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Tackling obstructive sleep apnea with pharmacotherapeutics: expert guidance

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Abstract

Introduction: The efficacy of non-pharmacotherapeutic treatment of obstructive sleep apnea, a highly prevalent condition with serious cardiometabolic and neurocognitive health consequences, is well established. Supplementing traditional treatment strategies with medications can improve symptoms and reduce side effects. Efforts to identify medications that target the causes of sleep apnea have met with mixed success. However, this remains a worthwhile objective for researchers to pursue, given the potential benefit pharmacotherapy could bring to those patients who reject or struggle to adhere to existing treatments.

Areas covered: This article presents the case for obstructive sleep apnea pharmacotherapy including drugs that reduce the occurrence of apnea events, such as weight loss agents, ventilation activators and muscle and nervous system stimulants, drugs that alleviate symptoms, such as wake-promoting agents for excessive daytime sleepiness, and drugs that improve adherence to existing treatments, such as hypnotics. Literature was accessed from PubMed between 1 March 2024 and 18 April 2024.

Expert opinion: Exciting recent advances in both our understanding of obstructive sleep apnea pathology and in the techniques used to identify therapeutic agents and their targets combine to embolden a positive outlook for the expanded use of drugs in tackling this consequential disease.

Keywords

CPAP; sleep apnea; pharmacotherapy; treatment

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Declaration of interest

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1. Introduction

Obstructive sleep apnea (OSA) is a disease in which repetitive pharyngeal collapse during sleep leads to a reduction or cessation of airflow [1]. Lifetime risk of developing OSA is high, with up to a billion predicted sufferers worldwide [2], and is sensitive to demographic variables including age and race [3]. OSA has serious adverse consequences, such as cardiometabolic [4] and neurocognitive sequelae [5,6], which result in higher health care utilization and costs among OSA patients compared to age and sex matched individuals [7]. To date, no single pharmacotherapeutic has been identified as an effective treatment for OSA [8,9]. Nevertheless, advancements toward this goal and an increasing appreciation of the role drugs may play in OSA mean that pharmacotherapeutics must be considered as an important facet of disease management [10,11]. In contrast with contemporaneous efforts to systematically review the literature of only those pharmacological OSA interventions that directly reduce respiratory events [12,13], we provide here an overview of how drugs can be incorporated into all aspects of OSA management.

2. Do we need alternatives to PAP?

When judging the merits of new treatment pathways, it is important to compare them with existing treatments. Currently, the first-line treatment for OSA is Nasal Positive Airway Pressure (PAP). Airway splinting with PAP is highly efficacious at managing both primary health outcomes of OSA: intermittent hypoxemia and sleep fragmentation [14]. PAP treatment improves hypoxemia as evidenced by reduced numbers of apneas and hypopneas that occur per hour of sleep [15] (apnea hypopnea index – AHI). PAP treatment also reduces subjective and objective measures of sleepiness [14,16], with benefits accruing in a matter of weeks. Furthermore, chronic PAP treatment is considered a cost-effective treatment with costs per quality adjusted life year (QALY) below usual care after the first year [7,17,18].

Despite these endorsements of PAP, there are legitimate limitations that warrant the investigation of pharmacological alternatives and/or supplementation. Though adherence to PAP is generally high, averaging at 75% and rising up to 87% when employing modern engagement strategies [19-21], major barriers remain for some patients [22]. For instance, despite having a two-fold risk of severe OSA compared to demographically matched Caucasians [23,24], African-Americans are 5.5 times less likely to adhere to PAP, particularly among those with low socioeconomic status [25,26]. Adherence measures also do not account for the high proportion of patients, 5–50% in some studies, who outright refuse PAP treatment [27,28]. In these cases, non-adherence is clearly not related to PAP therapy itself but rather stems from predisposed negative opinions [22], driven by factors like perceived confining nature of PAP machines and associations with hospital-like settings [29]. Pharmacological OSA treatment alternatives unburdened by these preconceptions could help reach those patients not currently benefiting from PAP treatment.

In addition to non-adherence, other limitations of PAP exist, which may be ameliorated by pharmacotherapeutic interventions. First, residual excessive sleepiness persists after PAP treatment in up to 6–13% of compliant patients [30-32], impacting patient lifestyles with higher fatigue, altered quality of life and high rates of self-reported ill health [33]. Second,

there is growing evidence suggesting PAP treatment may theoretically exert unwanted side effects on cardiovascular health [34]. PAP therapy is associated with increased levels of endothelial inflammation factors, providing a potential explanation as to why higher pressure settings are associated with worse cardiovascular outcomes [35,36]. Foregoing PAP as the primary treatment option for OSA based on these potential limitations would go against a large body of work which suggest the therapy is safe, effective and beneficial to the patient. For some participants who remain adherent, PAP therapy can provide transformative benefits [37]. Not only does long-term usage improve subjective measures such as sleepiness [38], it also improves objective health measures including blood pressure [39]. Nevertheless, exploring pharmacological alternatives is essential to broaden treatment options.

3. Targeting OSA causes

Pharmacotherapeutics that reduce the number of hypoxemia and apnea events have been explored as potential targets in OSA [40] (Table 1). Anatomical factors including parapharyngeal and tongue fat contribute to upper airway collapsibility in many OSA patients [41-44]. Addressing excess fat through weight loss has shown efficacy, with studies showing that for every 1% decrease in weight there is a corresponding reduction in AHI of 2.6% [45,46], prompting further research into pharmaceutical interventions to aid in weight loss [47]. For instance, the combination of phentermine, an appetite suppressant, and extended-release topiramate has shown promising results. When compared to a placebo alongside a supplementary diet and exercise regimen, this medication reduced AHI by 14.9 events/hour, improved subjective sleep quality, and was associated with greater weight loss [48]. Additionally, glucagon-like peptide-1 (GLP-1) receptor agonists have been the focus of intense recent attention for their potential in addressing OSA. Liraglutide, in particular, demonstrated efficacy, with reports of a decrease in AHI of 6.1 events/hour when compared to placebo, as well as a reduction in daytime sleepiness among obese patients with type 2 diabetes [49]. Despite these promising results, concerns remain about the durability of weight loss treatments for OSA and the potential for adverse effects given the short lengths of follow-up in current studies [50]. For instance, whilst OSA is a chronic disease requiring life-long treatment, studies show that up to 70% of patients on GLP-1 receptor agonists stop using the drug at 2 years due to adverse effects and/or cost [51,52]. Trials to determine whether treatment of OSA is an indication of the next generation of GLP-1 receptor agonists, such as the SURMOUNT-OSA trial for tirzepatide [11], are ongoing and must account for these limitations.

Upper airway collapsibility can also be compromised in a state-dependent manner whereby OSA patients compensate for vulnerable airway anatomy by increasing muscle activity (e.g. genioglossus) during wakefulness [53-56] but not during sleep [57]. Overnight delivery of drugs to increase pharyngeal airway patency has been proposed as a solution. Multiple studies have trialed combination therapy of a noradrenergic agent, proposed to combat non-rapid eye movement (NREM)-related genioglossus hypotonia, with an antimuscarinic agent, proposed to combat rapid eye movement (REM)-related pharyngeal hypotonia [10,58,59]. Although the high expectations driven by early results showing a 60% decrease in AHI using atomoxetine – oxybutynin have since been blunted, a recent systematic review suggests this therapy does produce a modest reduction in AHI [58,60]. Two large multicenter phase

3 randomized trials of atomoxetine + aroxybutynin (LunAIRo/SynAIRgy) are ongoing [61,62].

Dronabinol, synthetic tetrahydrocannabinol (THC), taken daily before bed was found to lower AHI by 12.9 events/hour and reduced daytime sleepiness when compared to placebo after 6 weeks of treatment [63] and similar results were obtained using noradrenergic stimulation with desipramine [64]. Additionally, nocturnal delivery of drugs that target the parasympathetic nervous system (e.g. physostigmine, donepezil) demonstrated positive results for AHI reduction in early trials, particularly for REM sleep events [65-67], but subsequent meta-analysis has failed to confirm this finding [68].

Two strictly non-anatomical factors believed to contribute to OSA in many sufferers of the disease are a high loop gain and a low arousal threshold [69]. The respiratory control system regulates blood oxygenation by acting on breathing rate. Ventilatory loop gain quantifies how strongly this system responds to disturbances such as obstructions. A high loop gain, which causes ventilatory instability (i.e. oversensitivity) leading to worse sleep apnea, can be reduced by acetazolamide, a carbonic anhydrase inhibitor that increases ventilation via hyperchloremic metabolic acidosis [70-72]. Across trials, acetazolamide showed an AHI reduction of 13.8 event/hour when compared to placebo; however, daytime sleepiness was unaltered and side effects were common [73]. Ventilatory arousal threshold, which quantifies the magnitude of ventilatory disturbance required to cause an arousal from sleep [74,75], is also thought to contribute to OSA. When ventilatory arousal threshold is low, it promotes OSA sufferers to arouse before state-dependent compensation measures can initiate. Pharmacotherapeutic-induced increase of the arousal threshold using hypnotics has been explored as a solution to prevent arousals in these patients. Eszopiclone 3 mg reduced AHI and improved sleep quality compared with placebo, particularly for patients with the lowest arousal threshold at baseline, and can be combined effectively with supplemental oxygen to target high loop gain [76,77]. Trazodone 100 mg is also effective at increasing the respiratory arousal threshold but it’s effects on AHI are less consistent [78,79]. Importantly, complete resolution of OSA using sedatives has yet to be shown and the small improvements attained may be outweighed by potentially harmful side-effects such as delayed arousal from marked hypoxemia, at least in theory [78].

Less well-understood routes of OSA pathogenesis that can be targeted with drug interventions include airway diameter and resistance. In the case of the former, topical nasal decongestants such as alpha-adrenergic agonists and corticosteroids have been hypothesized as a means of increasing upper airway diameter and reducing nasal congestion, promoting nasal breathing [68]. Delivery of decongestants was found to reduce AHI in a subset of patients diagnosed with nasal congestion prior to treatment but not in general OSA populations [80,81]. In the case of airway resistance, application of surfactants has been explored as a way of reducing surface tension so as to decrease the pressure required to reopen the pharynx [82,83]. A trial of surfactant treatment demonstrated a reduction in AHI and pharyngeal collapsibility, but had no influence on daytime sleepiness [84].

4. Supplementing PAP therapy with pharmacotherapeutics

Rather than replacing the need for PAP therapy, a less challenging but potentially high yield strategy is to use drugs to supplement existing PAP treatment (Table 1). Such an approach could increase PAP's performance at treating the symptoms of OSA whilst removing barriers to successful PAP usage such as low adherence rates in certain groups, alleviating known side effects.

Both reduction in hypoxia and improvement in sleep quality (e.g. fragmentation, daytime sleepiness) are necessary for effective treatment of OSA with regard to reducing the healthcare burden of the disease considering that both may be causally related to cardiovascular and neurocognitive morbidity. As such, pharmacotherapeutic intervention can have value in supplementing PAP therapy in cases where AHI is reduced but sleep complaints persist. Trials of wake-promoting agents (eugeroics) that target various pathways have been conducted with OSA patients already using PAP therapy to further reduce excessive daytime sleepiness. For example, modafanil, a dopamine reuptake inhibitor, improves wakefulness, ability to sustain attention and reduces the impact of excessive sleepiness on daily functioning when compared to placebo [33,85,86]. Despite known side effects such as congenital malformations resulting from *in utero* exposure, modafinil is currently recommended by the Standards of Practice Committee of the American Academy of Sleep Medicine [87-89]. Alternatives to modafinil include solriamfetol, a norepinephrine-dopamine reuptake inhibitor, which improves excessive daytime sleepiness in PAP adherent OSA patients without reducing 1-year adherence, although some side effects have been observed [90,91]. Pitolisant, a histamine 3 (H3) receptor antagonist, also significantly reduces excessive daytime sleepiness compared to placebo with a favorable adverse event profile [92,93].

As PAP adherence is loosely related to OSA severity [94] and by implication the objective benefits it bestows, increasing adherence requires tackling barriers other than efficacy. Eszopiclone, a hypnotic agent, led to an increase in PAP usage in terms of both number of nights and nightly hours of use compared to placebo [95] and may be related to a low respiratory arousal threshold [96]. Some evidence suggests that depression is related to reduced PAP adherence [97,98] but the directionality of this relationship is unclear given that high PAP adherence may be related to a low occurrence of self-harm events [99]. More research is needed to understand whether mood is itself a target for pharmacotherapeutic enhancement of PAP adherence. Another barrier to PAP treatment, which may grow as scrutiny develops, is the occurrence of side effects such as the aforementioned increased endothelial inflammation [35]. Recent evidence shows that the PAP-related increase in circulating Ang-2, a proangiogenic factor that amplifies endothelial inflammation, is reversed by statin delivery potentially due to increased expression of endothelial complement protectors [100]. As such, statins could be considered as an adjunct therapy to PAP.

5. Expert opinion

Though PAP should still be considered the ‘gold-standard’ treatment for sleep apnea, considerable progress has been made in our understanding of OSA and potential drug therapies, with the future promising exciting advances. A major advantage of pharmacotherapy is the possibility of personalized treatment. While PAP offers a ‘one-size-fits-all’ solution for OSA, drug interventions can be tailored to target the specific causes of OSA within patient subpopulations. The rationale for personalized treatment originates from studies showing that OSA is a multifactorial disorder in which the relative contribution of different physiological traits varies substantially between individuals, suggesting unique mechanisms of pathogenesis or so-called ‘endotypes’ [101-105]. Further work is required to understand whether differences in patient pathophysiological traits covary with well-established symptomatic profiles [106-109] in a way that suggests causality. Nevertheless, evidence already points to the clinical expression of OSA being driven in part by pathophysiology [110], providing impetus to the idea of personalized treatment. Current barriers to this strategy include the modest effect sizes of available drugs to target endotypes and the difficulty of identifying receptive patient groups. Both these barriers may be overcome in the future by leveraging artificial intelligence (AI) and machine learning (ML) techniques. Appropriate targeting of OSA patient subtypes using AI and ML may revolutionize the process of identifying drug candidates. In previous drug efficacy trials, therapeutic signal may have been masked by the inclusion of patients with OSA caused by factors unrelated to the drug’s mode-of-action. By using unsupervised clustering approaches to characterize patterns in OSA endotypes and phenotypes, researchers could select patient cohorts in a way that justifiably ‘stacks the deck’ to reveal the full efficacy of candidate drugs that reduce AHI.

New technologies will both expand the potential mechanisms of drug-based therapies and facilitate the identification of novel targets and treatment strategies. Chemogenetic activation of pharyngeal muscle is an attractive proposition, combining the temporal specificity of traditional pharmacotherapy with the spatial specificity of gene therapy [111]. The potential for such interventions in the context of OSA treatment has been explored in mouse models where Designer Receptor’s Exclusively Activated by Designer Drugs (DREADDs) introduced into the hypoglossal motoneurons facilitate increased tone during NREM and REM sleep when activated by clozapine-N-oxide administration [112,113]. Whilst ethical concerns and technical challenges have so far prevented extensive trials of similar therapies in humans [114], the future prospects are encouraging. Regarding the identification of pharmacotherapeutic targets in OSA, AI and ML techniques can be utilized to search large biological datasets for connections between diseases, genes, and biological processes to facilitate the identification of candidate drugs, some of which are already entering clinical trials [115]. A genetic basis for OSA has been long established but translating this into targeted therapies has not yet occurred, perhaps due to absence of specific sleep apnea genes [116]. AI and ML techniques may be able to detect subtle or non-linear connections between genes and sleep apnea that were previously missed, facilitating gene-based therapies.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Malhotra A, White DP. Obstructive sleep apnoea. Lancet. 2002 Jul 20;360(9328):237–245. doi: 10.1016/S0140-6736(02)09464-3 [PubMed: 12133673]
2. 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 Aug;7 (8):687–698. doi: 10.1016/S2213-2600(19)30198-5 [PubMed: 31300334]
3. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. JAMA. 2004 Apr 28;291(16):2013–2016. doi: 10.1001/jama.291.16.2013 [PubMed: 15113821]
4. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation. 2010 Jul 27;122(4):352–360. doi: 10.1161/CIRCULATIONAHA.109.901801 [PubMed: 20625114]
5. Lal C, Strange C, Bachman D. Neurocognitive impairment in obstructive sleep apnea. Chest. 2012;141(6):1601–1610. doi: 10.1378/chest.11-2214 [PubMed: 22670023]
6. Djonlagic IE, Guo M, Igue M, et al. Continuous positive airway pressure restores declarative memory deficit in obstructive sleep apnea. Am J Respir Crit Care Med. 2021 May 1;203(9):1188–1190. doi: 10.1164/rccm.202011-4253LE [PubMed: 33347378]
7. Sterling KL, Alpert N, Cistulli PA, et al. Healthcare resource utilisation and costs in patients with treated obstructive sleep apnea. J Sleep Res. 2023 Nov;14:e14099. doi: 10.1111/jsr.14099
8. Lin CM, Huang YS, Guilleminault C. Pharmacotherapy of obstructive sleep apnea. Expert Opin Pharmacother. 2012 Apr;13(6):841–857. doi: 10.1517/14656566.2012.666525 [PubMed: 22424320]
9. Hudgel DW. Pharmacologic treatment of obstructive sleep apnea. [Review] [66 refs]. J Lab Clin Med. 1995;126(1):13–18. [PubMed: 7602229]
10. Schweitzer PK, Taranto-Montemurro L, Ojile JM, et al. The combination of aroxybutynin and atomoxetine in the treatment of obstructive sleep apnea (MARIPOSA): a randomized controlled trial. Am J Respir Crit Care Med. 2023 Oct 9;208(12):1316–1327. doi: 10.1164/rccm.202306-1036OC. [PubMed: 37812772] • Major clinical trial.
11. Malhotra A, Bednarik J, Chakladar S, et al. Tirzepatide for the treatment of obstructive sleep apnea: rationale, design, and sample baseline characteristics of the SURMOUNT -OSA phase 3 trial. Contemp Clin Trials. 2024 Mar 26;141:107516. doi: 10.1016/j.cct.2024.107516 [PubMed: 38547961]
12. Perger E, Bertoli S, Lombardi C. Pharmacotherapy for obstructive sleep apnea: targeting specific pathophysiological traits. Expert Rev Respir Med. 2023 Aug 03;17(8):663–673. doi: 10.1080/17476348.2023.2241353 [PubMed: 37646222]
13. Nobre ML, Sarmento ACA, de Oliveira PF, et al. Pharmacological treatment for obstructive sleep apnea: a systematic review and meta-analysis. Clinics. 2024;79:79. doi: 10.1016/j.clinsp.2024.100330
14. Jenkinson C, Davies RJ, Mullins R, et al. Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. Lancet. 1999;353(9170):2100–2105. doi: 10.1016/S0140-6736(98)10532-9 [PubMed: 10382693]
15. Sullivan CE, Issa FG, Berthon-Jones M, et al. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet. 1981;317(8225):862–865. doi: 10.1016/S0140-6736(81)92140-1
16. Patel SR, White DP, Malhotra A, et al. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: results of a meta-analysis. Arch Intern Med. 2003 Mar 10;163(5):565–571. doi: 10.1001/archinte.163.5.565 [PubMed: 12622603]

17. Pachito DV, Bagattini ÂM, Drager LF, et al. Economic evaluation of CPAP therapy for obstructive sleep apnea: a scoping review and evidence map. Sleep Breathing. 2022 Mar;26(1):17–30. doi: 10.1007/s11325-021-02362-8 [PubMed: 33788132]
18. Ayas NT, FitzGerald JM, Fleetham JA, et al. Cost-effectiveness of continuous positive airway pressure therapy for moderate to severe obstructive sleep apnea/hypopnea. Arch Intern Med. 2006 May 8;166(9):977–984. doi: 10.1001/archinte.166.9.977 [PubMed: 16682570]
19. Cistulli PA, Armitstead J, Pepin JL, et al. Short-term CPAP adherence in obstructive sleep apnea: a big data analysis using real world data. Sleep Med. 2019 Jul;59:114–116. doi: 10.1016/j.sleep.2019.01.004 [PubMed: 30799254]
20. Drager LF, Malhotra A, Yan Y, et al. Adherence with positive airway pressure therapy for obstructive sleep apnea in developing versus developed countries: a big data study. J Clin Sleep Med. 2021;17(4): 703–709. doi: 10.5664/jcsm.9008 [PubMed: 33206044]
21. Malhotra A, Crocker ME, Willes L, et al. Patient engagement using new technology to improve adherence to positive airway pressure therapy: a retrospective analysis. Chest. 2018 Apr;153(4):843–850. doi: 10.1016/j.chest.2017.11.005 [PubMed: 29154970]
22. Broström A, Nilsen P, Johansson P, et al. Putative facilitators and barriers for adherence to CPAP treatment in patients with obstructive sleep apnea syndrome: a qualitative content analysis. Sleep Med. 2010 Feb;11(2):126–130. doi: 10.1016/j.sleep.2009.04.010 [PubMed: 20004615]
23. Ancoli-Israel S, Klauber MR, Stepnowsky C, et al. Sleep-disordered breathing in African-American elderly. Am J Respir Crit Care Med. 1995;152(6 Pt 1):1946–1949. doi: 10.1164/ajrccm.152.6.8520760 [PubMed: 8520760]
24. Redline S, Young T. Epidemiology and natural history of obstructive sleep apnea. Ear Nose Throat J. 1993;72(1):20–1, 24–6. doi: 10.1177/014556139307200106 [PubMed: 8444122]
25. Platt AB, Field SH, Asch DA, et al. Neighborhood of residence is associated with daily adherence to CPAP therapy. Sleep. 2009 Jun;32(6):799–806. doi: 10.1093/sleep/32.6.799 [PubMed: 19544757]
26. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc. 2008 Feb;5(2):173–178. doi: 10.1513/pats.200708-119MG [PubMed: 18250209]
27. Engelman H, Wild MR. Improving CPAP use by patients with the sleep apnea/hypopnea syndrome (SAHS). Sleep Med Rev. 2003;7 (1):81–99. doi: 10.1053/smrv.2001.0197 [PubMed: 12586532]
28. Lin HS, Zuliani G, Amjad EH, et al. Treatment compliance in patients lost to follow-up after polysomnography. Otolaryngol Head Neck Surg. 2007 Feb;136(2):236–240. doi: 10.1016/j.otohns.2006.08.007 [PubMed: 17275546]
29. Shaw R, McKenzie S, Taylor T, et al. Beliefs and attitudes toward obstructive sleep apnea evaluation and treatment among blacks. J Natl Med Assoc. 2012 Nov;104(11–12):510–519. doi: 10.1016/S0027-9684(15)30217-0 [PubMed: 23560353]
30. Pepin 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 May;33(5):1062–1067. doi: 10.1183/09031936.00016808 [PubMed: 19407048]
31. Schweitzer PK, Mayer G, Rosenberg R, et al. Randomized controlled trial of solriamfetol for excessive daytime sleepiness in OSA: an analysis of subgroups adherent or nonadherent to OSA treatment. Chest. 2021 Feb 22;160(1):307–318. doi: 10.1016/j.chest.2021.02.033 [PubMed: 33631141]
32. Steier JS, Bogan RK, Cano-Pumarega IM, et al. Recommendations for clinical management of excessive daytime sleepiness in obstructive sleep apnoea - a Delphi consensus study. Sleep Med. 2023 Oct 9;112:104–115. doi: 10.1016/j.sleep.2023.10.001 [PubMed: 37839271]
33. Pack AI, Black JE, Schwartz JRL, et al. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. Am J Respir Crit Care Med. 2001;164(9):1675–1681. doi: 10.1164/ajrccm.164.9.2103032 [PubMed: 11719309]
34. Castrogiovanni A, Bonsignore MR. May continuous positive airway pressure (CPAP) treatment be detrimental in obstructive sleep apnea? EBioMedicine. 2024 Mar;101:105052–105052. doi: 10.1016/j.ebiom.2024.105052 [PubMed: 38432082]

35. Gottlieb DJ, Lederer DJ, Kim JS, et al. Effect of positive airway pressure therapy of obstructive sleep apnea on circulating Angiopoietin-2. Sleep Med. 2022 Aug;96:119–121. doi: 10.1016/j.sleep.2022.05.007 [PubMed: 35636149]
36. Peker Y, Celik Y, Behboudi A, et al. CPAP may promote an endothelial inflammatory milieu in sleep apnoea after coronary revascularization. EBioMedicine. 2024 Mar;101:105015–105015. doi: 10.1016/j.ebiom.2024.105015 [PubMed: 38403558]
37. Weaver TE, Maislin G, Dinges DF, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. Sleep. 2007;30(6):711–719. doi: 10.1093/sleep/30.6.711 [PubMed: 17580592]
38. Sánchez AI, Martínez P, Miró E, et al. CPAP and behavioral therapies in patients with obstructive sleep apnea: effects on daytime sleepiness, mood, and cognitive function. Sleep Med Rev. 2009 Jun 01;13(3):223–233. doi: 10.1016/j.smrv.2008.07.002 [PubMed: 19201228]
39. 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(21):2280–2293. doi: 10.1001/jama.2015.16303 [PubMed: 26624827]
40. Schmickl CN, Edwards BA, Malhotra A. Drug therapy for obstructive sleep apnea: are we there yet? Am J Respir Crit Care Med. 2022 Mar 23;205(12):1379–1381. doi: 10.1164/rccm.202202-0301ED [PubMed: 35320066]
41. Welch K, Foster G, Ritter C, et al. A novel volumetric magnetic resonance imaging paradigm to study upper airway anatomy. Sleep. 2002;25(5):530–540. doi: 10.1093/sleep/25.5.530
42. Isono S, Remmers JE, Tanaka A, et al. Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. J Appl Physiol. 1997;82(4):1319–1326. doi: 10.1152/jappl.1997.82.4.1319 [PubMed: 9104871]
43. Malhotra A, Huang Y, Fogel R, et al. Aging influences on pharyngeal anatomy and physiology: the predisposition to pharyngeal collapse. Am J Med. 2006 Jan;119(1):72 e9–14. doi: 10.1016/j.amjmed.2005.01.077
44. Wang SH, Keenan BT, Wiemken A, et al. Effect of weight loss on upper airway anatomy and the apnea-hypopnea index. the importance of tongue fat. Am J Respir Crit Care Med. 2020 Mar 15;201(6):718–727. doi: 10.1164/rccm.201903-0692OC [PubMed: 31918559]
45. Peppard P, Young T, Palta M, et al. Longitudinal study of moderate weight change and sleep disordered breathing. JAMA. 2000;284(23):3015–3021. doi: 10.1001/jama.284.23.3015 [PubMed: 11122588]
46. Schwartz AR, Gold AR, Schubert N, et al. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. Am Rev Respir Dis. 1991 ;144(3 Pt 1):494–498. doi: 10.1164/ajrccm/144.3_Pt_1.494 [PubMed: 1892285]
47. O'Donnell C, Crilly S, O'Mahony A, et al. Continuous positive airway pressure but not GLP1-mediated weight loss improves early cardiovascular disease in obstructive sleep apnea: a randomized proof-of-concept study. Ann Am Thorac Soc. 2024 Mar;21(3):464–473. doi: 10.1513/AnnalsATS.202309-821OC [PubMed: 38096106]
48. 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 Nov;35(11):1529–1539. doi: 10.5665/sleep.2204 [PubMed: 23115402]
49. 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 (Lond). 2016 Aug;40(8):1310–1319. doi: 10.1038/ijo.2016.52 [PubMed: 27005405]
50. Le KDR, Le K, Foo F, et al. The impact of glucagon-like peptide 1 receptor agonists on obstructive sleep apnoea: a scoping review. Pharmacy. 2024 Jan;12:11. doi: 10.3390/pharmacy12010011 [PubMed: 38251405]
51. Weiss T, Carr RD, Pal S, et al. Real-world adherence and discontinuation of glucagon-like peptide-1 receptor agonists therapy in type 2 diabetes mellitus patients in the United States. Patient Preference Adherence. 2020;14:2337–2345. doi: 10.2147/PPA.S277676 [PubMed: 33273810]

52. Weiss T, Yang L, Carr RD, et al. Real-world weight change, adherence, and discontinuation among patients with type 2 diabetes initiating glucagon-like peptide-1 receptor agonists in the UK. BMJ Open Diabetes Res Care. 2022 Jan;10(1):e002517. doi: 10.1136/bmjdrc-2021-002517
53. Mezzanotte WS, Tangel DJ, White DP. Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). J Clin Invest. 1992;89 (5):1571–1579. doi: 10.1172/JCI115751 [PubMed: 1569196]
54. Horner RL. The neuropharmacology of upper airway motor control in the awake and asleep states: implications for obstructive sleep apnoea. Respir Res. 2001;2(5):286–294. doi: 10.1186/rr71 [PubMed: 11686898]
55. Horner RL. Pathophysiology of obstructive sleep apnea. J Cardiopulm Rehabil Prev. 2008 Sep;28(5):289–298. doi: 10.1097/01.HCR.0000336138.71569.a2 [PubMed: 18784537]
56. Horner RL, Hughes SW, Malhotra A. State-dependent and reflex drives to the upper airway: basic physiology with clinical implications. J Appl Physiol (1985). 2014 Feb 1;116(3):325–336. doi: 10.1152/japplphysiol.00531.2013 [PubMed: 23970535]
57. McGinley BM, Schwartz AR, Schneider H, et al. Upper airway neuromuscular compensation during sleep is defective in obstructive sleep apnea. J Appl Physiol (Bethesda, Md: 1985). 2008;105 (1):197–205. doi: 10.1152/japplphysiol.01214.2007
58. 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 May 15;199(10):1267–1276. doi: 10.1164/rccm.201808-1493OC [PubMed: 30395486] • Strong AHI reduction.
59. Rosenberg R, Abaluck B, Thein S. Combination of atomoxetine with the novel antimuscarinic aroxybutynin improves mild to moderate OSA. J Clin Sleep Med. 2022;18(12):2837–2844. doi: 10.5664/jcsm.10250 [PubMed: 35975547]
60. Lee Y-C, Lu C-T, Chuang L-P, et al. Pharmacotherapy for obstructive sleep apnea - a systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev. 2023 Aug 01;70:101809. doi: 10.1016/j.smrv.2023.101809 [PubMed: 37423095]
61. Apnimed. Parallel Arm Trial of AD109 and Placebo with Patients with OSA (LunAiro) ClinicalTrials.Gov identifier: NCT05811247. [Updated 2024 May 1;cited 2024 May 24]. Available from: https://www.clinicaltrials.gov/study/NCT05811247?id=NCT05811247&rank=1
62. Apnimed. Parallel-arm study to compare ad109 to placebo with patients with OSA (SynAirgy Study) ClinicalTrials.Gov identifier: NCT05813275. [Updated 2024 May 2;cited 2024 May 24]. Available from: https://www.clinicaltrials.gov/search?id=NCT05813275
63. 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 Jan 1;41(1). doi: 10.1093/sleep/zsx184
64. 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 Nov;48(5):1340–1350. doi: 10.1183/13993003.00823-2016 [PubMed: 27799387]
65. Hedner J, Kraiczi H, Peker Y, et al. Reduction of sleep apnea after the orally available cholinesterase inhibitor donepezil. Sleep Med. 2005;6(2):e545–e545.
66. Hedner J, Kraiczi H, Peker Y, et al. Reduction of sleep-disordered breathing after physostigmine. Am J Respir Crit Care Med. 2003 Nov;168(10):1246–1251. doi: 10.1164/rccm.200211-1344OC [PubMed: 12958052]
67. Li Y, Owens RL, Sands S, et al. The effect of donepezil on arousal threshold and apnea-hypopnea index. a randomized, double-blind, cross-over study. Ann Am Thorac Soc. 2016 Nov;13(11):2012–2018. doi: 10.1513/AnnalsATS.201605-384OC [PubMed: 27442715]
68. 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 Aug;46:74–86. doi: 10.1016/j.smrv.2019.04.009 [PubMed: 31075665]
69. Schmickl CN, Owens RL, Edwards BA, et al. OSA endotypes: what are they and what are their potential clinical implications? Curr Sleep Med Rep. 2018 Sep;4(3):231–242. doi: 10.1007/s40675-018-0121-8. • Explanation of endotyping-driven approach to pharmacotherapy.

70. Schmickl CN, Landry S, Orr JE, et al. Effects of acetazolamide on control of breathing in sleep apnea patients: mechanistic insights using meta-analyses and physiological model simulations. Physiol Rep. 2021 Oct;9(20):e15071. doi: 10.14814/phy2.15071 [PubMed: 34699135]
71. Schmickl CN, Landry SA, Orr JE, et al. Acetazolamide for OSA and central sleep apnea: a comprehensive systematic review and meta-analysis. Chest. 2020 Dec;158(6):2632–2645. doi: 10.1016/j.chest.2020.06.078 [PubMed: 32768459]
72. Schmickl CN, Landry SA, Orr JE, et al. Acetazolamide for OSA and central sleep apnea. Chest. 2020 Dec;158(6):2632–2645. doi: 10.1016/j.chest.2020.06.078 [PubMed: 32768459]
73. Eskandari D, Zou D, Grote L, et al. Acetazolamide reduces blood pressure and sleep-disordered breathing in patients with hypertension and obstructive sleep apnea: a randomized controlled trial. J Clin Sleep Med. 2018 Mar;14(3):309–317. doi: 10.5664/jcsm.6968 [PubMed: 29510792]
74. Berry RB, Gleeson K. Respiratory arousal from sleep: mechanisms and significance. [Review] [83 refs]. Sleep. 1997;20(8):654–675. doi: 10.1093/sleep/20.8.654 [PubMed: 9351134]
75. Gleeson K, Zwillich CW, WHite DP. The influence of increasing ventilatory effort on arousal from sleep. Am Rev Respir Dis. 1990;142(2):295–300. doi: 10.1164/ajrccm/142.2.295 [PubMed: 2382892]
76. 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 (Lond). 2011 Jun;120(12):505–514. doi: 10.1042/CS20100588 [PubMed: 21269278]
77. 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 Nov 1;39(11):1973–1983. doi: 10.5665/sleep.6226 [PubMed: 27634790]
78. 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 Apr 1;37(4):811–819. doi: 10.5665/sleep.3596 [PubMed: 24899767]
79. Smales ET, Edwards BA, Deyoung PN, et al. Trazodone effects on obstructive sleep apnea and non-REM arousal threshold [research-article]. 2015 May 12. Available from: https://doiorg/101513/AnnalsATS201408-399OC
80. Clarenbach CF, Kohler M, Senn O, et al. Does nasal decongestion improve obstructive sleep apnea? J Sleep Res. 2008 Dec;17(4):444–449. doi: 10.1111/j.1365-2869.2008.00667.x [PubMed: 18710420]
81. Koutsourelakis I, Minaritzoglou A, Zakynthinos G, et al. The effect of nasal tramazoline with dexamethasone in obstructive sleep apnoea patients. Eur Respir J. 2013 Oct;42(4):1055–1063. doi: 10.1183/09031936.00142312 [PubMed: 23397296]
82. Van Der Touw T, Crawford ABH, Wheatley JR. Effects of a synthetic lung surfactant on pharyngeal patency in awake human subjects. J Appl Physiol. 1997;82(1):78–85. doi: 10.1152/jappl.1997.82.1.78 [PubMed: 9029201]
83. Kirkness JP, Christenson HK, Garlick SR, et al. Decreased surface tension of upper airway mucosal lining liquid increases upper airway patency in anaesthetised rabbits. J Physiol. 2003 Mar 1;547(Pt 2):603–611. doi: 10.1113/jphysiol.2002.031013 [PubMed: 12562967]
84. Morrell MJ, Arabi Y, Zahn BR, et al. Effect of surfactant on pharyngeal mechanics in sleeping humans: implications for sleep apnoea. Eur Respir J. 2002;20(2):451–457. doi: 10.1183/09031936.02.00273702 [PubMed: 12212981]
85. Weaver TE, Chasens ER, Arora S. Modafinil improves functional outcomes in patients with residual excessive sleepiness associated with CPAP treatment. J Clin Sleep Med. 2009 Dec;5(6):499–505. doi: 10.5664/jcsm.27648 [PubMed: 20465014]
86. Dinges DF, Weaver TE. Effects of modafinil on sustained attention performance and quality of life in OSA patients with residual sleepiness while being treated with nCPAP. Sleep Med. 2003 Sep;4(5):393–402. doi: 10.1016/S1389-9457(03)00108-4 [PubMed: 14592280]
87. Morgenthaler TI, Kapen S, Lee-Chiong T, et al. Practice parameters for the medical therapy of obstructive sleep apnea. Sleep. 2006 Aug;29(8):1031–1035. doi: 10.1093/sleep/29.8.1031 [PubMed: 16944671]

88. Damkier P, Broe A. First-trimester pregnancy exposure to modafinil and risk of congenital malformations. JAMA. 2020 Jan;323(4):374–376. doi: 10.1001/jama.2019.20008 [PubMed: 31990303]

89. Kaplan S, Braverman DL, Frishman I, et al. Pregnancy and fetal outcomes following exposure to modafinil and armodafinil during pregnancy. JAMA Intern Med. 2021 Feb;181(2):275–277. doi: 10.1001/jamainternmed.2020.4009 [PubMed: 33074297]

90. 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 Med. 2019 Nov 6;64:S241. doi: 10.1016/j.sleep.2019.11.674

91. 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 Jun 1;199(11):1421–1431. doi: 10.1164/rccm.201806-1100OC [PubMed: 30521757]

92. 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 Apr;159(4):1598–1609. doi: 10.1016/j.chest.2020.09.281 [PubMed: 33121980]

93. Pépin JL, Attali V, Caussé C, et al. Long-term efficacy and safety of pitolisant for residual sleepiness due to OSA. Chest. 2024 Mar;165(3):692–703. doi: 10.1016/j.chest.2023.11.017 [PubMed: 37979718]

94. Engleman HM, Wild MR. Improving CPAP use by patients with the sleep apnoea/hypopnoea syndrome (SAHS). Sleep Med Rev. 2003;7(1):81–99. doi: 10.1053/smrv.2001.0197 [PubMed: 12586532]

95. Lettieri CJ, Shah AA, Holley AB, et al. Effects of a short course of eszopiclone on continuous positive airway pressure adherence: a randomized trial. Ann Intern Med. 2009 Nov 17;151(10):696–702. doi: 10.7326/0003-4819-151-10-200911170-00006 [PubMed: 19920270] • Demonstrates potential for pharmacotherapy for improving PAP adherence.

96. Schmickl CN, Lettieri CJ, Orr JE, et al. The arousal threshold as a drug target to improve continuous positive airway pressure adherence: secondary analysis of a randomized trial. Am J Respir Crit Care Med. 2020 Dec 1;202(11):1592–1595. doi: 10.1164/rccm.202003-0502LE [PubMed: 32673496]

97. Kjelsberg FN, Ruud EA, Stavem KSS, et al. Predictors of symptoms of anxiety and depression in obstructive sleep apnea. Sleep Med. 2005;6(4):341–346. doi: 10.1016/j.sleep.2005.02.004 [PubMed: 15946899] • Elsevier.

98. Law M, Naughton M, Ho S, et al. Depression may reduce adherence during CPAP titration trial. J Clin Sleep Med. 2014;10(2):163–163. doi: 10.5664/jcsm.3444 [PubMed: 24532999]

99. Wickwire EM, Cole KV, Dexter RB, et al. Depression and comorbid obstructive sleep apnea: association between positive airway pressure adherence, occurrence of self-harm events, healthcare resource utilization, and costs. J Affect Disord. 2024 Mar;349:254–261. doi: 10.1016/j.jad.2023.12.055 [PubMed: 38159653]

100. Shah R, Patel N, Emin M, et al. Statins restore endothelial protection against complement activity in obstructive sleep apnea: a randomized clinical trial. Ann Am Thorac Soc. 2023 Jul;20(7):1029–1037. doi: 10.1513/AnnalsATS.202209-761OC [PubMed: 36912897]

101. Wellman A, Eckert DJ, Jordan AS, et al. A method for measuring and modeling the physiological traits causing obstructive sleep apnea. J Appl Physiol. 2011 Jun;110(6):1627–1637. doi: 10.1152/japplphysiol.00972.2010 [PubMed: 21436459]

102. Wellman A, Edwards BA, Sands SA, et al. A simplified method for determining phenotypic traits in patients with obstructive sleep apnea. J Appl Physiol. 2013 Apr;114(7):911–922. doi: 10.1152/japplphysiol.00747.2012 [PubMed: 23349453]

103. Jen R, Grandner MA, Malhotra A. Future of sleep-disordered breathing therapy using a mechanistic approach. Can J Cardiol. 2015 Jul;31(7):880–888. doi: 10.1016/j.cjca.2015.02.007 [PubMed: 26044800]

104. Malhotra A, Mesarwi O, Pepin JL, et al. Endotypes and phenotypes in obstructive sleep apnea. Curr Opin Pulm Med. 2020 Nov;26(6):609–614. doi: 10.1097/MCP.0000000000000724 [PubMed: 32890019]

105. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet. 2014 Feb 22;383(9918):736–747. doi: 10.1016/S0140-6736(13)60734-5 [PubMed: 23910433]
106. Keenan BT, Kim J, Singh B, et al. Recognizable clinical subtypes of obstructive sleep apnea across international sleep centers: a cluster analysis. Sleep. 2018 Mar 1;41(3). doi: 10.1093/sleep/zsx214
107. 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 Aug 15;200(4):493–506. doi: 10.1164/rccm.201808-1509OC [PubMed: 30764637]
108. Mazzotti DR, Lim DC, Sutherland K, et al. Opportunities for utilizing polysomnography signals to characterize obstructive sleep apnea subtypes and severity. Physiol Meas. 2018 Sep 13;39(9):09TR01. doi: 10.1088/1361-6579/aad5fe
109. Ye L, Pien GW, Ratcliffe SJ, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. Eur Respir J. 2014 Dec;44(6):1600–1607. doi: 10.1183/09031936.00032314 [PubMed: 25186268]
110. Schmickl CN, Orr JE, Sands SA, et al. Loop gain as a predictor of blood pressure response in patients treated for obstructive sleep apnea: secondary analysis of a clinical trial. Ann ATS. 2024 Feb;21(2):296–307. doi: 10.1513/AnnalsATS.202305-437OC
111. Sternson SM, Bleakman D. Chemogenetics: drug-controlled gene therapies for neural circuit disorders. Cell Gene Ther Insights. 2020 Aug;6(7):1079–1094. doi: 10.18609/cgti.2020.112 [PubMed: 34422319]
112. Horton GA, Fraigne JJ, Torontali ZA, et al. Activation of the hypoglossal to tongue musculature motor pathway by remote control. Sci Rep. 2017 Apr;7(1). doi: 10.1038/srep45860
113. Herlihy R, Frasson Dos Reis L, Gvritishvili A, et al. Chronic intermittent hypoxia attenuates noradrenergic innervation of hypoglossal motor nucleus. Respir Physiol Neurobiol. 2023 Dec 21;321:104206. doi: 10.1016/j.resp.2023.104206 [PubMed: 38142024]
114. Mueller JS, Tescarollo FC, Sun H. DREADDs in epilepsy research: network-based review. Front Mol Neurosci. 2022;15:863003. doi: 10.3389/fnmol.2022.863003 [PubMed: 35465094]
115. Pun FW, Ozerov IV, Zhavoronkov A. AI-powered therapeutic target discovery. Trends Pharmacol Sci. 2023 Sep;44(9):561–572. doi: 10.1016/j.tips.2023.06.010 [PubMed: 37479540]
116. Redline S, Tishler PV. The genetics of sleep apnea. Sleep Med Rev. 2000 Dec;4(6):583–602. doi: 10.1053/smrv.2000.0120 [PubMed: 12531037]

Article highlights

- Whilst nasal positive airway pressure continues to be an effective treatment for obstructive sleep apnea (OSA), there is a strong interest in exploring pharmacological interventions.
- Pharmacotherapeutics, such as atomoxetine – oxybutynin combination therapy, can effectively reduce the number of respiratory events during the night.
- Drugs may also serve a purpose in supporting existing therapies by supplementing their effects on symptoms and increasing their tolerability to facilitate increased adherence.
- Recent advances in determining the pathophysiology of OSA pave the way for new candidate drugs targeted to specific patients.
- Additional novel therapeutic targets, such as gene-based therapies, may be detected by leveraging machine learning (ML) and artificial intelligence (AI) technologies.

Table 1.

Examples of pharmacological interventions in the management of OSA.

Purpose	Target	Intervention	Study	Effect
AHI reduction	Weight	Phentermine + Topiramate	Winslow et al., 2012	AHI reduction of 14.9 events/h
		Liraglutide	Gomez-Paralta et al., 2015; Blackman et al., 2016	AHI reduction of 6.1 events/h
		Tirzepatide	~	Preliminary only
	Low upper airway patency	Noradrenergic + Antimuscarinic	Taranto-Montemurro et al.,2019	AHI reduction of 23.1 events/h
		“	Rosenburg et al., 2022	AHI reduction of 4.1 events/h
		“	Schweitzer et al., 2023	AHI reduction of 9.9 events/h
		Desipramine	Taranto-Montemurro et al.,2016	AHI(NREM) reduction of 7.7 events/h
		Dronabinol	Carley et al., 2018	AHI reduction of 12.9 events/h
		Physostigmine	Hedner et al., 2003	AHI reduction of 13.6 events/h
		Donepezil	Hedner et al., 2005	AHI reduction of events/h
		“	Li et al., 2016	No change in AHI
	High loop gain	Acetazolomide	Eskandari et al., 2018	AHI reduction of 13.8 events/h
	Low ventilatory arousal threshold	Eszopiclone	Eckert et al., 2011	AHI reduction of 7.0 events/h
		“ + Oxygen	Edwards et al., 2016	AHI reduction of 22.4 events/h
		Trazodone	Eckert et al., 2014	No change in AHI
		“	Smales et al., 2015	AHI reduction of 10.2 events/h
	Airway diameter	Xylometazoline	Clarenbach et al., 2008	No change in AHI
		Tramazoline + Dexmethasone	Koutsourelakis et al., 2013	AHI reduction of 6.1 events/h
	Airway resistance	Natural bovine surfactant	Morrell et al., 2002	No change in AHI
Residual sleepiness	Wake-promotion	Modafanil	Pack et al., 2001	Reduced daytime sleepiness
		“ + PAP	Dinges et al., 2003	Improved vigilance
		“	Weaver at al., 2009	Improved daily functioning
		Solriamfetol	Malhotra et al., 2019	Reduced daytime sleepiness
		“	Schweitzer et al., 2019	Reduced daytime sleepiness
		Pitolisant	Pépin et al., 2021	Reduced daytime sleepiness
		“	Pépin et al., 2024	Reduced daytime sleepiness
PAP adherence	Low ventilatory arousal threshold	Eszopiclone	Lettieri et al., 2009	Increased PAP adherence

PAP = nasal positive airway pressure. AHI = apnea-hypopnea index.