Drug Therapy in Obstructive Sleep Apnea

Jan Hedner, MD, PhD*, Ding Zou, MD, PhD

KEYWORDS

• Sleep • Obstructive sleep apnea • Drug • Medication • Therapy

KEY POINTS

- Current, mainly mechanical, therapies in obstructive sleep apnea (OSA) are frequently hampered by limited compliance (continuous positive airway pressure) or efficacy (mandibular advancement devices).
- Previous attempts to identify a drug therapy in OSA, in order to overcome these limitations, have been unsuccessful; there is currently no available pharmacologic alternative in this condition.
- Relevant experimental models of OSA are lacking, as sleep disordered breathing is a heterogeneous condition that involves multiple dominating pathophysiological traits.
- The current trend is to identify drug candidates that address selective mechanisms in OSA. This approach will provide a better understanding of the OSA condition and enable phenotyping OSA patients in future drug development programs.

GENERAL ASPECTS OF DRUGS IN OBSTRUCTIVE SLEEP APNEA

Overview

Obstructive sleep apnea (OSA) is a common condition that has turned out to provide a major challenge for physicians and the health care systems. This form of sleep disordered breathing is characterized by recurrent episodes of complete or partial obstruction of the upper airway, which causes periodic hypoxia and hypercapnia during sleep.[1] OSA leads to not only transient cortical arousals and sleep fragmentation but also to increased oxidative stress, autonomic dysregulation, and hemodynamic changes during sleep.[2] These consequences have been linked to daytime sleepiness as well as increased cardiovascular/metabolic morbidities in terms of arterial hypertension, coronary heart disease, stroke, type 2 diabetes and mortality in patients with OSA.[3]

Despite the high prevalence, treatment options for OSA are limited. So far there is no generally effective drug available for this condition. Nevertheless, several drug candidates have been proposed; there are currently steps taken toward more strategic development programs in OSA. Previous attempts to generate a drug therapy were more or less serendipity driven, and the literature in the area is characterized by small-scale studies. These studies have been reviewed in several publications in the area[4,5] as well as in a recent Cochrane review.[6] There are now better designed trials, which adequately address many of the potential pitfalls encountered in previous studies, under way. There is also considerable literature on interventional strategies that reside on the physiologic mechanisms, which appear during upper airway collapse in sleep.[7,8]

Disclosure Statement: Dr J. Hedner reports grants from the Swedish Heart-Lung Foundation and from the University of Gothenburg, grants from ResMed and from PhilipsRespironics related to European database work (ESADA), and personal fees from Itamar and AstraZeneca outside the submitted work. Dr J. Hedner has 2 patents related to OSA therapy, one pending and one issued. Dr D. Zou reports no conflicts of interest.

Department of Internal Medicine and Clinical Nutrition, Center for Sleep and Vigilance Disorders, Sahlgrenska Academy, University of Gothenburg, Medicinaregatan 8B, Box 421, Gothenburg SE-40530, Sweden
* Corresponding author.
E-mail address: Jan.hedner@lungall.gu.se

Sleep Med Clin 13 (2018) 203–217
https://doi.org/10.1016/j.jsmc.2018.03.004
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This article addresses some major methodologic problems encountered when designing clinical drug trials in OSA. The authors describe some major outcomes addressed in previous and ongoing studies, which more specifically include drugs with a potential effect on the various pathophysiologic mechanisms that have been associated with the sleep and breathing disorder. The authors also briefly address drugs with an effect on associated conditions, including sleepiness, obesity, arterial hypertension, gastroesophageal reflux, and conditions of the oronasal airway. Finally, the authors review endocrine mechanisms, including menopausal hormone replacement therapy, hypothyroidism, and acromegaly, that may be relevant to OSA pathophysiology.

Current Treatment Options

OSA is known to, pathophysiologically, during sleep involve anatomic predisposition for airway collapse, reduced compensatory neuromuscular control of the upper airway, and labile central neurochemical ventilatory control.[1] Continuous positive airway pressure (CPAP), a highly efficacious treatment in OSA, splints the upper airway but does not seem to modulate these fundamental underlying mechanisms. Moreover, the clinical utility of CPAP has been extremely well established for many years, but CPAP therapy is clearly limited by the incomplete tolerability and poor compliance.[9] Not only do several patients reject this form of therapy completely but there are also many who use CPAP only during part of the night. Partial use of the device will frequently leave several hours of residual sleep apnea every night and thereby tentatively only provide partial therapy for the sleep and breathing disorder.[10] Most outcome studies in the area have introduced a cutoff threshold of 4 hours per night, and there is evidence that this amount of use represents a minimum for long-term efficacious therapy.[11] However, there is considerable interindividual variation in the subjective sleep need, which probably should be better accounted for. Although the 4 hours may be close to adequate in some patients, they may only represent a fraction of a relevant sleep period in others.

With these limitations in mind, there is certainly an incentive to identify potential pharmacologic remedies in OSA. In fact, in a comparative sense, it may be argued that a drug therapy with only partial efficacy, for example, 50% reduction of OSA but present during 8 hours of sleep (alleviation of 50% of OSA), may result in a better therapeutic response than a mechanical device that induces a 100% reduction of OSA but only during 2 hours (alleviation of 25% of OSA) in an 8-hour sleeper. Clearly, future trials of pharmacologic therapies in OSA should introduce the component habitual sleep length in order to adequately compute effectiveness and the influence of therapy on various outcomes.[12] Incomplete compliance is also relevant for other mechanical therapies, such as intraoral devices, whereby the possibility to monitor and quantify use is in fact even more restricted compared with in CPAP.

Obstructive Sleep Apnea as a Target in Clinical Trials

There are no established regulatory guidelines related to the design of clinical trial programs in sleep disordered breathing. There is also uncertainty about appropriate clinical endpoints in trials and whether these should be focused on frequency markers, such as the apnea hypopnea index (AHI), markers of hypoxia, such as the oxygen desaturation index (ODI) or mean nocturnal oxygen saturation, daytime symptoms such as excessive daytime sleepiness, or comorbid disorders such as hypertension or metabolic disease.

Multicenter trials need to observe the risk of interscorer variability in studies using polysomnography and potentially apply centralized scoring functions. The choice of the recording technique applied, for instance, use of thermistor or pressure cannula in protocols, may markedly influence the results. Other challenges in clinical trials in OSA include night-to-night variability of the breathing disorder, variability resulting from the influence of body position change, variability related to differences between nights in sleep stage distribution (particularly in those with sleep stage–dependent apnea) or changes in OSA severity induced by external factors, such as drug or alcohol intake (**Table 1**). Although there are guidelines addressing scoring rules of sleep and breathing events, there is a need to better define general standards to be applied in large-scale clinical trials. Finally, as discussed later in this article, there is emerging evidence for distinct subphenotypes of OSA. This finding suggests that a particular pharmacologic remedy may be specifically effective in some patients but not in others. Hence, insights gained in clinical trials may help us to subselect and better define such specific groups of patients. The stricter, with respect to subphenotype, our protocols are designed, the better the efficacy of the intervention will be in this context.

Another problematic dimension related to drug development in OSA is the choice of appropriate outcome variables in clinical drug trials. Most

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