Current and novel treatment options for obstructive sleep apnoea

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Shareable abstract (@ERSpublications)
The analysis of individual pathophysiological composition opens new directions towards personalised treatment of OSA, focusing not only on pharyngeal dilation, but also on technical or pharmaceutical interventions on muscle function or breathing regulation https://bit.ly/3sayhkd

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Abstract

Obstructive sleep apnoea is a challenging medical problem due to its prevalence, its impact on quality of life and performance in school and professionally, the implications for risk of accidents, and comorbidities and mortality. Current research has carved out a broad spectrum of clinical phenotypes and defined major pathophysiological components. These findings point to the concept of personalised therapy, oriented on both the distinct clinical presentation and the most relevant pathophysiology in the individual patient. This leads to questions of whether sufficient therapeutic options other than positive airway pressure (PAP) alone are available, for which patients they may be useful, if there are specific indications for single or combined treatment, and whether there is solid scientific evidence for recommendations. This review describes our knowledge on PAP and non-PAP therapies to address upper airway collapsibility, muscle responsiveness, arousability and respiratory drive. The spectrum is broad and heterogeneous, including technical and pharmaceutical options already in clinical use or at an advanced experimental stage. Although there is an obvious need for more research on single or combined therapies, the available data demonstrate the variety of effective options, which should replace the unidirectional focus on PAP therapy.

Phenotyping, multifaceted pathophysiology and a concept of individualised therapy

Since the 1980s, three core principles have described respiratory sleep medicine: 1) the clinical pattern of male obese patients who snore and experience excessive daytime sleepiness (EDS); 2) the definition and grading of obstructive sleep apnoea (OSA) based on the apnoea–hypopnoea index (AHI); and 3) the predominant treatment with positive airway pressure (PAP) [1]. Nowadays, OSA is considered a heterogeneous disease, determined by various symptoms, anthropometric dispositions, polysomnographic patterns, long-term outcomes and comorbidities (figure 1) [2, 3]. The AHI correlates only slightly with symptoms and adverse health outcomes and there is an urgent need for alternative outcome-related biomarkers [4]. Although PAP remains the backbone of treatment as it improves symptoms, driving performance and cardiovascular outcomes, it is limited by variable or long-term adherence, insufficient response in subgroups and missing proof of survival benefits [5–7]. These aspects require the development of tailored treatment based on patient-reported outcome parameters, individual risk and availability of therapeutic options [8].

The identification of OSA phenotypes may guide this approach [9–13]. Recent scientific progress has facilitated steps towards personalised medicine, although such an approach is not aetiologically based. The

FIGURE 1 Current considerations on the heterogeneity of obstructive sleep apnoea (OSA). Patients commonly present with breathing disturbances during sleep, associated with upper airway obstruction. However, the various OSA phenotypes can be differentiated based on clinical symptoms, polysomnographic findings, underlying pathophysiology, measurable biomarkers, anthropometric parameters, comorbidities and outcome. Each of these components includes various characteristics such as sleepiness, insomnia or minimal symptoms within symptoms, or rapid eye movement (REM)- or positional OSA within polysomnography. PROMs: patient-reported outcome measures.

evolving understanding of the pathophysiology represents another crucial step to individualised therapy, based on four essential traits: upper airway obstruction, responsiveness of the upper airway muscles, arousability and breathing regulation [14–19]. These components contribute to various degrees in individual patients and may differ with sleep stages or body position. There is growing evidence applying these experimental findings and theoretical considerations to standard clinical diagnostics and therapeutic decision making [20, 21].

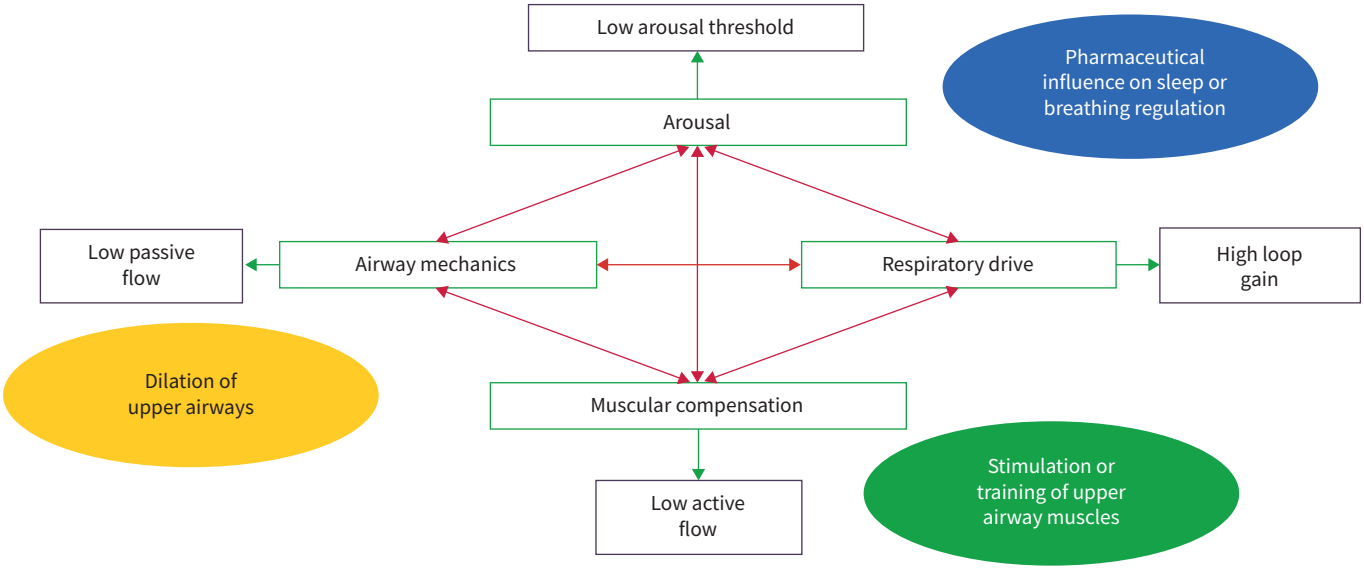

FIGURE 2 Pathophysiological concept and therapeutic traits. The concept as described by Wellman and Eckert and co-workers [14–16] identified four major pathophysiological components. Mechanical obstruction of the upper airways, the muscular response of the upper airway muscles, the respiratory drive and the brain reactivity (arousability). This offers new therapeutic options, addressing each of these components in an individual patient.

The aim of this review is to present current knowledge and perspectives on the treatment of OSA. It focuses on an individualised treatment approach, based on specific phenotypes, and follows the distinct pathophysiological traits (figure 2). As these concepts represent a highly dynamic and progressing development, the components are not exclusive, may partially overlap and can be combined. Importantly, they highlight that the future of OSA treatment must not follow single biomarkers, but should consider a comprehensive interpretation of symptoms and decide on the best possible therapeutic options.

Mechanical obstruction

Weight reduction

Obesity is one of the most important risk factors for the development of OSA. Approximately 70% of OSA patients are obese (body mass index (BMI) ⩾30 kg·m^{-2}) [22, 23]. In morbidly obese patients (BMI ⩾40 kg·m^{-2}), the prevalence of OSA varies between 40% and 90% [22, 23]. The severity level of OSA is also more pronounced than in less obese patients. Excess adipose tissue surrounding the upper airway can cause airway narrowing and increase the propensity for collapse during sleep [24]. Central obesity decreases lung volume and tracheal traction forces on the upper airway, and also increases upper airway collapsibility during sleep [25, 26]. Moreover, an increased deposition of fat tissue within the genioglossus muscle has been shown. Relative weight changes in overweight patients with milder OSA have been reported in epidemiological studies [27]. In a clinical cohort, Georgoulis *et al*. [28] found that even a <5% weight loss can reduce respiratory events, but ⩾5% and ideally ⩾10% weight loss was necessary for reducing the prevalence of severe OSA. Weight loss is not only associated with a decrease in AHI, but also with an improvement of hypoxaemia [29]. Therefore, weight reduction can be an important strategy in the management of OSA, alone or in combination with conventional therapy [30, 31] (figure 3). Diet-only interventions reduce BMI by the greatest amount (−4 kg·m^{-2}), while minimal, nonsignificant reductions with exercise-only interventions (aerobic training, interval training, muscle training) have been reported (−0.5 kg·m^{-2}) [32]. Combined interventions to reduce BMI could be beneficial (−2 kg·m^{-2}). One potential reason explaining why diet-only interventions demonstrate greater reductions in BMI is that they usually apply very low-calorie diets, compared to the combined intervention studies, in which more modest reductions in daily caloric intake are employed [33]. In order to achieve long-term benefits and avoid weight regain, lifestyle modification programmes are highly recommended [34]. Finally, weight loss not only reduces OSA severity, but also alters cardiometabolic comorbidities, with improvement in hypertension, lipids and glycaemic control [35–37].

Pharmacological interventions to reduce obesity have the potential to reduce upper airway collapsibility, and hence OSA severity [38, 39]. Limited studies have been performed in OSA patients with phentermine 15 mg plus topiramate 92 mg [38], orlistat (a gastrointestinal lipase inhibitor that reduces the intestinal

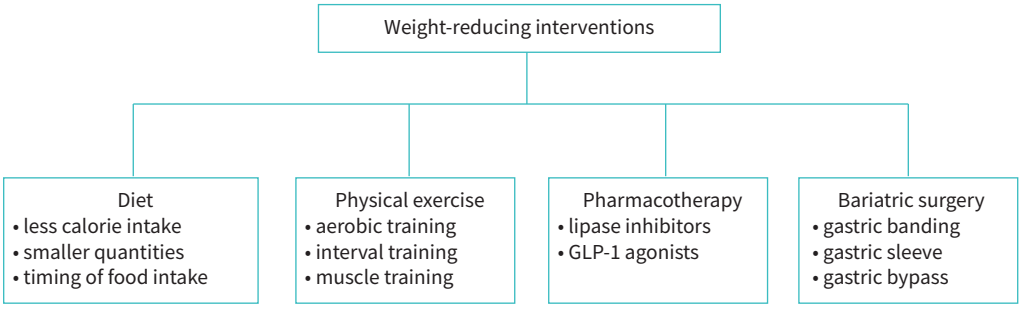

FIGURE 3 Weight-reduction interventions. GLP: glucagon-like peptide.

absorption of fat) [40], liraglutide (a glucagon-like peptide 1 (GLP1) agonist) [39], metformin added to liraglutide [41], and empagliflozin (an inhibitor of the sodium-glucose co-transporter 2) [42]. This approach results in a 10.2% decrease in weight compared to 4.3% in placebo (or an AHI reduction of 31.5 events·h^{-1} *versus* 16.6 events·h^{-1}) with phentermine/topiramate [38]; a weight loss of −5.7% *versus* −1.6% (or −12.2 *versus* −6.1 events·h^{-1}) with liraglutide *versus* placebo [39]; −3.5 kg with orlistat [40]; −7.6 kg (9.2%) with liraglutide, but −9.2 kg if combined with metformin (*versus* −7.4 kg without) [41]; while empagliflozin results in a modest, but larger, effect in OSA *versus* no OSA (−2.9 kg *versus* −1.9 kg) [42]. Other GLP1 agonists are available, but have not yet been studied in the context of OSA [43, 44].

Currently, there is a growing popularity of bariatric surgery as a permanent remedy. The aims of bariatric surgery are to reduce caloric intake, to modify the hormonal milieu and to alter nutritional absorption. Procedures can be classified in restrictive (gastric banding, gastric balloon and sleeve gastroplasty) and malabsorptive interventions (Scopinaro technique) or a combination of both (Roux-en-Y gastric bypass). Overall, gastric bypass surgery is more efficacious than gastric banding or gastroplasty, but with higher complication rates. In symptomatic cases, patients may be more willing to accept surgical intervention and related adverse events. In addition, variability could be introduced by age, occupation, severity of the underlying condition and comorbidities. OSA remission can be obtained in the majority (59.2%) of patients with obesity [45]. The nadir of weight loss reported following bariatric surgery occurs after 1 year, and subsequently weight is regained [46]. OSA can relapse, even if weight loss is maintained. Therefore, regular follow-up is required. Recently, international scientific societies (European Respiratory Society (ERS), American Thoracic Society) have recommended gastric bypass surgery in obese OSA patients [31, 47]. Compliance to active lifestyle and healthy food intake in this context is paramount. Finally, the consumption of food during the circadian evening and/or night plays an important role in body composition [48]. This has yet to be explored in the context of OSA, but opens new perspectives.

Positive airway pressure treatment

PAP is the first-line treatment for OSA [49], targeting on the most relevant pathophysiological trait, the compromised upper airway anatomy. The mechanism of PAP involves maintenance of a positive pharyngeal transmural pressure, so that the intraluminal pressure exceeds the surrounding pressure [49]. This therapy is indicated based on the severity of OSA, the clinical and pathophysiological phenotypes as well as the presence of cardiometabolic comorbidities [2].

PAP is considered the most effective treatment to reduce the AHI and to improve patient-reported outcomes, including daytime sleepiness, quality of life, cognitive function, depression and the rate of motor vehicle crashes [50, 51]. According to early observational data, long-term PAP usage improves blood pressure and reduces the risk of stroke and other cardiovascular events [52, 53]. In addition, several randomised controlled trials (RCTs) and meta-analyses have consistently demonstrated a clinically meaningful reduction in blood pressure, particularly in uncontrolled hypertension [54, 55]. In contrast, recent RCTs have failed to demonstrate a reduction in incident major cardiovascular outcome [56, 57]. This lack of evidence should be interpreted with caution, due to important limitations including low PAP adherence, sample selection bias, short follow-up time and use of combined cardiovascular outcome. Taking these limitations into account, new prospective studies should include different phenotypes integrating symptomatology and comorbidities as proposed by the Baveno classification [5, 56, 58].

Poor PAP adherence remains a challenge for clinicians. It varies substantially: between 29% and 83% of patients use the devices for <4 h per night [59]. Despite this, the objective adherence, which is now

available through telemonitoring of data from PAP devices [60] seems to exceed objectively assessed adherence of medications used for other respiratory diseases [61, 62]. It depends mainly on recognition of the relevance of the disease, awareness of the treatment effect on symptoms, social support, and acceptance during the initial treatment period. Nonadherence is of crucial relevance, especially in minimally symptomatic patients, in whom evidence of the effects of PAP therapy is less definitive [63]. Recognition of nonadherence is important, because there are a variety of educational, behavioural and troubleshooting interventions, including optimal mask fitting and use of telemedicine [64], that may allow a more personalised follow-up.

The most common modes of PAP administration include continuous positive airway pressure (CPAP), which delivers PAP at a constant level throughout the respiratory cycle; autotitrating positive airway pressure (APAP), which increases or decreases PAP in response to changes of upper airway obstruction; and bilevel positive airway pressure (BPAP). BPAP delivers a pre-set inspiratory positive airway pressure and expiratory positive airway pressure. Earlier studies indicated that CPAP was generally favoured as initial therapy, because it was the most familiar and best studied [65]. However, APAP appears to be as effective as CPAP, with no identified substantial harm, while delivering lower mean pressures [50, 66]. Furthermore, APAP *versus* CPAP had similar effects on adherence and patient-reported outcomes [50]. Some investigators used unattended single-night APAP titration to manage patients with uncomplicated OSA [18]. BPAP also conferred no clinically significant advantage over CPAP, but may be beneficial in patients with comorbidities, high PAP requirements or intolerance to CPAP or APAP [50, 67, 68]. Additional factors contributing to the selection of treatment mode or device may be associated symptoms or comorbid medical conditions, and utility of digital health and access to online data management and patient portals [69].

The heterogeneous response to PAP remains a major issue in long-term treatment and requires continual follow-up to assess efficacy of the therapy, technical problems and residual symptoms. Considering this, the identification of responder phenotypes, showing improvement on the multiple outcomes of OSA, would be particularly helpful, especially for asymptomatic or minimally symptomatic OSA patients.

Mandibular advancement devices

Mandibular advancement device (MAD) therapy is an anatomical intervention, reducing pharyngeal collapsibility in a dose-dependent manner in OSA patients [70]. Responders have a low to moderate pharyngeal collapsibility and no nonanatomical pathophysiological traits of OSA, such as a high loop gain [70–72].

The 2021 ERS guideline compared custom-made, adjustable, dual-block MAD (figure 4) with CPAP in patients with mild to severe OSA, with a dominance of patients within the milder range of severity [47]. It was recommended that CPAP should generally be used, mainly based on the higher decrease of AHI with CPAP over MAD. however, in mild to moderate OSA, these treatments were regarded as equal, since MAD therapy usually resulted in AHI values close to the normal range and had similar impact on EDS as CPAP. In patients with comorbidities and increasing severity of OSA, CPAP should be considered, because of a higher impact on systolic night-time blood pressure in severe OSA.

In studies of MAD, AHI is generally used for inclusion of patients. Some patients are often excluded based on this measure, concomitant diseases or oral health issues. Good responding phenotypes to MAD therapy are characterised by milder severity, younger age, lower BMI and female sex [73]. Two recent studies in more severe OSA patients reported that only CPAP, not MAD, had beneficial effects on night-time blood pressure dipping and variability after 1–2 months treatment [74, 75].

During longer-term MAD treatment, patients might change indications for this therapy. Follow-up of 318 patients after 3–17 years showed that the efficacy of MAD may persist [76–79], although impairment was also described [80–83]. At a 10-year follow-up, both MAD and CPAP were effective in the majority of the continuing patients, although they constituted only one-third of the original sample [81]. Weight increase might be an explanatory factor to a worsened effect of MAD [84]. Bite changes might also introduce a risk of reduced efficacy, if the device is left unadjusted. Stable blood pressure effects from MAD have been reported [76, 85], while a lack of effect on blood pressure from both MAD and CPAP was found in other studies in mild and moderate OSA patients after 1 year [86, 87]. One recent study observed significant reverse left ventricular hypertrophic remodelling after 6 months' successful MAD therapy [88]. Finally, one study found that only CPAP, not MAD, was effective on metabolic outcomes after 1 year's treatment of mild OSA patients [89].

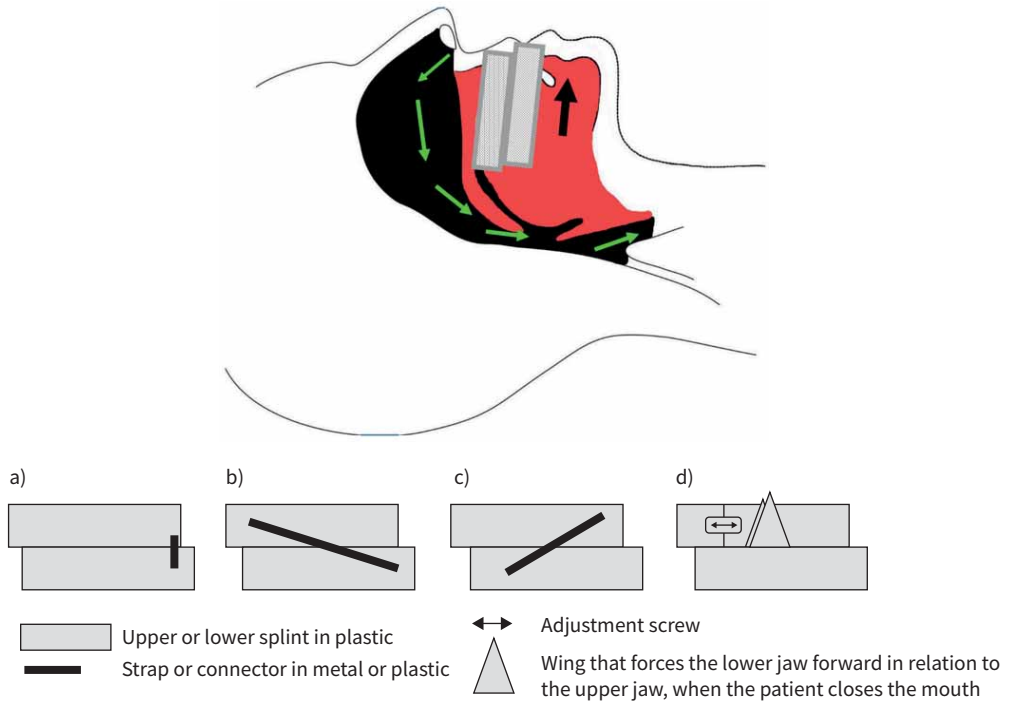

FIGURE 4 Schematic presentation of adjustable, dual-block mandibular advancement devices. The adjustment mechanisms can be located either a) in the midline or b–d) laterally. These mechanisms may allow more or less mouth opening or lateral movements of the lower jaw during sleep.

For the future, it will be important to use new grading systems that consider more aspects of OSA severity than AHI [58] to identify responders to MAD therapy. Furthermore, there is a need for long-term evaluation of beneficial phenotypic and endotypic traits, including the influence of various comorbidities and bite changes on the overall outcome, in order to define more precise indications for MAD in relation to CPAP that is more stable in its mechanism of action.

Positional therapy

Originally, positional OSA (POSA) was suggested for patients with an AHI in the supine posture double or greater than that in the nonsupine postures (supine-predominant OSA) [90]. This definition has been refined, in which the AHI in the nonsupine posture should be at a nonpathological level (AHI <5 events·h^{-1} or <10 events·h^{-1}, described as supine isolated OSA) [91, 92]. Recent studies have provided insight into the mechanisms of action [93]. When OSA patients shift from the supine to lateral position, they experience a significant increase in awake functional residual capacity, passive V'_0 (ventilation off CPAP when the upper airway dilator muscles are quiescent), and active V'_0 (ventilation off CPAP when the muscles are activated), and a significant decrease in critical positive end-expiratory pressure (P_{crit}). The loop gain and arousal threshold are not altered by changes in body position [94]. Moreover, POSA patients have a significantly more favourable ability to stiffen and dilate the airway (upper airway gain) and P_{crit}, which helps to almost completely avert OSA in the lateral position [94]. The folding geometry of the lateral wall is also critically important in determining collapsibility of the airway. When a POSA patient lies in the lateral direction, there is an opening up of the lateral portions of the airway, so that the overall shape of the velopharynx becomes more circular [95] (figure 5). Moreover, the tongue and soft palate now lie perpendicular to the gravitational pull (and now constitute the lateral wall of a 90° rotated airway), resulting in an airway that is less likely to collapse when passive and in the lateral position [96].

Avoidance of supine position should improve the AHI, especially if the nonsupine AHI is low. Positional therapy is not recommended for patients who for any reason (physical disability interfering with the lateral position) cannot avoid the supine posture during sleep. In addition, this therapy is not an optimal solution for POSA patients who continue to snore loudly while sleeping in the lateral postures. Diverse devices have been designed for positional therapy: tennis balls, pillows, bulky backpacks and position alarms [97–99]. The optimal position to achieve ⩾80% reduction in AHI is >30° lateral rotation with >70 mm of

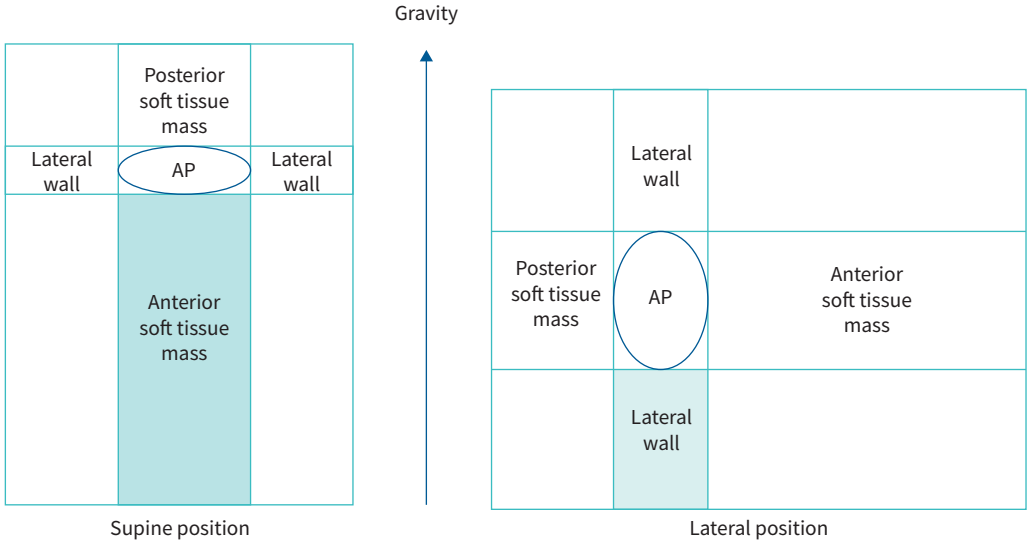

FIGURE 5 Upper airway and geometry in positional obstructive sleep apnoea when in the supine and lateral postures. AP: anteroposterior.

cervical head-tilt support and an elevation underneath the scapula of >20 mm [100]. Although the "tennis-ball" technique effectively reduces the AHI, compliance is hampered by discomfort, resulting in disappointing long-term results [101]. The more recent position alarms attached to either the neck [102], chest [103] or forehead [104] and are less cumbersome. These devices generate fine-tuned vibrational stimuli in a progressive manner, thereby alerting the user to react to the signal and to turn to a nonsupine position. Short- and long-term results of these devices showed a reduction in AHI combined with high compliance rates [99, 105]. However, in real-life registries, <60% of the patients remains adherent, and only 25% are willing to purchase the device, related to poor objective results, intolerance to the vibrations, cost of the device, persistent symptoms or preference for another treatment option [106, 107]. In general, patients expressed a preference for position training *versus* CPAP. However, longer term follow-up is lacking. Not suprisingly, sleeping in an upright position is very effective in reducing the AHI, but has an underestimated value and is not well documented in the literature [108]. It could be considered as a salvage solution in case of device problems, lack of electricity (when travelling in remote areas …) or when conventional treatments fail. Positional therapy can also be used as part of a multimodality therapeutic approach, but evidence is limited [109, 110].

Maxillomandibular advancement

Maxillomandibular advancement (MMA) is skeletal surgery, which has been performed for OSA since the 1980s. It increases both the dimension of the upper airway and the stability of the pharyngeal dilator muscles [111–113]. In the latest ERS guideline on non-PAP therapies, it was recommended that (although acceptability can vary between patients) both MMA and CPAP are good options in adult patients with OSA [47]. Initially, MMA was primarily indicated for overweight, skeletal and dental class II patients with an AHI $\geqslant$30 events·h^{-1} and often after unsuccessful uvulopalatopharyngoplasty and/or mandibular osteotomy/genioglossus advancement with hyoid suspension [114, 115]. The conventional MMA surgical plan was based on two-dimensional cephalometric analyses and cast model surgery. It routinely consisted of a Le Fort I osteotomy of the maxilla and bilateral sagittal split osteotomy of the mandible with a 10 mm advancement of the bimaxillary complex [116].

Presently, MMA selection is more individualised and based on patient phenotyping, taking into account clinical (*e.g.* age, comorbidities, neck circumference, BMI and dentofacial deformity) and polysomnographic evaluation [117, 118]. Complete lateral pharyngeal wall collapse and complete concentric velum collapse in drug-induced sleep endoscopy have also been found to be indicative for MMA [118, 119]. In contrast, MMA has been shown to be less effective when complete anteroposterior epiglottis collapse is present [120].

Nowadays virtual surgical planning and three-dimensional (3D) printing have further aided in individualising the MMA surgical plan [121]. These 3D tools have proven to decrease pre-operative

planning time, reduce surgical time and increase accuracy of osteotomies [122–125]. A more recent advance for individualisation of MMA is the implementation of the splintless orthognathic protocol [126, 127], in which patient-specific osteotomy guides and fixation plates are used to osteotomise and fixate the bimaxillary complex.

Although MMA warrants overnight intensive care unit monitoring, it is still considered relatively safe surgery, with transient (76.9%) and persistent (18.5%) facial paraesthesia as frequent complications [128, 129]. Facial change after MMA is inevitable and consists of a more pronounced lower facial third, widening of the alar base and slight nasal tipping [128, 130]. Current evidence suggests that by adding counterclockwise rotation to the advancement of the bimaxillary complex, greater AHI decrease, greater airway enlargement and a more acceptable aesthetic result can be achieved [118, 131, 132].

With a surgical success rate of 85%, MMA has proven to be the most effective surgical option [117, 128]. Of note, our unpublished data suggest that in addition to OSA, MMA can significantly reduce central and mixed apnoeas. In addition, patients' quality of life was found to be improved and maintained higher in the long term [130]. However, in order to more adequately select between CPAP or MMA and to further increase the success rate of MMA, more research is necessary, more stringent selection criteria should be applied, and a more personalised treatment plan is needed. Possibly, combining MMA with other therapies will prove to be useful in the future.

Maxillary expansion

Maxillary transverse deficiency is considered as a predisposing factor for the development of OSA [133], which is associated with increased nasal resistance [134] and posterior tongue displacement that compromises tongue support and facilitates pharyngeal collapse [135].

Maxillary expansion was first described in 1860 by Angell [136] as a solution to maxillary transverse deficiency. The benefits of rapid maxillary expansion (RME) in relation to psediatric OSA have been widely demonstrated [137]. RME may be considered as a treatment approach in children with residual OSA after adenotonsillectomy or in cases where maxillary constriction is the underlying cause of OSA [138–140].

Current adult maxillary expansion techniques include surgically assisted rapid maxillary expansion (SARME), distraction osteogenesis maxillary expansion (DOME) and segmental Le Fort I osteotomy [141–143]. SARME requires an osteotomy, in order to release the closed sutures resisting the expansion forces, which usually involves a Le Fort I osteotomy with pterygomaxillary disarticulation and midpalatal split [144]. With the development of custom-fabricated orthodontic mini-implants, DOME has been updated from SARME and requires the use of limited osteotomies, which is less invasive compared to SARME [143, 145]. Segmental Le Fort I osteotomy is primarily considered as part of orthognathic surgery when the required amount of expansion is <6–7 mm [146].

Adult maxillary expansion was initially utilised for treating dental–maxillary discrepancies, but recently, more and more researchers have found that maxillary expansion in adults can expand the nasal cavity and floor in addition to the palate, which reduces nasal airflow [147, 148]. The expansion also allows a higher tongue position, which may contribute to the opening of the airway [135]. Furthermore, maxillary expansion may increase tension on the muscles attached to the palate (*e.g.* palatoglossal and palatopharyngeal muscles), reducing upper airway collapsibility during sleep [149].

Several studies [143, 150, 151] have been conducted to investigate the effect of maxillary expansion on adult OSA. In 2016, a meta-analysis [152] of six such studies (n=36) reported that maxillary expansion can significantly improve the AHI (from 24.3±27.5 events·h^{-1} to 9.9±13.7 events·h^{-1}) and lowest oxygen desaturation for adult OSA patients. More recently, Yoon *et al.* [143] reported that in 75 adult OSA patients with narrow maxilla and nasal floor, DOME effectively reduced the severity of OSA, refractory nasal obstruction and daytime sleepiness (Epworth Sleepiness Scale score (ESS) from 10.5±5.4 to 6.7±4.8).

However, more research is necessary to further understand the role of maxillary expansion in the management of adult OSA, such as long-term outcome, the efficacy of maxillary expansion for the different severity of OSA, comparison of the effects of different expansion techniques in OSA improvement, amount of skeletal expansion necessary for improvement of OSA, and effects of combining expansion with other OSA treatment options.

Upper airway muscle activity

Myofunctional therapy

In terms of pathophysiological traits, upper airway muscular activity and anatomy can be modified by means of the dilator muscle function. Myofunctional therapy is a relatively new non-CPAP therapy, training the movement, strength, endurance and neuromuscular activation of the upper airway, pharyngeal and tongue muscles to facilitate a state in which snoring and sleep disordered breathing are diminished when asleep. The current recommendation by the ERS guidelines found a very low level of evidence of data from RCTs. Myofunctional therapy should not be considered when CPAP therapy is available; however, it may be considered if there is no other treatment that can be offered [47].

The description of positive effects in sleepiness, AHI and partner rating of sleep disturbance when playing didgeridoo for 20 min, at least five times a week, for a 4-month period started a discussion around the benefit of myofunctional exercise in awake patients with OSA [153]. More recently, a systematic review described an improvement of ∼50% in the AHI which was complemented by a significant improvement in the ESS [154].

Muscle stimulation

The use of electrical stimulation in the awake patient has been tested with various outcomes. In a double-blind, randomised and placebo-controlled study of 67 patients, using 20 min of stimulation over 8 weeks, snoring, but not the AHI, improved with intervention [155]. In addition, the method was tested in two separate reports of the same registered clinical trial, firstly, in 70 patients [156], and secondly in 125 patients [157] with snoring and mild OSA for 20 min (once daily) over a 6-week period. It was confirmed that snoring improved [156] while there was a modest improvement in the AHI in a subgroup [156].

Hypoglossal nerve stimulation

There remains limited evidence for hypoglossal nerve stimulation (HNS) and it is currently not recommended to be used as first-line treatment. It should be used as a salvage treatment when standard therapy cannot be tolerated. Responders to treatment are likely to have an AHI <50 events·h^{-1}, lower neck circumference, BMI <32 kg·m^{-2} and single-level, nonconcentric obstruction of the upper airway [47].

The use of electrical current to stimulate skeletal muscles is not new. However, transcutaneous electrical nerve stimulation and implantable devices, including cardiac and, more recently, neurological pacemakers, have been established in standard clinical practice. HNS is a relatively new treatment for patients with OSA.

In the 1980s, a study of transcutaneous electrical current described the successful normalisation of the nocturnal breathing pattern [158], although a different research group found that the electrical current may cause arousal from sleep and was not suitable to normalise the breathing when patients remained asleep [159].

In recent years, the method has been further refined using transcutaneous [160] and invasive approaches [161]. The Stimulation Therapy for Apnea Reduction trial described a 68% reduction of AHI after 12 months [162] using HNS in a RCT with a therapy-withdrawal design. The Transcutaneous Electrical Stimulation in Sleep Apnoea (TESLA) trial tested transcutaneous electrical stimulation of the upper airway dilator muscles in a crossover RCT design. Patients were kept asleep while offsetting the upper airway obstruction with a modest response in the AHI [163–166]. The lasting long-term efficacy and safety of HNS has been studied and proven over a 5-year period [167]. Based on the original concept, novel devices have been designed and tested trialling bilateral HNS [168].

Data to test the safety and efficacy of HNS have been published by the National Institute for Health and Care Excellence, including a clinical audit tool [169]. A systematic review and meta-analysis published the pooled improvement in the AHI using the invasive (AHI −24.9 events·h^{-1}, 95% CI −28.5– −21.2 events·h^{-1}) and the noninvasive approach (AHI −16.5 events·h^{-1}, 95% CI −25.1– −7.8 events·h^{-1}), while the ESS improved by −5.0 points (95% CI − 5.9– − 4.1) ($p<0.001$) [170].

Health-economical assessment of cost-effectiveness of HNS was undertaken for the United States [171] and the NHS [172] and, by now, various healthcare systems have approved HNS, including Germany and the United States.

Further developments are to be expected using more defined methods. The ongoing TESLA home trial (clinicaltrials.gov identifier NCT03160456) testing a noninvasive approach in the domiciliary setting will determine whether electrical stimulation can be a treatment modality for a wider patient cohort with OSA.

Upper airway muscle activity: pharmacologial approach

Recent insights into the physiological control of the upper airway muscles has resulted in systematic attempts to develop a pharmacological therapy in OSA related to an impaired upper airway muscle function. A specific target to master in this context is to manipulate differences in neuromodulator activity between wake and sleep. The currently explored avenues in this field of research include serotoninergic, noradrenergic and muscarinergic modulation of upper airway muscles (figure 6).

Serotoninergic modulation of upper airway motorneurons is mediated *via* 5-HT2a/c receptors, while 5-HT1a receptors participate in the regulation of respiratory neurons. Peripheral 5-HT3 receptors also contribute to the overall influence on serotoninergic influences on upper airway motor control [173]. Serotoninergic drive is decreased from wakefulness to non-rapid-eye movement (NREM) sleep and further during REM sleep. The bulk of documentation in this field includes the serotoninergic agents mirtazepin [174], paroxetine [175] and fluoxetine [176]. These drugs were shown to reduce the AHI, particularly during REM sleep, in small explorative studies of patients with OSA. However, inconsistent results, mainly in terms of efficacy or side-effects, have led to termination of further clinical development in this area.

Noradrenergic modulation was explored using the tricyclic antidepressants protriptyline [177] and desipramine [178] both resulting in a mild reduction of the AHI. More recent approaches have focused on the selective norepinephrine reuptake inhibitor atomoxetine [179]. This latter compound had only moderate effects on the AHI when administered alone, but it was speculated that the physiological limitation of the effect was of muscarinergic nature. In subsequent studies, Taranto-Montemurro *et al*. [180] combined atomoxetine with the antimuscarinergic oxybutynin, resulting in a reduction of the AHI by 62% in a pilot trial. Genioglossus muscle responsiveness was reduced along with the reduction of the AHI. A subsequent trial using a combination of adrenergic drug reboxetine and hyoscine butylbromide [181] recorded an effect of 35%, while the combination of reboxetine and oxybutynin lowered the AHI from 49 events·h^{-1} to 18 events·h^{-1} in a 7-night placebo-controlled trial [182]. The study protocols used so far in this field are of short duration and limited size. Extensive clinical trials of longer duration and with focus on subjective outcomes are needed in this field.

Carbonic anhydrase inhibitors: pharmacological approach

The carbonic anhydrase enzymes catalyse the interconversion between carbon dioxide and water on the one hand, and bicarbonate and hydrogen ions on the other [183]. Carbonic anhydrases thereby secure the maintenance of the physiological acid–base balance. There are data to suggest that this equilibrium is modified in some forms of OSA characterised by a high respiratory loop gain [184].

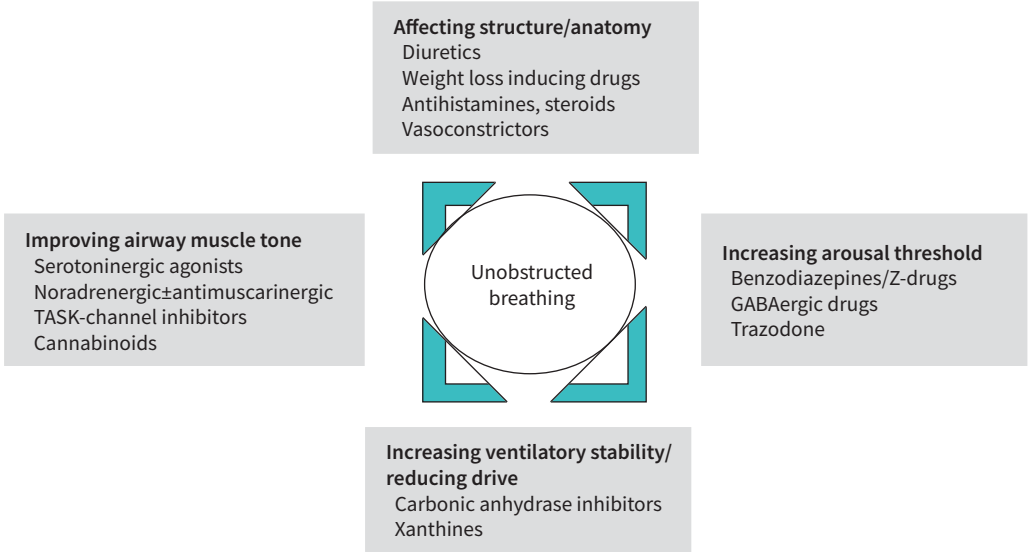

FIGURE 6 Principal current strategies for drug development in obstructive sleep apnoea. GABA: γ-aminobutyric acid.

Carbonic anhydrase activity is reduced after a carbonic anhydrase inhibitor. Acetazolamide, a frequently used carbonic anhydrase inhibitor, is known to reduce periodic breathing at high altitude [185] and to stabilise periodic breathing in cardiac failure [186]. However, carbonic anhydrase inhibitors have several biological effects that may link to conventional OSA. The evaluation of this drug in OSA should therefore include multiple effects (targets) that may be induced by a carbonic anhydrase inhibitor including respiratory (reduced AHI and improved oxygenation), cardiovascular (reduction of blood pressure) and metabolic (weight loss in obesity, reduced lipids) effects.

Acetazolamide (250 mg four times daily) induced an ∼50% placebo-adjusted AHI reduction in a small 2-week RCT [187], and an earlier uncontrolled short-term study [188] had used 250 mg (once daily) to reduce the AHI by 28%. Subsequent studies, with doses ranging from 500 mg to 750 mg three times daily, reported effect sizes of 40–52% [189, 190]. Finally, in a recent 4-week RCT of the carbonic anhydrase inhibitor sulthiame that included 68 patients with moderate to severe OSA, the AHI was reduced by 41% [191]. Carbonic anhydrase inhibition appears to reduce an elevated loop gain and to increase a low arousal threshold [189] which may be characteristics of a responding phenotype. Carbonic anhydrase inhibitors were well tolerated in these studies, but isolated paresthaesias were common [191]. More data on subjective sleepiness symptoms are needed.

Comorbid cardiovascular disease is a potential target for carbonic anhydrase inhibitor therapy in OSA. Several diuretics used to treat hypertension have carbonic anhydrase inhibitory properties [192], Acetazolamide induced vasodilation in experimental studies [193] and potently reduced blood pressures in hypertensive patients with OSA [190]. Another comorbidity target in OSA is weight loss. Zonisamide and topiramate [38, 194], carbonic anhydrase inhibitors used in epilepsy, induced 9.4% and 10.2% weight loss, respectively, after ∼6–8 months' therapy. Weight loss in this order of magnitude would be an added benefit in overweight or obese patients with OSA

Arousal threshold: pharmacological approach (sedatives and hypnotics)

Drugs with sedative, respiratory depressant or myorelaxant properties have traditionally been advised against in patients with OSA. Arguably, all such therapy might reinforce hypoventilation and respiratory gas derangement or suppress upper airway dilatory muscle function leading to a worsening of sleep apnoea. While drugs such as opiates might induce severe respiratory depression [195], others such as benzodiazepines may have a paradoxical beneficial effect. Indeed, a high ventilatory drive, which typically accompanies an obstructive event, may be detrimental in subjects with a low arousal threshold, since early arousal tends to destabilise sleep and to prevent stable breathing [196, 197]. Frequent arousals that occur during minor airway collapse are therefore believed to facilitate cyclic breathing events. Hence, arousals may be adequate to prevent excessive hypoxaemia in patients with a high arousal threshold, but they may lead to unstable breathing in those with a low arousal threshold [198]. This paradox has provided a rationale to explore the effects of certain sedatives in carefully selected patients with a low arousal threshold.

However, the potential clinical importance of a low arousal threshold is still under debate and there are few interventional studies in the field. Overall, the effect is proportionally limited and there is a delicate balance between beneficial and negative effects, as a delayed arousal would be expected to reinforce blood gas derangement. It could also be argued that several drugs in this class have myorelaxant properties that might worsen obstruction. However, available studies suggest a neutral response or an improvement after sedatives in subjects with moderate OSA [199, 200].

Most early studies on benzodiazepines on unselected groups of patients showed no effect, or a moderate increase of the AHI [201]. These studies also pointed to a high interindividual variability, although there was no severe worsening of OSA, a pattern which was supported by subsequent RCTs in the area [202, 203]. A similar pattern was found after z-drugs including zolpidem, zopiclone and eszopiclone. Both worsening and reduction of OSA were reported after higher doses in unselected patients. However, even with an unchanged AHI there was better sleep efficiency and fewer spontaneous arousals after eszopiclone [203]. In their study, Eckert *et al.* [202] demonstrated that eszopiclone reduced the AHI by 43% in a subgroup of patients with a low arousal threshold at baseline. However, this finding could not be repeated in a subsequent small controlled trial of zopiclone in patients with OSA [204].

Several other drugs with sedative/hypnotic properties including sodium oxybate and trazodone [205, 206] have been explored in OSA based on the rationale of altered arousal threshold. However, there is currently no approved therapy based on this rationale and benzodiazepines as well as z-drugs have only limited effects on the AHI in controlled trials.

Combination therapy

Although the concept of combining therapeutic options addressing different pathophysiological traits is intriguing, available evidence is limited [47, 207].

Several investigators addressed the combination of CPAP with MADs. Premaraj *et al.* [208] focused on patients nonadherent to automatic PAP. The combination significantly increased PAP adherence by 23.1% and decreased ESS by 1.4. However, PAP pressures, AHI and mask leak did not change significantly. Liu *et al.* [209] retrospectively reviewed data from patients with severe OSA, who could not tolerate high PAP pressures. AHI and oxygen desaturation index improved under combination of PAP and MAD compared to no therapy. More importantly, therapeutic pressure was substantially reduced. Tong *et al.* [26] compared CPAP alone with CPAP combined with MAD either with open or closed oral airway for one night each. Both combination therapies reduced PAP pressure significantly as compared to CPAP alone.

Dieltjens *et al.* [110] compared the combination of positional therapy and MADs with either treatment alone. Both single treatments improved respiratory disturbances significantly and similarly, while the combination was more effective and normalised the AHI.

Messineo *et al.* [210] addressed pharmaceutically the pathophysiological components of arousability and muscle responsiveness. They combined atomoxetine/oxybutynin with the sedative zolpidem or placebo in a double-blind randomised crossover design. The addition of zolpidem led to improved sleep efficiency and increased the arousal threshold with no change of respiratory disturbances, but negatively influenced driving simulator performance.

Edwards *et al.* [71] compared the combination of eszopiclone and oxygen with placebo in moderate to severe OSA. Active treatment reduced AHI and the ventilation associated with arousals and loop gain significantly. Responders were characterised by lower severity of OSA, higher muscle responsiveness and lower upper airway collapsibility.

In conclusion, the combination of various therapeutic options is the evident consequence of the concept of pathophysiological traits. This might address neglected components (arousability, respiratory drive, muscle responsiveness), improve PAP adherence or replace PAP.

Pharmacological treatment of residual sleepiness

Residual excessive daytime sleepiness (RES) despite sufficient reduction of respiratory disturbances characterises a specific phenotype. Underlying causes and pathophysiology are not yet sufficiently elucidated. RES should only be diagnosed if treatment-associated problems (*e.g.* adherence), concurrent internal, neurological or somnological diseases have been excluded or sufficiently been treated. RES can impair patients' quality of life (QoL), ability to work and participate in traffic and may therefore require treatment with wake-promoting drugs. Modafinil and armodafinil are dual dopamine-norepinephrine reuptake inhibitors. Castilho de Avellar *et al.* performed a meta-analysis of 8 placebo-controlled RCTs. Modafinil/ armodafinil improved EDS, attention and alertness as well as the clinical condition, but failed to improve quality of life and other cognitive domains [211]. Despite a significant number of dropouts, no severe adverse effects were seen.

Solriamfetol is a dopamine and norepinephrine reuptake inhibitor [212]. Schweitzer *et al.* [213] demonstrated an improvement of quality-of-life scores, Maintenance of Wakefulness Test and ESS in a double-blind placebo-controlled RCT over 12 weeks. Most adverse events were mild or moderate (headache, nausea, decreased appetite, anxiety, nasopharyngitis). These results were confirmed by Strollo *et al.* [214].

Pitolisant is a selective H3-receptor antagonist/inverse agonist at pre-synaptic neurons of the tuberomammillary nuclei. It increases the histamine synthesis and release promoting wakefulness. The drug has been evaluated in two recent placebo-controlled RCTs (HAROSA I, II) [215, 216]. They included patients with moderate to severe OSA with RES who were either sufficiently treated with PAP or could not tolerate PAP therapy. Both studies showed significant improvement of sleepiness and fatigue based on patient-reported outcomes and physician-assessed disease severity. Side-effects included headache, insomnia, nausea and vertigo without substantial differences as compared to placebo. Pitolisant increases the QT interval.

Wake-promoting drugs offer new therapeutic options for patients with the RES phenotype, as they may improve quality of life and work and traffic performance. The treatment should be initiated by a sleep

specialist in order to treat any concurrent internal, neurological or somnological diseases and optimise treatment-associated problems.

Conclusions

The crucial proceedings in our understanding of the pathophysiology and heterogeneity of clinical phenotypes urge for new approaches to individual patients, in contrast to the traditional focus on PAP only. We are aware that these perspectives require more research on the efficacy of the non-CPAP therapies, the recombination of various options and outcomes in specific phenotypes. The identification of the traits remains difficult in clinical practice. However, the concept of targeting treatment on the distinct components of upper airway collapsibility, muscle responsiveness and the central aspects of breathing and sleep regulation, either with single or combined therapies, offers fascinating options.

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