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Personalized Management Approach for OSA

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OSA is a heterogeneous disorder. If left untreated, it has major health, safety, and economic consequences. In addition to varying levels of impairment in pharyngeal anatomy (narrow/collapsible airway), nonanatomical "phenotypic traits" are also important contributors to OSA for most patients. However, the majority of existing therapies (eg, CPAP, oral appliances, weight loss, positional therapy, upper airway surgery) target only the anatomical cause. These are typically administered as monotherapy according to a trial and error management approach in which the majority of patients are first prescribed CPAP. Despite its high efficacy, CPAP adherence remains unacceptably low, and second-line therapies have variable and unpredictable efficacies. Recent advances in knowledge regarding the multiple causes of OSA using respiratory phenotyping techniques have identified new targets or "treatable traits" to direct therapy. Identification of the traits and development of therapies that selectively target one or more of the treatable traits has the potential to personalize the management of this chronic health condition to optimize patient outcomes according to precision medicine principles. This brief review highlights the latest developments and emerging therapies for personalized management approaches for OSA. CHEST 2018; 153(3):744-755

KEY WORDS: phenotyping; sleep apnea; sleep-disordered breathing; sleep medicine; upper airway

OSA is an increasingly common sleep-related breathing disorder.[1,2] It is characterized by repetitive upper airway narrowing (hypopnea) and closure (apnea) during sleep. This action causes intermittent hypoxemia, hypercapnia, and frequent cortical arousals. If left untreated, OSA can adversely affect the cardiovascular system,[3] cause neurocognitive impairment[4] and daytime sleepiness, and increase the risk of motor vehicle accidents.[5] OSA is more common in men than in women.[1,2] The continual rise in prevalence to approximately 9% of adults is related to increased rates of obesity and an aging population, two major risk factors for OSA.[6]

There are multiple causes or "phenotypic traits" that contribute to the pathogenesis of OSA. These traits include anatomical (narrow/crowded/collapsible upper airway) and nonanatomical (waking up too easily during airway narrowing [a low respiratory arousal threshold], ineffective or reduced pharyngeal dilator muscle activity during sleep, and unstable ventilatory control [high loop gain] components (Fig 1).[7,8] The

ABBREVIATIONS: AHI = apnea/hypopnea index; DREADDs = Designer Receptors Exclusively Activated by Designer Drugs; PALM = Pcrit, arousal threshold, loop gain, and muscle responsiveness; Pcrit = critical closing pressure; REM = rapid eye movement

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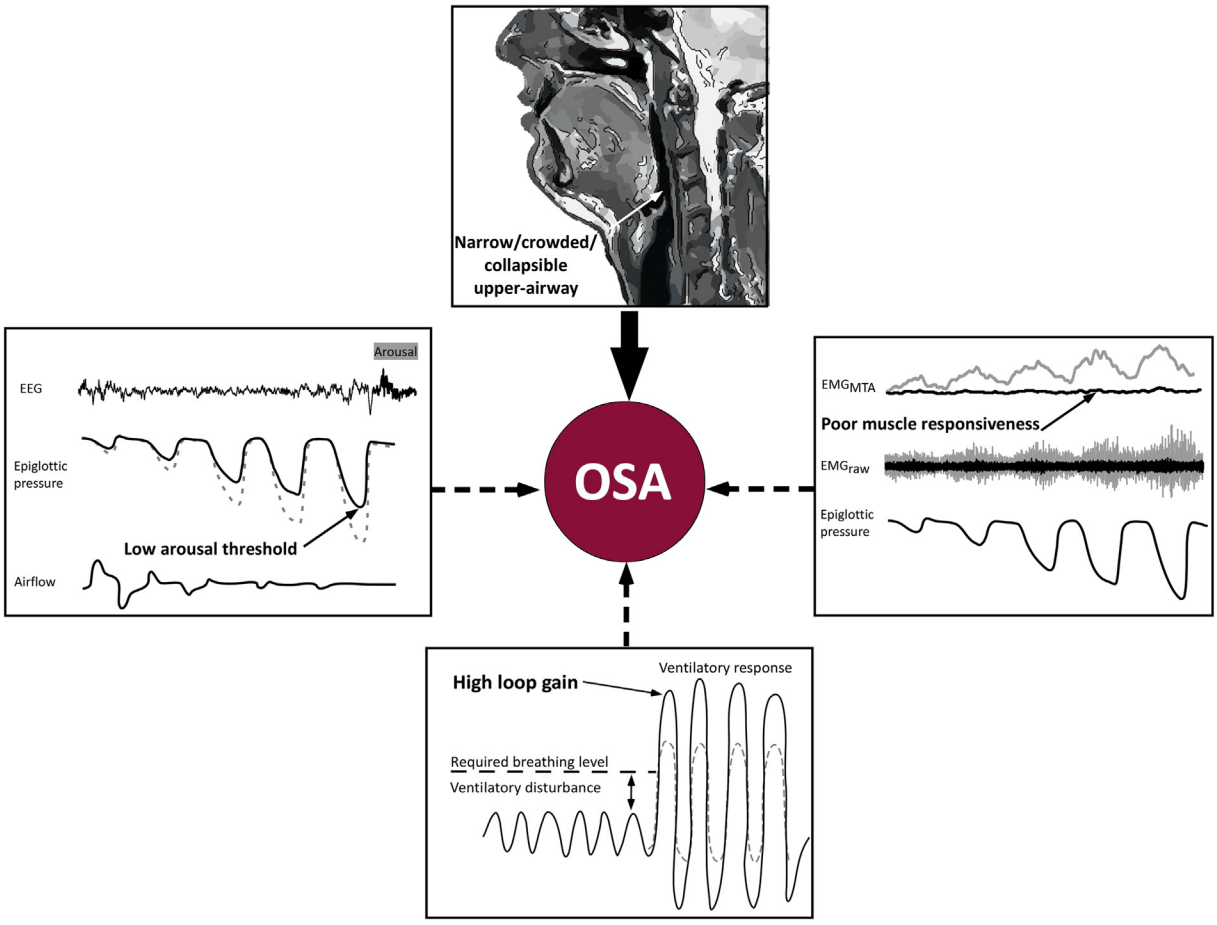

Figure 1 – *Schematic of the phenotypic traits that cause OSA. Some degree of "impaired" upper airway anatomy is a prerequisite for OSA (narrow/crowded/collapsible upper airway) indicated by the thick solid arrow and MRI schematic. Impairment in the nonanatomical traits (ie, low arousal threshold, poor muscle responsiveness, high loop gain) also importantly contributes to the pathogenesis of OSA in the majority of patients (dashed arrows). Schematic representation of impairment in each of the nonanatomical traits (solid black lines with adjacent arrows) is given, along with a more desirable response for each nonanatomical trait (gray lines). EMG = genioglossus electromyographic activity; MTA = moving time average (100 ms) of the rectified EMG signal. The text provides further details.*

contribution of these traits to OSA pathogenesis varies among individuals.[7]

Treatment for OSA has traditionally targeted the anatomical trait. This approach includes CPAP, oral appliances, upper airway surgery, weight loss, and positional therapy. These therapies are either often poorly tolerated (eg, CPAP), difficult to achieve (eg, weight loss), or have variable and unpredictable efficacy (eg, oral appliances, upper airway surgery, positional therapy). The diagnostic and treatment steps can be time-consuming, costly, and frustrating, especially for the many patients who fail CPAP (Fig 2).[9] Indeed, although advances in CPAP technology and optimal mask selection can improve CPAP comfort and tolerance,[10] failure rates are often high (> 50% in some cases).[11,12] Thus, most people with OSA remain undiagnosed, untreated, or undertreated.[6] Given the direct health, safety, and economic burden of untreated OSA,[13] this outcome is a major public health concern.

Recent evidence indicates that nonanatomical contributors play a prominent role in the pathogenesis of OSA for many patients, particularly in certain groups (eg, nonobese patients).[7,14] Thus, new and emerging therapies that target specific phenotypic or "treatable traits" (rather than a one-size-fits-all approach) show promise as an alternative to traditional therapies that focus on the anatomical problem. The present brief review summarizes the major pathophysiological causes of OSA, highlights current therapies and their limitations, and describes potential novel therapeutic options directed toward the nonanatomical traits that could be used independently or in combination with

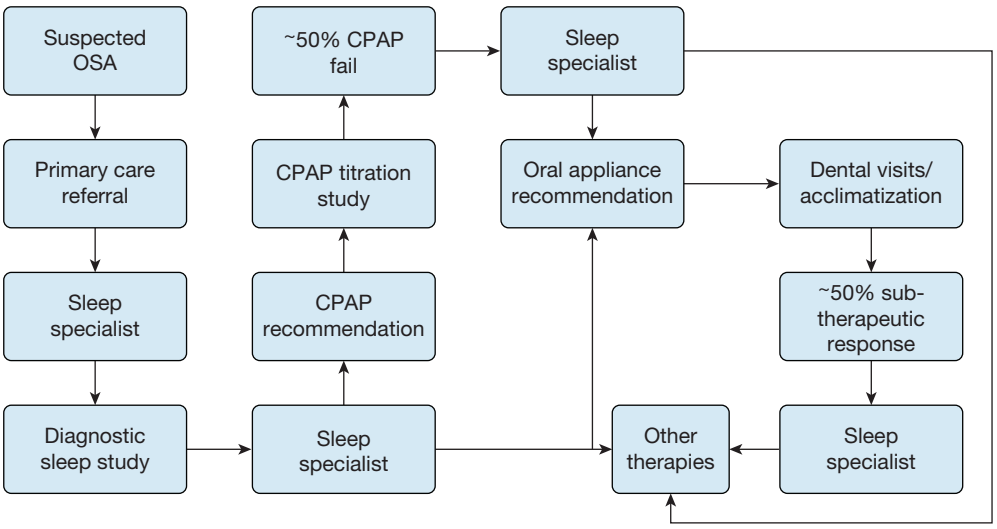

Figure 2 – *Example of current diagnosis and treatment flow diagram for someone with suspected OSA. As shown by the large number of potential steps, particularly for those who fail CPAP therapy, this schematic highlights the potentially cumbersome, time-consuming, and often frustrating process that many patients with OSA face in their diagnosis and treatment journey. (Note: several therapies and treatment pathways have been omitted for simplicity.) Not surprisingly, many patients are lost to follow-up at various stages throughout the process depending on their experiences and responses to prescribed therapy. Advances in technology (eg, autotitrating CPAP and home sleep testing) have emerged to streamline some of the steps. Similarly, simplified models of care that do not require a sleep specialist have been trialed*[9] *and have been shown to yield comparable outcomes for certain patient groups (eg, those with severe OSA and minimal comorbidities). However, rather than trial and error, the ultimate goal remains to personalize the management process to deliver one or more targeted therapies according to phenotypic characterization as first-line therapy with high predictive success rates. The text and Figures 1, 3, and 4 provide further details.*

existing therapies to treat OSA according to a precision medicine approach.

Upper Airway Anatomy and Collapsibility

Although OSA is a heterogeneous disorder, a prerequisite cause of its development is some level of anatomical compromise/increased upper airway collapsibility. Static imaging during wakefulness shows reduced pharyngeal lumen size in patients with OSA compared with non-OSA control subjects.[15] Obesity is a major contributor to pharyngeal narrowing. Increased fat deposition in the soft tissues, tongue, and lateral pharyngeal walls directly reduces the pharyngeal airspace in obese patients with OSA.[16-19] Central adiposity may also contribute to increased pharyngeal collapsibility via reductions in lung volume and caudal traction mechanisms.[20,21] In addition, the size and shape of craniofacial structures can impede the pharyngeal airspace.[22] Although anatomical abnormalities are key determinants of OSA, upper airway collapsibility during sleep (as measured by using the gold standard critical closing pressure [Pcrit] technique) varies considerably among patients with OSA (approximately –5 to > +5 cm H_2O).[7] Furthermore, approximately 20% of patients with OSA have upper airway collapsibility (Pcrit) during sleep similar to many people who do not have OSA.[7] OSA also occurs exclusively during sleep. Thus, there is clearly more to the disorder than "impaired upper airway anatomy." Nonetheless, impaired anatomy remains a key target for therapy and, as outlined in the following discussions, is the focus of most existing treatments.

Current Treatments That Target Impaired Upper Airway Anatomy

Anatomical treatments for OSA work by altering upper airway structure to prevent pharyngeal collapse during sleep.

CPAP

CPAP remains the first-line and most efficacious treatment for OSA. Delivered via a nasal or oronasal mask, CPAP acts as a pneumatic splint to directly increase the pharyngeal cross-sectional area and prevent collapse. CPAP also increases end-expiratory lung volume, which may indirectly improve airway function.[20,21,23] The therapeutic pressure, determined via an in-laboratory titration or autotitration device, ranges from approximately 4 to 20 cm H_2O.

Limitations: Due to its perceived invasiveness, CPAP acceptance, tolerance, and compliance are unacceptably low.[12] Indeed, although daytime sleepiness was minimal in this cohort, which may have affected adherence,

average nightly CPAP use was only 3.3 h in the largest randomized trial of CPAP therapy.[11] This level of use did not have any cardiovascular benefit.

Oral Appliances

Oral appliances are used as an alternative to CPAP or as second-line therapy following CPAP failure. They are typically custom-fitted by a dentist and are designed to protrude the mandible. Although the precise mechanisms are unresolved, oral appliances are generally thought to work by moving the tongue and soft palate forward to enlarge the oropharynx and velopharynx. Oral appliances may also prevent airway collapse by stiffening the pharyngeal soft tissues[24,25] and altering tissue properties in conjunction with cranial-anterior movement of the hyoid bone.[24,26] Measured using the closing pressure (Pclose) technique (similar to Pcrit) or via estimation of changes in minute ventilation during reductions in CPAP therapy, oral appliances reduce upper airway collapsibility by approximately 140%.[27,28] A recent dose-response study using the Pcrit technique indicates that oral appliances reduce Pcrit by approximately 2 cm H_2O with 50% advancement and by approximately 5 cm H_2O with 100% advancement.[29] However, there is considerable interindividual variability and other mechanisms such as improved pharyngeal muscle function may also contribute to the therapeutic effectiveness of oral appliances.

Clinically, oral appliances have variable efficacy. Complete responder rates (apnea/hypopnea index [AHI]$<$ 5 events/h) range from 21% to 71% (average, 48%).[30] This responder rate includes approximately 25% of patients with severe OSA.[30,31] Partial responder rates ($>$ 50% reduction in AHI, AHI $\geq$ 10 events/h) range from 6% to 63% (average, 35%).[30] Patients tend to prefer oral appliances to CPAP in crossover trials, and self-reported adherence rates are typically higher than those for CPAP by approximately 1.5 h/night.[30,31] Many patients also have health benefits similar to CPAP.[31]

Limitations: Given the variable efficacy of oral appliances and the need for multiple visits to the dentist and costs involved, a major clinical challenge is accurate prediction of which patients will respond favorably. In addition, not all patients are eligible for oral appliance therapy due to dental exclusions such as insufficient teeth and periodontal disease. Unwanted dental changes, temporal mandibular pain, and excess salivation can also occur with oral appliance therapy, which may reduce treatment adherence.

Weight Loss

Excess body weight (BMI $\geq$ 25 kg/m^2) is estimated to be responsible for 58% of moderate to severe OSA and 41% of mild OSA in US adults.[32] Thus, weight reduction is an obvious therapeutic target. Both "medical" and surgical weight loss strategies have been investigated. Medical weight loss involves one or a combination of factors, including low-calorie diet, lifestyle changes (eating behavior, exercise), counseling, and pharmacologic agents. Surgical weight loss via bariatric surgery is generally only reserved for those with BMI $>$ 35 kg/m^2 who have failed nonsurgical weight loss options.[33]

A 7% reduction in body weight in obese patients with moderate to severe OSA reduces the parapharyngeal fat pad volume by 17% coupled with a 19% increase in velopharyngeal volume.[34] Obese patients with mild OSA achieve similar improvements, whereby a 11% decrease in BMI reduces the parapharyngeal fat pad volume by 19%.[35] On average, a 17% reduction in BMI has a major beneficial effect on upper airway collapsibility, reducing Pcrit by 7.5 cm H_2O.[36] Weight loss has consistently been shown to reduce the severity of OSA, albeit to varying degrees between subjects, both with medical (3%-18% weight reduction = 3%-62% decrease in AHI) and surgical (12%-37% weight reduction = 48%-90% decrease in AHI) approaches.[37] There are several reasons for intersubject variability, including baseline BMI and regional distribution of adipose tissue. Small craniofacial skeletal structure may also be a moderator of the effect size of weight loss on AHI reductions.[18]

Limitations: Clinically, substantial weight loss can be difficult to achieve and even harder to maintain. Weight loss also tends to resolve OSA (AHI $<$ 5 events/h) in a minority of patients, usually those with mild OSA[38] and in those in whom Pcrit falls below approximately –4 cm H_2O.[36] Regardless, given the range of health benefits associated with weight loss beyond reductions in OSA, weight loss should be incorporated as part of a treatment plan for this chronic health condition in overweight and obese patients.

Positional Therapy

Body position is an important mediator of OSA severity for most patients.[39,40] Positional therapy to prevent supine sleep ranges from strapping a tennis ball or bulky object to the back, to wearable electronic devices that vibrate or deliver a tone when sleeping supine to prompt the patient to shift to a lateral

position. This therapy can reduce Pcrit by 2.2 cm H_2O[41] and the AHI by approximately 50%.[40] As is common knowledge among anesthetists, alterations in head/neck posture can also have a major effect on airway collapsibility. Indeed, Pcrit decreases by approximately 13 cm H_2O when head posture shifts from flexion to extension.[42]

Limitations: There is a lack of long-term clinical efficacy and adherence data. OSA may not resolve in many patients when applied in isolation. Bulky devices that severely limit sleeping position may also cause other problems such as back pain. Current approaches focus on whole body position rather than head position.

Upper Airway Surgery

Upper airway surgery has been described as "salvage therapy" following failure of other treatments.[43] Surgeries that target upper airway anatomy can be a useful adjunct to improve the efficacy of other treatments such as CPAP and oral appliance therapy. For example, surgery to reduce nasal resistance reduces therapeutic CPAP requirements[44] and can improve the effectiveness and/or tolerance of CPAP.[43] There are a range of pharyngeal surgical procedures for OSA. Knowledge of the physiologic effects of the different surgical procedures on upper airway physiology is limited. However, uvulopalatopharyngoplasty reduces Pcrit and closing pressure by approximately 2 to 3.5 cm H_2O.[45,46] Clinical success for upper airway surgery is typically defined as a $>$ 50% reduction in AHI to $<$ 20 events/h. Success rates vary widely from 5% to 78%.[47] Baseline pharyngeal anatomy and changes in upper airway muscle activity from wakefulness to sleep may be important predictors of treatment response.[48]

Limitations: Surgical procedures are costly and have variable and largely unpredictable efficacy. They are also often painful and carry the risks associated with other surgeries, such as infection and potential complications with anesthesia.

Nonanatomical Contributors to OSA and Potential Targeted Therapies

In addition to the importance of impaired upper airway anatomy to the pathogenesis of OSA, recent advances in OSA phenotyping and respiratory neurobiology have identified nonanatomical causes and novel targets for therapy.[7,8] Approximately 70% of patients with OSA have impairment in one or more nonanatomical contributors.[7] These are briefly summarized below.

Muscle Control and Function

The pharyngeal muscles play a pivotal role in the maintenance of upper airway patency. They receive complex neural input from respiratory pattern-generator neurons. This action includes synchronized drive with inspiration to stiffen and dilate the airway to oppose inspiratory collapse.[49] Upper airway dilator muscles also receive reflex input from pressure-sensitive mechanoreceptors in the airway and from chemoreceptors via changes in CO_2 or oxygen. The genioglossus is the largest dilator muscle and most-studied in the context of OSA pathogenesis. State-dependent reductions in muscle activity and reflex control contribute to upper airway collapsibility.[50,51] However, although most people with OSA retain the capacity to respond to changes in pharyngeal pressure and chemical stimuli during sleep, increased stimuli is required for adequate pharyngeal muscle recruitment compared with wakefulness.

The relationship between upper airway muscle activation to respiratory stimuli (negative pressure, measured via an epiglottic catheter) is known as muscle responsiveness.[7,8] More than 30% of patients with OSA have minimal muscle responsiveness to negative airway pressure during sleep ($<$ 0.1% of maximum electromyography per negative cm H_2O),[7] which is a key contributor to OSA pathogenesis. Conversely, excellent muscle responsiveness during sleep can protect certain individuals with pharyngeal anatomical impairment from OSA.[52] In addition to muscle responsiveness, other factors such as muscle fiber angulation, biomechanics, and neural coordination can also importantly influence the ability of the pharyngeal muscles to effectively dilate the upper airway during sleep.[8,25,53] Improved understanding of each of these components may provide novel targets for therapy to optimize new and emerging therapies directed toward this trait.

Potential Therapies for Impaired Muscle Control and Function

Hypoglossal Nerve Stimulation

Stimulation of the hypoglossal nerve, which innervates intrinsic and extrinsic muscles of the tongue, improves upper airway patency during sleep. Sustained

reductions in AHI (> 50%) after 6, 12, and 36 months of follow-up, as well as subjective measures of sleepiness and quality of life, have been reported.[54-57] Prediction of successful treatment response may be dependent on an individual's Pcrit, pharyngeal shape, and site of airway collapse.[57,58]

Limitations: Limitations of this procedure are similar to other forms of upper airway surgery. In the most extensive study conducted to date,[57] one third of patients were deemed "nonresponders."

Muscle Training

A systematic review and meta-analysis that includes data from nine studies involving a total of 120 adult patients with OSA showed that oropharyngeal training reduces the AHI by approximately 50% and increases nadir oxygen saturation by > 2.5%.[59] Subjective and objective snoring also decreases, a finding confirmed in a randomized trial.[60] Subjective sleepiness also improves by approximately 45% (> 6.5-point reduction in the Epworth Sleepiness Scale).[59] These findings indicate a beneficial role for upper airway muscle training in OSA. However, the precise mechanisms remain unknown. Possibilities include reductions in tongue fat, which would increase pharyngeal size and reduce collapsibility, and changes in pharyngeal muscle properties and dynamic function.

Limitations: This technique currently involves a trial-and-error approach. To allow for further refinement, optimization and widespread clinical implementation of pharyngeal muscle training using a targeted mechanistic approach, as well as physiologic studies to identify mechanisms of action, are required.

Pharmacologic and Experimental Therapies

Recent advances have been made in knowledge of pharmacologic targets to improve upper airway muscle function. Mechanoreceptor activation by topical administration of a potassium channel blocker via the nostrils in a pig model showed potential to increase pharyngeal muscle activity and reduce airway collapsibility.[61] Similarly, targeted blocking of potassium channels at the hypoglossal motor pool reversed sleep-induced reductions in genioglossus muscle activity in rats.[62] However, a recent study using 10 mg of 4-aminopyridine orally, a voltage-gated K^+ channel blocker, only modestly increased genioglossus muscle activity during rapid eye movement (REM) sleep but not during non-REM sleep in healthy adults without OSA.[63] The role of serotonergic, noradrenergic, and antimuscarinic pathways has also been investigated in animals and humans (as reviewed by White[64]). Recent human studies have shown that the tricyclic antidepressant desipramine, with combined serotonergic, noradrenergic, and antimuscarinic effects, prevents sleep-induced reductions in genioglossus muscle activity, improves upper airway collapsibility,[65] and reduces OSA severity in certain patients with OSA (those with poor muscle compensation at baseline).[66]

A recently developed approach using Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) allows for selective targeting of a group of neurons via introduction of an engineered macromolecule (designer receptor) with viral vectors that can be activated with a specific drug (designer drug). Chemogenetic stimulation of hypoglossal neurons in mice with the use of DREADDs has recently been shown to increase genioglossus muscle activity and airway patency in an anesthetized preparation.[67] Similarly, DREADDs can substantially increase genioglossus activity during REM sleep and non-REM sleep in mice, an effect that lasts in excess of 8 h.[68] However, it will likely be some time before this form of gene therapy can be refined to optimize safety and be implemented in humans. Nonetheless, these exciting new findings offer promise for development of pharmacologic agents to treat OSA.

Limitations: Currently, no pharmacologic agents to increase muscle activity are approved for the treatment of OSA.

Arousal Threshold

Cortical arousals from sleep during an obstructive event occur when increasing negative intra-thoracic pressure reaches a certain threshold (ie, the arousal threshold).[69] Repetitive cycling between wakefulness and sleep can destabilize breathing, prevent deep sleep, and perpetuate OSA severity.[69,70] Evidence indicates that 30% to 50% of all patients with OSA[7,71,72] (and > 85% of nonobese patients)[14] wake up too easily to small changes in intra-thoracic pressure (between zero and –15 cm H_2O). This action may also prevent adequate recruitment of the upper airway muscles.[69]

Potential Therapies for a Low Arousal Threshold

Hypnotic Agents

Standard doses of eszopiclone (3 mg), zopiclone (7.5 mg), and trazodone (100 mg) increase the

threshold for arousal to negative pressure[71,73,74] and can reduce the AHI by approximately 25% to 50%[71,75] without increasing hypoxemia. However, high doses of certain hypnotic agents in severe OSA may prolong apneic events and worsen hypoxemia.[73,76] Other sleep-promoting agents such as nitrazepam (5 mg or 10 mg) and tiagabine (12 mg) do not reduce the AHI[77,78] or arousal threshold[77] and are unlikely to be clinically beneficial. One major concern regarding the use of hypnotic agents in OSA is reduced pharyngeal muscle activity. However, recent findings in people with and without OSA indicate that standard doses of temazepam (10 mg), zopiclone (7.5 mg), and zolpidem (10 mg) do not reduce genioglossus activity during sleep.[79] Paradoxically, genioglossus activity increases almost threefold during airway narrowing with zolpidem. These findings highlight the therapeutic potential for certain hypnotic agents in carefully selected patients (those with a low threshold for arousal and oxygen desaturations $>$ 70%).

Limitations: The potential for worsening of hypoxemia in certain patients exists with these agents. Only modest increases in the threshold for arousal and reductions in AHI have been shown with the standard doses of hypnotic agents tested thus far. The risk of addiction, withdrawal effects, and tolerance after prolonged use also must be considered. However, these potential issues are rare with Z drugs in people with insomnia.[80-82] Additional studies using different doses/drugs over a longer time period are required to determine the risk/benefit profile of targeted hypnotic use in OSA.

Loop Gain

During sleep, Pa_{CO_2} tightly regulates ventilation via afferent feedback from chemoreceptors. The sensitivity of the ventilatory control system involves two principal components: controller (chemoresponsiveness) and plant (excretion of CO_2) gain. Overall "loop gain" is quantified as the ventilatory response/ventilatory disturbance ratio. High loop gain indicates unstable ventilatory control. Specifically, an individual with high loop gain has an excessively large ventilatory response to very small changes in CO_2. This scenario leads to hypocapnia and subsequent reductions in respiratory drive, which can perpetuate recurrent upper airway collapse. Approximately 30% of patients with OSA have high loop gain.[7]

Potential Therapies for High Loop Gain

Oxygen Therapy

Supplemental oxygen has been used as a treatment for OSA in unselected patients with variable efficacy.[83] Oxygen therapy reduces loop gain by approximately 50% and lowers the AHI by approximately 50% in patients with OSA with high loop gain.[84]

Limitations: Although oxygen therapy may be appropriate in select patients (high loop gain, or patients with major nocturnal intermittent hypoxia), it may not be appropriate in others. In a randomized trial, CPAP but not oxygen therapy improved blood pressure in patients with cardiovascular comorbidities.[85] Delivery in the home also remains somewhat cumbersome.

Carbonic Anhydrase Inhibitors

Acetazolamide, a carbonic anhydrase inhibitor (500 mg administered twice daily for 1 week), decreases loop gain by approximately 40% in patients with OSA without altering the other treatable traits.[86] Similarly, acetazolamide reduces the non-REM AHI by approximately 50%, an effect that correlates with reduced ventilatory response to arousal.[86,87] Zonisamide, which has carbonic anhydrase inhibitor properties, also decreases the AHI in obese patients with severe OSA.[88]

Limitations: Reported side effects (eg, dry mouth, bad taste and dizziness) may limit the long-term tolerability of the carbonic anhydrase inhibitors.

Targeted Therapy for OSA

Figure 3 summarizes some of the existing and experimental targeted therapies to treat OSA.

Pcrit, Arousal Threshold, Loop Gain, and Muscle Responsiveness Scale to Inform Targeted Therapy

The Pcrit, arousal threshold, loop gain, and muscle responsiveness (PALM) scale was developed based on the phenotyping concepts described in this review to inform tailored therapy.[7,8] The goal of the PALM scale is to complement existing clinical measures (eg, AHI, symptoms, comorbidities) to facilitate a more comprehensive personalized approach to inform treatment decisions in which patients are prescribed one or more therapies according to their specific underlying cause of OSA. The hope is that this strategy will reduce some of the problems associated with the current time-consuming trial-and-error management approach, which

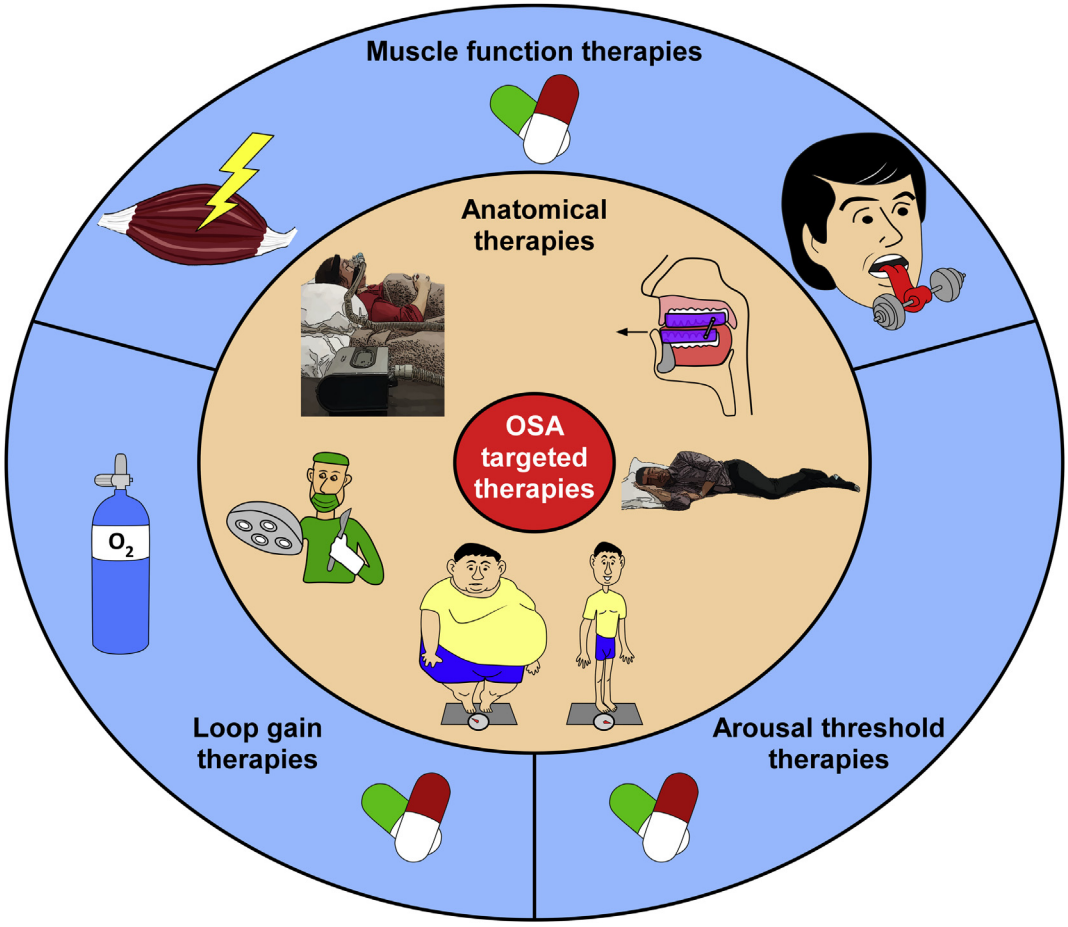

Figure 3 – *Schematic summary of existing and experimental targeted therapies to treat OSA. Anatomical therapies (clockwise from left to right, inner peach-colored circle) include: CPAP, oral appliance therapy (eg, mandibular advancement splint), positional therapy, weight loss, and upper airway surgery. Nonanatomical therapies (blue outer circle) to improve pharyngeal muscle function include: hypoglossal nerve stimulation, pharmacotherapies (experimental), and pharyngeal muscle training; hypnotic sleep promotion agents to increase the respiratory arousal threshold (experimental); and oxygen therapy and pharmacotherapies (experimental) to decrease loop gain. The text provides further details.*

fails too many patients (Fig 1), to yield greater acceptance, tolerance, and optimization of patient outcomes with the prescribed treatments.

Briefly, given that impairment in pharyngeal anatomy is the key driver of OSA, this trait is predicted to be the most important determinant of treatment outcome for most therapies. Accordingly, as described in detail elseware,[7,8] the PALM scale categorizes patients into three levels of pharyngeal anatomical impairment (mild, moderate, and severe) via the Pcrit method. The relative importance of the nonanatomical traits to OSA pathophysiology and as therapeutic targets is expected to be highly dependent on the extent of anatomical impairment. Thus, treatments that target the nonanatomical traits are predicted to be more efficacious in those with mild anatomical impairment compared with those with severe impairment (Fig 4).

Combination Therapy

Recent studies highlight the potential for combination therapy as an efficacious alternative to using existing therapies alone for many patients.[89] For example, combining two therapies that target the anatomical trait (ie, positional therapy and an oral appliance) reduces the AHI by approximately 75% compared with approximately 50% when each therapy is applied alone.[90] Combination therapy using a targeted phenotypic approach with non-CPAP therapies (including a hypocaloric diet) and pharmacologic agents (acetazolamide and/or trazodone) reduces the AHI by 65% and improves symptoms.[91] Consistent with the PALM scale concept, a recent study also showed that oxygen therapy to reduce loop gain combined with a hypnotic agent to increase the arousal threshold reduced the AHI in 95% of the patients studied; it was most

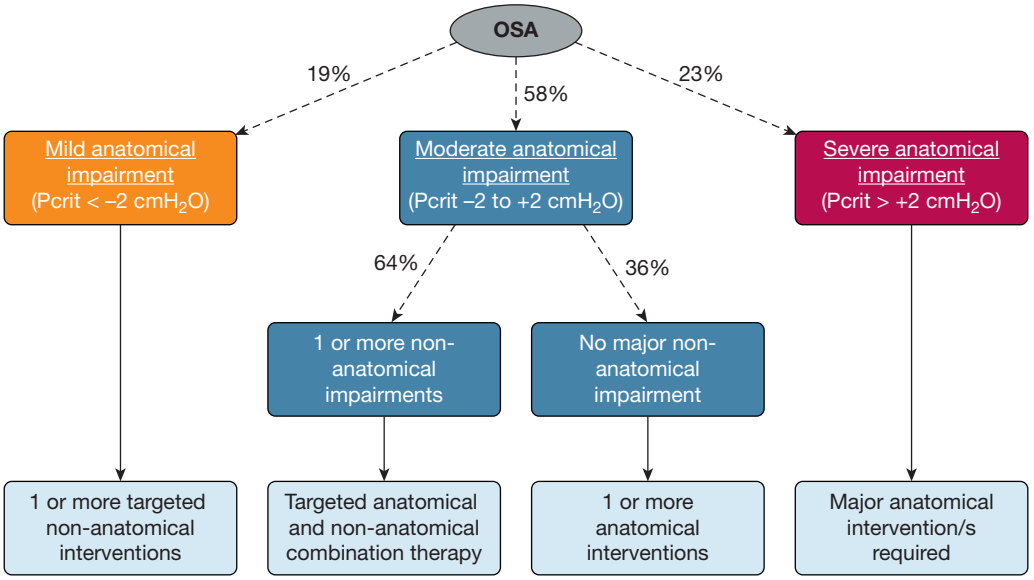

Figure 4 – *Potential treatment decision tree according to a targeted mechanistic approach. Patients with OSA are separated into three categories (Pcrit, arousal threshold, loop gain, and muscle responsiveness [PALM] scale categorization) according to their level of anatomical impairment (mild, moderate, or severe) defined by using the upper airway critical closing pressure technique (Pcrit).*[7] *Patients with only mild anatomical impairment (approximately 19%) all have nonanatomical impairment. Targeted nonanatomical interventions are predicted to resolve OSA in these patients. Fifty-eight percent of patients with OSA have moderate anatomical impairment. Approximately two thirds of these patients also have impairment in one or more of the nonanatomical traits. Targeted anatomical and nonanatomical combination therapy (eg, oral appliance + oxygen therapy) is predicted to yield therapeutic benefit in these individuals. The remaining one third of patients with moderate anatomical impairment without major impairment in the nonanatomical traits likely require one or more therapies directed toward the anatomical problem (eg, CPAP, positional therapy, upper airway surgery). Finally, 23% of patients with OSA have severe anatomical impairment and likely require a major anatomical intervention (eg, CPAP). The text and Figure 3 provide further details.*

efficacious in those with mild upper airway collapsibility.[92]

Simplified Phenotypic Tools to Advance Tailored Therapy

A major obstacle to implementation of phenotyping concepts into clinical care is that the current gold standard measurement techniques are too complex and not feasible beyond research.[7,8] However, several recent studies have made substantial progress in development of simplified phenotyping tools to advance tailored therapy. For example, simple wakefulness tests that use brief negative pressure pulses delivered via a nasal mask during quiet breathing either during expiration[89] or inspiration[90] show promise as surrogates for upper airway collapsibility (Pcrit).[93,94] Similarly, the therapeutic CPAP level (ie, < 8 cm H_2O) from a clinical titration study may be helpful for identifying patients with mild upper airway collapsibility[95] in whom non-CPAP therapies are predicted to be efficacious.[7,8] Prospective treatment studies are now required to determine how effective these approaches are in terms of optimizing responses to a range of therapies.

Standard polysomnography signals can also be used to estimate several of the phenotypic traits.[72,96,97] For example, signal-processing techniques can be used to estimate the ability of the pharyngeal dilator muscles to improve airway collapsibility[96] and loop gain[97] by using the nasal flow signal. In addition, the respiratory arousal threshold can be accurately estimated with three polysomnography parameters (AHI, nadir oxygen saturation, and the ratio of apneas to hypopneas).[72] It is also possible to perform CPAP manipulations in a manner similar to a CPAP titration study without the use of potentially invasive recording equipment (eg, epiglottic catheter and genioglossus intramuscular electrodes) to accurately estimate all four phenotypic traits and predict responses to a range of non-CPAP therapies.[89,98]

Conclusions

There has been substantial recent progress toward personalized management for OSA via advances in knowledge on the multiple causes of OSA, identification of new therapeutic targets, promising proof-of-concept data for targeted therapies including combination therapy, and ongoing development of

simplified phenotyping tools to be used in the clinic to inform targeted therapies for OSA. This research has the potential to realign treatment and management approaches for this common, chronic health condition.

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