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Novel avenues to approach non-CPAP therapy and implement comprehensive OSA care

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"Take home" message

Continuous positive airway pressure (CPAP) treatment of obstructive sleep apnoea (OSA) is often inadequate. Recent advances in knowledge of OSA pathogenesis, alternatives or adjuncts to CPAP and novel approaches will allow more personalized treatments.

Abstract

Recent advances in obstructive sleep apnoea (OSA) pathophysiology and translational research have opened new lines of investigation for OSA treatment and management. Key goals of such investigations are to provide efficacious, alternative treatment and management pathways that are better tailored to individual risk profiles to move beyond the traditional, continuous positive airway pressure (CPAP)-focused, “one size fits all”, trial and error approach which is too frequently inadequate for many patients. Identification of different clinical manifestations of OSA (clinical phenotypes) and underlying pathophysiological phenotypes (endotypes), that contribute to OSA have provided novel insights into underlying mechanisms and have underpinned these efforts. Indeed, this new knowledge has provided the framework for precision medicine for OSA to improve treatment success rates with existing non-CPAP therapies such as mandibular advancement devices and upper airway surgery, and newly developed therapies such as hypoglossal nerve stimulation and emerging therapies such as pharmacotherapies and combination therapy. These concepts have also provided insight into potential physiological barriers to CPAP adherence for certain patients. This review summarises the recent advances in OSA pathogenesis, non-CPAP treatment, clinical management approaches and highlights knowledge gaps for future research. OSA endotyping and clinical phenotyping, risk stratification and personalised treatment allocation approaches are rapidly evolving and will further benefit from the support of recent advances in e-health and artificial intelligence.

Introduction

Obstructive sleep apnoea (OSA) is a highly prevalent, but often undiagnosed, chronic respiratory condition estimated to affect nearly 1 billion individuals worldwide [1]. It is characterised by repeated episodes of apnoea (complete cessation of breathing) and hypopnea (partial reduction in breathing) during sleep producing intermittent hypoxia and sleep fragmentation. OSA generates bothersome symptoms including daytime sleepiness, impairment of daily functioning, deterioration of memory and cognition, and increased risk for the development of cardiovascular, metabolic and cerebrovascular disease. This results in considerable economic and social burden [2, 3].

A substantial body of evidence has recently demonstrated the complexity of OSA, the extreme heterogeneity of underlying aetiologies and the variety of clinical presentations. Thus, the usual "one size fits all" management by Continuous Positive Airway Pressure (CPAP) although can be effective for many has limitations including poor adherence [4] and remains far from ideal in terms of the expectations of personalised and precision medicine [5] desired by patients and caregivers. In short, a redesign of routine care pathways for OSA should be designed that carefully considers a more systematic physio-pathological and clinical phenotyping approaches with the aim of providing patients with better tailored treatments.

The objectives of this review are firstly, to describe the physio-pathological endotypes and clinical phenotypes that will form the basis for identifying optimal therapeutic options for the different OSA subtypes. Secondly, to describe the current therapeutic indications of alternatives to CPAP including well validated mandibular advancement devices, positional therapy and the emerging pharmacological solutions. Thirdly, to describe the new stimulation techniques under development and their respective indications. Fourthly, the importance of

implementing combined therapies to integrate care and optimise the management of OSA comorbidities is highlighted.

o Physiological phenotypes/endotypes and treatable traits

In addition to different clinical manifestations of OSA, the underlying pathophysiology varies considerably between patients. Current evidence indicates that there are at least four key “pathophysiological phenotypes” or more recently termed “endotypic traits” that contribute to OSA pathophysiology (Figure 1) [6-8]. The most influential trait to OSA pathogenesis is impaired pharyngeal anatomy. Indeed, all patients with OSA have some degree of impaired pharyngeal anatomy. However, the underlying causes and the magnitude of impaired pharyngeal anatomy varies widely between patients.

For example, excess adipose tissue surrounding the upper airway due to obesity can cause airway narrowing and increase the propensity for collapse during sleep [9]. Central obesity decreases lung volume which can also increase upper airway collapsibility during sleep [9, 10]. Other mechanisms such as increased adipose tissue within genioglossus, the largest pharyngeal dilator muscle, craniofacial abnormalities, and inherent viscoelastic and structural properties of the airway can also contribute to increased propensity for pharyngeal narrowing during sleep [11-15]. In addition, rostral fluid shifts when supine can increase pharyngeal tissue pressure, reduce pharyngeal cross-sectional area, and increase airway collapsibility [16]. The net result is that some people with OSA only have mildly impaired pharyngeal anatomy while others have highly collapsible airways. Indeed, quantification of upper airway collapsibility during sleep using the gold standard critical closing pressure or “Pcrit” technique, indicates that approximately 25% of patients with OSA have highly collapsible pharyngeal airways (Pcrit >+ 2cmH₂O). More than half of the OSA patient

population have pharyngeal airways that collapse at or near atmospheric pressure (P_{crit} range -2 to +2 cmH_2O). However, the remaining approximately 20% require a “suction pressure” between -5 and -2 cmH_2O to collapse the airway during sleep. This mild degree of pharyngeal collapsibility overlaps with many individuals who do not have OSA [6, 8]. Thus, in addition to impaired pharyngeal anatomy, many patients with OSA also have non-anatomical traits that contribute to OSA pathogenesis.

Approximately 70% of people with OSA have one or more non-anatomical traits that contribute to their OSA [6, 8]. 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) (Figure 3) [6, 8]. Current therapies for OSA however, mainly target the anatomical endotype. This includes CPAP which although efficacious, is often poorly tolerated [17], as well as other existing non-CPAP anatomical interventions such as mandibular advancement devices, positional therapy, and upper airway surgery. All these non-CPAP anatomical interventions serve to reduce upper airway collapsibility (lower P_{crit}) during sleep [18-20]. However, the non-anatomical endotypes or “treatable traits” also represent potential therapeutic targets for OSA. Indeed, as outlined in the following sections, detailed physiological studies that have quantified key OSA endotypes and delivered targeted interventions to improve one or more of the non-anatomical treatable traits can reduce OSA severity [21-26]. These concepts, which are underpinned by advances in knowledge of the pathophysiological causes of OSA, have opened new lines of investigation for the development of new targeted therapies for OSA. Identification of patients with certain endotypes may also help identify individuals who will respond unfavourably to certain existing OSA therapies. For example, non-obese patients with a low respiratory arousal threshold endotype may respond poorly to CPAP therapy [27-

29]. Similarly, 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 [30, 31]. Thus, these treatable trait concepts hold promise for delivery of precision medicine for OSA [32].

o Clinical and sleep phenotypes

At present, all OSA patients are considered to have the same generic diagnosis, despite OSA being characterized by different contexts of occurrence including age, sex, menopausal status, obesity, and lifestyle (e.g. low physical activity and nutrition). Moreover, patients with cardiovascular and/or metabolic diseases represent populations at particularly high risk of OSA but with minimally symptomatic presentations at diagnosis [33]. Thus, there is a complex interaction between underlying pathophysiology and various clinical and polysomnographic features. OSA diagnosis is mainly based on the apnoea/hypopnoea index captured by single-night polysomnography or respiratory polygraphy. However, there is now broad agreement that this simple metric [34] poorly reflects disease severity and its consequences. Hypoxic burden, sleep alterations and sympathetic activation are increasingly considered as important determinants of long-term poor outcomes [35-37]. This diversity in OSA at diagnosis should translate into greater plurality in treatment indications designed for different distinct homogeneous groups of patients [38, 39] which, in turn, should lead to improved treatment adherence, patient engagement and better prediction of anticipated treatment responses.

Distinct clinical OSA phenotypes have been primarily identified through various methodologies of cluster analysis such as latent class analysis, hierarchical ascendant clustering or K-means clustering. Clustering is an analytical technique that aims to minimize the dissimilarities between two individuals with the same subtype and maximize the

disparities between two patients with different phenotypes. Available literature has identified three to eight clusters. These not only reflect the variety of clustering methods but also the different assortments and mixtures of variables included in the clustering analyses. Cluster analyses have focussed on anatomical and maxilla-facial characteristics, subjective complaints [40, 41], polysomnographic features [42-44], comorbidities [45, 46] and primarily on a combination of comorbidities and symptoms [47-49]. Until recently, it has been difficult to envision a reliable landscape that contains all OSA phenotypes across different patient populations [50]. Apart from three studies [39, 48, 51], most datasets were regional or national whereas geographical factors, lifestyle, behaviours and genetic background might also impact OSA phenotypes. Other contextual factors that characterise patients' ecosystems include pollution, outside temperature or socio-economic status, all of which have been poorly addressed in current cluster analyses.

Despite these limitations, clustering studies have identified key areas for further research investigation and revealed important information that has the potential to be translated into routine practice management. Examples include:

- (i) There is an easy to manage clinical phenotype including "excessively sleepy/symptomatic" patients with disabling complaints, altered health-related quality of life who insistently request OSA management and show an expected high treatment adherence.
- (ii) Half of the reported clusters are sex-based, constituted by nearly exclusive populations of men or women, thus highlighting the crucial need to better delineate personalized therapies with respect to sex-specific differences.
- (iii) Two clusters predominantly including women were nearly always consistently reported across studies. One includes middle-aged women with insomnia or

complaints of poor sleep, moderate AHI and low CPAP adherence [50]. More widely, co-morbid insomnia and sleep apnoea (COMISA) is a specific phenotype with a prevalence of up to 40% that necessitates multi-faceted treatment approaches including cognitive behavioural therapies [52]. The other female cluster comprises women with pulmonary disease (essentially asthma).

- (iv) Another prominent clinical phenotype corresponds to the accumulation of 2 or more cardio-metabolic comorbidities in middle-aged to elderly obese individuals with few symptoms, and poor CPAP adherence [17]. Moreover, in such cases, CPAP is insufficient to reduce cardiovascular risk and should be combined with change in lifestyle interventions.
- (v) The overlap syndrome associating COPD and OSA constitutes a phenotype with a different clinical presentation including more persistent fatigue and dyspnoea while sleepiness is not imminent. This subtype is less responsive to CPAP with lower adherence to treatment.

In recognition of the heterogeneity of OSA [53] and as recently outlined by the Sleep Disordered Breathing Working Group of the European Respiratory and Sleep Research Societies [32], there is the potential to implement some of these concepts into routine management of OSA towards analytical step-by-step approaches and reasoning, distinguishing symptomatic versus non-symptomatic phenotypes, easy to identify endotypes (treatable conditions) and predict poor outcomes based on hypoxic burden, sympathetic overactivity and "disturbed sleep" (documented by polysomnography or simpler techniques). No doubt, in the future, advanced analytics including artificial intelligence will support clinicians for phenotype-based indication of the best treatment strategy (Figure 2).

The final objective of such a management pathway is to collect and interpret the full range of information relevant to therapeutic decision making in routine practice and to predict and characterize the evolution of patients' responses to treatment. The following points should be addressed in the coming years to achieve the full potential of this OSA care reshaping [54]

- (i) Clustering of phenotypes has been developed cross-sectionally, but we now need to implement longitudinal clustering as patients may change from one cluster to another during lifetime trajectories and require treatment adjustments.
- (ii) Data science algorithms and artificial intelligence-based research tools can currently exploit polysomnography measurements giving the hypoxic burden and sympathetic activity, or characterise endotypes (loop gain, arousal thresholds), but should be more widely deployed in every sleep laboratory.
- (iii) The OSA field is crucially lacking biomarkers of the hypoxic signature. Companion biomarkers of response to treatment in relation to different disease consequences remain to be validated [55]

o Alternatives to CPAP

• Mandibular advancement devices

Mandibular advancement devices have traditionally been recommended for second-line therapy in patients intolerant or refusing CPAP. In many countries, indications and usage have now been expanded as a primary indication at the same level as CPAP for mild to moderate

symptomatic OSA with a low burden of comorbidities. MADs have been extensively studied in terms of reduction of OSA severity, patient reported outcomes (PROMs), cardiovascular consequences, adherence, and short- or long-term side effects [56].

MADs have lower efficacy as measured by AHI compared to CPAP. Approximately two-thirds of OSA patients will achieve more than 50% reduction in AHI, with at least one-third achieving a complete response with AHI normalization [56]. Multiple attempts have been made to predict MAD efficacy from clinical characteristics, OSA endotype and polysomnographic indices. However, while comprehensive OSA endotyping approaches hold promise (Table 1) [30, 57-60], the reliability of most other prediction approaches is often weak and uncertainty regarding the level of efficacy in individual OSA patients remains a concern for the widespread prescription and use of MADs [56]. The incomplete reduction of AHI is partly counterbalanced by greater adherence and more regular nightly usage. Consequently, the Mean Disease Alleviation (MDA) defined by the ratio of adherence to treatment over total sleep time divided by the percentage of therapeutic efficacy is equivalent between CPAP and MADs [61, 62]. Indeed, overall, MADs provide similar health outcomes to CPAP [63]. The equivalent efficacy of MAD and CPAP in terms of MDA is consistent with the results of a recent individual participant data meta-analysis including seven randomised controlled trials. MADs had similar effectiveness to CPAP on major patient-centred outcomes including sleepiness and quality of life [64]. Both treatments improved sleep architecture, objectively measured by polysomnography, with an increase in N3 and REM sleep [64]. As comparable symptomatic improvement is achieved, combined with MADs being less cumbersome, studies consistently show that adherence and patient preference favours MADs versus CPAP.

Data regarding the impact of MADs on cardiometabolic outcomes are scarce. There are no available long-term interventional randomised trials on the impact of MADs on incident

cardiovascular events and all-cause mortality [65]. However, CPAP and MADs yield similar reductions in blood pressure [66].

By pooling efficacy and patient preference data, it was expected that the respective indications for CPAP and MADs would evolve. However, practical limitations to the implementation and titration (adjustment of the degree of protrusion to optimise therapy) of MADs [67] continue to limit their application in routine practice. Firstly, for one third of OSA patients, MADs are contraindicated mainly due to dental problems (insufficient teeth, periodontal problems with tooth mobility), but also to temporomandibular joint disorders, or limited maximum protrusive distance (<6mm) [68, 69]. Long term MAD wear can induce tooth movements and bite changes depending on adherence to MAD and to the mandibular advancement levels. Guidelines recommend regular follow-up by qualified practitioners every six months to inspect dental side effects or occlusal changes [56]. Secondly, the reference technical choice for MADs is not clearly established with new MAD blueprints continuously emerging on the market without clear evidence regarding the best cost-effectiveness balance [70]. Titratable two-piece custom-made MADs administered by dentists are widely accepted as the gold standard in clinical guidelines [71] but at the price of higher costs and delays in the implementation of treatment, which can reach several months [72]. Thermoplastic MADs constructed of a material that becomes mouldable when warmed by immersion in hot water [73] have become titratable and as such, provide an affordable and fast-tracked alternative to test efficacy [74]. However, there remains debate regarding their specific indications. Importantly, because the only high level of evidence for MAD efficacy has been provided by studies using titratable two-piece custom-made devices, it is not yet possible to extrapolate these findings to simpler devices without additional validation. Also, the MAD titration procedures are poorly standardised, and the process can last several months.

All these considerations are confusing for prescribing respiratory/sleep physicians, who are also discouraged by the complexity of the multidisciplinary care pathway, which requires them to share close patient supervision with dental specialists. There is a need to better define the respective roles of CPAP, MADs and alternatives to avoid inefficiency and redundancy both in the management pathway and in reimbursement models.

In summary, MADs are by far the best and most documented alternative to CPAP. To increase take up of this therapeutic modality, it is necessary to clarify the diverse technological options, better describe the care pathway and its reimbursement and optimise treatment outcome prediction strategies. CPAP treatment currently benefits from objective daily measurements of efficacy and adherence to treatment accessible by remote monitoring [38, 75]. This is informative for follow-up and much appreciated by all caregivers. In terms of benchmarking between treatments, MADs need to include an objective measure of treatment adherence through temperature-sensing data chips embedded in the appliance [76] and the development of multidisciplinary digital medicine platforms for monitoring.

- **Positional therapy**

Position-dependant OSA (POSA) is commonly defined as a supine to non-supine apnoea 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 [77, 78] and represents a specific clinical phenotype, easily identifiable from polysomnographic indices. POSA patients are overall less adherent to CPAP treatment [79]. Positional therapy (PT) aims to prevent supine sleep to reduce OSA burden. This approach has been undervalued for decades owing to the archaic or non-aesthetic methods initially proposed to reduce the amount of time patients sleep lying on their backs. Originally, diverse objects were strapped to the back (tennis balls, rigid backpacks, pillows) to prevent patients from sleeping in a supine

position. New generation PT solutions have now been successfully developed. These less cumbersome small devices attached to the neck, forehead [80] or chest [81] provide fine-tuned vibrating stimuli that progressively train patients night after night to adopt a lateral position during sleep [82]. A recent Cochrane review [83] summarised findings from eight randomised controlled trials that included 323 participants to compare the efficacy of positional therapy versus CPAP or versus an inactive control (a sham intervention or no positional therapy intervention). CPAP was superior at reducing the AHI while positional therapy was better than inactive controls for improving subjective sleepiness and AHI. Short-term adherence to PT was reported as good, with patients generally expressing a preference for PT versus CPAP. However, there is a lack of reliable data on long-term adherence and new tools to objectively measure adherence to PT are being developed. The certainty of evidence for positional therapy's efficacy remains moderate and further multinational, multicentric [ClinicalTrials.gov Identifier: NCT04211350] and long-term high-quality studies are needed before PT can be integrated more widely into OSA treatment algorithms. In particular, the respective roles of positional therapy as a standalone or in combination treatment with weight loss and/or oral appliances remains to be better established. Potential long term side effects from limiting movement during sleep such as back discomfort will also need to be carefully followed in future appropriately designed studies. While it is quite straight forward to identify the clinical phenotype of supine dependent OSA from polysomnography, OSA endotype studies of positional therapy have provided insight into the mechanisms of action (improvements in airway collapsibility and pharyngeal muscle function) [84] and knowledge of OSA endotypes may further help identify which patients will benefit from this therapy (Table 1) although this has not been investigated [85, 86].

- **Pharmacotherapy for OSA**

In cases where OSA is primarily driven by obesity related mechanisms, pharmacological interventions to reduce obesity have the potential to reduce upper airway collapsibility and OSA severity [87-90]. Although the effect size is modest, diuretics to minimise the potential for fluid redistribution to increase pharyngeal collapsibility during sleep may help reduce OSA severity especially in people with conditions where fluid accumulation (e.g. renal and heart disease) is common [91-94]. In addition, the relatively recent recognition of the importance of OSA endotypes beyond anatomy has provided the opportunity for development of new pathways for therapy including pharmacotherapy [95]. These are summarised in Figure 3.

- o Targeting the upper airway muscles

Recent advances in understanding of the mechanisms that control upper airway motor circuitry during sleep have identified several promising drug target priorities for OSA pharmacotherapy [96]. There is increasing consensus that for pharmacotherapy strategies for OSA to be effective, they will need to be targeted according to individual underlying pathophysiology/endotype characterisation [95, 97, 98].

Pharyngeal dilator muscle activity, which is crucial for maintaining a patent airway in people with impaired anatomy, abruptly reduces at sleep onset [99, 100]. Activity of the largest pharyngeal dilator, genioglossus, is dependent on the level of breathing effort and sleep stage and progressively reduces from N3, to N2 and REM sleep [101, 102]. Impaired pharyngeal muscle responsiveness (lack of dilator muscle recruitment during airway narrowing) contributes to OSA pathogenesis in over one-third of people with OSA [103]. Thus, strategies to increase pharyngeal dilator muscle activation during sleep is an important target for OSA pharmacotherapy.

Multiple neurotransmitters and receptor types can modulate neural control of pharyngeal dilator muscle activity. These include excitatory serotonin type 3 (5-HT₃) and inhibitory cannabinoid type 1 (CB₁) receptors in nodose ganglion cells, and noradrenergic, serotonergic and glutamatergic-mediated excitatory inputs to cranial motor neuron pools [104-108]. Withdrawal of noradrenergic drive is a key mediator of pharyngeal dilator muscle hypotonia during non-REM sleep [96]. Muscarinic receptor-mediated inhibition of pharyngeal dilator muscle activity is particularly important mediator of hypotonia during REM sleep [109]. While a universally effective pharmacologic therapy for OSA has not been identified, the mechanistic pathways highlighted above show considerable promise for targeted therapy for OSA.

Dronabinol, a nonselective CB₁ and CB₂ receptor agonist, modestly reduces OSA severity as measured via the apnoea/hypopnea index (AHI) by ~10 events/h at doses of 2.5 and 10 mg/day [110, 111]. Selective serotonin reuptake inhibitors (SSRIs) have shown mixed results. An early study with the selective serotonin reuptake inhibitors (SSRI), paroxetine, reduced the AHI during non-REM but not during REM sleep [112]. Fluoxetine also reduced the non-REM AHI but with substantial inter-individual variability [113]. Mirtazapine, a mixed 5-HT₂/5-HT₃ antagonist and α 2A antagonist showed promising results in an initial small, randomised trial [114]. However, two larger subsequent studies failed to replicate this finding [115]. Agents that target cannabinergic pathways require further investigation. However, current evidence suggests that any potential beneficial effect is likely to be modest. While serotonergic agents have not yielded consistent benefit, further investigation of these agents in patients according to endotypic characterisation may be insightful and may have therapeutic benefit for certain patients.

To date, noradrenergic and muscarinic pathways are the most promising class of agents to target the pharyngeal dilator muscles to treat OSA. Indeed, several recent drug repurposing studies highlight the importance of these pathways in mediating pharyngeal muscle activity and stabilising breathing during sleep. For example, desipramine, a tricyclic antidepressant that inhibits norepinephrine reuptake, reduces sleep onset-related reductions in genioglossus muscle activity in healthy individuals [116]. Desipramine also reduces upper airway collapsibility and OSA severity in those with impaired upper airway muscle activity [117]. The combination of atomoxetine, a norepinephrine reuptake inhibitor, and oxybutynin, an antimuscarinic, increases pharyngeal muscle responsiveness during sleep three-fold and markedly reduces the AHI and overnight hypoxemia [24, 118]. However, while modest improvements in airway stability occur in people with OSA when atomoxetine is combined with other more selective antimuscarinics [119], improvements are much less pronounced when compared to the combination of atomoxetine and oxybutynin [24]. Another norepinephrine reuptake inhibitor, reboxetine, when combined with the antimuscarinic hyoscine butylbromide, also improves pharyngeal dilator muscle control during sleep [120] and reduces OSA severity [121]. Findings from a recently completed trial indicates that reductions in OSA severity also occur when reboxetine is delivered alone without an antimuscarinic (ACTRN12620000662965). Thus, while larger, long-term studies are required to provide insight into the long-term efficacy and safety of these interventions, this class of agents show considerable promise for OSA pharmacotherapy.

Novel strategies to enhance pharyngeal dilator muscle reflexes to reduce airway collapsibility have shown promise in a pig model [122] and have recently been tested in people with OSA [123], require further investigation in humans which are currently underway (NCT04236440, NCT04713826). In addition, viral vectors to deliver excitatory designer

receptors to hypoglossal motoneurons is a novel and exciting concept with considerable potential for future translation to humans assuming the safety profile of this new technology can be established. These *designer receptors exclusively activated by designer drugs* (DREADDs) have recently been investigated in animal models with promising results [124-126]. Conceptually, targeting a designer receptor, not found elsewhere in the body, would alleviate the undesirable off-target effects associated with traditional drug therapy approaches for OSA.

o Targeting loop gain

People with inherently unstable or overly sensitive responses to CO₂ (*high loop gain*) during sleep are at increased risk of OSA [127]. Unstable respiratory control/high loop gain which is a key endotypic trait for approximately one third of people with OSA [8]. Pharmacological agents that reduce loop gain may therefore help to stabilise breathing and reduce OSA severity.

The metabolic acidosis induced by the carbonic anhydrase inhibitor acetazolamide increases ventilation, alters the hypercapnic ventilatory response, and lowers the PaCO₂ apnoea threshold [128, 129]. Acetazolamide also reduces key components of high loop gain (plant gain) [130] and increases the response time to changes in PaCO₂ secondary to increased cerebral blood flow [131]. These complementary mechanisms (i.e., increased minute ventilation combined with decreased plant gain) serve to reduce the overall propensity for unstable breathing/high loop gain.

A meta-analysis of eight randomised trials found improvements in AHI, periodic breathing, and increased nocturnal oxygen saturation with acetazolamide in people from low altitudes ascending above 2500 meters [132]. One week of 500mg of sustained-release acetazolamide twice daily reduces loop gain and the AHI in people with moderate-to-severe

OSA without negatively alerting the other key OSA endotypic traits [133]. Zonisamide, another carbonic anhydrase inhibitor, also reduces the AHI by ~30% in patients with moderate-to-severe OSA [134]. While, loop gain was not directly measured in this study, the effect on AHI was heterogeneous. This suggests that zonisamide improved OSA in patients with high loop gain but not in those in whom other OSA endotypes predominate [134]. Recent studies with the norepinephrine reuptake inhibitors atomoxetine and reboxetine also indicate that these agents can stimulate breathing frequency and also reduce the overall propensity for respiratory instability (lower loop gain) which may further contribute to their therapeutic benefit in people with OSA [24, 98, 119, 135].

Supplemental oxygen reduces peripheral chemosensitivity and can also stabilise breathing during sleep. For example, 3 to 5 L/min of supplemental oxygen reduces loop gain and the AHI in OSA patients with high loop gain [136] without altering the other key OSA endotypes [137]. OSA endotype characterisation either via awake chemosensitivity testing [138] or via signal processing of the sleep study signals [26] may help to provide a personalised medicine approach to identify those who are mostly likely to benefit from oxygen therapy.

- o Targeting the arousal threshold

Respiratory stimuli, such as blood gas disturbances and increased negative pressure swings during airway narrowing and closure augment breathing effort and often trigger brief cortical arousals from sleep [139]. Waking up too easily to airway narrowing (low respiratory arousal threshold), prevents more stable deeper sleep, compensatory pharyngeal muscle activation and can perpetuate breathing instability [139, 140]. A low respiratory arousal threshold is a common endotype in patients with OSA, especially in patients who are not obese [103, 141]. Thus, sleep promotion aids that raise the arousal threshold may therefore

promote breathing stability and reduce OSA severity in those with a low arousal threshold endotype.

Sedative medications have traditionally been avoided in people with OSA due to concerns of pharyngeal muscle relaxation and delayed responses to hypoxia. Indeed, high doses of the benzodiazepine triazolam can worsen hypoxemia in people with severe OSA [142]. However, more recent detailed physiological studies in people with and without OSA indicate that zolpidem, zopiclone, trazadone and temazepam increase the arousal threshold and do not impair pharyngeal dilator muscle responsiveness during sleep [143-147]. Eszopiclone has been shown to increase the respiratory arousal threshold and reduce OSA severity by ~45% in people with a low arousal threshold endotype [148]. Reductions in OSA severity in unselected patients have also been reported with trazodone [149]. When oxygen therapy is combined with eszopiclone, consistent with endotyping concepts, reductions in AHI occur in those with less collapsible pharyngeal airways and increased upper airway muscle effectiveness [23]. These data suggest that benefits occur through a reduction in loop gain and an increase in arousal threshold. These proof-of-concept studies suggest a potential role for hypnotics in patients with a low arousal threshold endotype. Hypnotics such as zolpidem also markedly increase sleep efficiency in people with OSA which may be helpful in people with comorbid OSA and insomnia [147]. Indeed, non-pharmacological approaches to promote sleep such as cognitive behavioural therapy for insomnia reduce OSA severity in people with OSA and insomnia [150]. However, most hypnotic trials in people with OSA do not systematically alter the AHI [139, 143, 151-154]. In addition, while non-benzodiazepine hypnotics and trazodone are considered to be relatively safe drugs [155, 156] with a low incidence of dependence versus benzodiazepines, patients with a history of abuse or dependence and those with psychiatric diseases may be at increased risk of abuse of these

agents [155]. Thus, further studies, including longer term efficacy, safety and tolerability trials in different patient populations are required before pharmacologically increasing the arousal threshold can be recommended as a treatment for OSA.

- **Stimulation therapy**

While recent evidence highlights the potential for multilevel upper airway surgery as an efficacious therapy for a substantial proportion of OSA patients [157] and the potential role that weight loss surgery may play for severely obese patients [158], these topics are beyond the scope of the current review which focussed on new stimulation techniques.

- o Hypoglossal nerve stimulation

A decrease in pharyngeal dilator muscle tone is a normal physiological response to sleep and usually results in a small increase in upper airway resistance [159]. However, in predisposed individuals this loss in tone can lead to upper airway narrowing and collapse during sleep, both being cardinal characteristics of OSA. Recognition of this relationship between pharyngeal muscle tone and patency has led to many studies investigating methods by which to minimise or reverse the sleep-related loss in pharyngeal muscle activity, and thereby decrease or prevent the detrimental changes in pharyngeal patency. The genioglossus is the major pharyngeal dilator muscle and has consequently been a major target for such studies.

The genioglossus muscle is innervated bilaterally by its motor nerve, the hypoglossal nerve [160] and surgical access to the nerve can be via an incision in the neck. Early 'proof of concept' studies were undertaken by Eisele et al [161] and Schwartz et al [162] who showed that unilateral stimulation of the hypoglossal nerve could improve airflow during sleep and decrease the severity of OSA. While these studies demonstrated the feasibility and therapeutic potential for hypoglossal nerve stimulation (HNS) in OSA, long term use of the

method was limited by technology problems with electrodes and sensors. Over the next decade improvements in lead construction, sensor development, implantable pacemaker construction and programming, and nerve cuff construction led to this being revisited.

In the mid-2000's several companies produced implantable devices that stimulated one of the hypoglossal nerves via a cuff electrode with resulting inspiratory phasic [163, 164] or continuous [165] contraction of the genioglossus muscle during sleep. Despite using different techniques, the studies reported remarkably similar results with decreases in AHI from 50-70% at 6-12 months post-implant, clinically significant improvements in subjective measurements of sleepiness and sleep-related quality of life and all were accompanied by good safety profiles.

Since its approval by the US Food and Drug Administration a device based on the seminal study by Strollo et al [164] has been implanted in many thousands of patients in North America and Europe (Figure 4). This has led to many valuable publications and insights based on additional research studies, case studies, post-market analyses and clinical audits. Some of the main findings are that the technique: is safe to use over prolonged periods of time with minimal side effects [166]; is effective in improving objective measures of OSA severity and subjective measures of OSA-related symptoms [166, 167]; and is reliant on careful implementation of titration algorithms and manipulation of stimulation settings [168, 169]. Improved understanding of these factors has led to marked improvements in therapeutic effectiveness with recent postmarket studies reporting improvements in AHI of 75% or greater [167, 170]. A new generation device has been developed with several differences to other devices [171, 172] (Figure 5). Firstly, it delivers bilateral HNS via an implantable 'paddle' electrode that lies over the genioglossus muscles near their insertion on the mandible. Secondly, due to electrode positioning only the genioglossus muscle is stimulated. Thirdly,

the small paddle electrode, which incorporates a receiver, is the only implantable component. Finally, the system delivers intermittent stimulation at a pre-programmed rate and duty cycle, adjusted to stimulate at a rate near the participants own breathing frequency but not specifically timed to the respiratory cycle. Long term data are not yet available for this device but published short term results (6 months post-implant) show similar therapeutic efficacy to the other cuff-based stimulating devices. Specifically, a 47% decrease in AHI, significant improvements in symptoms and an acceptable safety profile [171]. Hypoglossal nerve stimulation is now considered an acceptable alternative for patients who are intolerant of or fail CPAP therapy. However, a major challenge remains in identifying those individuals, before implantation, who will benefit from the therapy. Current guidelines recommend that the therapy is suitable for individuals who have an AHI between 20 and 50 events/h, body mass index (BMI) less than 32 kg/m², central or mixed apnoea index [173] <25% of the AHI and absence of circumferential pharyngeal airway during drug-induced sleep endoscopy [164, 174]. Despite application of these criteria and optimisation of stimulation settings, approximately one-third of patients are considered partial- or non-responders due to the presence of residual OSA while on therapy [170]. Importantly, the current evidence base for HNS remains very limited with only one study fulfilling (partly) the criteria of a randomized controlled trial [164]

A great deal of work continues to be undertaken to identify factors that influence outcomes for HNS. Approaches include analyses of data from published studies [175], clinical registries [176] and prospective studies [177, 178]. Recently, Op de Beeck et al [179] used baseline polysomnography records from implanted patients to show that several non-anatomical endotypes (low arousal threshold, low pharyngeal muscle compensation, high loop gain) were associated with reduced HNS treatment efficacy (Table 1). In contrast, Yu and

Younes [180] did not find a significant difference in polysomnography-derived odds ratio product, a measure of arousal propensity, between responders and non-responders to HNS therapy. These studies highlight the complex nature of OSA and its underlying pathophysiology, the understanding of which remains incomplete but essential to selecting the most suitable patients for HNS therapy.

- o Other stimulation techniques

Several other stimulation techniques have been proposed to treat OSA. Of these, the most studied has been transcutaneous electrical stimulation (TENS) of the submental muscles via electrodes attached to the skin of the submental region. A recent study has shown that, when applied to individuals with OSA over time (i.e. 'training' the tongue muscles), such stimulation results in an improvement in posttreatment AHI. However, the impact on quality of life remains unclear [181]. Electrical stimulation has also been applied to the muscles of the tongue to cause muscle contraction and increase strength and fatigue resistance and has been shown to reduce time spent snoring [182]. Daytime electrical stimulation of the calf muscles while seated has recently been shown to reduce leg fluid, decrease the sleep-related fluid shift from the legs to the neck and reduce snoring, presumably by mucosal water content in the peripharyngeal tissues, thereby decreasing pressure applied to the pharynx and decreasing airway narrowing and collapsibility [183]. Finally, a recent electrophysiology experiment in a single participant with OSA reported that neurostimulation of the ansa cervicalis branch innervating the sternothyroid muscle can increase inspiratory airflow and retropalatal area during sedation, presumably by increasing tracheal traction and decreasing pharyngeal collapsibility [184]. A great deal more research is required to determine the feasibility and therapeutic efficacy of these new techniques. While it is beyond the scope of this review, it should be noted that other approaches to improve

muscle activity are being tested such as the application of sleep therapy techniques to ‘train’ the tongue muscles [185]. While results to date are promising, randomised and high-quality studies still need to be undertaken [186].

- **Combined therapies**

Obstructive sleep apnoea (OSA) is a chronic condition with multifactorial pathophysiology which requires a comprehensive chronic disease management model [54], rather than the predominant CPAP monotherapy approach. Accordingly, similar to other conditions in which one or more underlying mechanisms are targeted with therapy (e.g. asthma where both the smooth muscle and inflammation components of the condition are targeted with therapy) there is considerable scope for combination therapy for OSA. For example, the combination of MAD and CPAP lowers CPAP requirements [187] which may help improve tolerance for people with high therapeutic CPAP requirements [188, 189] although this requires further investigation. Combination therapy directed towards the anatomical endotype with non-CPAP therapies may also be a viable alternative to CPAP for many patients. For example, positional therapy combined with MAD therapy (Table 1) [190], upper airway surgery combined with positional therapy [191] and MAD therapy combined with end expiratory pressure valves [192]. Combining two non-anatomical interventions (eszopiclone to increase the arousal threshold and oxygen to lower loop gain) reduces the AHI by ~50% in unselected patients [23]. Thus, while still in the research investigation stage, these findings provide proof of concept support for the potential for combination therapy for OSA. Indeed, it is estimated that more than 50% of all OSA patients could be treated with one or more non-CPAP therapies directed towards to the appropriate endotypes [193]. A major prospective trial is currently underway in which OSA endotypes are quantified at baseline

using gold standard methodology and the ultimate goal of the study is to treat all patients with one or more targeted therapies according to endotype characterisation (ACTRN12618001995268).

Consistently, study findings and a meta-analysis suggests that short term continuous positive airway pressure (CPAP) treatment may cause weight gain in obstructive sleep apnea (OSA) [194, 195] which of itself could impact on associated cardiometabolic comorbidities. The final goal of holistic management is not only to improve the patient reported outcomes but also to manage cardio-metabolic risk to attain the best possible health outcomes. In more than 50% of cases OSA patients are obese and multimorbid and should be efficiently treated for their cardio-metabolic co-morbidities. This includes support to follow weight loss programs and lifestyle interventions promoting physical activity. Behavioural and lifestyle interventions not only target overall risk reduction but also are effective in reducing the severity of OSA [196]. When indicated in isolation they cannot be expected to totally resolve OSA in most patients but might generate major reductions in disabilities and prove superior to CPAP in improving cardio-metabolic risk factors. Therefore, clinicians should more systematically use lifestyle interventions as adjuncts to primary OSA therapy.

Effect of body weight loss, changes in lifestyle habits and rehabilitation programs

Previous studies have largely documented the benefits of weight loss programs and physical activity to correct or attenuate OSA [196]. In obese patient's weight loss achieved either by bariatric surgery (Roux-en-Y gastric bypass, vertical-banded gastroplasty) or by lifestyle interventions was associated with an improvement in sleep-related breathing disorders. Weight loss not only reduces OSA severity but also reduces the burden of comorbidities and improves hypertension and diabetes control [197, 198]. While bariatric surgery is associated with dramatic weight reduction, it is also nowadays considered as a

metabolic intervention that decreases hypertension, improves control of diabetes and thus reduces morbi-mortality [199]. In morbidly obese OSA patients, as CPAP has only a limited impact on cardio-metabolic risk, when possible, a surgical method of body weight reduction should be proposed. As recently supported by American Thoracic Society consensus guidelines, additional therapies for body weight reduction should be encouraged for overweight or obese patients with OSA initiated on CPAP [90]. Moreover, weight loss plus CPAP have synergistic effects on weight and metabolic parameters compared with each intervention taken alone [200].

Both maximal exercise capacities [201] and the level of spontaneous physical activity [202] are lower than normal in OSA patients. A sedentary lifestyle is associated with sleep disordered breathing and may be corrected by lifestyle intervention programs [202]. In obese patients with OSA on CPAP, NIV or respiratory muscle training as supports to increase exercise duration and intensity have recently been shown to significantly reduce waist circumference and blood pressure [203]. All these considerations argue in favour of a combined treatment strategy for obese OSA.

Residual sleepiness in CPAP-treated OSA patients

Excessive daytime sleepiness (EDS) is one of the chief symptoms reported by patients with obstructive sleep apnoea (OSA). 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 [204, 205]. The need for pharmacotherapy as adjunct therapy in CPAP-treated patients is now acknowledged in this population with residual EDS. Recently, the efficacy of Solriamfetol, a dopamine/norepinephrine reuptake inhibitor [206, 207], and Pitolisant, a selective histamine receptor-3 antagonist, [208, 209] have been established in large multicentre 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 assessed by MWT or Osler tests. Further evaluation remains necessary to assess long term benefits and safety, specifically in OSA with cardiometabolic comorbidities.

Integrated follow-up with the help of remote monitoring and telemedicine platforms

OSA is typically an ambulatory disease for which e-health solutions supported by artificial intelligence will in the future improve workflow for clinicians and caregivers and enable patients to process their own data to promote better health (Figure 6). The use of several different home care services each managing an individual disease/comorbidity is clearly duplicative and inefficient and is potentially unsafe for patients because of poor coordination and integration. A major goal in the field of holistic management of OSA will be to create integrated telemedicine and home care services for the follow-up of multimorbid OSA and risk prediction [54]. Patient transmitted self-measured blood pressure, CPAP adherence and residual events, number of steps per day and PROMS questionnaires are starting to be deployed on integrated telemedicine platforms and allow clinicians to prioritize actions and health education in the care of patients with OSA [210].

o Perspectives

Recent advances in knowledge of clinical OSA phenotypes and pathophysiological endotypes have provided new pathways and opportunities for precision medicine approaches for OSA including novel strategies to direct targeted non-CPAP therapies. Further investigation is required to establish the stability of clinical phenotypes across different cohorts and ultimately standardisation of clusters/phenotypes so that they can be evaluated systematically in prospective studies/cohorts. Recent work has led to the development of

simplified tools to estimate the key OSA endotypes for scalable use in the clinic. A future priority will be to continue to refine and enhance these approaches and integrate into clinical practice. A major step on this translation journey will be to systematically assess and update these tools in clinical practice in pragmatic trials to determine if the conceptual physiological framework of OSA endotyping delivers better outcomes for patients (e.g. better prospective prediction/tailored therapy from the onset rather than trial and error etc.).

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Table 1. Potential advantages and disadvantages of non-CPAP therapies and potential utility of personalised care

Advantages	Disadvantages	Personalisation potential
Mandibular advancement devices		
<ul style="list-style-type: none"> Well-tolerated, often preferred to CPAP Comparable health benefits to CPAP 	<ul style="list-style-type: none"> Variable and currently largely unpredictable efficacy (overall less efficacious vs. CPAP) Often not reimbursed Teeth movement/potential dental symptoms 	<ul style="list-style-type: none"> Endotyping studies indicate that consideration of OSA endotypes may help direct patient selection/increase success rates E.g., patients with less collapsible airways tend to do better whereas those with high loop gain tend to do poorly
Positional therapy		
<ul style="list-style-type: none"> -Well-tolerated, often preferred to CPAP Affordable and efficacious for a substantial proportion of patients 	<ul style="list-style-type: none"> RCT's to assess long term compliance, efficacy and effects on key health outcomes required Less efficacious vs. CPAP Potential to cause back discomfort in some cases 	<ul style="list-style-type: none"> Supine dependent clinical phenotype Conceptually, patients with less collapsible airways without major impairment in non-anatomical endotypes expected to do best (not yet known) Given that supine avoidance also improves pharyngeal muscle function baseline muscle function may be an important mediator of treatment outcome (not yet known)
Pharmacotherapy to treat OSA		
<ul style="list-style-type: none"> Strong desire from many patients for a non-device medication therapy Recent studies show promise for multiple mechanistic targets for OSA pharmacotherapy 	<ul style="list-style-type: none"> Not yet available clinically Further discovery, and RCT's required to establish long-term efficacy, safety and tolerability profile and potential health benefits 	<ul style="list-style-type: none"> As highlighted in the initial proof of concept studies, knowledge of OSA endotypes is likely to be crucial to deliver the right pharmacotherapy to the right patient to optimise efficacy
Stimulation therapy		
<ul style="list-style-type: none"> Strong desire from many patients for a non-CPAP therapy 	<ul style="list-style-type: none"> Less efficacious vs. CPAP and not without risk 	<ul style="list-style-type: none"> Recent endotyping findings indicate that consideration of OSA

<ul style="list-style-type: none"> Once in place, minimal patient input required and thus, high compliance 	<ul style="list-style-type: none"> Current treatment prediction approaches are imperfect Costly and not widely available Further longer-term data required on potential health benefits (difficult to blind subjective outcomes) 	<p>endotypes may help direct patient selection/ increase success rates</p> <ul style="list-style-type: none"> E.g., patients with baseline impairment in non-anatomical OSA endotypes tend to do poorly
Combined therapies		
<ul style="list-style-type: none"> Considerable potential for those who do not respond to conventional monotherapy Some options are readily available and inexpensive (e.g., adding positional therapy when MAD monotherapy in incompletely efficacious) 	<ul style="list-style-type: none"> Further research investigation and long-term clinical evaluation of all the various potential combinations (including existing and emerging approaches) required 	<ul style="list-style-type: none"> As highlighted in the initial proof of concept studies, knowledge of OSA endotypes is likely to be crucial to deliver the right targeted combinations of therapies to the right patient to optimise efficacy
Pharmacotherapy to treat residual sleepiness		
<ul style="list-style-type: none"> Strong clinical need and desire from many patients for a medication-based approach to reduce sleepiness, especially when not fully resolved with other therapies 	<ul style="list-style-type: none"> Further clinical evaluation required to assess long term benefits and safety in different patient populations E.g., people with OSA and cardiometabolic comorbidities 	<p>Endotypic characteristics of patients who are most likely to benefit from this approach, beyond the clinical sleepiness phenotype, is not currently known</p>

CPAP= continuous positive airway pressure, MAD= mandibular advancement device, OSA= obstructive sleep apnoea, RCT= randomised controlled trial. Refer to the text for further detail.

Figure Legends

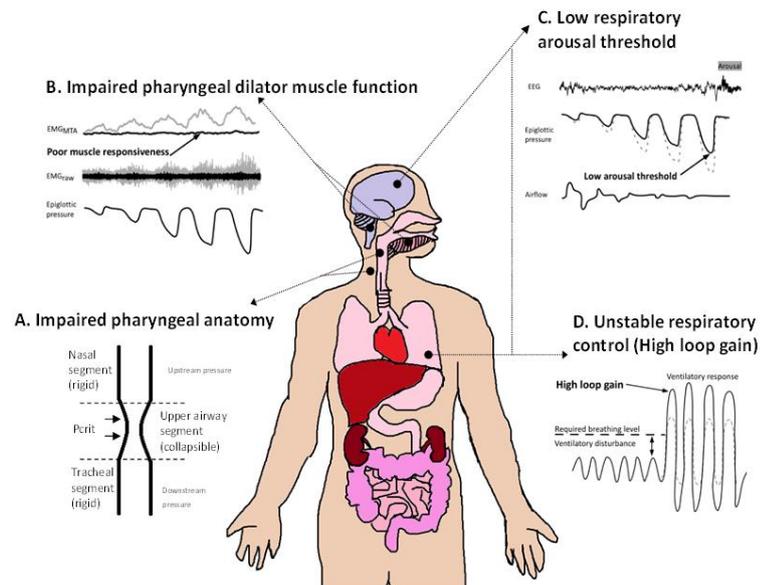


Figure 1. Schematic of the 4 key endotypic traits that contribute to OSA pathophysiology

A. Impaired pharyngeal anatomy (elevated critical closing pressure [P_{crit}] of the upper airway during sleep). Non-anatomical endotypes include: **B.** Poor pharyngeal dilator muscle function including inadequate responsiveness/activation to negative pharyngeal pressure/airway narrowing, **C.** A low respiratory arousal threshold (waking up too easily to minor pharyngeal narrowing); and **D.** Unstable respiratory control/increased sensitivity to minor changes in CO_2 (High loop gain). Each of these endotypes is a target for therapy or a “treatable trait”. Adapted from Carberry et al, *Chest*, 2018 [72] and Aishah and Eckert, *Curr Opin Pulm Med*, 2019 [95].

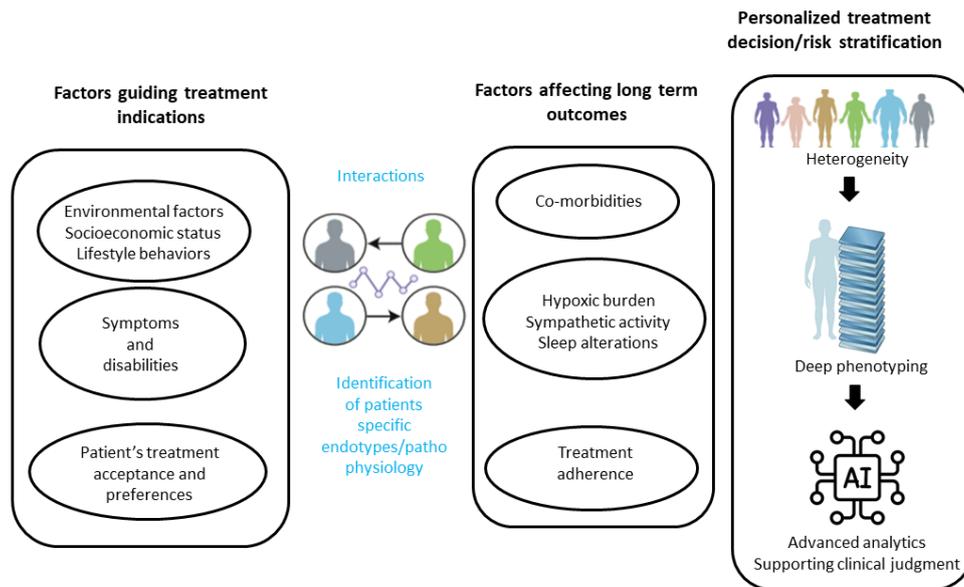


Figure 2. Routine management of OSA can now be conducted using analytical step-by-step approaches and reasoning, distinguishing symptomatic versus non-symptomatic phenotypes, easy to identify endotypes (treatable conditions) and predict poor outcomes by advanced analytics.

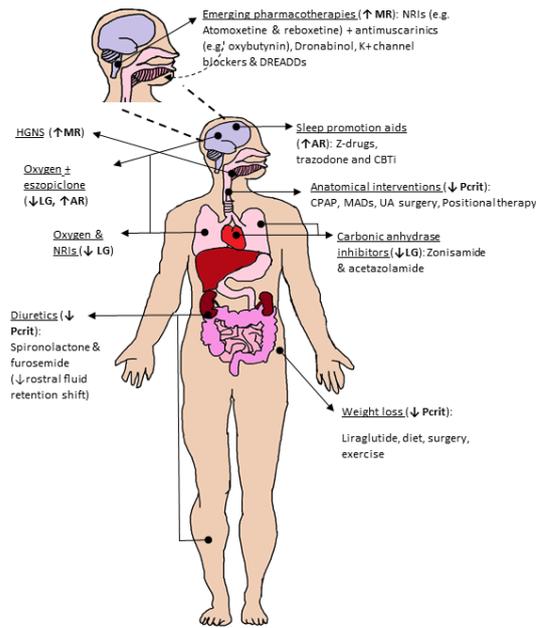


Figure 3. Schematic highlighting examples of existing and emerging targeted therapies for obstructive sleep apnoea.

Bold abbreviations indicate the endotypes to which the various anatomical and non-anatomical interventions are targeted where: MR= muscle responsiveness/dilator muscle function, LG= loop gain/respiratory control, Pcrit= critical closing pressure of the upper airway/pharyngeal anatomy and AT= arousal threshold. Refer to the text for further detail. CBTi= cognitive behavioural therapy for insomnia, CPAP= continuous positive airway pressure, DREADDs= designer receptors exclusively activated by designer drugs, HGNS= hypoglossal nerve stimulation, MADs= mandibular advancement devices, NRI= norepinephrine reuptake inhibitor, UA= upper airway.

Adapted from Aishah and Eckert, *Curr Opin Pulm Med*, 2019 [95].

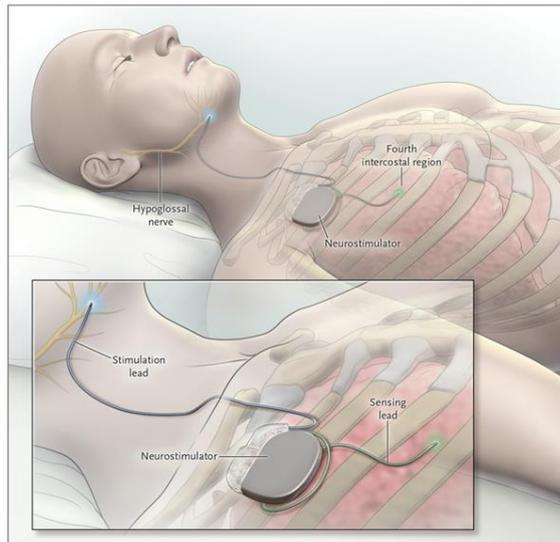


Figure 4. Example of an upper airway stimulator system which is based on delivering stimulation the hypoglossal nerve via a unilateral cuff electrode.[164]

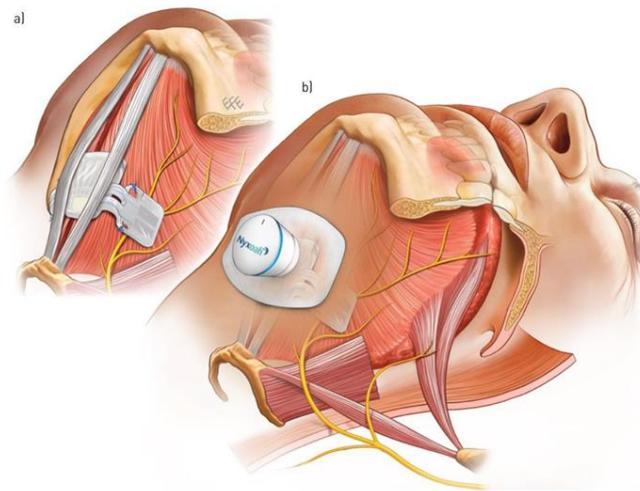


Figure 5. Example of a bilateral system which is based on delivering stimulation to the hypoglossal nerve via bilateral paddle electrodes. [171]

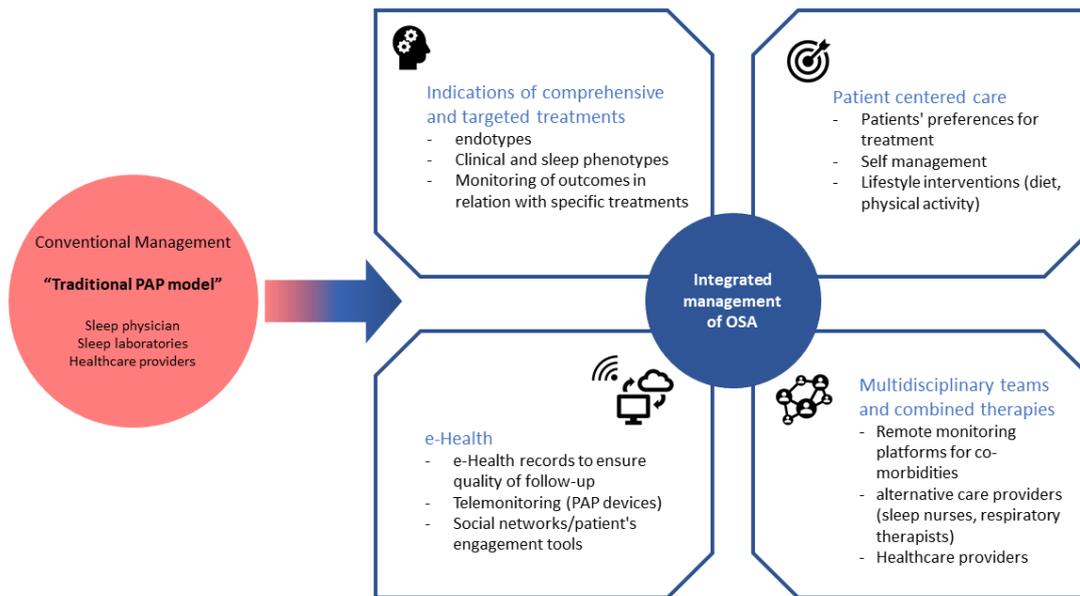


Figure 6: Reshaping sleep apnoea care: moving from conventional to integrated management of OSA and value-based care [54]