

Treatment of Obstructive Sleep Apnea

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Indications for treatment

- The AASM recommends offering PAP therapy to all patients who have been diagnosed with OSA.

OSA is defined as either

- an obstructive respiratory disturbance index (RDI) ≥ 15 events per hour with or without symptoms

or

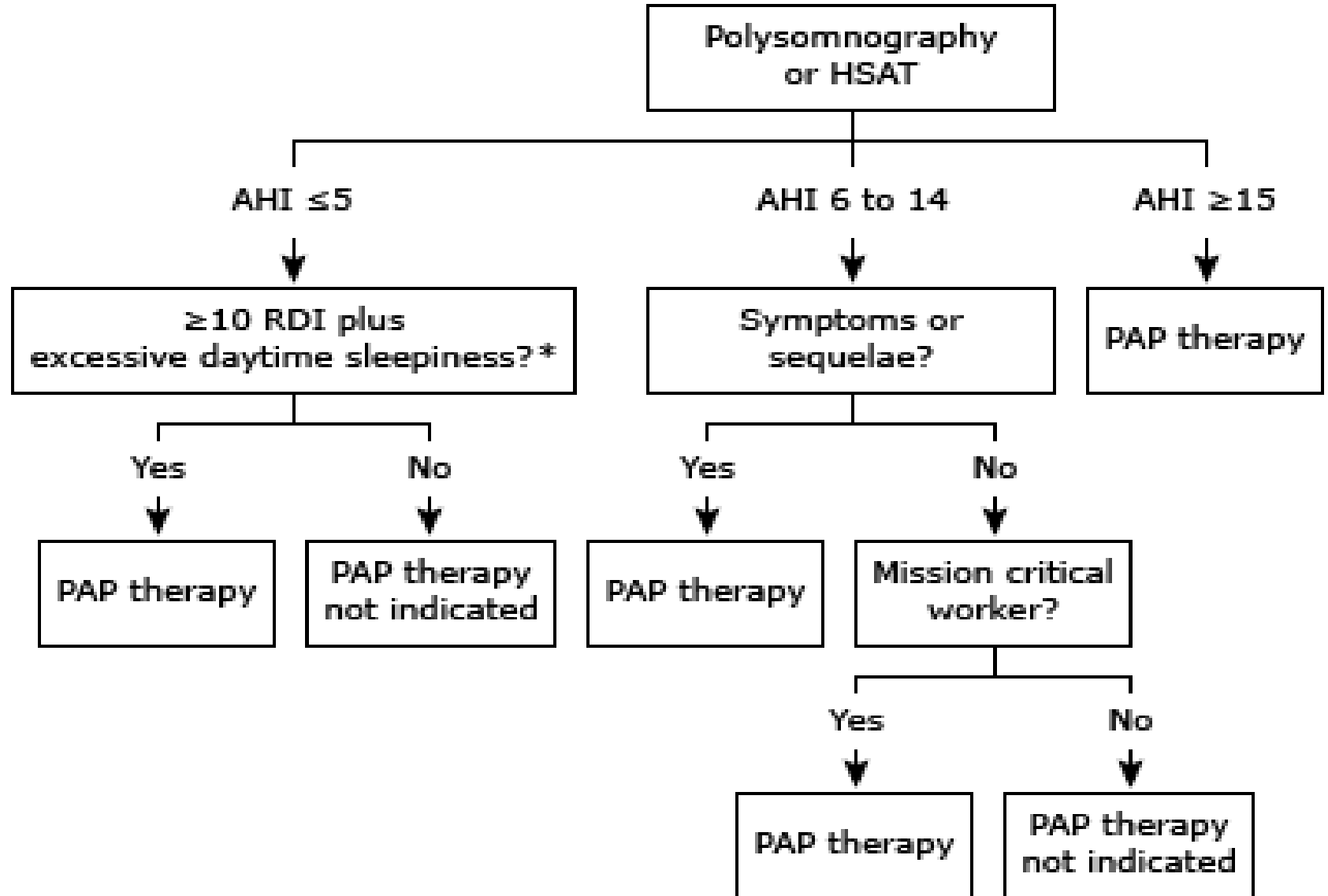
- an obstructive RDI between 5 and 14 events per hour that is accompanied by any of the following: sleepiness, nonrestorative sleep, fatigue, or insomnia symptoms; waking up with breath holding, gasping, or choking; habitual snoring and/or breathing interruptions; hypertension, mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes.

Indications for treatment

Our approach is to also initiate therapy in the following groups of patients:

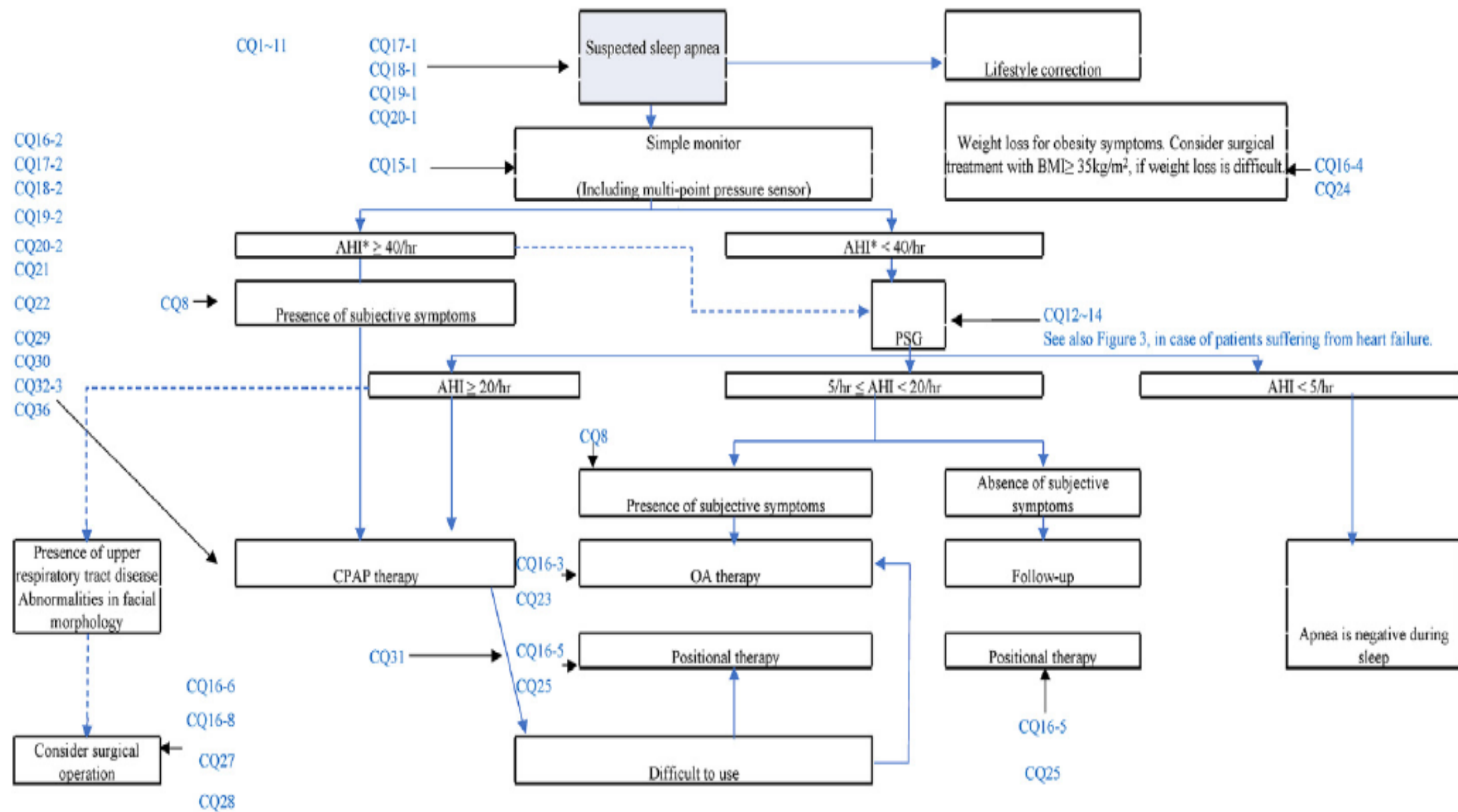
- Patients with an AHI >5 events per hour of sleep plus one or more clinical or physiologic sequelae attributable to OSA.
- Patients with an AHI ≥ 15 events per hour of sleep, even in the absence of symptoms.
- Patients who perform mission critical work (eg, airline pilots, air traffic controllers, locomotive engineers, bus and truck drivers) and have an AHI between 5 and 15 events per hour of sleep, even if there are no clinical or physiological symptoms attributable to OSA.
- Patients with an increased number of RERAs (eg, ≥ 10 per hour) and excessive daytime sleepiness, even if the AHI is ≤ 5 events per hour.

Indications for positive
airway pressure therapy
in adults with
obstructive sleep apnea



Indications for treatment

- The Centers for Medicare and Medicaid Services (CMS) in the United States has its own guidelines for reimbursement of PAP therapy.
- PAP therapy for OSA is reimbursed when the AHI is ≥ 15 events per hour, or between 5 and 14 events per hour and associated with excessive daytime sleepiness, impaired neurocognitive function, mood disorders, insomnia, cardiovascular disease (eg, hypertension, ischemic heart disease), or a history of stroke.



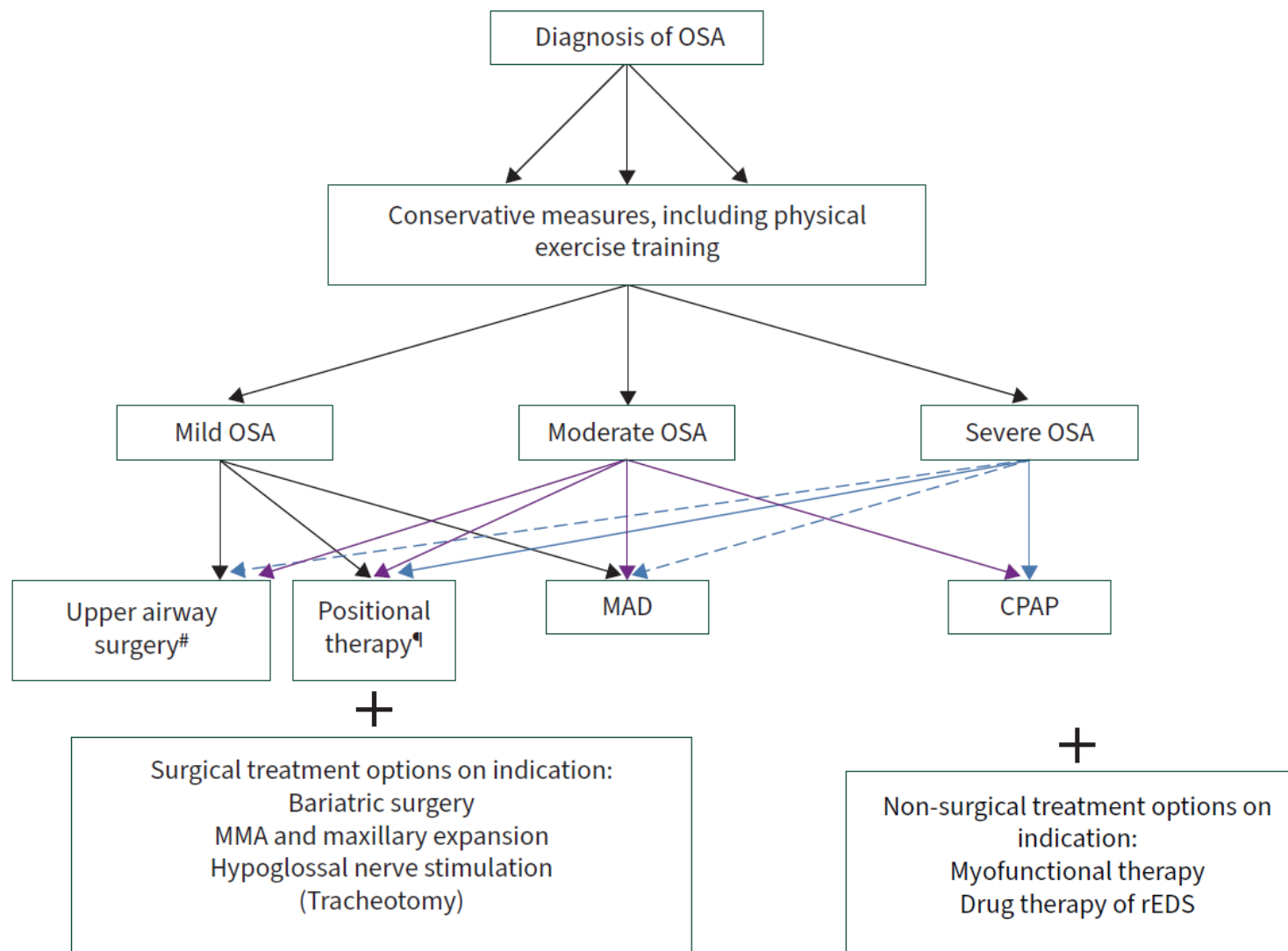


FIGURE 1 Current treatment modalities in obstructive sleep apnoea (OSA). Dashed arrows: mandibular advancement device (MAD) therapy or upper airway surgery indicated in patients who do not tolerate continuous positive airway pressure (CPAP). MMA: maxillomandibular advancement; rEDS: residual excessive daytime sleepiness. [#]: in selected patients (drug-induced sleep endoscopy); [¶]: if position dependent.

Treatment of Adult OSA with Positive Airway Pressure: An AASM Clinical Practice Guideline

- We recommend that clinicians use PAP, compared to no therapy, to treat OSA in adults with excessive sleepiness. (STRONG)
- We suggest that clinicians use PAP, compared to no therapy, to treat OSA in adults with impaired sleep-related quality of life. (CONDITIONAL)
- We suggest that clinicians use PAP, compared to no therapy, to treat OSA in adults with comorbid hypertension. (CONDITIONAL)
- We recommend that PAP therapy be initiated using either APAP at home or in-laboratory PAP titration in adults with OSA and no significant comorbidities. (STRONG)
- We recommend that clinicians use either CPAP or APAP for ongoing treatment of OSA in adults. (STRONG)
- We suggest that clinicians use CPAP or APAP over BPAP in the routine treatment of OSA in adults. (CONDITIONAL)
- We recommend that educational interventions be given with initiation of PAP therapy in adults with OSA. (STRONG)
- We suggest that behavioral and/or troubleshooting interventions be given during the initial period of PAP therapy in adults with OSA. (CONDITIONAL)
- We suggest that clinicians use telemonitoring-guided interventions during the initial period of PAP therapy in adults with OSA. (CONDITIONAL)

GOOD PRACTICE STATEMENTS

- Treatment of OSA with PAP therapy should be based on a diagnosis of OSA established using **objective testing**.
- Adequate follow-up, including troubleshooting and monitoring of objective efficacy and usage data to ensure adequate treatment and adherence, should occur following PAP therapy initiation and during treatment of OSA.

Positive airway pressure treatment

- The most common modes of PAP administration include continuous positive airway pressure (**CPAP**), which delivers PAP at a constant level throughout the respiratory cycle; autotitrating positive airway pressure (APAP), which increases or decreases PAP in response to changes of upper airway obstruction; and bilevel positive airway pressure (BPAP).
- Earlier studies indicated that CPAP was generally favored as initial therapy, because it was the most familiar and best studied. However, **APAP** appears to be as effective as CPAP, with no identified substantial harm, while delivering lower mean pressures.
- **BPAP** also conferred no clinically significant advantage over CPAP, but may be beneficial in patients with comorbidities, high PAP requirements or intolerance to CPAP or APAP.

OSA Treatment

- Continuous positive airway pressure (**CPAP**) is the current **standard of treatment** of obstructive sleep apnea (OSA), since its description in the early 1980s, and is highly effective in **suppressing respiratory disturbances** during sleep as well as **improving several patient clinical manifestations**.
- However, advances in the pathophysiological understanding of OSA have shown that not only **anatomical narrowing of the upper airways**, but also **impairment of muscle responsiveness**, **arousability** and **respiratory drive** all contribute to the pharyngeal collapse that is the hallmark of the disorder.

OSA Treatment

- The heterogeneous pathophysiology and the focus on patient-related outcome parameters, in addition to limited positive airway pressure adherence in many patients encourage the search for reliable alternatives to CPAP.

Endotypes and Phenotypes of Obstructive Sleep Apnea

- Some researchers and clinicians have begun categorizing OSA as a heterogeneous disease with classifications based on **endotypes** (underlying mechanisms) or **phenotypes** (clinical expression).
- The endotypes that can be identified in OSA include **impaired anatomical compromise, impaired pharyngeal dilator muscle function, high loop gain, and low arousal threshold**, which is the predisposal of waking up due to respiratory disturbances.
- In contrast, OSA phenotypes can be classified into five distinct groups: **disturbed sleep, minimal symptoms, upper airway symptoms with sleepiness, upper airway symptoms dominant, and sleepiness dominant**. Because endotypes are associated with different underlying mechanisms of OSA, adopting this idea of OSA being a heterogeneous chronic disease could be beneficial since it would allow a more patient-specific treatment approach.

Oral appliances

- The American Academy of Sleep Medicine recommends sleep physicians consider prescription of oral appliances, rather than no treatment, for adult patients with obstructive sleep apnea who **are intolerant of CPAP therapy** or **prefer alternate therapy**. Level of Evidence: Moderate
- An oral appliance is a custom-fit, molded mouthpiece that is fitted by a dental professional to enlarge the upper airway and/or decrease upper airway collapsibility.
- There are two types of oral appliances: **mandibular advancement devices** (MADs), which advance the mandible with respect to the resting position and cover the upper and lower teeth, and **tongue-retaining devices**, which do not reposition the mandible but hold the tongue forward relative to the resting position.

Ann Intern Med. 2013;159(7):471-483.

J Clin Sleep Med. 2009;5(3):263-276.

Oral appliances

- The most frequently prescribed type of oral appliance is the mandibular advancement device (**MAD**), which represents the main noninvasive CPAP alternative for patients with OSA. These devices are worn intraorally at night to keep the lower jaw anteriorly positioned during sleep. The mechanism of action of the MAD is usually assumed to be an **enlargement** of the **cross-sectional upper airway dimensions** by **anterior displacement of the mandible** and the attached **tongue**, resulting in **improved upper airway patency**.
- Furthermore, the MAD aims at **resisting** the **downward rotation of the mandible** during sleep and the accompanying retrusion of the mandible, compromising upper airway patency.

Oral appliances

- One-third of patients under MAD therapy showed a complete resolution of the OSA disease obtaining an AHI <5 events·h⁻¹ under MAD therapy,
- Another third of patients showed a decrease in AHI of 50% or more,
- The last one-third of patients only showed a negligible improvement in OSA severity.

Mandibular advancement devices

- **Good responding** phenotypes to MAD therapy are characterized by **milder severity**, **younger age** (<60 years) and **lower BMI** (<30 kg/m²) **and female sex**.
- One recent study observed significant reverse left ventricular hypertrophic remodelling after 6 months' successful MAD therapy. Finally, one study found that only CPAP, not MAD, was effective on metabolic outcomes after 1 year's treatment of mild OSA patients.



Figure 2. A mandibular advancement splint fitted to upper and lower dentition used to protrude the mandible forward during sleep.

MRI axial slice
velopharynx

Without MAS



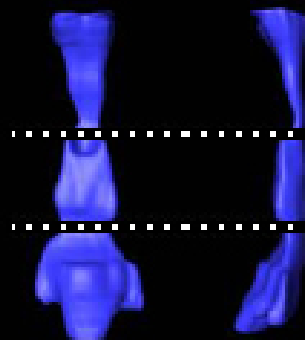
With MAS



3-D reconstruction

Lateral

A-P



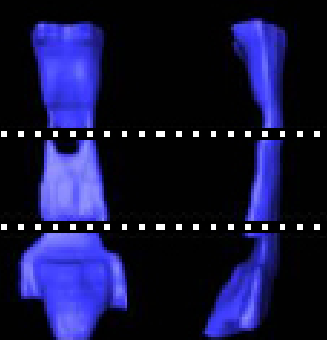
Velopharynx

Oropharynx

Hypopharynx

Lateral

A-P



Total airway
volume (cm³)

16.3

19.7
(21% increase)

Tongue-retaining devices

- TRDs use a suction cavity to pull the tongue out of the mouth, thus improving retrolingual dimensions.
- These devices have not been well studied. However, one clear advantage is that they can be used in edentulous patients or patients who cannot use MAS (eg, due to occlusal changes).



Upper airway surgery

- Surgery may be preferable to oral appliances in those who have an anatomic upper airway narrowing that is causing or exacerbating OSA and can be ameliorated surgically (eg, nasal obstruction, adenotonsillar hypertrophy).

Surgery of the upper airway

- In severe forms of OSA, surgery can be indicated in case of an unfavorable outcome with non-surgical therapies, such as CPAP or MAD therapy. Surgery can also be considered as a first-line treatment in mild OSA. At the same time, there are also patients who do not want to be dependent on a lifelong aid.
- In all cases, surgical treatment of OSA aims to correct anatomical abnormalities in the upper airway that contribute to its collapse during sleep. Surgery may also be considered to correct anatomic deficiencies that compromise other therapies or to improve acceptance and tolerance of other OSA treatments.
- Various surgical modifications of the upper airway have been proposed to manage, and in some cases, treat OSA. When DISE shows obstruction at the level of the palate-tonsil many surgical techniques are indicated, such as radiofrequency thermotherapy (RFTT), uvulopalatopharyngoplasty (UPPP) and some modifications.
- Tonsillectomy is only recommended for adult patients with tonsillar hypertrophy or as part of UPPP. UPPP is accompanied by considerable morbidity. This intervention is painful and there is temporary velopharyngeal insufficiency, post-operative bleeding, nasopharyngeal stenosis, voice changes and alterations in speech. This usually resolves within a month of surgery.

Surgery of the upper airway

- Chances of success of UPPP (50% reduction in AHI and AHI <20 events·h⁻¹) for OSA seem to be ~40% in unselected patients, or a ~30% chance of a post-operative AHI below 10 events·h⁻¹, but this rises to 70–80% if the location of the upper airway obstruction is determined with DISE.

Maxillomandibular surgery

- Overall, this type of surgery has the best record of success as a treatment for OSA, and **response rates of 86%** have been published, while **cure** (AHI <5 events·h⁻¹) is present **in about 43%.**

Weight reduction

- Approximately **70% of OSA patients are obese** (body mass index (BMI) ≥ 30 kg·m⁻²). In morbidly obese patients (BMI ≥ 40 kg·m⁻²), the prevalence of OSA varies between 40% and 90%.
- In a clinical cohort, GEORGOULIS et al. found that even a <5% weight loss can reduce respiratory events, but $\geq 5\%$ and **ideally $\geq 10\%$ weight loss** was necessary for reducing the prevalence of severe OSA.
- These changes do not guarantee a reduction in OSA severity in all cases. For example, a reduction of 10 events·h⁻¹ in a patient with a starting AHI of 15 events·h⁻¹ reduces the severity class, whereas the same reduction in a patient with 45 events·h⁻¹ does not change the severity class.
- Weight loss is not only associated with a decrease in AHI, but also with an improvement of hypoxemia. Finally, weight loss not only reduces OSA severity, but also alters cardiometabolic comorbidities, with improvement in hypertension, lipids and glycemic control.

Bariatric surgery

- Bariatric surgery is an effective means to achieve major weight loss and is indicated in individuals with a **body mass index (BMI) ≥ 40 kg·m⁻²** or those with a **BMI ≥ 35 kg·m⁻² with important comorbidities** (arterial hypertension, diabetes, OSA) and in whom dietary attempts at weight control have been ineffective.
- Different studies have shown the beneficial effects of bariatric surgery on OSA, with **a reduction in AHI of 77%** and **cure of OSA in 64–86%** of the cases.

Breathe 2022; 18: 220164

Eur Respir Rev 2021; 30: 210200

Weight Loss Medications

- Current pharmacological agents that have been approved by the Food and Drug Administration (FDA) for weight loss include orlistat, liraglutide, naltrexone/bupropion, and phentermine/topiramate extended-release (ER). However, only phentermine/topiramate ER, liraglutide, and orlistat have studies evaluating weight loss in those with OSA.
- Phentermine 15 mg plus topiramate 92 mg extended-release.
- Liraglutide 0.6 mg/day and titrated weekly by 0.6-mg increments until a 3.0 mg daily dose.
- Orlistat 60 mg or 120 mg three times a day.

Medicina 2022, 58, 225.

ERJ Open Res 2022; 8: 00126-2022

Positional therapy

- Diverse devices have been designed for positional therapy: tennis balls, pillows, bulky backpacks and position alarms.
- When a positional OSA (POSA) patient lies in the lateral direction, there is an opening up of the lateral portions of the airway, so that the overall shape of the velopharynx becomes more circular. Moreover, the tongue and soft palate now lie perpendicular to the gravitational pull (and now constitute the lateral wall of a 90° rotated airway), resulting in an airway that is less likely to collapse when passive and in the lateral position.
- The optimal position to achieve $\geq 80\%$ reduction in AHI is $>30^\circ$ lateral rotation with >70 mm of cervical head-tilt support and an elevation underneath the scapula of >20 mm.

Positional therapy

- **Position-dependant OSA (POSA)** is commonly defined as a **supine to non-supine apnea hypopnea index (AHI) ratio ≥ 2** and an AHI that normalizes (AHI < 5 or 10 events/h) in the non-supine posture.
- POSA occurs in more than 50% of OSA patients.

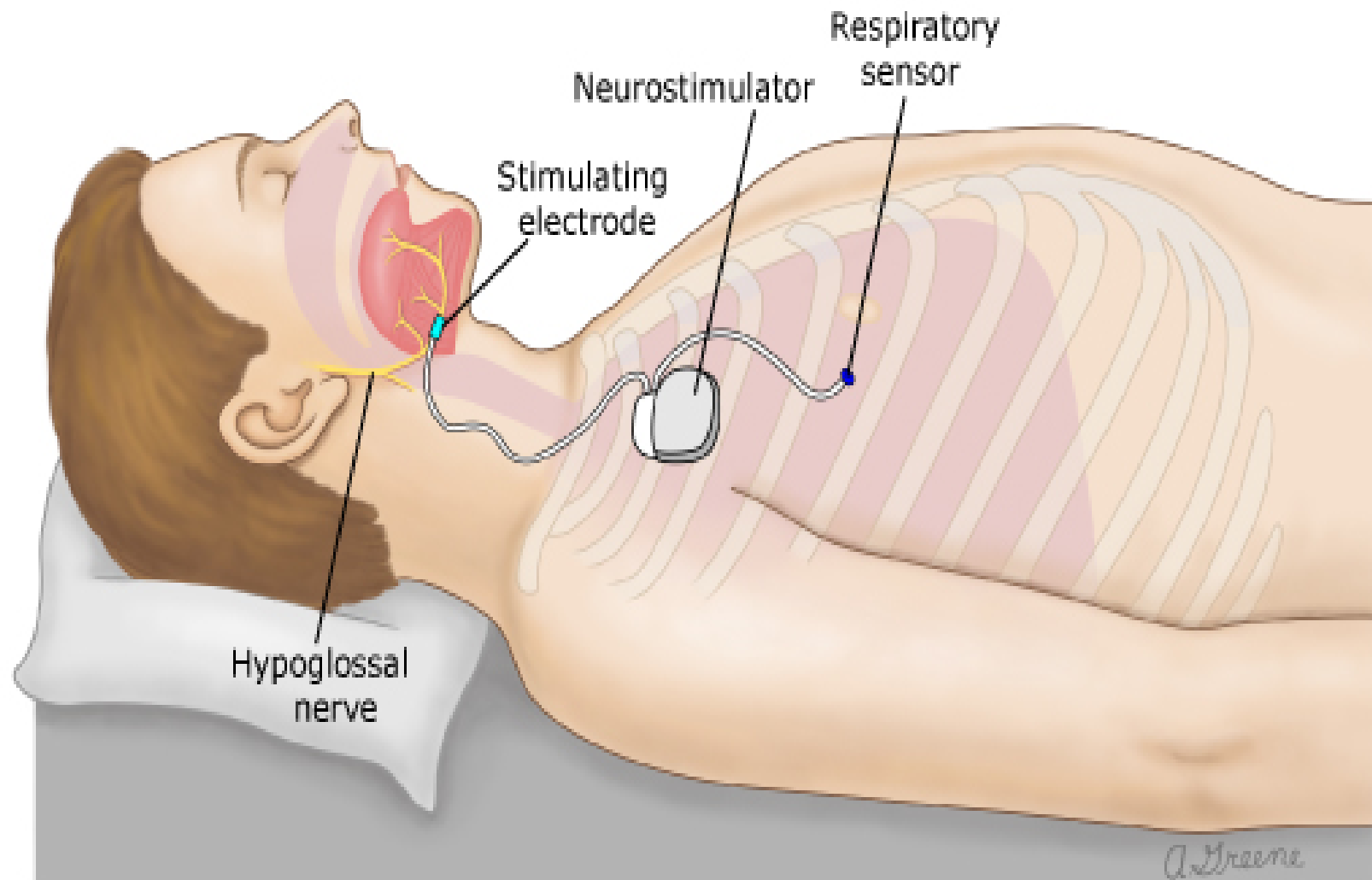


Figure 3. A vibratory sleep device placed around the neck which vibrates when patient is in supine position. Vibration will stop when patient rolls out of supine position.



Hypoglossal nerve stimulation

- Electrical stimulation of the hypoglossal nerve (i.e. the motor nerve of the genioglossus muscle) causes tongue protrusion and stiffening of the anterior pharyngeal wall.
- There remains limited evidence for hypoglossal nerve stimulation (HNS) and it is currently not recommended to be used as first-line treatment. It should be used as a salvage treatment when standard therapy cannot be tolerated.
- **Responders** to treatment are likely to have an **AHI <50 events·h⁻¹, lower neck circumference, BMI <32 kg·m⁻² and single-level, nonconcentric (noncircumferential) obstruction of the upper airway.**
- Hypoglossal nerve stimulator implantation, showed a surgical response in 75% of participants in a 5-year clinical trial.



Drug treatment

- Approximately 70% of people with OSA have one or more non-anatomical traits that contribute to their OSA. These include **impaired pharyngeal dilator muscle function during sleep, unstable respiratory control (high loop gain) and waking up too easily to minor airway narrowing during sleep (low respiratory arousal threshold)**.
- For example, non-obese patients with a low respiratory arousal threshold endotype may respond poorly to CPAP therapy.
- Patients with unstable respiratory control (high loop gain) are more likely to have a suboptimal therapeutic response to mandibular advancement splint therapy and upper airway surgery.

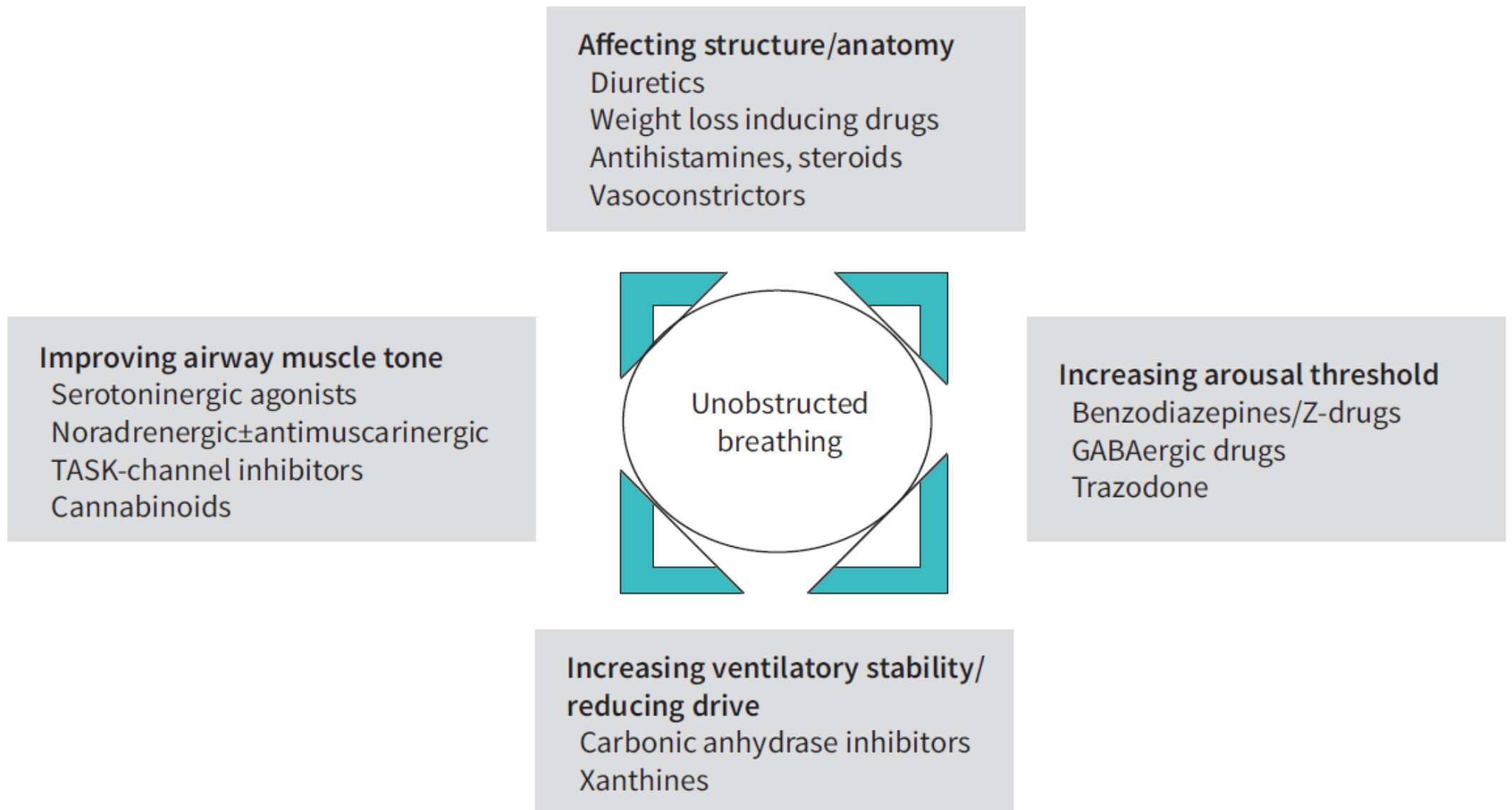


FIGURE 6 Principal current strategies for drug development in obstructive sleep apnoea. GABA: γ -aminobutyric acid.

Upper airway muscle activity: pharmacological approach

- Serotonergic drive is decreased from wakefulness to non-rapid-eye movement (NREM) sleep and further during REM sleep. The bulk of documentation in this field includes the **serotonergic agents** mirtazepin, paroxetine and fluoxetine.
- These drugs were shown to **reduce the AHI**, particularly during REM sleep, in small explorative studies of patients with OSA. However, inconsistent results, mainly in terms of efficacy or side-effects, have led to termination of further clinical development in this area.

Improving Pharyngeal Dilator Function

- **Serotonin** displays predominantly **excitatory** central effects on 5-HT receptor activity of the upper airway motor neurons and respiratory neurons.
- This **activity** is **diminished** centrally **during REM** sleep and is believed to cause upper airway collapse in patients with OSA. Peripherally, serotonin exhibits inhibitory effects.

Improving Pharyngeal Dilator Function Serotonergic Medications

- A randomized, double-blind, placebo-controlled trial tested the combination of **fluoxetine** and **ondansetron**, 5-HT₃ receptor antagonists, in 44 patients with OSA.
- The result was a **40% reduction in AHI** in the high-dose combination group (**fluoxetine 10 mg daily and ondansetron 24 mg daily**; $p < 0.03$) compared to baseline, which was predominantly attributed to fluoxetine use as the ondansetron monotherapy group showed a trend toward increased AHI post-treatment that was not statistically significant in REM and supine sleep.
- The study suggested that a high-dose combination treatment may yield an entirely therapeutic response in only a subset of patients with mild-moderate OSA. Thus, fluoxetine may have some benefits as a pharmacological option for OSA.
- Furthermore, several NREM and REM sleep studies have shown that serotonin SRIs have a strong association with reducing AHI in OSA severity.

Upper airway muscle activity: pharmacological approach

- **Noradrenergic modulation** was explored using the tricyclic antidepressants protriptyline and desipramine both resulting in a mild reduction of the AHI. More recent approaches have focused on the selective norepinephrine reuptake inhibitor atomoxetine. This latter compound had only moderate effects on the AHI when administered alone, but it was speculated that the physiological limitation of the effect was of muscarinic nature.
- TARANTO-MONTEMURRO et al. combined **atomoxetine** with the antimuscarinic **oxybutynin**, resulting in a **reduction of the AHI by 62%** in a pilot trial.
- A subsequent trial using a combination of adrenergic drug reboxetine and hyoscine butylbromide recorded an effect of 35%, while the combination of reboxetine and oxybutynin lowered the AHI from 49 events·h⁻¹ to 18 events·h⁻¹ in a 7-night placebo-controlled trial.
- The study protocols used so far in this field are of short duration and limited size.

High Loop Gain

- **Loop gain** is quantified as the **instability of ventilatory chemoreflex control**. Loop gain functions as the system that controls ventilation via a negative feedback loop. This mechanism manages blood gas tension levels between narrow limits. The feedback loop consists of various components (i.e., the circulatory delay, the plant, and the controller) and works consecutively to prevent any shift in blood gas tension due to ventilation.
- A high loop gain signifies the unbalanced response to minor changes in PCO₂, leading to hyperventilation mixed with hypoventilation. Patients with a collapsible upper airway and high loop gain experience negative inspiratory pressures that overwhelm the airway and force it closed. Because of this, there has been a growing interest in discovering possible OSA treatments that work through mechanisms that alter ventilatory chemoreflex control.

Front Neurol 2018, 9, 896.

Medicina 2022, 58, 225.

Carbonic anhydrase inhibitors: pharmacological approach

- Acetazolamide, a frequently used carbonic anhydrase inhibitor, is known to reduce periodic breathing at high altitude and to stabilize periodic breathing in cardiac failure.
- However, **carbonic anhydrase inhibitors** have several biological effects that may link to conventional OSA. The evaluation of this drug in OSA should therefore include multiple effects (targets) that may be induced by a carbonic anhydrase inhibitor including respiratory (**reduced AHI and improved oxygenation**), cardiovascular (**reduction of blood pressure**) and metabolic (**weight loss in obesity, reduced lipids**) effects.

Carbonic anhydrase inhibitors: pharmacological approach

- **Acetazolamide** (250 mg four times daily) induced an **~50%** placebo-adjusted **AHI reduction** in a small 2-week RCT, and an earlier uncontrolled short-term study had used 250 mg (once daily) to reduce the AHI by 28%.
- Subsequent studies, with doses ranging from 500 mg to 750 mg three times daily, reported effect sizes of 40–52%.
- Finally, in a recent 4-week RCT of the carbonic anhydrase inhibitor sulthiame that included 68 patients with moderate to severe OSA, the AHI was reduced by 41%.
- Preliminary findings in 56 patients with moderate or severe OSA who were intolerant of PAP reported that the carbonic anhydrase inhibitor sulthiame reduced the AHI from 55.2 to 33.0 events/hour (400 mg group; placebo group 53.9 events/hour) and from 61.1 to 40.6 events/hour (200 mg; placebo 50.9 events/hour).
- Carbonic anhydrase inhibition appears **to reduce an elevated loop gain** and **to increase a low arousal threshold** which may be characteristics of a responding phenotype. Carbonic anhydrase inhibitors were well tolerated in these studies, but isolated paresthesias were common.

Carbonic anhydrase inhibitors: pharmacological approach

- Another comorbidity target in OSA is weight loss. **Zonisamide** and **topiramate**, carbonic anhydrase inhibitors used in epilepsy, induced 9.4% and 10.2% weight loss, respectively, after ~6–8 months' therapy. Weight loss in this order of magnitude would be an added benefit in overweight or obese patients with OSA.

Low Respiratory Arousal Threshold

- In patients with OSA, sleep arousal is the sudden awakening from sleep due to airway obstruction. Approximately 30–50% of OSA patients have low respiratory arousal thresholds, making them more subject to frequent and premature nighttime awakenings, leading to sleep fragmentation, breathing instability, and impaired dilator muscle.
- Because of this, further efforts have been made to investigate drugs with sedative and hypnotic effects with the intent of increasing arousal threshold while maintaining appropriate upper airway muscle activity, to reduce AHI and OSA severity.

Arousal threshold: pharmacological approach (sedatives and hypnotics)

- Drugs with sedative, respiratory depressant or myorelaxant properties have traditionally been advised against in patients with OSA. Arguably, all such therapy might reinforce hypoventilation and respiratory gas derangement or suppress upper airway dilatory muscle function leading to a worsening of sleep apnea. While drugs such as opiates might induce severe respiratory depression, others such as benzodiazepines may have a paradoxical beneficial effect.
- Indeed, a high ventilatory drive, which typically accompanies an obstructive event, may be detrimental in subjects with a low arousal threshold, since early arousal tends to destabilize sleep and to prevent stable breathing.
- Frequent arousals that occur during minor airway collapse are therefore believed to facilitate cyclic breathing events. Hence, arousals may be adequate to prevent excessive hypoxemia in patients with a high arousal threshold, but they may lead to unstable breathing in those with a low arousal threshold. This paradox has provided a rationale to explore the effects of certain sedatives in carefully selected patients with a low arousal threshold.

Low Respiratory Arousal Threshold

Z-Drugs

- Z-drugs are non-benzodiazepine agents that work on GABA_A receptors to produce inhibitory effects. However, unlike benzodiazepines, z-drugs do not produce myorelaxant effects and are associated with fewer adverse side effects, which their increased selectivity could explain GABA_Aα1 subunits interaction.
- In a physiological study, **eszopiclone (3 mg)** was found to significantly increase the arousal threshold by approximately 30% ($p < 0.01$) from stage one to stage two sleep and reduce AHI by about 45% ($p = 0.52$) in OSA patients with a low arousal threshold.
- Another study looked at the effects of **zolpidem 10 mg** and **zopiclone 7.5 mg** in patients with and without OSA. Results showed that zolpidem and zopiclone **increased the arousal threshold by 27%** ($p = 0.02$) and 37% ($p < 0.001$), respectively, without inhibiting upper airway muscle response.
- However, a different study looked at the effects of zolpidem (10 mg) in patients with severe OSA and low-moderate arousal threshold and found that although arousal threshold increased by 15% ($p = 0.010$), it was not shown to reduce AHI and improve OSA severity .

Eur Respir J. 2017, 50, 1701344.

Sleep Med. Rev. 2021, 58, 101492.

Clin Sci 2011, 120, 505–514.

Low Respiratory Arousal Threshold

Other Alternative Hypnotics

- **Trazodone**, a tricyclic antidepressant, is another drug that is being investigated for OSA patients with a low arousal phenotype because of the sedative effects it can produce by blocking muscarinic α -adrenoceptors.
- A study looked at the effect of **trazodone 100 mg** in OSA patients with a low arousal threshold and found that it significantly **increased the respiratory arousal threshold by 32%** without altering upper airway muscle activity. No significant reduction in AHI and OSA severity was noted.
- Another study did find that trazodone (100 mg) significantly reduced AHI when compared to placebo (38.7 vs. 28.5 events/h, $p = 0.041$) in OSA patients with $AHI \geq 10$.

J Physiol 2020, 598, 4681–4692.

Sleep 2014, 37, 811–819.

Residual sleepiness in CPAP-treated OSA patients

- While successful treatment of OSA with CPAP or other primary therapies typically improves symptoms, **between 10 and 15% of patients continue to experience EDS** and alterations in quality of life despite adequate therapy.
- Recently, the efficacy of **Solriamfetol**, a **dopamine/norepinephrine reuptake inhibitor** (Initial oral dosing is 37.5 mg once daily, titrated up to a maximum dose of 150 mg/day), and **Pitolisant**, a **selective histamine receptor-3 antagonist**, have been established in large multicenter randomized controlled trials. The two compounds have demonstrated significant improvements in subjective ESS scores by ~2 to 5 points and a reduction of objective sleepiness.

Eur Respir J 2022 Jun 2;59(6):2101788.

ERJ Open Res 2022; 8: 00126-2022

Breathe 2022; 18: 220164

Oxygen Therapy

- Oxygen therapy is not considered a useful treatment for obstructive sleep apnea, as it has been found that it can lengthen the duration of apneas. However, it is sometimes used to relieve hypoxemia. Resolution of hypoxemia must be documented to justify continued use, especially in patients with comorbid respiratory disease who are at an increased risk of hypercapnia with oxygen therapy.

Combination therapy

- Several investigators addressed the combination of CPAP with MADs. The combination significantly increased PAP adherence by 23.1% and decreased ESS by 1.4. However, PAP pressures, AHI and mask leak did not change significantly.
- LIU et al. retrospectively reviewed data from patients with severe OSA, who could not tolerate high PAP pressures. AHI and oxygen desaturation index improved under combination of PAP and MAD compared to no therapy. More importantly, therapeutic pressure was substantially reduced.
- TONG et al. compared CPAP alone with CPAP combined with MAD either with open or closed oral airway for one night each. Both combination therapies reduced PAP pressure significantly as compared to CPAP alone.

Eur J Dent 2021; in press

PLoS One 2017; 12: e0187032.

J Appl Physiol 2020; 129:1085–1091.

Combination therapy

- DIELTJENS et al. compared the combination of **positional therapy and MADs** with either treatment alone.
- Both single treatments improved respiratory disturbances significantly and similarly, while the combination was more effective and normalized the AHI.



The average attention span during a presentation is 10 minutes.