Obstructive Sleep Apnea Disease State

Disclaimer

- This information is provided in response to your unsolicited request and is intended for your scientific and/or educational purpose and is not intended for promotional use and its use is at your discretion.
- This information may contain substantive discussion of developmental compound(s) not approved for marketing and/or products approved for marketing but for uses, dosages, formulations, and/or populations different than those discussed in these materials.
- For marketed products, please consult the product labelling for information on the specific uses, dosages, formulations and populations for which they are approved. Refer to www.lilly.com for labelling material if it has not been provided.

Content Overview

Disease Overview

Background and Classification

Global Prevalence

Disease Symptoms

Etiology

Risk Factors and Causes

Weight Reduction and OSA

OSA-related Comorbidities

Diagnosis

OSA Screening

Diagnostic Tools

- Polysomnography
- Home Sleep Apnea Testing

Management

Treatment Methods

Success Rate and Efficiency of Treatment Methods for OSA

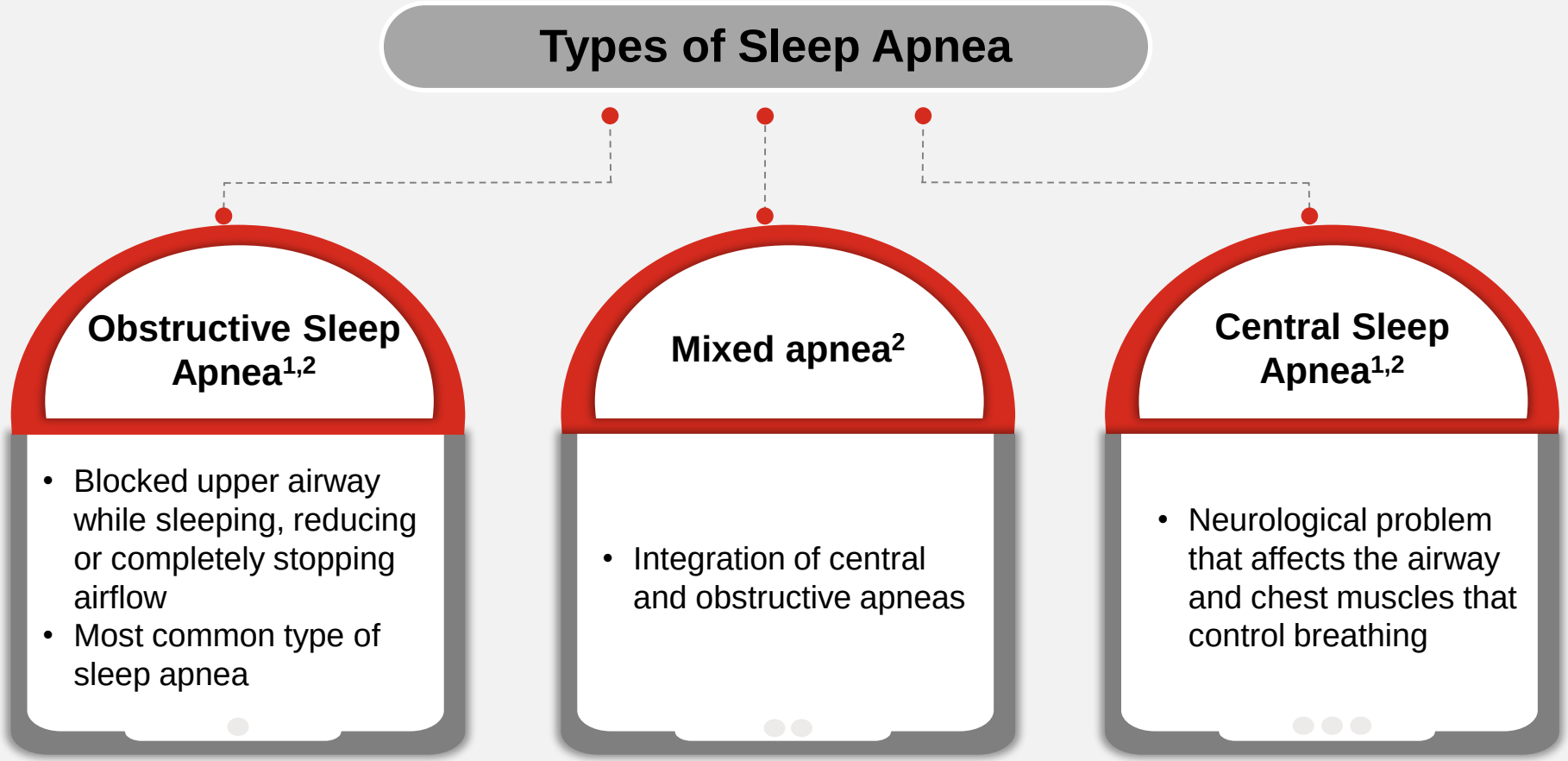
Pharmacological Therapy

OSA=Obstructive Sleep Apnea.

Obstructive Sleep Apnea Overview

Background

Sleep apnea is characterized by a temporary interruption of breathing during sleep[1,2]

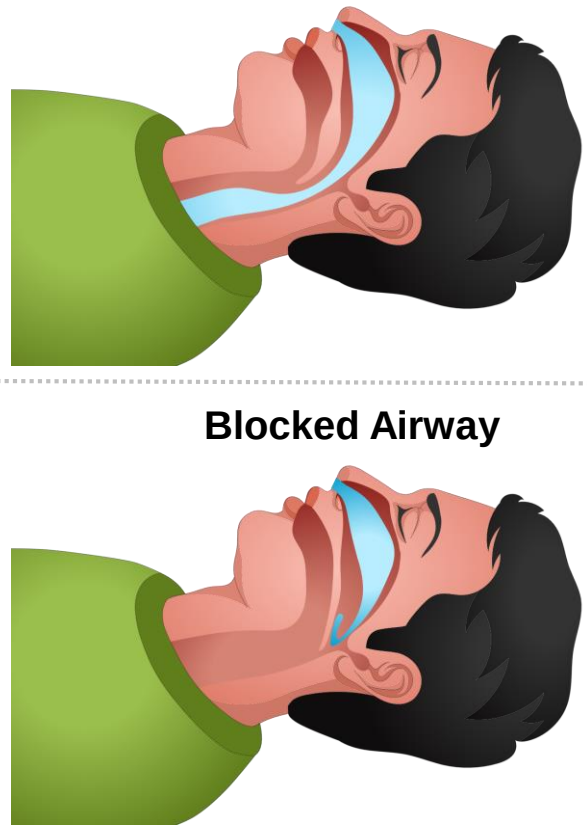


1. Sleep Apnea - What Is Sleep Apnea? | NHLBI, NIH. https://www.nhlbi.nih.gov/health/sleep-apnea. Updated 24 March, 2022; Accessed 24 June 2022. 2. Yang X, et al. *Sleep Breath*. 2019;23(2):559-565.

Obstructive Sleep Apnea

Obstructive sleep apnea is characterised by:

- **Apnea** - A drop in air flow by ≥90% of pre-event baseline for ≥10 sec
- **Hypopnea** - A drop in air flow by ≥30% of pre-event baseline for ≥10 sec and a ≥3% oxygen desaturation from baseline or the event is associated with an arousal



Chang J, et al. *Int Forum Allergy Rhinol.* 2022;doi:10.1002/alr.23079 (Online ahead of print).

Severity and Prevalence of OSA

Severity of OSA is quantified by AHI[1]

AHI defines the number of apneas or hypopneas per hour of sleep

Mild OSA: ≥5 AHI to <15 AHI per h

Moderate OSA: ≥15 AHI to <30 AHI per h

Severe OSA: ≥30 AHI per h

Estimated Prevalence[2]

AHI ≥5 events/h	936 million†
AHI ≥15 events/h	425 million†

AHI defines the number of apneas or hypopneas per hour of sleep[1]
*Estimated prevalence in the USA in individuals who are 30-69 years old using AHI ≥5 events per h with hypopnea defined as ≥30% decrease in flow from baseline with an associated oxygen desaturation of ≥4%.
†Prevalence of global OSA estimated in individuals in the age group of 30-69 years with hypopnea defined as ≥30% decrease in flow from baseline with an associated oxygen desaturation of ≥3% or an associated arousal

AHI=Apnea-Hypopnea Index; OSA=Obstructive Sleep Apnea.

1. Chang JL. *Int Forum Allergy Rhinol*. 2022. doi:10.1002/alr.23079. 2. Benjafield AV, et al. *Lancet Respir Med*. 2019;7(8):687-698.

Estimated Global Prevalence of OSA (1/2)

Top 10 countries with the highest estimated number of individuals with OSA based on the AASM 2012 criteria*

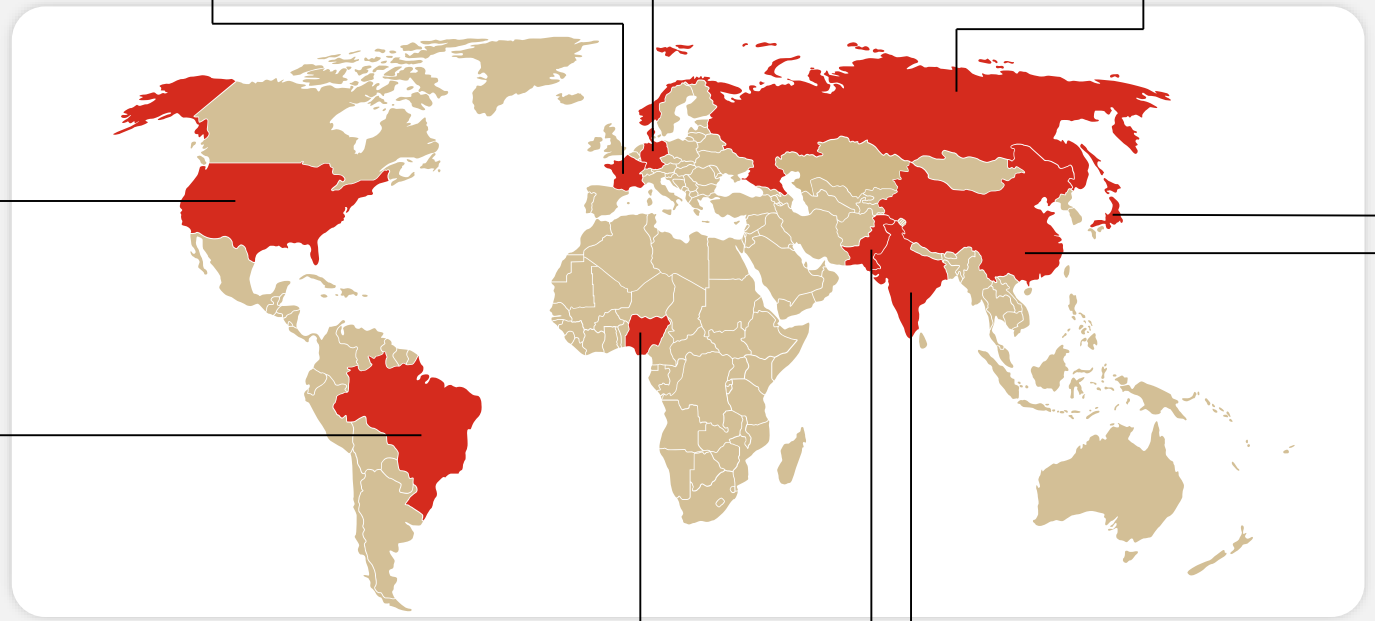
USA
AHI ≥5 events per h: 54 million (33.2%)
AHI ≥15 events per h: 24 million (14.5%)

France
AHI ≥5 events per h: 24 million (72.1%)
AHI ≥15 events per h: 12 million (36.3%)

Germany
AHI ≥5 events per h: 26 million (60.1%)
AHI ≥15 events per h: 14 million (32.9%)

Russia
AHI ≥5 events per h: 40 million (51.4%)
AHI ≥15 events per h: 20 million (25.6%)

Japan
AHI ≥5 events per h: 22 million (32.7%)
AHI ≥15 events per h: 9 million (14.0%)



Brazil
AHI ≥5 events per h: 49 million (49.7%)
AHI ≥15 events per h: 25 million (26.0%)

Nigeria
AHI ≥5 events per h: 31 million (60.2%)
AHI ≥15 events per h: 12 million (22.8%)

Pakistan
AHI ≥5 events per h: 42 million (65.9%)
AHI ≥15 events per h: 17 million (27.0%)

India
AHI ≥5 events per h: 52 million (9.6%)
AHI ≥15 events per h: 29 million (5.4%)

China
AHI ≥5 events per h: 176 million (23.6%)
AHI ≥15 events per h: 66 million (8.8%)

*Estimates of OSA prevalence focused on individuals aged 30-69 years.

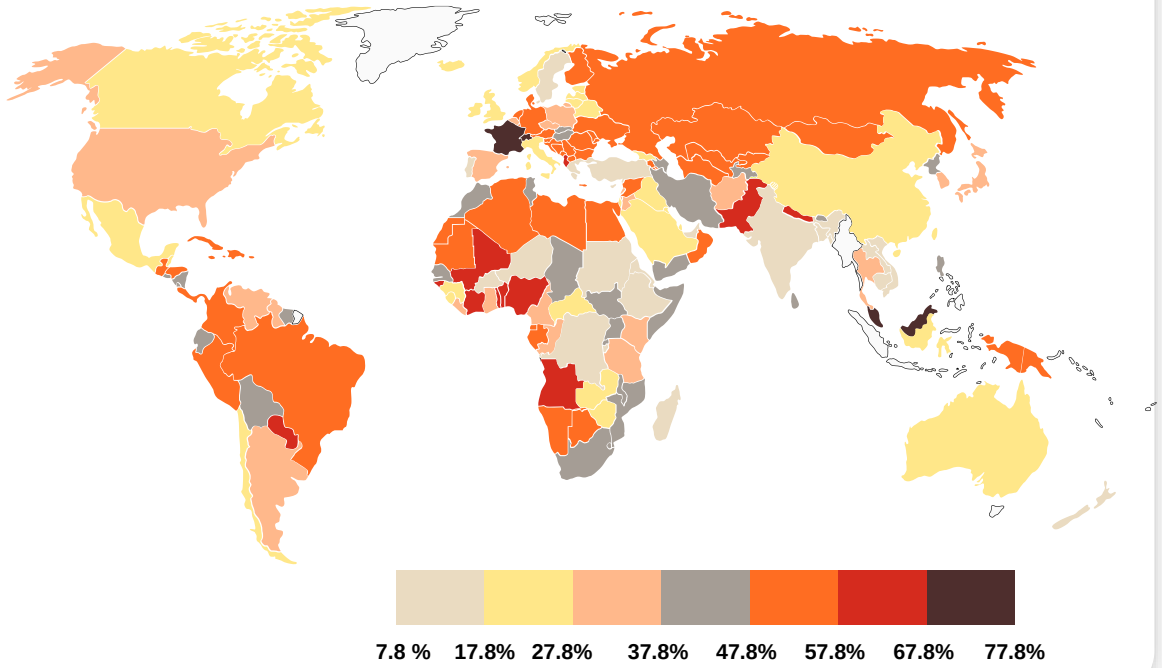
AASM=American Academy of Sleep Medicine; AHI=Apnea-Hypopnea Index; OSA=Obstructive Sleep Apnea.

Benjafield AV, et al. *Lancet Respir Med*. 2019;7(8):687-698.

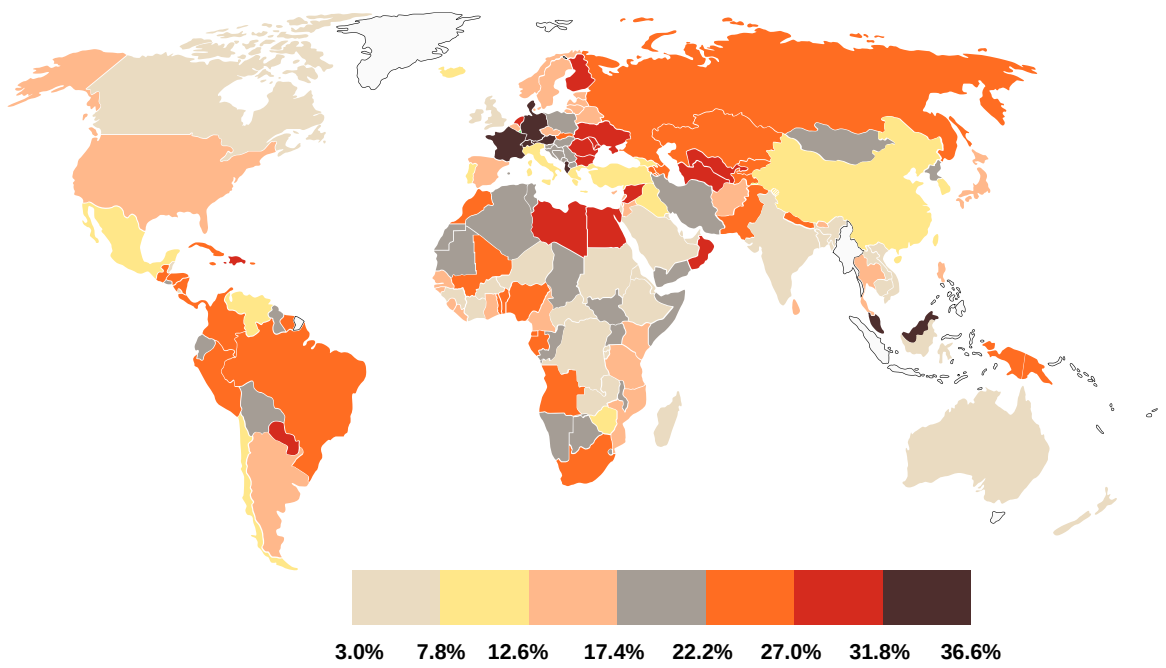
Estimated Global Prevalence of OSA (2/2)

Global heat map of estimated prevalence of OSA*

OSA with AHI ≥5 events/h



Moderate-to-severe OSA with AHI ≥15 events/h



*Estimation based on AASM 2012 criteria.

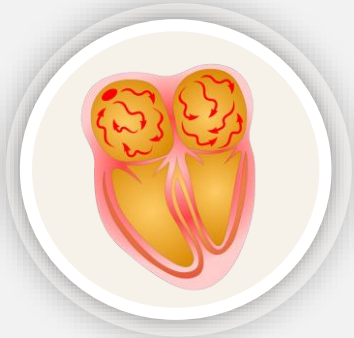
AHI=Apnea-Hypopnea Index; OSA=Obstructive Sleep Apnea.

Benjafield AV, et al. *Lancet Respir Med*. 2019;7(8):687-698.

Prevalence of OSA in Select Diseases

73-82%

Resistant hypertension[1]

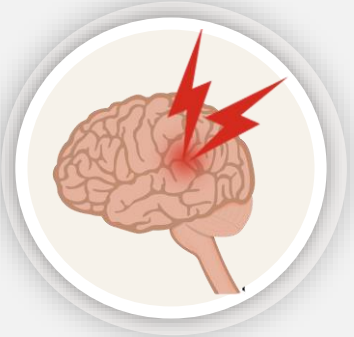


76-85 %

Atrial fibrillation[1]

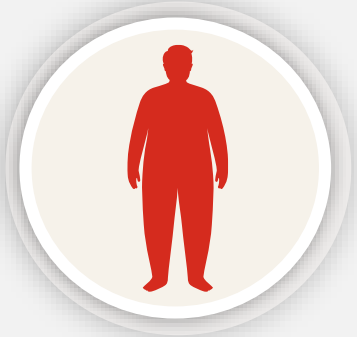
65-85 %

Type 2 diabetes[1]



71%

Stroke[1]



71-95 %

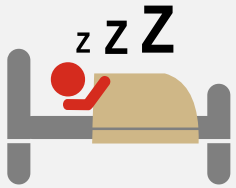
Obesity[2]

OSA=Obstructive Sleep Apnea.

1. Gottlieb DJ and Punjabi NM. *JAMA*. 2020;323(14):1389-1400. 2. Lopez PP, et al. *Am Surg*. 2008;74(9):834-838.

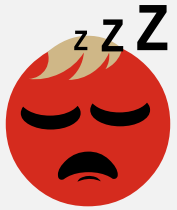
Symptoms of OSA

Daytime sleepiness[1,2]



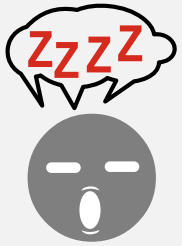
Unrefreshing sleep[1]

Fatigue[1,2]

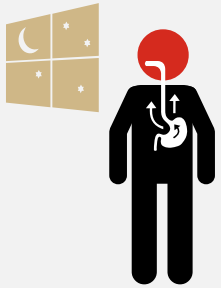


Breathing pauses, choking or gasping during sleep[1,2]

Morning headaches[1,2]

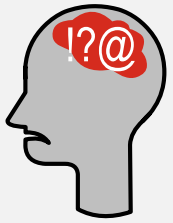


Snoring[1,2]



Nocturnal gastroesophageal reflux[1]

Nocturia[1,2]



Concentration and memory problems[2]

Irritability[2]

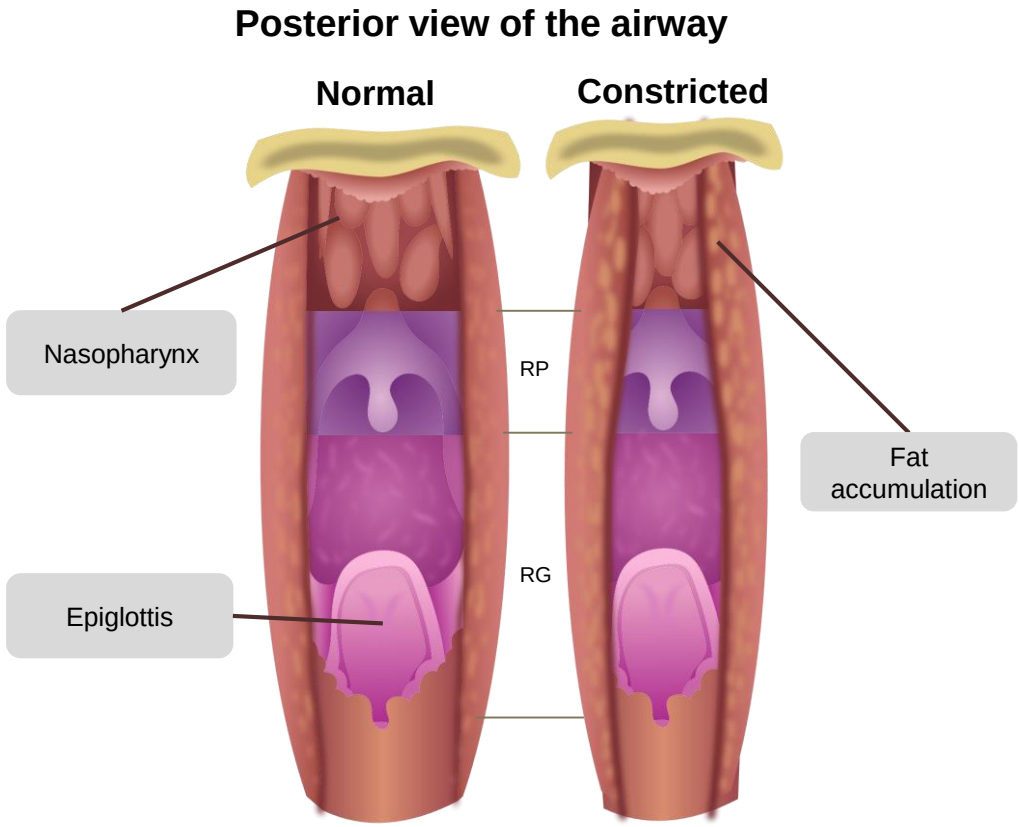
OSA=Obstructive Sleep Apnea.

1. Gottlieb DJ, Punjabi NM. *JAMA*. 2020;323(14):1389-1400. 2. Yeghiazarians Y, et al. *Circulation*. 2021;144(3):e56-e67.

Aetiology of OSA

Factors associated with the pathogenesis of OSA:

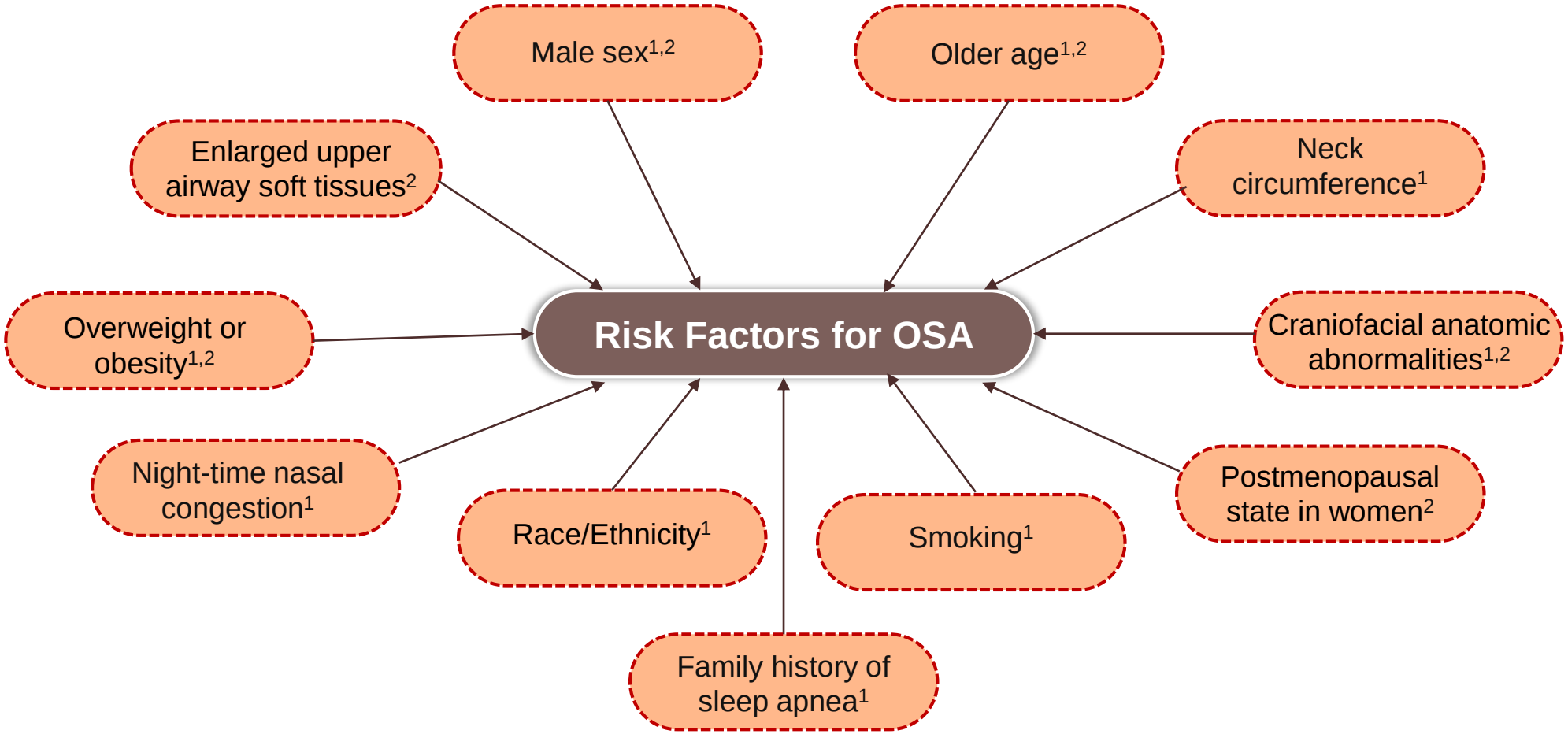
- Decreased muscle airway tone[1]
- Narrow upper airways caused by fat deposition or less commonly abnormalities in craniofacial structure[2]



OSA=Obstructive Sleep Apnea; RG=Retroglossal; RP=Retropalatal.

1. Slowik JM, Collen JF. 2022. http://www.ncbi.nlm.nih.gov/books/NBK459252. Accessed June 30, 2022. 2. Gottlieb DJ, Punjabi NM. *JAMA*. 2020;323(14):1389-1400.

Risk Factors for OSA

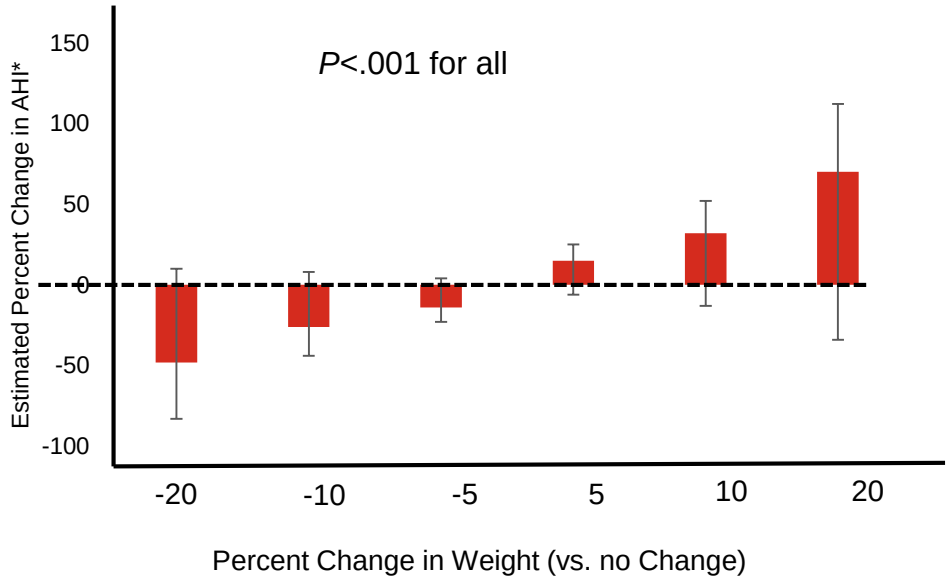


OSA=Obstructive Sleep Apnea.

1. Yeghiazarians Y, et al. *Circulation*. 2021;144(3):e56-e67. 2. Gottlieb DJ, Punjabi NM. *JAMA*. 2020;323(14):1389-1400.

Change in AHI by Change in Body Weight

10% weight gain predicted ~32% increase in AHI and a 6-fold increase in the risk for developing moderate-to-severe sleep-disordered breathing



*AHI adjusted for gender, change in cigarette packs per week, baseline BMI and baseline age.
Error bars indicate 95% CI (in addition to change expected if weight remained stable).

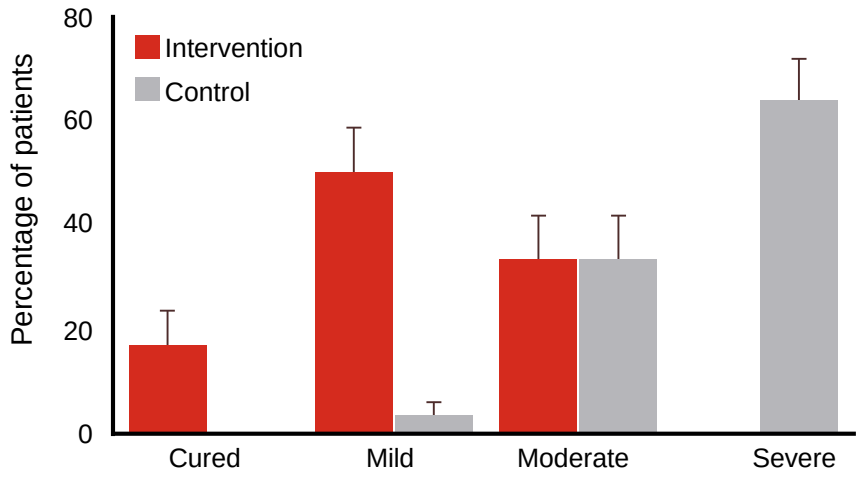
AHI=Apnea Hypopnea Index; BMI=Body Mass Index; CI=Confidence Interval; OSA=Obstructive Sleep Apnea.

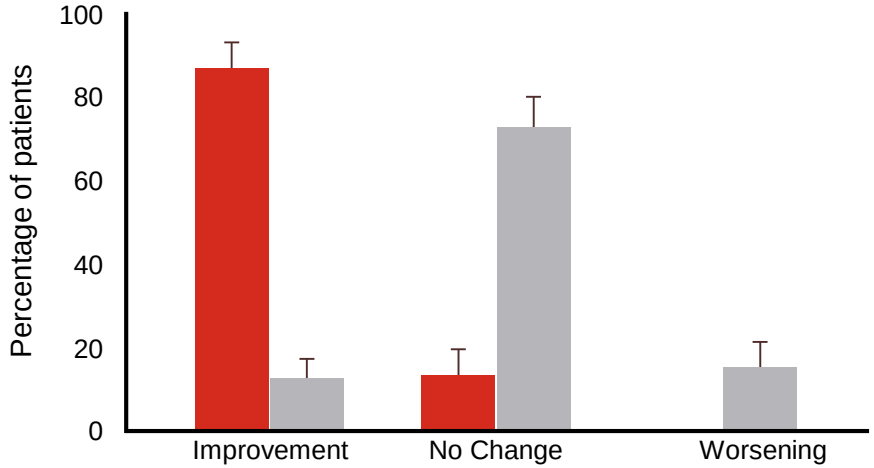
Peppered PE et al. *JAMA*. 2000;284(23):3015-3021.

Weight Reduction Was Associated With Improvements in OSA

Weight reduction from a low-energy diet improved OSA in men with obesity in a 9-week study

At Week 9, the intervention group's mean body weight was 19.8 kg lower than that of the control group





Note: Error bars indicate 95% confidence intervals

Definitions:

Cured: AHI <5 events/h; Mild: 5-14.9 events/h, Moderate: AHI 15-30 events/h; Severe >30 events/h.

Improvement in OSA: Shift in severity of OSA (ie. moderate to cured or mild; or severe to cured, moderate or mild)

Worsening of OSA: opposite direction of improvement

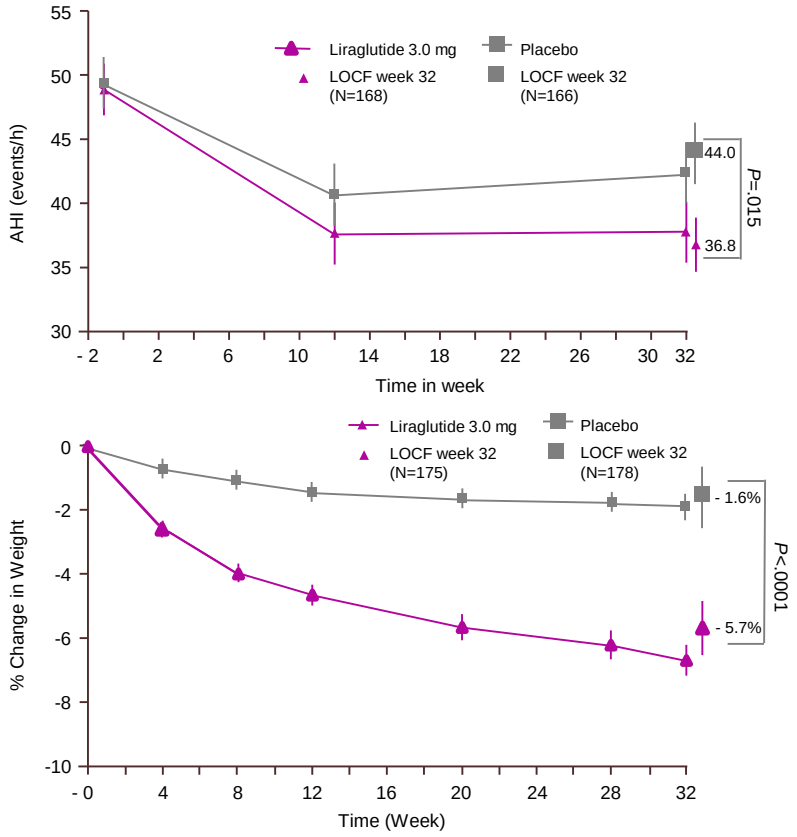
No change in OSA: remaining within the same category of severity of OSA

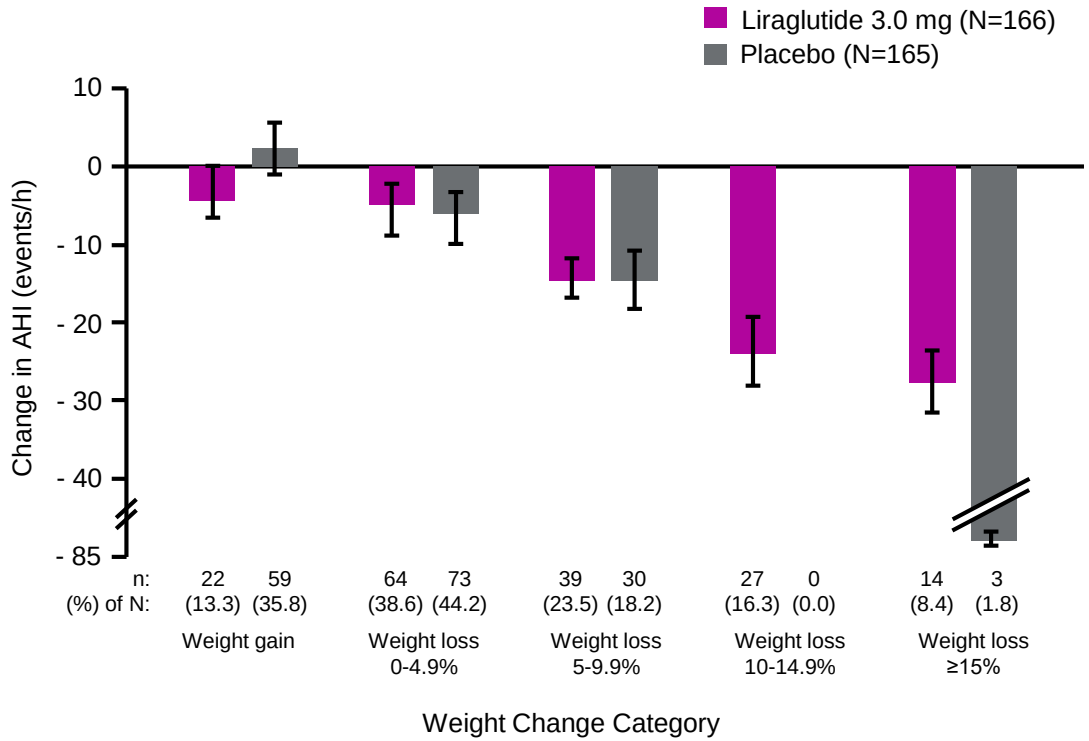
AHI=Apnea-Hypopnea Index; OSA=Obstructive Sleep Apnea.

Johansson K, et al. *BMJ*. 2009;339:b4609.

Relationship Between Weight Reduction and Change in AHI

In both liraglutide and placebo groups, greater weight reduction was associated with greater reduction in AHI



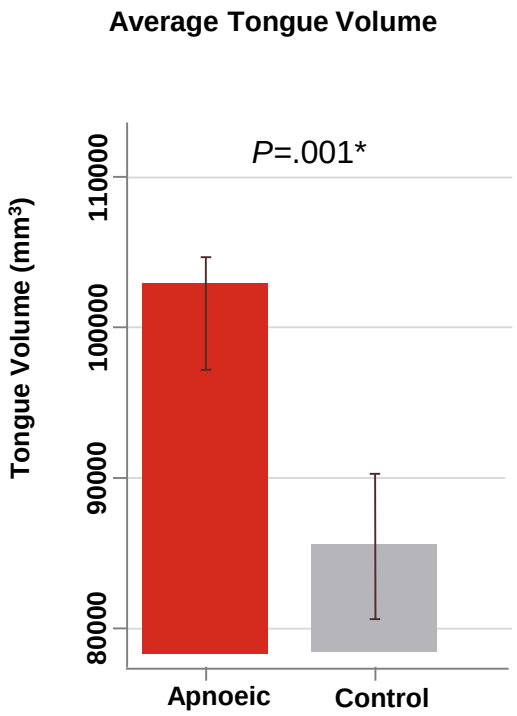


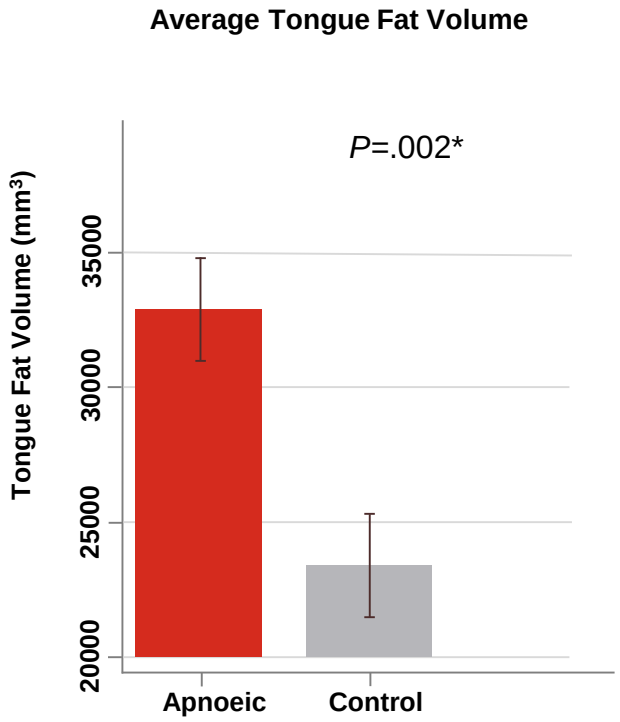
AHI=Apnea-Hypopnea Index; LOCF=Last Observation Carried Forward.

Blackman A, et al. *Int J Obes (lond)*. 2016;40(8):1310-9.

Relationship Between Tongue Fat and OSA

Significant difference in tongue volume and tongue fat between patients with OSA and controls





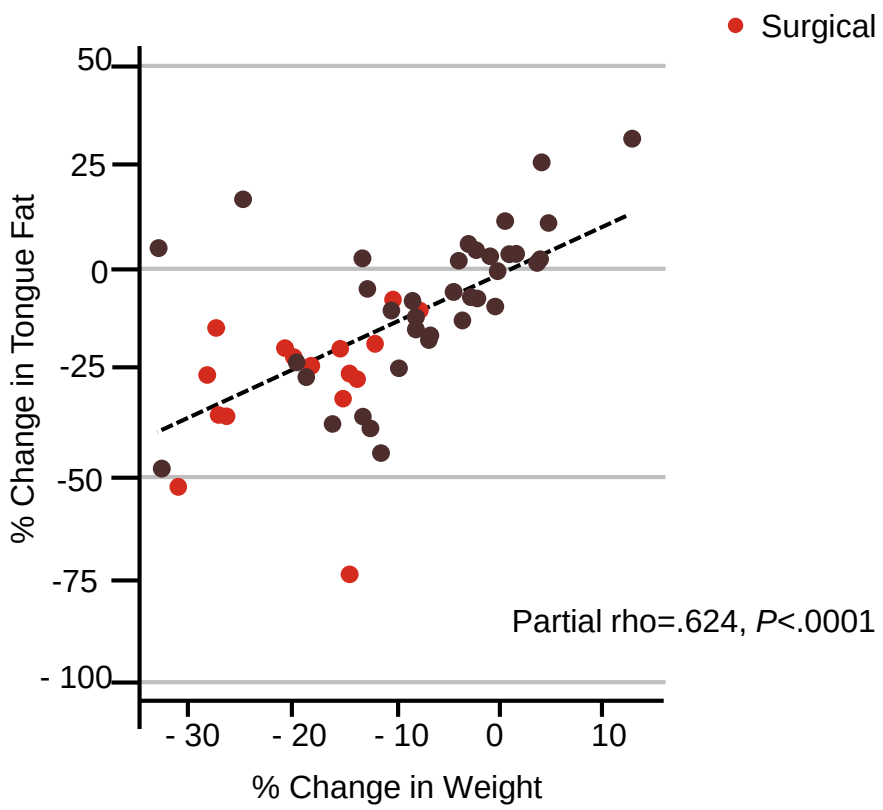
*After adjustment for age, BMI, gender and race.

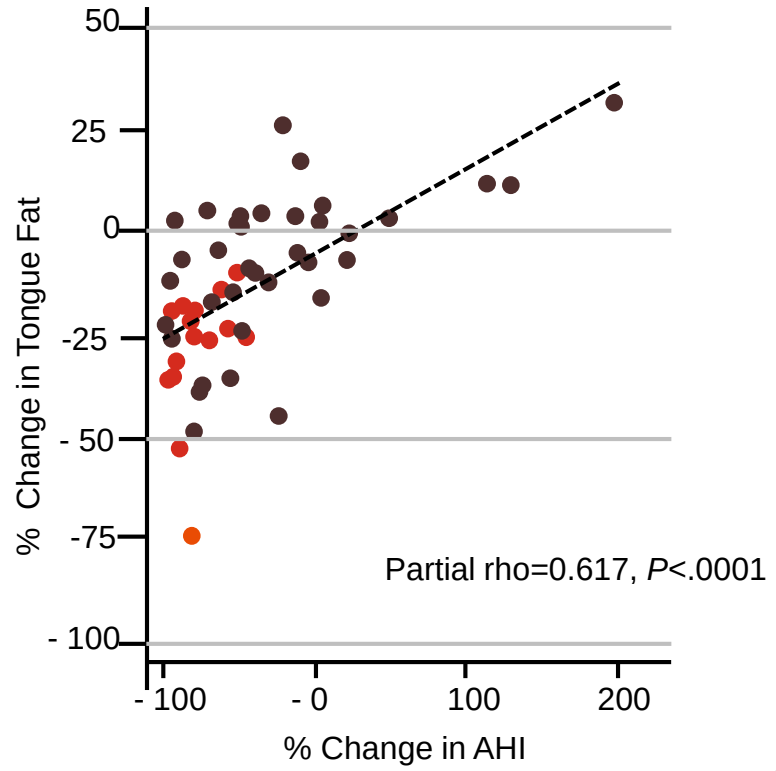
AHI=Apnea-Hypopnea Index; BMI=Body Mass Index; OSA=Obstructive Sleep Apnea.

Kim AM, et al. *Sleep*. 2014;37(10):1639-1648.

Changes in Tongue Fat Are Related to Weight Reduction and OSA

Association between percentage change in tongue fat with weight reduction or AHI change

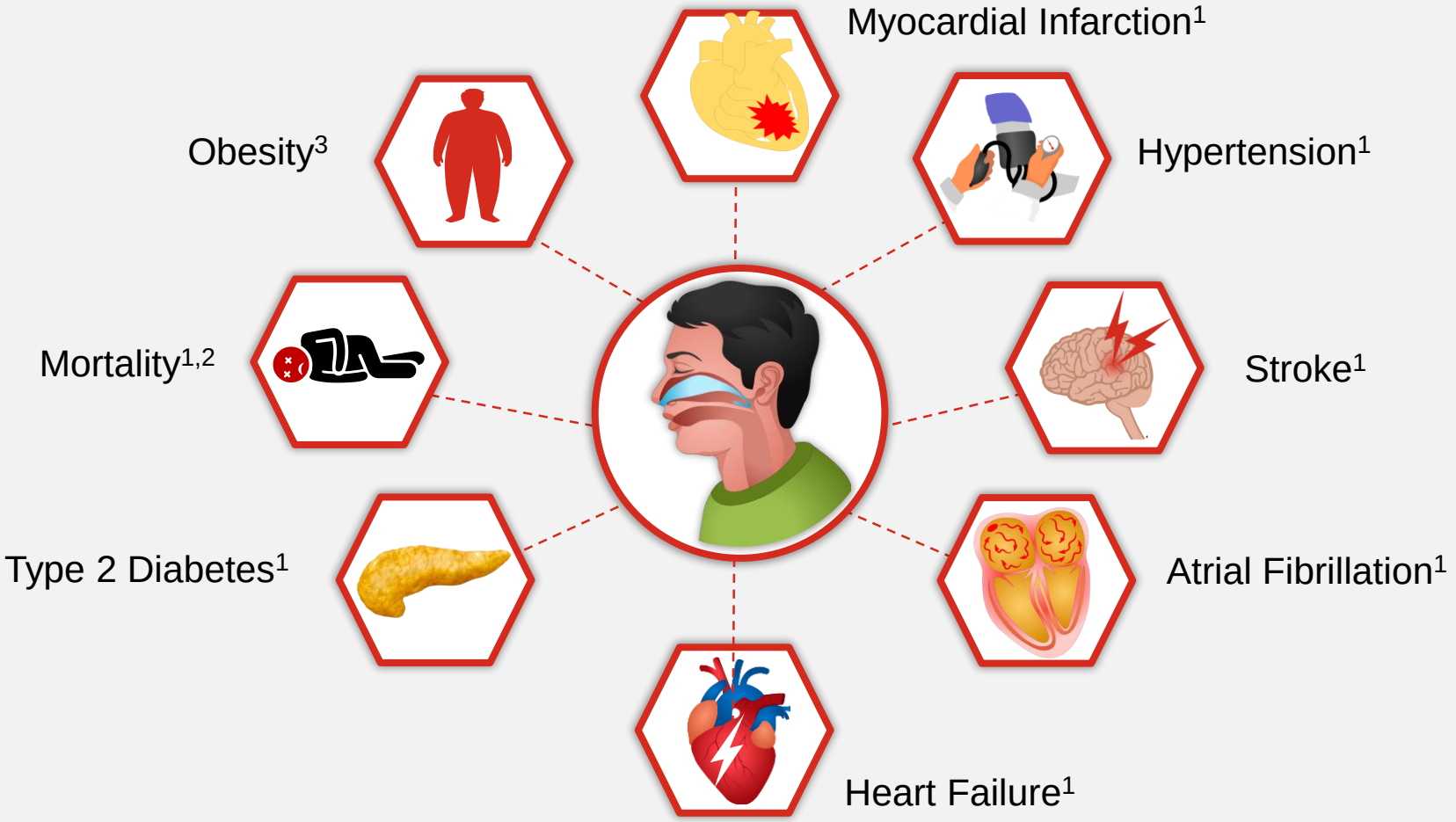




Note: Correlation is based on covariate-adjusted analyses.
Correlations include subjects with obesity and OSA undergoing surgical or medical lifestyle interventions for weight reduction.

AHI=Apnea-Hypopnea Index; OSA=Obstructive Sleep Apnea.
Wang SH et al. *Am J Respir Crit Care Med*. 2020;201(6):718-727.

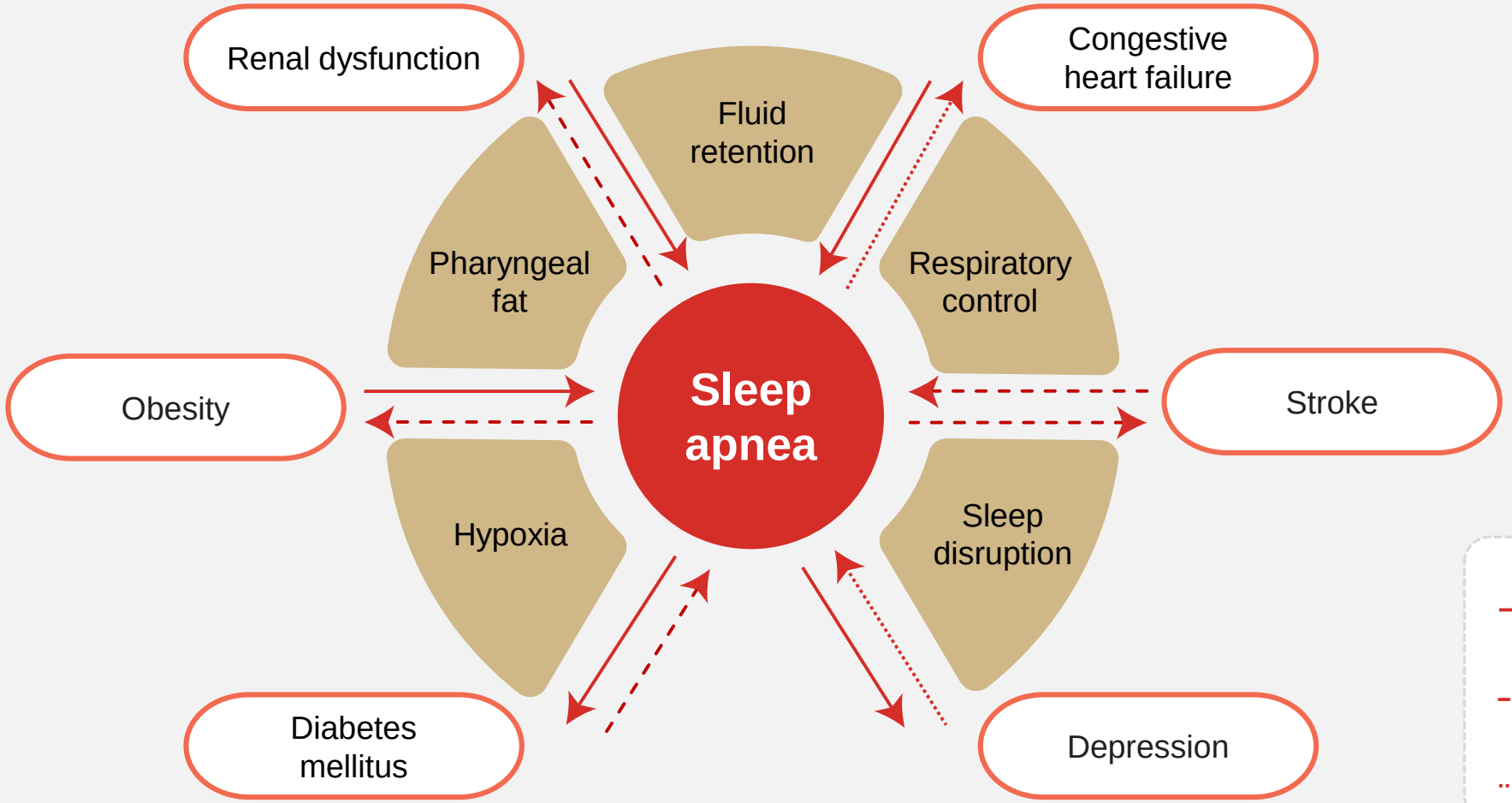
Untreated OSA Is Associated With Increased Prevalence of Cardiometabolic Disease



OSA=Obstructive Sleep Apnea.

1. Arredondo E, et al. *Cureus*. 2021;13(9):e17843. 2. Budhiraja R, et al. *Pulm Crit Care*. 2021;23:23-35. 3. Chang J, et al. *Int Forum Allergy Rhinol*. 2022. doi: 10.1002/alr.23079.

Bidirectional Relationships of Comorbidities With OSA

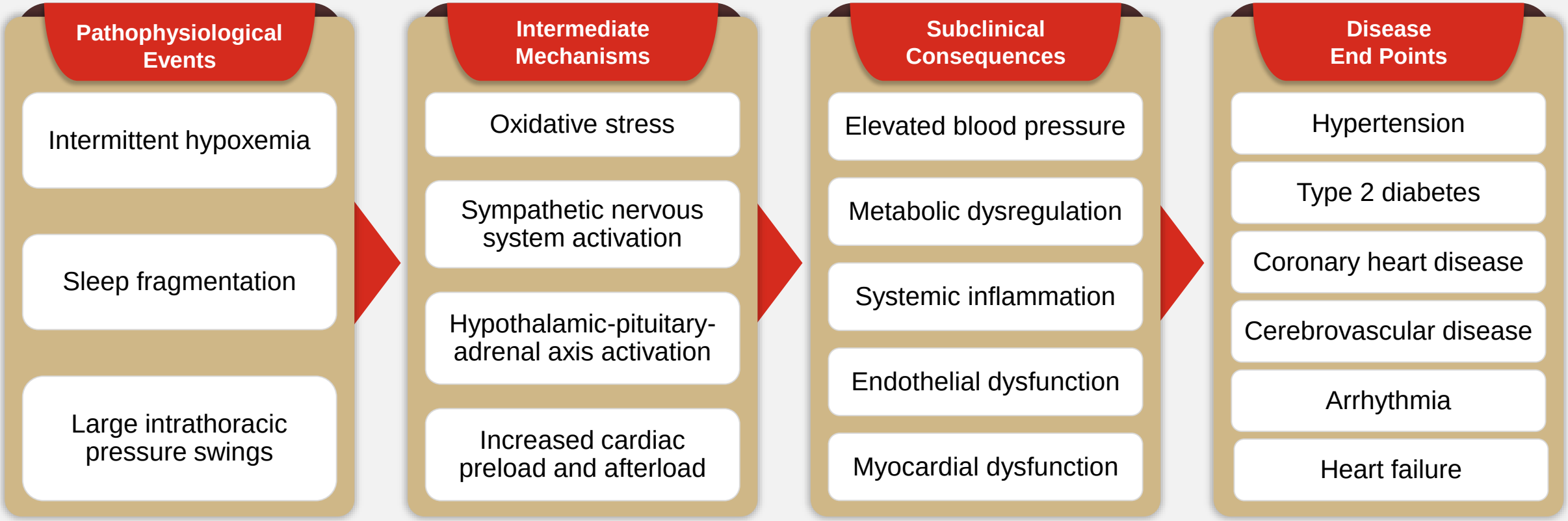


Note: The levels of evidence favouring inter-relationships ranging from strong to weak are the authors' opinions based on the available evidence.

OSA=Obstructive Sleep Apnea.

Gleeson M, McNicholas WT. *Eur Respir Rev*. 2022;31(164):210256.

Probable Causal Mechanisms of OSA-related Cardiovascular and Metabolic Disease



- OSA probably causes 3 proximate pathophysiological events: intermittent hypoxemia, sleep fragmentation and large swings in intrathoracic pressure
- These events leads to interacting processes that contribute to adverse health outcomes: hypertension, T2D, CV diseases

CV=Cardiovascular; OSA=Obstructive Sleep Apnea; T2D=Type 2 Diabetes.
Gottlieb DJ, Punjabi NM. *JAMA*. 2020;323(14):1389-1400.

Diagnosis of Obstructive Sleep Apnea

OSA Screening

Questionnaires for assessing the risk of OSA[1]

Questionnaire	Description
Berlin Questionnaire[1,2]	11 items grouped in 3 domains: snoring/apneas, fatigue/sleepiness and obesity/hypertension[1]
STOP-Bang questionnaire[1,2]	8 item survey assesses snoring, sleepiness, apneas, hypertension, obesity, neck girth, age and sex[1]
Epworth Sleepiness Scale[1,2]	Self-administered assessment of sleep tendency in 8 common situations[1]

- Sleep apnea-focused questionnaires are for screening for OSA as they lack diagnostic accuracy[3]

OSA=Obstructive Sleep Apnea.

1. Gottlieb DJ, Punjabi NM. *JAMA*. 2020;323(14):1389-1400. 2. Chang JL. *Int Forum Allergy Rhinol*. 2022. doi:10.1002/alr.23079. 3. Kapur VK, et al. *J Clin Sleep Med*. 2017;13(3):479-504.

Diagnostic Tools for OSA*

Polysomnography (1 of 2)

Description

- PSG is the standard diagnostic test for OSA
- PSG uses sensors to closely monitor and record patients' sleep and respiratory parameters
- Measures number of apneas and hypopneas per hour during sleep

Pros

- PSGs permit diagnosis of sleep apnea and other sleep disorders

Cons

- Labour-intensive, relatively 5X costlier than HSAT
- Laboratory-based with trained attendant, inconvenient to patient

PSG

*PSG and HSAT are accepted tools used to diagnose OSA per current AASM clinical guidelines.

AASM=American Academy of Sleep Medicine; HSAT=Home Sleep Apnea Test; OSA=Obstructive Sleep Apnea; PSG=Polysomnography.

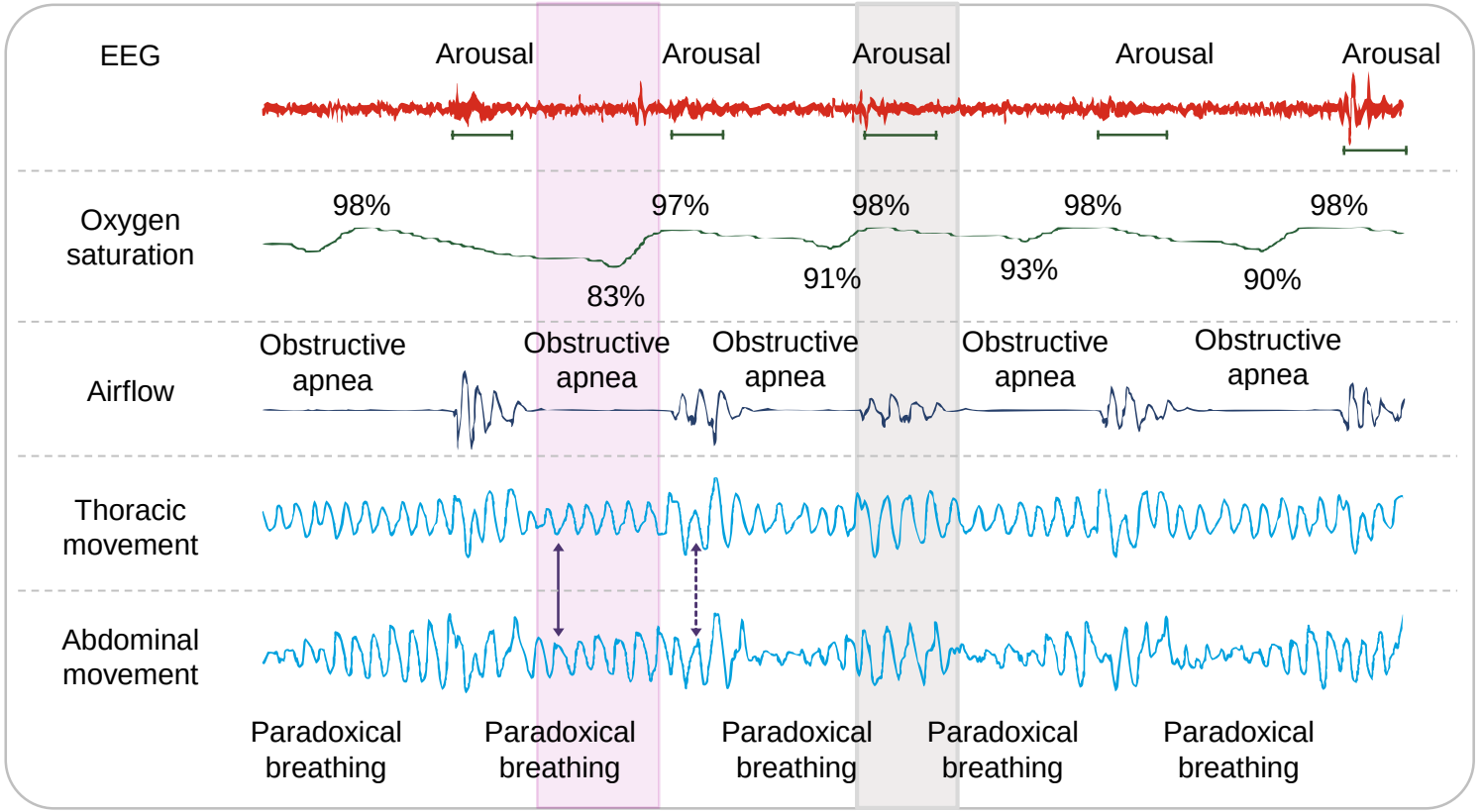
Gottlieb DJ, Punjabi NM. *JAMA*. 2020;323(14):1389-1400.

Diagnostic Tools for OSA

Polysomnography (2 of 2)

A 5-minute PSG tracing of OSA events

- PSG measurements associated with an obstructive apnea event ( ):
  - Absence of air flow
  - Paradoxical breathing - out of phase movement of the thorax and abdomen (solid arrow)
  - Decrease in oxygen saturation
- PSG measurements associated with termination of the obstructive event ( )
  - Arousal measured by EEG
  - Resumption of normal airflow and breathing (dashed arrow)
  - Restoration of oxygen saturation
- Transition back to sleep after each arousal is associated with collapse of upper airway and recurrent apneic/hypopneic events



EEG= Electroencephalogram; OSA=Obstructive Sleep Apnea; PSG=Polysomnography.

Gottlieb DJ, Punjabi NM. *JAMA*. 2020;323(14):1389-1400.

Diagnostic Tools for OSA*

Home Sleep Apnea Testing

Description

- Used for OSA diagnosis and supported by guidelines[1]
- Factors evaluated: airflow, respiratory effort and oxygen saturation[2]
- Measures number of apneas and hypopneas per hour[2]

Pros

- Cost-effective and greater convenience compared with PSG[2]

Cons

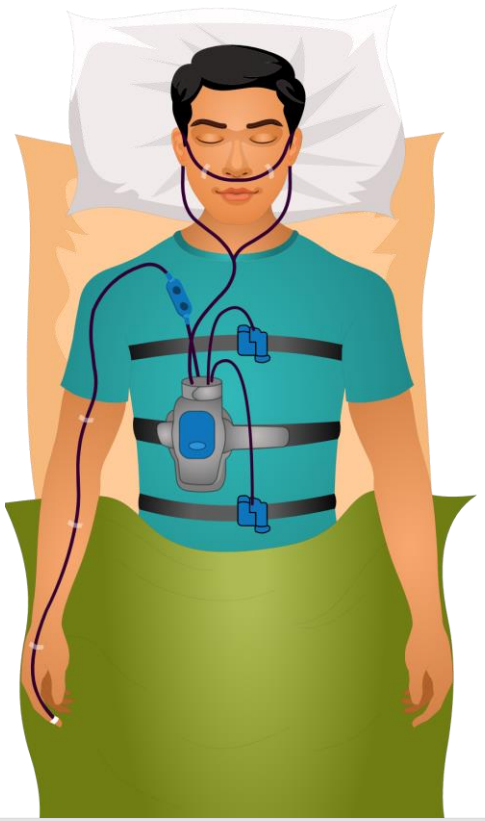
- False-negative results possible[2]
- Unable to diagnose disorders other than sleep apnea[2]

Additional Information

- Innovative wireless PSG and disposable HSAT solutions have been cleared by regulatory authorities[3,4]

*PSG and HSAT are accepted tools used to diagnose OSA per current AASM clinical guidelines.

HSAT

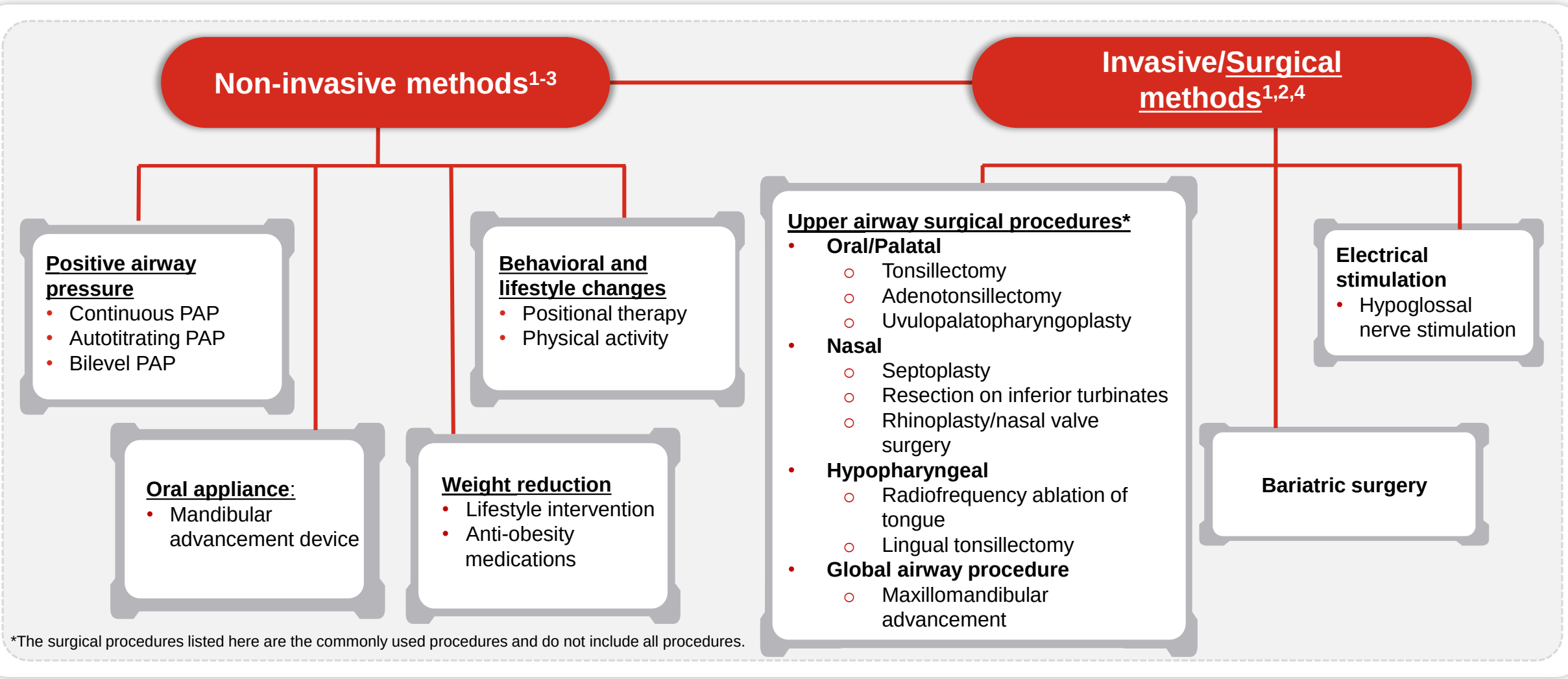


AASM=American Academy of Sleep Medicine; HSAT=Home Sleep Apnea Testing; OSA=Obstructive Sleep Apnea; PSG=Polysomnography.

1. Kapur VK, et al. *J Clin Sleep Med.* 2017;13(3):479–504. 2. Gottlieb DJ, Punjabi NM. *JAMA*. 2020;323(14):1389-1400. 3. https://www.onerahealth.com/newsroom-articles/fda-grants-510-k-clearance-to-onera-sts-a-system-for-at-home-and-in-lab-polysomnography-studies. Accessed 2 March 2023. 4. https://aasm.org/fda-clears-disposable-home-sleep-apnea-test/. Accessed 6 February 2023.

Management of Obstructive Sleep Apnea

Management of OSA



*The surgical procedures listed here are the commonly used procedures and do not include all procedures.

OSA=Obstructive Sleep Apnea; PAP=Positive Airway Pressure.

1. Xia F, Sawan M. *Sensors (Basel)*. 2021;21(5):1784. 2. Yeghiazarians Y, et al. *Circulation*. 2021;144(3):e56-e67. 3. Gottlieb DJ, Punjabi NM. *JAMA*. 2020;323(14):1389-1400. 4. Smith DF, et al. *Chest*. 2015;147(6):1681-1690.

Treatments for OSA (1 of 2)

Success Rate

	Methods							
	Non-invasive Methods			Invasive Methods				
Analysis	**PAP**	**OAT**	**Weight loss**	**MMA**	**UPPP**	**UPPP+TE**	**AT**	**HGNS**
Severity of OSA	Mild-severe	Mild-severe	Mild-severe	Severe	Moderate-severe	Moderate-severe	Moderate-severe	Severe
No. of samples	463	425	132	29	212	31	578	584
Follow-up	7 years	4 years	1 year	12.5±3.5 years	≥34 months	3 months	Immediately	1 year
Pre-AHI (mean)	48.6±31.8	27.5±16.3	27.6±24.6	36.7±14*	39.9±18.3	33.7±14.6	18.2±21.4	33.8±15.5
Post-AHI (mean)	5.7±8.4	12±12.5	9.9±11.2	4.7±3.2*	21.5±15.6	15.4±14.1	4.1±6.4	11±13.6
AHI<5 or AHI reduction>50%	59.3%	68%	27%	27.6%	44.35%	64.5%	-	77.1%
AHI<1	-	-	-	-	-	-	27.2%	-

Note: Treatment success criteria defined as AHI index of <5 or more than 50% reduction of AHI in adults with OSA, and AHI less than 1 or reduction of AHI >50% for children.
Pre(mean) is the mean AHI value before treatment; Post(mean) is the mean AHI value after treatment. More '+' sign indicates a higher treatment outcome.
*Analysis only in patients that had a good (successful) response to MMA surgery.

AHI=Apnea-Hypopnea Index; AT=Adenotonsillectomy; PAP=Positive Airway Pressure; HGNS=Hypoglossal Nerve Stimulation; MMA=Maxillomandibular Advancement; OAT=Oral Appliance Therapy; OSA=Obstructive Sleep Apnea; TE=Tonsillectomy; UPPP=Uvulopalatopharyngoplasty.

Xia F, Sawan, M. *Sensors (Basel)*. 2021;21(5):1784.

Treatments for OSA (2 of 2)

Efficiency and Limitations

	Methods							
	Non-invasive Methods			Invasive Methods				
Analysis	**PAP**	**OAT**	**Weight loss**	**MMA**	**UPPP**	**UPPP+TE**	**AT**	**HGNS**
Efficiency	+++++	+++	+	+++++	+++	++++	++	+++++
Limitations	Poor adherence	Strict teeth structure, long-term overjet and overbite	Difficult to achieve weight loss and maintain	Highly invasive and complicated procedure, side effects include malocclusion, haemorrhage, facial numbness, etc.	Velopharyngeal insufficiency, dysphagia, swallow difficulty	Velopharyngeal insufficiency, dysphagia, swallow difficulty	Post-operative bleeding, infection of wound	High cost, tongue abrasion, device malfunction, abnormal sensations, etc.

Treatment success criteria defined as AHI index of <5 or more than 50% reduction of AHI in adults with OSA, and AHI less than 1 or reduction of AHI >50% for children.

AHI=Apnea-Hypopnea Index; AT=Adenotonsillectomy; HGNS=Hypoglossal Nerve Stimulation; MMA=Maxillomandibular Advancement; OAT=Oral Appliance Therapy; OSA=Obstructive Sleep Apnea; PAP=Positive Airway Pressure; TE=Tonsillectomy; UPPP=Uvulopalatopharyngoplasty.
Note: Pre(mean) is the mean AHI value before treatment; Post(mean) is the mean AHI value after treatment. More '+' sign indicates higher treatment outcome.
Xia F, Sawan, M. *Sensors (Basel)*. 2021;21(5):1784.

Summary of Some OSA Management Principles

1. Effective treatment for OSA includes non-invasive and invasive methods[1]
2. Weight reduction should be recommended for patients with over weight or obesity in conjunction with other therapies[1]
3. Lifestyle interventions, bariatric surgery and antiobesity medications are each associated with improved OSA severity[1]
4. PAP is the primary therapy for symptomatic OSA of any severity[1]
5. Oral appliances (mandibular repositioning devices) are effective treatment options, particularly for individuals with mild-to-moderate OSA[1]
6. Surgical modification of the upper airway is suitable for select patients and often recommended for symptomatic patients unable to tolerate PAP therapy[1]
7. The most common surgical procedures for OSA modify upper airway soft tissue, including palate, tongue base and lateral pharyngeal wall[1]
8. HGNS is a surgical procedure that increases pharyngeal dilator muscle tone during sleep[1]
9. Pharmacologic therapies for OSA may include drugs proposed to increase airway muscle tone, increase ventilatory drive or raise the arousal threshold[1]
10. Currently, approved pharmacotherapy for OSA is limited to management of OSA associated symptoms[2]

HGNS=Hypoglossal Nerve Stimulation; OSA=Obstructive Sleep Apnea, PAP=Positive Airway Pressure.

1. Gottlieb DJ, Punjabi NM. *JAMA*. 2020;323(14):1389-1400. 2.. Panahi L, et al. *Medicina (Kaunas)*. 2021;57(11):1173.

Pharmacological Therapy for Adults With OSA

Pharmacological Therapy for Adults With OSA

- There are no pharmacological therapy that is universally used, or approved by the FDA for the treatment of OSA[1]
- The role of currently available pharmacotherapy for OSA is limited to management of OSA-associated symptoms and disease[1]

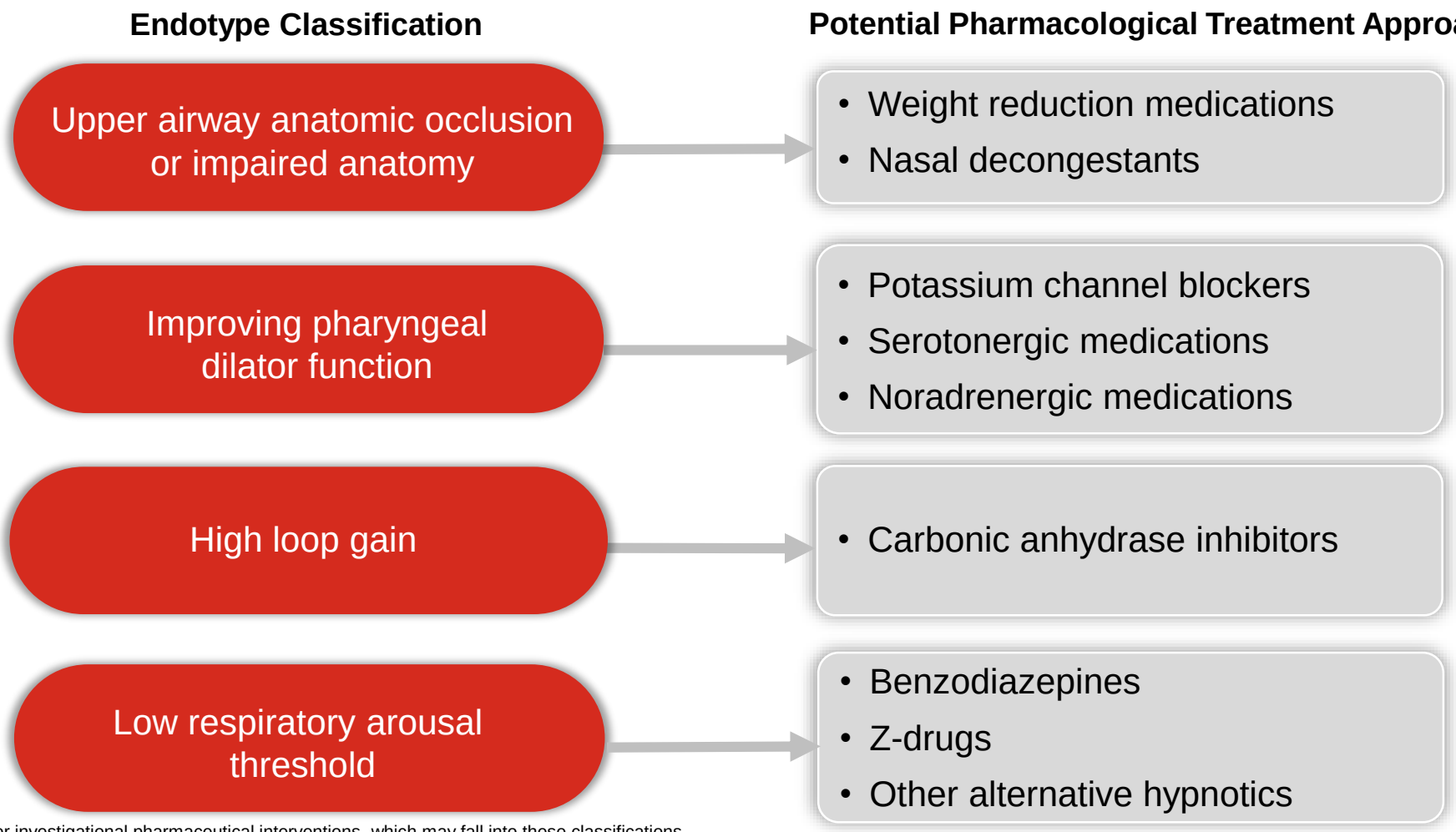
Drug	Company	MOA	FDA Approval	EU Approval	Indication
Sunosi™ solriamfetol	Jazz pharma[1,2]	CNS stimulant[1]	2019[2]	2020[3]	Improve **wakefulness** in adult patients with excessive daytime sleepiness associated with narcolepsy or OSA[2]
Nuvigil® armodafinil†	Teva[4]	CNS Stimulant[1]	2007[4]	NA	Improve **wakefulness** in adult patients with excessive sleepiness associated with OSA, narcolepsy or shift work disorder[4]
Provigil Modafinil	Cephalon[5]	CNS Stimulant[1]	1998[5]	NA	Improve **wakefulness** in adult patients with excessive sleepiness associated with narcolepsy, OSA or shift work disorder[5]
Saxenda® liraglutide	Novo Nordisk[6]	GLP1-RA[6]	2010[6,*]	2015[7]	OSA included in **EU label only**[7] An adjunct to a reduced-calorie diet and increased physical activity for weight management in adult patients with an initial body mass index of • ≥30 kg/m² (with obesity), or • ≥27 kg/m² to ≥30 kg/m² (with overweight), in the presence of at least one weight-related comorbidity such as dysglycemia (pre-diabetes or T2DM), hypertension, dyslipidemia or OSA[4]

*OSA is not included in the indication in the US product information.
Note: Not an extensive list of pharmacotherapies for OSA-associated symptoms.

CNS=Central Nervous System; DRNI=Dopamine and Norepinephrine Reuptake Inhibitor; EU=European Union; FDA=Food and Drug Administration; GLP1-RA=Glucagon-like Peptide-1 Receptors Agonist; MOA=Mechanism of Action; NA=Not Approved; OSA=Obstructive Sleep Apnea.

1. Panahi L, et al. *Medicina (Kaunas)*. 2021;57(11):1173. 2. Sunosi. [Highlights of Prescribing Information]. Jazz Pharmaceuticals, Inc.: Palo Alto, CA, USA, 2019. Accessed 20 November 2022. 3. Sunosi | European Medicines Agency (europa.eu). Accessed 16 December 2022. 4. Nuvvigil [Highlights of Prescribing Information]; Teva Pharmaceuticals USA, 2018. Accessed 16 December 2022. 5. Provigil m. [Highlights of Prescribing Information]; Cephalon Inc. USA, 2010. Accessed 16 December 2022. 6. Saxenda. [Highlights of Prescribing Information]. Novo Nordisk, USA. Accessed 20 November 2022. 7. Saxenda | European Medicines Agency (europa.eu). Accessed 20 November 2022.

Potential Pharmacological Treatment Approaches for Adults With OSA by Endotype Classification



*Refer to the Phase 2 trials for investigational pharmaceutical interventions, which may fall into these classifications.

OSA=Obstructive Sleep Apnea.

Arredondo et al. Medicina 2022; 58(2):225.

Ongoing Phase 3 Studies for OSA

Drug (brand)	Company	Indication	MOA	Clinical trial design and NCT number	Hypothesis	Key outcome measures*	Status
Tirzepatide	Eli Lilly and Company	OSA, obesity	GIP and GLP-1 receptor agonist	Phase 3 randomized double-blind study SURMOUNT-OSA (NCT05412004[1])	Weight reduction reduces upper airway occlusion	• Reduction in AHI	• Study start: June 2022 • Est. Study completion: March 2024
AD109 (atomoxetine + aroxybutynin)	Apnimed	OSA	Atomoxetine: NRI Aroxybutynin: Antimuscarinic agent	Phase 3 randomized double-blind study SynAIRgy (NCT05813275[2])	Activation of upper airway (pharyngeal dilator) muscles maintains upper airway during sleep	• Reduction in AHI	• Not yet recruiting • Study start: April 2023 • Est. Study completion: February 2025
AD109 (atomoxetine + aroxybutynin)	Apnimed	OSA	Atomoxetine: NRI Aroxybutynin: Antimuscarinic agent	Phase 3 randomized double-blind study LunAIRo (NCT05811247[3])	Activation of upper airway (pharyngeal dilator) muscles maintains upper airway during sleep	• Reduction in AHI	• Not yet recruiting • Study start: April 2023 • Est. Study completion: June 2025

*Not an extensive list. Additional outcomes may apply.

AHI=Apnea-hypopnea Index; Est=Estimated; NRI= Norepinephrine Reuptake Inhibitor; OSA=Obstructive Sleep Apnea.

1. https://clinicaltrials.gov/ct2/show/NCT05236842. NCT05412004. Accessed 6 March 2023. 2. https://clinicaltrials.gov/ct2/show/NCT05813275. Accessed 20 April 2023. 3. https://clinicaltrials.gov/ct2/show/NCT05811247. Accessed 20 April 2023.

Key Takeaways

1. OSA is a sleep-related breathing disorder in which a blocked upper airway reduces or prevents airflow
2. OSA is highly prevalent with nearly a billion adults (aged 30-69 years old) worldwide
3. Obesity is a primary risk factor for OSA and weight reduction is recommended in patients with higher BMI
4. Effective treatment for OSA includes non-invasive and invasive methods
5. Current FDA-approved pharmacologic therapies are limited to symptom management

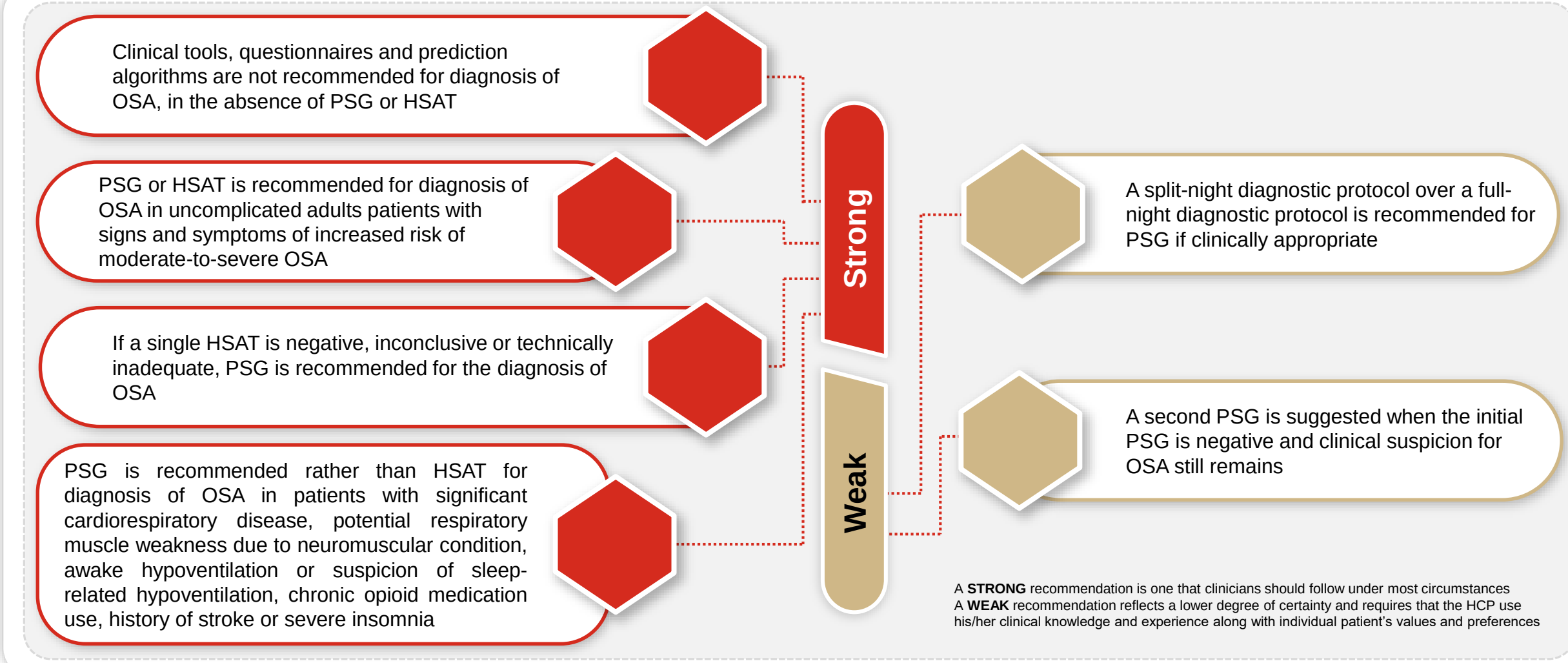
FDA=Food and Drug Administration; OSA=Obstructive Sleep Apnea.

Appendix

Guidelines and Additional Information

Clinical Practice Guidelines for Diagnosis of OSA in Adults

AASM Guidelines Recommendations

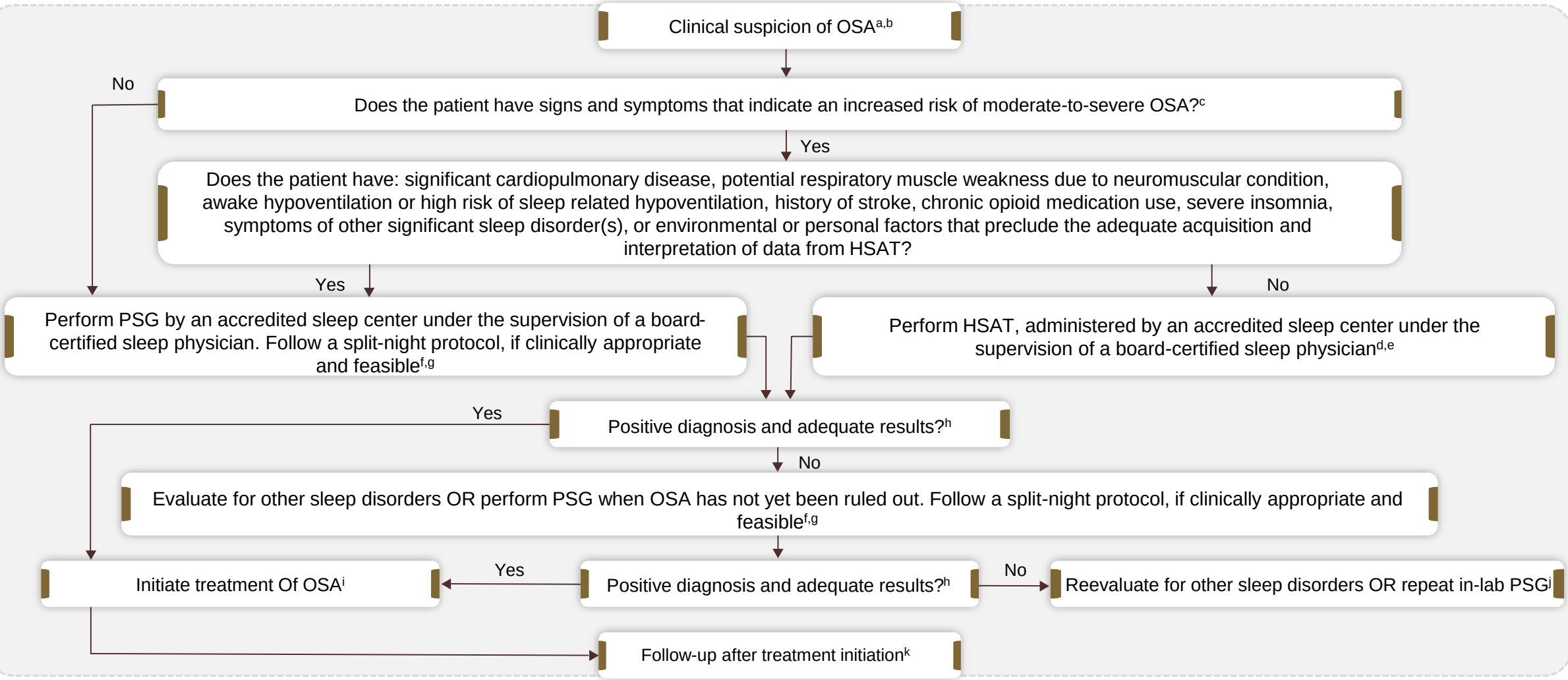


AASM=American Academy of Sleep Medicine; HSAT=Home Sleep Apnea Test; OSA=Obstructive Sleep Apnea; PSG=Polysomnography.

Kapur VK, et al. *J Clin Sleep Med.* 2017;13(3):479-504.

Diagnosis of OSA

Clinical Algorithm for Implementation of AASM Clinical Practice Guidelines



Note: Description for a,b,c,d,e,f,g,h,I,j,k provided in the speaker notes.
AASM=American Academy of Sleep Medicine; HSAT=Home Sleep Apnea Test; OSA=Obstructive Sleep Apnea; PSG=Polysomnography.
Kapur VK, et al. *J Clin Sleep Med*. 2017;13(3):479-504.

Primary Treatments for OSA

Medical Devices

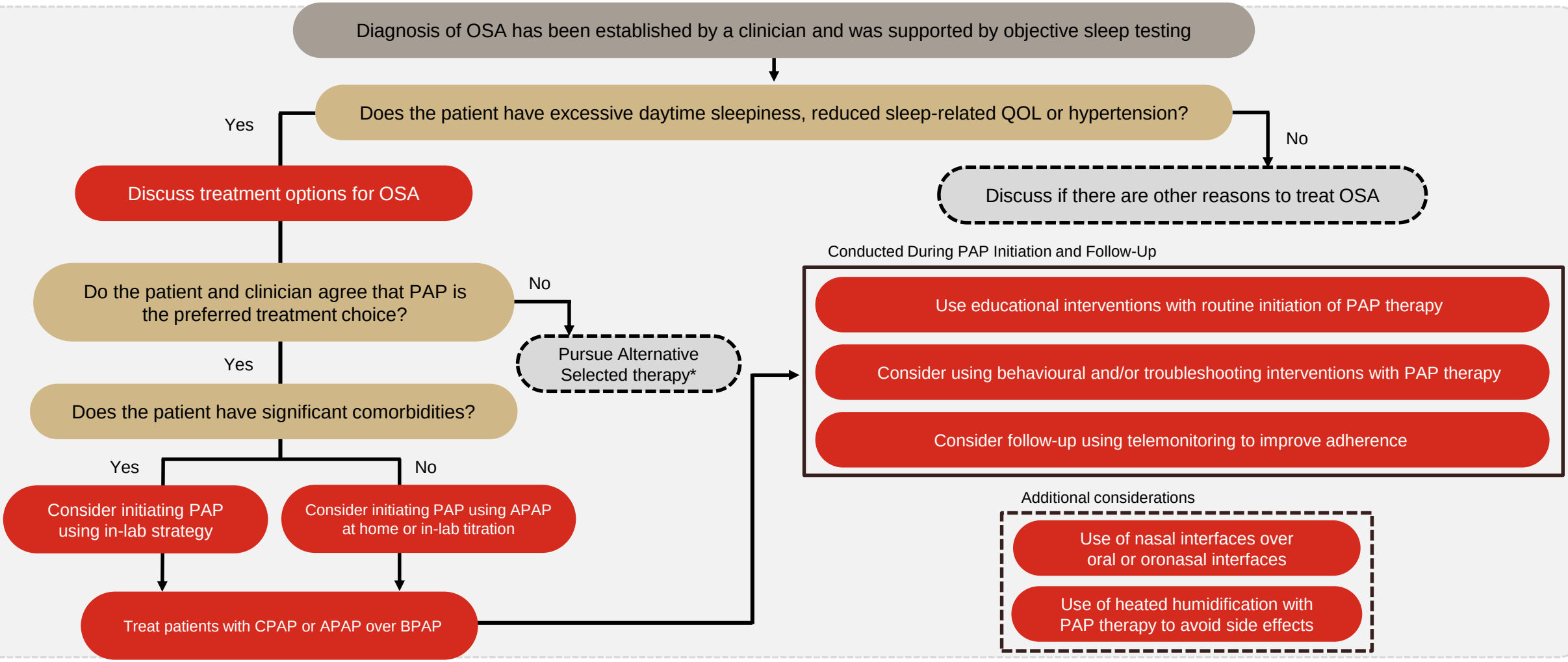
Treatment Method[1]	Details[2]	Guideline Recommendations
PAP	• Air pressure generated by the device is introduced into the airway via a mask worn over the nose or both nose and mouth • This pressure acts as a splint to prevent airway collapse during inspiration	PAP is the treatment of choice for mild, moderate and severe OSA and should be offered as an option to all patients diagnosed with OSA[2,3]
Oral appliances (mandibular repositioning devices)	• Designed to fit the upper and lower teeth • Provide adjustable forward advancement of the mandible during sleep	Sleep physicians to consider prescription of oral appliances, rather than no treatment, for adult patients with OSA who are intolerant of CPAP therapy or prefer alternate therapy[4]

CPAP=Continuos Positive Airway Pressure; OSA=Obstructive Sleep Apnea; PAP=Positive Airway Pressure.

1. Gottlieb DJ, Punjabi NM. *JAMA*. 2020;323(14):1389-1400. 2. Epstein LJ. *J Clin Sleep Med*. 2009;5(3):263-276. 3. Qasim A, et al. *Ann Intern Med*. 2013; doi:10.7326/0003-4819-159-7-201310010-00704. 4. Ramar K, et al. *J Clin Sleep Med*. 2015;11(7):773-827.

Treatment of OSA in Adults With Positive Airway Pressure

Flow Chart for Implementation of AASM Clinical Practice Guidelines



*Alternative therapies may include, but are not limited to, weight reduction, positional therapy, oral appliance therapy or surgical interventions.

APAP=Auto-adjusting Positive Airway pressure, BPAP=Bilevel Positive Airway Pressure, CPAP=Continuous Positive Airway Pressure, OSA=Obstructive Sleep Apnea, PAP=Positive Airway Pressure, QOL=Quality of Life.

Patil SP, et al. *J Clin Sleep Med*. 2019;15(2):335-343.

Primary Treatments for OSA

Behavioural Interventions

Treatment method	Details	Guideline recommendations
Weight reduction[1,2]	• Lifestyle interventions for weight reduction[1] • Also, effective when achieved by antiobesity medications or bariatric surgery[1]	• Successful dietary weight loss may improve the AHI in patients with obesity and OSA[2,3] • Weight loss should be recommended for all patients with overweight and OSA. Weight loss should be combined with a primary treatment for OSA[2,3]
Behavioral and lifestyle changes[1,2,3]	• Avoidance of supine sleep position[1,4] • Maintain side sleep position through positioning pillows or devices[1,4] • Additional lifestyle changes include restraining from alcohol, regular physical activity aerobic exercise[1]	• Positional therapy is an effective secondary therapy or can be a supplement to primary therapies for OSA in patients who have a low AHI in the non-supine versus that in the supine position

OSA=Obstructive Sleep Apnea.

1. Gottlieb DJ, Punjabi NM. *JAMA*. 2020;323(14):1389-1400. 2. Epstein LJ. *J Clin Sleep Med*. 2009;5(3):263-276. 3. Qaseem A. *Ann Intern Med*. 2013; doi:10.7326/0003-4819-159-7-201310010-00704. 4. Omobomi O, Quan SF. *Sleep Breath*. 2015;22:297-304.

Role of Weight Management in OSA

American Thoracic Society Clinical Practice Guideline

For patients with OSA and with overweight or obesity (BMI ≥25 kg/m^2)	Comprehensive lifestyle intervention program that includes a reduced-calorie diet, exercise/increased physical activity and behavioural counselling rather than no program (strong recommendation)
For patients with OSA with BMI ≥27 kg/m^2, with no weight improvement despite lifestyle intervention program and with no contraindications	Evaluate for anti-obesity pharmacotherapy (conditional recommendation)
For patients with OSA with BMI ≥35 kg/m^2, with no weight improvement despite lifestyle intervention programme and with no contraindications	Referral for bariatric surgery evaluation (conditional recommendation)

Note: In recommending weight management strategies for patients with OSA and with overweight or obesity, it is recommended that clinicians discuss options and involve patients in shared decision-making, considering their values and preferences.

BMI=Body Mass Index; OSA=Obstructive Sleep Apnea.

Hudgel DW, et al. *Am J Respir Crit Care Med*. 2018;198(6):e70-e87.

Primary Treatments for OSA
Surgical Procedures*

Treatment	Description	Advantages	Disadvantages and adverse effects
Uvulopalato-pharyngoplasty and related soft tissue procedures	• Surgical removal of uvula and a portion of soft palate • Other soft tissue procedures focus on increasing pharyngeal volume by reducing lateral pharyngeal walls or base of tongue	• Widely studied procedure • Improved OSA severity in many patients • Ensured adherence to therapy	• Lower efficacy than PAP • Effectively manages airway collapse only at the level of the velopharynx • Postsurgical pain • Small risk of velopharyngeal insufficiency • Disease recurrence with weight gain
Maxillomandibular advancement	Expansion of skeletal facial framework of the maxilla and mandible with LeFort I osteotomy	• Efficacious regardless of disease severity, level of airway collapse, or body weight • Ensured adherence to therapy	• Complex surgical procedure involving bony structures (recovery time: 2 to 10 weeks) • Complications include malocclusion, poor cosmetic result and facial numbness or paresthesia
Tracheostomy (rarely used)	Surgical incision at the trachea, or windpipe in front of the neck	• Curative technique in most patients regardless of disease severity, level of airway collapse, or body weight • Ensured adherence to therapy	• Unacceptable cosmetic result • Affects speech • Need long-term tracheostomy care
Hypoglossal nerve stimulation	Enhances tongue protrusion and stabilize the upper airway during inspiration through surgically implanted electrode stimulating the hypoglossal nerve	Highly effective and well tolerated in select patients (BMI <32 and absence of concentric collapse of the retropalatal airway on drug-induced sleep endoscopy)	• Expensive • Complications include temporary tongue weakness and tongue soreness and discomfort from stimulation

*The surgical procedures listed here are the commonly used procedures and do not include all procedures.

BMI=Body Mass Index; OSA=Obstructive Sleep Apnea; PAP=Positive Airway Pressure.

Gottlieb DJ, Punjabi NM. *JAMA*. 2020;323(14):1389-1400.

Referral of Adults With OSA for Surgical Consultation

AASM Clinical Practice Guideline

Strong

Clinicians discuss referral to a sleep surgeon with adults with OSA and BMI <40 kg/m^2 who are intolerant or unaccepting of PAP as part of a patient-oriented discussion of alternative treatment options

Clinicians discuss referral to a sleep surgeon with adults with OSA, BMI <40 kg/m^2 and persistent inadequate PAP adherence due to pressure-related side effects as part of a patient-oriented discussion of adjunctive or alternative treatment options

Conditional

Clinicians discuss referral to a bariatric surgeon with adults with OSA and obesity (class II/III,BMI≥35) who are intolerant or unaccepting of PAP as part of a patient-oriented discussion of alternative treatment options

Clinicians recommend PAP as initial therapy for adults with OSA and a major upper airway anatomic abnormality prior to consideration of referral for upper airway surgery

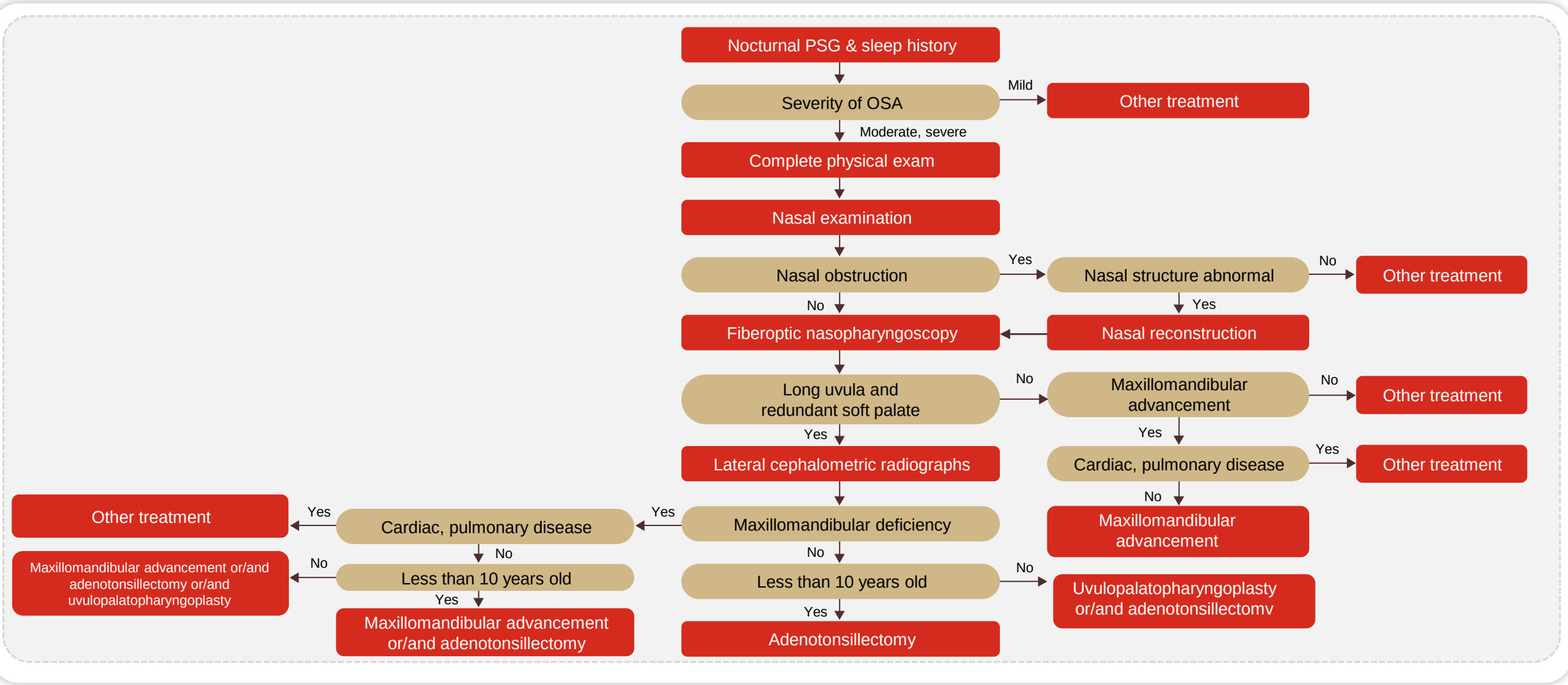
A **STRONG** recommendation is one that clinicians should follow under most circumstances.

A **CONDITIONAL** recommendation is one that requires that the clinician use clinical knowledge and experience and strongly consider the patient's values and preferences to determine the best course of action.

BMI=Body Mass Index; OSA=Obstructive Sleep Apnea; PAP= Positive Airway Pressure; PSG=Polysomnography.

Kent D, et al. *J Clin Sleep Med*. 2021;17(12):2499-2505.

Surgical Considerations for Patients With OSA



OSA=Obstructive Sleep Apnea; PSG=Polysomnography.

Xia F, Sawan, M. *Sensors (Basel)*. 2021;21(5):1784.

Phase 2 Clinical Studies for OSA

Disclaimer

- The following is a list of ongoing and completed Phase 2 studies for OSA to be used as a reference only
- Please note that the information may not be updated
- Please refer to references for up-to-date information

Phase 2 Studies for OSA

Ongoing Randomised-controlled Trials

Drug (brand)	Company/Sponsor	MOA	NCT number	Key outcome measures*	Status
Sulthiame	Desitin Arzneimittel GmbH	Carbonic anhydrase inhibitor	NCT05236842[1]	• Change in AHI	• Recruiting • Study start: November 2021 • Est. Study completion: May 2023
Acetazolamide, Eszopiclone, Venlafaxine combination therapy	University of California, San Diego	Acetazolamide: Carbonic anhydrase inhibitor; Eszopiclone: GABA receptor agonist Venlafaxine: SNRI	NCT04639193[2]	• AHI during supine NREM sleep	• Recruiting • Study start: January 2020 • Est. Study completion: December 2023
Atomoxetine Oxybutynin combination therapy	Brigham and Women's Hospital	Atomoxetine: Norepinephrine reuptake inhibitor Oxybutynin: Antimuscarinic agent	NCT03919955[3]	• AHI • Hypoxic Burden • Arousal index	• Recruiting • Study start: September 2019 • Est. Study completion: August 2023
AD113 or Atomoxetine	Apnimed	Norepinephrine reuptake inhibitors	NCT04905979[4]	• Change in hypoxic burden • Change in AHI	• Ongoing • Study start: July 2021 • Est. Study completion: May 2023
Atomoxetine and DAW2022	Brigham and Women's Hospital	Atomoxetine: Norepinephrine reuptake inhibitor DAW2022: NR	NCT05350215[5]	• OSA severity (AHI events) • Arousal index	• Recruiting • Study start: June 2022 • Est. Study completion: June 2023
LTM1201	Brigham and Women's Hospital	NA	NCT03858751[6]	• AHI	• Ongoing • Study start: March 2019 • Est. Study completion: December 2022
Quetiapine	Flinders University	Antipsychotic age	NCT05303935[7]	• AHI	• Recruiting • Study start: May 2022 • Est. Study completion: December 2024

*Not an extensive list. Additional outcomes may apply; Note: Last update can be noted in the reference section of the speaker notes.

AHI=Apnea-Hypopnea Index; Est=Estimated; NR=Not Reported; MOA=Mechanism of Action; NREM=Non-Rapid Eye Movement; ODI=Oxygen Desaturation Index; OSA=Obstructive Sleep Apnea; SNRI=Serotonin-norepinephrine Reuptake Inhibitor.

References are provided in the speaker notes.

Phase 2 Studies for OSA

Completed Randomised-controlled Trials With Outcomes

Drug (brand)	Company/ Sponsor	MOA	NCT number	Key outcome measures*	Outcomes
AD128 (Reboxetine and oxybutynin)	Apnimed	Reboxetine:NRI Oxybutynin: Antimuscarinic agent	NCT04449133[1,2]	• Change in AHI • AHI decrease ≥50% • AHI<15/h	• Median reduction in AHI events/h (%): Placebo=6% Reboxetine and oxybutynin=59% (*P*<.001)
AD036 (Atomoxetine and oxybutynin)	Apnimed	Atomoxetine:NRI Oxybutynin: Antimuscarinic agent	NCT04445688[3,4]	• AHI • HB • ODI	• AHI events/h, Median (IQR): Placebo=14.2 (5.4-22.3) AD036=6.2 (2.8-13.6) *P*<.0001 Atomoxetine=4.8 (1.4-11.6); *P*<.0001
AD109 (Atomoxetine and aroxybutynin)	Apnimed	Atomoxetine:NRI Aroxybutynin: Antimuscarinic agent	NCT04631107[5,6]	• Change in HB • AHI	• AHI events/h, Median (IQR): Placebo=13.2 (8.0-19.1) AD109 75/2.5 mg=5.5 (2.2-9.6) *P*<0.001 AD109 37.5/2.5 mg=7.8 (4-13.7); *P*<.05
Ramelteon	Takeda	$Melatonin_1$/$Melatonin_2$-receptor agonist	NCT00672061[7,8]	• AHI • Central apnea index • Mean oxygen saturation	• AHI events/h, LSM (SE) Placebo=11.1 (1.9) Ramelteon=11.4 (1.9); *P*=.812
BAY2253651	Bayer	Genioglossus muscle activator (via potassium channel blocker)	NCT03603678[9,10]	• AHI reduction ≥50% • Incidence of TEAEs	• A single dose of 100 µg BAY 2253651, applied nasally, did not lead to a reduction in AHI in people with moderate to severe OSA off CPAP

*Not an extensive list. Additional outcomes may apply.
Note: Last update can be noted in the reference section of the speaker notes.
AHI=Apnea-Hypopnea Index; CI=Confidence Interval; CPAP=Continuous Positive Airway Pressure; HB=Hypoxic Burden; IQR=Interquartile Range; LSM=Least-Squares Mean; MOA=Mechanism of Action; NA=Not Available; NRI= Norepinephrine Reuptake Inhibitor; ODI=Oxygen Desaturation Index; OSA=Obstructive Sleep Apnea; SE=Standard Error; TEAE=Treatment-emergent Adverse Event.
References are provided in the speaker notes.

Phase 2 Studies for OSA

Completed Randomised-controlled Trials With Outcomes

Drug (brand)	Company/Sponsor	MOA	NCT number	Key outcome measures*	Outcomes
Dronabinol	University of Illinois at Chicago Northwestern University University of Chicago Hektoen Institute for Medical Research, NHLBI	Cannabinoid receptor agonist	NCT01755091[1,2]	• Change in AHI • Change in Epworth Sleepiness Scale Change in Sleep Latency	• Compared to placebo, dronabinol significantly reduced AHI by 10.7±4.4 (*P*=.02) at 2.5 mg/d and 12.9±4.3 (*P*=.003) events/hr at 10 mg/d
Desipramine	Brigham and Women's Hospital	NRI	NCT02436031[3,4]	• Change in Pharyngeal Critical Collapsing Pressure • AHI	• Median AHI NREM supine events/hr sleep (IQR)[4]: Placebo=42.0 (30.8) Desipramine=34.3 (54.9); *P*>.5
Atomoxetine and Oxybutynin	Brigham and Women's Hospital	Atomoxetine:NRI Oxybutynin: Antimuscarinic agent	NCT02908529[5,6]	• AHI • Genioglossus muscle responsiveness to increased ventilatory drive	• Atomoxetine and oxybutynin lowered AHI (events/h % change) by 63% (34-86%), from 28.5 (10.9-51.6) events/h to 7.5 (2.4–18.6) events/h (*P*<.001)
VI-0521 (Phentermine and topiramate)	VIVUS LLC	Appetite suppression	NCT00745251[7]	• Change in AHI • % change in weight	• Change in AHI (SE): Placebo= -16.6 (4.15) Phentermine and topiramate=-31.46 (4.25); *P*=.0084 • Percent change in weight (SE) Placebo= -10.26 (1.17) Phentermine and topiramate 15mg/92 mg= -4.21 (1.15)
DAW1033B2	Brigham and Women's Hospital	NA	NCT03426631[8]	• AHI	• AHI events/h, Median (IQR): Placebo=33 (24.1 to 41.9) DAW1033B2=20.4 (6.4 to 47.9); *P*=.47

*Not an extensive list. Additional outcomes may apply.

Note: Last update can be noted in the reference section of the speaker notes.

AHI=Apnea-Hypopnea Index; CI=Confidence Interval; CPAP=Continuous Positive Airway Pressure; IQR=Interquartile Range; MOA=Mechanism of Action; NA=Not Available; NHLBI=National Heart Lung and Blood Institute; NREM=Non-Random Eye Movement; NRI=Norepinephrine Reuptake Inhibitor; ODI=Oxygen Desaturation Index; OSA=Obstructive Sleep Apnea; SE=Standard Error.

References are provided in the speaker notes.

Phase 2 Studies for OSA

Completed Randomised-controlled Trials With Outcomes

Drug (brand)	Company/ Sponsor	MOA	NCT number	Key outcome measures*	Outcomes
AD109 (Atomoxetine and Aroxybutynin) AD504 (Atomoxetine and Trazodone)	Apnimed	Atomoxetine: NRI Aroxybutynin: Antimuscarinic agent Trazodone: Serotonin uptake inhibitor	NCT05071612[1] MARIPOSA	• Change in AHI	• AHI reduced from 20.5 to 10.8 events/h with AD109 75 mg/2.5 mg and from 19.4 to 9.5 events/h with AD109 75mg/5mg[2] • 41% of patients achieved AHI<10 with AD109[2] • 44% of patients achieved >50% reduction in AHI and 15% achieved >80% reduction in AHI from baseline[2]
Tiagabine	Brigham and Women's Hospital	GABA reuptake inhibitor	NCT02387710[3]	• AHI • Slow wave sleep • Arousal Threshold	• AHI supine events/h, Median (IQR)[4]: Placebo=41.5 (20.3) Tiagabine=39.5 (16.5); *P*>.5
LTM1201	Brigham and Women's Hospital	NA	NCT03640052[5]	• AHI • Collapsibility of the Upper Airway	• AHI events/h, Mean (SE) : Placebo=20.8 (8) LTM1201L=24.4 (11.3); *P*>.5 LTM1201LN= 18.8 (11.3); *P*>.5 LTM1201LB=14 (11.3); *P*>.5; LTM1201LD=9.1 (11.9); *P*=.33
DAW1033D	Brigham and Women's Hospital	NA	NCT03383887[6]	• AHI • Collapsibility of the Upper Airway	• AHI events/h, Median (IQR): Placebo=21.6 (9.1 to 49.8) DAW1033D=37.9 (5.1 to 55.4); *P*=.56

*Not an extensive list. Additional outcomes may apply.
Note: Last update can be noted in the reference section of the speaker notes.
AHI=Apnea-Hypopnea Index; IQR=Interquartile Range; MOA=Mechanism of Action; NA=Not Available; NRI= Norepinephrine Reuptake Inhibitor; OSA=Obstructive Sleep Apnea; SE=Standard Error.
References are provided in the speaker notes.

Phase 2 Studies for OSA

Completed Randomised-controlled Trials With Outcomes

Drug (brand)	Company/ Sponsor	MOA	NCT number	Key outcome measures*	Outcomes
AD036 Atomoxetine and oxybutynin	Apnimed	Atomoxetine: NRI Oxybutynin: Antimuscarinic agent	NCT03845023[9]	• AHI • ODI • Epworth Sleepiness Scale	• People with 50% reduction in AHI (%) Placebo=8.3% AD036 Dose 1=5.6% AD036 Dose 2=17.6% AD036 Dose 3=23.5%
AD109 (Atomoxetine and Aroxybutynin)	Apnimed	Atomoxetine: Norepinephrine reuptake inhibitor Aroxybutynin: Antimuscarinic agent	NCT04580394[2]	• Change in Hypoxic Burden (HB) • AHI	• Change in HB LSM (95% CI) AD109=-0.41 (-0.54 to -0.28) Atomoxetine=-0.36 (-0.49 to -0.23); R-oxybutynin=-0.04 (-0.17 to 0.09) Placebo=-0.06 (-0.18 to 0.07)
Dimethyl Fumarate	University of Michigan	Antiinflammatory and cytoprotective agent	NCT024381377[3]	• Mean change in apnea Severity as measured by the respiratory disturbance index	• Respiratory events/h, Mean (SD) Placebo=10.2 (13.1) Dimethyl Fumarate=-3.11 (12.9); *P*=.0124

*Not an extensive list. Additional outcomes may apply

Note: Last update can be noted in the reference section of the speaker notes.

AHI=Apnea-Hypopnea Index; HB=Hypoxic Burden; IQR=Interquartile Range; LSM=Least Square Mean; MOA=Mechanism of Action; NA=Not Available; NRI= Norepinephrine Reuptake Inhibitor; ODI=Oxygen Desaturation Index; OSA=Obstructive Sleep Apnea; SD=Standard Deviation.

References are provided in the speaker notes.

Phase 2 Studies for OSA

Completed Randomised-controlled Trials

Drug (brand)	Company/ Sponsor	MOA	NCT number	Key outcome measures*	Outcomes
AD182 (Atomoxetine and orexin antagonist) AD504 (atomoxetine and trazodone)	Apnimed	Atomoxetine: Norepinephrine reuptake inhibitor Orexin antagonist Trazodone: serotonin uptake inhibitor	NCT04645524[1]	• AHI	NA
BF2.649	Bioprojet	Histamine H3 receptor inverse agonist	NCT01620554[2]	• Change in Epworth Sleepiness Scale scores (ESS)	NA
Eszopiclone	Sunovion	Sedative-Hypnotic - GABA Receptor modulator	NCT00685269[3]	• AHI (frequency of apnea and hypopnea episodes) • The mean duration of apnea and hypopnea episodes • Oxygen saturation during apnea and hypopnea	NA
AVE0657	Sanofi	NA	NCT00614250[4]	• Change in AHI	NA
Zonisamide	Goteborg University Eisai Inc.	Carbonic anhydrase inhibitor	NCT01765608[5]	• AHI • ODI	NA
BAY2586116	Bayer	Protein channel blocker	NCT04713826[6]	• Reduction in AHI from baseline ≥50% • TEAE	NA
AD313+ Atomoxetine	Apnimed	Atomoxetine: Norepinephrine reuptake inhibitor	NCT05101122[7]	• Change in AHI	NA
AD128 Mannitol	Apnimed Raphael Heinzer	NA	NCT04394143[8]	• AHI • ODI	NA
SAS0421 a,b, & c	Apnimed Brigham and Women's Hospital	NA	NCT03892772[9]	• AHI • Hypoxic Burden • Arousal Index	NA

*Not an extensive list. Additional outcomes may apply

Note: Last update can be noted in the reference section of the speaker notes.

AHI=Apnea-Hypopnea Index; NA=Not Available; MOA=Mechanism of Action; NA=Not Available; ODI=Oxygen Desaturation Index; OSA=Obstructive Sleep Apnea; TEAE=Treatment-emergent Adverse Event.

References are provided in the speaker notes.