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CLINICAL REVIEW

Pharmacological treatment of sleep apnea: Current situation and future strategies

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Summary Current forms of mechanical treatment in obstructive sleep apnea (OSA) are generally effective in eliminating sleep and breathing disorders. However, they do have drawbacks, such as incomplete tolerability and non-compliance. Several attempts have been made to identify pharmacological treatments for OSA, but no drug has consistently reduced the severity of the condition by more than 50%. OSA, in most cases, is a condition characterized by considerable comorbidity, including hypertension, obesity, metabolic derangement and hormonal dysfunction. Daytime sleepiness and cognitive dysfunction represent common, but not consistent, findings in people with this nocturnal sleep and breathing disorder. Hence, future pharmacological treatments for OSA may need to take aspects other than the nocturnal breathing events alone into consideration. Drug research into OSA has been hampered by the lack of useful experimental systems and animal models for drug screening. In addition, the phenotypic characterization of OSA seems to be incomplete, and this limits the possibility of using stringent criteria for patient selection in drug studies. Finally, the criteria for defining the severity of OSA and disease impact seem to be insufficient for adequate definition of efficacy end points in clinical trials. This review will list some potential shortcomings and possibilities of pharmacological treatment in OSA, and discuss some of the already attempted modes of treatment.

Background

Current forms of treatment for obstructive sleep apnea (OSA) are almost exclusively mechanical. Properly applied and used mechanical devices can effectively eliminate sleep-disordered breathing. For example, continuous positive airway pressure (CPAP), which is the most effective form of treatment, usually eradicates episodes of airway collapse during sleep. However, the overall clinical utility of this device is hampered by incomplete tolerability and compliance, sometimes reaching as low as 50% in certain clinic populations.[1] On the other hand, practical use of oral appliances may be

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limited by incomplete efficacy, particularly in severe cases. Upper airway surgery is also limited by the success rate and insufficient long-term efficacy, despite guaranteed compliance.

It is evident that the treatment approach for sleep apnea aims to deal with the breathing disorder itself. However, it may eventually be necessary to target multiple aspects of the disease. Strategies that also address typical comorbidity in OSA (e.g., hypertension, obesity, metabolic derangement and insulin resistance) are important for reducing the risk of cardiovascular complications. Similarly, successful apnea reduction, such as that achieved during CPAP therapy, does not always preclude clinically persisting daytime somnolence. Thus, the key symptom of sleepiness in OSA may be a more complex problem than just a matter of sleep-disordered breathing events. It is possible that elimination of daytime sleepiness in some people with OSA needs to include measures other than mechanical treatment.

In view of the limitations of current treatment modalities for OSA, it is surprising that few systematic attempts have been made to identify pharmacological modes of treatment. This is also surprising when the high prevalence of OSA and the functional effect of OSA on daytime performance and the cardiovascular system are taken into account. However, the exact target for pharmacological treatment in OSA still remains to be defined, and we lack promising drug candidates. Other shortcomings include insufficient phenotypic characterization for people with OSA in studies of new drug candidates. The optimal metrics for definition of disease severity, in addition to insufficient definition of outcome measures to be used in the clinical trials, is also uncertain. In this review, we will outline some previous drug trials in OSA and highlight future considerations useful for rational drug development for OSA.

Lack of adequate experimental systems and animal models

Systematic drug development is time consuming, and may take decades from early drug discovery to final commercial production. This development traditionally requires adequate biological experimental systems or animal models. In OSA, few models have addressed the composite fundamental pathogenetic mechanisms of the disease. Some models of intermittent hypoxemia were developed to investigate on the biological consequences of periodic breathing. Other pharmacotherapeutic models of OSA reflect additional, but limited, aspects of the disease. Unless we develop adequate models of the disorder, we will have to rely on experimental testing of specific compounds in patients with induced disease. This is a time-consuming and complex task. It is possible that new drug targets will evolve from serendipitous findings (e.g., a certain drug is clinically observed to reduce OSA or its sequels). In fact, some of the existing attempts to identify drug treatments for OSA were initially serendipitous findings.

Patient recognition in clinical trials

Sleep-disordered breathing is a 'young' disease because systematic epidemiological mapping was not launched until the mid-1980s. It is evident that the condition presents in fundamentally different forms: as predominantly central or obstructive apneas. A drug proven to be effective in OSA may not be equally useful in central sleep apnea (CSA) or vice versa. Moreover, patients with purely obstructive apneas differ in phenotypic characteristics, such as gender, age of onset, obesity, body composition or craniofacial structure.

This apparent phenotypic heterogeneity in OSA suggests that stratification measures are needed in trials aiming to identify new drug candidates. For instance, an obese person with compromised upper airway patency throughout the sleep period may have activated completely different operational compensatory mechanisms than a lean person with airway collapse that solely occurs during rapid-eye-movement (REM) sleep periods. The application of CPAP, for example, will not differentiate clinically between these different types of patients, as both are likely to experience a similar benefit from the airway splint generated by the positive airway pressure. With a drug, it may be a different story. If the specific mechanism involved in upper-airway collapse differs, various OSA phenotypes should not be expected to respond uniformly well upon 'local' intervention with various modulator systems. On the contrary, different subgroups of people with OSA would be expected to be selectively responsive to a given pharmacological treatment. Although the critical descriptors for this phenotypic classification are still imprecise in OSA, components such as control of ventilation, obesity, craniofacial abnormalities, circadian rhythm and sleep regulation have been proposed to contribute to the development of the disorder.

Clearly, there is a need to understand the effect of each and every factor in order to properly identify suitable study candidates in future clinical