LETTER TO THE EDITOR

Precision Medicine in Obstructive Sleep Apnea

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To the Editor,

Obstructive sleep apnea is characterized by repetitive episodes of upper airway narrowing during sleep and is defined as more than five apneas or hypopneas per hour. Treating this anatomical abnormality with continuous positive airway pressure (CPAP) has long been considered the gold standard of OSA treatment. Despite the efficacy of CPAP in reducing apnea–hypopnea index (AHI), it has been shown the major caveat is poor adherence and noncompliance to CPAP therapy.[1] Thus, it has become imperative to find treatment alternatives for OSA. This requires understanding the pathogenesis of OSA. Apart from the anatomical narrowing of the upper airway either because of increased fat deposition or craniofacial abnormalities, abnormal response to this narrowing during sleep plays a major role in the development.

Adequate compensation would require enough pharyngeal dilator muscle activity to stiffen or dilate the upper airway, a higher arousal threshold to allow enough time for upper airway muscle compensation and a smaller increase in ventilatory drive in response to a given decrease in ventilation. Thus, OSA is found to arise due to the following four abnormal physiological traits: Increased pharyngeal collapsibility, increased loop gain, decreased muscle response (decreased upper airway gain), and lower arousal threshold.[2] Research has found multiple interventions to treat each of these pathophysiological traits.

Pharyngeal collapsibility (the anatomical abnormality) can be improved by CPAP, upper airway surgery, and oral devices. Upper airway surgery aims to modify or remove upper airway structures to increase the upper airway caliber. Maxillomandibular advancement surgery although highly efficacious depends on the preoperative AHI, and is best reserved for severe OSA refractory to CPAP and intraoral devices.[3] Uvulopalatopharyngoplasty, although shown to reduce AHI by 46%, is associated with slow relapse of OSA with an increase in AHI over the long term.[4] The response in AHI also is not consistent in all patients of OSA when done as a standalone procedure.[5] Loop gain may be reduced using oxygen or acetazolamide.[6,7]

Upper airway muscle response can be improved using hypoglossal nerve stimulation and a combination of atomoxetine and oxybutynin. Genioglossus is the main pharyngeal dilator muscle that helps increase upper airway caliber. Branches of the hypoglossal nerve that supply the genioglossus are primarily motor and hypoglossal nerve stimulation has been shown to reduce AHI, improve oxygen desaturation index, subjective sleepiness, and quality of life along with high adherence.[8] Decreased activity of genioglossus as measured by the electromyographic response in genioglossus in response to a drop in the pharyngeal pressure (measured by an epiglottic transducer) is due to the reduction in the noradrenergic drive during nonrapid eye movement (NREM) sleep and increased muscarinic suppression during rapid eye movement (REM) sleep. Atomoxetine is a selective norepinephrine reuptake inhibitor while atomoxetine is an antimuscarinic agent. The combination of atomoxetine and oxybutynin has been shown to increase upper airway muscle response and reduce AHI.[9] Arousal threshold can be increased using hypnotics like the non-benzodiazepine sedative eszopiclone.[10] Acetazolamide also has been shown to reduce AHI in patients in whom high loop gain is shown to contribute to OSA. A meta-analysis found that acetazolamide reduces AHI in OSA and CSA equally, the effect is higher with higher doses. It also improved the oxygen saturation nadir, sleep quality, and BP.[11]

A recent randomized controlled crossover trial studied the effects of the combination of acetazolamide and atomoxetine and oxybutynin in patients of moderate-to-severe OSA with AHI above 15 events/hour.[12] A total of 23 patients were enrolled, out of which 4 were excluded as their baseline AHI was below 15. A total of 19 patients were studied and randomly allocated to 1 of 4 treatment sequences. Each sequence had 4 treatment periods lasting 7 days including atomoxetine 80 mg, oxybutynin 5 mg (Ato-oxy), Ato-oxy and acetazolamide 500 mg (Acz), acetazolamide 500 mg alone, and placebo. The drugs were given at half the dose on the first day and full doses on the second and third days. Polysomnography (PSG) was done on day 3 followed by 4 days of treatment-free washout period. Half-lives of all the drugs were less than 8 hours thus allowing for around 15 half-lives between different interventions. The primary outcome studied was AHI, with secondary outcomes being a hypoxic burden and arousal index. AHI as measured by percent reduction from baseline, was found to be reduced with all three interventions compared to placebo. There was no additional

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reduction with Ato-oxy plus acetazolamide compared to Ato-oxy. Also, Ato-oxy showed a greater reduction in AHI compared to acetazolamide. There were similar effects in hypoxic burden (measured as the respiratory event-related area under the SpO_2 curve per hour of sleep). Ato-oxy alone group, and Ato-oxy and acetazolamide combination group improved pharyngeal collapsibility, although acetazolamide alone group did not. All three interventions reduced loop gain and the arousal threshold. Interestingly, the triple combination intervention reduced loop gain more than the Ato-oxy and acetazolamide alone, although this did not translate into a greater reduction in AHI. A sensitivity analysis was done to examine the effect on primary outcomes in different subgroups. It was shown that a greater AHI reduction was found in patients with moderate OSA, milder pharyngeal collapsibility, good muscle compensation, and lower loop gain. This implies that patients with milder diseases and milder physiological abnormalities were more likely to benefit from these interventions compared to patients with more severe abnormalities. The lack of benefit of Ato-oxy-Acz compared to Ato-oxy could be explained by the following three reasons: (1) Both drugs Ato-oxy and Acz act through a common mechanism, that is, increasing muscle activity; thus, leading to the combination being rendered less efficacious; (2) Atomoxetine promotes wakefulness being a noradrenergic agent, and acetazolamide increases ventilatory drive closer to the arousal threshold; thus, the efficacy of the combination could be limited by the ceiling effect on the arousal threshold; and (3) There could be a pharmacological ceiling effect for the present interventions in reducing pharyngeal collapsibility.

The limitations of this study were a smaller population and a shorter duration of treatment being studied. The median age of the study population was 45 years, thus the applicability of the findings to an older population with more comorbidities is not known. However, the study did show that there was a greater reduction in AHI in patients below 45 years of age compared to patients above 45 years of age. Furthermore, Ato-oxy and the combination reduce REM duration, although the reduction in AHI and improvement in hypoxic burden was found in NREM too, indicating that REM suppression is not solely responsible for the benefit.

Future studies are warranted to study Ato-oxy and acetazolamide further in patients with OSA separately, as the combination was found not to be beneficial. Also, the discovery of more potent agents that could improve more severely deranged physiological traits remains important. Studies designed to find the most ideal candidates that could derive the maximum benefit from these interventions need to be done. To conclude, precision medical therapeutics in obstructive sleep apnea need further research to find the ideal agent for the ideal population.

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