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REVIEW

Current perspectives on the use of GLP-1 receptor agonists in obesity-related obstructive sleep apnea: a narrative review

Ali A. El-Solh [a,b,c], Erin Gould[b], Keziah Aibangbee[b], Tanya Jimerson[b] and Rebecca Hartling[b]

[a]Sleep Disorders Research Center, Western New York Healthcare System, Buffalo, NY, USA; [b]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, NY, USA; [c]Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, Buffalo, NY, USA

ABSTRACT

Introduction: Traditionally, obstructive sleep apnea (OSA) management has focused on continuous positive airway pressure therapy, oral appliances, and in some cases, surgical interventions. However, these treatments do not directly address the underlying metabolic issues contributing to OSA. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), originally developed for type 2 diabetes management, have demonstrated substantial efficacy in promoting weight.

Areas covered: This review aims to summarize the potential impact of liraglutide, semaglutide, and tirzepatide in managing obese patients with OSA.

Expert opinion: The introduction of GLP-1 RAs has gained attention not only for their ability to produce significant and sustained weight loss but also for their potential to improve OSA symptoms by reducing fat deposition around the upper airway and decreasing systemic inflammation. Emerging clinical trials suggest that GLP-1 RAs may enhance traditional OSA treatments, offering an integrated approach targeting the root cause of obesity in OSA. Additionally, GLP-1 RAs may provide benefits for other obesity-related comorbidities, including hypertension and cardiovascular disease, which are commonly associated with OSA. The future integration of GLP-1 RAs into OSA treatment protocols could mark a paradigm shift toward more comprehensive management strategies, ultimately improving patient outcomes in this complex patient population.

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Glucagon-like peptide-1 receptor agonists; obesity; sleep apnea; weight loss; continous positive airway pressure; hypoglossal nerve stimulation

1. Introduction

Obstructive sleep apnea (OSA) is a highly prevalent sleep condition associated with many chronic resource-draining ailments. The sleep disorder is characterized by recurrent episodes of cessation (apnea) or decreased inspiratory airflow (hypopnea) during sleep, often associated with reduced oxyhemoglobin saturation and cortical arousals [1]. These physiologic perturbations result in sleep fragmentation manifested as snoring, excessive daytime sleepiness, witnessed apnea, decreased libido, cognitive impairment, and reduced quality of life [2,3]. OSA also induces chronic neurohumoral and metabolic derangements leading to chronic hypertension, type II diabetes, cardiovascular morbidity and mortality [4–6], and even cancer [7,8].

Population-based studies on the prevalence of OSA in adult populations showed consistent estimates despite variability in definitions, sample construction, and statistical techniques. Most recent updates on OSA prevalence revealed that 13–15% of men and 5–6% of women have clinically moderate to severe OSA (defined by an apnea-hypopnea index [AHI] > 15/h) [9,10]. Assuming a 15% population prevalence, more than 39 million people in the United States alone are expected to have OSA [11]. The global estimates of OSA exceed 930 million people worldwide with a vast swath of the population being undiagnosed or undertreated [12]. Not surprisingly, the annual economic burden of untreated sleep apnea among US adults is approximately $149.6 billion divided into $86.9 billion in lost productivity, $26.2 billion in motor vehicle accidents, and $6.5 billion in workplace accidents [13].

It is long-established that obesity plays a prominent role in the pathogenesis of OSA [14,15]. While the prevalence of OSA in the general population is estimated at 15% [16], the diagnosis of OSA approaches 50% to 77% in individuals with morbid obesity (Body Mass Index [BMI]≥ 45 kg/m^2) [17]. In those with BMI ≥60 kg/m^2, OSA is present in nearly 90% of patients [18]. According to the Wisconsin Sleep Cohort Study data, an increase of one standard deviation in BMI is associated with a four-fold increase in the prevalence of sleep apnea [19]. Alternatively, a 10% increase in body weight is associated with a six-fold increase in the risk of developing OSA over 4 years. Notwithstanding, the relationship between body weight and OSA is not straightforward. The severity of sleep apnea does not always correlate with BMI [20]. It is the indices of central obesity (i.e. central fat mass) that have been shown to have a more robust association with moderate to severe sleep apnea than BMI [21]. The strength of this relationship between obesity and OSA is further substantiated by experimental and longitudinal cohort studies documenting a substantial relief from sleep-disordered breathing events

CONTACT Ali A. El-Solh solh@buffalo.edu Sleep Disorders Research Center, VA Western New York Healthcare System, 3495 Bailey Avenue, Buffalo, NY 14215-1129, USA

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Article highlights

- In obese patients with OSA, GLP-1 RAs promote substantial weight loss, which can reduce fat deposits around the upper airway, helping to alleviate upper airway obstruction potentially lowering the need for high CPAP pressure.
- GLP-1 RAs help mitigate the cardiovascular risks associated with both OSA and obesity by lowering blood pressure, improving metabolic profiles, and reducing inflammation.
- In obese patients with OSA, GLP-1 RAs can complement existing therapies, such as mandibular advancing devices or hypoglossal nerve stimulation to address residual respiratory events.
- While effective for weight loss, GLP-1 RAs are not substitute for CPAP therapy in patients with OSA.
- Common side effects like nausea and vomiting, although transient in nature, may limit the tolerability of GLP-1 RAs in some patients.
- While short-term improvements in OSA severity have been observed in obese patients with OSA, long-term data on the sustained impact of GLP-1 RAs on OSA outcomes are still limited.

after weight loss [22–25]. Both prospective and randomized controlled trials (RCTs) incorporating weight loss interventions in OSA suggest a dose-response relationship between BMI and improvement in apnea-hypopnea index (AHI) [25–27]. Although a precise formula is yet to be deciphered, as a rule of thumb, it is estimated that for every 7-pound drop in weight, a corresponding change in AHI of 7% is expected [28].

The mechanisms linking obesity to sleep apnea are multifactorial, although they are mostly attributed to direct mechanical effects on the upper airway patency and the respiratory system [29]. Fat deposition in the anterolateral region of the pharynx and posterior tongue exerts a centripetal force on the walls of the upper airway reducing its luminal diameter [30]. When combined with abdominal visceral adiposity, pharyngeal collapsibility is accentuated by a reduction in functional residual capacity, resulting in a loss of caudal traction on the mediastinal structures, thus engendering repeated upper airway closure [31,32]. Moreover, obesity appears to confer a state of leptin resistance to its respiratory and metabolic effects [33]. The diminished response to leptin despite higher circulating levels than those observed in lean individuals alters the neuromuscular control of the pharyngeal lumen leading to higher pharyngeal collapsibility [34].

Although effective management of sleep apnea alleviates the symptoms of excessive daytime sleepiness, ameliorates cognitive function, and improves sleep quality of life, it does little to alter the trajectory of obesity [35,36]. When used in conjunction with a weight loss program (i.e. lifestyle interventions or diet modification), OSA treatment does not always lead to significant changes in BMI [37]. To complicate matters further, even with exemplary adherence to diet and high-intensity exercise programs, the magnitude of weight loss is considered modest at best. In addition, most patients who lose considerable weight with these regimens regain at least 50% of it in 2 to 3 years [38].

Anti-obesity medications (AOMs) have been recommended for OSA patients with BMI ≥27 kg/m2 who were unable to achieve or sustain weight loss despite comprehensive lifestyle modification [39]. Up until 2014, the US Food and Drug Administration (FDA) has approved five AOM agents. Two of those, Phentermine/topiramate ER (Qsymia) and Orlistat (Xenical) were evaluated in two separate RCTs involving patients with sleep apnea [40]. Both agents improved quality of life, but, changes in AHI were only reported with the combination of phentermine/topiramate ER and were modestly correlated with the amount of weight loss [40,41]. However, it is the entry of glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-I RA) into the arena of diabetes management that promises to cause a paradigm shift in the treatment of obese patients with OSA. An excellent review on the pharmacological mechanisms of GLP-1 RAs, their effectiveness across multiple body systems, and their potential impact of on obstructive sleep apnea-associated metabolic dysregulation was recently published [42]. This narrative review aims to synthesize the utility of FDA-approved GLP-1 RAs about obesity management in the context of sleep apnea with emphasis on recently published clinical trials, and provide an expert opinion on therapeutic algorithm for the use of these agents in patients with coexisting OSA and obesity.

2. Methods

A search of PubMed, Medline, and Embase for articles published between 2010 and 2024 was conducted by combining the terms 'GLP-1,' 'GLP-1 RA,' 'obese,' 'obesity,' 'randomized clinical trials,' 'OSA,' and 'sleep apnea.' The search was restricted to articles published in English. Clinical guidelines and relevant meta-analyses were included. Abstracts from conferences and commentaries, retrospective studies, preclinical studies, and articles focusing solely on animal models were excluded. Studies conducted entirely in pediatric cohorts, or studies of medications withdrawn from the market were discarded. All papers underwent title and abstract screening for relevance to the aims of this narrative review by two investigators. Potential eligible articles were retrieved for full-text review. Reference lists were also screened for additional studies. Discrepancies were resolved through consensus by a third investigator.

3. GLP-1 analogs

Glucagon-like peptide-1 (GLP-1) is an endogenous hormone secreted by the enteroendocrine L-cells of the lower gastrointestinal tract [43]. The hormone is expressed constitutively but rises briskly following food ingestion potentiating the glucose-dependent insulin secretion from pancreatic islets, a mechanism known as the *incretin* phenomenon [44]. GLP-1 is also released from the brain's preproglucagon neurons in the nucleus tractus solitarii and mediates its extra-pancreatic effects by directly suppressing the appetite-regulating centers and slowing gastric emptying, thus promoting satiety and reducing hunger and food-seeking behavior [45]. It exerts its biological functions via binding GLP-1 receptors expressed in pancreatic beta cells, gastric mucosa, and heart, but also in the hindbrain, amygdala, and the hypothalamus (Figure 1) [46]. Aside from restoring neuronal insulin signaling, GLP-1 reduces inflammation, stimulates neurogenesis, and promotes mitochondrial biogenesis [46]. The half-life of endogenous GLP-1

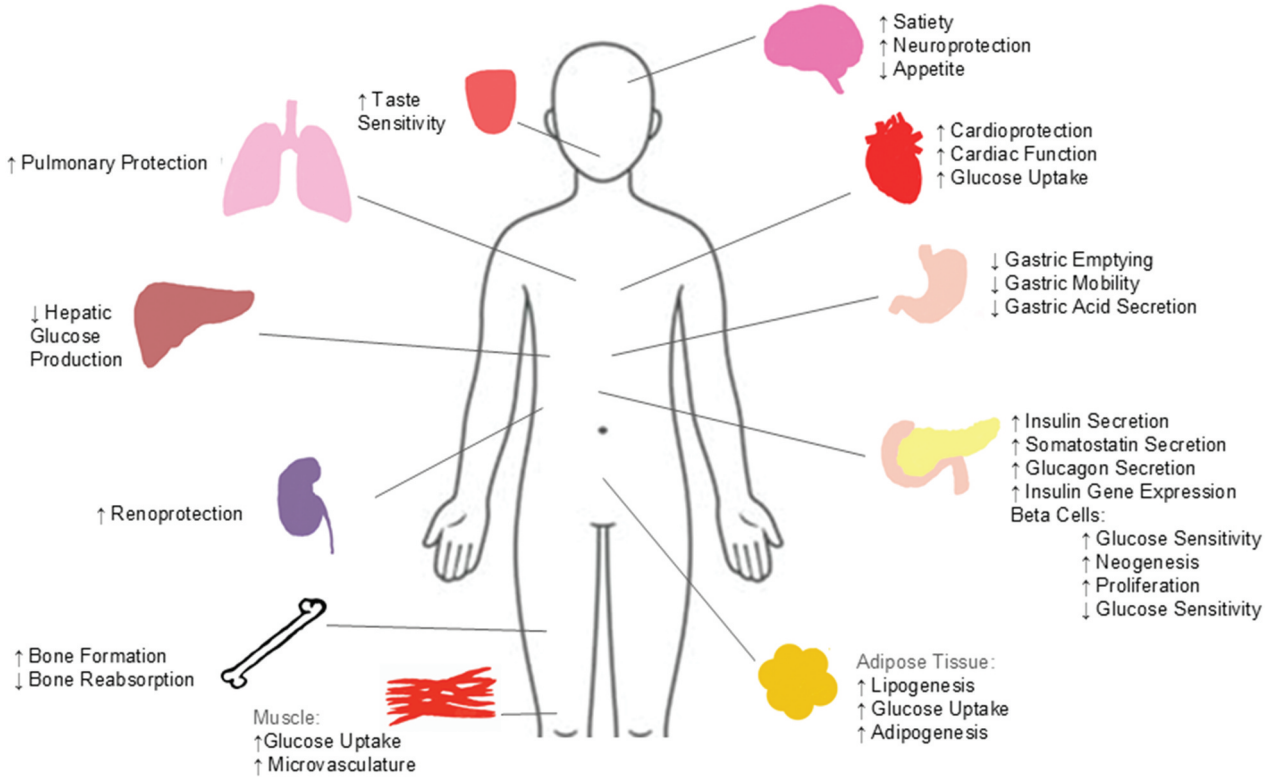

Figure 1. Effect of GLP-1 on peripheral organs.

is very short, estimated at less than 2 minutes. This rapid turnover is due to its rapid degradation by the ubiquitous proteolytic enzyme dipeptidyl peptidase 4 (DPP-4) [47]. The kidneys subsequently eliminate the resulting metabolites via glomerular filtration and tubular catabolism [48]. Synthetically modified analogs of GLP-1 are designed to overcome this degradation. To date, three FDA-approved GLP-1-RAs (liraglutide, semaglutide, and tirzepatide) for chronic weight management in adults with obesity have been investigated in patients with moderate to severe OSA. The pharmacodynamic properties of these agents are shown in Table 1.

3.1. Liraglutide

Liraglutide was the first medication in the class of GLP-1 to be studied in the setting of OSA and obesity. It shares 97% homology with the amino acid sequence of the human endogenous GLP-1 [49]. The liraglutide extended duration of action

Table 1. Pharmacodynamic properties of fda-approved GLP-1 drugs for management of obesity tested in patients with sleep apnea.

	Liraglutide	Semaglutide	Tirzepatide
Molecular Structure	GLP-1 analog (97% homologous to human GLP-1), with C16 acyl chain	GLP-1 analog with a modified backbone at position 8 (Aib substitution) and fatty acid derivatization	Synthetic dual incretin mimetic with modifications for GIP/GLP-1 activity
Receptor Activity	Selective for GLP-1 receptors	Highly selective for GLP-1 receptors	Binds both GLP-1 and GIP receptors
Dosing Frequency	Once daily (subcutaneous)	Once weekly (subcutaneous)	Once weekly (subcutaneous)
Absorption (Tmax)	8–12 hours	1–3 days	1–2 days
Bioavailability	~55%	~89%	~80%
Volume of Distribution (Vd)	~11–17 L	~12.5 L	~11–15 L
Peak Plasma Concentration (Cmax)	12–24 hours post-injection	1–3 days post-injection	1–3 days post-injection
Time to Steady State	3–4 days	4–5 weeks	4–5 weeks
Metabolism	Proteolytic degradation, not primarily through liver	Primarily proteolytic, resistant to DPP-4 enzymes	Proteolytic degradation similar to endogenous incretins
Excretion	<2% excreted unchanged; primarily via urine	Mostly through renal excretion of metabolites	Excreted mostly via urine as metabolites
Elimination Half-Life (T1/2)	~13 hours	~168 hours	~120 hours
FDA Approval for Obesity	Yes (Saxenda, 2014)	Yes (Wegovy, 2021)	Yes (Zepbound, 2023)

is attributed to replacing Lys 34 with Arg 34 and adding a C16 fatty acid chain to Lys 26. This structural change permits liraglutide to bind avidly to albumin (99%), reducing its degradation by DPP4, thus limiting its renal clearance.

The first case report of using liraglutide in OSA occurred in a 62-year-old man with human immunodeficiency virus infection, obesity, and type 2 diabetes mellitus (DM) [50]. The patient was initiated at 0.6 mg/day and titrated gradually to 1.2 mg/day in conjunction with metformin (1700 mg/d) and Levemir (30 IU/day). At 24 weeks after starting liraglutide, the patient lost 16 kg, a drop of 14% in body weight. Although the report did not disclose the average daily use of continuous positive airway pressure (CPAP) while liraglutide was being administered, polysomnography revealed abatement of sleep apnea severity from an initial apnea-hypopnea index (AHI) of 27/h down to 7.1/h.

Several RCT studies were published on the use of liraglutide in patients with moderate to severe OSA [51–53]. The SCALE Sleep Apnea trial randomized 359 non-diabetic participants with obesity (BMI ≥30) and moderate to severe sleep apnea (AHI ≥15) unwilling or unable to use CPAP to receive either liraglutide 3 mg/d or placebo, in combination with diet restriction and exercise [51]. After 32 weeks of treatment, liraglutide resulted in a higher percentage of weight loss compared with placebo (5.7% versus 1.6%) with consequent greater reduction in AHI in the liraglutide-treated arm than in the placebo-treated participants (12.2 versus 6.1 events/h). However, the mean residual AHI in the treatment group remained severe at 36.8 events/h. Secondary analysis also found no significant improvements in self-reported quality of life or sleep propensity. A similar randomized, controlled, nonblinded trial evaluated the efficacy of liraglutide in 90 patients with type II diabetes mellitus (T2DM) with moderate to severe OSA (AHI >15/h) [52]. Liraglutide was administered subcutaneously starting at 0.6 mg/d and titrated up to 1.8 mg/d over 2 weeks. The control group was provided the usual care. No placebo was given. Both groups were allowed to continue the use of their CPAP. At the end of 3 months, the liraglutide group had a nearly 8% drop in BMI compared to 0.4% for the control group ($p < 0.001$). In parallel, AHI decreased by 16% during the same time in the liraglutide but increased by 5% in the control group ($p < 0.0001$). The 24-hour mean systolic blood pressure was also significantly lower in the liraglutide group than in the control group. CPAP utilization was not reported in either group. A more recent proof-of-concept, 24-week, RCT involving 30 obese patients (BMI 30–40 kg/m^2) diagnosed with moderate to severe OSA with no prior history of cardiovascular events was performed to evaluate the effect of CPAP on atherosclerotic processes [53]. Participants were randomized to either CPAP alone, an escalating dose of liraglutide from 0.6 mg up to 2.4 mg/d, or a combination of liraglutide and CPAP. Both the liraglutide and the liraglutide plus CPAP interventions resulted in significant weight loss (6% and 4%, respectively) while patients on CPAP alone experienced a small increase in body weight (2%). In comparison, liraglutide-mediated weight loss was accompanied by 22% improvement in AHI but was inferior to both CPAP (94%) and CPAP plus liraglutide (90%). This was reflected in high residual AHI (42 ± 16 events/h) in the liraglutide group compared with CPAP (3 ± 3 events/h) and CPAP plus liraglutide (5 ± 5 events/h), respectively. In tandem, there was a significant reduction in the vascular inflammation of the aortic wall in the CPAP and the CPAP plus liraglutide group but not in the liraglutide group. Low attenuation coronary artery plaque volume also decreased with CPAP alone and with combination therapy but not with liraglutide alone. The lack of liraglutide to abate OSA-related inflammation might have been related to the persistence of intermittent hypoxia. Future studies are required to elucidate these observations. It is noteworthy that the use of CPAP machine was 5.8 ± 1.4 h in the CPAP group and 4.7 ± 1.8 h in the combined treatment group.

Last but not least, an ongoing single-centered, open-labeled, prospective, phase IV randomized controlled trial (ROMANCE) is currently underway in the United Kingdom to examine the impact of liraglutide-induced weight loss alone or in combination with CPAP on the severity of OSA [54]. The study plans to recruit 132 patients with newly diagnosed OSA (AHI ≥15 events/hour), and existing obesity and T2DM. Patients are assigned on 1:1:1:1 to each of the four treatment arms for 26 weeks: (1) liraglutide (1.8 mg once per day) alone, (2) liraglutide 1.8 mg once per day with CPAP, (3) CPAP alone (conventional care) or (4) no treatment. The primary outcome measure is the change in AHI from baseline. The results are anticipated in the last quarter of 2025.

3.2. Semaglutide

Semaglutide was the second GLP-1RA approved for the treatment of obesity and the first to yield a double-digit reduction in weight [55]. Semaglutide was approved by the FDA in 2021 for weight loss management and currently comprises more than 40% of the United States market share of GLP-1 agonists. Semaglutide, a 31 amino acid-containing peptide, shares 94% structural homology with endogenous human GLP. The substitution of alanine at position 8 with α-aminoisobutyric acid prevents dipeptidyl peptidase-4-mediated degradation [56]. In addition, the replacement of lysine residue at with arginine at position 34 facilitates the production of semaglutide via recombinant DNA technology. Compared to liraglutide, which is administered once daily, semaglutide has an even longer half-life, allowing for once-weekly administration. This marked prolongation in plasma half-life is attributed to the acetylation of lysine residue at 26th position with a C18 fatty diacid resulting in higher binding affinity to albumin and reduced renal clearance [57]. The medication is prescribed on an escalating dose via weekly subcutaneous injection at doses starting with 0.25 mg and up to 2.4 mg to minimize gastrointestinal side effects.

Semaglutide efficacy as AOM was demonstrated in the semaglutide treatment in people (STEP) with obesity trials. In a seminal 68-week RCT (STEP 1) involving 1961 participants with BMI ≥30 kg/m^2 free of diabetes (or BMI ≥27 kg/m^2 with at least one weight-related comorbidity), semaglutide at a dose of 2.4 mg once weekly resulted in a 14.9% weight loss versus 2.4% in the placebo group, with 34.8% of participants achieving more than 20% weight loss [55]. The weight loss was sustainable at week 104 with 36.1% maintaining ≥ 20% weight

loss in the semaglutide versus 2.3% in the placebo group (STEP 5) [58]. The benefits of semaglutide also included a reduction in the incidence of death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke [59]. Incorporating intensive behavioral therapy along with semaglutide increased the mean body weight change to 16% compared to 5.7% for placebo [60]. As of to date, there hasn't been a published clinical trial investigating semaglutide's direct effect on OSA.

3.3. Tirzepatide

Tirzepatide is a synthetic peptide of 39-amino acid designed to function as dual glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide (GLP-1/GIP) receptor agonists. Tirzepatide is conjugated to C20 fatty diacid side chain through a glutamic acid linker. This modification prolongs its half-life allowing it to bind to albumin, reducing renal clearance, and degradation by DDP-4 [61]. The structure is further optimized with glycine and amide substitutions to improve its therapeutic potential. Tirzepatide activates GIP receptors with a similar affinity to native GIP, but its affinity for GLP-1 receptor is about fivefold weaker than that of native GLP-1. The activation of both receptors offers a synergistic effect by enhancing insulin secretion and sensitivity [62]. Tirzepatide is marketed under the name of Mounjaro® for T2DM and Zepbound® for chronic weight management. It is administered once weekly via subcutaneous injection using single-dose prefilled pens with doses ranging from 2.5 to 15 mg.

In 2022, the FDA granted approval of tirzepatide for the treatment of T2DM following the publication of SURPASS Clinical Trials that showed considerable improvement in glycemic control and weight loss in a dose-dependent manner [63–65]. Based on these observations, a series of pivotal trials, known as the SURMOUNT clinical program, established the superiority of tirzepatide over other existing treatments for weight management including semaglutide. In the pivotal SURMOUNT-1 trial, the study enrolled 2,539 adults with obesity (BMI ≥30) or overweight (BMI ≥27) with at least one weight-related comorbidity, but without type 2 diabetes [66]. Participants were randomized to receive tirzepatide (5 mg, 10 mg, or 15 mg) or placebo once weekly via subcutaneous injection for 72 weeks, along with lifestyle interventions (low-calorie diet and increased physical activity). At the end of the trial, the percentage change in body weight compared to the baseline was 15%, 19.5%, and 20.9% with tirzepatide 5, 10, and 15 mg, corresponding to a mean body weight reduction of 11.9, 16.4 and 17.8 kg, respectively [66]. More than 50% of participants who received 15 mg dose achieved a weight reduction greater than 20% compared to baseline. On November 2023, the FDA approved tirzepatide for chronic weight management promising to revolutionize the treatment of obesity. The new drug presented a potential therapeutic modality for reducing the severity of OSA, considering the profound degrees of weight loss garnered from these trials and the bidirectional association between weight loss and OSA. Shortly after, a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial, known as the SURMOUNT-OSA trial, was conducted to explore whether weight loss induced by tirzepatide can reduce the severity of OSA [67]. The trial enrolled adults with obesity (BMI ≥30 kg/m^2 or ≥27 kg/m^2 with at least one weight-related comorbidity) and moderate to severe OSA (AHI ≥15). Individuals with other significant sleep disorders, non-obese participants, or those with mild OSA were excluded from the study. Two participant populations were included: Study 1 comprised patients who were unable or unwilling to use PAP therapy, and Study 2 included participants who had been using PAP therapy for at least 3 consecutive months at the time of screening and who planned to continue PAP therapy during the trial. All participants were randomly assigned to receive placebo or tirzepatide (10 mg or 15 mg) once weekly via subcutaneous injection for a period of 52 weeks in conjunction with standard lifestyle counseling, including advice on diet, physical activity, and sleep hygiene. In study 1, tirzepatide led to a mean AHI reduction from baseline of 25.3 events/hour (50.7%) compared to a mean AHI reduction from baseline of 5.3 events/hour (3.0%) for placebo while in study 2, the mean AHI reduction from baseline was 29.3 events/h (58.7%) with tirzepatide compared to 5.5 events/h (2.5%) with placebo. In tandem, tirzepatide led to a mean body weight reduction of 17.7% and 19.6% from baseline in Study 1 and Study 2, compared to 1.6% and 2.3% from baseline for placebo, respectively. The trial demonstrated that tirzepatide alone could significantly improve OSA parameters, suggesting that weight loss from the drug had a direct impact on reducing upper airway obstruction. The reduced severity of OSA was also manifested by an improvement in hypoxic burden. In about 50% of those who received tirzepatide, the improvements in OSA were significant enough to meet the criteria under which CPAP therapy may not be recommended (AHI <5 events/h or 5 to 14 events/h and an ESS of 10 or less). Interestingly, adherence to CPAP in study 1 was not provided. The study reported that 3.9% of participants discontinued trial drug over the 52-week period compared with 4.3% in the placebo group. The rate of tirzepatide discontinuation in this study was consistent or slightly lower than the rates observed in other trials of GLP-1 RAs.

4. Adverse events

Many of the undesirable reactions reported with GLP-1 drugs are considered class effects although differences do exist. The most frequent side effects associated with GLP-1 RAs are gastrointestinal (GI) in nature and are often attributed to the direct effects on the central nervous system in the area postrema and to the change in gastric motility, leading to prolonged transit time and delayed gastric emptying [68]. Studies report nausea and vomiting in approximately 44% and 25%of users, respectively, depending on the dose and agent used. These events are mostly mild-to-moderate in severity, tend to be more frequent at initiation of treatment, and rarely result in discontinuation of therapy (less than 5%). Nausea and vomiting can usually be abrogated by slowly titrating the medications to the highest tolerable dose. Diarrhea and constipation occur also with all GLP-1 RAs in 4% to 20%, are usually dose-independent, and are more pronounced with long-acting GLP-1 RAs (i.e. liraglutide, semaglutide, tirzepatide). Used as

monotherapy, GLP-1 RAs have a low incidence of hypoglycemia, ranging between 0% and 12.3% [47]. The risk is increased however when used in combination with insulin or oral hypoglycemics. Other significant adverse effects include acute pancreatitis (0.2%) and cholelithiasis (1.8%) [69]. Among the predisposing factors identified are a history of T2DM, tobacco use, and advanced chronic kidney disease. Two subsequent studies disputed these findings [70,71]. A meta-analysis derived from three long-term clinical trials that covered a total of 9347 GLP-1 RA-treated and 9353 placebo-treated T2DM patients found no association between GLP-1 RA use and acute pancreatitis [70]. The other meta-analysis encompassing 113 trials, 100 of which included information on the incidence of pancreatitis, demonstrated similar rates between patients assigned to GLP-1 RAs and those in the comparator arms [71]. Increased risk of diabetic retinopathy complications was raised with semaglutide injection [72,73] but data obtained from Medicare beneficiaries did not substantiate this claim [74,75] although temporary worsening of retinopathy is a recognized phenomenon known to occur following rapid improvement in blood glucose in patients with diabetes [76].

Recently, several reports linking suicidality and self-harm to the use of GLP-1 RAs emerged in Europe and in the United States [77]. However, a retrospective analysis of the TriNetX Analytics Network involving more than 240,000 patients with overweight or obesity found lower risk for incident and recurrent suicidal ideation in patients prescribed semaglutide compared with non-GLP-1 RAs [78]. A post hoc analysis of pooled data from phase 3a STEP 1, 2, and 3 trials and phase 3b STEP 5 trials confirmed the lack of association between semaglutide and the risk of developing depression, suicidal ideation, or suicidal behavior relative to placebo [79]. It should be noted that these trials involved a single agent and excluded patients with a history of major depression, bipolar disorder, or schizophrenia in the 2 years prior to enrollment. Whether these findings extend to the entire class of GLP-1 RAs awaits future trials.

GLP-1 RAs are contraindicated in patients with a history of medullary thyroid cancers or multiple endocrine neoplasia syndrome given previous associations with thyroid tumors in rodent studies [80]. In terms of using these agents during pregnancy, the evidence so far does not suggest an increased risk of major congenital malformations above the risk conferred by maternal T2DM requiring insulin treatment [81].

5. Conclusion

The advent of incretin-based therapies, such as glucagon-like peptide 1 (GLP1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, represents a new frontier for treating OSA that occurs in the context of obesity. While CPAP remains the cornerstone for the symptomatic management of OSA, liraglutide, semaglutide, and tirzepatide have been shown to lead to clinically significant reductions in body weight, and ostensibly AHI making them a valuable adjunct or even alternative to traditional OSA treatments.

6. Expert opinion

CPAP is generally considered the current gold standard therapy for OSA given its efficacy in preventing upper airway collapse, reducing cortical arousals associated with respiratory events, reversing hypoxemia, and ameliorating cognitive impairment and overall sleep quality of life. Yet, despite all technological advances in machine design and the introduction of novel algorithms in airflow delivery, adherence to CPAP remains suboptimal. It is estimated that between 8% to 15% of patients with OSA decline using CPAP treatment after the first few days and that 50% or more of those recently initiated therapy discontinue its usage within 1 year from the treatment [82]. More importantly, while CPAP may increase the upper airway caliber by reducing tissue edema [83], it does little to alter the underlying pathophysiology of OSA. The strong association between BMI and OSA has led professional societies to issue a call for implementing integrative treatment approaches for the management of obesity in OSA [36,84]. The American Thoracic guidelines ascribe a strong recommendation for instituting comprehensive lifestyle intervention that includes reduced caloric intake, increased physical activity and behavioral guidance [36]. Unfortunately, the impact of these regimens on OSA and cardiovascular complications from the burden of obesity has been inconsistent [85–88]. Only a minority of highly motivated patients can achieve long-term, clinically meaningful, and sustainable weight loss. Earlier pharmacotherapies that were investigated in weight loss trials comprised appetite suppressants such as sibutramine, phentermine-topiramate, or the lipase inhibitor, orlistat. These agents had modest efficacy in reducing OSA severity [40,89]. However, the doses required to show clinically meaningful results in reducing AHI were associated with a high frequency of adverse events including serious complications such as psychiatric derangements, nonfatal strokes, and myocardial infarction [90,91]. The advent of GLP-1 RAs has brought a paradigm shift from traditional OSA management focused on symptom control to a more comprehensive approach that targets underlying metabolic dysfunction in specific populations (Table 2).

6.1. How does the introduction of GLP-1 RAs alter the management of OSA treatment?

GLP-1 RAs align with the trend toward personalized medicine, offering a tailored approach to OSA management based on a patient's specific risk factors and comorbidities. In patients whose OSA endotype is predominantly driven by obesity, GLP-1 RAs can be prioritized as a central component of the treatment strategy. By reducing OSA severity, GLP-1 RAs can potentially lower CPAP requirements which may increase adherence to treatment. In OSA patients with T2DM, GLP-1 RAs also improve glycemic control, reduce blood pressure, and attenuate inflammation, leading to a healthier cardiovascular system. All the novel pharmacological therapies (atomoxetine and oxybutynin, TASK potassium channel antagonist, carbonic anhydrase inhibitor sulthiame) targeting non-anatomical factors induced-OSA (i.e. high loop gain, low arousal threshold, impaired pharyngeal dilator muscle function) have limited

benefits in patients with higher upper airway collapsibility [92–94]. By reducing parapharyngeal fat pads, and lessening central obesity, GLP-1 RAs advance the potential for complementing endotype-based treatments to be effective in those with residual OSA [95]. In particular, for patients unwilling to use CPAP or struggle with CPAP adherence, GLP-1 RAs may increase the effectiveness of mandibular advancing devices by reducing fat accumulation within the genioglossus muscle [96]. The benefits of these agents also extend to the overall respiratory system, as reduced abdominal fat can improve functional residual capacity, further boosting airflow during sleep. Similarly, combining GLP-1 RAs with hypoglossal nerve stimulation (HGNS) offers an alternative multimodal approach to treating OSA. Recently, the FDA extended the upper BMI eligibility threshold range of HGNS OSA candidates to 40 kg/m^2. However, the odds of achieving a satisfactory treatment response with HGNS decrease with rising BMI [97]. The success rate drops precipitously for BMI above 35 kg/m^2. The availability of GLP-1 RAs can theoretically expand the pool of candidates for HGNS implantation by providing a pharmaceutical pathway to lowering BMI. These drugs can also improve the tolerability of these devices by allowing a reduced stimulation amplitude for genioglossal recruitment.

6.2. Would GLP-1RAs render CPAP obsolete in the treatment of OSA?

The SURMOUNT-OSA clinical trial demonstrated that GLP-1 receptor agonists are efficacious in lowering AHI, reducing the propensity of sleepiness, and improving sleep-related quality of life measurements in patients with obesity [67]. However, the statement related to the discontinuation of CPAP garnered the most attention. By achieving the threshold set by the Centers for Medicare and Medicaid Services for CPAP coverage [98], the study implied that more than half of patients with OSA may not require CPAP. Despite the overwhelming enthusiasm displayed with GLP-1 receptor agonists, the role of CPAP therapy in managing OSA is indispensable. First, CPAP's effective and rapid onset of action in reducing sleep-related symptoms establishes it as a benchmark against which other therapeutic options are assessed. Currently, none of the GLP-1 RAs outcomes match CPAP efficacy in treating OSA. Second, qualifying criteria for CPAP coverage under the CMS rule include six additional symptoms and comorbidities related to AHI other than sleepiness. Hypertension is one of those qualifying conditions that was present in > 75% of the SURMOUNT-OSA trial population [67]. Third, although weight loss can be substantial with GLP-1 RAs, only a subset of patients will achieve sufficient weight loss to 'cure' OSA. CPAP is still required for residual OSA after initial weight loss. Third, GLP-1 RA-induced weight loss may take months before a considerable drop in BMI occurs, as demonstrated by the SURMOUT-OSA trial [67]. Given that untreated sleep apnea is associated with a nearly 40% increase in all-cause mortality in just the first year after diagnosis [99], delaying or withholding CPAP therapy is ethically an untenable position. Fourth, although GLP-1 receptor agonists are generally well tolerated, a large segment of eligible patients with obesity and OSA do not have access to these medications due to availability or cost. Finally, this class of AOM is relatively new and its long-term safety profile has yet to be fully established, making it too premature to sign off on CPAP obituary.

6.3. What are the determinants for the duration of GLP-1 RAs use in OSA patients?

The answer to this question hinges on several factors: a) *Degree of Weight Loss*: The effectiveness of GLP-1 RAs in improving OSA symptoms largely depends on the amount of weight loss achieved. Comparative clinical trials among GLP-1RAs are limited (Figure 2). Existing studies demonstrate a clear hierarchy, with tirzepatide showing the greatest effectiveness, followed by semaglutide and liraglutide [100,101]. Based on prior clinical trials, tirzepatide, with its dual GLP-1 and GIP action, resulted in the most substantial weight reduction (~21% of initial body weight) in the SURMOUNT-4 trial [102], even outperforming semaglutide, which itself has set a new standard for pharmacologic weight management compared to liraglutide. In the SCALE Obesity and Prediabetes trial, liraglutide (3 mg) led to an average weight loss of

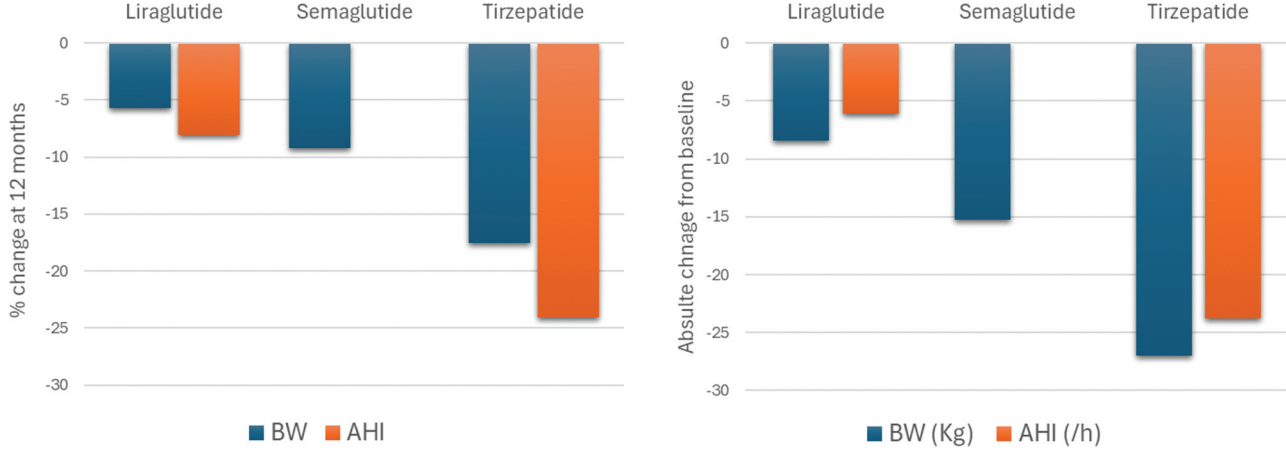

Figure 2. Mean percentage (a) and absolute change (b) in body weight and apnea-hypopnea index at 12 months of patients receiving liraglutide (3.0 mg), Semaglutide (2.4 mg), and tirzepatide (15 mg).

Table 2. A summary of GLP-1 clinical trials addressing obesity in sleep apnea.

	Study population	Intervention (baseline)	Placebo/control (baseline)	Follow up (weeks)	Outcomes
Liraglutide 3.0 mg					
Blackman [51]	359 (72% male)	Age (48.6 ± 9.9) AHI (49.0 ± 27.5) BMI (38.9 ± 6.4) ODI ≥4% (43.7 ± 26.1)	Age (48.4 ± 9.5) AHI (49.3 ± 27.5) BMI (39.4 ± 7.4) ODI ≥4% (44.1 ± 26.1)	32	The mean reduction in AHI was greater with liraglutide than with placebo (−12.2 vs − 6.1 events h − 1, $p = 0.015$). Liraglutide produced greater mean percentage weight loss compared with placebo (−5.7% vs − 1.6%, $p < 0.0001$). There was a drop in ODI ≥ 4% albeit non-significant (−9.5 vs −5.2 events h − 1, $p = 0.06$)
Jiang [52]	90 (70% male)	Age (55.7 ± 7.4) AHI (31.0 ± 7.3) BMI (26.5 ± 4.4) SpO_2%, nadir (80.3 ± 5.8)	Age (54.8 ± 5.5) AHI (30.1 ± 6.2) BMI (27.0 ± 2.4) SpO_2%, nadir (80.4 ± 5.0)	12	The mean reduction in AHI was greater with liraglutide than with placebo (−4.9 vs 0.5 events h − 1, $p < 0.001$). Liraglutide produced a greater BMI drop compared with placebo (−2.1 vs 0.1, $p = 0.001$). There was an improvement in SpO_2%, nadir (3.1 vs 0, $p = 0.017$)
O'Donnell [53]	30 (80% male)	Age (50 ± 9 for Lir and 50 ± 5 for Lir+CPAP) AHI (53 ± 20 for Lir and 47 ± 16 for Lir+CPAP) BMI 35.0 ± 3.1 for Lir and 34.0 ± 3.3 for Lir+CPAP) ODI (45 ± 22 for Lir and 43 ± 17 for Lir+CPAP)	Age (51 ± 8 for CPAP) AHI (50 ± 21 for CPAP) BMI (36.0 ± 3.2 for CPAP) ODI (40 ± 17 for CPAP)	24	Lir+CPAP and CPAP resulted in greater reduction in AHI than Lir (mean difference, −45 and − 43 events/h, respectively, vs.-12 events/h; $p < 0.05$). Both Lir and Lir+CPAP resulted in greater drop in weight than CPAP (mean difference −6.17 and −3.67 kg, respectively, vs 2.73; $p < 0.05$). Lir+CPAP and CPAP resulted in greater reduction in ODI than Lir (mean difference 38 and 34, events h − 1, respectively, vs 13; $p < 0.05$)
Tirzepatide 15 mg					
Malhotra [110] Trial 1	114 (68% male)	Age (47.3 ± 11.0) AHI (52.9 ± 30.5) BW (116.7 ± 24.6) BMI (39.7 ± 7.3)	Age (48.4 ± 11.9) AHI (50.1 ± 31.5) BW (112.8 ± 22.6) BMI (38.6 ± 6.7)	52	The percent change in body weight from baseline to week 52 was − 17.7 in the tirzepatide group as compared with −1.6 kg in the placebo group (estimated treatment difference, −16.1 kg; $p < 0.001$). The mean change in AHI was − 25.3 events per hour with tirzepatide and − 5.3 events per hour with placebo, for an estimated treatment difference of − 20.0 events per hour; $p < 0.001$)
Malhotra [110] Trial 2	120 (72% male)	Age (50.8 ± 10.7) AHI (46.1 ± 22.4) BW (115.8 ± 21.5) BMI (38.6 ± 6.1)	Age (52.7 ± 11.3) AHI (53.1 ± 30.2) BW (115.1 ± 22.7) BMI (38.7 ± 6.0)	52	The percent change in body weight from baseline to week 52 was − 19.6 in the tirzepatide group as compared with − 2.3 in the placebo group (estimated treatment difference, −17.3; $p < 0.001$). The mean change in AHI was − 29.3 events per hour with tirzepatide and − 5.5 events per hour with placebo, for an estimated treatment difference of − 23.8 events per hour; $p < 0.001$)

AHI = Apnea Hypopnea Index; BMI = Body Mass Index; BW = Body Weight; CPAP = Continuous Positive Airway Pressure; Lir = Liraglutide; ODI = Oxygen Desaturation Index; SpO2 = Oxygen Saturation.

8–10% of initial body weight over 56 weeks [103]. In the STEP trials, semaglutide 2.4 mg showed impressive results, with patients losing an average of 15–17% of their body weight over 68 weeks [55,104]. The latest GLP-1 RA, Retatrutide, is a novel triple agonist at GLP-1, glucose-dependent insulinotropic polypeptide (GIP), and glucagon receptors with superior efficacy to dual receptor co-agonists [105]. In a phase II multicenter, double-blind, randomized controlled trial, 338 adults with obesity were administered retatrutide (1, 4, 8, and 12 mg) over 48 weeks [106]. At the highest dose of 12 mg, retatrutide was responsible for an average weight loss of 24% with a reduction up to 30% from the baseline weight in 25% of participants [106]. As such, the discovery of more potent GLP-1RAs can potentially shorten the duration of treatment to achieve the desired target weight loss. b) *Co-existing Metabolic Conditions*: Many patients with OSA also have comorbidities such as type 2 diabetes or cardiovascular disease. GLP-1 RAs have additional benefits in improving glycemic control, reducing inflammation, and reducing major adverse cardiovascular events [107,108]. These benefits may justify long-term use in patients who not only require weight management but also need ongoing control of these other conditions. Recently, an observational cohort study noted that bariatric metabolic surgery had a larger reduction in mortality compared to those treated with GLP-1 RAs among individuals with diabetes duration of 10 years or less [109]. However, there was no difference in the risk of mortality among those with a longer duration of diabetes, nor in the risk of MACEs among all patients, indicating that the full benefits of GLP-1 RAs may require prolonged treatment. c) *Rebound Weight Gain*: A major concern with discontinuing GLP-1 RAs is the potential of regaining weight, which can exacerbate OSA symptoms. Studies have shown that cessation of GLP-1 RA therapy often leads to gradual weight gain over time, which could reverse the improvements in OSA [102]. This concern supports the long-term use of GLP-1 RAs for sustained weight management and continued OSA symptom control. d) *Access and Affordability*: As of now, there is no FDA-approved GLP-1 RA for treating OSA. GLP-1 RAs are expensive and can cost several thousand dollars annually without insurance. The high cost of these medications coupled with the wide prevalence of OSA can only exacerbate the health disparity between economically disadvantaged populations and those with greater access to healthcare resources, further widening the gap in health outcomes. For those insurance plans that do cover these drugs, the approval is granted for use in type 2 diabetes, but rarely for weight management or obesity treatment. In some cases, demand for GLP-1RAs has outpaced supply. This has been particularly true for semaglutide, where high demand for weight loss treatment has led to periodic supply shortages, further complicating access.

The outlook for sleep apnea treatment is increasingly promising with the advent of GLP-1 RAs. As we gain a deeper understanding of the intricate connections between obesity, metabolic health, and sleep disorders, we are advancing toward more effective, targeted therapies that can enhance both sleep quality and overall cardiovascular health for the millions affected by sleep apnea globally.

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ORCID

Ali A. El-Solh http://orcid.org/0000-0003-4237-8776

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