Review Article

# Personalised therapy in obstructive sleep apnea

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**Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder mainly characterised by repetitive upper airway narrowing (hypopnea) and closure (apnea) during Sleep[1]. This leads to intermittent hypoxia, hypercapnia and frequent cortical arousals. Untreated OSA can adversely affect the cardiovascular system, neuro cognitive impairment, daytime sleepiness, and increase the risk for motor vehicle accidents[2-5]. Traditional therapy mainly targets anatomical problem irrespective of aetiology But this one size fit all approach is not effective in all patients and there is need to identify specify phenotype and accordingly treatment which is called personalised treatment. But still these phenotypes are not fully characterised.**

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***Key words*** **: Obstructive Sleep Apnea, phenotypes, PALM scale, no anatomical intervention.**

There are multiple risk factors of OSA like advancing age, male gender, obesity, and craniofacial morphology or upper airway soft tissue abnormalities. Additional factors include smoking, nasal congestion, menopause, and family history. Rates of OSA are also increased in association with certain medical conditions, such as pregnancy, end-stage renal disease, congestive heart failure, chronic obstructive pulmonary disease, post-traumatic stress disorder, and stroke[6].

## Pathogenesis :

There are multiple causes or 'phenotypic traits' that contribute to OSA pathogenesis. But mainly four key traits or phenotypes contribute to OSA pathogenesis. These include anatomical (narrow/crowded/collapsible upper airway) and non-anatomical components (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][7-8] (Fig 1). The relative contribution of these phenotypes, each of which is a therapeutic target, varies widely between patients. All obstructive sleep apnea patients have some degree of impairment in upper airway anatomy. However, this phenotype varies widely between patients. Approximately 19% have impairment in upper airway collapsibility to many people who do not have obstructive sleep apnea. There are also at least three other non-anatomical phenotypes that contribute to obstructive sleep apnea pathogenesis which collectively are present in almost 70% of obstructive sleep apnoea patients. So non-anatomical factors also play a prominent role in OSA pathogenesis for many patients particularly in certain groups (eg, non-obese patients).

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## Personalised (Phenotypic) Treatment :

Treatment for OSA has traditionally targeted the anatomical trait, which includes: continuous positive airway pressure (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. Indeed, while advancement in CPAP technology and better mask selection can improve CPAP comfort and tolerance, failure rates are still high (>50% in some cases)[9-10]. Thus, most people with OSA remain undiagnosed, untreated or undertreated. Recent evidence indicates that non-anatomical contributors play a prominent role in OSA pathogenesis for many patients particularly in certain groups (e.g. non-obese patients)[11]. 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.

In addition to the importance of impaired upper-airway anatomy to OSA pathogenesis, recent advances in OSA phenotyping and respiratory neurobiology have identified non-anatomical causes and novel targets for therapy[7]. Treatment of OSA should include targeting both Anatomical & non anatomical component of OSA (Fig 1).

## Ineffective Upper Airway Dilator Muscle:

The pharyngeal muscles play a pivotal role in maintenance of upper airway patency. The genioglossus is the largest dilator muscle and most studied in the context of OSA pathogenesis. Over 30% of OSA patients have minimal muscle responsiveness to negative airway pressure during sleep, which is a key contributor to OSA,

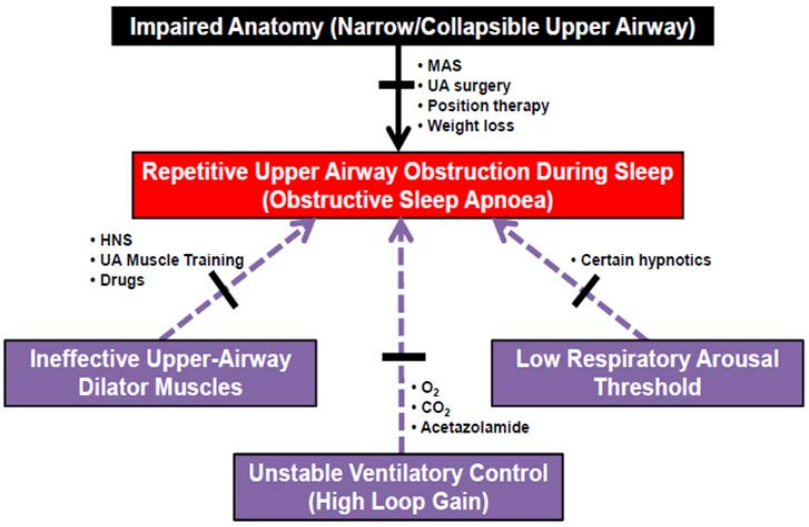


Fig 1 — Summarises existing and experimental targeted therapies to treat OSA

pathogenesis. Conversely, excellent muscle responsiveness during sleep can protect certain individuals with pharyngeal anatomical impairment from OSA. Stimulation of the hypoglossal nerve which innervates intrinsic and extrinsic muscles of the tongue, improves upper-airway patency during sleep[12]. A systematic review and meta-analysis that includes data from nine studies involving a total of 120 adult OSA patients recently showed that oropharyngeal training reduces the AHI by ~50% and increases nadir $O_2$ saturation by >2.5%, There have been recent advances in knowledge of pharmacological targets to improve upper airway muscle function. Mechano-receptor activation by topical administration of a potassium channel blocker via the nostrils in a pig model shows potential to increase pharyngeal muscle activity and reduce airway collapsibility.

## Arousal Threshold :

Arousals from sleep during an obstructive event occur when increasing negative intrathoracic pressure reaches a certain threshold called arousal threshold. Recent evidence indicates that 30-50% of all OSA patients (and over 85% of non-obese patients) wake up too easily to small changes in intra-thoracic pressure. This may also prevent adequate recruitment of the upper-airway muscles. Standard doses of Hypnotic like trazadone increase the threshold for arousal to negative pressure and can reduce the AHI by ~25-50% without increasing hypoxemia[13].

## Loop Gain :

$PaCO_2$ tightly regulates ventilation via afferent feedback from chemoreceptors during sleep. The sensitivity of the ventilatory control system involves two principal components: controller (chemorespon-siveness) and plant (excretion of $CO_2$) gain. Overall 'loop gain' is quantified as the ventilatory response/ ventilatory disturbance ratio. High loop gain indicates unstable ventilator control. Specifically, an individual with high loop gain has an excessively large ventilator response to very small changes in $CO_2$. This leads to hypocapnia and subsequent reductions in respiratory drive which can perpetuate recurrent upper-airway collapse. ~30% of OSA patients have high loop gain[7].

$O_2$ therapy has been used as a treatment for OSA in unselected patients with variable efficacy. $O_2$ therapy reduces loop gain by ~50% and lowers the AHI by ~50% in OSA patients with high loop gain. Acetazolamide, a carbonic anhydrase inhibitor (500 mg administered twice daily for one week), decreases loop gain by ~40% in OSA patients without altering the other treatable traits.

## PALM Scale for Targeted Therapy :

The Pcrit, Arousal threshold, Loop gain, Muscle responsiveness (PALM) scale was developed based on the phenotyping of OSA. PALM scale complement existing clinical measures (eg, AHI, symptoms and 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/s of OSA. Impairment in pharyngeal anatomy is the key driver of OSA, and this trait is predicted to be the most important determinant of treatment outcome for most therapies. OSA patients are separated into three categories (PALM scale categorization) according to their level of anatomical impairment (mild, moderate or severe) by using the upper airway critical closing pressure technique (Pcrit). Almost one fifth (19%) of OSA patients have mild anatomical impairment and all have predominantly non-anatomical impairment. Targeted non-anatomical interventions are predicted to resolve OSA in these patients. 58% of OSA patients have moderate anatomical impairment. Approximately two thirds (64%) of these patients also have impairment in one or more of the non-anatomical traits. Targeted anatomical and non-anatomical combination therapy (eg, oral appliance + $O_2$ therapy) is predicted to yield therapeutic benefit in these individuals. The remaining one third (36%) of patients with moderate anatomical impairment without major impairment in the non-anatomical traits likely require one or more therapies directed towards the anatomical problem (eg, CPAP, positional therapy, upper airway surgery). Finally, approximately one fourth of OSA patients (23%) have severe anatomical impairment and likely require a major anatomical intervention (eg, CPAP) (Fig 2).

Recent studies concluded that combination therapy as an efficacious alternative to using existing therapies alone for many patients[14]. For example, like combining two treatment that target the anatomical trait, positional therapy and an oral appliance, reduces the AHI by ~75% compared to ~50% when each therapy is applied alone[15]. Combination therapy using a targeted phenotypic approach with non-CPAP therapies (like hypocaloric diet) and pharmacological agents (acetazolamide) reduces the AHI by 65% and improves symptoms[16]. Consistent with the PALM scale concept, a recent study[17] also showed that O2therapy to reduce loop gain combined with a hypnotic to increase the arousal threshold reduces the AHI in 95% of the patients studied and was most effective in those with mild upper airway narrowing or collapsibility.

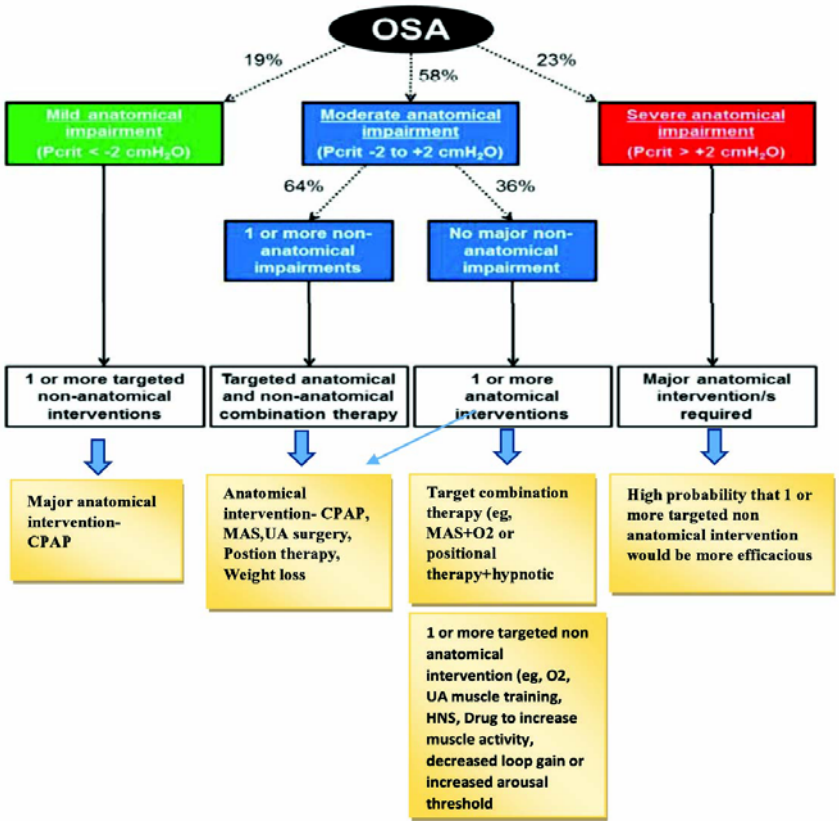


Fig 2 — Treatment decision tree according to a PALM approach (CPAP- Continuous positive airway pressure, MAS- Mandibular advancing surgery, UA- Upper airway, HNS- Hypoglossal Nerve stimulation)

## *Summary :*

OSA is a now recognised as a heterogeneous disorder with different phenotype. Along with anatomical trait, non-anatomical trait is also important in etio-pathogenesis of OSA especially in non-obese patient. Conventional treatment mainly target anatomical problem irrespective of aetiology and this one size fit all approach is not effective in all patients and there is need to identify specify phenotype and treatment accordingly which is called personalised treatment.

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