# Pharmacologic Therapy for Obstructive Sleep Apnea

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**KEYWORDS**

• Obstructive sleep apnea • Pharmacologic • Treatment • Review • Targets

**KEY POINTS**

- Current pharmacotherapy for sleep apnea is adjunctive, but its role can be transformed as we learn more about the various risk factors and interrelated pathology underlying the pathophysiology of sleep apnea.
- Because obesity is present in two-thirds of patients with documented sleep apnea, novel antiobesity medications may help in weight control and may secondarily improve breathing abnormalities.
- Medications addressing endothelial dysfunction, combined with positive airway pressure therapy, may help prevent hypoxemic sequelae of sleep apnea.
- New medications that can increase upper airway muscle tone and target fibrillin to improve connective-tissue laxity may also be useful.
- Determining the molecular signatures of sleep apnea may help identify diagnostic, prognostic, and surrogate markers for obstructive sleep apnea, and identify markers for drug-response phenotypes.

## INTRODUCTION

Obstructive sleep apnea (OSA) is a major health hazard that is estimated to affect 12 million Americans. Up to 5% of adults in Western countries remain undiagnosed.[1] Severity of OSA is defined by the number of apneic and hypopneic events per hour of sleep, also known as the apnea-hypopnea index (AHI). Among Americans between the ages of 30 and 60 years, 24% of men and 9% of women have mild OSA (AHI $\geq$5), and 9% of men and 4% of women have at least moderate OSA (AHI $\geq$15).[1]

Sleep apnea is multifactorial in origin. Obesity, craniofacial abnormalities, age, gender, congenital and acquired conditions, and environmental factors may increase collapsibility of the upper airway during inspiration; combined with insufficient neuromuscular compensation, these factors may lead to failure to keep the airway patent. Ventilatory instability, pharyngeal neuropathy, and fluid shifts toward the pharynx have been implicated in the pathophysiology of OSA. OSA has been associated with accidents, hypertension, ischemic heart disease, strokes, insulin resistance, and increased mortality.[2–4]

Primary treatment modalities attempt to prevent upper airway collapse through a positive airway pressure (PAP) device, an oral appliance (OA), or surgical modification of the upper airway. However, at least 8% to 9% of new OSA patients decline continuous PAP (CPAP),[5] and adherence rates vary from 30% to 60%.[6] Dropout rates in OA users vary from 0% to 38% because of lack of efficacy or side effects.[7] A review of placebo-controlled crossover trials of OAs reported that the AHI decreased from 25 to 14 in 64% of OSA patients.[8] Adjustable OAs are preferable over fixed OA devices.[9] In a group of 602 OSA patients, mean AHI decreased from a baseline of 30 to fewer than 5 events per hour in 57% of individuals with an adjustable OA, compared with 47%

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fixed-OA subjects.[9] Surgical success rates for OSA vary depending on the procedure. A review compared the percent reduction in mean AHI postoperatively relative to baseline mean AHI: maxilla-mandibular advancement, 87%; uvulopalatopharyngoplasty, 33%; laser uvuloplasty, 18%; radiofrequency to the soft palate, base of the tongue, or multilevel treatment, 34%; and soft-palate implants, 26%.[10] Adjunctive surgeries for OSA include nasal procedures to relieve nasal obstruction or bariatric surgery to address obesity.

Medical therapy for sleep apnea includes weight reduction, positional therapy, supplemental oxygen therapy, and pharmacotherapy. Drugs can potentially improve OSA by maintaining patency of the upper airway during sleep, increasing respiratory drive, reducing the proportion of rapid eye movement (REM) sleep, facilitating cholinergic tone during sleep, or reducing upper airway resistance/surface tension. Unfortunately, agents that have been investigated have inadequately prevented upper airway collapse or have improved AHI insufficiently to warrant their use as primary therapy. Pharmacotherapy in OSA remains in a secondary or adjunctive role. This article discusses current pharmacotherapy and the treatment goals for sleep apnea.

## PHARMACOTHERAPEUTIC AGENTS

### *Medications that Promote Alertness in Treated OSA Patients*

Residual excessive sleepiness (RES) can persist in all categories of OSA-treated patients.[11–14] Reported RES prevalence (defined subjectively) among CPAP users varies from 207 of 4129 (5%)[11] to 60 of 502 (12%),[12] and up to as many as 106 of 149 (71%) individuals.[13]

#### *Modafinil and armodafinil use in CPAP users with RES*

For patients with RES on CPAP therapy, it is important to objectively verify hours of use per night (the prevalence of Epworth Sleepiness Scale [ESS] score <10 is higher with more usage hour per night),[13] monitor adequacy of pressure settings based on AHI from device data, and reevaluate and treat coexisting comorbid psychiatric illnesses, medical conditions, and other primary sleep disorders.[11,12] The value of treating RES in these patients has been questioned[15] because the percentage of sleepy subjects (ESS >10) among 572 CPAP users (mean body mass index [BMI] 35 kg/m$^2$) at 16% did not significantly differ from a "normal" control group of 525 subjects (mean BMI 27 kg/m$^2$) at 14%.[15] In the usual clinical setting, however, OSA-treated patients with unexplained hypersomnolence are considered for supplemental stimulant therapy to improve their quality of life and reduce their risk of accidents.

Modafinil and armodafinil are the main stimulants used to address RES in treated OSA. Modafinil is metabolized into the R and S enantiomers, whereas armodafinil is the R and longer-lasting enantiomer of modafinil. Modafinil induces wakefulness by inhibiting dopamine and noradrenaline reuptake transporters. Peak plasma absorption (fasting state) occurs at 2 to 4 hours for modafinil and 2 hours for armodafinil. Both drugs have an elimination half-life of 13 hours, with similar mean maximum plasma drug concentration.[16] Compared with modafinil on a milligram-to-milligram basis, armodafinil achieves higher plasma concentrations late in the day.[16] There are no head-to-head studies comparing the efficacy of modafinil with that of armodafinil in reducing sleepiness in OSA subjects.

Modafinil is started at either 100 mg or 200 mg each morning and titrated upwards to 300 to 400 mg if needed. Split dosing (AM and mid-afternoon) is an alternative if mid-afternoon sleepiness occurs. Armodafinil is started at 150 mg in the morning and is increased after 1 week to 250 mg if needed. Both drugs are metabolized by the liver, with renal excretion of metabolites. Interactions with other drugs are due to their effect on cytochrome P450 enzymes. The most frequent side effects are headache, nausea, anorexia, dry mouth, and diarrhea. Serious rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, have been reported with modafinil. Patients should be advised to discontinue modafinil or armodafinil if rash develops. Caution should be exercised in prescribing either medication to patients with a history of heart disease (particularly left ventricular dysfunction and mitral valve prolapse) or arrhythmias, because palpitations and electrocardiographic T-wave ischemic changes have been reported with modafinil. Users should be informed that the efficacy of birth-control tablets may be reduced, and advised to consider alternative/supplemental contraception.

Modafinil does not reduce AHI, but does improve vigilance and quality of life.[17–19] In 2 randomized, double-blind, placebo-controlled trials of modafinil (4 weeks,[17] 12 weeks[18]), ESS scores improved,[17,18] with normalization (ESS <10) in 51% of modafinil-treated subjects, compared with 27% in the placebo group.[17] Multiple Sleep Latency Test (MSLT) sleep-onset latencies did not improve.[17] ESS and sleep-related functional status continued to improve over a 12-week open-label trial of modafinil in 125 moderate to severe OSA patients who had previously completed