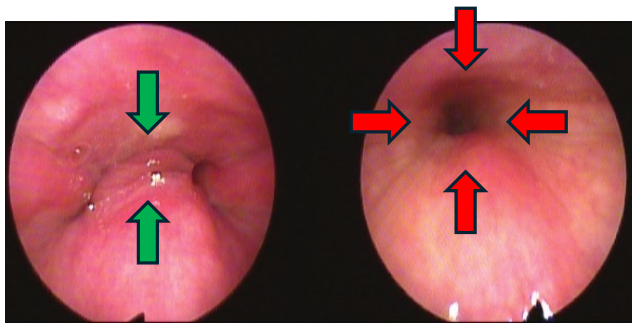
- Variable options:
  - Nonadjustable, OTC “boil and bite” appliances
  - Custom-made one-piece “monobloc” devices
  - Adjustable two-piece devices with ability to titrate protrusion
- Rx and LMN for E0486 device
- Referral to AADSM-certified dentist
- Follow up testing – HSAT vs in-lab titration
- DISE may be helpful to predict outcomes
- Recent study in JCSM (Mosca et al 2025) demonstrating high efficacy in reducing SASHB

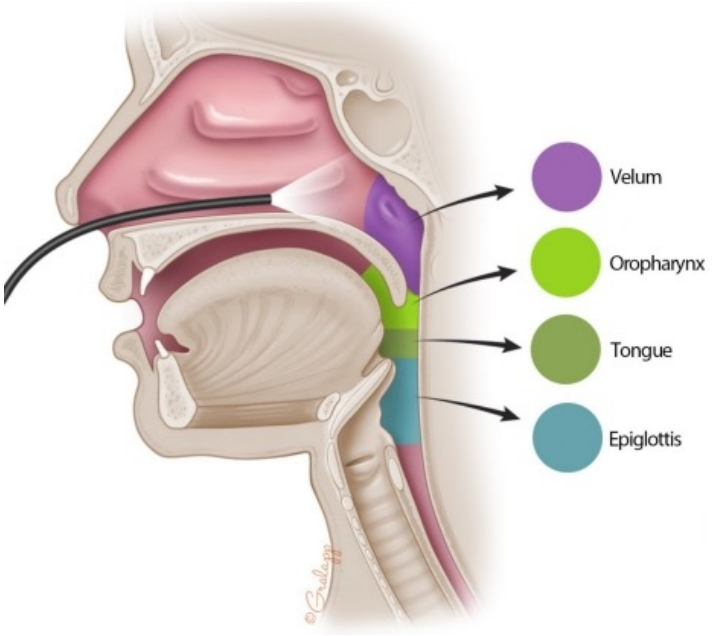
Upper Airway Surgery

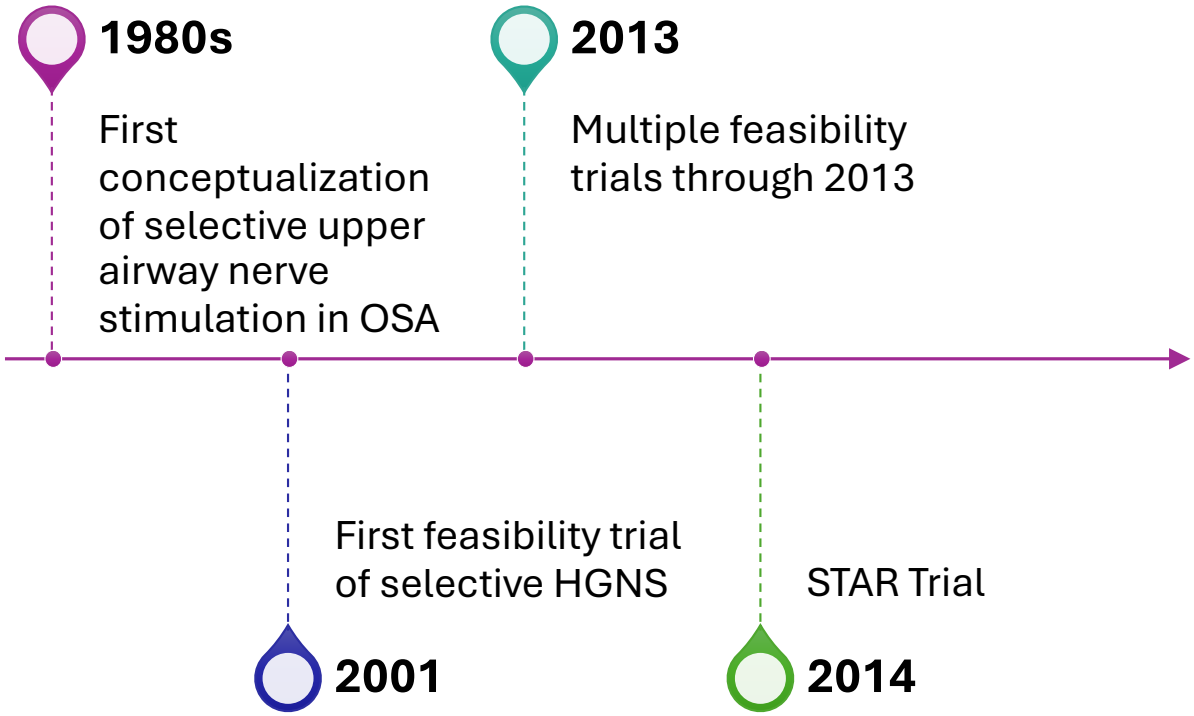
- Surgical Options:
  - Nasal surgery
  - Palate suspension
  - Tonsillectomy
  - Uvulopalatopharyngoplasty (UPPP)
  - Hyoid suspension
  - Maxillomandibular advancement
- Sher criteria for treatment success:
  - Reduction in AHI by 50%
  - Final AHI <20
- DISE for surgical planning

Drug Induced Sleep Endoscopy (DISE)

- Evaluate upper vs lower airway collapse
- Assess candidacy for hypoglossal nerve stimulation (rule out complete concentric collapse)

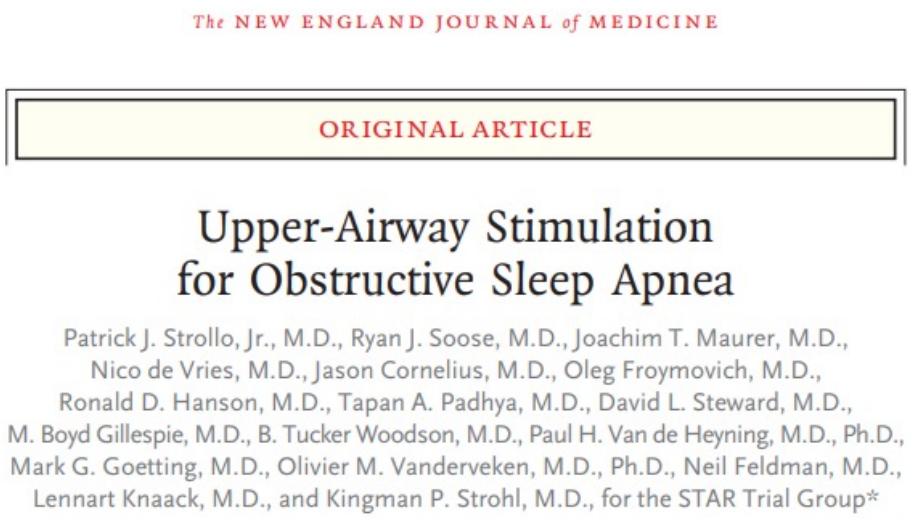






Hypoglossal Nerve Stimulation (HGNS)

2014 STAR Trial



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Upper-Airway Stimulation for Obstructive Sleep Apnea

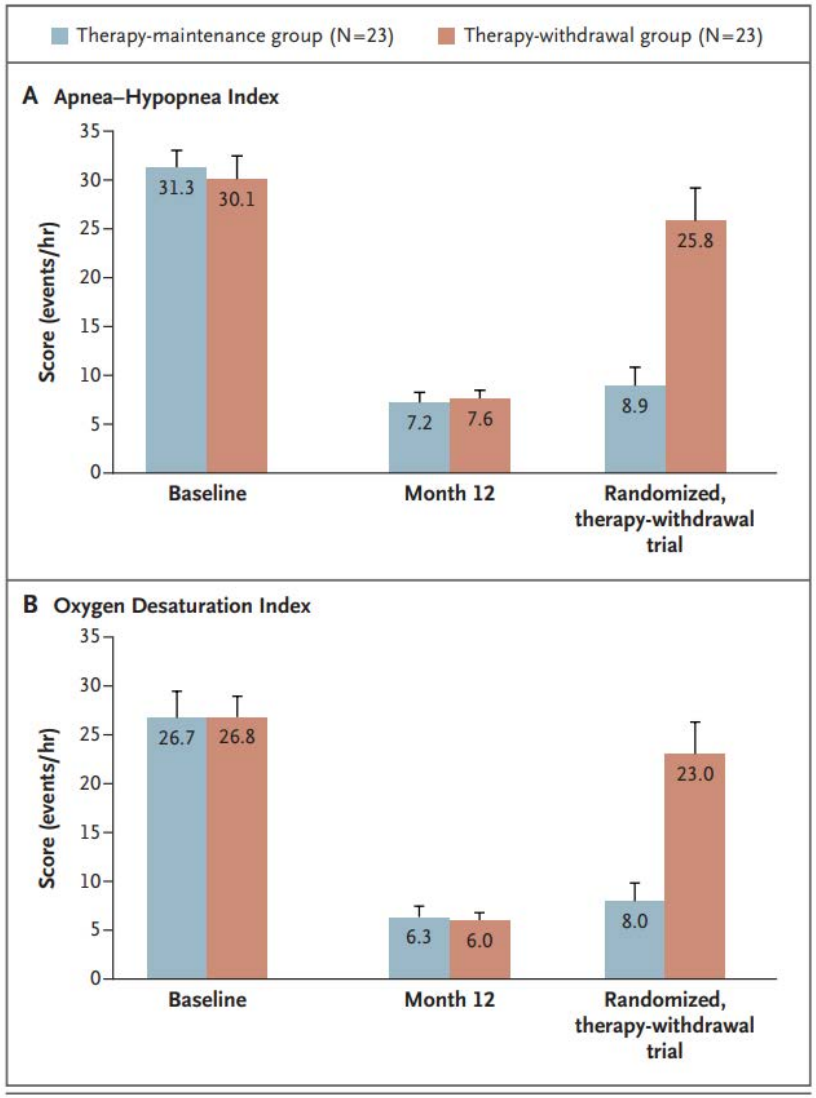
Patrick J. Strollo, Jr., M.D., Ryan J. Soose, M.D., Joachim T. Maurer, M.D., Nico de Vries, M.D., Jason Cornelius, M.D., Oleg Froymovich, M.D., Ronald D. Hanson, M.D., Tapan A. Padhya, M.D., David L. Steward, M.D., M. Boyd Gillespie, M.D., B. Tucker Woodson, M.D., Paul H. Van de Heyning, M.D., Ph.D., Mark G. Goetting, M.D., Olivier M. Vanderveken, M.D., Ph.D., Neil Feldman, M.D., Lennart Knaack, M.D., and Kingman P. Strohl, M.D., for the STAR Trial Group*

- Inclusion/Exclusion Criteria:
  - AHI 20-50
  - BMI <32
  - CPAP intolerance
  - <25% central/mixed apneas
  - Non-supine AHI >=10
  - DISE did not show complete concentric collapse
- 126 participants
  - 83% men
  - Mean age 54.5
  - Mean BMI 28.4
  - Median AHI 29.3

STAR Trial1-year Outcomes

Table 2. Primary and Secondary Outcome Measures.*

Outcome	Baseline	12 Months	Change	P Value
Primary outcomes				
AHI score†	32.0±11.8	15.3±16.1	−16.4±16.7	<0.001
Median	29.3	9.0	−17.3	
Interquartile range	23.7 to 38.6	4.2 to 22.5	−26.4 to −9.3	
ODI score‡	28.9±12.0	13.9±15.7	−14.6±15.8	<0.001
Median	25.4	7.4	−15.7	
Interquartile range	19.5 to 36.6	3.5 to 20.5	−24.0 to −8.6	
Secondary outcomes				
FOSQ score§	14.3±3.2	17.3±2.9	2.9±3.1	<0.001
Median	14.6	18.2	2.4	
Interquartile range	12.1 to 17.1	16.2 to 19.5	0.7 to 4.7	
Epworth Sleepiness Scale score¶	11.6±5.0	7.0±4.2	−4.7±5.0	<0.001
Median	11.0	6.0	−4.0	
Interquartile range	8.0 to 15.0	4.0 to 10.0	−8.0 to −1.0	
Percentage of sleep time with oxygen saturation <90%	8.7±10.2	5.9±12.4	−2.5±11.1	0.01
Median	5.4	0.9	−2.2	
Interquartile range	2.1 to 10.9	0.2 to 5.2	−6.6 to −0.3	



Strollo et al NEJM 2014

ADHERE Registry – Long Term Outcomes

Figure 1: Changes of Apnea Hypopnea Index (AHI) from Baseline to Post-Titration and Final Visit Results

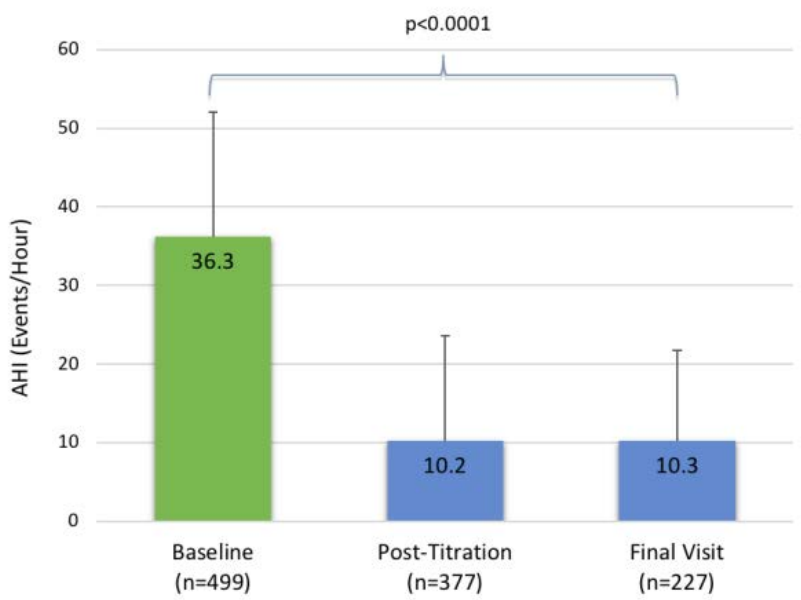
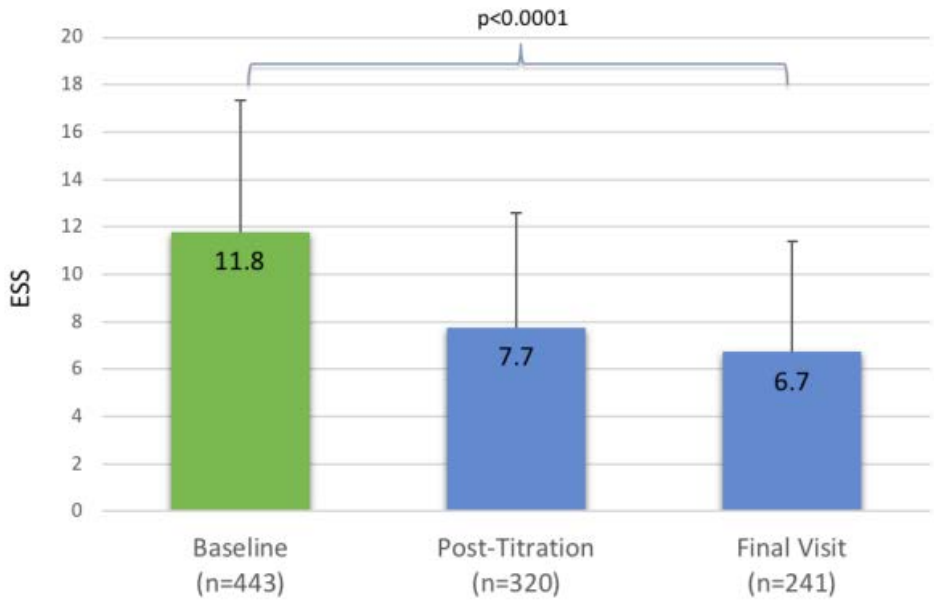


Figure 2: Changes of Epworth Sleepiness Scale (ESS) from Baseline to Post-Titration and Final Visit Results.



Heiser et al 2018 Eur Respir J

Similar response to HGNS in higher BMI group

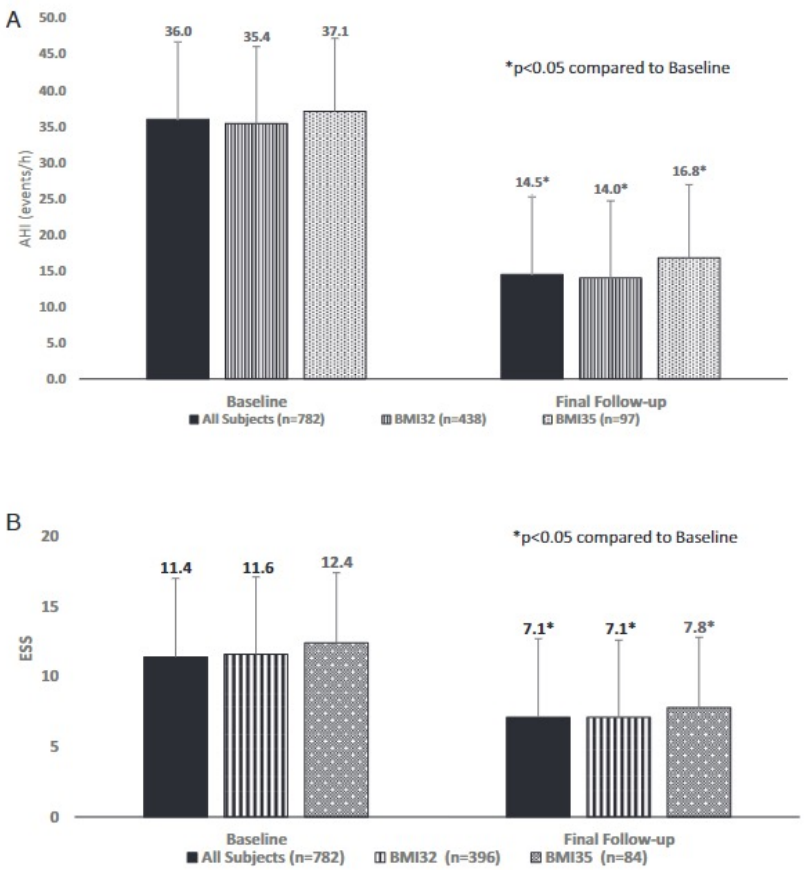
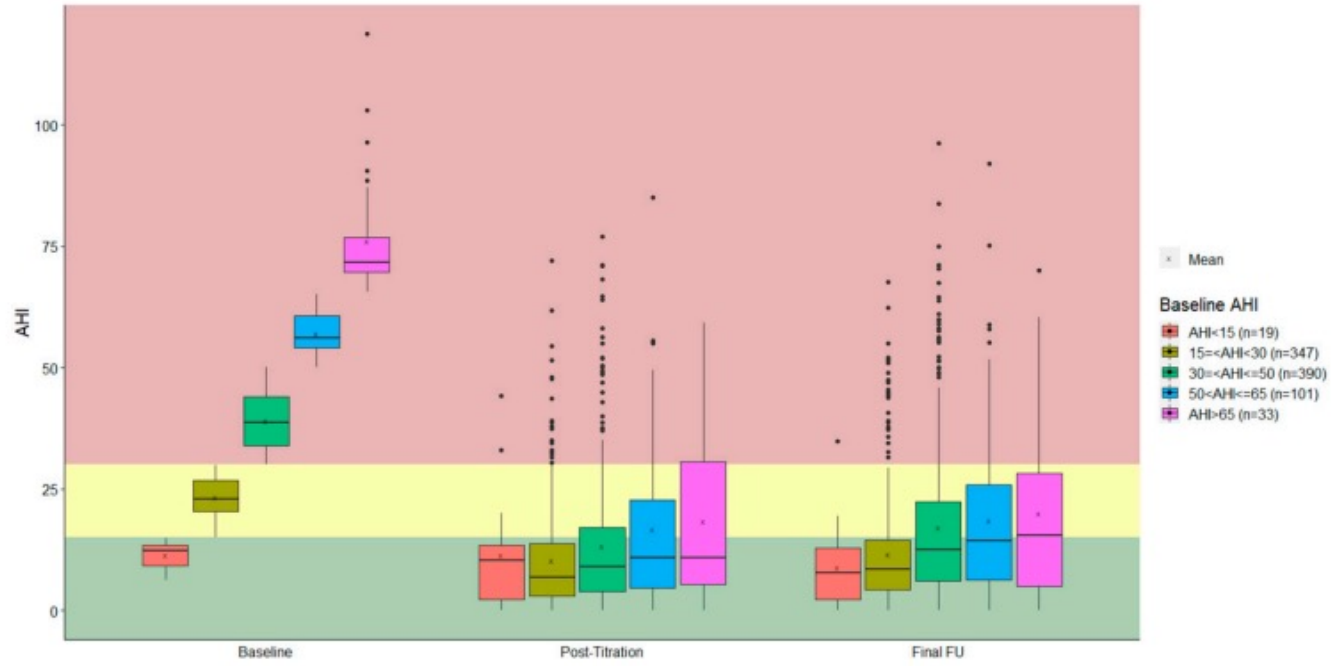


Fig. 2. A, Apnea hypopnea index (AHI) change over time (by body mass index [BMI] group); B, Epworth sleepiness scale (ESS) over time (by BMI group)

Suurna et al 2021 Laryngoscope

Similar effect of HGNS with varying disease severity

Figure 1—Therapy outcomes (AHI).



AHI = apnea-hypopnea index.

Bosschieter et al 2022 JCSM

Inspire Device – FDA approved 2014

FDA Approved Indications for HGNS

Adults >=18* yo

- Moderate to severe OSA
  (AHI >=15 and <=100)
- <25% Central + Mixed Sleep Apnea
- CPAP failure or inability to tolerate CPAP
- No complete concentric collapse at soft palate
- BMI <=40
- *Ages 18-21 if adenotonsillectomy contraindicated or ineffective
- Patients with Down Syndrome >12yo

Qualifying Criteria per Payors

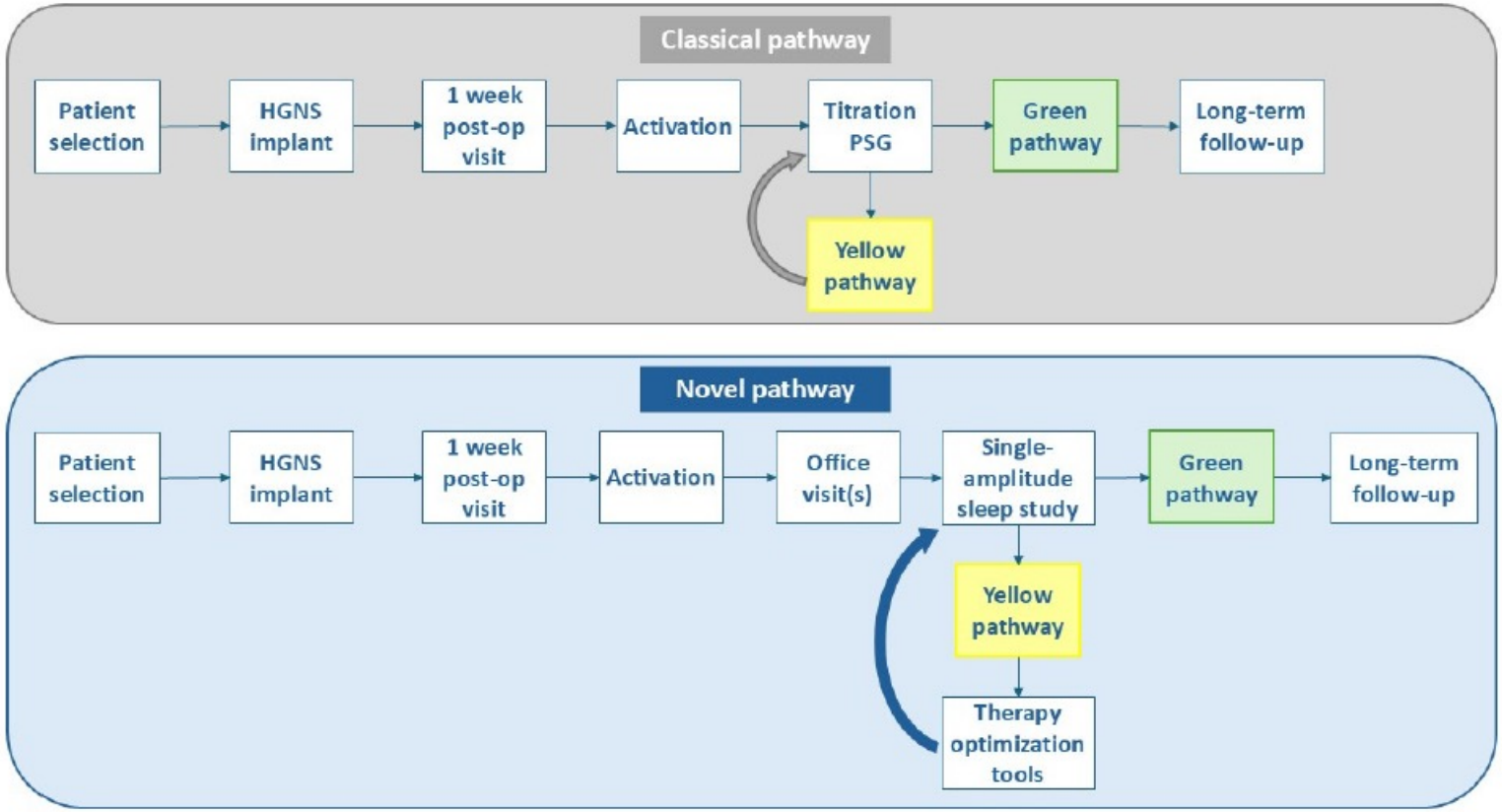
Adults >=22 yo

- Moderate to severe OSA
  (AHI >=15 and <=65) (AHI-4% CMS)
- <25% Central + Mixed Sleep Apnea
- CPAP failure or inability to tolerate CPAP
- No complete concentric collapse at soft palate
- BMI <=32 (<=35 CMS)

HGNS Pre-Implant Process

- Sleep consult
- ENT consult
- Diagnostic sleep study within past 24 months (ideally in-lab PSG)
- History of PAP intolerance or failure confirmed
- DISE (drug induced sleep endoscopy)
- Surgery
- Activation 1 month after surgical implant

Clinical Care Pathway for HGNS Therapy



Van Loo et al Journal Clin Med 2025

Factors Affecting HGNS Adherence

- Comfort:
  - Difficulty falling asleep or staying asleep during stimulation
  - Tongue being “grabbed” or “pulled”
  - Tongue abrasion
  - Dry mouth
- Sleep hygiene
- Management of comorbid sleep disorders
- ***Patient education, support and close clinical follow up***
- Remote/Connection Issues

Improving Outcomes with HGNS Therapy

- Review findings from in-lab titration
  - Consider HSAT if poor sleep efficiency or body position effect
- Electrode configuration change
- Consider positional therapy
- Retesting after any major therapy change
- Awake endoscopy with supplemental testing
- Advanced titration or “fine tuning” study
- Adjunctive therapy – weight loss, chinstrap or mouth tape, MAD, ENT surgery

Challenges to HGNS Therapy

- ❑ Patient selection
- ❑ Patient counseling (especially pre-implant)
- ❑ Defining treatment success
- ❑ Other factors that affect sleep
- ❑ Investment of time and effort (and $) for patients
- ❑ **May need combination/multimodal therapy**

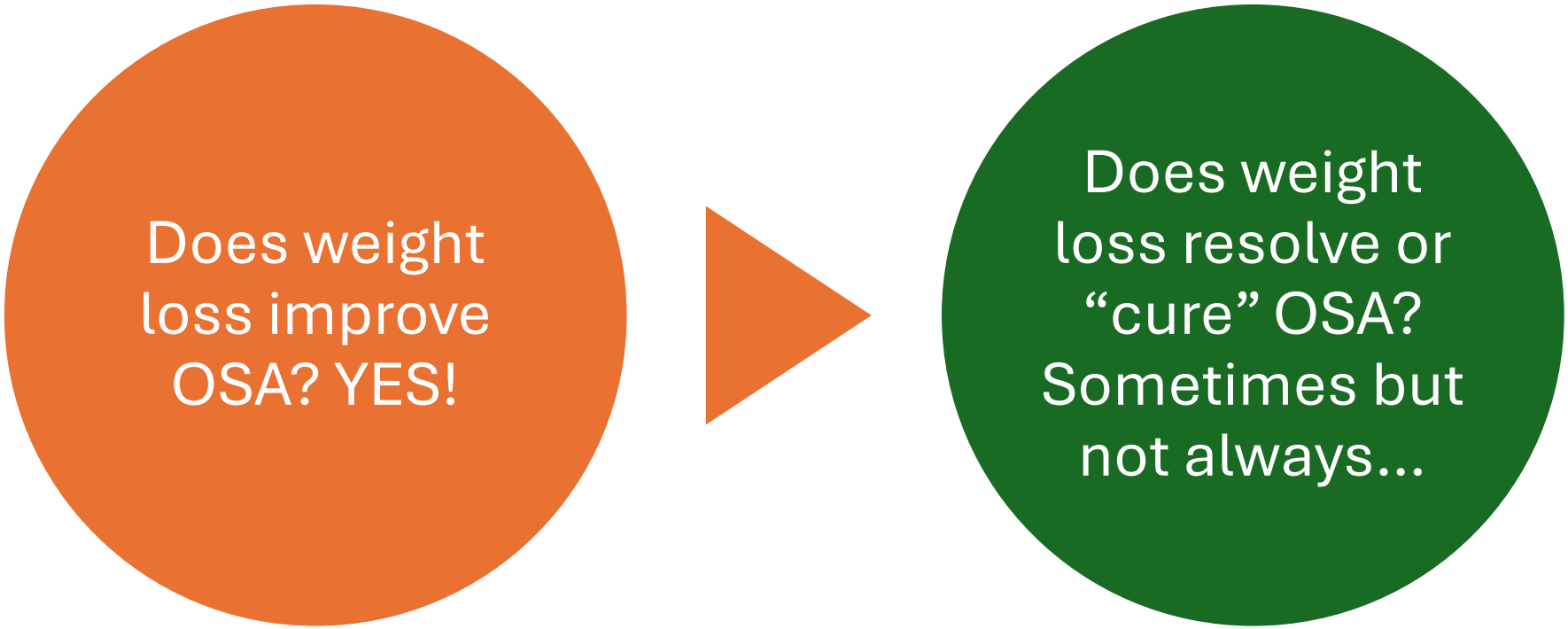
Keys to a Successful Program

- ✓ Collaboration between ENT and Sleep
- ✓ Managing expectations
- ✓ Patient education
- ✓ Patient navigator
- ✓ Long-term follow-up

Bilateral HGNS – FDA approved 8/2025

- DREAM Trial 2025:
  - 113 participants
  - Primary endpoints: reduction in AHI and ODI at 12 months
  - Similar inclusion/exclusion criteria to STAR trial
  - 63.5% with significant treatment response for both primary endpoints
  - Acceptable safety profile
- Genio System by Nyxoah – FDA approved in August 2025
  - Surgically inserted under the chin – unique surgical approach
  - Externally powered using disposable adhesive patch connected to external battery (activation chip) under the chin which is charged daily

Obesity is the greatest risk factor for OSA…



Effects of Surgical Weight Loss on OSA

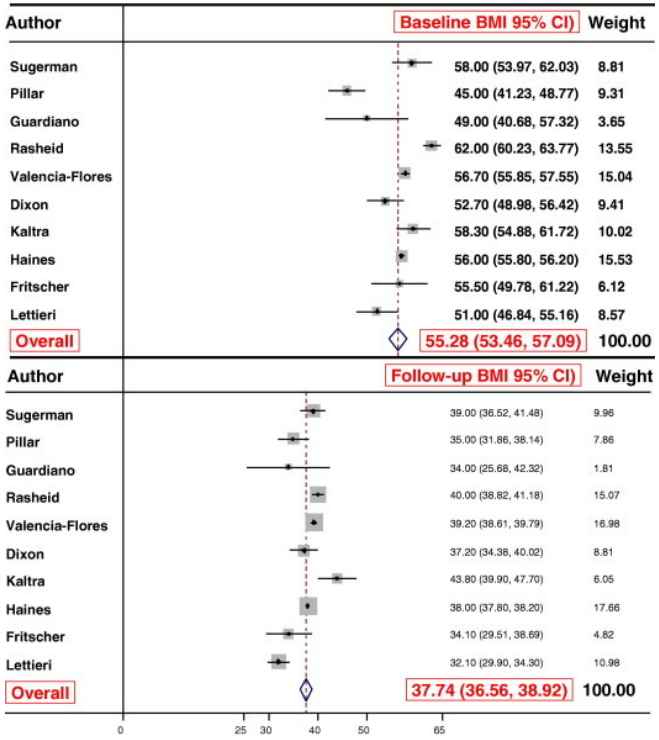


Figure 2. BMI at baseline and after bariatric surgery.; BMI = body mass index; CI = confidence interval.

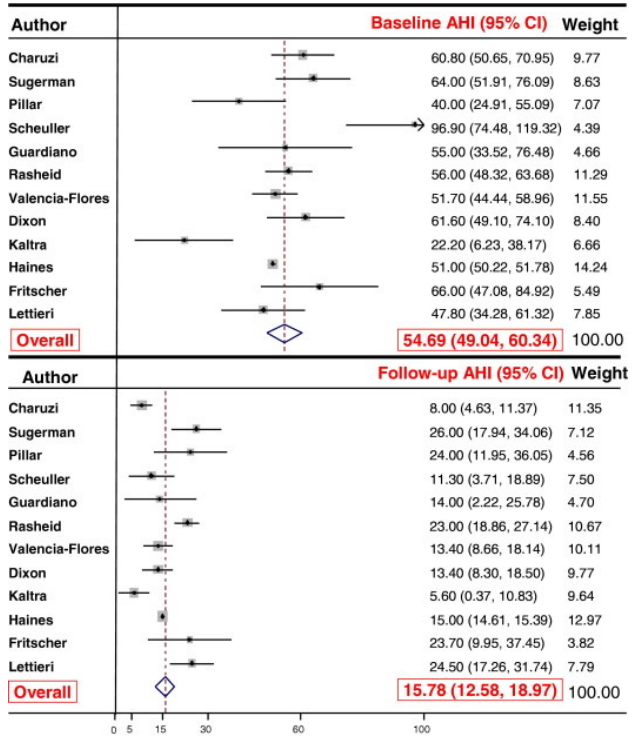


Figure 3. AHI at baseline and after bariatric surgery. AHI = apnea-hypopnea index; CI = confidence interval.

Greenburg et al Am J Med 2009

Impact of Bariatric Surgery on HGNS Outcomes

TABLE 2 | Comparing post-surgical outcomes between patients with and without a history of previous bariatric surgery.

Characteristic	N	Overall, N = 72[a]	No previous bariatric surgery, N = 48[a]	Previous bariatric surgery, N = 24[a]	p[b]
Post-op AHI	72	13.97 (15.18)	16.53 (17.39)	8.85 (7.26)	0.076
AHI change	72	−21.27 (20.28)	−17.68 (21.23)	−28.44 (16.39)	0.009
Post-op OSA Severity	72				0.053
Normal (AHI < 5)		20 (28%)	9 (19%)	11 (46%)	
Mild OSA (AHI 5–15)		30 (42%)	22 (46%)	8 (33%)	
Moderate OSA (AHI 15–30)		16 (22%)	11 (23%)	5 (21%)	
Severe OSA (AHI ≥ 30)		6 (8.3%)	6 (12%)	0 (0%)	
Post-op ESS	71	6.37 (4.46)	6.17 (4.63)	6.78 (4.17)	0.5
ESS change	69	−3.81 (4.39)	−3.44 (4.50)	−4.67 (4.08)	0.2
Post-op SpO2 nadir	72	83.06 (7.94)	82.86 (6.67)	83.48 (10.18)	0.2
Change in SpO2 nadir	71	4.16 (10.91)	3.42 (8.79)	5.72 (14.50)	0.4
Post-op BMI	72	29.98 (4.20)	29.59 (3.96)	30.77 (4.62)	0.4
BMI change	72	−0.28 (2.71)	−0.22 (2.29)	−0.42 (3.46)	0.2
Sher15 treatment response	72	44 (61%)	27 (56%)	17 (71%)	0.2

[a]Mean (SD); *n* (%).
[b]Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test.

Retrospective study of 72 patients with HGNS

Bariatric surgery group had greater reduction in AHI even when adjusting for baseline BMI, AHI, age and sex

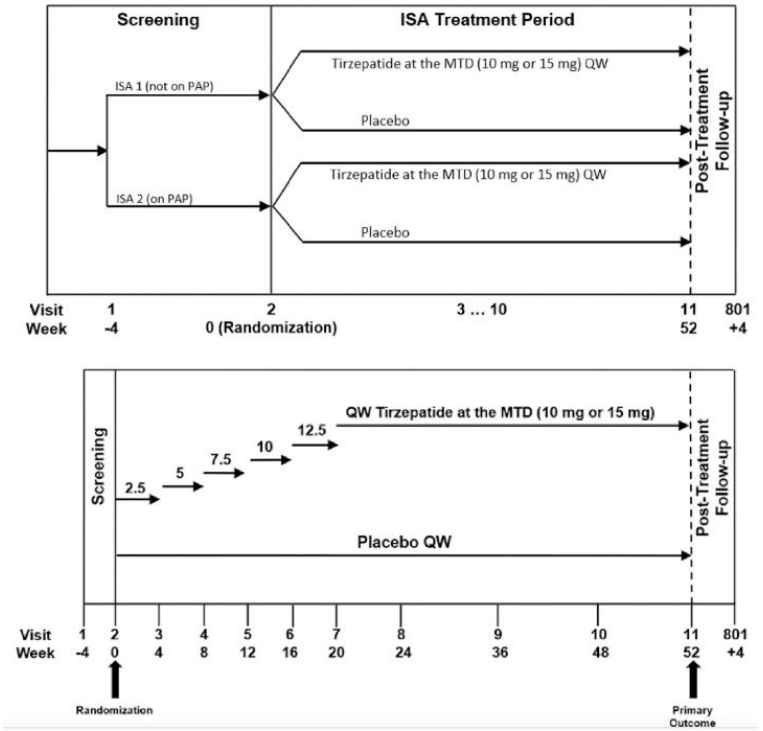
Reduction in AHI after weight loss largely mediated by loss of tongue fat

Increased compensatory upper airway muscle activation/tone may persist in patients with previous severe obesity

Kaki et al The Laryngoscope 2025

SURMOUNT-OSA: Tirzepatide for OSA

- Randomized, parallel-arm, double-blind, placebo-controlled phase 3 trial
- Aim: Evaluate the efficacy and safety of tirzepatide at maximum tolerated dose (10 or 15mg) vs placebo in patients with obesity (BMI >=30) and moderate to severe OSA (AHI>=15).
- Randomized 1:1 placebo vs tirzepatide
- Primary outcome: change in AHI at 52 weeks
- Trial 1: 234 patients not on PAP
- Trial 2: 235 patients on PAP



Malhotra et al NEJM 2024

Mean age: 48yo
33% female
Mean BMI 39
Mean AHI 51.5
Mean ESS 10.6

Trial 1: no PAP **Trial 2: PAP**

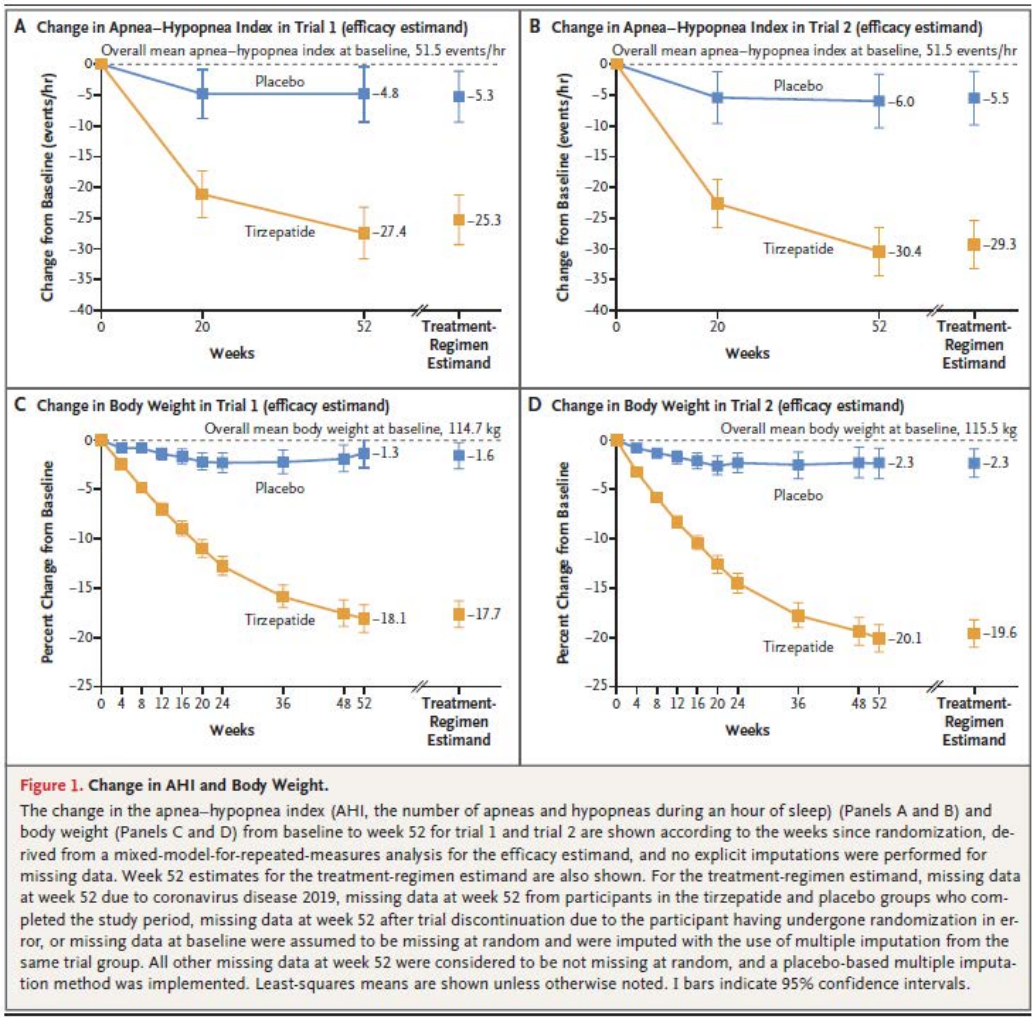


Figure 1. Change in AHI and Body Weight.

The change in the apnea–hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep) (Panels A and B) and body weight (Panels C and D) from baseline to week 52 for trial 1 and trial 2 are shown according to the weeks since randomization, derived from a mixed-model-for-repeated-measures analysis for the efficacy estimand, and no explicit imputations were performed for missing data. Week 52 estimates for the treatment-regimen estimand are also shown. For the treatment-regimen estimand, missing data at week 52 due to coronavirus disease 2019, missing data at week 52 from participants in the tirzepatide and placebo groups who completed the study period, missing data at week 52 after trial discontinuation due to the participant having undergone randomization in error, or missing data at baseline were assumed to be missing at random and were imputed with the use of multiple imputation from the same trial group. All other missing data at week 52 were considered to be not missing at random, and a placebo-based multiple imputation method was implemented. Least-squares means are shown unless otherwise noted. I bars indicate 95% confidence intervals.

Mean age: 52yo
28% female
Mean BMI 39
Mean AHI 49.5
Mean ESS 10.2

Effect of tirzepatide on reducing AHI attributed to weight loss

Malhotra et al NEJM 2024

Can’t I just take a pill to treat my OSA?

Pharmacological Therapy

- Zepbound (tirzepatide) **FDA-approved** for moderate to severe OSA in obese patients
- 2023 MARIPOSA Trial: combination of aroxybutynin (antimuscarinic) and atomoxetine (noradrenergic)
  - AHI-4% reduced by 45% vs placebo over 1-month treatment period
  - 44% of participants had >50% reduction in AHI-4%
  - 42% of participants had AHI-4% <10 after treatment
- 2018 PACE Trial: dronabinol (no change in AHI, 6 patients potential “responders”)
- Wake-promoting drugs – real-world effectiveness and tolerability contrasts with RCT’s
  - Modafinil
  - Armodafinil
  - Solriamfetol

Schweitzer et al AJRCCM 2023
Carley et al Sleep 2018
Roberts et al JCSM 2026

Daytime NMES

- Daily transoral NMES device (ExciteOSA)
- 65 participants (68% male) with mild OSA
  - 6 weeks of daily therapy x 20 min
  - AHI reduced from 10.2 to 6.8 among all participants
  - AHI reduced from 10.4 to 5.0 in responders
  - Adherence 85%
  - Improvements in ESS, PSQI, snoring
- FDA approved for mild OSA and primary snoring
- Insurance coverage varies – cost is issue

Fig. 2 The exciteOSA device as well as associated application interface

Nokes et al Sleep Breath 2023

Take Home Points

- OSA is NOT a “one size fits all” sleep disorder.
- CPAP is the most effective therapy for OSA and should be considered in all patients diagnosed with OSA…but CPAP is not the ONLY therapy for OSA.
- Referral to a sleep specialist is recommended for PAP intolerant patients and/or patients with more severe or complex sleep disordered breathing.
- Multimodal therapy should be anticipated in more complicated patients, especially PAP intolerant patients
- Management of OSA is often multidisciplinary (ENT, dentist, PCP, endocrinologist, psych)
- Managing expectations and patient education are KEY components of any successful OSA treatment.

Thank you!

Questions?
Please contact me at swappel@gbmc.org