REVIEW ARTICLE

Drug Therapy for Obstructive Sleep Apnoea

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Abstract

Obstructive sleep apnea (OSA) is a common disorder that is characterized by obstructive apnoeas and hypopneas due to the repetitive collapse of the upper airway during sleep. A variety of effective behavioral and airway-specific therapies are available for the treatment of OSA, including weight loss, positive airway pressure therapy, oral appliances, and surgical procedures. Behavior modification is indicated for most patients who have OSA. This includes losing weight, exercising, abstaining from alcohol, and avoiding certain medications. For patients with severe OSA, positive airway pressure is recommended as initial therapy. Oral appliance may be tried for patients with mild to moderate OSA. Surgical therapy is usually for the surgically correctable obstructing lesion. Hypoglossal nerve stimulation via an implantable neurostimulator device is a novel treatment strategy. Patients who continue to have excessive daytime sleepiness despite adequate OSA-specific therapy that is severe enough to warrant treatment may benefit from adjunctive pharmacologic therapy like modafinil and armodafinil. Other drugs have been tried in the management of OSA. In small trials, benefits have been found sporadically with remifentanil, zolpidem, triazolam, eszopiclone, and sodium oxybate. Further large multicentric trials are required to prove their efficacy. There is also a scope for research for thedevelopment of some novel group of drugs for the primary treatment for OSA.

Keywords: Obstructive sleep apnoea (OSA), Drug therapy, Modafinil, Armodafinil, Positive airway pressure therapy (PAP).

Introduction

Obstructive sleep apnoea (OSA) is characterized by obstructive apnoeas and hypopnoeas due to therepetitive collapse of the upper airway during sleep. Untreated OSA has many potential consequences including excessive daytime sleepiness, impaired daytime function, metabolic dysfunction, and an increased risk of cardiovascular disease and mortality[1]. Management of OSA with more detailed discussion on its drug therapy is being discussed in this article.

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Therapy for OSA

Behavior and lifestyle modification:

Weight loss and exercise are recommended to obese patients[2]. Weight loss decreases the apnea-hypopnea

index, and also decreases daytime sleepiness[3]. Patients whose OSA improves or resolves after weight loss should strive to maintain their weight loss, since weight gain has been associated with worsening or recurrence of OSA[4]. Counseling regarding ongoing diet modification and exercise, as well as referral to a nutritionist, may be beneficial. A supervised exercise program was found to be associated with significantly improved AHI, and subjective sleepiness, with minimal change in body weight in a recently published meta-analysis[5].

Patients are advised to avoid alcohol and drugs like benzodiazepines and sedating antidepressants, barbiturates, antihistamines, and opiates. Antidepressants that cause weight gain (e.g., mirtazapine) should also be avoided.

Positive Airway Pressure (PAP) Therapy:

PAP therapy is the mainstay of therapy for OSA. Discussion on PAP therapy is beyond the scope of this article. Interested readers may go through other literature available on this topic[6].

Management of co-morbidity:

OSA has been associated with other medical conditions, such as diabetes, hypertension, heart failure, and ischemic heart disease. Any co-morbid condition that may be impacted by OSA should be monitored closely following the initiation of OSA-specific therapy. Therapy directed at such co-morbidities may need to be modified once therapy for OSA is instituted.

Oral appliances:

Mandibular advancement devices and tongue retaining devices are alternative therapeutic strategies that may be offered to patients with mild to moderate OSA, who decline or fail to adhere to positive airway pressure therapy and who have a preference for such treatment[7].

Hypoglossal nerve stimulation:

Hypoglossal nerve stimulation via an implantable neurostimulator device is a novel treatment strategy that may have a role in selected patients with moderate to severe OSA, although early results are mixed and further data are needed[8].

Upper airway surgery:

It is considered when positive airway pressure or an oral appliance is declined or ineffective. It is most effective in patients who have OSA due to a severe,obstructing lesion of the upper airway, correctable surgically[9].

Pharmacologic agents in OSA:

A variety of pharmacologic agents has been investigated in randomized trials as primary therapeutic agents for the management of sleep-disordered breathing on OSA, with the goal of replacing the more burden some therapies described above. Pharmacologic therapy (with agents such as modafinil or armodafinil) may be beneficial as an adjunctive therapy for excessive daytime sleepiness that persists despite documentation of adequate and successful conventional therapy (e.g., positive airway pressure, oral appliances). Other drugs are undergoing trials, and some of them have been found to be either useful in a special group of patients or found being not useful in controlled trial or in the meta-analysis.

Wakefulness-promoting agents:

A trial of a wakefulness-promoting agent is recommended for patients with OSA who have persistent daytime sleepiness that is burdensome enough to require therapy, have had alternative causes of daytime sleepiness excluded, and have had the efficacy of their conventional therapy confirmed. Both modafinil and armodafinil have prove to improve symptoms in randomized trials.10-12 The decision to prescribe a wake-promoting medication is generally based on patient symptoms. Epworth Sleepiness Scale (ESS) score is most commonly used to guide decision making about initiating adjunctive. ESS scores of 10 to 12 or higher are a reasonable threshold for initiating a treatment trial.

Modafinil and armodafinil:

Modafinil and the active R-enantiomer, armodafinil, act on the central nervous system to enhance alertness. Probably, these medications enhance dopamine signaling, but the precise mechanism of effect is unknown.

The effectiveness of modafinil for treatment of residual sleepiness in patients with OSA has been demonstrated in multiple randomized trials. As an

example, a double-blind crossover trial randomly assigned 157 patients with OSA who had persistent daytime sleepiness despite adequate conventional therapy to receive modafinil (titrated upward from 200 to 400 mg) or placebo once daily for four weeks. Excessive daytime sleepiness (EDS) resolved in a greater proportion of patients in the modafinil group than in the placebo group (51 versus 27 percent), as measured by the ESS. A subsequent analysis that pooled data from this trial with data from another trial,[13] confirmed that modafinil improved productivity, activity, and vigilance compared with placebo[14].

Modafinil given once in the morning promotes wakefulness into the early evening without disrupting nighttime sleep. The drug is started with 100 or 200 mg each morning and then titrated up to 300 or 400 mg. Patients with persistent afternoon sleepiness may benefit from divided dosing with 200 mg in the morning and 200 mg in the early to mid-afternoon. Patients generally report improvement within days of starting therapy or increasing a dose.

As per the randomized trials, armodafinil is similarly effective[15,16]. It can be started at 150 mg once daily and titrated up to 250 mg once daily as needed.

Modafinil and armodafinil should be used cautiously in people with angina, the recent history of myocardial infarction, or with left ventricular hypertrophy). But adverse cardiovascular effects are less common with these drugs than with stimulants such as amphetamines.

There are conflicting data regarding the impact of wake-promoting medications on the primary OSA therapy (e.g., positive airway pressure [PAP] therapy). Some studies suggest that reduced daytime sleepiness due to modafinil therapy prompts patients to reduce their use of continuous PAP (CPAP), while other studies suggest that modafinil does not alter CPAP usage. In light of the conflicting data, it is important to closely monitor adherence with conventional therapy in all patients who receive pharmacologic therapy.

Other drugs for OSA: 2013 Cochrane review:

The following drugs have been reviewed by Manson M et al in their 2013 Cochrane review:Protriptyline, Paroxetine, Mirtazapine, Ondansetron,Buspirone, Salmeterol, Aminophylline, Theophylline, Acetazolamide, Medroxyprogesterone, Naloxone, Naltrexone, Almitrine, Clonidine, Mibefradil, Nasal lubricant, Saleluzone, Physostigmine, Donepezil and Eszopiclone[17].

Other drugs for OSA: 2015 Cochrane review:

Manson et al again did their 2015 Cochrane review with meta-analysis with the following drugs:Remifentanil, Eszopiclone, Nitrazepam,Temazepam, Triazolam, Sodium oxybate and Ramelteon[18].

The findings of these reviews show that currently, no evidence suggests that the pharmacological compounds assessed have a deleterious effect on the severity of OSA as measured by change in AHI. Significant clinical and statistical decreases in minimum overnight SpO_2 were observed with remifentanil, zolpidem 20 mg, and triazolam 0.25 mg. Eszopiclone 3 mg and sodium oxybate 4.5 g showed a beneficial effect on the severity of OSA with a reduction in AHI and may merit further assessment as a potential therapeutic option for a subgroup of patients with OSA. Only one trial assessed the effect of an opioid (remifentanil). Most studies were small and of short duration, with indiscernible methodological quality. Caution is therefore required when such agents are prescribed for patients with OSA, especially outside the severity of the OSA cohorts and the corresponding dose of compounds given in the particular studies. Larger, longer trials involving patients across a broader spectrum of OSA severity are needed to clarify these results.

Conclusion

Cardinal features of obstructive sleep apnea (OSA) include irregular and abnormal respiratory patterns during sleep, loud snoring and, and symptoms attributable to disrupted sleep. There are several interventions that may benefit patients with OSA. These include behavior modifications including weight loss, and OSA-specific therapies (e.g., positive airway pressure, oral appliances, and surgery). Patients with severe untreated OSA are at increased risk for all-cause mortality. Modafinil and armodafinil are used for patients who has residual daytime sleepiness even after appropriate use of their CPAP therapy. In two Cochrane based meta-analysis, a few drugs have been found to be sporadically useful in OSA. But larger trials are warranted. There is scope for the invention of a novel group of drugs for OSA patients.

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