Treatment of Obstructive Sleep Apnea in 2026

Atul Malhotra, MD
Vice Chair of Medicine for Research Peter C. Farrell Presidential Chair and Tenured
Professor of Respiratory Medicine
President American Thoracic Society (2015-2016)
University of California San Diego, La Jolla, CA, USA

18th Annual Sleep Medicine CME Course

Conflict of Interest Disclosures for Speakers

Eli Lilly, Livanova, Zoll, Powell Mansfield; ResMed philanthropic to UCSD

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UCLA 2026

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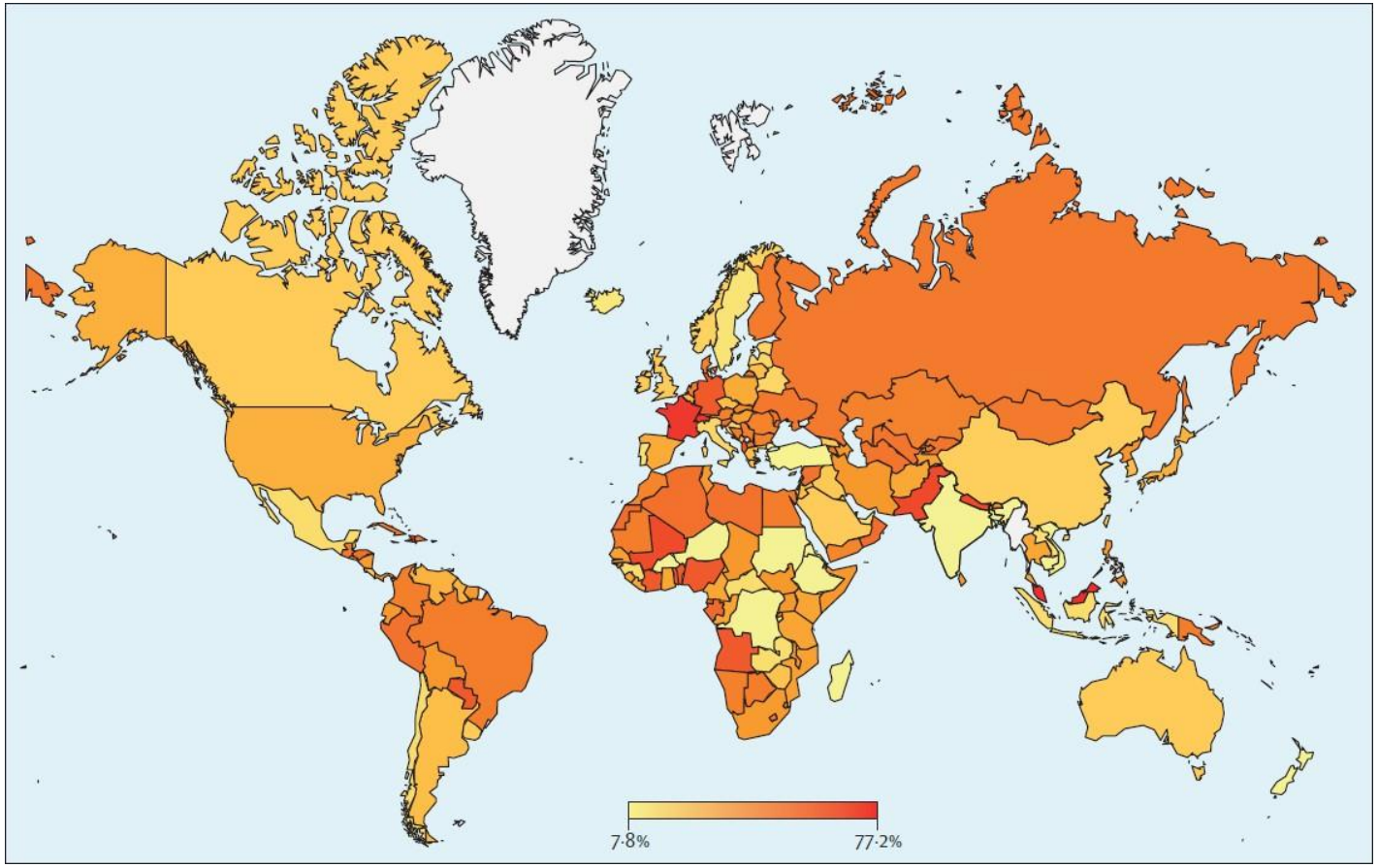
Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis

Adam V Benjafield, Najib T Ayas, Peter R Eastwood, Raphael Heinzer, Mary S M Ip, Mary J Morrell, Carlos M Nunez, Sanjay R Patel, Thomas Penzel, Jean-Louis D Pépin, Paul E Peppard, Sanjeev Sinha, Sergio Tufik, Kate Valentine, Atul Malhotra

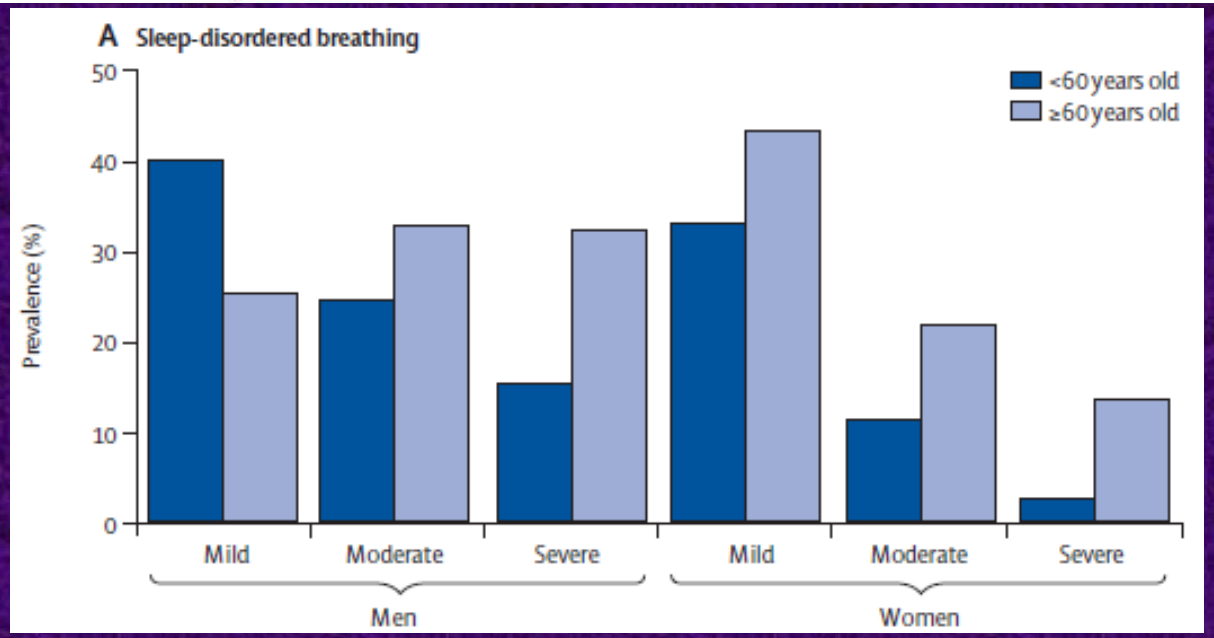
AHI ≥ 5
936,360,689



Lancet Respiratory Medicine 2019

Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study

R Heinzer, S Vat, P Marques-Vidal, H Marti-Soler, D Andries, N Tobback, V Mooser, M Preisig, A Malhotra, G Waeber, P Vollenweider, M Tafti,* J Haba-Rubio*



Lancet Respiratory Medicine 2015

(7·2–27·1) in men. The prevalence of moderate-to-severe sleep-disordered breathing (≥15 events per h) was 23·4% (95% CI 20·9–26·0) in women and 49·7% (46·6–52·8) in men. After multivariable adjustment, the upper quartile

Multivariate: AHI predicts HTN, DM, depression

Concept: OSA is highly prevalent, but not all are likely to get cardiovascular benefit from CPAP

NIH Funding (author)

Projecting the 30-year burden of obstructive sleep apnoea in the USA: a prospective modelling study

Elroy Boers, Meredith A Barrett, Adam V Benjafield, Jodi H Barnet, Laurel A Ravelo, Leanne Kaye, Peter A Cistulli, Jean-Louis Pépin, Jeff Armitstead, Kimberly L Sterling, Carlos M Nunez, Paul E Peppard, Atul Malhotra

Summary

Background Obstructive sleep apnoea is a common disorder that is associated with major public health and economic burden across the USA. Previous studies have assessed the prevalence of the condition. In the present study, we aimed to estimate the burden of obstructive sleep apnoea across the USA from 2020 to 2050, to guide public health policies and management pathways.

Lancet Respir Med 2025
Published Online
August 26, 2025
https://doi.org/10.1016/S2213-2600(25)00243-7

OSA prevalence is increasing particularly in women
GLP1RA have some effect but not major at a population level

OSA will increase 34.7% to 76.6 million cases

Females will increase 65.4% while males projected to increase 19.3%

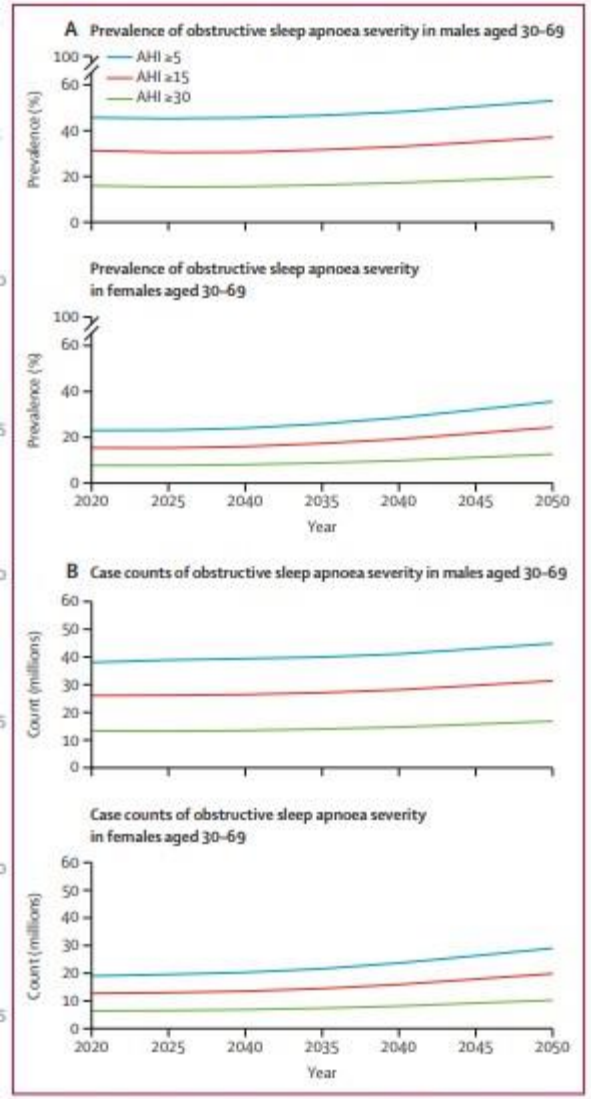
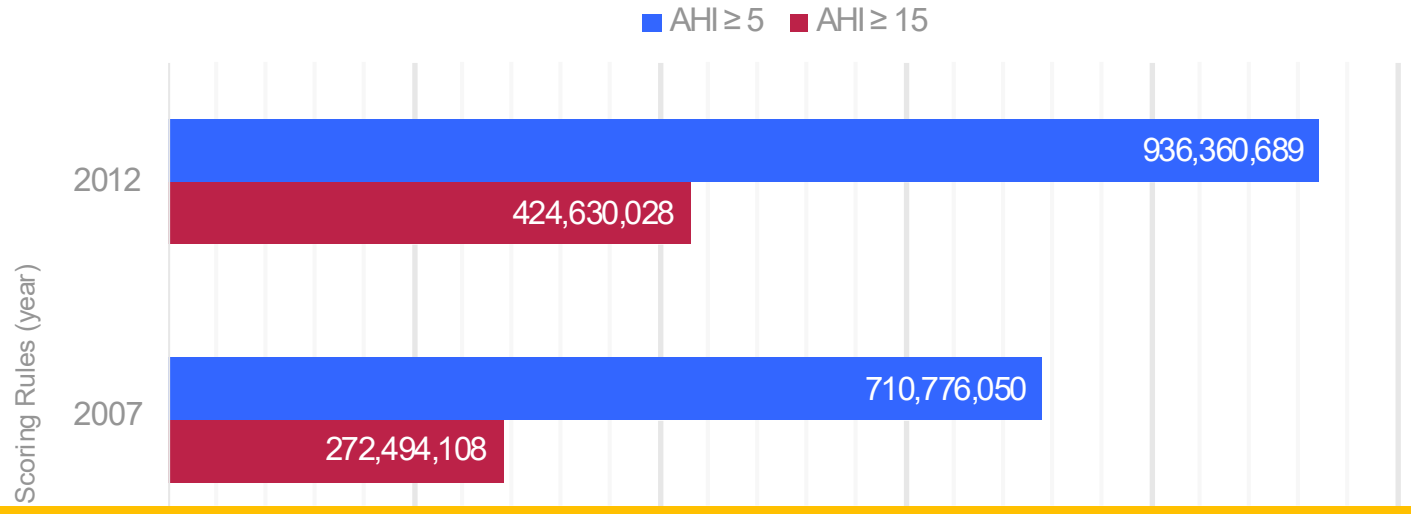


Figure 2: Projected prevalence and number of obstructive sleep apnoea cases (in millions) in the USA from 2020 to 2050, stratified by AHI severity, assuming the introduction of GLP-1 therapy
AHI=apnoea–hypopnoea index. GLP-1=glucagon-like peptide-1.

Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis

Adam V Benjafield, Najib T Ayas, Peter R Eastwood, Raphael Heinzer, Mary S M Ip, Mary J Morrell, Carlos M Nunez, Sanjay R Patel, Thomas Penzel, Jean-Louis D Pépin, Paul E Peppard, Sanjeev Sinha, Sergio Tufik, Kate Valentine, Atul Malhotra

Results – Scoring Rule Impact



Take Home:
OSA affects up to 1 billion people. Numbers vary with scoring criteria and equipment but we need to think how to address this global burden

ORIGINAL ARTICLE

CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea

R. Doug McEvoy, M.D., Nick A. Antic, M.D., Ph.D., Emma Heeley, Ph.D., Yuanming Luo, M.D., Qiong Ou, M.D., Xilong Zhang, M.D., Olga Mediano, M.D., Rui Chen, M.D., Luciano F. Drager, M.D., Ph.D., Zhihong Liu, M.D., Ph.D., Guofang Chen, M.D., Baoliang Du, M.D., Nigel McArdle, M.D., Sutapa Mukherjee, M.D., Ph.D., Manjari Tripathi, M.D., Laurent Billot, M.Sc., Qiang Li, M.Biostat., Geraldo Lorenzi-Filho, M.D., Ferran Barbe, M.D., Susan Redline, M.D., M.P.H., Jiguang Wang, M.D., Ph.D., Hisatomi Arima, M.D., Ph.D., Bruce Neal, M.D., Ph.D., David P. White, M.D., Ron R. Grunstein, M.D., Ph.D., Nanshan Zhong, M.D., and Craig S. Anderson, M.D., Ph.D., for the SAVE Investigators and Coordinators*

Therapy with CPAP plus usual care, as compared with usual care alone, did not prevent cardiovascular events in patients with moderate-to-severe obstructive sleep apnea and established cardiovascular disease. (Funded by the National Health and Medical Re-

NEJM 2016

ORIGINAL ARTICLE

CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea

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Need better therapies/adherence
Need to identify high risk patients better
Need more basic research re: mechanisms
Need to treat the underlying cause?

Therapy with CPAP plus usual care, as compared with usual care alone, did not prevent cardiovascular events in patients with moderate-to-severe obstructive sleep apnea and established cardiovascular disease. (Funded by the National Health and Medical Re-

NEJM 2016

Therapeutic Approaches in OSA

1. CPAP to hold airway open

   -oral appliance, upper airway surgery

2. Treat underlying cause based on mechanism

   -weight loss, promoting UA muscle tone, lowering loop gain etc

3. Treatments to facilitate PAP therapy

   - Hypnotics Schmickl et al. AJRCCM 2020; Lettieri et al. Annals IM 2009
   - Nasal patency Weaver et al.

4. Treatments to improve symptoms in OSA

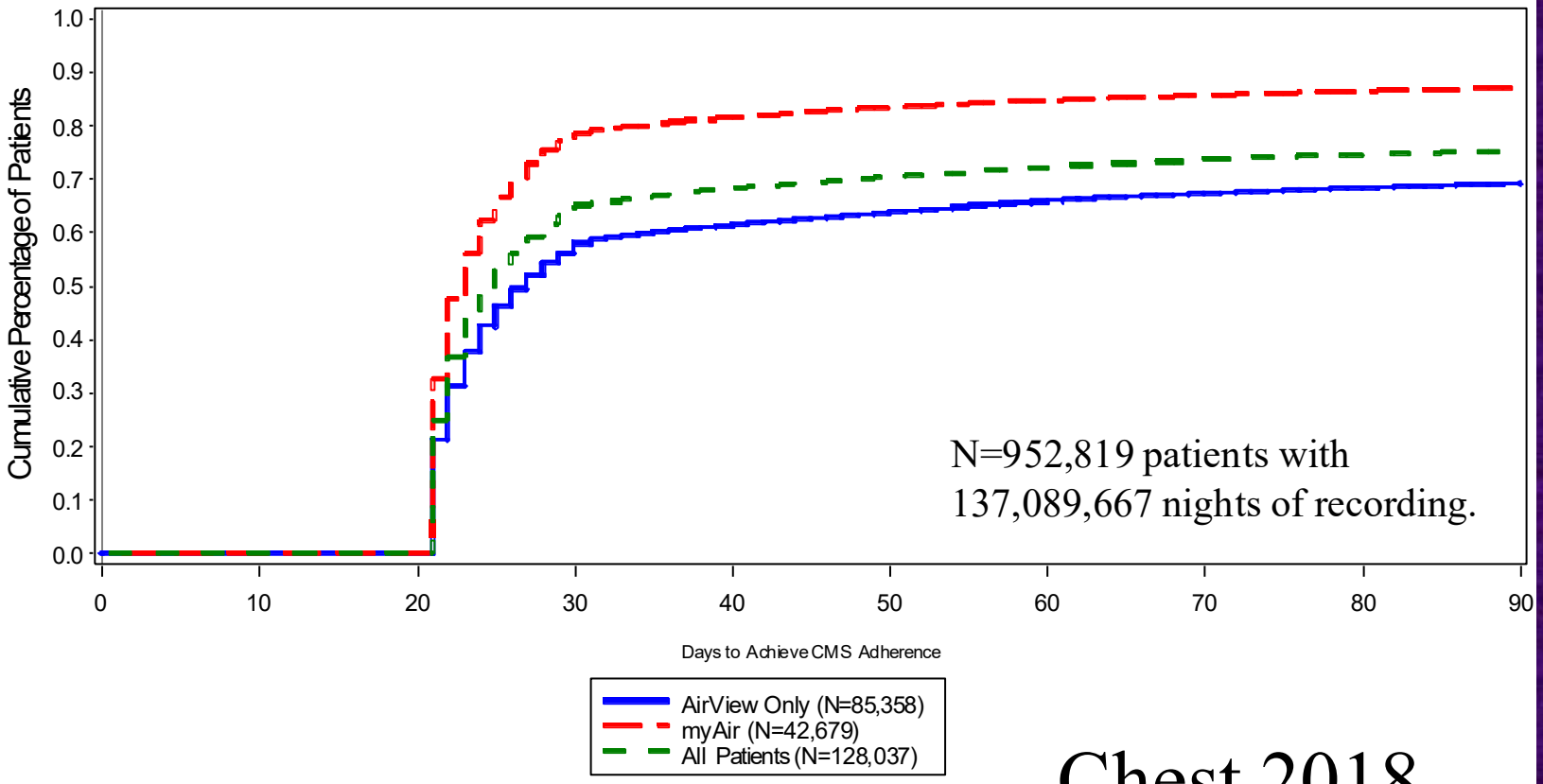
   -Solriamfetol JCSM 2022, AJRCCM 2019, Steier et al. Sleep Med 2023

5. Treatments to block complications of OSA

Patient Engagement Using New Technology to Improve Adherence to Positive Airway Pressure Therapy

A Retrospective Analysis

Atul Malhotra, MD; Maureen E. Crocker, BS; Leslee Willes, MS; Colleen Kelly, PhD; Sue Lynch, RN; and Adam V. Benjafield, PhD



Chest 2018

Version:24JUN16:13:12:06

Sleep Medicine 59 (2019) 114–116

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Brief Communication

Short-term CPAP adherence in obstructive sleep apnea: a big data analysis using real world data

Peter A. Cistulli [a, g, *], Jeff Armitstead [b, g], Jean-Louis Pepin [c, g], Holger Woehrle [d, g], Carlos M. Nunez [e, g], Adam Benjafield [e, g], Atul Malhotra [f, g]

Table 1
Adherence data from the first 90 days of therapy.

Adherence measures	Values (n = 2,621,182) Median (IQR)[a]
CMS compliance in first 90 days, n (%)	1,955,961 (74.6)
Time to achieve CMS compliance, days	23.00 (21.00, 27.00)
Device usage, h/session	6.18 (4.79, 7.35)
Daily usage (all days), h/night	5.54 (3.42, 7.84)
Proportion of days with non-zero usage, %	93.3 (72.2, 98.9)
Proportion of days compliant (usage ≥ 4 h/night), %	80.0 (46.7, 95.6)

CMS, Center for Medicare and Medicaid Services; IQR, interquartile range; SD, standard deviation. CMS Compliance definition: ≥4 hours' PAP use on 70% of nights in a consecutive 30-day period in the first 90 days of therapy.

medXcloud

J Clin Sleep Med. 2021 Apr 1;17(4):703-709. doi: 10.5664/jcsm.9008.

Adherence with positive airway pressure therapy for obstructive sleep apnea in developing vs. developed countries: a big data study

Luciano F Drager [1 2], Atul Malhotra [3], Yang Yan [4], Jean-Louis Pépin [5 6], Jeff P Armitstead [7], Holger Woehrle [8], Carlos M Nunez [9], Peter A Cistulli [10 11], Adam V Benjafield [7], medXcloud group

N= 4,132,884 US; 31,672 Brazil; 16,394 Mexico

Adherence74% in US, 71.7% Brazil vs. 66.4% Mexico, Patient engagement tools were assoc with 2x benefit and grossly underutilized

80% of patients meeting CMS criteria were using at 1 yr

CPAP benefits HFpEF, HFrEF, DM, AF, HCRU, COPD etc

Journal of the American Heart Association

ORIGINAL RESEARCH

Positive Airway Pressure Adherence and Health Care Resource Utilization in Patients With Obstructive Sleep Apnea and Heart Failure With Reduced Ejection Fraction

Atul Malhotra, MD; Kate V. Cole, MS; Anita S. Malik, PhD; Jean-Louis Pépin, MD; Fatima H. Sert Kuniyoshi, PhD; Peter A. Cistulli, MD, PhD; Adam V. Benjafield, PhD; Virend K. Somers, MD, PhD; on behalf of the medXcloud group*

Journal of the American Heart Association
Volume 12, Issue 14, 18 July 2023
https://doi.org/10.1161/JAHA.122.028733

ORIGINAL RESEARCH

Positive Airway Pressure Therapy Adherence and Health Care Resource Use in Patients With Obstructive Sleep Apnea and Heart Failure With Preserved Ejection Fraction

Peter A. Cistulli, MD, PhD; Atul Malhotra, MD; Kate V. Cole, MS; Anita S. Malik, PhD; Jean-Louis Pépin, MD; Fatima H. Sert Kuniyoshi, PhD; Adam V. Benjafield, PhD; Virend K. Somers, MD, PhD

Check for updates

ORIGINAL RESEARCH

Dose-Response Relationship between Obstructive Sleep Apnea Therapy Adherence and Healthcare Utilization

Atul Malhotra[1], Kimberly L. Sterling[2], Peter A. Cistulli[3], Jean-Louis Pépin[4], Jiaming Chen[2], Caleb Woodford[5], Naomi Alpert[2], Suyog More[5], Carlos M. Nunez[2], and Adam V. Benjafield[6]; on behalf of the medXcloud Group

[1]University of California, San Diego, La Jolla, California; [2]ResMed Science Center, San Diego, California; [3]Charles Perkins Centre and Faculty of Medicine and Health, University of Sydney, Sydney, Australia; [4]HP2 Laboratory (Hypoxia: Pathophysiology), Grenoble Alpes University, Grenoble, France; [5]ResMed Science Center, Halifax, Nova Scotia, Canada; and [6]ResMed Science Center, Sydney, Australia

ORIGINAL ARTICLE

Impact of Positive Airway Pressure Therapy Adherence on Outcomes in Patients with Obstructive Sleep Apnea and Chronic Obstructive Pulmonary Disease

Kimberly L. Sterling[1], Jean-Louis Pépin[2], Walter Linde-Zwirble[3], Jiaming Chen[1], Adam V. Benjafield[4], Peter A. Cistulli[5], Kate V. Cole[1], Hussein Emami[1], Caleb Woodford[6], Jeff P. Armitstead[4], Carlos M. Nunez[1], Jadwiga A. Wedzicha[7], and Atul Malhotra[8]; on behalf of the medXcloud group

American Journal of RESPIRATORY AND CRITICAL CARE MEDICINE
ATS. We help the world breathe
www.thoracic.org

Annals ATS 2023 and JAHA 2023a; 2023b

medXcloud

Positive airway pressure therapy and all-cause and cardiovascular mortality in people with obstructive sleep apnoea: a systematic review and meta-analysis of randomised controlled trials and confounder-adjusted, non-randomised controlled studies

Adam V Benjafield, Jean-Louis Pepin, Peter A Cistulli, Alison Wimms, Florent Lavergne, Fatima H Sert Kuniyoshi, Sibyl H Munson, Brendan Schuler, Shrikar Reddy Badikol, Kelly C Wolfe, Leslee Willes, Colleen Kelly, Tetyana Kendzerska, Dayna A Johnson, Raphael Heinzer, Chi-Hang Lee, Atul Malhotra, on behalf of the medXcloud Group

Lancet Respir Med 2025
Published Online March 18, 2025
https://doi.org/10.1016/S2213-2600(25)00002-5

Summary

Background Data regarding the effect of positive airway pressure (PAP) therapy for obstructive sleep apnoea (OSA) on

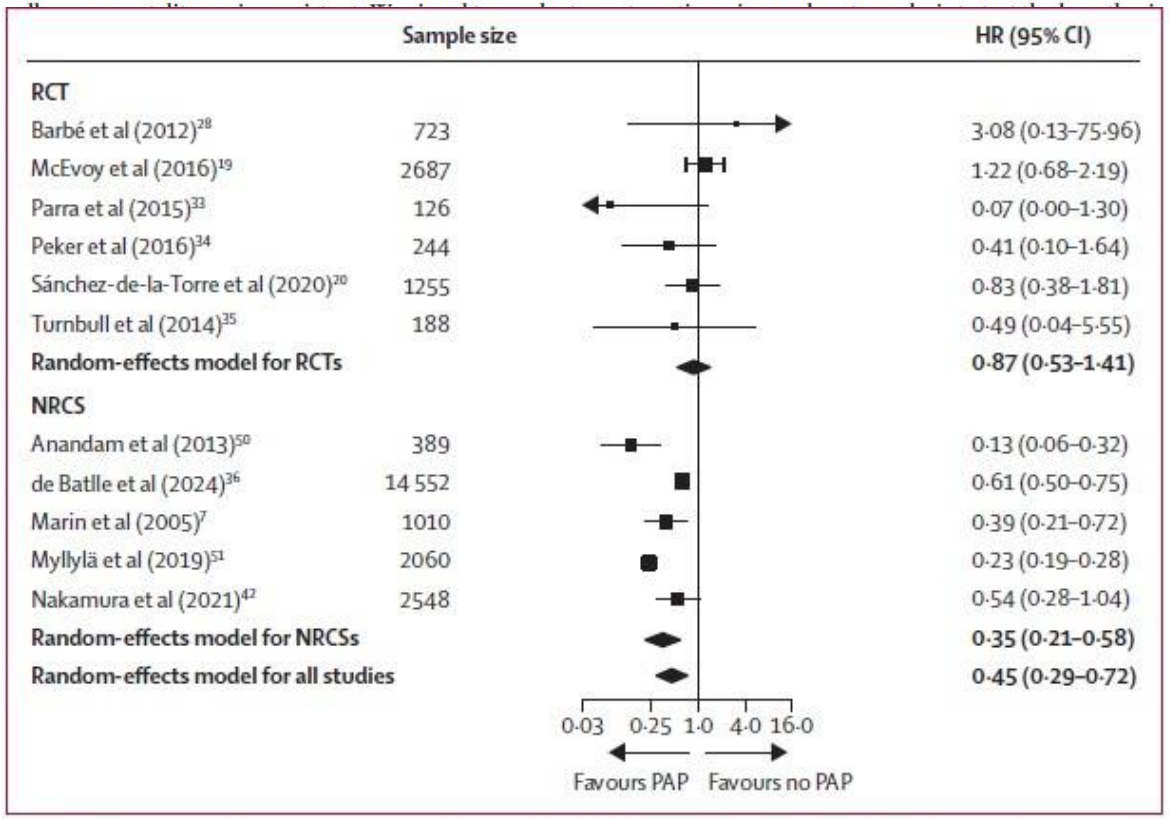


Figure 3: Forest plot showing the risk of cardiovascular death in the PAP *vs* no PAP therapy groups

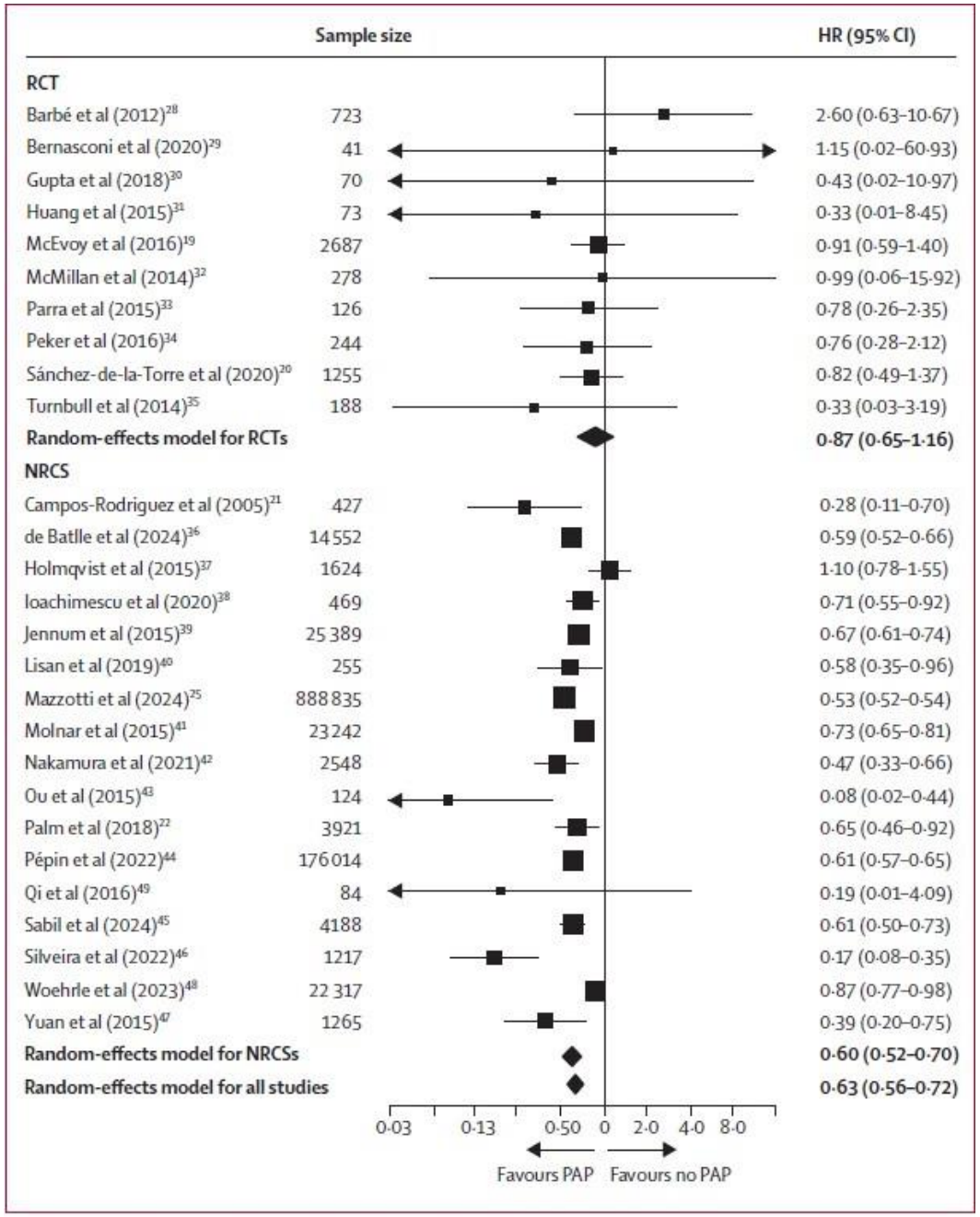


Figure 2: Forest plot showing the risk of all-cause death in the PAP *vs* no PAP therapy groups

Nasal CPAP is The First Line Treatment for OSA

- Improves symptoms
- Improves blood pressure
- Transformative for some patients
- A defeatist attitude towards CPAP is not justifiable

- Need new therapies based on ongoing research

Therapeutic Approaches in OSA

1. CPAP to hold airway open

   -oral appliance, upper airway surgery

2. Treat underlying cause based on mechanism

   -weight loss, promoting UA muscle tone, lowering loop gain etc

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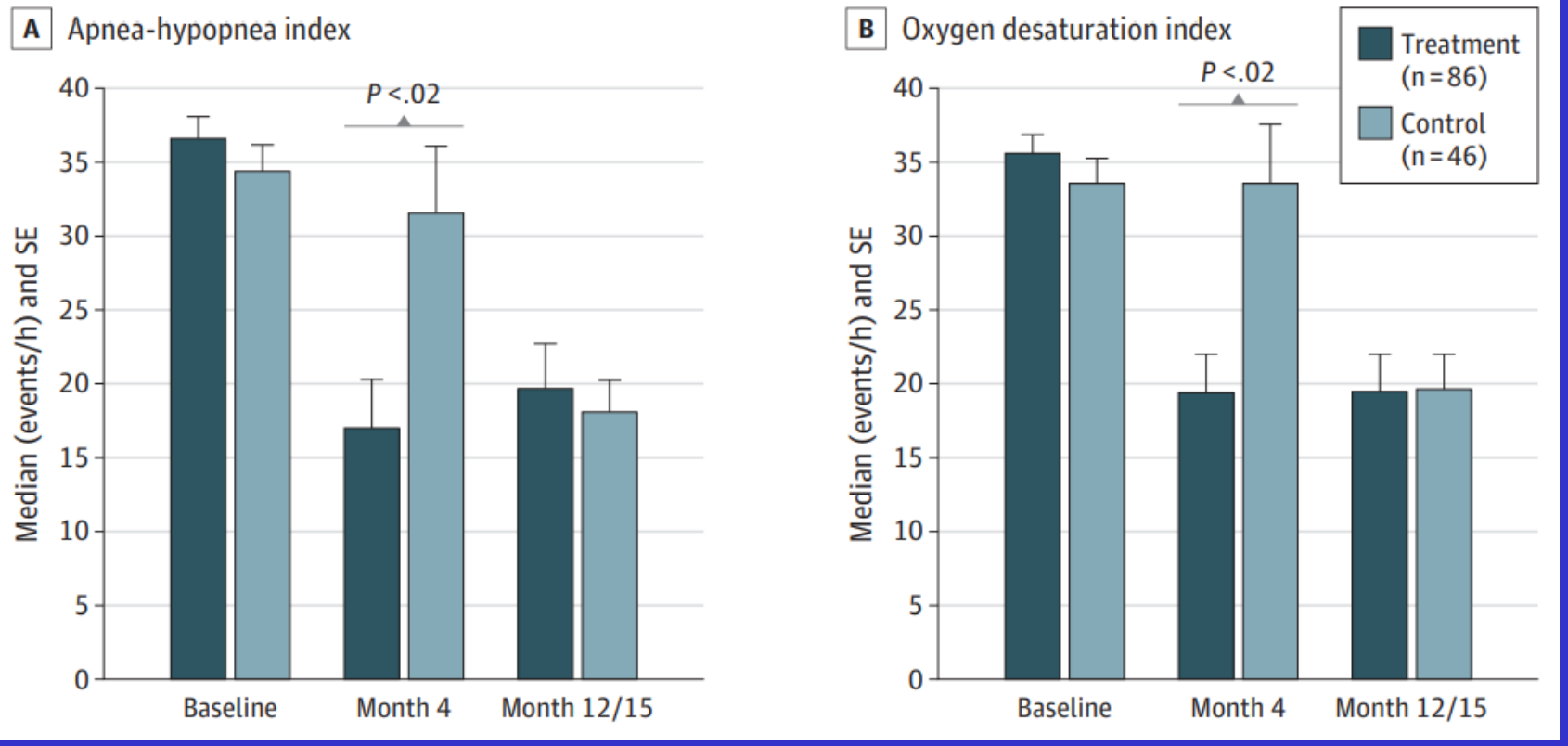
5. Treatments to block complications of OSA

JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Targeted Hypoglossal Nerve Stimulation for Patients With Obstructive Sleep Apnea
A Randomized Clinical Trial

Alan R. Schwartz, MD; Ofer Jacobowitz, MD, PhD; David W. Eisele, MD; Samuel A. Mickelson, MD; Mitchell B. Miller, MD; Arie Oliven, MD; Victor Certal, MD, PhD; Martin L. Hopp, MD, PhD; David H. Winslow, MD; Tod C. Huntley, MD; Nathan E. Nachlas, MD; Luu V. Pham, MD; M. Boyd Gillespie, MD; Brian H. Weeks, MD; Eric G. Lovett, PhD; John Shen, MS; Atul Malhotra, MD; Joachim T. Maurer, MD



JAMA ENT 2024

Proximal Hypoglossal Nerve Stimulation Improves Sleep-Disordered Breathing in Obstructive Sleep Apnea: The OSPREY Randomized, Controlled Trial

Atul Malhotra MD, Alan R Schwartz MD, Richard K. Bogan MD, Shaun A. Nguyen MD, Samuel A. Mickelson MD, Jose Barrera MD, Mitchell B. Miller MD, Neerav Goyal MD, Haresh Boghara MD, Paul Schalch MD, Deborah A. Goss MD, Randall A. Ow MD, John Webb MS, Nadine Juran RN, Eric G. Lovett PhD, Ofer Jacobowitz MD PhD

ATS 2025 San Francisco May 16-21

Annals of Internal Medicine in revision

Contemporary Clinical Trials 119 (2022) 106804

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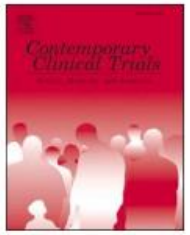
Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial



Check for updates

Design and rationale for the treating Obstructive Sleep Apnea using Targeted Hypoglossal Nerve Stimulation (OSPREY) trial

Ofer Jacobowitz [a,*], Alan R. Schwartz [b], Eric G. Lovett [c], Giovanni Ranuzzi [d], Atul Malhotra [e]

LivaNova
Health innovation that matters

About Us | News & Events | Investors | Therapeutic Areas

LivaNova Announces OSPREY Clinical Study Meets Primary Safety and Efficacy Endpoints

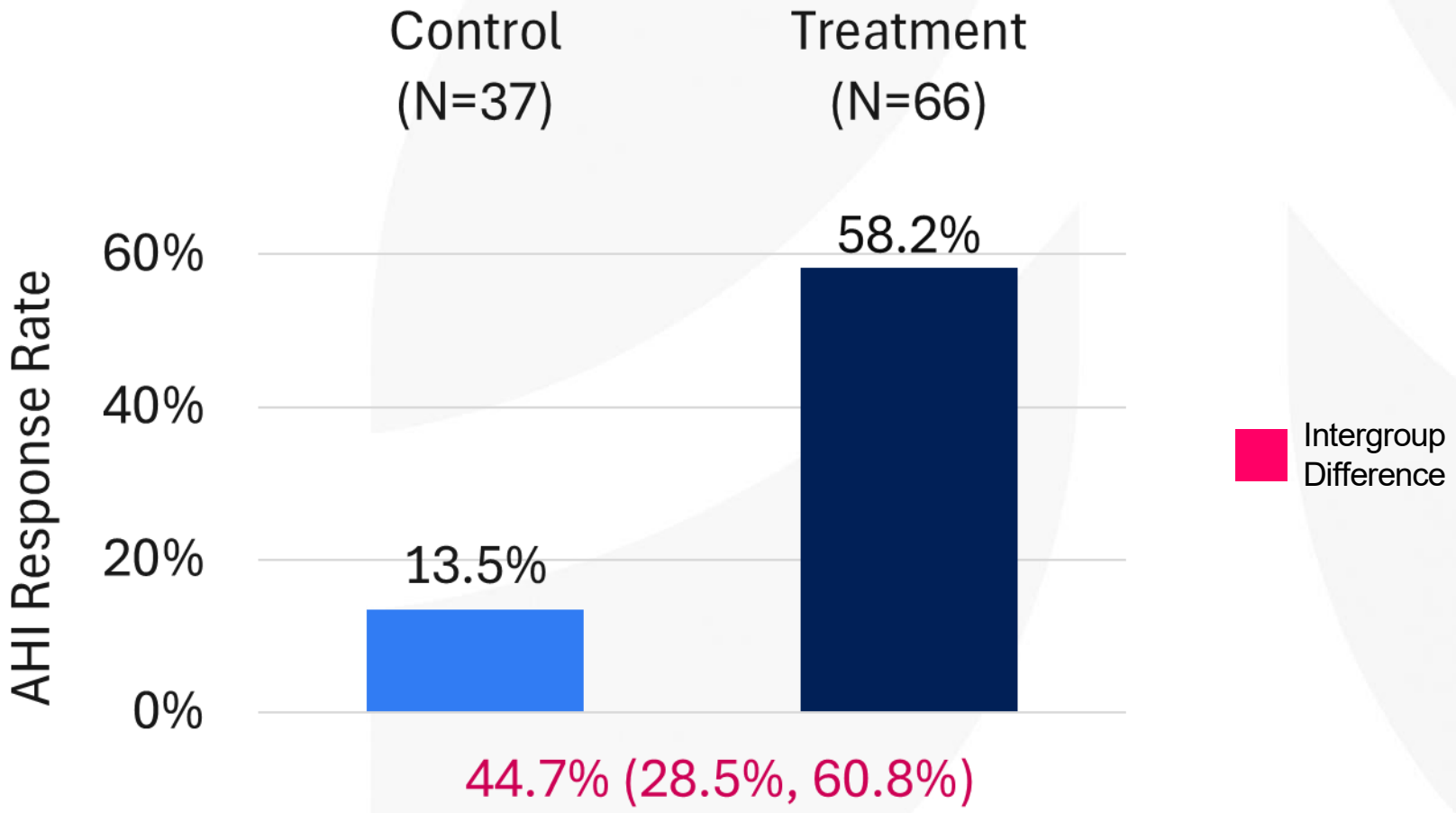
November 11, 2024

Top-line results compared to baseline at six months:
Median apnea-hypopnea index reduction of 66.2%
Median oxygen desaturation index reduction of 63.3%

PDF Version

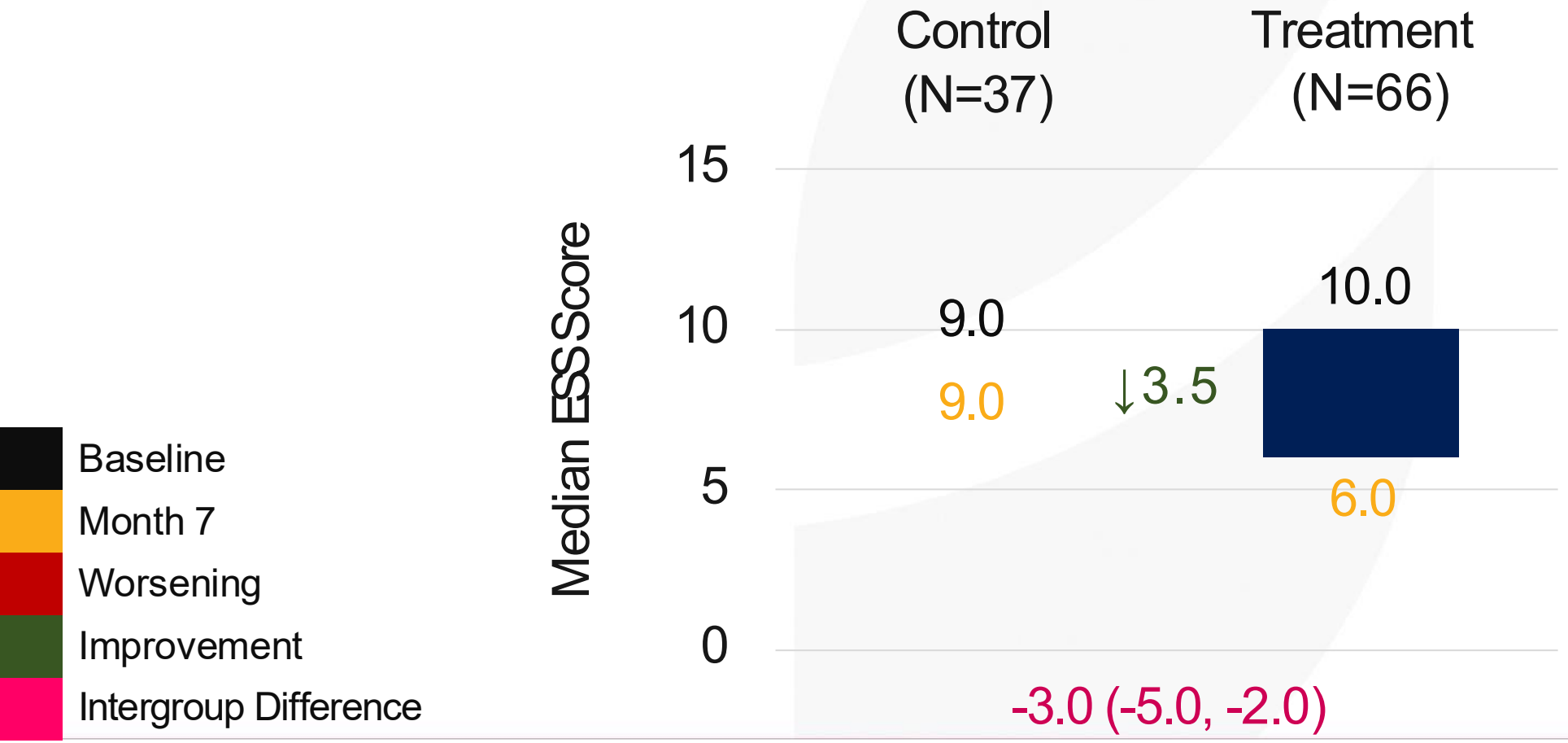
Manuscript in prep

Primary Endpoint: AHI Response Rate

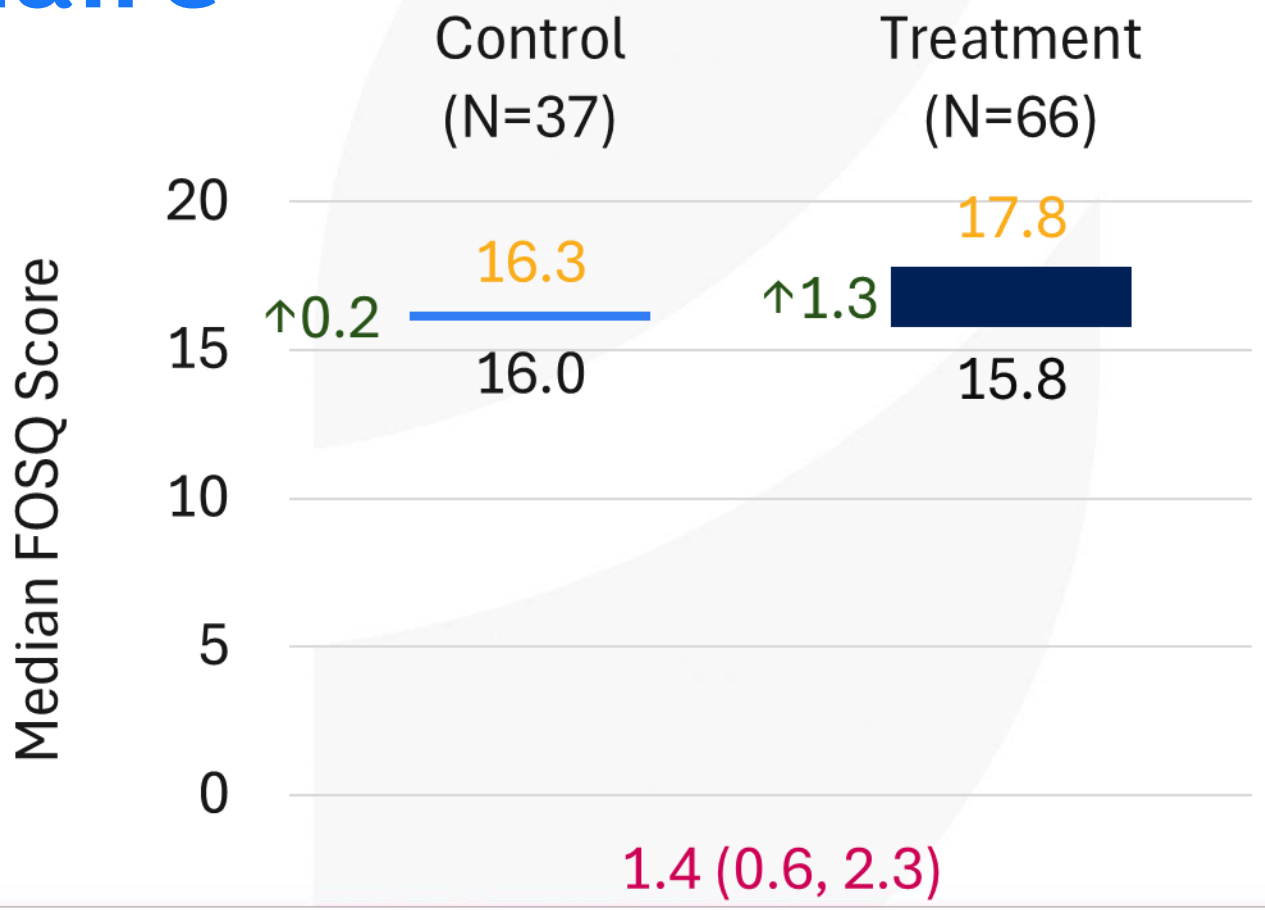


p<0.001

Epworth Sleepiness Scale



Functional Outcomes of Sleep Questionnaire



Baseline
Month 7
Worsening
Improvement
Intergroup Difference

Long-Term Outcomes

Treatment Group at Month 13:

➢Response Rate 65%

- Median AHI 34.3→11.0/hr

➢68% Reduction

- Median ODI 34.9→11.1/hr

➢68% Reduction

LivaNova
Health innovation that matters

NEWS RELEASE

LivaNova Announces 12-month Data from OSPREY Clinical Study for Moderate to Severe Obstructive Sleep Apnea, Demonstrating Strong Response and Durability of Therapy

Top-line results at 12 months of treatment show meaningful improvement over time:
Overall responder rate of 65%
Overall reduction in median apnea-hypopnea index of 68%
Overall reduction in median oxygen desaturation index of 68%

London, May 7, 2025 – LivaNova PLC (Nasdaq: LIVN), a market-leading medical technology company, today announced 12-month, top-line data from its OSPREY randomized controlled trial (RCT), evaluating outcomes with the aura6000™ System for the treatment of moderate to severe obstructive sleep apnea (OSA). At 12 months of therapy, the treatment arm responder rate was 65% with responders defined as those who realized at least a 50% improvement from the baseline apnea-hypopnea index (AHI) and an AHI value below 20. The study features a differentiated neurostimulation modality called proximal hypoglossal nerve stimulation (p-HGNS), which utilizes six electrodes placed on the proximal trunk of the hypoglossal nerve, offering broad access to the muscles controlling the airway and providing customized titration.

Conclusions

- pHGNS provided safe and effective treatment for sleep-disordered breathing, oxygenation, and quality of life in an OSA cohort that closely resembled the target clinical population
- OSPREY had unique strengths:
  - RCT design
  - High BMI cutoff
  - No sleep endoscopy screening
  - Racial/ethnic diversity
  - Short procedure with no inpatient stays
  - Many patient-reported outcomes
- Together with the THN3 RCT, the positive outcomes of OSPREY establish Level 1 evidence for pHGNS; we are now at FDA

Therapeutic Approaches in OSA

1. CPAP to hold airway open

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2. Treat underlying cause based on mechanism

   -weight loss, promoting UA muscle tone, lowering loop gain etc

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5. Treatments to block complications of OSA

Obstructive Sleep Apnea
Underlying Mechanisms (Endotypes)

- Anatomy
- Pharyngeal dilator muscle control during sleep
- Arousal Threshold
- Loop gain
- Lung volume
- Vascular

Obstructive Sleep Apnea Endophenotypes

Janna Rae Raphelson Ana Lucia Fuentes Breanna Holloway Atul Malhotra

School of Medicine, University of California San Diego, La Jolla, CA, United States

Address for correspondence Atul Malhotra (e-mail: amalhotra@ucsd.edu).

Sleep Sci 2025;18(1):e109–e113.

- Patients don’t all get sleep apnea for the same reason
- The one-size-fits-all strategy has largely failed

The different clinical faces of obstructive sleep apnoea: a cluster analysis

Lichuan Ye[1], Grace W. Pien[2], Sarah J. Ratcliffe[3], Erla Björnsdottir[4,5], Erna Sif Arnardottir[4,5], Allan I. Pack[6], Bryndis Benediktsdottir[4,5] and Thorarinn Gislason[4,5]

Clusters:

1. Disturbed sleep group 33%
2. Minimally symptomatic 25%
3. Severe excessive daytime sleepiness 43%

Differential susceptibility

ERJ 2014
AJRCCM 2019

Received: 14 April 2022 | Revised: 2 June 2022 | Accepted: 5 June 2022
DOI: 10.14814/phy2.15360

ORIGINAL ARTICLE

The Physiological Society · American Physiological Society · Physiological Reports

The impact of daytime transoral neuromuscular stimulation on upper airway physiology – A mechanistic clinical investigation

Brandon Nokes[1,2] | Christopher N. Schmickl[1] | Rebbecca Brena[1] | Nana Naa-Oye Bosompra[1] | Dillon Gilbertson[1] | Scott A. Sands[3] | Rakesh Bhattacharjee[4] | Dwayne L. Mann[5] | Robert L. Owens[1] | Atul Malhotra[1] | Jeremy E. Orr[1]

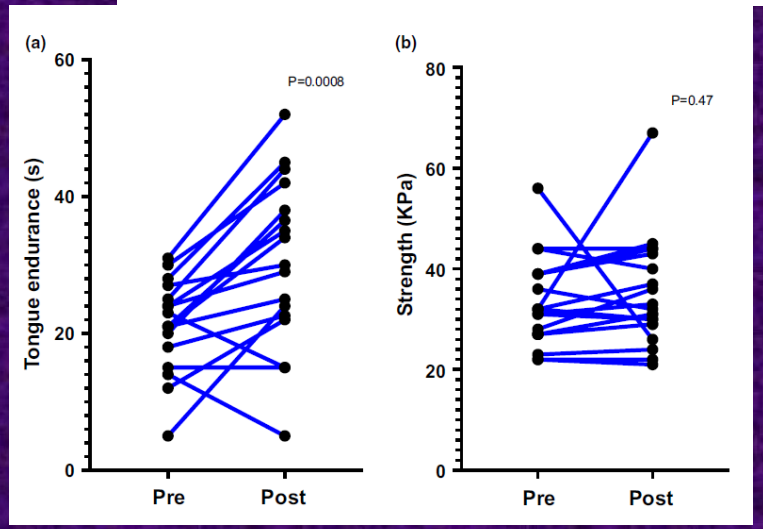


Table 3 Changes in sleep indices pre-to post-therapy among responders

	Pre-therapy	Post-therapy	Change (mean ± SD)	95% CI	2-tailed *p*-value
Any reduction in AHI (n = 51)					
AHI (events/hour)	10.4	5.0	5.4 ± 2.8	4.7–6.2	< 0.01
ODI 4% (events/hour)	8.6	4.3	4.3 ± 2.7	3.6–5.1	< 0.01
Objective snoring > 40 dB (%)	37.1	20.2	16.9 ± 16.7	12.2–21.6	< 0.01
ESS (/24 points)	9.3	5.4	3.9 ± 3.7	2.8–4.9	< 0.01
PSQI (21 points)	7.2	5.5	1.7 ± 2.3	1.0–2.3	< 0.01
≥ 50% reduction in AHI (n = 28)					
AHI (events/hour)	10.8	3.5	7.2 ± 2.1	6.4–8.0	< 0.01
ODI 4% (events/hour)	9.0	3.2	5.8 ± 2.1	5.0–6.6	< 0.01
Objective snoring > 40 dB (%)	39.0	20.7	18.3 ± 20.8	10.2–26.4	< 0.01
ESS (/24 points)	9.5	5.2	4.4 ± 4.3	2.7–6.0	< 0.01
PSQI (21 points)	6.6	4.8	1.8 ± 2.6	0.8–2.8	< 0.01

Sleep and Breathing
https://doi.org/10.1007/s11325-022-02644-9

SLEEP BREATHING PHYSIOLOGY AND DISORDERS • ORIGINAL ARTICLE

Check for updates

Transoral awake state neuromuscular electrical stimulation therapy for mild obstructive sleep apnea

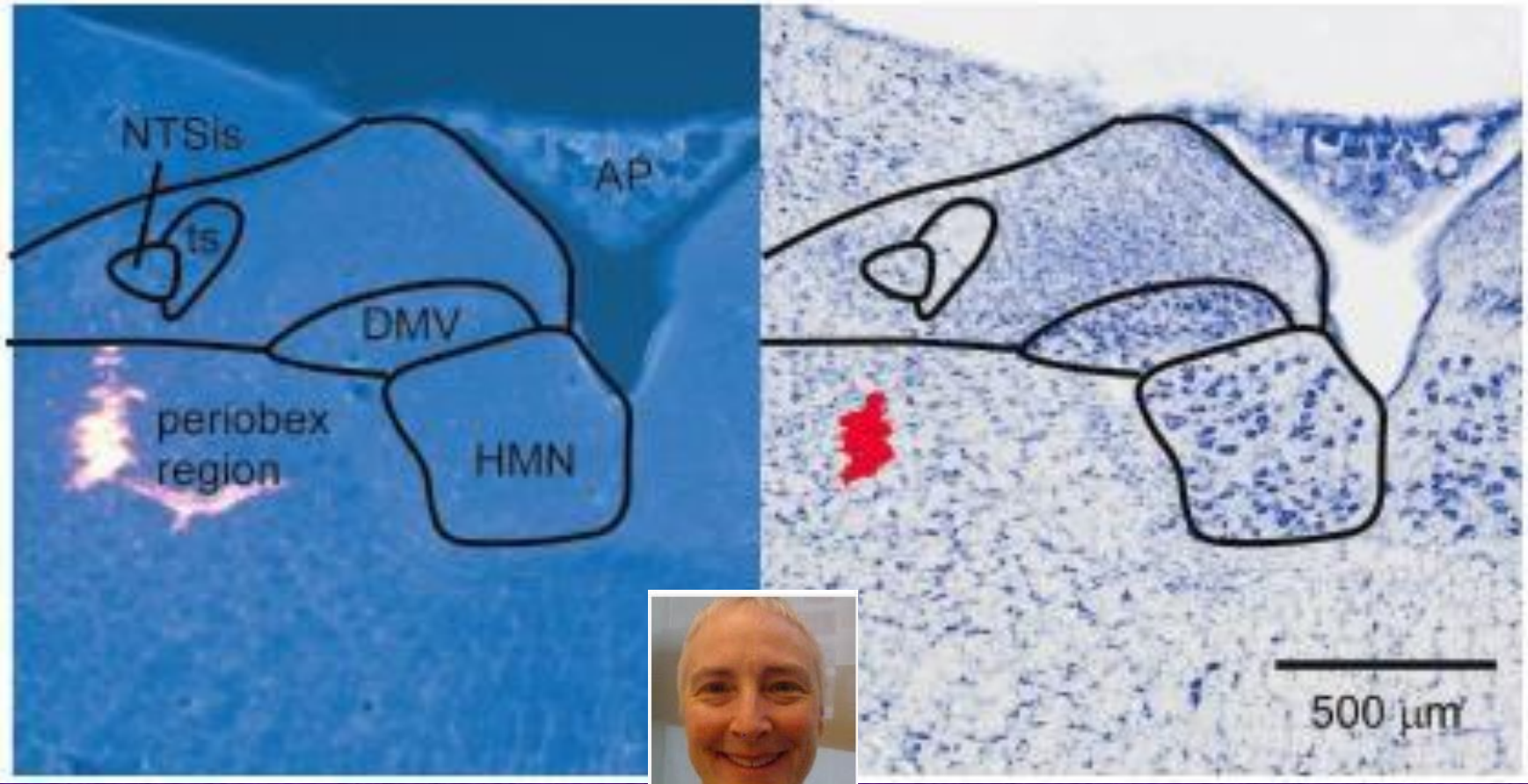
Brandon Nokes[1,2] · Peter M. Baptista[3] · Paula Martínez Ruiz de Apodaca[4] · Marina Carrasco-Llatas[4] · Secundino Fernandez[3] · Bhik Kotecha[5] · Phui Yee Wong[5] · Henry Zhang[5] · Amro Hassaan[5] · Atul Malhotra[1]

We got FDA approval for ExciteOSA

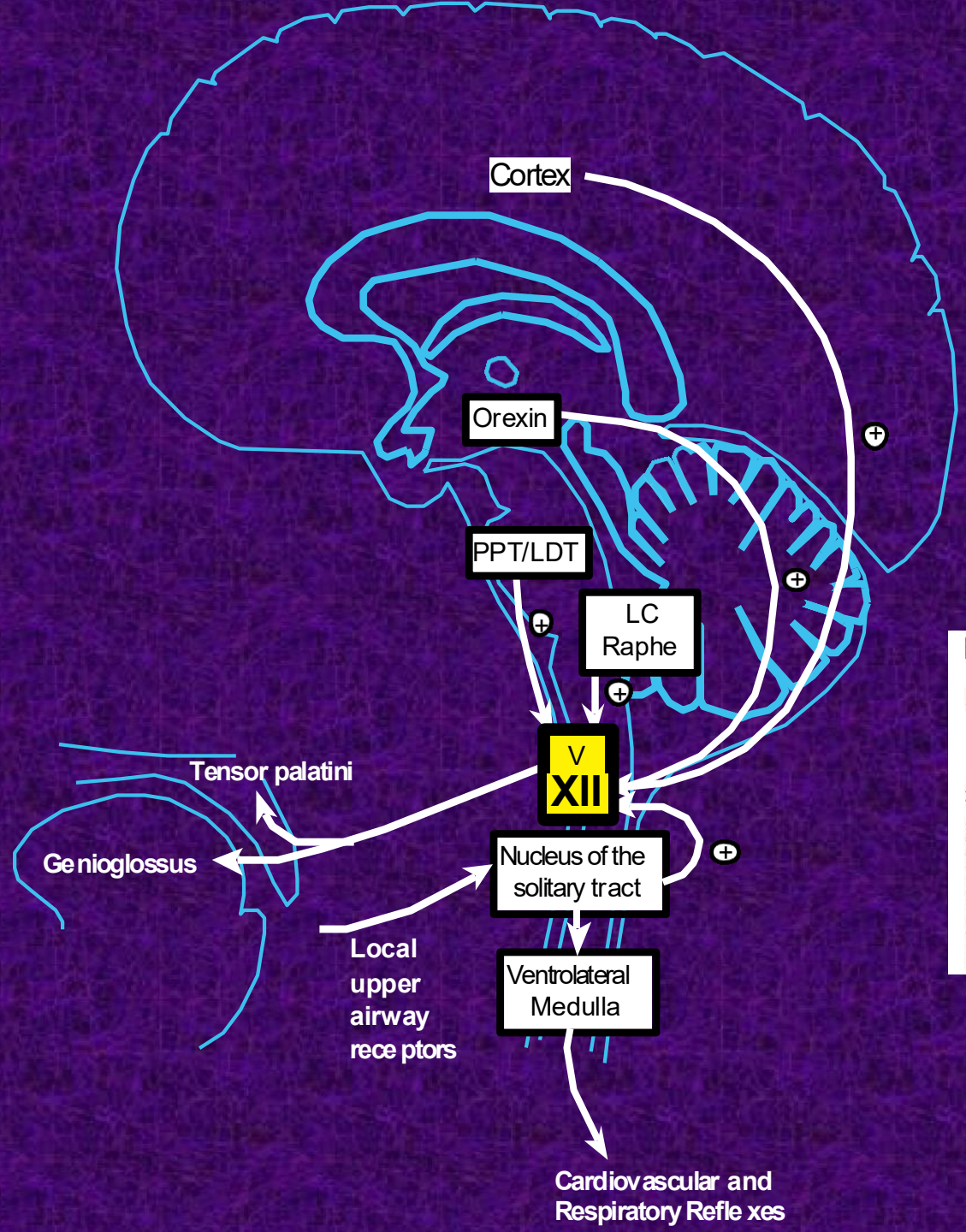
Genioglossus premotoneurons and the negative pressure reflex in rats

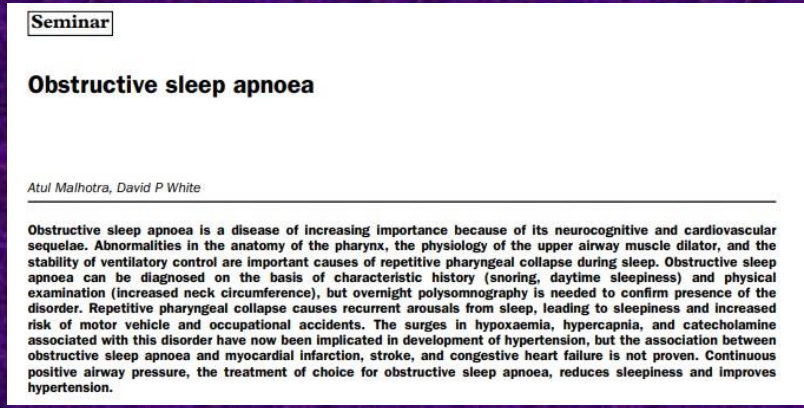
Nancy L. Chamberlin[1], Matthias Eikermann[2], Philipp Fassbender[1], David P. White[2] and Atul Malhotra[2]

[1]*Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA 02115, USA*
[2]*Divisions of Sleep Medicine and Pulmonary/Critical Care Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115 USA*



J Physiol 2007





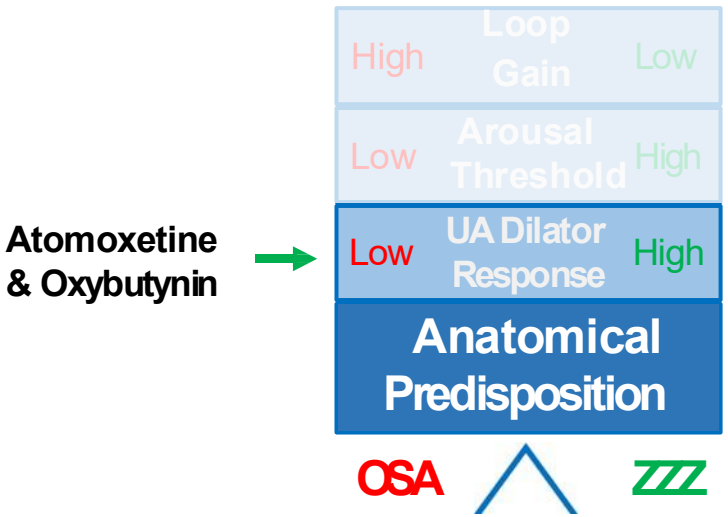
Seminar

Obstructive sleep apnoea

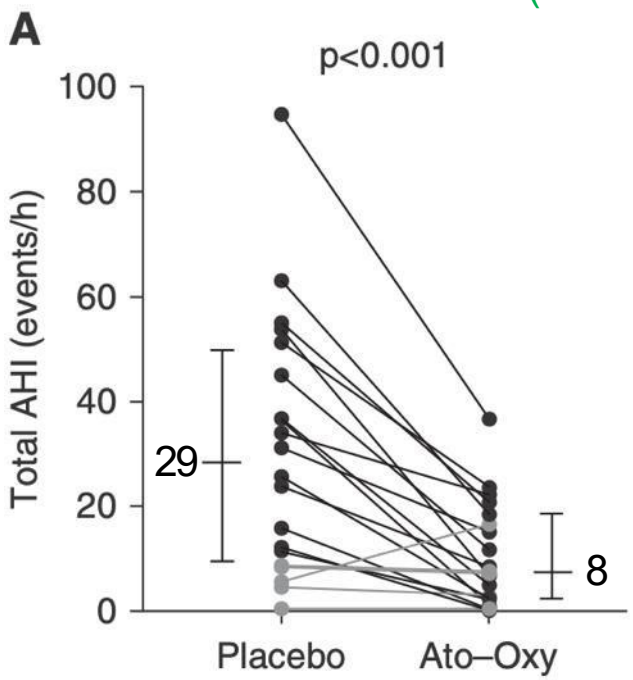
Atul Malhotra, David P White

Obstructive sleep apnoea is a disease of increasing importance because of its neurocognitive and cardiovascular sequelae. Abnormalities in the anatomy of the pharynx, the physiology of the upper airway muscle dilator, and the stability of ventilatory control are important causes of repetitive pharyngeal collapse during sleep. Obstructive sleep apnoea can be diagnosed on the basis of characteristic history (snoring, daytime sleepiness) and physical examination (increased neck circumference), but overnight polysomnography is needed to confirm presence of the disorder. Repetitive pharyngeal collapse causes recurrent arousals from sleep, leading to sleepiness and increased risk of motor vehicle and occupational accidents. The surges in hypoxaemia, hypercapnia, and catecholamine associated with this disorder have now been implicated in development of hypertension, but the association between obstructive sleep apnoea and myocardial infarction, stroke, and congestive heart failure is not proven. Continuous positive airway pressure, the treatment of choice for obstructive sleep apnoea, reduces sleepiness and improves hypertension.

Malhotra and White
Lancet 2002



median reduction 63% (-16/h)



?Low UA Dilator Tone in Sleep due to:

- drop in noradrenergic tone in NREM
- cholinergic (muscarinic) inhibition in REM

Oxybutynin counters alerting effects of atomoxetine

Subset with $AHI_{Placebo}$ >10/h (n=15)

	Placebo	ato–oxy	Median Change	*P* Value
Total sleep time, min	212 (155 to 264)	289 (221 to 307)	45 (−6 to 97)	0.0496
Sleep efficiency, %TIB	56 (38 to 72)	69 (63 to 81)	12 (1 to 29)	0.018
N1, % TST	29 (19 to 53)	32 (25 to 38)	2 (−25 to 13)	0.323
N2, % TST	20 (15 to 38)	33 (24 to 47)	12 (4 to 17)	0.0175
N3, % TST	3 (0 to 16)	0 (0 to 5)	−2 (−9 to 0)	0.21
REM, % TST	5 (0 to 10)	6 (0 to 12)	0 (−6 to 7)	0.85
Subjective sleep quality, VAS score	5 (2 to 8)	7 (4 to 8)	1 (0 to 2)	0.036
Heart rate, beats/min	70 (62 to 77)	74 (69 to 80)	6 (1 to 7)	0.003
Systolic blood pressure, mm Hg	140 (130 to 149)	143 (144 to 148)	1 (−7 to 7)	0.83
Diastolic blood pressure, mm Hg	84 (75 to 91)	86 (77.5 to 92)	2 (−15 to 10.5)	0.99

Taranto-Montemurro L, et al. AJRCCM 2019

ORIGINAL ARTICLE

The Combination of Aroxybutynin and Atomoxetine in the Treatment of Obstructive Sleep Apnea (MARIPOSA)

A Randomized Controlled Trial

Paula K. Schweitzer[1], Luigi Taranto-Montemurro[2], Joseph M. Ojile[3], Stephen G. Thein[4], Christopher L. Drake[5], Russell Rosenberg[6], Bruce Corser[7], Brian Abaluck[8], R. Bart Sangal[9,10], and James Maynard[11]

[1]Sleep Medicine and Research Center, St. Luke's Hospital, Chesterfield, Missouri; [2]Apnimed Inc., Cambridge, Massachusetts; [3]Clayton Sleep Institute, St. Louis, Missouri; [4]Pacific Research Network, an Evolution Research Group Portfolio Site, San Diego, California; [5]Thomas Roth Sleep Disorders and Research Center, Henry Ford Health System, Detroit, Michigan; [6]NeuroTrials Research Inc., Atlanta, Georgia; [7]Intrepid Research, Cincinnati, Ohio; [8]Sleep Medicine, Brian Abaluck, M.D., Malvern, Pennsylvania; [9]Sleep & Attention Disorders Institute, Sterling Heights, Michigan; [10]Oakland University William Beaumont School of Medicine, Rochester, Michigan; and [11]CTI Clinical Research Center, Cincinnati, Ohio

AJRCCM 2023

Measurements and Main Results: Of 211 randomized patients, 181 were included in the pre-specified efficacy analyses. Sleep was assessed by two baseline and two treatment polysomnograms. Apnea-hypopnea index (AHI_4, 4% desaturation criterion, primary outcome) was reduced from median (IQR) of 20.5 (12.3-27.2) to 10.8 (5.6-18.5) in the AD109 2.5/75 mg arm (-47.1%), from 19.4 (13.7-26.4) to 9.5 (6.1-19.3) in the 5/75 mg arm (-42.9%, both $p<0.0001$ vs placebo), and from 19.0 (11.8-28.8) to 11.8 (5.5-21.5) with atomoxetine alone (-38.8%, $p<0.01$ vs placebo). Placebo AHI_4 went from 20.1 (11.9 - 25.9) to 16.3 (11.1 - 28.9).

	Arm	Baseline	Treatment	Placebo-adjusted change from baseline
AHI_4 events/h	Placebo	20.1 (11.9 - 25.9)	16.3 (11.1 - 28.9)	
	Ato75	19.0 (11.8 - 28.8)	11.8 (5.5 - 21.5)	-5.19 (-8.6 to -1.8) **
	AD109 2.5/75	20.5 (12.3 - 27.2)	10.8 (5.6 - 18.5)	-7.16 (-11.0 to -3.3)***
	AD109 5/75	19.4 (13.7 - 26.4)	9.5 (6.1 - 19.3)	-7.20 (-10.97 to -3.4) ***

Table 6. Adverse Events

	Placebo ($n = 63$)	Ato75 ($n = 63$)	AD109 2.5/75 mg ($n = 42$)	AD109 5/75 mg ($n = 41$)
Any adverse event	25 (39.7%)	51 (81%)	26 (61.9%)	32 (78%)
Adverse event leading to discontinuation	1 (2%)	12 (19%)	5 (12%)	5 (12%)
Most common adverse events*				
Dry mouth	3 (5%)	17 (27%)	10 (24%)	24 (59%)
Insomnia	2 (3%)	23 (37%)	11 (26%)	9 (22%)
Urinary hesitation/flow decrease	0	14 (22%)	3 (7%)	9 (22%)
Constipation	2 (3%)	2 (3%)	0	5 (12%)
Nausea	2 (3%)	4 (6%)	5 (12%)	4 (10%)
Decreased appetite	1 (2%)	5 (8%)	2 (5%)	4 (10%)
Feeling jittery	1 (2%)	2 (3%)	2 (5%)	3 (7%)
Somnolence	1 (2%)	0	1 (2%)	3 (7%)

Definition of abbreviation: Ato75 = atomoxetine 75 mg.
*Most common adverse events are those reported in at least three participants in any treatment group.

Table 7. Difference in Heart Rate and Blood Pressure between Placebo and Active Treatment Arms at Different Time Points

	HR, beats/min			SBP, mm Hg		DBP, mm Hg	
Arm	Evening	Overnight*	Morning	Evening	Morning	Evening	Morning
Ato75	3.7 (−0.5 to 7.8)	7.7 (5.7 to 9.6)	7.0 (3.3 to 10.6)	−2.7 (−8.9 to 3.6)	−0.8 (−5.3 to 3.8)	1.5 (−1.7 to 4.7)	1.2 (−2.1 to 4.5)
AD109 2.5/75 mg	2.0 (−2.8 to 6.7)	5.1 (2.9 to 7.4)	5.5 (1.4 to 9.6)	3.4 (−3.6 to 10.3)	1.9 (−3.2 to 7.0)	4.7 (1.1 to 8.3)	4.2 (0.5 to 7.9)
AD109 5/75 mg	1.5 (−3.1 to 6.1)	5.5 (3.3 to 7.7)	7.4 (3.4 to 11.4)	−3.3 (−10.1 to 3.5)	−4.0 (−9.0 to 1.1)	0.5 (−3.0 to 4.0)	−0.8 (−4.4 to 2.8)

Definition of abbreviations: Ato75 = atomoxetine 75 mg, HR = heart rate, DBP = diastolic blood pressure, SBP = systolic blood pressure.
Data show mean (95% confidence interval) difference from placebo derived from the average of the two treatment polysomnography nights.
Evening values were obtained before dosing.
*HR overnight data are additionally adjusted for baseline.

No serious adverse events; some htn and tachycardia

Apnimed Announces Positive Topline Results in the First Landmark Phase 3 Clinical Trial of AD109, an Investigational Once-daily Oral Pill for Obstructive Sleep Apnea

Apnimed

NEWS PROVIDED BY
Apnimed, Inc. →
May 19, 2025, 06:00 ET

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Press Release Not Peer Reviewed Yet

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NEWS PROVIDED BY
Apnimed, Inc. →
May 19, 2025, 06:00 ET

- *AD109 met the primary endpoint, mean change in apnea-hypopnea index (AHI, p=0.001) at 26 weeks, across a broad range of people with mild, moderate and severe obstructive sleep apnea*
- *Study participants treated with AD109 achieved a mean reduction in AHI of 55.6% from baseline and achieved significantly improved oxygenation and reduced disease severity*
- *AD109 is a first-in-class, anti-apneic neuromuscular modulator which targets the root cause of OSA by increasing upper airway muscle tone during sleep*
- *Apnimed expects topline results in Q3'25 from its second Phase 3 clinical trial, LunAIRo, and plans to submit an NDA to the U.S. FDA for AD109 by early 2026*

Summary re: Ato/Oxy

- Ato/oxy has fairly consistent though modest effects on OSA
- AHI improved by 3.3-4.0 events in mITT analysis
- 1/3 to ½ dropped out of phase III studies
- Side effects will need to be considered carefully in context of hard OSA outcomes especially compared to other pharmacotherapy
- Now at FDA being reviewed

Therapeutic Approaches in OSA

1. CPAP to hold airway open

   -oral appliance, upper airway surgery

2. Treat underlying cause based on mechanism

   -weight loss, promoting UA muscle tone, lowering loop gain etc

3. Treatments to facilitate PAP therapy

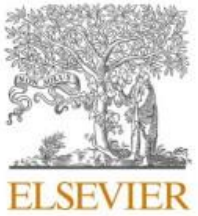
   - Hypnotics Schmickl et al. AJRCCM 2020; Lettieri et al. Annals IM 2009
   - Nasal patency Weaver et al.

4. Treatments to improve symptoms in OSA

   -Solriamfetol JCSM 2022, AJRCCM 2019, Steier et al. Sleep Med 2023

5. Treatments to block complications of OSA

Sleep Medicine 112 (2023) 104–115



Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Recommendations for clinical management of excessive daytime sleepiness in obstructive sleep apnoea – A Delphi consensus study

Joerg S. Steier[a,*,1], Richard K. Bogan[b], Irene M. Cano-Pumarega[c], John A. Fleetham[d], Giuseppe Insalaco[e], Chitra Lal[f], Jean-Louis Pépin[g], Winfried J. Randerath[h], Susan Redline[i], Atul Malhotra[j,1]

- Global consensus challenging
- Actigraphy and MSLT are not universally available
- General acknowledgment that 10-20% of well managed OSA patients on PAP have residual sleepiness
- Emphasis on primary therapy for OSA
- Modafanil and/or Solriamfetol may be reasonable for some OSA

Solriamfetol (Sunosi) was developed by trials run at UCSD and is now **FDA approved** and SOC

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Incidence and duration of common early-onset adverse events in randomized controlled trials of solriamfetol for treatment of excessive daytime sleepiness in obstructive sleep apnea and narcolepsy

Russell Rosenberg, PhD[1]; Michael J. Thorpy, MD[2]; Yves Dauvilliers, MD, PhD[3]; Paula K. Schweitzer, PhD[4]; Gary Zammit, PhD[5,6]; Mark Gotfried, MD[7]; Shay Bujanover, MD[8]; Brian Scheckner, PharmD, BCPP, CMPP[9]; Atul Malhotra, MD[10]

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Sleep Medicine 100 (2022) 165–173

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

ELSEVIER

Effects of solriamfetol treatment on body weight in participants with obstructive sleep apnea or narcolepsy

Atul Malhotra [a,*], Patrick J. Strollo Jr [b], Jean-Louis Pepin [c], Paula Schweitzer [d], Gert Jan Lammers [e,f], Jan Hedner [g], Susan Redline [h], Dan Chen [i], Patricia Chandler [i], Shay Bujanover [i], Kingman Strohl [j]

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[b] University of Pittsburgh/Veterans Administration Pittsburgh Health System, Pittsburgh, PA, USA
[c] Université Grenoble Alpes, INSERM U1300, CHU Grenoble Alpes, HP2, 38000, Grenoble, France
[d] Sleep Medicine and Research Center, St. Luke's Hospital, Chesterfield, MO, USA
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[f] Department of Neurology, Leiden University Medical Centre, Leiden, Netherlands
[g] Sahlgrenska University Hospital, Gothenburg University, Gothenburg, Sweden
[h] Brigham and Women's Hospital, Harvard University, Boston, MA, USA
[i] Jazz Pharmaceuticals, Palo Alto, CA, USA
[j] Case Western Reserve University, Cleveland, OH, USA

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Long-term effects of solriamfetol on quality of life and work productivity in participants with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea

Terri E. Weaver, PhD[1]; Jean-Louis Pepin, MD[2]; Richard Schwab, MD[3]; Colin Shapiro, PhD, MBBCh[4]; Jan Hedner, MD[5]; Mansoor Ahmed, MD[6]; Nancy Foldvary-Schaefer, DO, MS[7]; Patrick J. Strollo Jr, MD[8]; Geert Mayer, MD[9,10]; Kathleen Sarmiento, MD, MPH[11]; Michelle Baladi, PhD[12]; Morgan Bron, PharmD, MS[12]; Patricia Chandler, MD[12]; Lawrence Lee, PhD[12]; Atul Malhotra, MD[13]

[1]College of Nursing, University of Illinois Chicago, Chicago, Illinois; [2]Grenoble Alpes University and INSERM, Grenoble, France; [3]University of Pennsylvania, Philadelphia, Pennsylvania; [4]University of Toronto, Toronto, Ontario, Canada; [5]Sahlgrenska University Hospital, Gothenburg University, Gothenburg, Sweden; [6]Cleveland Sleep Research Center, Cleveland, Ohio; [7]Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio; [8]University of Pittsburgh/Veterans Administration Pittsburgh Health System, Pittsburgh, Pennsylvania; [9]Hephata Klinik, Schwalmstadt, Germany; [10]Philipps University, Marburg, Germany; [11]San Francisco Veterans Administration Health Care System, San Francisco, California; [12]Jazz Pharmaceuticals, Palo Alto, California; [13]Division of Pulmonary, Critical Care, and Sleep Medicine, University of California, San Diego, La Jolla, California

Solriamfetol for Excessive Sleepiness in Obstructive Sleep Apnea (TONES 3)

A Randomized Controlled Trial

AJRCCM

Paula K. Schweitzer[1], Russell Rosenberg[2,3], Gary K. Zammit[4,5], Mark Gotfried[6], Dan Chen[7], Lawrence P. Carter[7,8], Hao Wang[7], Yuan Lu[7], Jed Black[7,9], Atul Malhotra[10], and Kingman P. Strohl[11]

[1]Sleep Medicine and Research Center, St. Luke's Hospital, Chesterfield, Missouri; [2]NeuroTrials Research, Atlanta, Georgia; [3]Atlanta School of Sleep Medicine, Atlanta, Georgia; [4]Clinilabs Drug Development Corporation, New York, New York; [5]Icahn School of Medicine at Mount Sinai, New York, New York; [6]Pulmonary Associates, PA, Phoenix, Arizona; [7]Jazz Pharmaceuticals, Palo Alto, California; [8]University of Arkansas for Medical Sciences, Little Rock, Arkansas; [9]Stanford Center for Sleep Sciences and Medicine, Palo Alto, California; [10]University of California, San Diego, San Diego, California; and [11]Case Western Reserve University, Cleveland, Ohio

OXFORD | Sleep Research Society

SLEEPJ, 2020, 1–11

doi: 10.1093/sleep/zsz220
Advance Access Publication Date: 6 November 2019
Original Article

ORIGINAL ARTICLE

Long-term study of the safety and maintenance of efficacy of solriamfetol (JZP-110) in the treatment of excessive sleepiness in participants with narcolepsy or obstructive sleep apnea

Atul Malhotra[1,*] Colin Shapiro[2], Jean-Louis Pepin[3,4], Jan Hedner[5], Mansoor Ahmed[6], Nancy Foldvary-Schaefer[7], Patrick J. Strollo Jr[8], Geert Mayer[9,10], Kathleen Sarmiento[11], Michelle Baladi[12], Patricia Chandler[12], Lawrence Lee[12] and Richard Schwab[13]

[1]Division of Pulmonary, Critical Care and Sleep Medicine, University of California San Diego, La Jolla, [2]University of Toronto, ON, Canada, [3]HP2 Laboratory, INSERM U1042, University Grenoble Alpes, France, [4]EFCR Laboratory, Pole Thorax et Vaisseaux, Grenoble Alpes University Hospital, France, [5]Sahlgrenska University Hospital, Gothenburg University, Sweden, [6]Cleveland Sleep Research Center, OH, [7]Cleveland Clinic Lerner College of Medicine, OH, [8]University of Pittsburgh/Veterans Administration Pittsburgh Health System, PA, [9]Hephata Klinik, Schwalmstadt, Germany, [10]Philipps University, Marburg, Germany, [11]San Francisco Veterans Administration Healthcare System, CA, [12]Jazz Pharmaceuticals, Palo Alto, CA and [13]University of Pennsylvania, Philadelphia

Therapeutic Approaches in OSA

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5. Treatments to block complications of OSA

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 25, 2013 VOL. 368 NO. 17

Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk

W.H. Wilson Tang, M.D., Zeneng Wang, Ph.D., Bruce S. Levison, Ph.D., Robert A. Koeth, B.S., Earl B. Britt, M.D., Xiaoming Fu, M.S., Yuping Wu, Ph.D., and Stanley L. Hazen, M.D., Ph.D.

TMAO leads to atherosclerosis
can block with probiotics or antibiotics
to present atherosclerosis

now controversial

Intermittent Hypoxia and Hypercapnia Accelerate Atherosclerosis, Partially via Trimethylamine-Oxide

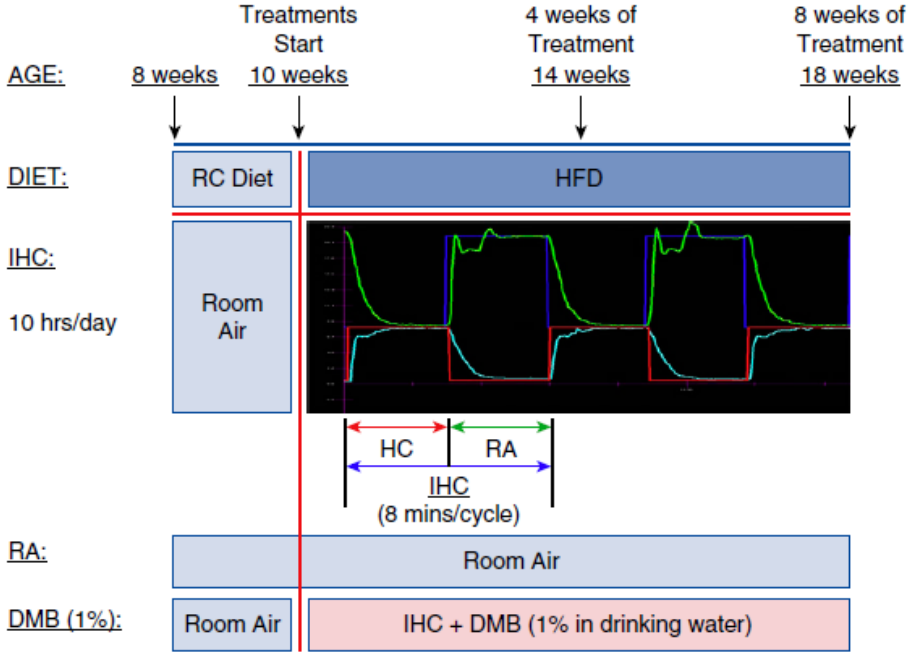
Jin Xue[1], Dan Zhou[1], Orit Poulsen[1], Toshihiro Imamura[1], Yu-Hsin Hsiao[1], Travis H. Smith[1], Atul Malhotra[2], Pieter Dorrestein[1,3,4], Rob Knight[1,4,5], and Gabriel G. Haddad[1,3,5,6]

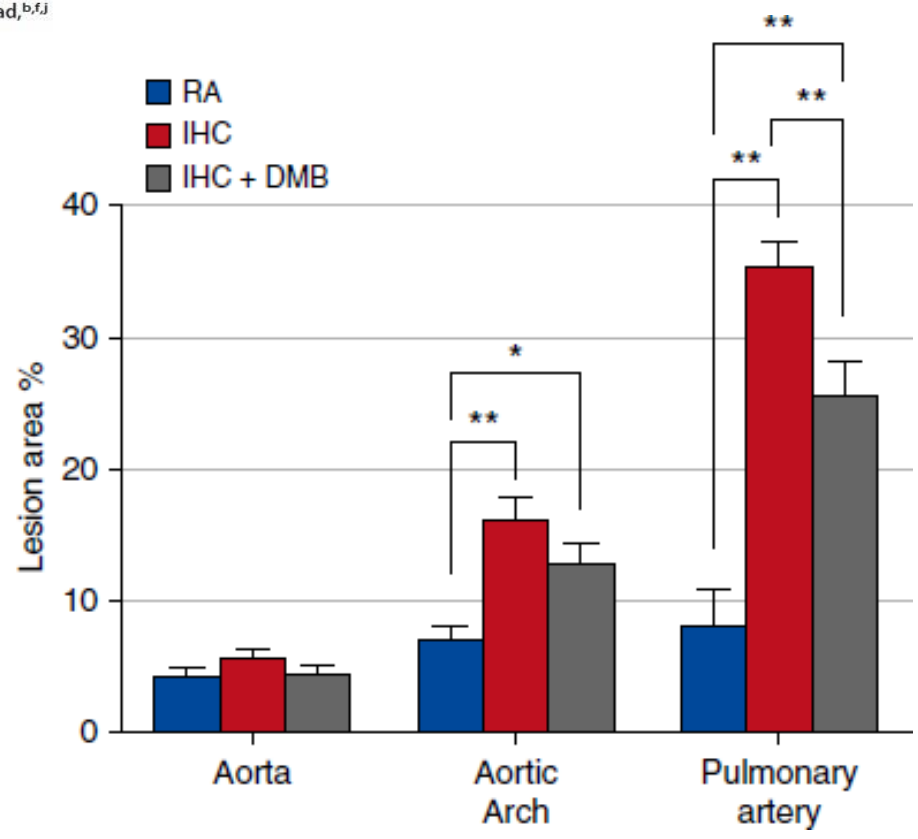
Departments of [1]Pediatrics, [2]Internal Medicine, and [3]Neurosciences, School of Medicine, [4]School of Pharmacy and Pharmaceutical Sciences, and [5]Department of Computer Sciences and Engineering, School of Engineering, University of California San Diego, La Jolla, California; and [6]The Rady Children's Hospital, San Diego, California

Intermittent Hypoxia and Hypercapnia Reproducibly Change the Gut Microbiome and Metabolome across Rodent Model Systems

AJRCMB 2017, mSystems 2019

Anupriya Tripathi,[a,b,c] Zhenjiang Zech Xu,[d] Jin Xue,[b] Orit Poulsen,[b] Antonio Gonzalez,[b] Gregory Humphrey,[b] Michael J. Meehan,[c] Alexey V. Melnik,[c] Gail Ackermann,[b] Dan Zhou,[b] Atul Malhotra,[e] Gabriel G. Haddad,[b,f,j] Pieter C. Dorrestein,[b,g,h] Rob Knight[b,h,i]





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   -Solriamfetol JCSM 2022, AJRCCM 2019, Steier et al. Sleep Med 2023

5. Treatments to block complications of OSA

Sleep Medicine 121 (2024) 26–31

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Weight reduction and the impact on apnea-hypopnea index: A systematic meta-analysis

Atul Malhotra [a], Cory R. Heilmann [b], Kushal K. Banerjee [c], Julia P. Dunn [b], Mathijs C. Bunck [b], Josef Bednarik [b,*]

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SLEEP, 2023, 46, 1–7
https://doi.org/10.1093/sleep/zsad224
Advance access publication 5 September 2023
Perspective

Perspective

Giving weight to incretin-based pharmacotherapy for obesity-related sleep apnea: a revolution or a pipe dream?

Ronald R Grunstein[1,2,3,*], Thomas A Wadden,[4] Julia L Chapman[1], Atul Malhotra[5] and Craig L Phillips[1,6]

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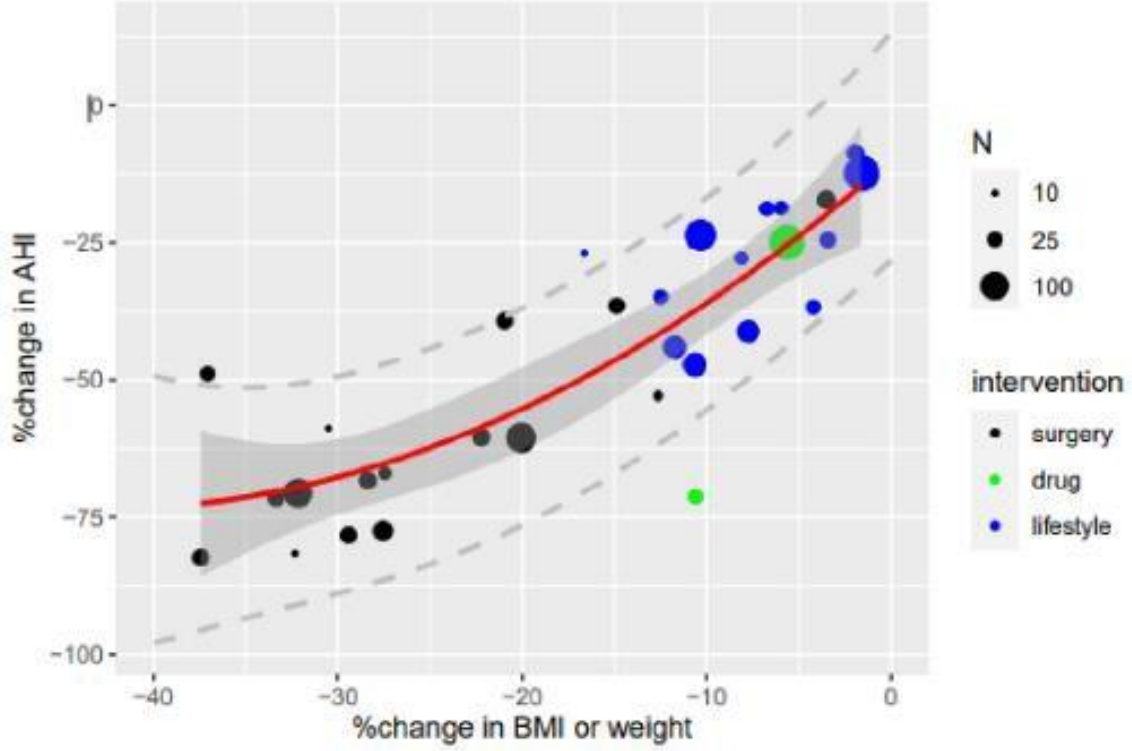

Fig. 2. Apnea-hypopnea index versus weight reduction inference. Abbreviations: AHI, apnea-hypopnea index; N, population size.

SURMOUNT-OSA

Design, Efficacy and Safety

Contemporary Clinical Trials 141 (2024) 107516

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Tirzepatide for the treatment of obstructive sleep apnea: Rationale, design, and sample baseline characteristics of the SURMOUNT -OSA phase 3 trial

Atul Malhotra [a,*], Josef Bednarik [b], Sujatro Chakladar [b], Julia P. Dunn [b], Terri Weaver [c,d], Ron Grunstein [e], Ingo Fietze [f], Susan Redline [g], Ali Azarbarzin [g], Scott A. Sands [g], Richard J. Schwab [h], Mathijs C. Bunck [b]

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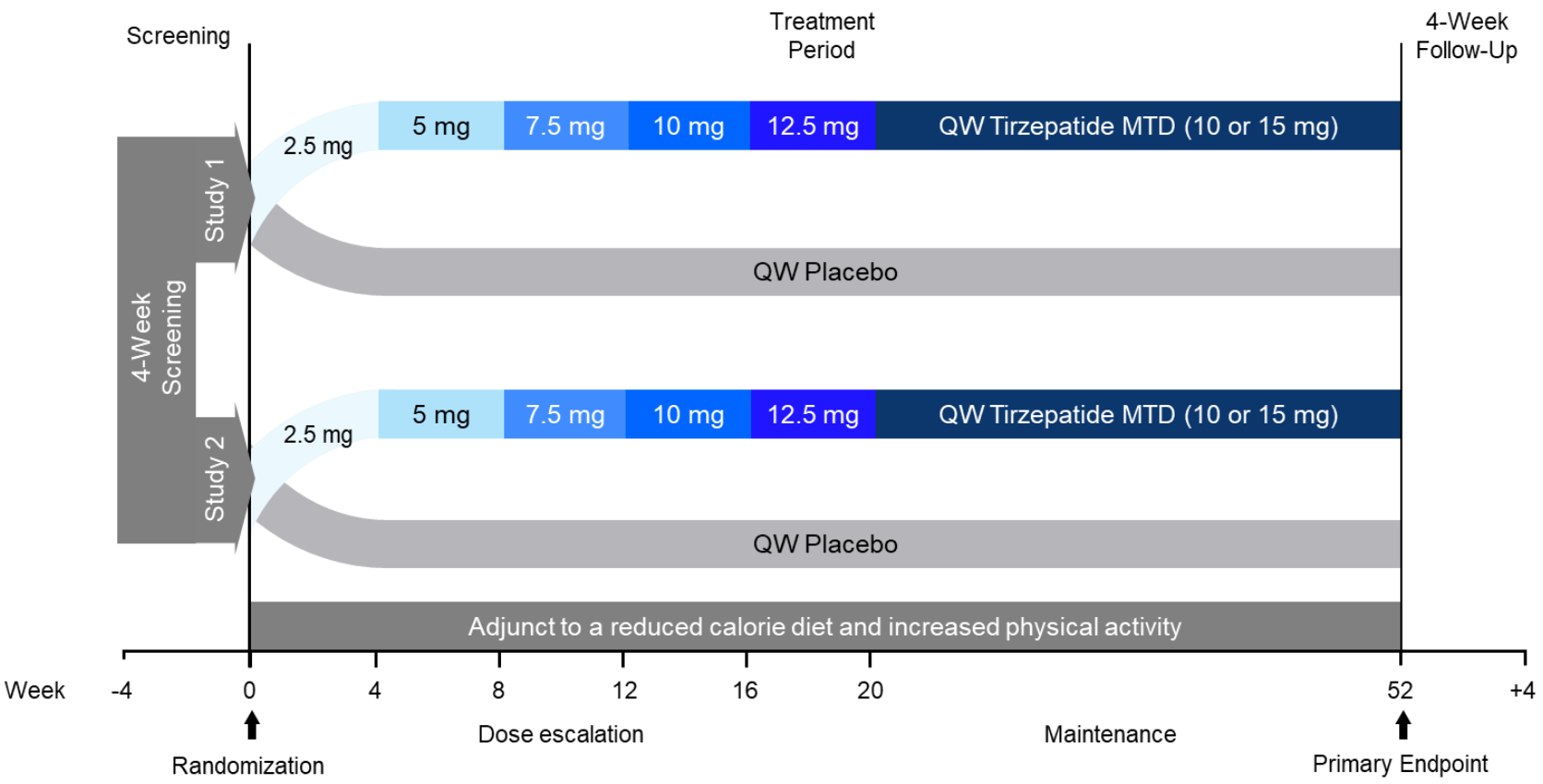
[f] Centre of Sleep Medicine, Charité University Hospital Berlin, Berlin, Germany
[g] Harvard Medical School, Boston, MA, USA
[h] Division of Sleep Medicine, Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

SURMOUNT-OSA Master Protocol Design

Two Randomized, Double-Blind, Multicenter, Placebo-Controlled Trials



KEY FEATURES:

- Study 1 not on PAP therapy
- Study 2 on PAP therapy
- Randomization stratified by study, country/geographic region, baseline AHI category and sex
- Upper limit of 70% enrollment of men to ensure a sufficiently large sample of female participants
- Dose escalated in 2.5 mg increments up to the maximum-tolerated dose of 10 mg or 15 mg in Week 20
- All participants received regular lifestyle counseling sessions for
  - healthy nutrition with a 500 kcal/day deficit and
  - ≥150 min/week of physical activity
- In Study 2, participants were to suspend PAP 7 days prior to PSG

Abbreviations: AHI = apnea-hypopnea index; MTD = maximum-tolerated dose; OSA = obstructive sleep apnea; PAP = positive airway pressure; PSG = polysomnography; QW = once weekly.

Malhotra A, et al. *Contemp Clin Trials* 2024;141:107516

Key Inclusion and Exclusion Criteria

- Key Inclusion Criteria
  - Age ≥18 years
  - Moderate-to-severe OSA with AHI ≥15 events/hour
  - BMI ≥30 kg/m^2
- Key Exclusion Criteria
  - Type1 or Type 2 Diabetes

Malhotra A, et al. *Contemp Clin Trials 2024;141:107516*

Primary Objective

- To demonstrate that tirzepatide at the maximum-tolerated dose (10 mg or 15 mg) once-weekly is superior to placebo for change in AHI from baseline to Week 52

CURRENT OPINION

Glucagon-like peptide-1 receptor agonists for the treatment of obstructive sleep apnea

Danielle A. D'Annibale[a], Mizuho Mimoto[a,c], Karen C. McCowen[a,c] and Atul Malhotra[a,b]

Journal of Diabetes

WILEY

Journal of Diabetes

COMMENTARY OPEN ACCESS

The Role of Incretins in Obstructive Sleep Apnea "GLP1RAs and GLP1RA/GIPRAs in OSA"

Ana Lucia Fuentes[1] | Gurleen Dhami[2] | Jeremy Pettus[3] | Praveen Akuthota[1] | Atul Malhotra[1]

[1]Department of Pulmonary, Critical Care, Sleep Medicine, and Physiology, University of California, San Diego, California, USA | [2]Department of Pharmacology, University of California, Santa Barbara, California, USA | [3]Department of Endocrinology, University of California, San Diego, California, USA

Malhotra A, et al. *Contemp Clin Trials 2024;141:107516; Current Opinion in Pulmonary Medicine 2025; J Diabetes 2025*

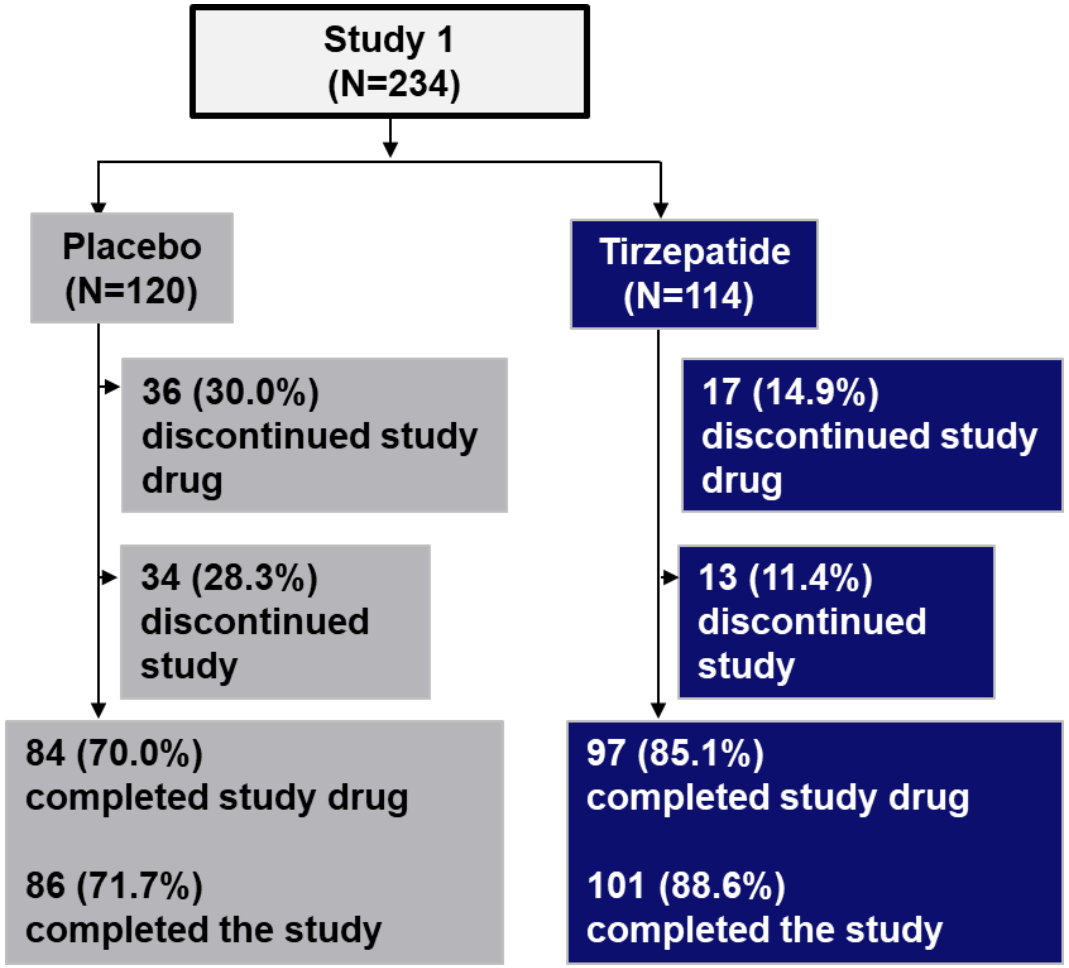
Key Secondary Objectives (Controlled for Type 1 Error)

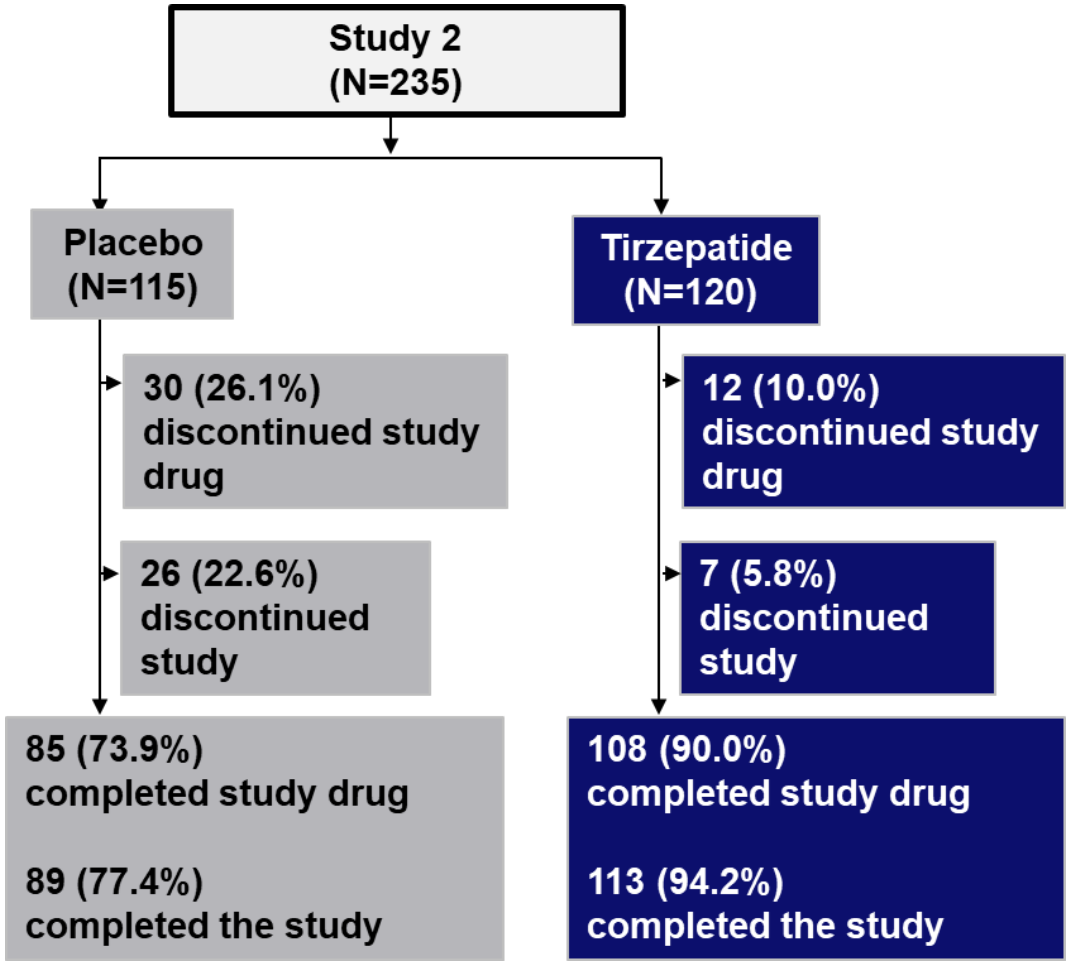
Sleep-Disordered Breathing-Related

- To demonstrate that tirzepatide is superior to placebo from baseline to Week 48-52 for:
  - Percent change in AHI
  - Change in sleep-specific hypoxic burden (SASHB, % min/hour)
  - SBP, hsCRP
  - Symptoms PROMIS scores

Malhotra A, et al. *Contemp Clin Trials 2024;141:107516*

Study and Treatment Completion Rates





Randomized population

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity

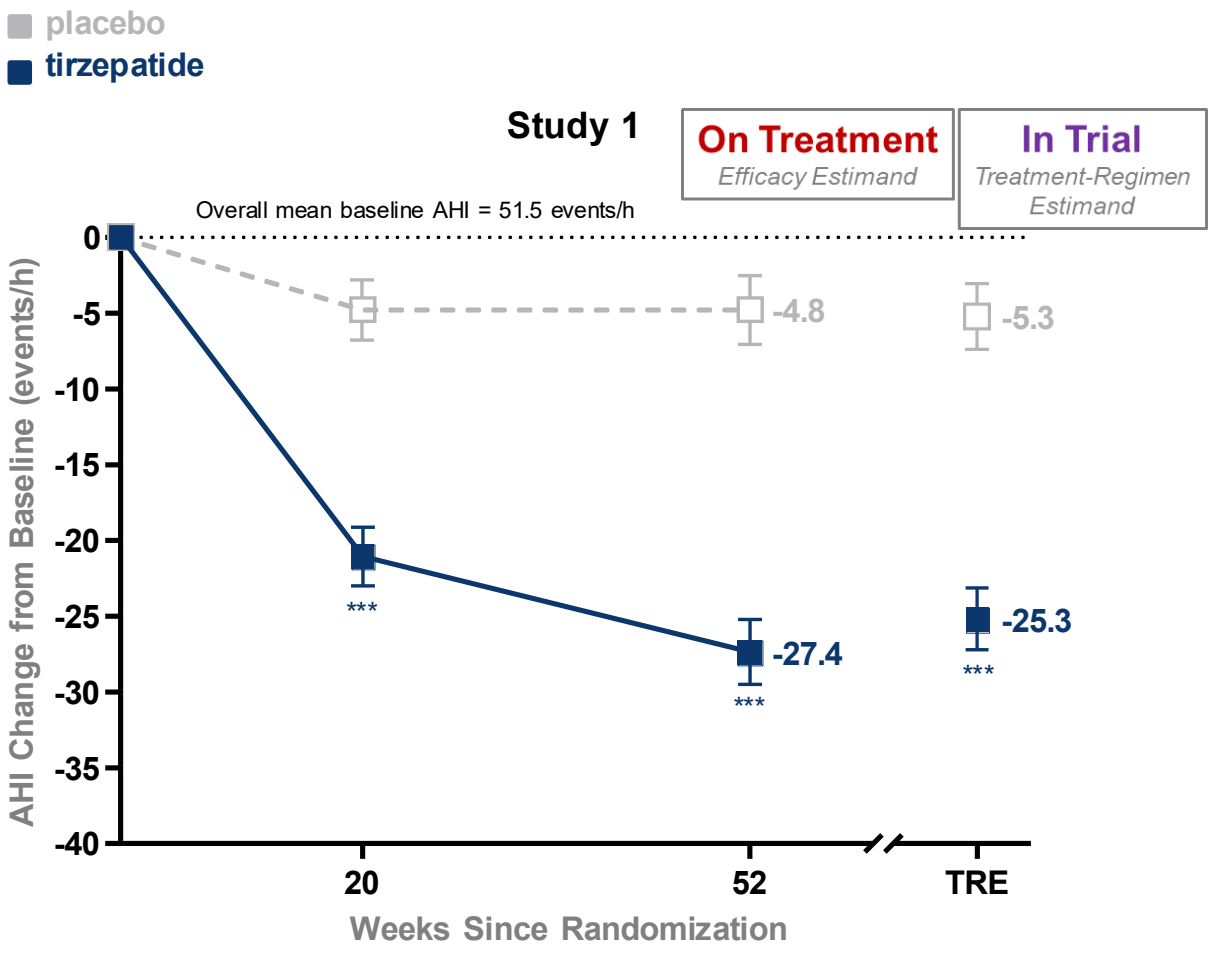
Atul Malhotra, M.D., Ronald R. Grunstein, M.D., Ph.D., Ingo Fietze, M.D., Terri E. Weaver, Ph.D., Susan Redline, M.D., M.P.H., Ali Azarbarzin, Ph.D., Scott A. Sands, Ph.D., Richard J. Schwab, M.D., Julia P. Dunn, M.D., Sujatro Chakladar, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Josef Bednarik, M.D., M.B.A., for the SURMOUNT-OSA Investigators*

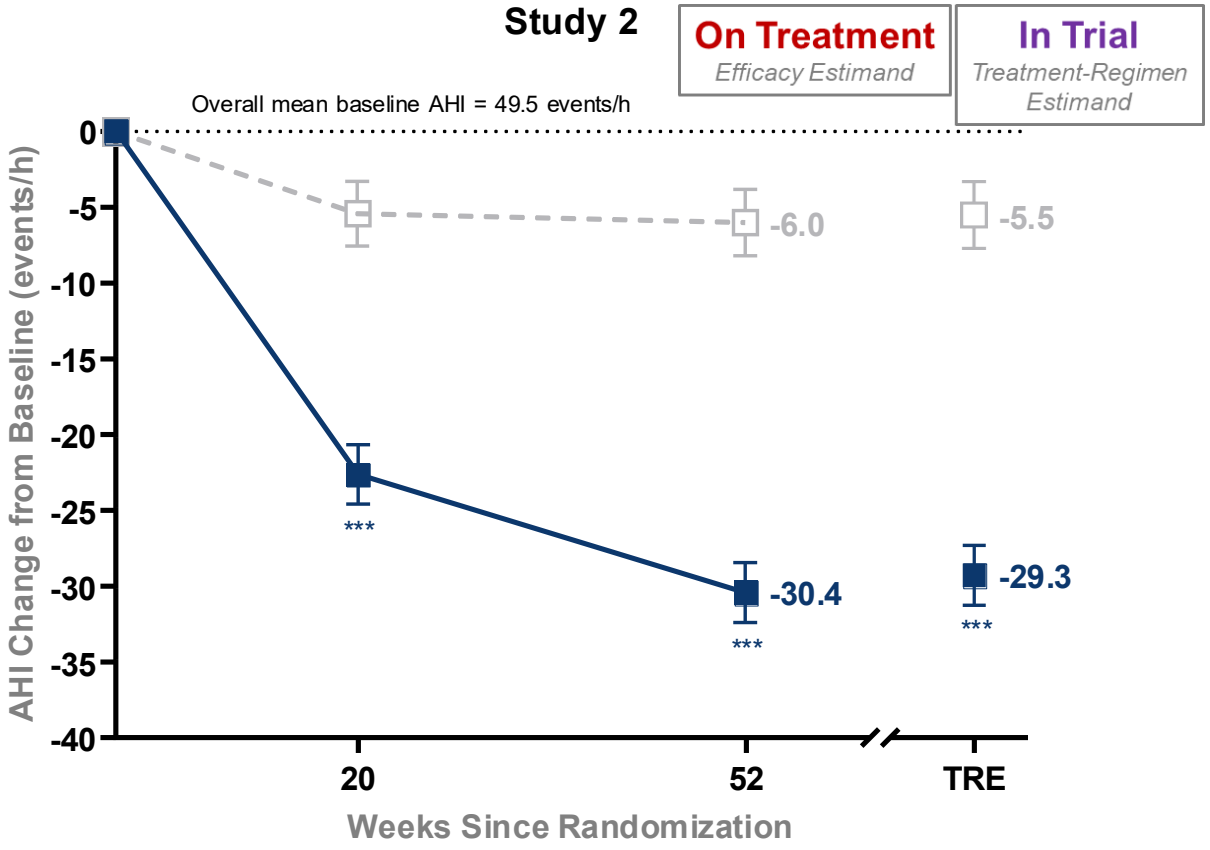
FDA approved 12/20/24

Primary Outcome

Change From Baseline in AHI Over 52 Weeks

Absolute Change





Tirzepatide vs. placebo ***p<0.001.

Key Secondary Outcomes
Cardiovascular-Related

EXPERT REVIEW OF CARDIOVASCULAR THERAPY
https://doi.org/10.1080/14779072.2025.2561067

Taylor & Francis
Taylor & Francis Group

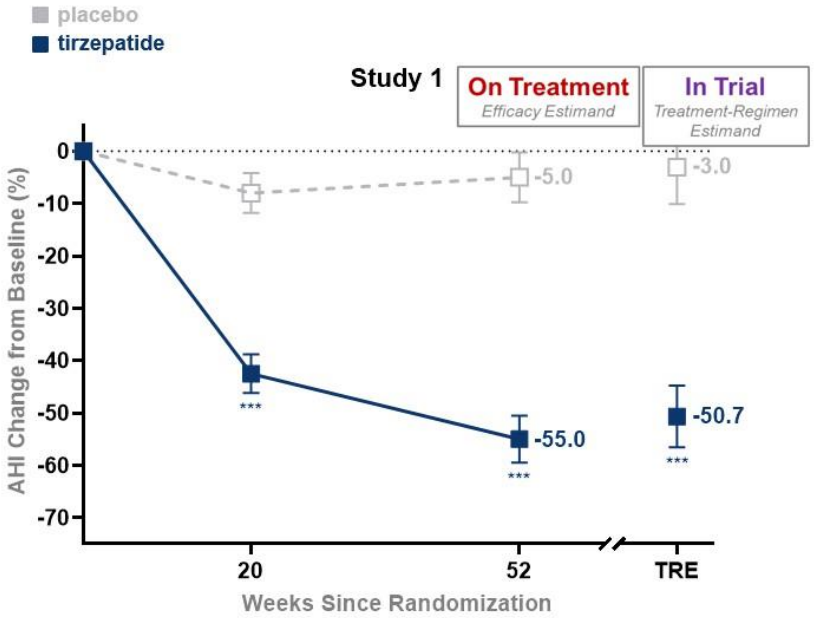
EDITORIAL

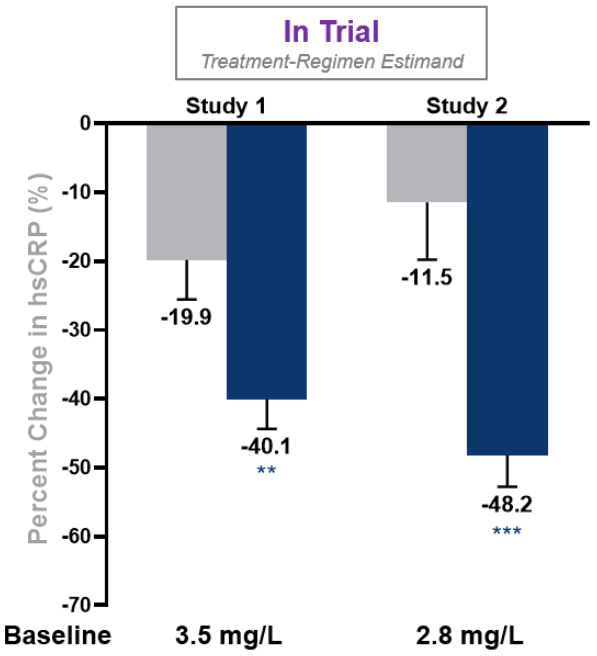
Check for updates

What impact could tirzepatide have on major cardiovascular complications in patients with obstructive sleep apnea?

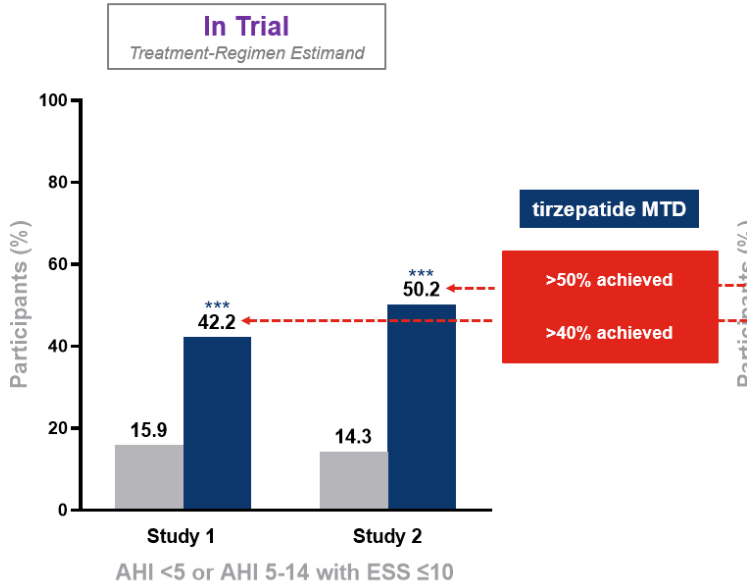
Avnee J. Kumar, Samantha Scroggie, Tia De Sarkar, Mark Hepokoski and Atul Malhotra

Division of Pulmonary, Critical Care, Sleep Medicine, and Physiology, University of California San Diego Department of Medicine, San Diego, CA, USA

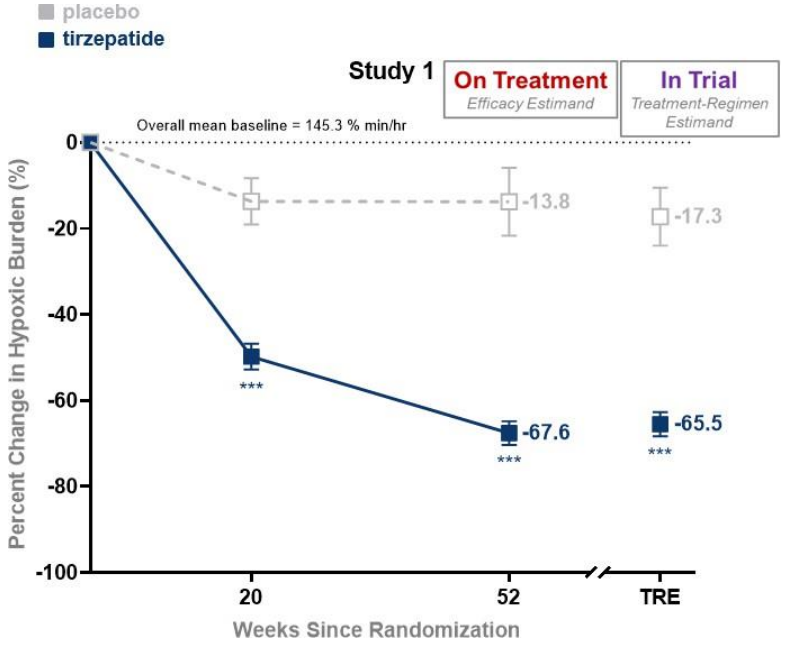


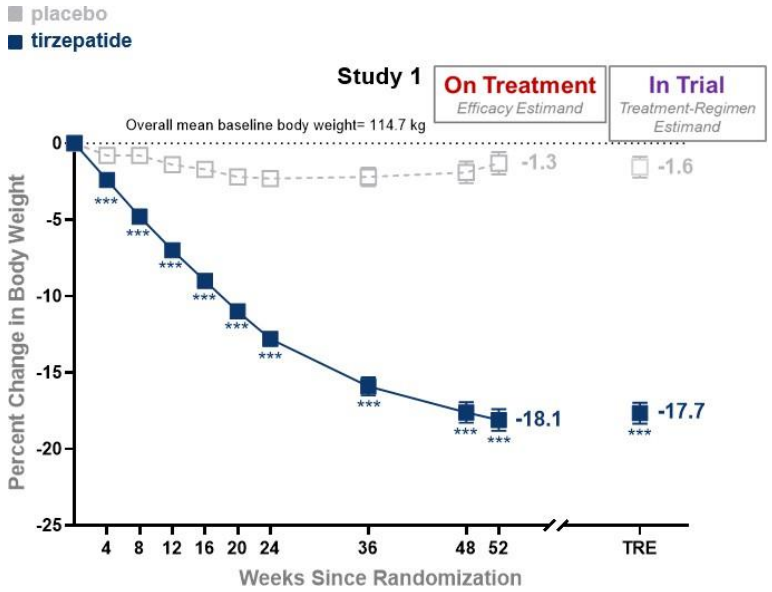


Percent of Participants With AHI < AHI 5-14 events/h with ESS ≤10 at



patide vs. placebo ***p<0.001, **p<0.01.





Key Secondary Outcomes
Patient-Reported Outcomes-Related

Sleep Medicine 134 (2025) 106719

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Effect of tirzepatide treatment on patient-reported outcomes among SURMOUNT-OSA participants with obstructive sleep apnea and obesity

Chisom Kanu [a,*], Shraddha Shinde [a], Sujatro Chakladar [a], Ellen B. Dennehy [a], Terri E. Weaver [b,c], Jiat Ling Poon [a], Atul Malhotra [d]

[a] Eli Lilly and Company, Indianapolis, IN, USA
[b] College of Nursing, University of Illinois Chicago, Chicago, IL, USA
[c] University of Pennsylvania School of Nursing, Philadelphia, PA, USA
[d] University of California San Diego, La Jolla, CA, USA

nature medicine

Article https://doi.org/10.1038/s41591-025-04071-1

Tirzepatide on obstructive sleep apnea-related cardiometabolic risk: secondary outcomes of the SURMOUNT-OSA randomized trial

Article https://doi.org/10.1038/s41591-025-04071-1

Atul Malhotra[1], Ronald Grunstein[2], Ali Azarbarzin[3], Scott Sands[3], Virend K. Somers[4], Louis J. Aronne[5], Ania M. Jastreboff[6], Jitong Lou[7], Sujatro Chakladar[7], Julia P. Dunn[7], Mathijs C. Bunck[7] & Josef Bednarik[7]

[1]University of California San Diego, La Jolla, CA, USA. [2]Woolcock Institute of Medical Research, Macquarie University and Royal Prince Alfred Hospital,

Mediation analyses show variable effects of OSA vs. obesity vs. GLP1RA

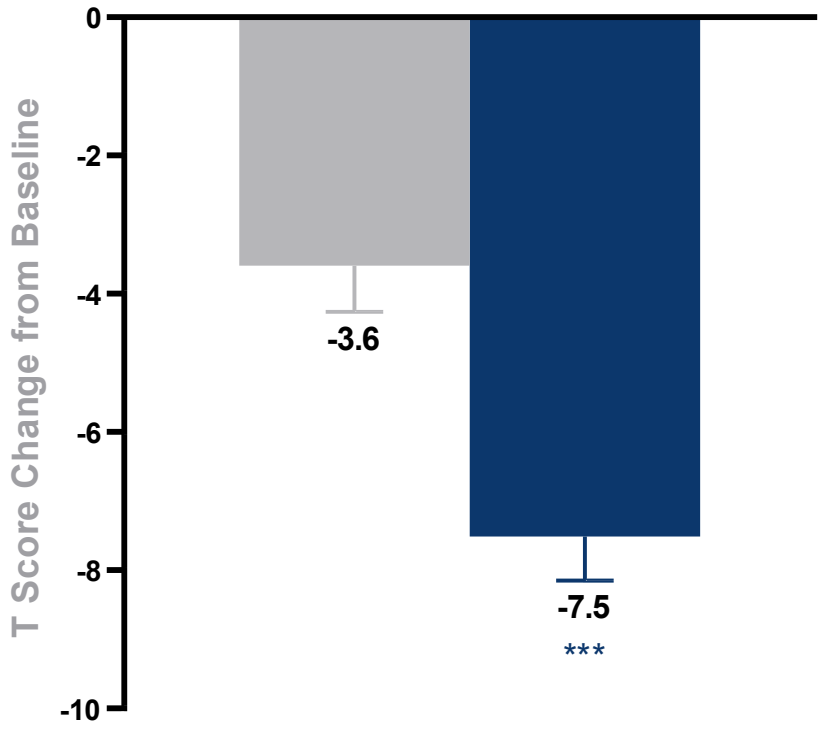
Change from Baseline in Pooled PROMIS Scores at Week 52

Absolute Change

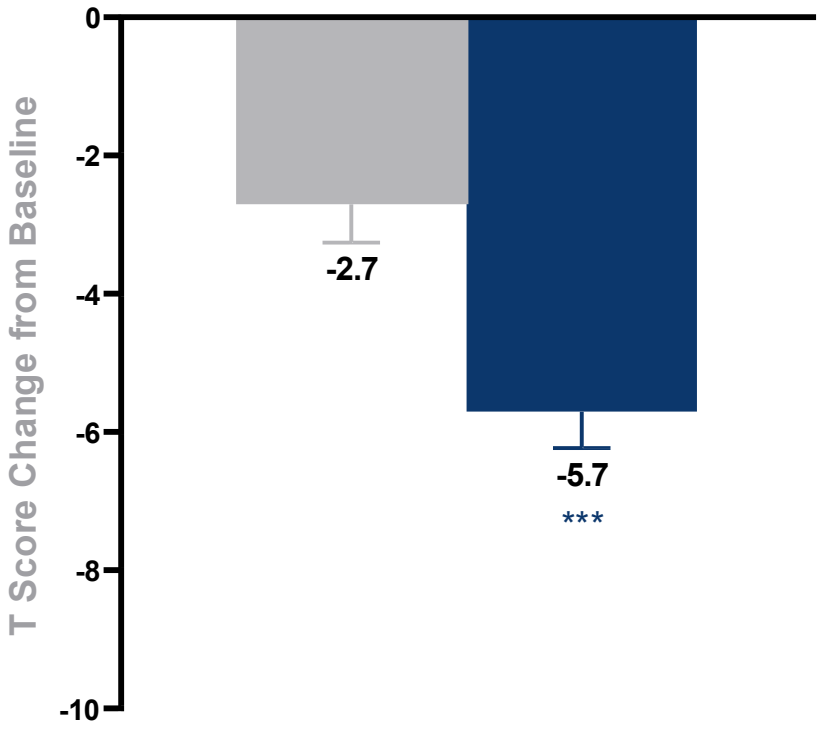
In Trial
Treatment-Regimen Estimand

placebo
tirzepatide

Pooled PROMIS Sleep-Related Impairment Score



Pooled PROMIS Sleep Disturbance Score



Sleep Medicine 2025

Tirzepatide vs. placebo ***p<0.001.

Safety

Overview of Adverse Events

	Study 1		Study 2	
Parameter	Placebo (N=120)	Tirzepatide (N=114)	Placebo (N=115)	Tirzepatide (N=120)
Deaths	0	0	0	0
Serious Adverse Events	7 (5.8)	9 (7.9)	12 (10.5)	7 (5.9)
Discontinuations from Study due to an AE	2 (1.7)	0	5 (4.4)	1 (0.8)
Discontinuations from Study Drug due to an AE	2 (1.7)	5 (4.4)	8 (7.0)	4 (3.4)
Treatment-Emergent Adverse Events	92 (76.7)	91 (79.8)	83 (72.8)	99 (83.2)

Data are number of participants (%).

Study 1 Treatment Emergent Adverse Events

With ≥5% Frequency in Any Treatment Arm

	Study 1	
Parameter	**Placebo** (N=120) **n (%)**	**Tirzepatide** (N=114) **n (%)**
Diarrhea	15 (12.5)	30 (26.3)
Nausea	12 (10.0)	29 (25.4)
Vomiting	5 (4.2)	20 (17.5)
Constipation	3 (2.5)	18 (15.8)
Eructation	0	9 (7.9)
Gastroesophageal reflux disease	1 (0.8)	9 (7.9)
Injection site reaction	1 (0.8)	8 (7.0)
Abdominal pain	4 (3.3)	7 (6.1)
Upper respiratory tract infection	10 (8.3)	7 (6.1)
COVID-19	10 (8.3)	6 (5.3)
Nasopharyngitis	8 (6.7)	3 (2.6)
Influenza	8 (6.7)	4 (3.5)
Hypertension	8 (6.7)	1 (0.9)
Arthralgia	6 (5.0)	3 (2.6)

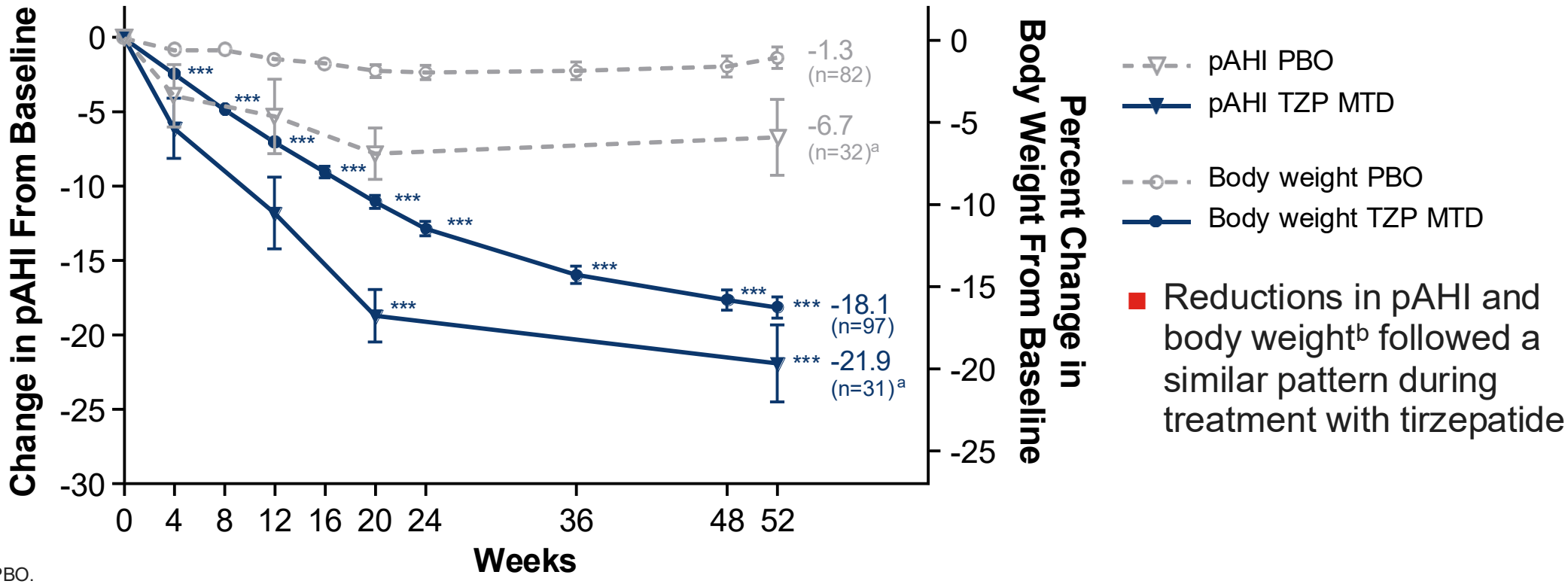
The majority of TEAEs were gastrointestinal in nature.

Adverse Events of Special Interest

	Study 1		Study 2	
Parameter	Placebo (N=120)	Tirzepatide (N=114)	Placebo (N=115)	Tirzepatide (N=120)
Severe hypoglycemia	1 (0.8)	0	1 (0.9)	0
Adjudication-confirmed MACE*	0	0	1 (0.9)	0
Treatment-emergent arrythmias and cardiac conduction disorders	9 (7.5)	7 (6.1)	2 (1.8)	6 (5.0)
Severe or serious gastrointestinal events	0	4 (3.5)	0	4 (3.4)
Severe or serious hepatic events	0	0	0	0
Severe or serious acute renal events	0	0	0	1 (0.8)
Adjudication-confirmed acute pancreatitis	0	0	0	2 (1.7)
C-cell hyperplasia and thyroid malignancies	0	0	0	0
Severe or serious major depressive disorder/suicidal ideation or behavior events	1 (0.8)	2 (1.8)	2 (1.8)	0
Severe or serious allergic/hypersensitivity reactions	0	0	0	0

Data are number of participants (%). *Major adverse cardiac events (MACE) included but not limited to cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, and hospitalization for heart failure.

Measurements of pAHI Demonstrated Early Reductions in Sleep-Disordered Breathing During Treatment With Tirzepatide



- Reductions in pAHI and body weight[b] followed a similar pattern during treatment with tirzepatide

***p<0.001 vs. PBO.

[a]Only participants with pAHI non-missing baseline value and ≥1 pAHI non-missing post-baseline value were included in the analysis; [b]Changes from baseline in body weight were previously reported[5].

Notes: Data are LSM (SE) unless specified otherwise. MMRM model for post-baseline measures: variable=Baseline+Geographic Region+Baseline OSA Severity Group (only for Body Weight)+Sex+Treatment+Time+Treatment*Time (Type III sum of squares); variance-covariance structure (change from baseline)=unstructured. Error bars not displayed for data points where the error bar is smaller than the symbol size. Week 0 pAHI (events/hour; LSM±SE) was 45.4±3.4 (n=58) for placebo and 45.4±3.4 (n=59) for tirzepatide MTD; Week 0 body weight (kg; LSM±SE) was 112.7±2.2 (n=115) for placebo and 117.0±2.3 (n=112) for tirzepatide MTD.

LS=least squares; MMRM=mixed model for repeated measures; MTD=maximum tolerated dose; OSA=obstructive sleep apnea; pAHI=peripheral apnea-hypopnea index; PBO=placebo; SE=standard error; TZP=tirzepatide.

5. Malhotra A, et al. *N Engl J Med*. 2024;391:1193-1205.

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- In the SURMOUNT-OSA Study 1 (not on PAP therapy), measurement of pAHI with WatchPAT demonstrated clinically meaningful improvement in sleep-disordered breathing with tirzepatide treatment in adults with moderate-to-severe OSA with obesity:
  - Significant improvements vs. baseline were observed as early as Week 4
  - Improvements were statistically significant compared with placebo at Week 20 and Week 52
- Reductions in pAHI were accompanied by statistically significant reductions in body weight

> Sleep Med. 2025 Oct 14:136:106853. doi: 10.1016/j.sleep.2025.106853. Online ahead of print.

Tirzepatide for sleep-disordered breathing in SURMOUNT-OSA: Time course and association with body weight

Atul Malhotra [1], Ronald R Grunstein [2], Ali Azarbarzin [3], Scott A Sands [3], Xiangnan Dang [4], Sujatro Chakladar [4], Julia P Dunn [4], Beverly Falcon [4], Josef Bednarik [5]

Affiliations + expand

PMID: 41135142 DOI: 10.1016/j.sleep.2025.106853

OSA=obstructive sleep apnea; pAHI=peripheral apnea-hypopnea index; PAP=positive airway pressure; PSG=polysomnography.

5. Malhotra A, et al. *N Engl J Med*. 2024;391:1193-1205.

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SURMOUNT-OSA Key Takeaways

- Tirzepatide MTD demonstrated superior and clinically meaningful improvement of OSA-related sleep-disordered breathing.
- Tirzepatide MTD demonstrated superior improvement of patient-reported quality of sleep and sleep-related functioning.
- Treatment with tirzepatide MTD translated to clinically meaningful improvements in OSA and obesity-related CV risk factors.
- The safety and tolerability profile of tirzepatide in people with moderate-to-severe OSA and obesity was generally consistent with the safety profile of tirzepatide and incretin-based therapies in people with obesity.
- Mediation analyses (obesity vs. OSA vs. GLP1ra)
  now in press at Nature Medicine

FAQ: What is in the future for GLP1RA

Aging Clinical and Experimental Research (2024) 36:185
https://doi.org/10.1007/s40520-024-02825-4

Check for updates

Effect of Bimagrumab on body composition: a systematic review and meta-analysis

Mehmet Kanbay[1] · Dimitrie Siriopol[2,3] · Sidar Copur[4] · Nuri Baris Hasbal[1] · Mustafa Güldan[4] · Kam Kalantar-Zadeh[5,6,7,8] · Tania Garfias-Veitl[9] · Stephan von Haehling[9]

Received: 25 March 2024 / Accepted: 30 July 2024
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Eloralintide, a selective amylin receptor agonist for the treatment of obesity: a 48-week phase 2, multicentre, double-blind, randomised, placebo-controlled trial

Liana K Billings, Stanley Hsia, Harold Bays, Beth Tidemann-Miller, Jessica O'Hagan, Lai San Tham, Annabelle Butler, Christof Kazda, Kieren J Mather, Tamer Coskun

Summary
Background Amylin-based therapies are emerging as promising obesity medications. Eloralintide is a novel, selective amylin receptor agonist in development for weight management. We performed a phase 2, double-blind, randomised, placebo-controlled trial with the aim of evaluating the efficacy and safety of a range of doses and dose escalation schemes of once-per-week eloralintide versus placebo in adults with obesity or overweight and had at least one weight-related comorbidity

Lancet 2025; 406: 2631–43
Published Online November 6, 2025
https://doi.org/10.1016/S0140-6736(25)02155-5

WVE007 for siRNA

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 7, 2023 VOL. 389 NO. 10

Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity

Sean Wharton, M.D., Thomas Blevins, M.D., Lisa Connery, M.D., Julio Rosenstock, M.D., Sohini Raha, Ph.D., Rong Liu, Ph.D., Xiaosu Ma, Ph.D., Kieren J. Mather, M.D., Axel Haupt, M.D., Deborah Robins, M.S., Edward Pratt, M.D., Christof Kazda, M.D., and Manige Konig, M.D., Ph.D., for the GZGI Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial

Ania M. Jastreboff, M.D., Ph.D., Lee M. Kaplan, M.D., Ph.D., Juan P. Frías, M.D., Qiwei Wu, Ph.D., Yu Du, Ph.D., Sirel Gurbuz, M.D., Tamer Coskun, M.D., Ph.D., Axel Haupt, M.D., Ph.D., Zvonko Milicevic, M.D., and Mark L. Hartman, M.D., for the Retatrutide Phase 2 Obesity Trial Investigators*

Ongoing studies with newer agents
ATTAIN – OSA
Triumph
Believe
? Combinations of therapies

FDA approval pending for these in 2026-27

Conclusion

- Exciting time for OSA field
- Pharmacotherapy is here
- a number of new FDA approved therapies
- Individualizing therapy may be viable
- Ongoing research

Frequently Asked Question 1: Are These drugs Long term

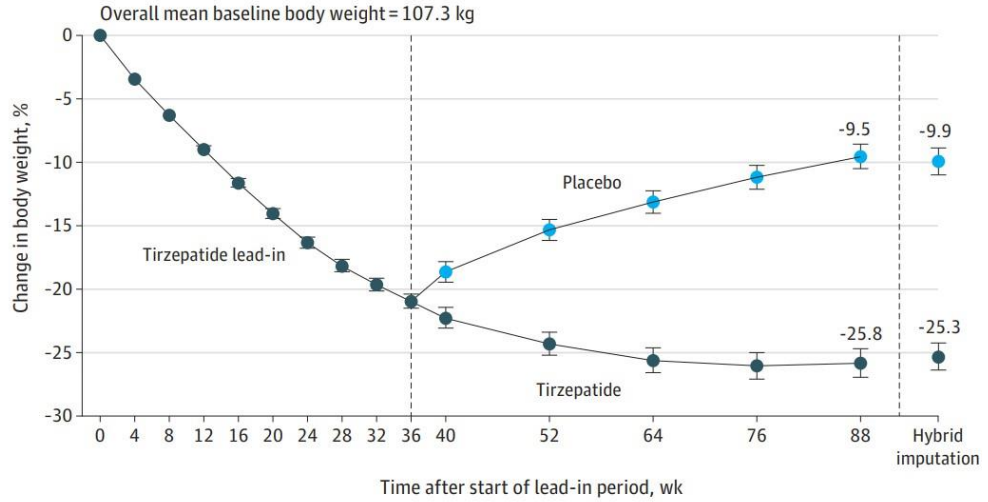
Short answer is yes

JAMA | Original Investigation

Continued Treatment With Tirzepatide for Maintenance of Weight Reduction in Adults With Obesity
The SURMOUNT-4 Randomized Clinical Trial

Louis J. Aronne, MD; Naveed Sattar, MD; Deborah B. Horn, DO, MPH; Harold E. Bays, MD; Sean Wharton, MD; Wen-Yuan Lin, MD, PhD; Nadia N. Ahmad, MD, MPH; Shuyu Zhang, MSc; Ran Liao, PhD; Mathijs C. Bunck, MD, PhD; Irina Jouravskaya, MD, PhD; Madhumita A. Murphy, MD; for the SURMOUNT-4 Investigators

Figure 2. Effect of Tirzepatide vs Placebo on Body Weight and Waist Circumference



No. at risk

Tirzepatide lead-in	670 666 669 668 667 667 669 663 659 670						
Tirzepatide	335 333	328	317	310	310	335	
Placebo	335 330	317	303	292	289	335	

Can maintain weight loss via diet and exercise perhaps
Newer agents are in development to maintain skeletal muscle and/or oral maintenance
Long term followup of SURMOUNT 1 shows 93% reduced incident DM at 3 years NEJM 2025

Frequently Asked Question 2: Should PCCSM Providers be Prescribing GLP1RA

Yes probably but some logistic challenges:

1. Insurance approvals/ prior authorizations/appeals
2. Registered dietician visits
3. Access to clinic backlogs
4. Need to be able to assess/handle complications

FAQ 3: Are They Expensive?

Short answer is yes

Insurance coverage is pretty good in general even for under-compensated

Reduced cost of complications including DM, dialysis etc

Reduced costs of food, alcohol, tobacco, gambling

Was $500/month on Lilly direct – maybe lower now with political influence

FAQ 4: Do You Lose Skeletal Muscle with GLP1RA ?

Short answer is yes

Can mitigate with resistance exercise
Potentially with protein intake food
Roughly 20% of the weight loss is skeletal muscle ? Estimates vary
Skeletal muscle agents are in development by many major companies

Some amount of loss of muscle and bone density is appropriate as class 3 obesity resolves

FAQ 6: Is the mechanism of improvement in SURMOUNT-OSA weight loss?

The degree of improvement in AHI is largely predictable from the change in BMI

However, the marked improvement in SBP and other variables to me suggests some off target effects

e.g. carotid body, orexinergic, dopamine reward

Hedonic eating

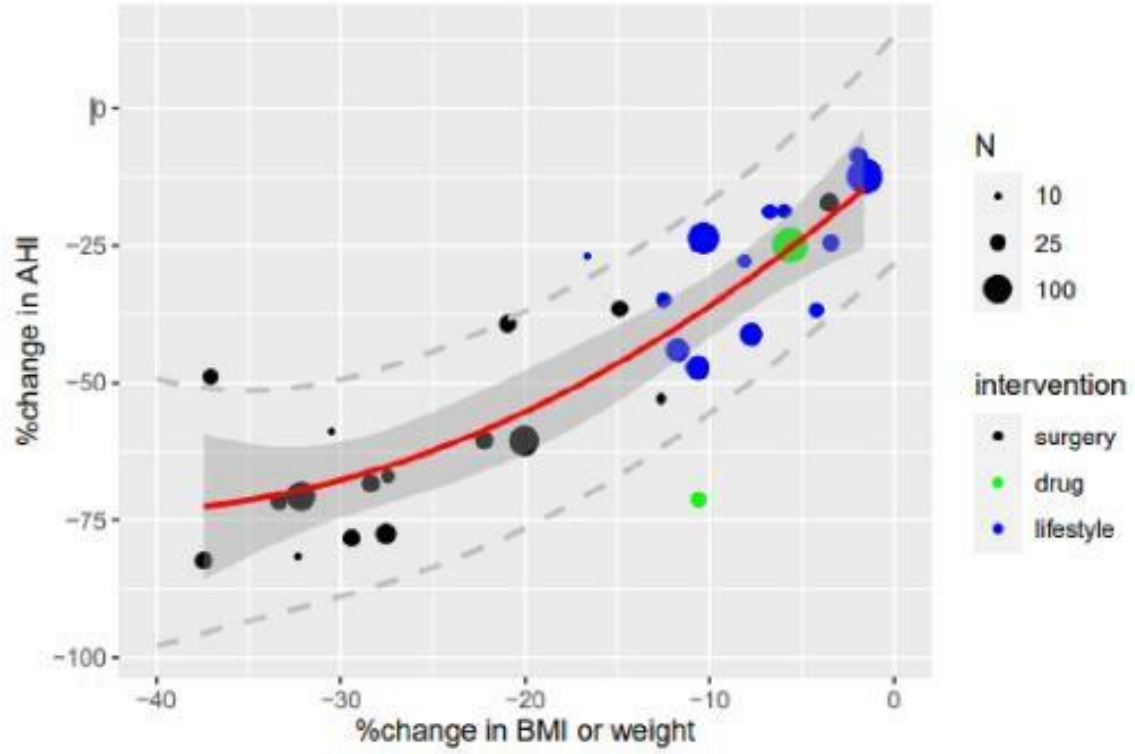


Fig. 2. Apnea-hypopnea index versus weight reduction inference. Abbreviations: AHI, apnea-hypopnea index; N, population size.

CPAP is Here to Stay
Malhotra and Pettus
Lancet Respiratory Medicine 2024

THE LANCET
Respiratory Medicine

1. Some OSA patients are lean or overweight
2. Some have huge BMI wont lose enough
3. Some lose weight and have residual AHI (Dixon JAMA 2012)
4. Some lose weight then regain it
5. Some lose weight and reacquire OSA even if they maintain weight loss (Pillar Chest 1994)
6. Treating both OSA and obesity is optimal for metabolic outcomes (Chirinos NEJM 2014)