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Pharmacotherapy of Obstructive Sleep Apnea: Is Salvation Just Around a Corner?

Obstructive sleep apnea (OSA) is recurrent upper airway obstruction caused by a loss of upper airway muscle tone during sleep, which leads to intermittent hypoxia and sleep fragmentation (1). OSA is a common disorder affecting 25–30% of the adult population, and more than 50% of obese individuals (2). Continuous positive airway pressure (CPAP) relieves OSA, but poor adherence severely limits its use (3). Mandibular advancement devices have better compliance, but are not as effective as CPAP (4). There is no effective pharmacotherapy.

Successful drug development is possible only when the pathogenesis of the disease is fully understood. Four key pathophysiological mechanisms of OSA have been identified: anatomically compromised or collapsible upper airway, inadequate compensatory responses of the upper airway dilator muscles during sleep, a low arousal threshold, and an overly sensitive ventilatory control drive (5). Anatomic predisposition plays a primary role in OSA pathogenesis (6), whereas faulty neuromuscular mechanisms during sleep fail to compensate adequately for compromised pharyngeal patency (7).

The tongue plays a critical role in the pathogenesis of OSA and has been targeted for therapy (8). The upper airway patency is regulated by lingual protrudors, including the biggest upper airway dilator, the genioglossus (GG) muscle. Hypoglossal nerve electrical stimulation has been effective in activation of the GG muscle and relieving OSA in a subpopulation of patients intolerant of CPAP, but it is invasive (8). Until now, pharmacological approach did not reveal drug candidates, which effectively restore pharyngeal patency and treat OSA (9, 10).

Multiple potential targets on hypoglossal motoneurons have been identified, but until now translational studies either failed or had limited success (9). Serotonin (5-hydroxytryptamine) exerts excitatory effects on hypoglossal motoneurons, and withdrawal of serotonergic mechanisms has been previously considered as the main mechanism for loss of neuromuscular input during sleep (11). However, "the serotonin hypothesis" has been downplayed, because activation of serotonergic mechanisms had limited success in preclinical models (12) and clinical trials (13).

Subsequent studies from Horner's laboratory proposed distinct mechanisms of hypoglossal motor pool activation during non-REM (NREM) and REM sleep (14, 15). The investigators examined the role of an endogenous noradrenergic drive in maintaining GG muscle tone during sleep in rats. Microdialysis perfusion of the α1 receptor antagonist terazosin into the hypoglossal nucleus decreased GG activity, whereas the α1 receptor agonist phenylephrine increased GG activity during wakefulness and NREM sleep, but not REM sleep (14). The same group demonstrated that GG muscle tone in REM sleep is regulated by muscarinic receptors with a significant increase in GG muscle tone by muscarinic blockers without pronounced effects during wakefulness and NREM sleep (15).

This experimental work laid a foundation for a phase 1 clinical trial of desipramine (9), a tricyclic antidepressant blocking norepinephrine reuptake. Desipramine reduced pharyngeal collapsibility (Pcrit), but it had a very limited effect on the main marker of OSA severity, apnea–hypopnea index (AHI).

In this issue of the *Journal*, Taranto-Montemurro and colleagues (pp. 1267–1276) (16) reasoned, based on this experimental work, that a combination of norepinephrine reuptake inhibitor and muscarinic blocker may optimally modulate the GG muscle tone across sleep stages. The investigators performed a one-night randomized placebo-controlled double-blind crossover trial of a fixed dose of a norepinephrine reuptake inhibitor atomoxetine and an antimuscarinic drug oxybutynin, which they named ato–oxy.

Originally Published in Press as DOI: 10.1164/rccm.201811-2135ED on December 6, 2018

The investigators studied 20 patients with predominantly mild to moderate OSA and found that ato–oxy dramatically improved OSA compared with the placebo night. As a result of treatment, the AHI decreased from 28.5 to 7.5 events/h, and this decrease was accompanied by an increase in the oxygen saturation nadir. In a subset of patients with AHI $\geq$ 10, AHI was lowered by 74%, and all patients exhibited $\geq$50% reduction of AHI with significant improvement in sleep quality. This dramatic effect was mechanistically investigated and attributed to improved GG muscle response to the obstructive events. Notably, atomoxetine or oxybutynin alone did not reduce AHI.

The striking results of the study represent the first significant advancement in the pharmacotherapy of OSA. Another significant advantage of ato–oxy is that both medications used in this combination are thoroughly studied and approved by the U.S. Food and Drug Administration for treating attention deficit hyperactivity disorder (atomoxetine) and overactive bladder (oxybutynin) at the doses used in the current study. Nevertheless, there are significant limitations. First of all, although the effect of the drug combination was remarkable on a single night, it remains to be tested whether therapeutic benefits will be sustainable over time. Second, ato–oxy did not reduce arousals, and the patients had low sleep efficiency on a treatment night. The latter effect may be attributable to atomoxetine. The low arousal threshold is a well-known adverse effect of this drug. Nevertheless, in a subset of patients with AHI $\geq$ 10, ato–oxy improved sleep efficiency. The authors argue that oxybutynin may counterbalance negative effects of atomoxetine on sleep continuity. Third, another consequence of ato–oxy is REM sleep suppression, which may be a consequence of the antimuscarinic effects of oxybutynin. Fourth, both drugs are associated with multiple adverse effects, and the safety of the combination is yet to be determined. Atomoxetine is contraindicated in patients with severe cardiovascular morbidity and can cause increases in blood pressure and heart rate in susceptible individuals (17). Such adverse effects as nausea, dry mouth, fatigue, decreased appetite, urinary hesitation, and erectile dysfunction were also reported (18). Oxybutynin is contraindicated in patients with urinary retention, glaucoma, and gastric motility disorders (19). All of the above suggests that several categories of patients with high prevalence of OSA, such as patients with cardiovascular diseases, may not be candidates for ato–oxy. Only a single dose of ato–oxy has been investigated, and the dose response should be examined carefully. Future clinical trials should determine the safety profile, specific indications, and contraindications for the proposed combination in patients with OSA.

In conclusion, the article by Taranto-Monemurro and colleagues represents a significant advancement in the field of sleep medicine, opening a possibility for the first effective pharmacotherapy of OSA. It may revolutionize treatment of OSA, but more work needs to be done to assure the safety and effectiveness of this pharmacotherapy. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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