Novel avenues to approach non-CPAP therapy and implement comprehensive obstructive sleep apnoea care

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Continuous positive airway pressure (CPAP) treatment of obstructive sleep apnoea (OSA) requires alternatives. Recent advances in knowledge of OSA pathogenesis, alternatives or adjuncts to CPAP and novel approaches will allow more personalised treatments. https://bit.ly/3ieyDRG

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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. Additionally, these concepts have 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 hypopnoea (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) therapy, which 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 is needed, which carefully considers more systematic physiopathological and clinical phenotyping approaches with the aim of providing patients with better tailored treatments.

The objectives of this review are first to describe the physiopathological endotypes and clinical phenotypes that will form the basis for identifying optimal therapeutic options for the different OSA subtypes; second, to describe the current therapeutic indications of alternatives to CPAP including well-validated mandibular advancement devices (MADs), positional therapy and the emerging pharmacological solutions; third, to describe the new stimulation techniques under development and their respective indications; and fourth, to highlight the importance of implementing combined therapies to integrate care and optimise the management of OSA comorbidities.

Physiological phenotypes/endotypes and treatable traits

In addition to different clinical manifestations of OSA, the underling 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 of 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.

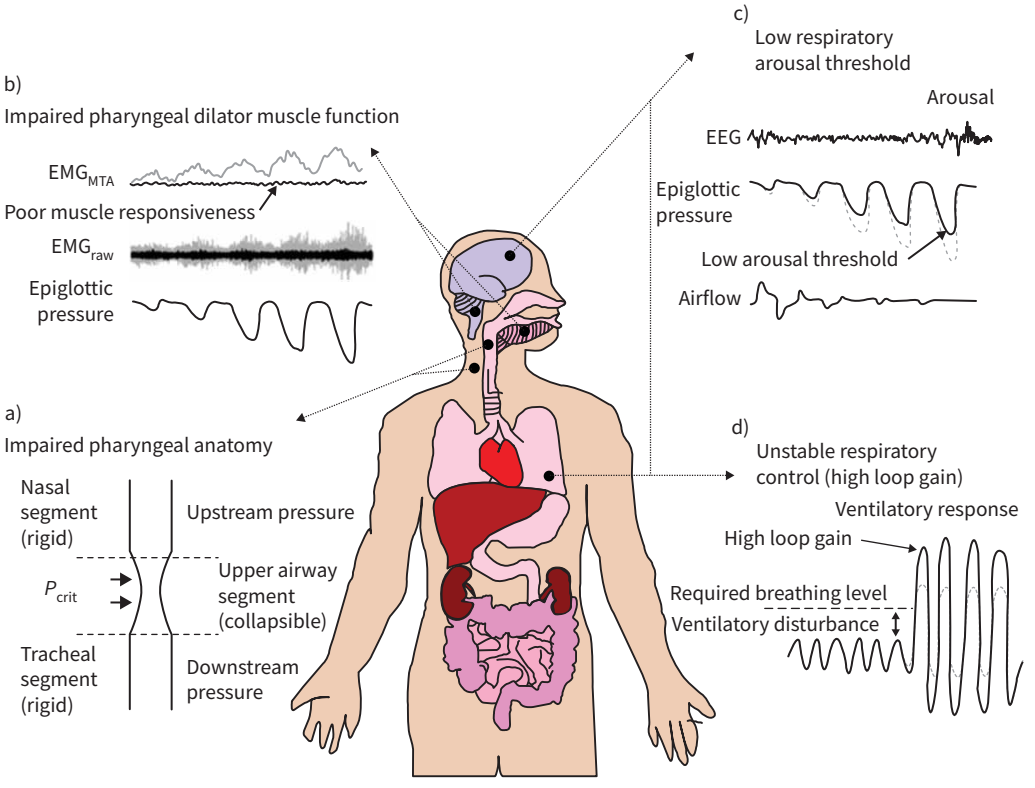

FIGURE 1 Schematic of the four key endotypic traits that contribute to obstructive sleep apnoea (OSA) pathophysiology. a) Impaired pharyngeal anatomy (elevated critical closing pressure (P_{crit}) of the upper airway during sleep). Nonanatomical endotypes include b) poor pharyngeal dilator muscle function 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 carbon dioxide (high loop gain). Each of these endotypes is a target for therapy or a "treatable trait". EMG: electromyogram; MTA: mean turn amplitude; EEG: electroencephalogram. Reproduced and modified from [72] and [95] with permission.

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 "P_{crit}" technique, indicates that ∼25% of patients with OSA have highly collapsible pharyngeal airways (P_{crit} >+2 cmH_2O). 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 ∼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 nonanatomical traits that contribute to OSA pathogenesis.

Approximately 70% of people with OSA have one or more nonanatomical 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 1) [6, 8]. However, current therapies for OSA 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 MADs, 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 nonanatomical 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 nonanatomical treatable traits and which 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, nonobese 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].

Clinical and sleep phenotypes

At present, all OSA patients are considered to have the same generic diagnosis, despite OSA being characterised 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 (AHI) 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 minimise the dissimilarities between two individuals with the same subtype and maximise 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 maxillofacial 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 socioeconomic 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 the following.

1) There is an easy-to-manage clinical phenotype including "excessively sleepy/symptomatic" patients with disabling complaints and altered health-related quality of life who insistently request OSA management and show an expected high treatment adherence.
2) 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 personalised therapies with respect to sex-specific differences.
3) 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, comorbid insomnia and sleep apnoea (COMISA) is a specific phenotype with a prevalence of up to 40% that necessitates multifaceted treatment approaches including cognitive behavioural therapies [52]. The other female cluster comprises women with pulmonary disease (essentially asthma).
4) Another prominent clinical phenotype corresponds to the accumulation of two or more cardiometabolic 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.
5) 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 Society and Sleep Research Society [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* nonsymptomatic 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 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 characterise 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].

1) 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.
2) 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.
3) 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].

Alternatives to CPAP

Mandibular advancement devices

MADs have traditionally been recommended for second-line therapy in patients intolerant of 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 studied extensively in terms of reduction of OSA severity, patient-reported outcomes measures (PROMs), cardiovascular consequences, adherence and short- or long-term side-effects [56].

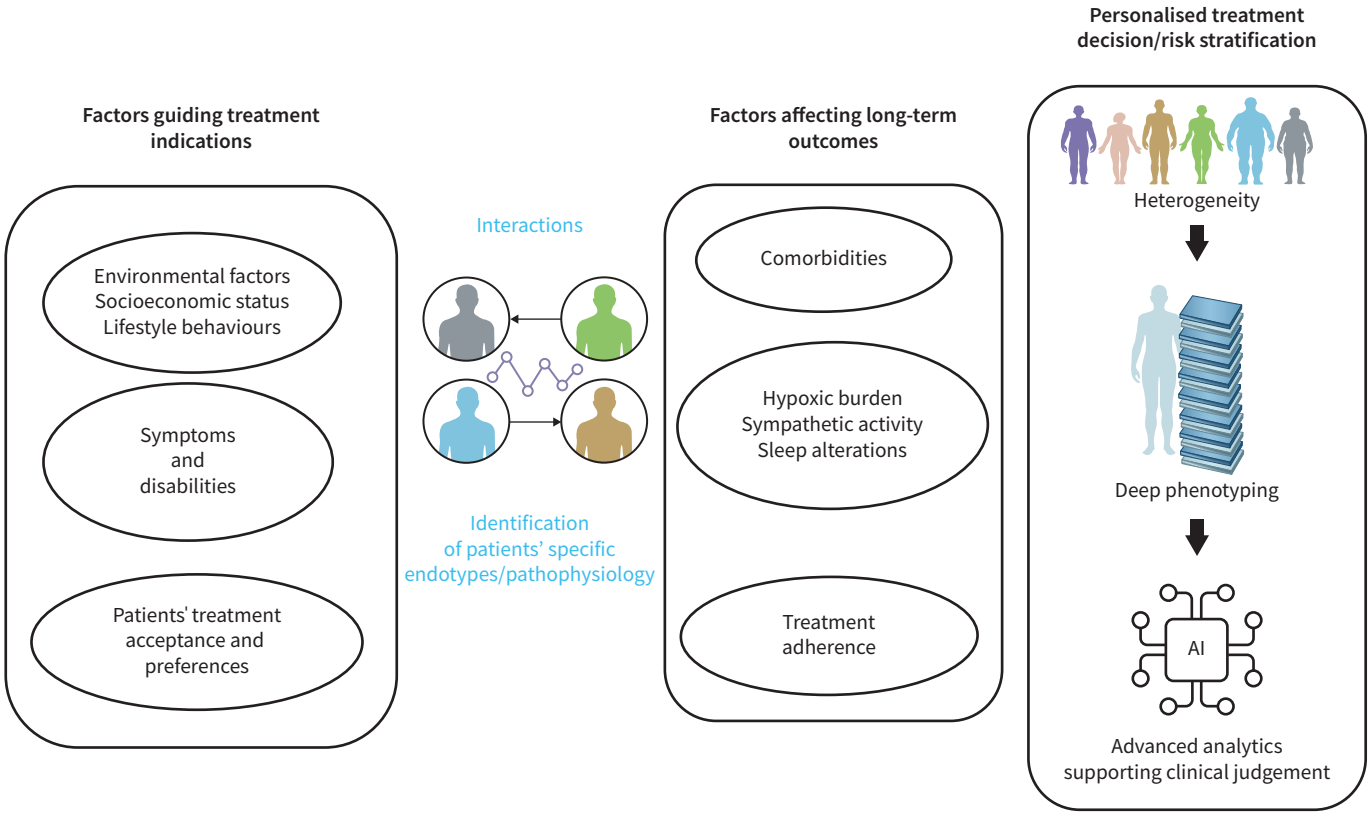

FIGURE 2 Routine management of obstructive sleep apnoea can now be conducted using analytical step-by-step approaches and reasoning, distinguishing symptomatic *versus* nonsymptomatic phenotypes and easy-to-identify endotypes (treatable conditions), and predicting poor outcomes by advanced analytics.

MADs have lower efficacy as measured by AHI compared to CPAP. Approximately two-thirds of OSA patients will achieve >50% reduction in AHI, with at least one-third achieving a complete response with AHI normalisation [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 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 mean disease alleviation 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 rapid eye movement (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

TABLE 1 Potential advantages and disadvantages of non-continuous positive airway pressure (CPAP) therapies and potential utility of personalised care

	Advantages	Disadvantages	Personalisation potential
Mandibular advancement devices	• Well-tolerated, often preferred to CPAP • Comparable health benefits to CPAP	• Variable and currently largely unpredictable efficacy (overall less efficacious *versus* CPAP) • Often not reimbursed • Movement of teeth/potential dental symptoms	• 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	• Well-tolerated, often preferred to CPAP • Affordable and efficacious for a substantial proportion of patients	• RCTs to assess long-term compliance, efficacy and effects on key health outcomes required • Less efficacious *versus* CPAP • Potential to cause back discomfort in some cases	• Supine-dependent clinical phenotype • Conceptually, patients with less collapsible airways without major impairment in nonanatomical 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	• Strong desire from many patients for a nondevice medication therapy • Recent studies show promise for multiple mechanistic targets for OSA pharmacotherapy	• Not yet available clinically • Further discovery and RCTs required to establish long-term efficacy, safety and tolerability profile and potential health benefits	• 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	• Strong desire from many patients for a non-CPAP therapy • Once in place, minimal patient input required, and thus, high compliance	• Less efficacious *versus* CPAP, and not without risk • 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)	• Recent endotyping findings indicate that consideration of OSA endotypes may help direct patient selection/ increase success rate, *e.g.* patients with baseline impairment in nonanatomical OSA endotypes tend to do poorly
Combined therapies	• 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 is incompletely efficacious	• Further research investigation and long-term clinical evaluation of all the various potential combinations (including existing and emerging approaches) required	• 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	• Strong clinical need and desire from many patients for a medication-based approach to reduce sleepiness, especially when not fully resolved with other therapies	• Further clinical evaluation required to assess long-term benefits and safety in different patient populations, *e.g.* people with OSA and cardiometabolic comorbidities	• Endotypic characteristics of patients who are most likely to benefit from this approach, beyond the clinical sleepiness phenotype, is not currently known

OSA: obstructive sleep apnoea; RCT: randomised controlled trial; MAD: mandibular advancement device.

practice. First, 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 (<6 mm) [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 6 months to inspect dental side-effects or occlusal changes [56]. Second, 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. Furthermore, 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 additionally 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-dependent OSA (POSA) is commonly defined as a supine to nonsupine AHI ratio $\geqslant 2$ and an AHI that normalises (AHI <5 or 10 events·h^{-1}) in the nonsupine posture. POSA occurs in >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 aims to prevent supine sleep to reduce OSA burden. This approach has been undervalued for decades owing to the archaic or nonaesthetic 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 positional therapy solutions have now been developed successfully. 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 positional therapy was reported as good, with patients generally expressing a preference for positional therapy *versus* CPAP. However, there is a lack of reliable data on long-term adherence and new tools to objectively measure adherence to positional therapy are being developed. The certainty of evidence for the efficacy of positional therapy remains moderate and further multinational, multicentric (*e.g.* ClinicalTrials.gov NCT04211350) and long-term high-quality studies are needed before positional therapy can be integrated more widely into OSA treatment algorithms. In particular, the respective roles of positional therapy as a standalone or as 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 straightforward 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.

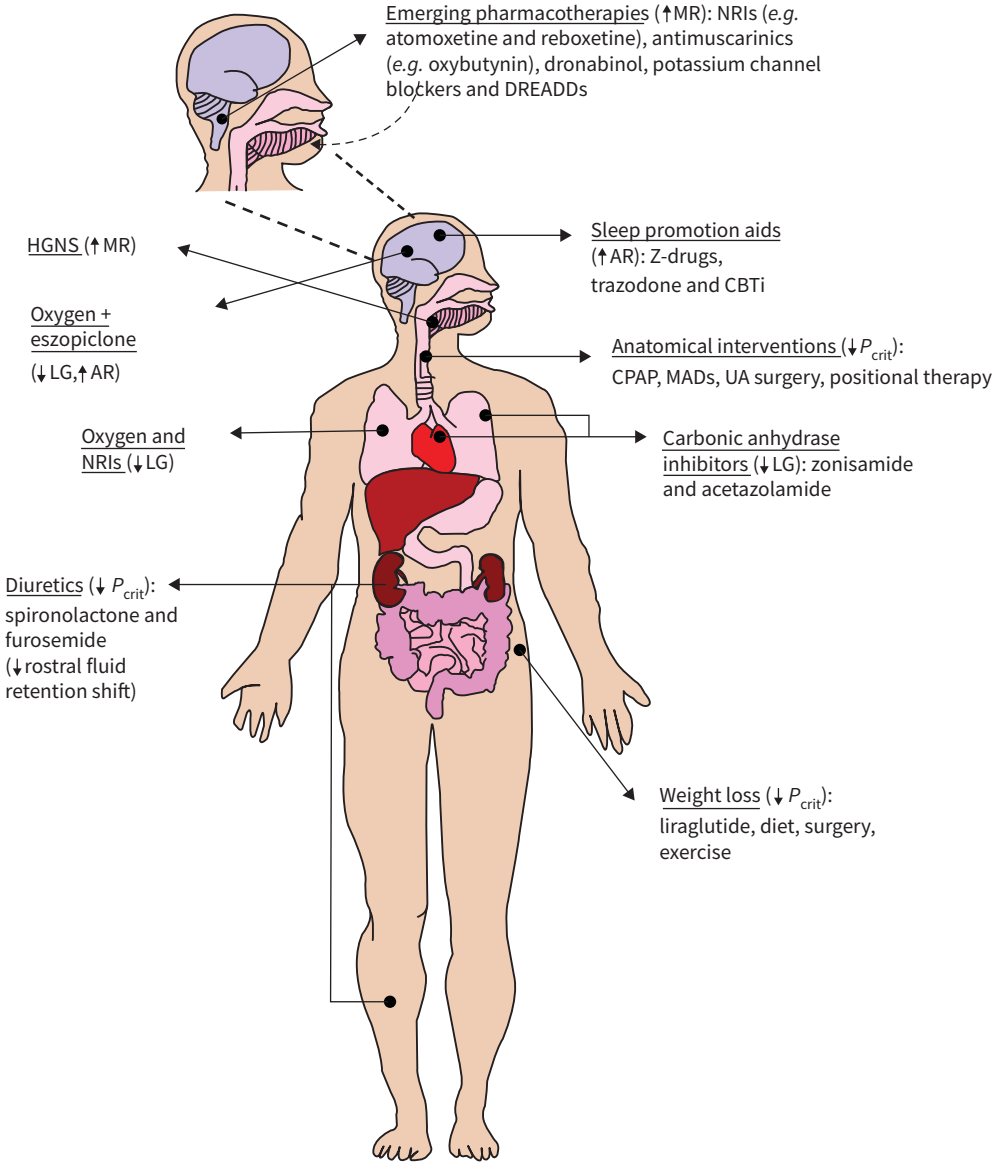

FIGURE 3 Schematic highlighting examples of existing and emerging targeted therapies for obstructive sleep apnoea. Abbreviations indicate the endotypes to which the various anatomical and nonanatomical interventions are targeted: muscle responsiveness/dilator muscle function (MR); loop gain/respiratory control (LG); critical closing pressure of the upper airway/pharyngeal anatomy (P_{crit}); and arousal threshold (AT). NRI: norepinephrine reuptake inhibitor; DREADDs: designer receptors exclusively activated by designer drugs; CBTi: cognitive behavioural therapy for insomnia; CPAP: continuous positive airway pressure; MADs: mandibular advancement devices; UA: upper airway; HGNS: hypoglossal nerve stimulation. Reproduced and modified from [95] with permission.

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 more than one-third of people with OSA [8]. 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-HT_3) and inhibitory cannabinoid type 1 (CB_1) receptors in nodose ganglion cells, and noradrenergic-, serotonergic- and glutamatergic-mediated excitatory inputs to cranial motor neuron pools [103–107]. 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 [108]. While a universally effective pharmacological therapy for OSA has not been identified, the mechanistic pathways highlighted here show considerable promise for targeted therapy for OSA.

Dronabinol, a nonselective CB_1 and CB_2 receptor agonist, modestly reduces OSA severity as measured *via* AHI by ~10 events·h^{-1} at doses of 2.5 and 10 mg·day^{-1} [109, 110]. Selective serotonin reuptake inhibitors (SSRIs) have shown mixed results. An early study with the SSRI paroxetine reduced the AHI during non-REM sleep, but not during REM sleep [111]. Fluoxetine also reduced non-REM AHI, but with substantial interindividual variability [112]. Mirtazapine, a mixed 5-HT_2/5-HT_3 antagonist and α2A antagonist showed promising results in an initial small randomised trial [113]. However, two larger subsequent studies failed to replicate this finding [114]. 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, drugs targeting the noradrenergic and muscarinic pathways are the most promising class of agents to control 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 [115]. In addition, desipramine reduces upper airway collapsibility and OSA severity in those with impaired upper airway muscle activity [116]. 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 hypoxaemia [24, 117]. However, while modest improvements in airway stability occur in people with OSA when atomoxetine is combined with other more selective antimuscarinics [118], 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 [119] and reduces OSA severity [120]. Findings from a recently completed trial indicates that reductions in OSA severity also occur when reboxetine is delivered alone without an antimuscarinic (anzctr.org.au 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, which have shown promise in a pig model [121] and have recently been tested in people with OSA [122] require further investigations in humans (currently underway: ClinicalTrials.gov 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 have recently been investigated in animal models with promising results [123–125]. 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.

Targeting loop gain

People with inherently unstable or overly sensitive responses to carbon dioxide (high loop gain) during sleep are at increased risk of OSA [126]. Unstable respiratory control/high loop gain 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 arterial carbon dioxide tension (P_{aCO_2}) apnoea threshold

[127, 128]. In addition, acetazolamide reduces key components of high loop gain (plant gain) [129] and increases the response time to changes in P_{aCO_2} secondary to increased cerebral blood flow [130]. 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 m [131]. 1 week of 500 mg 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 [22]. Zonisamide, another carbonic anhydrase inhibitor, also reduces the AHI by ∼30% in patients with moderate-to-severe OSA [132]. 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 [132]. 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, 118, 119].

Supplemental oxygen reduces peripheral chemosensitivity and can also stabilise breathing during sleep. For example, 3–5 $L \cdot min^{-1}$ of supplemental oxygen reduces loop gain and the AHI in OSA patients with high loop gain [133] without altering the other key OSA endotypes [134]. OSA endotype characterisation either *via* awake chemosensitivity testing [135] 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.

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 [136]. Waking up too easily to airway narrowing (low respiratory arousal threshold), prevents more stable deeper sleep and compensatory pharyngeal muscle activation and can perpetuate breathing instability [136, 137]. A low respiratory arousal threshold is a common endotype in patients with OSA, especially in patients who are not obese [8, 27]. Thus, sleep promotion aids that raise the arousal threshold may 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 hypoxaemia in people with severe OSA [138]. However, more recent detailed physiological studies in people with and without OSA indicate that zolpidem, zopiclone, trazodone and temazepam increase the arousal threshold and do not impair pharyngeal dilator muscle responsiveness during sleep [137, 139–142]. Eszopiclone has been shown to increase the respiratory arousal threshold and reduce OSA severity by ∼45% in people with a low arousal threshold endotype [21]. Reductions in OSA severity in unselected patients have also been reported with trazodone [143]. 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 [142]. Indeed, nonpharmacological approaches to promote sleep, such as cognitive behavioural therapy for insomnia, reduce OSA severity in people with OSA and insomnia [144]. However, most hypnotic trials in people with OSA do not systematically alter the AHI [136, 137, 145–148]. In addition, while nonbenzodiazepine hypnotics and trazodone are considered to be relatively safe drugs [149, 150] 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 [149]. 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 [151] and the potential role that weight-loss surgery may play for severely obese patients [152], these topics are beyond the scope of the current review, which focuses on new stimulation techniques.

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 [153]. 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 [154], 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.* [155] and SCHWARTZ *et al.* [156], 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 following decade, improvements in lead construction, sensor development, implantable pacemaker construction and programming and nerve cuff construction led to this being revisited.

In the mid-2000s several companies produced implantable devices that stimulated one of the hypoglossal nerves *via* a cuff electrode with resulting inspiratory phasic [157, 158] or continuous [159] contraction of the genioglossus muscle during sleep. Despite using different techniques, the studies reported remarkably similar results, with decreases in AHI of 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 United States Food and Drug Administration, a device based on the seminal study by STROLLO *et al.* [158] 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 [160]; is effective in improving objective measures of OSA severity and subjective measures of OSA-related symptoms [160, 161]; and is reliant on careful implementation of titration algorithms and manipulation of stimulation settings [162, 163]. Improved understanding of these factors has led to marked improvements in therapeutic effectiveness with recent post-market studies reporting improvements in AHI of ⩾75% [161, 164].

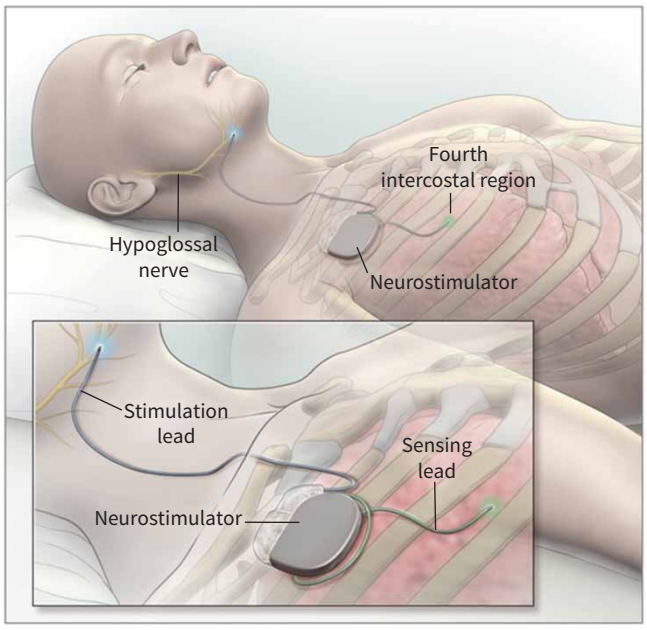

FIGURE 4 Example of an upper airway stimulator system which is based on delivering stimulation to the hypoglossal nerve *via* a unilateral cuff electrode. Reproduced from [158] with permission.

A new-generation device has been developed with several differences from other devices [165, 166] (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 participant's 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 [165]. 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 20–50 events·h^{-1}, body mass index <32 kg·m^{-2}, central or mixed apnoea index [167] <25% of the AHI and absence of circumferential pharyngeal airway during drug-induced sleep endoscopy [158, 168]. 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 [164]. Importantly, the current evidence base for HNS remains very limited, with only one study fulfilling (partly) the criteria of a randomised controlled trial [158].

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 [169], clinical registries [170] and prospective studies [171, 172]. Recently, Op de Beeck *et al.* [25] used baseline polysomnography records from implanted patients to show that several nonanatomical 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 [173] did not find a significant difference in polysomnography-derived odds ratio product, a measure of arousal propensity, between responders and nonresponders to HNS therapy. These studies highlight the complex nature of OSA and its underlying pathophysiology, the understanding of which remains incomplete, but which is essential to selecting the most suitable patients for HNS therapy.

Other stimulation techniques

Several other stimulation techniques have been proposed to treat OSA. Of these, the most studied has been transcutaneous electrical stimulation 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 post-treatment AHI. However, the impact on quality of life remains unclear [174]. Electrical stimulation has also been applied to the muscles of the tongue to cause muscle contraction and increase strength and fatigue resistance and

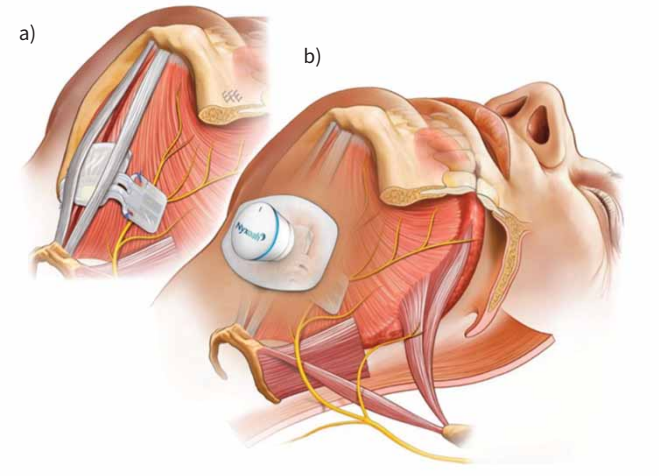

FIGURE 5 Example of a bilateral system which is based on delivering stimulation to the hypoglossal nerve *via* bilateral paddle electrodes. Reproduced with permission [165].

has been shown to reduce time spent snoring [175]. Daytime electrical stimulation of the calf muscles while seated has 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 [176]. 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 [177]. 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 speech therapy techniques to "train" the tongue muscles [178]. While results to date are promising, randomised and high-quality studies still need to be undertaken [179].

Combined therapies

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 [180], which may be help improve tolerance for people with high therapeutic CPAP requirements [181, 182], 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) [183], upper airway surgery combined with positional therapy [184] and MAD therapy combined with end-expiratory pressure valves [185]. Combining two nonanatomical 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 >50% of all OSA patients could be treated with one or more non-CPAP therapies directed towards to the appropriate endotypes [186]. 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 (AustralianClinicalTrials.gov.au ACTRN12618001995268).

Consistently, study findings and meta-analyses suggest that short-term CPAP treatment may cause weight gain in OSA [187, 188], 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 cardiometabolic risk to attain the best possible health outcomes. In >50% of cases OSA patients are obese and multimorbid and should be treated efficiently for their cardiometabolic comorbidities. This includes support to follow weight-loss programmes and lifestyle interventions promoting physical activity. Behavioural and lifestyle interventions not only target overall risk reduction, but are also effective in reducing the severity of OSA [189]. 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 cardiometabolic 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 programmes

Previous studies have largely documented the benefits of weight-loss programmes and physical activity to correct or attenuate OSA [189]. In obese patients, 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 [190, 191]. 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 [192]. In morbidly obese OSA patients, as CPAP has only a limited impact on cardiometabolic risk, when possible, a surgical method of body weight reduction should be proposed. As 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 has synergistic effects on weight and metabolic parameters compared with each intervention taken alone [193].

Both maximal exercise capacities [194] and the level of spontaneous physical activity [195] are lower than normal in OSA patients. A sedentary lifestyle is associated with sleep disordered breathing and may be corrected by lifestyle intervention programmes [196]. In obese patients with OSA on CPAP, noninvasive ventilation or respiratory muscle training as supports to increase exercise duration and intensity have been shown to significantly reduce waist circumference and blood pressure [197]. 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, 10–15% of patients continue to experience EDS and alterations in quality of life despite adequate therapy [198, 199]. 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 [199, 200], and pitolisant, a selective histamine receptor-3 antagonist [201, 202], have been established in large multicentre randomised controlled trials. The two compounds have demonstrated significant improvements in subjective Epworth Sleepiness Scale scores by ~2–5 points and a reduction of objective sleepiness assessed by Maintenance of Wakefulness or Oxford Sleep Resistance 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 prioritise actions and health education in the care of patients with OSA [203].

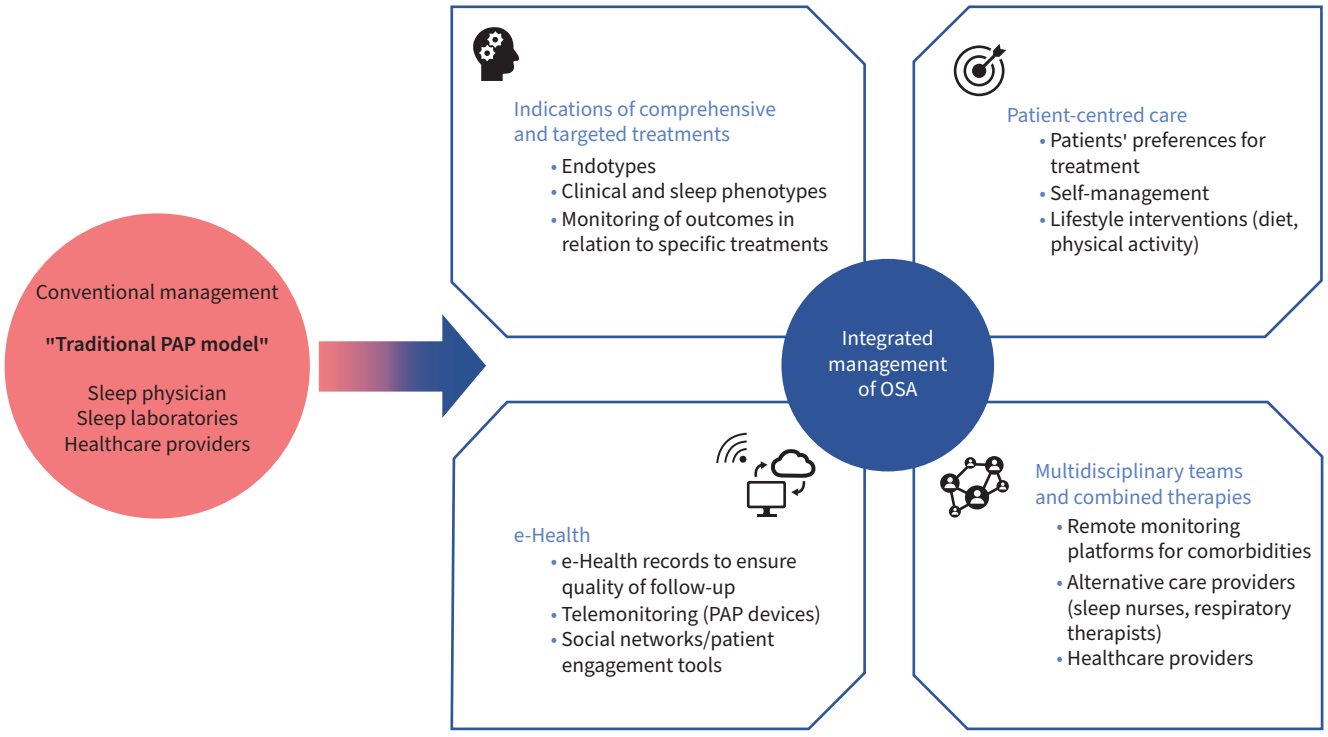

FIGURE 6 Reshaping sleep apnoea care: moving from conventional to integrated management of obstructive sleep apnoea (OSA) and value-based care. PAP: positive airway pressure. Reproduced and modified from [54] with permission.

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).

Previous articles in this series: No. 1: Osorio RS, Martínez-García MA, Rapoport DM. Sleep apnoea in the elderly: a great challenge for the future. *Eur Respir J* 2022; 59: 2101649. *No. 2:* Lévy P, Naughton MT, Tamisier R, *et al.* Sleep apnoea and heart failure. *Eur Respir J* 2022; 59: 2101640.

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References

1 Benjafield AV, Ayas NT, Eastwood PR, *et al.* Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019; 7: 687–698.
2 Lévy P, Kohler M, McNicholas WT, *et al.* Obstructive sleep apnoea syndrome. *Nat Rev Dis Primers* 2015; 1: 15015.
3 Streatfeild J, Smith J, Mansfield D, *et al.* The social and economic cost of sleep disorders. *Sleep* 2021; 44: zsab132.
4 Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proc Am Thorac Soc* 2008; 5: 173–178.
5 Martinez-Garcia MA, Campos-Rodriguez F, Barbé F, *et al.* Precision medicine in obstructive sleep apnoea. *Lancet Respir Med* 2019; 7: 456–464.
6 Eckert DJ. Phenotypic approaches to obstructive sleep apnoea – new pathways for targeted therapy. *Sleep Med Rev* 2018; 37: 45–59.
7 Malhotra A, Mesarwi O, Pepin JL, *et al.* Endotypes and phenotypes in obstructive sleep apnea. *Curr Opin Pulm Med* 2020; 26: 609–614.
8 Eckert DJ, White DP, Jordan AS, *et al.* Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. *Am J Respir Crit Care Med* 2013; 188: 996–1004.
9 Schwartz AR, Patil SP, Squier S, *et al.* Obesity and upper airway control during sleep. *J Appl Physiol* 2010; 108: 430–435.
10 Stadler DL, McEvoy RD, Sprecher KE, *et al.* Abdominal compression increases upper airway collapsibility during sleep in obese male obstructive sleep apnea patients. *Sleep* 2009; 32: 1579–1587.
11 Genta PR, Schorr F, Eckert DJ, *et al.* Upper airway collapsibility is associated with obesity and hyoid position. *Sleep* 2014; 37: 1673–1678.
12 Kim AM, Keenan BT, Jackson N, *et al.* Tongue fat and its relationship to obstructive sleep apnea. *Sleep* 2014; 37: 1639–1648.

13 Neelapu BC, Kharbanda OP, Sardana HK, *et al.* Craniofacial and upper airway morphology in adult obstructive sleep apnea patients: a systematic review and meta-analysis of cephalometric studies. *Sleep Med Rev* 2017; 31: 79–90.

14 Cheng S, Gandevia SC, Green M, *et al.* Viscoelastic properties of the tongue and soft palate using MR elastography. *J Biomech* 2011; 44: 450–454.

15 Malhotra A, Huang Y, Fogel RB, *et al.* The male predisposition to pharyngeal collapse: importance of airway length. *Am J Respir Crit Care Med* 2002; 166: 1388–1395.

16 White LH, Bradley TD. Role of nocturnal rostral fluid shift in the pathogenesis of obstructive and central sleep apnoea. *J Physiol* 2013; 591: 1179–1193.

17 Pépin JL, Bailly S, Rinder P, *et al.* CPAP therapy termination rates by OSA phenotype: a French Nationwide Database Analysis. *J Clin Med* 2021; 10: 936.

18 Bamagoos AA, Cistulli PA, Sutherland K, *et al.* Dose-dependent effects of mandibular advancement on upper airway collapsibility and muscle function in obstructive sleep apnea. *Sleep* 2019; 42: zsz049.

19 Penzel T, Möller M, Becker HF, *et al.* Effect of sleep position and sleep stage on the collapsibility of the upper airways in patients with sleep apnea. *Sleep* 2001; 24: 90–95.

20 Schwartz AR, Schubert N, Rothman W, *et al.* Effect of uvulopalatopharyngoplasty on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1992; 145: 527–532.

21 Eckert DJ, Owens RL, Kehlmann GB, *et al.* Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold. *Clin Sci* 2011; 120: 505–514.

22 Edwards BA, Sands SA, Eckert DJ, *et al.* Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea. *J Physiol* 2012; 590: 1199–1211.

23 Edwards BA, Sands SA, Owens RL, *et al.* The combination of supplemental oxygen and a hypnotic markedly improves obstructive sleep apnea in patients with a mild to moderate upper airway collapsibility. *Sleep* 2016; 39: 1973–1983.

24 Taranto-Montemurro L, Messineo L, Sands SA, *et al.* The combination of atomoxetine and oxybutynin greatly reduces obstructive sleep apnea severity. A randomized, placebo-controlled, double-blind crossover trial. *Am J Respir Crit Care Med* 2019; 199: 1267–1276.

25 Op de Beeck S, Wellman A, Dieltjens M, *et al.* Endotypic mechanisms of successful hypoglossal nerve stimulation for obstructive sleep apnea. *Am J Respir Crit Care Med* 2021; 203: 746–755.

26 Sands SA, Edwards BA, Terrill PI, *et al.* Identifying obstructive sleep apnoea patients responsive to supplemental oxygen therapy. *Eur Respir J* 2018; 52: 1800674.

27 Gray EL, McKenzie DK, Eckert DJ. Obstructive sleep apnea without obesity is common and difficult to treat: evidence for a distinct pathophysiological phenotype. *J Clin Sleep Med* 2017; 13: 81–88.

28 Zinchuk AV, Chu JH, Liang J, *et al.* Physiological traits and adherence to sleep apnea therapy in individuals with coronary artery disease. *Am J Respir Crit Care Med* 2021; 204: 703–712.

29 Zinchuk A, Edwards BA, Jeon S, *et al.* Prevalence, associated clinical features, and impact on continuous positive airway pressure use of a low respiratory arousal threshold among male United States veterans with obstructive sleep apnea. *J Clin Sleep Med* 2018; 14: 809–817.

30 Edwards BA, Andara C, Landry S, *et al.* Upper-airway collapsibility and loop gain predict the response to oral appliance therapy in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2016; 194: 1413–1422.

31 Joosten SA, Leong P, Landry SA, *et al.* Loop gain predicts the response to upper airway surgery in patients with obstructive sleep apnea. *Sleep* 2017; 40: zsx094.

32 Randerath W, Bassetti CL, Bonsignore MR, *et al.* Challenges and perspectives in obstructive sleep apnoea: report by an *ad hoc* working group of the Sleep Disordered Breathing Group of the European Respiratory Society and the European Sleep Research Society. *Eur Respir J* 2018; 52: 1702616.

33 Bonsignore MR, Suarez Giron MC, Marrone O, *et al.* Personalised medicine in sleep respiratory disorders: focus on obstructive sleep apnoea diagnosis and treatment. *Eur Respir Rev* 2017; 26: 170069.

34 Lévy P, Tamisier R, Pépin JL. Assessment of sleep-disordered-breathing: quest for a metric or search for meaning? *J Sleep Res* 2020; 29: e13143.

35 Azarbarzin A, Sands SA, Taranto-Montemurro L, *et al.* Hypoxic burden captures sleep apnoea-specific nocturnal hypoxaemia. *Eur Heart J* 2019; 40: 2989–2990.

36 Azarbarzin A, Sands SA, Taranto-Montemurro L, *et al.* The sleep apnea-specific hypoxic burden predicts incident heart failure. *Chest* 2020; 158: 739–750.

37 Blanchard M, Gervès-Pinquié C, Feuilloy M, *et al.* Hypoxic burden and heart rate variability predict stroke incidence in sleep apnoea. *Eur Respir J* 2021; 57: 2004022.

38 Pépin JL, Bailly S, Tamisier R. Big Data in sleep apnoea: opportunities and challenges. *Respirology* 2020; 25: 486–494.

39 Bailly S, Grote L, Hedner J, *et al.* Clusters of sleep apnoea phenotypes: a large pan-European study from the European Sleep Apnoea Database (ESADA). *Respirology* 2021; 26: 378–387.

40 Saaresranta T, Hedner J, Bonsignore MR, *et al.* Clinical phenotypes and comorbidity in European Sleep Apnoea Patients. *PLoS One* 2016; 11: e0163439.

41 Mazzotti DR, Keenan BT, Lim DC, *et al.* Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes. *Am J Respir Crit Care Med* 2019; 200: 493–506.

42 Nakayama H, Kobayashi M, Tsuiki S, *et al.* Obstructive sleep apnea phenotypes in men based on characteristics of respiratory events during polysomnography. *Sleep Breath* 2019; 23: 1087–1094.

43 Zinchuk AV, Jeon S, Koo BB, *et al.* Polysomnographic phenotypes and their cardiovascular implications in obstructive sleep apnoea. *Thorax* 2018; 73: 472–480.

44 Pépin JL, Bailly S, Tamisier R. Incorporating polysomnography into obstructive sleep apnoea phenotyping: moving towards personalised medicine for OSA. *Thorax* 2018; 73: 409–411.

45 Turino C, Bertran S, Gavalda R, *et al.* Characterization of the CPAP-treated patient population in Catalonia. *PLoS One* 2017; 12: e0185191.

46 Vavougios GD, George DG, Pastaka C, *et al.* Phenotypes of comorbidity in OSAS patients: combining categorical principal component analysis with cluster analysis. *J Sleep Res* 2016; 25: 31–38.

47 Ye L, Pien GW, Ratcliffe SJ, *et al.* The different clinical faces of obstructive sleep apnoea: a cluster analysis. *Eur Respir J* 2014; 44: 1600–1607.

48 Keenan BT, Kim J, Singh B, *et al.* Recognizable clinical subtypes of obstructive sleep apnea across international sleep centers: a cluster analysis. *Sleep* 2018; 41: zsx214.

49 Bailly S, Destors M, Grillet Y, *et al.* Obstructive sleep apnea: a cluster analysis at time of diagnosis. *PLoS One* 2016; 11: e0157318.

50 Zinchuk A, Yaggi HK. Phenotypic subtypes of OSA: a challenge and opportunity for precision medicine. *Chest* 2020; 157: 403–420.

51 Quan W, Zheng D, McEvoy RD, *et al.* High risk characteristics for recurrent cardiovascular events among patients with obstructive sleep apnoea in the SAVE study. *EClinicalMedicine* 2018; 2–3: 59–65.

52 Ong JC, Crawford MR, Wallace DM. Sleep apnea and insomnia: emerging evidence for effective clinical management. *Chest* 2021; 159: 2020–2028.

53 Sutherland K, Kairaitis K, Yee BJ, *et al.* From CPAP to tailored therapy for obstructive sleep apnoea. *Multidiscip Respir Med* 2018; 13: 44.

54 Pépin JL, Baillieul S, Tamisier R. Reshaping sleep apnea care: time for value-based strategies. *Ann Am Thorac Soc* 2019; 16: 1501–1503.

55 Ryan S, Cummins EP, Farre R, *et al.* Understanding the pathophysiological mechanisms of cardiometabolic complications in obstructive sleep apnoea: towards personalised treatment approaches. *Eur Respir J* 2020; 56: 1902295.

56 Sutherland K, Cistulli PA. Oral appliance therapy for obstructive sleep apnoea: state of the art. *J Clin Med* 2019; 8: 2121.

57 Bamagoos AA, Cistulli PA, Sutherland K, *et al.* Polysomnographic endotyping to select patients with obstructive sleep apnea for oral appliances. *Ann Am Thorac Soc* 2019; 16: 1422–1431.

58 Op de Beeck S, Dieltjens M, Azarbarzin A, *et al.* Mandibular advancement device treatment efficacy is associated with polysomnographic endotypes. *Ann Am Thorac Soc* 2021; 18: 511–518.

59 Vena D, Azarbarzin A, Marques M, *et al.* Predicting sleep apnea responses to oral appliance therapy using polysomnographic airflow. *Sleep* 2020; 43: zsaa004.

60 Marques M, Genta PR, Azarbarzin A, *et al.* Structure and severity of pharyngeal obstruction determine oral appliance efficacy in sleep apnoea. *J Physiol* 2019; 597: 5399–5410.

61 Grote L, Hedner J, Grunstein R, *et al.* Therapy with nCPAP: incomplete elimination of sleep related breathing disorder. *Eur Respir J* 2000; 16: 921–927.

62 Ravesloot MJ, de Vries N. Reliable calculation of the efficacy of non-surgical and surgical treatment of obstructive sleep apnea revisited. *Sleep* 2011; 34: 105–110.

63 Phillips CL, Grunstein RR, Darendeliler MA, *et al.* Health outcomes of continuous positive airway pressure *versus* oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med* 2013; 187: 879–887.

64 Trzepizur W, Cistulli PA, Glos M, *et al.* Health outcomes of continuous positive airway pressure *versus* mandibular advancement device for the treatment of severe obstructive sleep apnea: an individual participant data meta-analysis. *Sleep* 2021; 44: zsab015.

65 Anandam A, Patil M, Akinnusi M, *et al.* Cardiovascular mortality in obstructive sleep apnoea treated with continuous positive airway pressure or oral appliance: an observational study. *Respirology* 2013; 18: 1184–1190.

66 Bratton DJ, Gaisl T, Wons AM, *et al.* CPAP *vs* mandibular advancement devices and blood pressure in patients with obstructive sleep apnea: a systematic review and meta-analysis. *JAMA* 2015; 314: 2280–2293.

67 Dieltjens M, Vanderveken OM, Van de Heyning PH, *et al.* Current opinions and clinical practice in the titration of oral appliances in the treatment of sleep-disordered breathing. *Sleep Med Rev* 2012; 16: 177–185.

68 Clark GT. Mandibular advancement devices and sleep disordered breathing. *Sleep Med Rev* 1998; 2: 163–174.

69 Petit FX, Pépin JL, Bettega G, *et al.* Mandibular advancement devices: rate of contraindications in 100 consecutive obstructive sleep apnea patients. *Am J Respir Crit Care Med* 2002; 166: 274–278.

70 Sharples L, Glover M, Clutterbuck-James A, *et al.* Clinical effectiveness and cost-effectiveness results from the randomised controlled Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea-hypopnoea (TOMADO) and long-term economic analysis of oral devices and continuous positive airway pressure. *Health Technol Assess* 2014; 18: 1–296.

71 Johal A, Agha B. Ready-made *versus* custom-made mandibular advancement appliances in obstructive sleep apnea: a systematic review and meta-analysis. *J Sleep Res* 2018; 27: e12660.

72 Carberry JC, Amatoury J, Eckert DJ. Personalized management approach for OSA. *Chest* 2018; 153: 744–755.

73 Gagnadoux F, Nguyen XL, Le Vaillant M, *et al.* Comparison of titrable thermoplastic *versus* custom-made mandibular advancement device for the treatment of obstructive sleep apnoea. *Respir Med* 2017; 131: 35–42.

74 Pépin JL, Raymond N, Lacaze O, *et al.* Heat-moulded *versus* custom-made mandibular advancement devices for obstructive sleep apnoea: a randomised non-inferiority trial. *Thorax* 2019; 74: 667–674.

75 Pépin JL, Tamisier R, Hwang D, *et al.* Does remote monitoring change OSA management and CPAP adherence? *Respirology* 2017; 22: 1508–1517.

76 Sutherland K, Almeida FR, Kim T, *et al.* Treatment usage patterns of oral appliances for obstructive sleep apnea over the first 60 days: a cluster analysis. *J Clin Sleep Med* 2021; 17: 1785–1792.

77 Heinzer R, Petitpierre NJ, Marti-Soler H, *et al.* Prevalence and characteristics of positional sleep apnea in the HypnoLaus population-based cohort. *Sleep Med* 2018; 48: 157–162.

78 Omobomi O, Quan SF. Positional therapy in the management of positional obstructive sleep apnea – a review of the current literature. *Sleep Breath* 2018; 22: 297–304.

79 Sabil A, Blanchard M, Trzepizur W, *et al.* Positional obstructive sleep apnea within a large multicenter French cohort: prevalence, characteristics, and treatment outcomes. *J Clin Sleep Med* 2020; 16: 2037–2046.

80 Hidalgo Armas L, Ingles S, Vaca R, *et al.* New forehead device in positional obstructive sleep apnoea: a randomised clinical trial. *Thorax* 2021; 76: 930–938.

81 Berry RB, Uhles ML, Abaluck BK, *et al.* NightBalance sleep position treatment device *versus* auto-adjusting positive airway pressure for treatment of positional obstructive sleep apnea. *J Clin Sleep Med* 2019; 15: 947–956.

82 Ravesloot MJL, White D, Heinzer R, *et al.* Efficacy of the new generation of devices for positional therapy for patients with positional obstructive sleep apnea: a systematic review of the literature and meta-analysis. *J Clin Sleep Med* 2017; 13: 813–824.

83 Srijithesh PR, Aghoram R, Goel A, *et al.* Positional therapy for obstructive sleep apnoea. *Cochrane Database Syst Rev* 2019; 5: CD010990.

84 Joosten SA, Edwards BA, Wellman A, *et al.* The effect of body position on physiological factors that contribute to obstructive sleep apnea. *Sleep* 2015; 38: 1469–1478.

85 Joosten SA, O'Driscoll DM, Berger PJ, *et al.* Supine position related obstructive sleep apnea in adults: pathogenesis and treatment. *Sleep Med Rev* 2014; 18: 7–17.

86 Eckert DJ. Phenotypic approaches to positional therapy for obstructive sleep apnoea. *Sleep Med Rev* 2018; 37: 175–176.

87 Bray GA, Heisel WE, Afshin A, *et al.* The science of obesity management: an Endocrine Society scientific statement. *Endocr Rev* 2018; 39: 79–132.

88 Blackman A, Foster GD, Zammit G, *et al.* Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. *Int J Obes* 2016; 40: 1310–1319.

89 Winslow DH, Bowden CH, DiDonato KP, *et al.* A randomized, double-blind, placebo-controlled study of an oral, extended-release formulation of phentermine/topiramate for the treatment of obstructive sleep apnea in obese adults. *Sleep* 2012; 35: 1529–1539.

90 Hudgel DW, Patel SR, Ahasic AM, *et al.* The role of weight management in the treatment of adult obstructive sleep apnea. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med* 2018; 198: e70–e87.

91 Fiori CZ, Martinez D, Montanari CC, *et al.* Diuretic or sodium-restricted diet for obstructive sleep apnea – a randomized trial. *Sleep* 2018; 41: zsy016.

92 Bucca CB, Brussino L, Battisti A, *et al.* Diuretics in obstructive sleep apnea with diastolic heart failure. *Chest* 2007; 132: 440–446.

93 Gaddam K, Pimenta E, Thomas SJ, *et al.* Spironolactone reduces severity of obstructive sleep apnoea in patients with resistant hypertension: a preliminary report. *J Hum Hypertens* 2010; 24: 532–537.

94 Kasai T, Bradley TD, Friedman O, *et al.* Effect of intensified diuretic therapy on overnight rostral fluid shift and obstructive sleep apnoea in patients with uncontrolled hypertension. *J Hypertens* 2014; 32: 673–680.

95 Aishah A, Eckert DJ. Phenotypic approach to pharmacotherapy in the management of obstructive sleep apnoea. *Curr Opin Pulm Med* 2019; 25: 594–601.

96 Horner RL, Grace KP, Wellman A. A resource of potential drug targets and strategic decision-making for obstructive sleep apnoea pharmacotherapy. *Respirology* 2017; 22: 861–873.

97 Gaisl T, Haile SR, Thiel S, *et al.* Efficacy of pharmacotherapy for OSA in adults: a systematic review and network meta-analysis. *Sleep Med Rev* 2019; 46: 74–86.

98 Taranto-Montemurro L, Messineo L, Wellman A. Targeting endotypic traits with medications for the pharmacological treatment of obstructive sleep apnea. A review of the current literature. *J Clin Med* 2019; 8: 1846.

99 Nicholas CL, Jordan AS, Heckel L, *et al.* Discharge patterns of human tensor palatini motor units during sleep onset. *Sleep* 2012; 35: 699–707.

100 Wilkinson V, Malhotra A, Nicholas CL, *et al.* Discharge patterns of human genioglossus motor units during sleep onset. *Sleep* 2008; 31: 525–533.

101 Carberry JC, Jordan AS, White DP, *et al.* Upper airway collapsibility (P_{crit}) and pharyngeal dilator muscle activity are sleep stage dependent. *Sleep* 2016; 39: 511–521.

102 Eckert DJ, Malhotra A, Lo YL, *et al.* The influence of obstructive sleep apnea and gender on genioglossus activity during rapid eye movement sleep. *Chest* 2009; 135: 957–964.

103 Carley DW, Radulovacki M. Pharmacology of vagal afferent influences on disordered breathing during sleep. *Respir Physiol Neurobiol* 2008; 164: 197–203.

104 Chan E, Steenland HW, Liu H, *et al.* Endogenous excitatory drive modulating respiratory muscle activity across sleep-wake states. *Am J Respir Crit Care Med* 2006; 174: 1264–1273.

105 Fenik VB, Davies RO, Kubin L. REM sleep-like atonia of hypoglossal (XII) motoneurons is caused by loss of noradrenergic and serotonergic inputs. *Am J Respir Crit Care Med* 2005; 172: 1322–1330.

106 Sood S, Morrison JL, Liu H, *et al.* Role of endogenous serotonin in modulating genioglossus muscle activity in awake and sleeping rats. *Am J Respir Crit Care Med* 2005; 172: 1338–1347.

107 Burgess C, Lai D, Siegel J, *et al.* An endogenous glutamatergic drive onto somatic motoneurons contributes to the stereotypical pattern of muscle tone across the sleep-wake cycle. *J Neurosci* 2008; 28: 4649–4660.

108 Grace KP, Hughes SW, Horner RL. Identification of the mechanism mediating genioglossus muscle suppression in REM sleep. *Am J Respir Crit Care Med* 2013; 187: 311–319.

109 Prasad B, Radulovacki MG, Carley DW. Proof of concept trial of dronabinol in obstructive sleep apnea. *Front Psychiatry* 2013; 4: 1.

110 Carley DW, Prasad B, Reid KJ, *et al.* Pharmacotherapy of apnea by cannabimimetic enhancement, the PACE clinical trial: effects of dronabinol in obstructive sleep apnea. *Sleep* 2018; 41: zsx184.

111 Kraiczi H, Hedner J, Dahlöf P, *et al.* Effect of serotonin uptake inhibition on breathing during sleep and daytime symptoms in obstructive sleep apnea. *Sleep* 1999; 22: 61–67.

112 Hanzel DA, Proia NG, Hudgel DW. Response of obstructive sleep apnea to fluoxetine and protriptyline. *Chest* 1991; 100: 416–421.

113 Carley DW, Olopade C, Ruigt GS, *et al.* Efficacy of mirtazapine in obstructive sleep apnea syndrome. *Sleep* 2007; 30: 35–41.

114 Marshall NS, Yee BJ, Desai AV, *et al.* Two randomized placebo-controlled trials to evaluate the efficacy and tolerability of mirtazapine for the treatment of obstructive sleep apnea. *Sleep* 2008; 31: 824–831.

115 Taranto-Montemurro L, Edwards BA, Sands SA, *et al.* Desipramine increases genioglossus activity and reduces upper airway collapsibility during non-REM sleep in healthy subjects. *Am J Respir Crit Care Med* 2016; 194: 878–885.

116 Taranto-Montemurro L, Sands SA, Edwards BA, *et al.* Desipramine improves upper airway collapsibility and reduces OSA severity in patients with minimal muscle compensation. *Eur Respir J* 2016; 48: 1340–1350.

117 Taranto-Montemurro L, Messineo L, Azarbarzin A, *et al.* Effects of the combination of atomoxetine and oxybutynin on OSA endotypic traits. *Chest* 2020; 157: 1626–1636.

118 Aishah A, Lim R, Sands SA, *et al.* Different antimuscarinics when combined with atomoxetine have differential effects on obstructive sleep apnea severity. *J Appl Physiol* 2021; 130: 1373–1382.

119 Lim R, Carberry JC, Wellman A, *et al.* Reboxetine and hyoscine butylbromide improve upper airway function during nonrapid eye movement and suppress rapid eye movement sleep in healthy individuals. *Sleep* 2019; 42: zsy261.

120 Lim R, Messineo L, Grunstein RR, *et al.* The noradrenergic agent reboxetine plus the antimuscarinic hyoscine butylbromide reduces sleep apnoea severity: a double-blind, placebo-controlled, randomised crossover trial. *J Physiol* 2021; 599: 4183–4195.

121 Wirth KJ, Steinmeyer K, Ruetten H. Sensitization of upper airway mechanoreceptors as a new pharmacologic principle to treat obstructive sleep apnea: investigations with AVE0118 in anesthetized pigs. *Sleep* 2013; 36: 699–708.

122 Gaisl T, Turnbull CD, Weimann G, *et al.* BAY 2253651 for the treatment of obstructive sleep apnea a multi-center, double-blind, randomized controlled trial (SANDMAN). *Eur Respir J* 2021; 58: 2101937.

123 Horton GA, Fraigne JJ, Torontali ZA, *et al.* Activation of the hypoglossal to tongue musculature motor pathway by remote control. *Sci Rep* 2017; 7: 45860.

124 Fleury Curado T, Fishbein K, Pho H, *et al.* Chemogenetic stimulation of the hypoglossal neurons improves upper airway patency. *Sci Rep* 2017; 7: 44392.
125 Fleury Curado T, Pho H, Freire C, *et al.* Designer receptors exclusively activated by designer drugs approach to treatment of sleep-disordered breathing. *Am J Respir Crit Care Med* 2021; 203: 102–110.
126 Wellman A, Jordan AS, Malhotra A, *et al.* Ventilatory control and airway anatomy in obstructive sleep apnea. *Am J Respir Crit Care Med* 2004; 170: 1225–1232.
127 White DP, Zwillich CW, Pickett CK, *et al.* Central sleep apnea: improvement with acetazolamide therapy. *Arch Intern Med* 1982; 142: 1816–1819.
128 Nakayama H, Smith CA, Rodman JR, *et al.* Effect of ventilatory drive on carbon dioxide sensitivity below eupnea during sleep. *Am J Respir Crit Care Med* 2002; 165: 1251–1260.
129 Ginter G, Sankari A, Eshraghi M, *et al.* Effect of acetazolamide on susceptibility to central sleep apnea in chronic spinal cord injury. *J Appl Physiol* 2020; 128: 960–966.
130 Fan JL, Burgess KR, Thomas KN, *et al.* Effects of acetazolamide on cerebrovascular function and breathing stability at 5050 m. *J Physiol* 2012; 590: 1213–1225.
131 Liu HM, Chiang IJ, Kuo KN, *et al.* The effect of acetazolamide on sleep apnea at high altitude: a systematic review and meta-analysis. *Ther Adv Respir Dis* 2017; 11: 20–29.
132 Eskandari D, Zou D, Karimi M, *et al.* Zonisamide reduces obstructive sleep apnoea: a randomised placebo-controlled study. *Eur Respir J* 2014; 44: 140–149.
133 Wellman A, Malhotra A, Jordan AS, *et al.* Effect of oxygen in obstructive sleep apnea: role of loop gain. *Respir Physiol Neurobiol* 2008; 162: 144–151.
134 Edwards BA, Sands SA, Owens RL, *et al.* Effects of hyperoxia and hypoxia on the physiological traits responsible for obstructive sleep apnoea. *J Physiol* 2014; 592: 4523–4535.
135 Wang D, Wong KK, Rowsell L, *et al.* Predicting response to oxygen therapy in obstructive sleep apnoea patients using a 10-minute daytime test. *Eur Respir J* 2018; 51: 1701587.
136 Eckert DJ, Younes MK. Arousal from sleep: implications for obstructive sleep apnea pathogenesis and treatment. *J Appl Physiol* 2014; 116: 302–313.
137 Carter SG, Eckert DJ. Effects of hypnotics on obstructive sleep apnea endotypes and severity: novel insights into pathophysiology and treatment. *Sleep Med Rev* 2021; 58: 101492.
138 Berry RB, Kouchi K, Bower J, *et al.* Triazolam in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 1995; 151: 450–454.
139 Carberry JC, Fisher LP, Grunstein RR, *et al.* Role of common hypnotics on the phenotypic causes of obstructive sleep apnoea: paradoxical effects of zolpidem. *Eur Respir J* 2017; 50: 1701344.
140 Carter SG, Berger MS, Carberry JC, *et al.* Zopiclone increases the arousal threshold without impairing genioglossus activity in obstructive sleep apnea. *Sleep* 2016; 39: 757–766.
141 Eckert DJ, Malhotra A, Wellman A, *et al.* Trazodone increases the respiratory arousal threshold in patients with obstructive sleep apnea and a low arousal threshold. *Sleep* 2014; 37: 811–819.
142 Messineo L, Eckert DJ, Lim R, *et al.* Zolpidem increases sleep efficiency and the respiratory arousal threshold without changing sleep apnoea severity and pharyngeal muscle activity. *J Physiol* 2020; 598: 4681–4692.
143 Smales ET, Edwards BA, Deyoung PN, *et al.* Trazodone effects on obstructive sleep apnea and non-REM arousal threshold. *Ann Am Thorac Soc* 2015; 12: 758–764.
144 Sweetman A, Lack L, McEvoy RD, *et al.* Cognitive behavioural therapy for insomnia reduces sleep apnoea severity: a randomised controlled trial. *ERJ Open Res* 2020; 6: 00161-2020.
145 Jordan AS, O'Donoghue FJ, Cori JM, *et al.* Physiology of arousal in obstructive sleep apnea and potential impacts for sedative treatment. *Am J Respir Crit Care Med* 2017; 196: 814–821.
146 Messineo L, Eckert DJ, Lim R, *et al.* Zolpidem increases sleep efficiency and the respiratory arousal threshold without changing sleep apnoea severity and pharyngeal muscle activity. *J Physiol* 2020; 598: 4681–4692.
147 Carter SG, Carberry JC, Cho G, *et al.* Effect of 1 month of zopiclone on obstructive sleep apnoea severity and symptoms: a randomised controlled trial. *Eur Respir J* 2018; 52: 1800149.
148 Carter SG, Carberry JC, Grunstein RR, *et al.* Randomized trial on the effects of high-dose zopiclone on OSA severity, upper airway physiology, and alertness. *Chest* 2020; 158: 374–385.
149 Hajak G, Müller WE, Wittchen HU, *et al.* Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. *Addiction* 2003; 98: 1371–1378.
150 Jaffer KY, Chang T, Vanle B, *et al.* Trazodone for insomnia: a systematic review. *Innov Clin Neurosci* 2017; 14: 24–34.
151 MacKay S, Carney AS, Catcheside PG, *et al.* Effect of multilevel upper airway surgery *vs* medical management on the apnea-hypopnea index and patient-reported daytime sleepiness among patients with moderate or severe obstructive sleep apnea: the SAMS randomized clinical trial. *JAMA* 2020; 324: 1168–1179.

152 Arterburn DE, Telem DA, Kushner RF, *et al.* Benefits and risks of bariatric surgery in adults: a review. *JAMA* 2020; 324: 879–887.
153 Kay A, Trinder J, Bowes G, *et al.* Changes in airway resistance during sleep onset. *J Appl Physiol* 1994; 76: 1600–1607.
154 Mu L, Sanders I. Human tongue neuroanatomy: nerve supply and motor endplates. *Clin Anat* 2010; 23: 777–791.
155 Eisele DW, Smith PL, Alam DS, *et al.* Direct hypoglossal nerve stimulation in obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg* 1997; 123: 57–61.
156 Schwartz AR, Bennett ML, Smith PL, *et al.* Therapeutic electrical stimulation of the hypoglossal nerve in obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg* 2001; 127: 1216–1223.
157 Eastwood PR, Barnes M, Walsh JH, *et al.* Treating obstructive sleep apnea with hypoglossal nerve stimulation. *Sleep* 2011; 34: 1479–1486.
158 Strollo PJ Jr, Soose RJ, Maurer JT, *et al.* Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med* 2014; 370: 139–149.
159 Mwenge GB, Rombaux P, Dury M, *et al.* Targeted hypoglossal neurostimulation for obstructive sleep apnoea: a 1-year pilot study. *Eur Respir J* 2013; 41: 360–367.
160 Woodson BT, Strohl KP, Soose RJ, *et al.* Upper airway stimulation for obstructive sleep apnea: 5-year outcomes. *Otolaryngol Head Neck Surg* 2018; 159: 194–202.
161 Steffen A, Sommer UJ, Maurer JT, *et al.* Long-term follow-up of the German post-market study for upper airway stimulation for obstructive sleep apnea. *Sleep Breath* 2020; 24: 979–984.
162 Baptista PM, Costantino A, Moffa A, *et al.* Hypoglossal nerve stimulation in the treatment of obstructive sleep apnea: patient selection and new perspectives. *Nat Sci Sleep* 2020; 12: 151–159.
163 Pawlak D, Bohorquez D, König IR, *et al.* Effect of electrode configuration and impulse strength on airway patency in neurostimulation for obstructive sleep apnea. *Laryngoscope* 2021; 131: 2148–2153.
164 Heiser C, Steffen A, Boon M, *et al.* Post-approval upper airway stimulation predictors of treatment effectiveness in the ADHERE registry. *Eur Respir J* 2019; 53: 1801405.
165 Eastwood PR, Barnes M, MacKay SG, *et al.* Bilateral hypoglossal nerve stimulation for treatment of adult obstructive sleep apnoea. *Eur Respir J* 2020; 55: 1901320.
166 Lewis R, Pételle B, Campbell MC, *et al.* Implantation of the Nyxoah bilateral hypoglossal nerve stimulator for obstructive sleep apnea. *Laryngoscope Investig Otolaryngol* 2019; 4: 703–707.
167 Mayne RJ, Cochrane NJ, Cai F, *et al. In-vitro* study of the effect of casein phosphopeptide amorphous calcium fluoride phosphate on iatrogenic damage to enamel during orthodontic adhesive removal. *Am J Orthod Dentofacial Orthop* 2011; 139: e543–e551.
168 Vanderveken OM, Maurer JT, Hohenhorst W, *et al.* Evaluation of drug-induced sleep endoscopy as a patient selection tool for implanted upper airway stimulation for obstructive sleep apnea. *J Clin Sleep Med* 2013; 9: 433–438.
169 Steffen A. What makes the responder to upper airway stimulation in obstructive sleep apnea patients with positive airway pressure failure? *J Thorac Dis* 2018; 10: Suppl. 26, S3131–S3134.
170 Thaler E, Schwab R, Maurer J, *et al.* Results of the ADHERE upper airway stimulation registry and predictors of therapy efficacy. *Laryngoscope* 2020; 130: 1333–1338.
171 Seay EG, Keenan BT, Schwartz AR, *et al.* Evaluation of therapeutic positive airway pressure as a hypoglossal nerve stimulation predictor in patients with obstructive sleep apnea. *JAMA Otolaryngol Head Neck Surg* 2020; 146: 691–698.
172 Lee CH, Seay EG, Reese JW, *et al.* Clinical radiographic predictors of response to hypoglossal nerve stimulation for obstructive sleep apnea. *Otolaryngol Head Neck Surg* 2021; 164: 1122–1127.
173 Yu JL, Younes M. Relation between arousability and outcome of upper airway stimulation in the Stimulation for Apnea Reduction (STAR) trial. *J Clin Sleep Med* 2021; 17: 797–801.
174 Byun YJ, Yan F, Nguyen SA, *et al.* Transcutaneous electrical stimulation therapy in obstructive sleep apnea: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg* 2020; 163: 645–653.
175 Baptista PM, Martínez Ruiz de Apodaca P, Carrasco M, *et al.* Daytime neuromuscular electrical therapy of tongue muscles in improving snoring in individuals with primary snoring and mild obstructive sleep apnea. *J Clin Med* 2021; 10: 1883.
176 Vena D, Lyons O, Fernie GR, *et al.* Effect of calf muscle electrical stimulation on rostral fluid shift, snoring and obstructive sleep apnea. *Sleep Med* 2019; 57: 36–42.
177 Kent DT, Zealear D, Schwartz AR. Ansa cervicalis and hypoglossal nerve stimulation in a patient with obstructive sleep apnea. *Otolaryngol Head Neck Surg* 2021; 65: 602–604.
178 Guimarães KC, Drager LF, Genta PR, *et al.* Effects of oropharyngeal exercises on patients with moderate obstructive sleep apnea syndrome. *Am J Respir Crit Care Med* 2009; 179: 962–966.
179 de Felício CM, da Silva Dias FV, Trawitzki LVV. Obstructive sleep apnea: focus on myofunctional therapy. *Nat Sci Sleep* 2018; 10: 271–286.

180 Tong BK, Tran C, Ricciardiello A, *et al.* CPAP combined with oral appliance therapy reduces CPAP requirements and pharyngeal pressure swings in obstructive sleep apnea. *J Appl Physiol* 2020; 129: 1085–1091.

181 Liu HW, Chen YJ, Lai YC, *et al.* Combining MAD and CPAP as an effective strategy for treating patients with severe sleep apnea intolerant to high-pressure PAP and unresponsive to MAD. *PLoS One* 2017; 12: e0187032.

182 de Vries GE, Doff MHJ, Hoekema A, *et al.* Continuous positive airway pressure and oral appliance hybrid therapy in obstructive sleep apnea: patient comfort, compliance, and preference: a pilot study. *J Dental Sleep Med* 2016; 3: 5–10.

183 Dieltjens M, Vroegop AV, Verbruggen AE, *et al.* A promising concept of combination therapy for positional obstructive sleep apnea. *Sleep Breath* 2015; 19: 637–644.

184 Benoist LBL, Verhagen M, Torensma B, *et al.* Positional therapy in patients with residual positional obstructive sleep apnea after upper airway surgery. *Sleep Breath* 2017; 21: 279–288.

185 Lai V, Tong BK, Tran C, *et al.* Combination therapy with mandibular advancement and expiratory positive airway pressure valves reduces obstructive sleep apnea severity. *Sleep* 2019; 42: zsz119.

186 Owens RL, Edwards BA, Eckert DJ, *et al.* An integrative model of physiological traits can be used to predict obstructive sleep apnea and response to non positive airway pressure therapy. *Sleep* 2015; 38: 961–970.

187 Drager LF, Brunoni AR, Jenner R, *et al.* Effects of CPAP on body weight in patients with obstructive sleep apnoea: a meta-analysis of randomised trials. *Thorax* 2015; 70: 258–264.

188 Chen B, Drager LF, Peker Y, *et al.* Effect of continuous positive airway pressure on weight and local adiposity in adults with obstructive sleep apnea: a meta-analysis. *Ann Am Thorac Soc* 2021; 18: 1717–1727.

189 Edwards BA, Bristow C, O'Driscoll DM, *et al.* Assessing the impact of diet, exercise and the combination of the two as a treatment for OSA: a systematic review and meta-analysis. *Respirology* 2019; 24: 740–751.

190 Foster GD, Borradaile KE, Sanders MH, *et al.* A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. *Arch Intern Med* 2009; 169: 1619–1626.

191 Kuna ST, Reboussin DM, Strotmeyer ES, *et al.* Effects of weight loss on obstructive sleep apnea severity. ten-year results of the Sleep AHEAD study. *Am J Respir Crit Care Med* 2021; 203: 221–229.

192 Ashrafian H, le Roux CW, Rowland SP, *et al.* Metabolic surgery and obstructive sleep apnoea: the protective effects of bariatric procedures. *Thorax* 2012; 67: 442–449.

193 Chirinos JA, Gurubhagavatula I, Teff K, *et al.* CPAP, weight loss, or both for obstructive sleep apnea. *N Engl J Med* 2014; 370: 2265–2275.

194 Mendelson M, Marillier M, Bailly S, *et al.* Maximal exercise capacity in patients with obstructive sleep apnoea syndrome: a systematic review and meta-analysis. *Eur Respir J* 2018; 51: 1702697.

195 Mendelson M, Bailly S, Marillier M, *et al.* Obstructive sleep apnea syndrome, objectively measured physical activity and exercise training interventions: a systematic review and meta-analysis. *Front Neurol* 2018; 9: 73.

196 Vivodtzev I, Tamisier R, Croteau M, *et al.* Ventilatory support or respiratory muscle training as adjuncts to exercise in obese CPAP-treated patients with obstructive sleep apnoea: a randomised controlled trial. *Thorax* 2018; 730: 634–643.

197 Pépin JL, Viot-Blanc V, Escourrou P, *et al.* Prevalence of residual excessive sleepiness in CPAP-treated sleep apnoea patients: the French multicentre study. *Eur Respir J* 2009; 33: 1062–1067.

198 Gasa M, Tamisier R, Launois SH, *et al.* Residual sleepiness in sleep apnea patients treated by continuous positive airway pressure. *J Sleep Res* 2013; 22: 389–397.

199 Schweitzer PK, Rosenberg R, Zammit GK, *et al.* Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3). A randomized controlled trial. *Am J Respir Crit Care Med* 2019; 199: 1421–1431.

200 Malhotra A, Shapiro C, Pepin JL, *et al.* Long-term study of the safety and maintenance of efficacy of solriamfetol (JZP-110) in the treatment of excessive sleepiness in participants with narcolepsy or obstructive sleep apnea. *Sleep* 2020; 43: zsz220.

201 Pépin JL, Georgiev O, Tiholov R, *et al.* Pitolisant for residual excessive daytime sleepiness in OSA patients adhering to CPAP: a randomized trial. *Chest* 2021; 159: 1598–1609.

202 Dauvilliers Y, Verbraecken J, Partinen M, *et al.* Pitolisant for daytime sleepiness in patients with obstructive sleep apnea who refuse continuous positive airway pressure treatment. A Randomized Trial. *Am J Respir Crit Care Med* 2020; 201: 1135–1145.

203 Pépin JL, Jullian-Desayes I, Sapène M, *et al.* Multimodal remote monitoring of high cardiovascular risk patients with OSA initiating CPAP: a randomized trial. *Chest* 2019; 155: 730–739.