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## Abstract

**BACKGROUND:** Currently the treatment of choice for symptomatic obstructive sleep apnoea (OSA) is continuous positive airway pressure (CPAP). Some patients with OSA do not tolerate CPAP or have insufficiently severe symptoms to justify its use; for these patients, drug therapy would be a desirable potential therapeutic alternative. **OBJECTIVE:** To summarize the current evidence on the effectiveness of drug therapy in patients with OSA. **METHODS:** A systematic review of randomized controlled trials was performed to investigate the effects of drug therapy on OSA. **RESULTS/CONCLUSIONS:** Searches of bibliographical databases revealed 33 trials investigating the effects of 27 different drugs on OSA severity and/or symptoms. The mechanisms by which these drugs are supposed to improve OSA include, amongst others, an increase in tone of the upper airways, an increase in ventilatory drive, a reduction in airway resistance, and alterations in surface tension forces in the upper airway. In most of these studies there was no significant effect on OSA observed. However, there is evidence from a few small trials that some drugs, especially those thought to increase upper airway muscle tone, have the potential to reduce OSA severity; but further data from larger studies of adequate duration are needed.

# Pharmacological approaches to the treatment of obstructive sleep apnoea

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## ABSTRACT

**Background:** Currently the treatment of choice for symptomatic obstructive sleep apnoea (OSA) is continuous positive airway pressure (CPAP). Some patients with OSA do not tolerate CPAP or have insufficiently severe symptoms to justify its use; for these patients, drug therapy would be a desirable potential therapeutic alternative. **Objective:** To summarize the current evidence on the effectiveness of drug therapy in patients with OSA. **Methods:** A systematic review of randomized controlled trials was performed to investigate the effects of drug therapy on OSA. **Results/conclusions:** Searches of bibliographical databases revealed 33 trials investigating the effects of 27 different drugs on OSA severity and/or symptoms. The mechanisms by which these drugs are supposed to improve OSA include, amongst others, an increase in tone of the upper airways, an increase in ventilatory drive, a reduction in airway resistance, and alterations in surface tension forces in the upper airway. In most of these studies there was no significant effect on OSA observed. However, there is evidence from a few small trials that some drugs, especially those thought to increase upper airway muscle tone, have the potential to reduce OSA severity; but further data from larger studies of adequate duration are needed.

## 1. Introduction

Obstructive sleep apnoea (OSA) is caused by repetitive obstruction of the upper airway during sleep. This leads to apnoeas or hypopnoeas associated with arterial oxygen desaturations and arousals from sleep with consequent sleep fragmentation. Patients with OSA typically present with a history of habitual snoring, nocturnal apnoeas observed by the bed partner, unrefreshing sleep, and excessive daytime sleepiness.

Particularly in obese individuals, lateral fat deposits in the neck, hypertrophic pharyngeal walls, and pharyngeal mucosal oedema encroach on the lumen of the pharynx and thereby predispose to OSA [1]. Furthermore, subtle abnormalities of the cranio-facial skeleton, such as micro- and retrognathia, are common in patients with OSA [2]. However, in many patients no particular anatomic abnormalities can be found and the sleep-related upper airway obstruction appears to be purely functional. In these cases, it may result from a relatively greater reduction in tonic input to muscles dilating the upper airway during sleep, which promotes upper airway collapse [3]. Familial aggregation of OSA suggests a role of genetic factors that may control craniofacial shape [4].

It has been estimated that 2 – 4% of the adult population in Western countries suffer from moderate to severe OSA with daytime symptoms, and it is becoming more prevalent as the average population body weight rises [5]. The prevalence of milder or minimally symptomatic forms of OSA among middle-aged adults has been shown to be as high as 26% [5], making OSA one of the most frequent abnormalities and thus of potential epidemiologic interest.

In patients with OSA, excessive daytime sleepiness leads to impaired cognitive function and quality of life and is associated with an increased risk of traffic accidents, as has been demonstrated repeatedly in controlled studies. Treatment of OSA patients with CPAP has been shown to reduce this risk effectively [6].

OSA has been implicated as an important causal factor in the development of cardiovascular disease and appears to increase the risk of fatal and nonfatal cardiovascular events [7,8]. Multiple causal factors leading to vessel wall damage and atherosclerotic plaques have been proposed, including reflex sympathetic activation, surges in blood pressure, endothelial dysfunction, systemic inflammation and reactive oxygen species [9-12]. Several large cross-sectional studies have provided strong evidence that OSA is an independent risk factor for arterial hypertension, and randomized controlled studies have shown a positive effect of continuous positive airway pressure (CPAP) therapy on sympathetic activation, arterial stiffness and blood pressure [13,14].

Unfortunately, only 50 – 70% of all patients with OSA tolerate CPAP in the long term, and the daily use of CPAP varies considerably between individuals. This is particularly true for patients with milder or asymptomatic forms of OSA. As a result, patients with OSA and their doctors are interested in novel treatment modalities, especially pharmacological therapies. Thus a considerable number of randomised placebo-controlled trials investigating the effects of diverse medications on OSA have been conducted and published [15,16].

## 2. Nonpharmacological treatment modalities for OSA

Choose



Nocturnal application of CPAP via a nasal mask is the standard therapy for OSA [17]. It improves excessive daytime sleepiness and other symptoms, quality of life, vigilance, cognitive performance, nocturnal breathing disturbances and oxygenation [18,19]. Therefore, the indication for CPAP therapy is based on the combination of symptoms and an increased number of apnoeas in a sleep study. The compliance with CPAP therapy is strongly influenced by the severity of the patient's symptoms, the benefit they perceive from treatment, and the support given by their physician and other healthcare workers [20]. The nightly use of

patients refuse CPAP because of the inconvenience, side effects (such as mask discomfort), no perceived benefit, or for psychological reasons.

For patients who do not tolerate CPAP, a removable oral appliance that is snapped onto the upper and lower teeth during sleep is currently the only alternative treatment [23]. The device is designed to advance the mandible (usually by 5 – 10 mm), thereby enlarging the upper airway calibre. Several randomised trials have documented the effectiveness of oral appliance therapy for mild-to-moderate OSA regarding alleviation of symptoms, quality of life and sleep-disordered breathing [24]. The long-term effects on teeth and temporomandibular joints have to be carefully evaluated [25]. Unfortunately, compliance with this therapy is not well established.

With the exception of adenotonsillectomy in children, and adults with significantly enlarged adenoids and tonsils, surgical treatment is rarely indicated and effective as a therapy for OSA. Although commonly performed, uvulopalatopharyngoplasty (UPPP) and novel surgical techniques, such as radiofrequency tissue ablation and laser-assisted uvulopalatoplasty, have not been proven to be sufficiently effective treatments for OSA [26].

### 3. Pharmacological treatment for OSA

 

#### 3.1 Sleep apnoea severity, study design and outcome definition

There is no definitive consensus on the optimal variable to use for classification of OSA severity. Because more than five episodes of apnoea/hypopnoea per hour of sleep (apnoea/hypopnoea index, AHI) were rarely found in sleep studies of healthy young adults, this became the standard definition of OSA. The number of physiologic apnoea/hypopnoea events increases with age, and therefore many more events per hour of sleep can be normal in the elderly. Measures of hypoxaemia such as the number of oxygen desaturations per hour (oxygen desaturation index, ODI) and hypopnoeas with associated oxygen desaturations of  $\geq 4\%$  have been shown to be closely correlated with cardiovascular consequences of the disease [27].

As AHI and ODI do not describe daytime symptoms of OSA, additional assessment of a patients' daytime sleepiness is necessary to allow the diagnosis of obstructive sleep apnoea syndrome (OSAS). The subjective tendency to fall asleep during eight typical daytime situations can be assessed by the Epworth Sleepiness Scale (ESS), a widely used standardised questionnaire [28]. Measuring objective sleepiness in a meaningful way is very difficult; the multiple sleep latency test (MSLT) is regarded as the standard for measuring sleepiness [29]. This test measures how long it takes for an individual to fall asleep lying down in a darkened room on several occasions across the day. A variant of the MSLT, called the maintenance of wakefulness test (MWT), asks the individual to try to stay awake rather than trying to fall asleep [30]. A very popular way of assessing objective sleepiness is the Osler test, a sleep resistance challenge that tests the ability to stay awake in a darkened and sound-isolated room [31].

The lack of a universally used variable to define sleep apnoea severity, different recording devices to monitor respiration during sleep, and night-to-night variability in AHI and ODI (partly because of changes in body position, sleep stage distribution, and alterations in alcohol consumption) have made it difficult to produce universally acceptable and robust results in

many clinical trials. Furthermore, data from appropriately sized randomised controlled studies and multicentre trials on the effects of pharmacological treatment in patients with OSA are currently not available; for example, power calculation indicates that in a parallel-group trial with a single active treatment group, 32 patients with mild-to-moderate OSA (AHI/ODI > 5 and < 30) are required to detect clinically relevant differences in AHI/ODI to achieve a power of 80% (based on the assumption that a clinically relevant difference in AHI/ODI between active treatment and placebo is 10/h [SD 10] in such a group of OSA patients) [32]. These factors have to be considered when interpreting the outcomes of the randomised controlled studies that are discussed in the following review. Randomised placebo-controlled trials concerned with pharmacological treatment of adult OSA patients were identified by searches of the bibliographic databases EMBASE and PubMed as well as by hand-searching of journals. Search terms included 'sleep apnoea', 'sleep apnea' and 'therapy', 'treatment', 'trials', and 'pharmacotherapy'. Trials without a placebo control group, those including either normal subjects without OSA or patients on current CPAP therapy, or those investigating combined pharmacological/nonpharmacological treatments were excluded from this review.

### 3.2 Drugs proposed to act on the upper airway tone

#### 3.2.1 Protriptyline

The non-sedating tricyclic antidepressant protriptyline has been shown to suppress rapid eye movement (REM) sleep [33], a sleep stage often associated with more severe apnoea in patients with OSA, and to increase the tone in the upper airway muscles [34]. In three randomised placebo-controlled studies, the effect of protriptyline (10 – 20 mg daily for 2 – 3 weeks) on OSA severity was investigated in a total of 23 participants [35–37]. Protriptyline had no significant effect on AHI, ODI and sleep duration when compared with placebo. In two of these studies [35,36], patients reported improved subjective daytime sleepiness with protriptyline, but the methods used to assess sleepiness were limited. In the third study [37] no improvement in subjective sleepiness (assessed with a visual analogue scale) was found. Therefore current evidence from these small randomised controlled studies does not suggest that protriptyline improves OSA severity or symptoms to a clinically relevant degree.

#### 3.2.2 Paroxetine

Based on the findings obtained from a model of sleep-induced hypoglossal atonia, it has been suggested that the sleep-related loss of upper airway muscle activity may be caused by a withdrawal of serotonergic input to the hypoglossal nucleus. Serotonin (5-hydroxytryptamine [5-HT]) has also been shown to influence upper airway dilator motor neurons; experiments in awake healthy volunteers have proven that the serotonin reuptake inhibitor paroxetine increases genioglossus muscle activity [38]. To date, there is only one randomised controlled trial looking at the effects of paroxetine on OSA severity and symptoms [39]. In this crossover study, 17 male patients with a mean AHI of 36 were treated for 6 weeks with paroxetine (20 mg daily) or placebo, respectively. Paroxetine reduced the mean AHI during non-REM sleep significantly from 37.6 to 30.4, but not during REM sleep (24.7 to 21.7). Not surprisingly, this minimal reduction in AHI did not result in any alleviation of daytime symptoms.

#### 3.2.3 Mirtazapine

The antidepressant mirtazapine is a mixed 5-HT<sub>1</sub> agonist and 5-HT<sub>2</sub>, 5-HT<sub>3</sub> antagonist that has been shown to promote serotonin release in the brain, increase genioglossus muscle activity and suppress sleep apnoea in animal studies [40,41].

In a randomised, double-blind, placebo-controlled, three-way crossover study, Carley and colleagues [32] investigated the effects of mirtazapine on OSA severity and daytime symptoms in 12 patients with symptomatic OSA. Patients were randomised to either placebo, 4.5 mg mirtazapine, or 15 mg mirtazapine for 3 consecutive 7-day periods. In comparison to placebo treatment, 4.5 mg of mirtazapine significantly reduced the AHI in all sleep stages by 48% (AHI with mirtazapine was 13.5 and 22.3 with placebo) and 15 mg of mirtazapine reduced the number of apnoeas in all 12 patients; the reduction in AHI averaged 54% of baseline. Unfortunately, mirtazapine is also associated with weight gain and sedation, the latter side effect possibly explaining why subjective daytime alertness did not improve in this study [32].

These results are in contrast to those recently published by Marshall and co-workers, who performed two randomised placebo-controlled trials on the effects of different doses of mirtazapine on OSA severity [42]. The first study was a three-way crossover dose-finding study (7.5, 15, 30 and 45 mg of mirtazapine or placebo) for 2 weeks at each dose. Eighteen OSA patients completed the protocol; of these, 8 received placebo while 13 received 7.5 mg, 12 received 15 mg, 11 received 30 mg and 10 received 45 mg of mirtazapine. Mirtazapine did not improve OSA severity with any dose; in fact, a small increase in AHI was observed with 15 and 30 mg of mirtazapine [42]. In the second study (parallel-group design), 26 patients were randomised to 15 mg of mirtazapine and 13 to placebo; there was no significant change in AHI after 4 weeks of treatment with mirtazapine. Subjective daytime sleepiness assessed by the ESS did not improve with mirtazapine.

### 3.2.4 Ondansetron

The 5-HT<sub>3</sub> receptor antagonist ondansetron reduced the respiratory disturbance index (RDI) in REM sleep by 5.4% in a dog model of OSA [43]. In a small crossover randomised placebo-controlled study including 10 patients with moderate OSA, a single dose of 16 mg ondansetron had no significant effect on AHI or ODI [44]. Daytime sleepiness was not assessed in this study. It must be mentioned that the dose used in the study by Stradling and colleagues [44] was considerably lower per kilo body weight than that used in the dog model [43]. In addition, a longer period of treatment may be needed to achieve maximal therapeutic effects with ondansetron [45].

### 3.2.5 Buspirone

The azapirone anxiolytic buspirone has been proposed to act on serotonin receptors and increase respiratory rate in animal models [46]. The only data available derive from one small (n = 5) randomised placebo-controlled crossover trial looking at the effect of a single dose of 20 mg buspirone on OSA severity; although not statistically significant, buspirone tended to improve OSA severity as the mean AHI fell from 30.8 to 19.6 [47]. Data on daytime sleepiness were not presented in this paper.

### 3.2.6 Physostigmine

Cholinergic activity also influences the upper airway function via central and peripheral mechanisms [48]. Physostigmine, an inhibitor of acetylcholine esterase activity, leads to muscle contraction via muscle end-plate depolarisation at the neuromuscular junction. In a study of patients with multiple system atrophy, an association between reduced thalamic nerve terminal density and severity of OSA was found, suggesting that decreased pontine cholinergic projections may contribute to OSA [49].



Based on this hypothesis, Hedner and co-workers [50] performed a single-night, randomised, placebo-controlled crossover trial of physostigmine, administered by overnight infusion (0.12 µg/kg/min), in 10 male patients with OSA. Physostigmine reduced AHI by 13.6 corresponding to 21.4% (AHI with placebo 54). During the last third of the night (with steady-state plasma concentration of physostigmine), AHI during non-REM sleep decreased by 19.2, or 14.9%, and AHI during REM sleep by 33.8, or 67.5%, respectively. Daytime sleepiness was not assessed in this trial.

### 3.2.7 Donepezil

Donepezil is an inhibitor of the acetylcholine-esterase enzyme and thereby enhances cholinergic transmission. Donepezil is the drug most frequently used to treat cognitive symptoms in Alzheimer's disease. In a randomised placebo-controlled trial, 11 patients with OSA and Alzheimer's disease were treated with donepezil 5 mg daily or placebo for 3 months [51]. In the donepezil group, AHI and ODI decreased significantly from 20.0 to 9.9 and 15.4 to 5.8, respectively, whereas there was no significant change in the placebo group. No data on daytime sleepiness are presented in this study report.

In a randomised, placebo-controlled, parallel-group trial, published only as an abstract, 20 patients with OSA (without Alzheimer's disease) received donepezil (5 mg daily) and 18 patients received placebo for 3 weeks [52]. Donepezil treatment was associated with a statistically significant reduction of 31% in AHI (from 35.6 to 24.4), with no change in the placebo group. Data on daytime sleepiness are not available from this study.

## 3.3 Drugs proposed to act on ventilatory drive

### 3.3.1 Aminophylline and theophylline

The effect of a single night of intravenous aminophylline, a methylxanthine known to have respiratory stimulant properties, on OSA severity in 10 patients was investigated in a crossover, single-blind, randomised, placebo-controlled study [53]. There was no change in either frequency or duration of obstructive apnoeas. Mean and minimal arterial oxygen saturation values also remained unchanged. No data on daytime sleepiness are given in this study report.

To date, data from two crossover, randomised, placebo-controlled studies published on the effects of theophylline on OSA severity are available [54,55]. In the study by Mulloy and colleagues [55], 800 mg of theophylline was given daily for 4 weeks to 12 male patients with OSA. There was a small statistically significant difference in AHI after 4 weeks of theophylline compared with placebo (AHI 40 and 48, respectively). Daytime sleepiness was not assessed in this trial. In the study by Hein and co-workers [54], 14 patients with mild OSA were given theophylline (daily doses of 600 or 900 mg to maintain serum levels of  $\geq 8$  mg/l) or placebo for 14 days. A small, statistically significant, decrease in AHI was observed with theophylline in comparison to placebo treatment (AHI 6.7 with theophylline and 9.2 with placebo). Data on daytime sleepiness were not presented in this report.

### 3.3.2 Acetazolamide

In a randomised, controlled study, 10 patients with OSA were treated with either acetazolamide 1000 mg/day or placebo for 14 days [37]. Acetazolamide reduced AHI significantly compared with placebo (AHI with placebo, 50; with acetazolamide, 26) and



improve daytime symptoms and was associated with significant side effects such as paraesthesias [37].

### 3.3.3 Naloxone and naltrexone

Naloxone and naltrexone are opiate antagonists and are proposed to inhibit endogenous opiates, which are thought to suppress respiration. The effects of naloxone/naltrexone on OSA severity were investigated in two published randomised, placebo-controlled, crossover studies [56,57]. Atkinson and colleagues [56] treated 10 OSA patients with naloxone (infusion of 5 mg over 5 min followed by 50 mg/h) during one night and found no difference in ODI compared with placebo treatment. Ferber and co-workers [57] treated 12 patients with a single dose of naltrexone 50 mg and placebo, and found a small but statistically significant reduction in AHI with naltrexone (29.1 versus 37.6). Daytime sleepiness was not assessed in either study.

### 3.3.4 Doxapram

The effect of a single night of doxapram hydrochloride (bolus of 0.5 mg/kg followed by infusion of 1 mg/min), a respiratory stimulant both peripherally at the carotid body and centrally at the respiratory centre, was investigated in only one small, randomised, placebo-controlled crossover study including four patients with OSA [58]. There was no significant difference in ODI between doxapram and placebo. Data on daytime sleepiness were not presented in this study report.

### 3.3.5 Almitrine

Almitrine, a piperazine, is a respiratory stimulant proposed to activate peripheral chemoreceptors located on the carotid bodies. In a randomised, placebo-controlled crossover trial, nine male patients with OSA were given almitrine (2 or 3 mg/kg up to 200 mg/d) for 5 days [59]. There was no significant difference in AHI between almitrine and placebo. No data on daytime sleepiness are available from this study.

## 3.4 Topical drugs proposed to act on the upper airway

### 3.4.1 Fluticasone

Data from early observational studies suggested that chronic nasal obstruction may promote OSA. Excessive mucosal swelling of the nasal turbinates, which is the predominant cause of high nasal resistance in patients with chronic rhinitis, can be addressed by topical application of sympathomimetic vasoconstrictors or topical nasal steroids. There is one published randomised, placebo-controlled, crossover trial investigating the effects of intranasal fluticasone (100 µg twice daily) on OSA severity in 13 patients [60]. Four weeks of fluticasone apparently led to a significantly lower AHI compared with placebo (23.3 versus 30.3), although the reported confidence intervals crossed 0, and did not improve oxygen saturation derivatives. Daytime sleepiness was not assessed with a scientifically approved method.

### 3.4.2 Xylometazoline

In a recently published randomised, placebo-controlled, crossover trial on the effects of intranasal xylometazoline (0.15 mg daily before bedtime) for 7 days, the authors found that, at

reduced compared with placebo (27.3 vs 33.2) [61]. However, xylometazoline did not improve sleepiness assessed subjectively and objectively in this trial.

### 3.4.3 Phosphocholinamin

Phosphocholinamin, an intranasally applied topical lubricant, is thought to reduce surface tension forces in the upper airway. The authors of a single-night randomised, placebo-controlled, crossover study reported significantly lower AHI and arousals with phosphocholinamin (0.4 ml) compared with placebo (AHI: 14 vs 24; arousals: 24 vs 32) [62]. Data on daytime sleepiness were not available from this study.

### 3.4.4 Salmeterol

Salmeterol is a long-acting selective  $\beta_2$ -adrenoceptor agonist that induces bronchodilation through relaxation of bronchial smooth muscles. Based on the hypothesis that salmeterol may also relax the inner pharyngoconstricting muscles, Rasche and colleagues [63] conducted a crossover, randomised, placebo-controlled study on the effects of a single salmeterol inhalation (50  $\mu$ g) on OSA severity in 20 patients. Compared with placebo, salmeterol had no significant effect on AHI. Data on daytime sleepiness were not included in this paper.

### 3.4.5 Surfactant

Surfactant, which reduces surface tension forces, has been shown to decrease the pressure required to reopen the pharynx when it is collapsed and to decrease upper airway resistance in dogs [64].

In a randomised, placebo-controlled study including seven males with OSA, surfactant (1 ml) or saline was instilled via a pharyngeal catheter over 1 min for a single night [65]. RDI decreased significantly with surfactant treatment (from 79.7 to 59.6), but not with placebo. Daytime sleepiness was not assessed in this study.

## 3.5 Antihypertensive drugs

Data from animal models suggest that higher blood pressure itself is associated with increased upper airway collapsibility and blood pressure reduction is associated with a decrease in apnoea frequency [66,67].

### 3.5.1 Cilazapril

In a randomised, placebo-controlled, parallel-group trial, 54 OSA patients were either treated with the angiotensin-converting enzyme inhibitor cilazapril (2.5 mg/d) or placebo for 8 days [68]. There was no statistically significant effect of cilazapril found on measures of OSA severity. Daytime sleepiness was not assessed in this study.

### 3.5.2 Clonidine

Clonidine is an alpha-adrenergic agonist that also suppresses REM sleep. In a randomised, placebo-controlled, crossover study, the effect of a 10-day course of clonidine (0.2 mg daily at bedtime) was tested in eight male patients with OSA [69]. In this trial, clonidine had no significant effect on OSA severity as measured by AHI and oxygen saturation derivatives. Daytime sleepiness was not assessed in this study.

### 3.5.3 Mibefradil

In a randomised, placebo-controlled, parallel-group trial, 48 OSA patients were either treated with the calcium channel antagonist mibefradil (200 mg/d) or placebo for 8 days [70]. There was no statistically significant effect of mibefradil found on AHI. No data on daytime sleepiness were available from this study.

## 3.6 Miscellaneous

### 3.6.1 Sabeluzole and AR-R15896AR

Altered glutamatergic activity has been proposed as a patho-mechanism in OSA. It has been proposed that apnoea-related hypoxia may lead to increased glutamate release in the central nervous system, which in turn generates ventilatory oscillations caused by the feedback of the respiratory chemical controller. The effects of glutamate on respiration have been attributed to activation of postjunctional NMDA receptors; in animal models, glutamate injected into the nucleus tractus solitarius of the medulla induced apnoea, and injection of a L-glutamate uptake inhibitor prevented the occurrence of apnoea [71]. Sabeluzole, a putative glutamate antagonist, has been shown to increase survival time in rat models of hypoxia [72]. Based on this positive effect in the animal model, Hedner and colleagues [73] investigated the effects of 2 weeks of sabeluzole (10 mg twice daily) on OSA severity in 13 patients in a randomised, placebo-controlled, crossover trial. There was no significant change in ODI with sabeluzole when compared with placebo and no difference between in OSA symptoms (assessed by visual analogue scale).

In a randomised, placebo-controlled, single-dose, crossover study of the NMDA receptor antagonist AR-R<sub>15896</sub>AR in 15 male patients with OSA, seven patients received 120 mg and eight patients received 350 mg or corresponding placebo (as infusion) [74]. AHI and ODI were not significantly changed after either dose of AR-R<sub>15896</sub>AR. Daytime sleepiness was not assessed in this study.

### 3.6.2 Sex hormones

Sex steroids may have a protective effect against the development of OSA. Postmenopausal women were shown to have a reduced genioglossus activity by electromyography; this increased after hormone replacement therapy [75].

### 3.6.3 Estradiol and progesterone

In a randomised, controlled trial, the effects of estradiol (50 mg/d released by a transdermal patch) or estradiol + progesterone (50 mg/d of estradiol and 200 mg/d of progesterone as capsules) versus placebo on OSA severity were evaluated in six postmenopausal women with OSA [76]. Estradiol monotherapy was associated with a significant reduction in AHI (from 22.7 to 12.2); in contrast, the reduction in AHI with estrogen + progesterone did not achieve statistical significance. Daytime sleepiness was not assessed in this pilot-study.

Medroxyprogesterone is a synthetic progesterone that is supposed to increase ventilatory responsiveness. Ten male patients with OSA were entered into a randomised, controlled, crossover study using medroxyprogesterone acetate 150 mg/day and placebo for 1 week [77]. There was no significant difference between drug and placebo for AHI. Daytime sleepiness was not formally assessed in this study.

### 3.6.4 Pantoprazole

Pharyngeal acid reflux may cause mucosal swelling that contributes to upper airway obstruction. Based on this hypothesis, 60 patients with OSA and gastroesophageal reflux disease were randomly assigned to a 2-week treatment with pantoprazole 40 mg and placebo in a crossover trial [78]. Unfortunately, objective measures of OSA severity were not performed in the study; subjective daytime sleepiness assessed by the ESS improved significantly (- 0.5 points) with pantoprazole when compared with placebo.

## 4. Expert opinion and conclusion

Choose

We found 33 randomised, placebo-controlled trials investigating the effects of 27 different drugs on OSA severity and/or symptoms. In some studies, a statistically significant improvement in OSA severity indices such as AHI and ODI was found, but complete normalisation of nocturnal breathing patterns was not achieved. It must be mentioned that interpretation of the results of the reviewed studies is difficult, as many were not appropriately powered and duration of pharmacological treatment was often too short to draw definitive conclusions.

Based on the findings from physiological studies showing that the tone in the upper airway musculature is lower during sleep in patients with OSA compared with normal control subjects, recent pharmacological approaches to the treatment of OSA have mainly focused on increasing output from serotonergic neurones and on enhancing cholinergic activity, as both have been shown to augment upper airway tone. Among the drugs thought to act on the upper airway tone, paroxetine [39], mirtazapine [32], physostigmine [50] and donepezil [51,52] all improved OSA severity indices to some extent.

The most promising data comes from trials investigating the effects of acetylcholine inhibitors such as physostigmine [50] and donepezil [51,52]. It must be mentioned that the mean BMI of the patients included in the study on the effects of physostigmine was only mildly elevated (27 kg/m<sup>2</sup>) and therefore the results of this study may not apply to more obese patients with OSA [50]. Also, physostigmine is not available in an orally active form, which limits its use in clinical practice. Donepezil is available in an oral form and is associated with relatively mild and transient side effects such as diarrhoea, nausea, and nightmares, among others (unfortunately there were no data on side effects reported in the two reviewed trials [51,52]), making it an interesting drug for further evaluation in larger placebo-controlled studies that include outcomes such as subjective and objective measures of daytime sleepiness. Such future trials will have to include younger patients without dementia, as the pathogenic factors of OSA may be markedly different from those in studied elderly demented patients.

The antidepressant mirtazapine was until recently another promising substance, as it has been shown to reduce OSA severity indices up to > 50% [32]. The results of two recently published trials on the effect of mirtazapine have, however, been disappointing, as both showed no improvement in OSA severity [42]. Furthermore, mirtazapine is also associated with weight gain and sleepiness, which may further worsen OSA and its main symptom. Although more data from randomised, controlled studies are needed to clarify the contradictory results of the reviewed studies, mirtazapine cannot be recommended for the treatment of OSA. Although treatment with another antidepressant, the serotonin reuptake inhibitor paroxetine, was

associated with a minimal decrease in OSA severity, this change was not of clinical relevance, and paroxetine [39] seems not to improve OSA severity or symptoms enough to recommend it as a treatment for OSA.

Earlier pharmacological approaches to the treatment of OSA focused on respiratory stimulation. Among the drugs thought to increase respiratory drive, theophylline [54,55], acetazolamide [37] and naltrexone [57] all improved OSA severity to a small extent. However, the reduction in OSA severity observed with theophylline and naltrexone was not of clinical significance. Acetazolamide reduced the number of apnoeas/hypopnoeas by almost 50%, but this positive effect was not associated with an improvement in daytime symptoms, and side effects such as paraesthesias were reported [37]. It therefore seems that increasing respiratory drive is not a promising approach to the treatment of OSA.

Another approach to the treatment of OSA is local application of drugs directly into the upper airway, with the aim of decreasing mucosal swelling and adhesion forces. Fluticasone [60], xylometazoline [61], phosphocholinamin [62], and surfactant [65] all showed only very minor effects on OSA severity indices. Daytime sleepiness was only assessed in the study using xylometazoline, and did not improve after active treatment. From the available data, it must be concluded that topical drug therapy is not sufficiently effective to be recommended as a treatment for OSA.

Randomised, placebo-controlled studies on the effects of antihypertensive drugs were uniformly negative regarding amelioration of OSA severity [68-70]. Because moderate-to-severe OSA may also lead to arterial hypertension, the drug trials reviewed here were mainly designed to investigate the blood pressure-lowering effects in patients with OSA, rather than to explore the effect on OSA severity itself.

Decreased levels of estrogen may be a risk factor for OSA in postmenopausal women, as there is evidence from one pilot study that estradiol monotherapy reduced AHI by almost 50% [76]. Clearly, more data from larger randomised, controlled trials are needed to confirm this promising result. However, the applicability of estradiol treatment would be limited to postmenopausal women only, and potential side effects of hormone replacement therapy – such as increased risk for cardiovascular and thromboembolic disease, as well as breast cancer – are further limitations.

Another promising pharmacological approach to the treatment of OSA is via weight reduction, as there is a strong relationship between obesity and OSA. Over 50% of obese people were found to have OSA in a cross-sectional study, with BMI/neck circumference being the strongest predictor of OSA [79]. In a population-based prospective cohort study, a 10% weight loss predicted a 26% decrease in AHI [80]. In a recently published uncontrolled cohort study on the effects of 6 months of sibutramine, a weight loss of approximately 9% was associated with a 35% reduction in OSA severity indices and a significant improvement in subjective daytime sleepiness [81]. Randomised, controlled trials on the long-term effects (and side effects) of sibutramine and other drugs considered for weight reduction therapy (e.g., orlistat) are now needed to prove their effectiveness in patients with OSA.

It has to be pointed out that almost all of the reviewed negative studies were underpowered to draw definite conclusions. Future clinical trials investigating the effect of a drug on OSA should include a power analysis to ensure that an appropriate number of patients are studied, thus allowing useful conclusions to be drawn from a negative finding. Furthermore, many of the reviewed studies tended to look at patients who had moderate-to-severe OSA. The lack of

a clinically significant effect is perhaps to be expected in this patient group, as a drug would have to be extremely powerful to reverse severe OSA. It is generally accepted that more severe OSA has a complex and multifactorial pathophysiology, and the primary perturbations probably differ among individual patients. Thus future studies may benefit from the inclusion of patients with milder forms of OSA, or even just snoring patients; and the study population should be homogeneous (regarding the severity of OSA and anthropometric measures), as this will lessen the chances of diluting any therapeutic effect. This is particularly important when trying to ascertain whether there is any pharmacological effect, in order to inform further drug developments in this area.

To date, there is not enough evidence from randomised, controlled trials to recommend any particular pharmacological treatment for OSA. There is some evidence from small trials that some drugs (especially those considered to increase upper airway tone, such as acetylcholine esterase inhibitors) have the potential to reduce OSA severity. Further randomised, controlled studies of adequate duration – including a larger number of well-characterised OSA patients, and with scientifically approved objective outcomes – are urgently needed to better define the effects of these drugs on OSA.

#### Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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