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Pharmacologic Therapy for Obstructive Sleep Apnea: Are We Seeing Some Light at the End of the Tunnel?

Obstructive sleep apnea (OSA) is a substantial global health concern, with almost a billion adults affected (1). Continuous positive airway pressure (CPAP) therapy is considered the primary therapy for the disease. CPAP is highly effective in alleviating hypoxemia, sleep fragmentation, and daytime sleepiness; regular use of a CPAP device is also associated with improved long-term outcomes such as cardiovascular disease (2). However, one of the major challenges with CPAP is acceptance of and adherence to therapy. Although alternative therapies to CPAP exist (e.g., oral appliances, hypoglossal nerve stimulation, upper airway surgery, weight loss), we desperately need to develop other treatments. A variety of pharmacologic approaches have been attempted to treat individuals with OSA, including serotonin reuptake inhibitors (3), hormones (4), and nicotine (5), to name just a few; these attempts have not been successful, and to date, there are no approved pharmacologic therapies for this common disease (6).

In this issue of the *Journal*, Schweitzer and colleagues (pp. 1316–1327) report the results of MARIPOSA, a phase II trial of AD109, a combination of an anticholinergic (aroxybutynin) and a noradrenergic reuptake inhibitor (atomoxetine) (7). As shown by *in vivo* animal studies, these drugs can increase the activation of the genioglossus muscle and may thus reduce the upper airway collapse associated with OSA (8). The MARIPOSA investigators randomized 209 patients with OSA (age 18–65 yrs in men, 18–75 yrs in women, apnea–hypopnea index [AHI] 10–45 events/h, body mass index $\leqslant$ 38 kg/m^2 in men and $\leqslant$40 kg/m^2 in women) to one of four treatment arms—lower dose AD109 (2.5 mg aroxybutynin and 75 mg atomoxetine), higher dose AD109 (5.0 mg aroxybutynin and 75 mg atomoxetine), atomoxetine alone (75 mg), or placebo—for four weeks. In the modified intention-to-treat analysis (n = 181), there were significant reductions in 4% AHI (primary outcome) in all three active arms (placebo-adjusted reductions in AHI of 5.19 events/h with atomoxetine alone, 7.16 events/h with low-dose AD109, and 7.20 events/h with higher dose AD109).

The results of this trial are consistent with and extend those of a previous one-night crossover trial and represent an important step forward in the field (9). However, a number of issues should be considered. First, although there was a reduction in the Patient Reported Outcome Measurement Information System Fatigue score in the lower dose AD109 group, other patient-reported outcomes were not significantly improved (though this might have been due to the relatively low number of participants and short duration of the study). This lack of improvement in subjective outcomes might also be explained by the significant proportion of participants who had been previously exposed to primary OSA therapy, including CPAP. This previous negative experience with treatment might have partially biased evaluations of subjective outcomes.

Second, side effects were more frequent among participants who received the drug; adverse events were reported in 61.9% of

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participants in the lower dose AD109 group, 78% in the higher dose AD109 group, 81% in the atomoxetine-alone group, and 39.7% in the placebo group. Consistent with the known side effects of these drugs, the most common were dry mouth, insomnia, and urinary hesitancy. Of the 23 participants who discontinued the study for side effects, 22 were in one of the treatment arms (5 for each dose of AD109, 12 in the atomoxetine-alone group).

Finally, cardiovascular safety was poorly documented, but there was an increase in heart rate in the morning in all treatment arms and in diastolic blood pressure in the lower dose AD109 group. The elevation of diastolic blood pressure (about 4 mm Hg), if confirmed in the long term, might have an impact on cardiovascular outcomes. Such a blood pressure increase has previously been reported with solriamfetol, a selective dopamine and norepinephrine reuptake inhibitor wake-stimulant agent, leading insurers to not reimburse the highest dose (300 mg) for the indication of residual sleepiness in patients with OSA (10). Given the high prevalence of comorbidities in patients with OSA, any potential cardiovascular effects need to be cautiously monitored in longer trials.

The many concerns raised here may be addressed by ongoing large, phase III, multisite randomized controlled trials (LunAIRo [Parallel Arm Trial of AD109 and Placebo With Patients With OSA; NCT05811247], SynAIRgy [Parallel-Arm Study to Compare AD109 to Placebo With Patients With OSA; NCT05813275]) in which patients are randomized to AD109 or placebo for 6–12 months. These longer randomized controlled trials are required to establish the long-term efficacy, safety, tolerability, and potential health benefits of drug therapy for OSA.

The hope for a pharmaceutical approach to OSA is an exciting direction for the field, and MARIPOSA is one of the first steps toward this goal. This study also demonstrates the usefulness of translational animal work in upper airway neural circuitry in helping discover viable targets for sleep apnea therapies (11). Future studies should assess whether specific drugs may be more effective in particular physiologic endotypes (12) and whether the assessment of these endotypes may help match the right pharmacotherapy to the right patient. For example, patients with a reduced muscle response to respiratory stimuli may be more likely to respond to drugs that activate the genioglossus (such as AD109), while patients with high gain of the respiratory system may respond to drugs that dampen gain (13, 14). In addition, combined treatments targeting multiple physiologic targets may be a fruitful future direction. ■

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