EDITORIAL

Entering a New Era in Sleep-Apnea Treatment

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Obstructive sleep apnea is one of the most common respiratory disorders worldwide. Persons with obstructive sleep apnea can have loud snoring that is detrimental to social relationships and have breathing problems that result in recurrent nocturnal awakenings, unrefreshing sleep, and excessive daytime sleepiness — effects that together can substantially impair quality of life. Excess weight is the most important risk factor for obstructive sleep apnea; it is responsible for approximately 60% of moderate-to-severe cases of obstructive sleep apnea in the United States.[1] Clinical guidelines therefore recommend evidence-based weight-loss strategies as part of the comprehensive management of obstructive sleep apnea.[2] Unfortunately, the integration of obesity management into the approaches to care for obstructive sleep apnea has lagged, even though sleep specialists acknowledge the limitations of current treatments for obstructive sleep apnea — including continuous positive airway pressure (CPAP) therapy, which is abandoned by nearly 50% of patients within 3 years.[3] An effective medication to treat obesity is thus an obvious avenue to pursue as a pharmacologic treatment for obstructive sleep apnea.

Malhotra et al.[4] now report in the *Journal* results of the SURMOUNT-OSA trial evaluating tirzepatide, a dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, to treat participants with moderate-to-severe obstructive sleep apnea and coexisting obesity. The SURMOUNT-OSA trial included two substudies of tirzepatide therapy: one involving participants who were receiving stable CPAP therapy and one involving participants for whom CPAP therapy had failed or had proved unacceptable. Over a period of 52 weeks, treatment with tirzepatide at a dose of 10 to 15 mg weekly as compared with placebo resulted in a reduction in weight of approximately 16 to 17% across both substudies. The weight loss was accompanied by a reduction in the apnea–hypopnea index (AHI) as compared with placebo (the primary end point) of 20 to 24 events per hour, a relative reduction in events of 48 to 56%. Most of the reduction in the AHI was apparent as early as 20 weeks after the initiation of tirzepatide therapy, when participants had reached their appropriate adjusted doses of tirzepatide. A clinically important improvement in systolic blood pressure levels was also observed, particularly among participants who were not receiving CPAP therapy. Treatment with tirzepatide had an acceptable side-effect profile, with most side effects gastrointestinal in nature.

Whether tirzepatide improves patient-centered outcomes in obstructive sleep apnea remains unclear because a change in the AHI has not been validated as a surrogate marker of clinically relevant end points.[5] The investigators report significant improvements in nighttime sleep quality and in scores on assessments of daytime sleepiness (the Patient-Reported Outcomes Measurement Information System [PROMIS] assessments). However, experience with the performance of these novel metrics in treatment studies for obstructive sleep apnea is limited, and preliminary work indicates the minimal clinically important difference for both PROMIS instruments may be larger than the approximately 3-point reduction in T scores observed with tirzepatide as compared with placebo.[6] The investigators collected, but do not yet report analyses of, additional patient-reported

outcome measures with established minimal clinically important differences, such as the Epworth Sleepiness Scale and Functional Outcomes of Sleep Questionnaire. These additional data from the SURMOUNT-OSA trial will be necessary to fully understand the magnitude of clinical benefit and allow comparisons with existing therapies for obstructive sleep apnea.

The improvement in systolic blood pressure that was seen with tirzepatide was substantially larger than effects seen with CPAP therapy alone[7] and indicate that tirzepatide may be an attractive option for those patients who seek to reduce their cardiovascular risk. Long-term trials of tirzepatide with a focus on major cardiovascular events will be needed to confirm this approach.

The potential incorporation of tirzepatide into treatment algorithms for obstructive sleep apnea should include consideration of the challenges of adherence to treatment and the imperative to address racial disparities in medical care. A major limitation of CPAP therapy in obstructive sleep apnea has been suboptimal adherence to treatment. Although adherence to tirzepatide therapy in the SURMOUNT-OSA trial was high, real-world evidence suggests that nearly 50% of patients who begin treatment with a GLP-1 receptor agonist for obesity discontinue therapy within 12 months.[8] Thus, it is likely that any incorporation of tirzepatide into treatment pathways for obstructive sleep apnea will not diminish the importance of long-term strategies to optimize adherence to treatment. Furthermore, racial disparities in the use of GLP-1 receptor agonists among patients with diabetes arouse concern that the addition of tirzepatide as a treatment option for obstructive sleep apnea without directly addressing policies relative to coverage of care will only further exacerbate already pervasive disparities in clinical care for obstructive sleep apnea.[9,10]

The initial results from the SURMOUNT-OSA trial show the usefulness of tirzepatide as an adjunctive treatment to address coexisting obesity in patients with obstructive sleep apnea. Weight loss resulting from tirzepatide treatment may be leveraged to expand the populations that may benefit from second-line treatments for obstructive sleep apnea, such as mandibular-advancement devices or hypoglossal-nerve stimulation. Additional analyses of the effects of tirzepatide on a broader range of patient-reported outcome measures by the SURMOUNT-OSA team will be eagerly awaited to evaluate the potential utility of tirzepatide as a sole treatment for obstructive sleep apnea. If the results of those analyses are promising, the news of an addition of a pharmacologic option to the clinical armamentarium for obstructive sleep apnea will be welcomed by many patients and clinicians alike.

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