Obstructive Sleep Apnea: Advancing Clinical Outcomes with Incretin Mimetics

Obstructive sleep apnea (OSA) is associated with a higher risk of cardiometabolic complications, cardiovascular-related mortality, and all-cause mortality. Individuals with comorbid obesity are particularly vulnerable as obesity not only puts patients at a higher risk of developing OSA, but it is also linked to cardiometabolic complications. Despite the availability of effective treatment, many people with OSA, including those living with obesity, are underdiagnosed and undertreated. To address this gap in clinical practice, we propose an educational program for primary care physicians aimed at enhancing the identification of high-risk individuals and facilitating the initiation of evidence-based treatments to improve patient outcomes

Gaps	Learning Objective	Outcomes
Patients at high risk of OSA are not being screened	Identify patients who should be screened for OSA based on guideline recommendations	Use case-based multiple choice questions to measure clinicians' ability to recognize characteristics that should prompt screening and evaluation for OSA
Patients with OSA and obesity are undertreated	Summarize efficacy and safety data of incretin mimetics for the treatment of OSA Apply guideline recommendations and current evidence on incretin mimetics to patient care when managing patients with OSA.	Use multiple choice questions to measure clinicians' awareness of clinical trial findings Use case-based multiple choice questions to evaluate clinicians ability to utilize incretin mimetics based on guideline recommendations and current evidence

Needs Assessment

OSA is a common and potentially lethal condition that affects 34% and 17% of middle-aged men and women, respectively, in the US.[1] More than 900 million people are affected worldwide.[2] Males, older individuals, post-menopausal women, individuals with upper airway abnormalities, and those living with obesity are at higher risk of OSA.[3]

OSA is caused by the intermittent collapse of the upper airway during sleep. This leads to multiple brief episodes of apnea and hypoxia during sleep and their attendant consequences such as daytime sleepiness and fatigue, impaired mental health, reduced productivity, and increased risk of road traffic accidents.[4] OSA is also associated with a myriad of medical conditions, particularly cardiometabolic disorders.

About 70% of patients with resistant hypertension, 40% to 80% of patients with cardiovascular disease, and 45% of patients with obesity have OSA.[1,5,6] In addition to the high prevalence of OSA among patients with obesity, weight gain is associated with the progression of OSA.[6] The likelihood of a worse OSA severity is 14% greater per each point increase in body mass index (BMI) and 61 % higher per each 0.1 unit increase in waist/hip ratio.[7] A 10 % weight gain predicts a 6-fold odds of developing moderate to severe OSA.[7]

Like OSA, obesity is associated with cardiometabolic comorbidities and a higher risk of cardiovascular death. As such, patients with concomitant obesity and OSA have a high risk of cardiovascular morbidity and mortality. Considering the increasing prevalence of obesity, there is an urgent need to treat patients with obesity and OSA. Inadequate diagnosis and treatment of OSA impact not only the patient but the general public as well.

Positive airway devices, mandibular advancement, and weight loss are helpful treatment strategies. Weight loss not only improves OSA severity but also combats the cardiometabolic abnormalities common to OSA and obesity. Positive airway pressure is the mainstay of treatment as it improves apnea and alleviates symptoms associated with OSA. However, its effectiveness varies and is closely tied to patient adherence. These devices are often challenging to use, especially at the onset, as many patients find them a nuisance.[8] Furthermore, some randomized controlled trials failed to demonstrate a reduction in cardiovascular events with positive airway pressure therapy for patients with established cardiovascular disease and OSA.[9–11] These findings underscore an urgent need for alternative interventions that address the unmet clinical needs in patients with OSA, including those living with obesity. Until recently, there was no approved drug treatment for OSA. Given the recent approval of tirzepatide for OSA in adults with obesity and the unavailability of guideline recommendations to help clinicians identify patients who would benefit from pharmacotherapy, educational programs are warranted.

Gap 1: Many patients with OSA are undiagnosed.

Only approximately 10% of patients with OSA are diagnosed.[5] Undiagnosed OSA patients are unable to avail themselves of interventions that could improve sleep, thereby putting patients at risk of untoward sequelae. Additionally, patients with undiagnosed OSA have higher medical costs compared with those who do not have OSA, estimated at $1950 to $3899 each year.[4] Primary care physicians must make a concerted effort to diagnose patients.

Poor screening practices partially account for the high incidence of underdiagnosis. Other factors contributing to underdiagnosis are patients' lack of serious attention to symptoms, patients' negative perceptual framing of diagnosis and treatment of OSA, and poor coordination of health care services.[12] Although the U.S. Preventive Services Task Force (USPSTF) states that the current evidence is insufficient to assess the balance of benefits and harms of screening for OSA in the general adult population, screening is advocated in high-risk populations and symptomatic patients.[3] Screening for OSA is recommended in individuals with symptoms such as daytime sleepiness, loud snoring, or abrupt awakenings with gasping or choking.[13]

The American Heart Association also recommends screening for OSA in patients with resistant/poorly controlled hypertension, pulmonary hypertension, a nondipping nocturnal blood pressure profile on ambulatory blood pressure monitoring, repetitive bradyarrhythmias captured by electronic wearable devices during sleep, and recurrent atrial fibrillation after either cardioversion or ablation.[1,13] Other individuals who require screening are those with New York Heart Association class II to IV heart failure, tachy-brady and sick sinus syndrome, ventricular tachycardia, survivors of sudden cardiac death, and stroke.[13] In addition to these individuals, the American Academy of Sleep recommends screening for individuals with a body mass index ≥ 30 kg/m^2 and those undergoing bariatric surgery.[14] Approximately 40% of individuals on the waiting list for bariatric surgery meet the criteria for OSA.[7]

Validated screening tools such as STOP-BANG or Berlin are recommended for OSA screening.[14] Patients at high risk for OSA following screening should then receive a comprehensive sleep evaluation that includes an overnight sleep study in an accredited sleep center or a home sleep apnea test. To diagnose OSA, the frequency of respiratory events (respiratory disturbance index) should be at least 5 per hour on a sleep study.[13]

The benefits of timely diagnosis are profound given the vast consequences of undiagnosed and untreated OSA. Medical consequences include hypertension, obesity, type 2 diabetes mellitus, cardiovascular disease, stroke, impotence, anxiety, and depression. Patients with OSA have a higher risk of cardiovascular-related and all-cause mortality.[4] Perioperative complications, such as the need for prolonged intubation, need for re-intubation, pneumonias, aspiration, arrhythmias, and cardiac arrest more frequent in those with untreated sleep apnea. In addition, when sleep apnea is diagnosed before surgery, the risk of cardiac and neurovascular events is decreased by about 50%, highlighting the need for screening in high-risk patients such as those undergoing bariatric surgery. Beyond medical implications, OSA is associated with a higher risk of road traffic accidents and workplace accidents. In the year 2000, more than 800,000 drivers were involved in OSA-related vehicular accidents, and it cost $15.9 billion and 1,400 lives.[15] There is thus an urgent need for prompt diagnosis and treatment of OSA.

Gap 2: HCPs are unaware of the role of incretin mimetics in OSA management

Positive airway pressure (PAP) is the most effective treatment for OSA.[13] Continuous positive airway pressure is the gold standard, and it delivers a preset pressure that keeps the airway open during sleep.[5] OSA patients who are treated with continuous positive airway pressure cost $2700-$5200 less per year than those not receiving treatment. Other positive airway pressure devices are the automatic self-adjusting positive airway pressure and bilevel positive airway pressure.[5] However, adherence with positive airway pressure is often suboptimal, and barriers to their uptake include mask-related discomfort, psychological resistance, bulky machine, noise from the machine, travelling difficulties, and airway dryness.[16]

The need to treat patients cannot be overemphasized, given the deluge of medical, emotional, and economic consequences of untreated OSA. Pharmacologic interventions had hitherto shown limited benefits and had little to no role in OSA management.[17] However, incretin mimetics have recently shown promise in patients with OSA living with obesity.

Liraglutide

The SCALE sleep apnea randomized, double blind placebo trial investigated whether liraglutide 3mg would reduce OSA severity compared with placebo. All patients received CPAP. Three hundred and fifty-nine patients were randomized, but 276 completed the trial. Liraglutide was associated with greater mean reduction in apnea-hypopnea index (−12.2 vs −6.1 events h−1, estimated treatment difference: −6.1 events h−1 (95% confidence interval (CI), −11.0 to −1.2), P=0.0150). In addition, liraglutide led to significantly greater reductions than placebo in body weight, systolic blood pressure, and glycated hemoglobin levels in participants.[18]

Tirzepatide

The SURMOUNT OSA trials involving tirzepatide recently showed positive findings in patients with OSA living with obesity. Tirzepatide is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist popularly known as a twincretic approved for treating obesity and type 2 diabetes mellitus. The two 52-week phase 3 multicenter SURMOUNT-OSA trials consisted of 469 people with moderate to severe OSA and obesity (BMI ≥30 [≥27 in Japan]) who were randomly assigned in 1:1 ratio to receive maximum tolerated dose of tirzepatide (10mg or 15mg) or a placebo unwilling or unable to use PAP (trial 1) and participants who had been using PAP for at least 3 months who planned to continue using it (trial 2). In trial 1, the mean change in apnea-hypopnea index (AHI) at week 52 was −25.3 events per hour (95% confidence interval [CI], −29.3 to −21.2) with tirzepatide compared with −5.3 events per hour (95% CI, −9.4 to −1.1) with placebo (P<0.001).[2] Similarly, trial 2 led to a mean change in AHI at week 52 of −29.3 events per hour (95% CI, −33.2 to −25.4) with tirzepatide and −5.5 events per hour (95% CI, −9.9 to −1.2) with placebo (P<0.001).[2] Furthermore, tirzepatide reduced body weight and systolic blood pressure and improved sleep-related patient-reported outcomes.[2] The most commonly reported side effects with tirzepatide were gastrointestinal. The frequency of serious adverse events was similar in both groups.[2]

Based on the findings of the SURMOUNT-OSA trials, the FDA approved tirzepatide to be used in combination with a reduced-calorie diet and increased physical activity for the treatment of moderate to severe obstructive sleep apnea (OSA) in adults with obesity.[19] With this new approval, HCPs who care for patients who have obesity and OSA need updates on the efficacy and safety data of tirzepatide, recognition of patients who would benefit from it, and initiation of tirzepatide whilst implementing risk mitigating strategies.

Conclusion

Undiagnosed and untreated OSA poses an immense physical, mental, and economic burden on patients. Despite the high prevalence of the disorder, it remains grossly underdiagnosed. Screening of high-risk individuals, including individuals living with obesity, is crucial to timely recognition. With the recent approval of tirzepatide in individuals with obesity and moderate to severe OSA, educational initiatives are warranted.

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