Glucagon-like peptide-1 receptor agonists for the treatment of obstructive sleep apnea

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Purpose of review
This review highlights the emerging data on the use of incretin therapies, including glucagon-like peptide-1 receptor agonists (GLP-1RA) and dual GLP-1RA and glucose-dependent insulinotropic peptide (GIP) receptor agonists, on the treatment of obstructive sleep apnea (OSA). Given known cardiometabolic and neurocognitive consequences of OSA, optimizing treatment is essential. In the setting of widespread research efforts and clinical implementation of dual agonists in managing OSA, obesity and other cardiometabolic diseases, this review is timely.

Recent findings
Several randomized controlled trials and meta-analyses have shown GLP-1 and GIP receptor agonists to reduce apnea–hypopnea index (AHI) and body weight in patients with OSA. This impact has been demonstrated with the use of pharmacotherapy alone and in combination with traditional positive airway pressure (PAP) therapy. GLP-1RA may positively affect OSA through reducing systemic inflammation and decreasing adiposity, including via hormone changes, delayed gastric emptying, and central mechanisms impacting appetite regulation and sleep-wakefulness.

Summary
Novel pharmacological advances in individuals with OSA and obesity have shown promise in cardiometabolic disease control. Longitudinal follow-up to monitor the efficacy and adverse effects of incretin therapies, and further comparison studies with PAP therapy, are warranted.

Keywords
apnea–hypopnea index, glucagon-like peptide-1, obesity, obstructive sleep apnea, Tirzepatide

INTRODUCTION

Obstructive sleep apnea (OSA) affects up to 1 billion people worldwide and has major neurocognitive and cardiometabolic consequences [1,2]. OSA is common and has important effects, yet many of those afflicted with this condition remain undiagnosed and untreated [2,3]. While obesity is a major reversible risk factor for OSA, the mechanisms through which it predisposes to OSA are unclear [3,4]. Given the high obesity prevalence and association with multiorgan metabolic disease and mortality risk, considerable interest has focused on novel pharmacological advances in individuals with both OSA and obesity, including glucagon-like peptide-1 receptor agonists (GLP-1RA) and dual GLP-1RA and glucose-dependent insulinotropic peptide (GIP) receptor agonists [5,6].

PATHOPHYSIOLOGY OF OBSTRUCTIVE SLEEP APNEA

OSA is characterized by repetitive collapse of the pharyngeal airway during sleep [7]. This repetitive collapse results in oxygen desaturations and subsequent reoxygenation leads to oxidative stress [8]. Recurrent apneas also contribute to catecholamine surges which can increase the risk of stroke, coronary artery disease, and other serious conditions [9]. In the setting of obesity, OSA is also associated with diabetes mellitus and metabolic dysfunction-associated steatotic liver disease. Thus, treatment of OSA may be critical for reducing cardiometabolic risk [10,11]. Positive airway pressure (PAP) remains the gold standard therapy for OSA and functions by delivering positive pressure to keep the upper airway open

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KEY POINTS

- Glucagon-like peptide-1 receptor agonists (GLP-1RA) and combined GLP-1 and glucose-dependent insulinotropic peptide (GIP) receptor agonists have demonstrated benefits in reducing apnea–hypopnea index, body weight, and other cardiometabolic risk factors in multiple trials of patients with obstructive sleep apnea (OSA).
- There are several peripheral and centrally mediated mechanisms through which incretin therapies function; however, the degree to which these medications help treat OSA via direct impact on OSA pathophysiology, versus secondarily through weight loss impact, is unclear.
- A whole-person care approach considering healthy lifestyle practices, positive airway pressure therapy, pharmacotherapy involving GLP-1RA, and patient preferences is essential to optimizing OSA treatment.
- Further research on the longitudinal impact of GLP-1RA and combined GLP-1 and GIP receptor agonists on OSA is warranted.

and thereby prevent pharyngeal collapse [12]. However, there are challenges with PAP therapy tolerance and adherence in certain patients. Although there are compelling data that PAP therapy can lead to transformative benefits for some patients, there is general acknowledgement that additional mechanistic research is needed to develop new therapeutic approaches [13–15]. The addition of pharmacological treatments that target obesity may positively impact not only OSA outcomes but also associated metabolic diseases.

THE IMPACT OF OBESITY ON OBSTRUCTIVE SLEEP APNEA

Obesity may increase the risk of and exacerbate OSA through various mechanisms. OSA is now known to have multiple endotypes (i.e. pathophysiological mechanisms) which can lead to repetitive pharyngeal collapse [16]. Anatomical predisposition to OSA can result from excessive adiposity around the upper airway, including in the tongue and soft tissues [17]. Craniofacial structure can also contribute to OSA via compromise of pharyngeal mechanics [18]. Additionally, individuals with obesity and robust upper airway dilator muscle activity are protected from OSA, as compared to individuals with similar weight but poor function of these muscles [19]. Beyond anatomical features, control of breathing is also important in OSA pathogenesis as unstable ventilatory control can contribute to OSA by various pathways [20]. Of note, obesity may impact control of breathing through multiple mechanisms, and weight loss may stabilize breathing patterns, at least in theory. Obesity also has a major impact on end-expiratory lung volume (EELV), which has an important impact on pharyngeal patency [21–24]. Increased EELV can raise caudal traction forces on the upper airway and help maintain pharyngeal patency, which may improve sleep disordered breathing in patients with OSA [21–25]. Thus, obesity would be predicted to reduce pharyngeal patency due to decreasing EELV while weight loss should improve pharyngeal patency via increased EELV.

MECHANISMS OF ACTION OF GLP-1 AND DUAL GLP-1 AND GIP RECEPTOR AGONISTS

A major advance has occurred with the introduction of GLP-1 and GIP receptor agonists in the treatment of patients with metabolic disease. This class of agents has been available for twenty years, starting with the Food and Drug Administration's approval of Exenatide [Byetta] in 2005, but more recent developments in pharmacology have led to improved clinical outcomes [26]. GLP-1 and GIP are incretin hormones released by gut enteroendocrine cells in response to nutrient intake, and play key roles in regulating energy homeostasis by multiple mechanisms. GLP-1RAs improve glycemic control through stimulation of glucose-dependent insulin secretion from pancreatic beta cells and inhibition of glucagon secretion from pancreatic alpha cells [27]. GLP-1RAs also delay gastric emptying, promoting satiety and reduced food intake and have been shown to impact premeal satiety, suggesting the effects on appetite regulation are also centrally mediated [27]. In addition to effects on appetite-regulating centers, GLP1RAs have been postulated to impact reward-related pathways involving dopamine, leading to suppression of hedonic eating (i.e. food intake based on pleasure rather than hunger) and thereby reducing food intake [28,29]. This GLP-1 effect may also yield benefit in decreasing substance use, including tobacco, alcohol, and opioids, potentially benefiting other aspects of patient well being [30,31].

The development of combined GLP-1 plus GIP receptor agonists, such as Tirzepatide, has further advanced weight and glycemic control [6,32]. GIPs are also incretin hormones that stimulate glucose-dependent insulin secretion from the pancreas, which may potentiate the GLP-1RA effect. In addition, GIP has central-acting mechanisms that are less well understood but also serve to reduce hunger, appetite, and hedonic feeding [33]. Tirzepatide's effects are thought to be mediated more by GIP than

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GLP-1 receptor agonism [34]. Head-to-head comparisons in randomized comparative effectiveness studies of Tirzepatide versus the GLP-1RA Semaglutide demonstrate that Tirzepatide may be superior in reducing glycated hemoglobin level, waist circumference, and body weight [35,36].

THE IMPACT OF GLP-1 AND DUAL GLP-1 AND GIP RECEPTOR AGONISTS ON OSA MANAGEMENT

Although weight loss is purported to be the primary mechanism whereby GLP-1RAs lead to improvement in OSA, other mechanisms have been proposed. First, GLP-1RAs can lead to reduced inflammation independent of changes in adiposity, including through decreasing production of pro-inflammatory cytokines [37]. This anti-inflammatory impact may help lead to improved cardiometabolic health. Second, GLP-1RAs have direct actions at the carotid body which could affect autonomic function. Hyperglycemia's sympathoexcitatory effect on the carotid body can be attenuated with GLP1-RA [38]. Thus, improvements in systolic blood pressure observed in randomized trials may be mediated by reduced sympathoexcitation rather than solely from improvement in OSA or body weight per se. Third, GLP-1RAs have multiple central mechanisms described above that could impact appetite regulation, as well as sleep and wakefulness. These various mechanisms can lead to positive effects on the overall health and well being of patients with OSA.

Regarding OSA treatment, randomized trials have now been completed to examine the potential therapeutic role of GLP-1 and GIP receptor agonists. The SURMOUNT-OSA study was recently published in the NEJM showing the potential benefits of Tirzepatide on individuals with moderate to severe OSA with obesity [39▪], Table 1. The study had two arms, with trial one including patients who were not using PAP therapy for OSA management, and trial two including PAP-treated patients. Participants in both arms were randomized to receive either Tirzepatide or placebo with the primary outcome of change in the apnea–hypopnea index (AHI) at one year. In addition, secondary outcomes were prespecified and controlled for multiple comparisons including systolic blood pressure, high-sensitivity C-reactive protein (hsCRP), sleep apnea-specific hypoxic burden, body weight, and patient-reported outcomes including daytime and nighttime symptoms. The results showed that Tirzepatide was superior to placebo in both trials one and two. Tirzepatide led to a clinically and statistically significant improvement in the AHI as compared to placebo. Additionally, Tirzepatide led to marked improvement in systolic blood pressure up to 9.5 mmHg, hsCRP, sleep apnea-specific hypoxic burden, body weight with 18–20% reductions, and patient-reported outcomes [39▪] Table 1. In aggregate, the data demonstrated that Tirzepatide was superior to placebo for OSA treatment in patients with or without concomitant PAP therapy. Based on this study, the FDA approved Tirzepatide for the treatment of OSA in December 2024.

Additional studies of GLP-1RA have also been performed in people with OSA. Although mean percentage weight loss was modest with Liraglutide at –5.7%, there were small but significant improvements in AHI (–12.2 events per hour with Liraglutide, as compared to –6.1 events per hour with placebo) over

Table 1. Recent trials on GLP-1 receptor agonists or dual GLP-1 and GIP receptor agonists in OSA management

Study	Study design	Incretin therapy assessed	Intervention	Mean change in AHI from baseline (events per hour)	Change in body weight from baseline
Malhotra *et al.* [39▪]	Two phase 3, double-blind, randomized, controlled trials	Tirzepatide	Individuals with moderate to severe OSA and obesity not on PAP therapy (Trial 1) and on PAP (Trial 2) were randomized to receive Tirzepatide or placebo for 52 weeks	Trial 1: −25.3 with Tirzepatide and −5.3 with placebo Trial 2: −29.3 with Tirzepatide and −5.5 with placebo	Trial 1: −17.7% with Tirzepatide and −1.6% with placebo Trial 2: −19.6% with Tirzepatide and −2.3% with placebo
Jiang *et al.* [41▪]	Two-center, prospective randomized controlled trial	Liraglutide	Individuals with type 2 diabetes and severe OSA were randomized to receive CPAP and drug treatment without Liraglutide, or CPAP plus Liraglutide for 3 months	+1.5 with CPAP and no Liraglutide, and -4.9 with CPAP plus Liraglutide	−0.1 kg/m^2 change in BMI with CPAP and no Liraglutide, and −2.1 kg/m^2 change in BMI with CPAP plus Liraglutide
O'Donnell *et al.* [49▪]	Randomized proof-of-concept study	Liraglutide	Individuals with OSA were randomized to receive CPAP alone, Liraglutide alone, or CPAP plus Liraglutide for 24 weeks	−12 with Liraglutide alone, −45 with CPAP alone, and −43 on combined CPAP plus Liraglutide	−6.17 kg with Liraglutide alone, +2.73 kg with CPAP alone, and −3.67 kg on combined CPAP plus Liraglutide

AHI, apnea–hypopnea index; GIP, glucose-dependent insulinotropic peptide; GLP-1RA, glucagon-like peptide-1 receptor agonists; OSA, obstructive sleep apnea; PAP, positive airway pressure.

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32 weeks in patients with obesity and moderate to severe OSA in the SCALE Sleep Apnea randomized clinical trial [40]. This study also demonstrated statistically significant reductions in glycated hemoglobin and systolic blood pressure in patients receiving Liraglutide compared to placebo [40]. In another randomized controlled trial, patients with type 2 diabetes and severe OSA who received continous positive airway pressure (CPAP) plus Liraglutide therapy experienced significant reductions in AHI, body mass index, and mean systolic blood pressure after three months, as compared to individuals receiving CPAP and drug treatment without Liraglutide [41▪], Table 1. Further randomized controlled trials are being conducted, including the ROMANCE trial which will evaluate changes in OSA severity based on AHI in 132 patients with obesity, type 2 diabetes, and newly diagnosed OSA receiving either no treatment (control), CPAP alone, Liraglutide alone, or combined CPAP plus Liraglutide therapy for 26 weeks [42].

Meta-analyses in OSA have shown that the magnitude of weight reduction is likely a major driver of the improvement in the AHI, regardless of the weight loss intervention [43]. Beyond reducing AHI and body weight, meta-analyses have also demonstrated improvements in hsCRP, glucose, and blood pressure control, revealing the benefits of GLP-1RA in metabolic syndrome [44]. Notably, emerging studies have also demonstrated pleiotropic beneficial effects of GLP1RAs and dual GLP1 and GIP receptor agonists on improving cardiovascular disease, improving renal outcomes in patients with diabetes and chronic kidney disease, and in reducing mortality [45–47]. Further studies are ongoing to help determine the mechanisms whereby incretin therapies lead to these beneficial multiorgan effects, whether directly or indirectly related to weight reduction.

Considering the mind-body connection, studies have also evaluated the effects of GLP-1RA on cognitive impairment in OSA. Liraglutide has been shown to attenuate chronic intermittent hypoxia (CIH)-induced cognitive deficits in the setting of oxidative stress and neuroinflammation [48]. This effect is proposed to occur through activation of nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) and by inhibition of mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) pathways [48]. While Lv *et al.*'s study was performed in cells and animal models, the results are promising that GLP-1RA could potentially protect against CIH-induced brain injury through antioxidant and anti-inflammatory properties [48].

While GLP-1RAs have shown promising results in OSA and other metabolic diseases, it is also important to highlight the value of PAP therapy as standard of care for OSA treatment. O'Donnell *et al.* showed that CPAP alone and in combination with Liraglutide led to a more significant reduction in AHI compared to Liraglutide alone over 24 weeks [49▪], Table 1. This randomized proof-of-concept study also revealed that only CPAP improved vascular inflammation and decreased unstable coronary artery plaque volume in patients with OSA, supporting the potential benefits of CPAP therapy in cardiovascular disease modification [49▪]. However, given some patients are unable to tolerate CPAP and CPAP does not generally improve weight regulation, it is important to analyze combination therapies involving GLP-1RAs that possess weight loss and multiorgan effects.

FUTURE CONSIDERATIONS FOR INCRETIN-BASED THERAPIES

Despite the exciting advances in OSA pharmacotherapy, many important questions remain:

(1) *Should GLP-1RA and dual GLP-1 and GIP receptor agonists be used in place of CPAP for OSA treatment?* As a point of emphasis, the SURMOUNT-OSA study did not have a direct comparison between CPAP and Tirzepatide and thus no conclusions can be drawn based on the study design. Comparative effectiveness studies are being designed to account for patient preferences that may yield important results in the future [50]. At present, the data strongly suggest that treatment of both OSA and obesity is more important than treating either disease alone. Chirinos *et al.*'s randomized trial in NEJM showed more improvements in blood pressure, triglyceride level, and insulin sensitivity by treating OSA plus obesity versus treating either obesity or OSA in isolation [51].

(2) *Should GLP-1RA be prescribed by pulmonologists?* Many endocrine and bariatric clinics are well resourced with registered dieticians and diabetes nurses who can provide education to patients on nutrition, management of side effects and proper technique for administering the subcutaneous GLP-1RA injections. For instance, the SURMOUNT OSA study included monthly visits with registered dieticians for all participants. Counseling on healthy nutrition and exercise is an important part of providing whole-person care and may be necessary for the long-term success of these agents. This issue is particularly relevant as rapid weight loss in the setting of GLP-1RA use may impact musculoskeletal health, especially in older adults, and thus strength training exercises are important for preserving muscle mass. Guidance for maintaining

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adequate nutrition and aerobic and resistance exercises while on these medications has been provided in recent reviews, though additional research is warranted [52,53]. Furthermore, studies have demonstrated high rates of discontinuation of these medications for various reasons, including side effects or disparities in access [54,55]. Thus, healthy lifestyle practices that can be sustained, despite medication discontinuation, are essential. Regardless of which provider is prescribing the GLP-1RA, the therapy should be given in the context of a more holistic approach to patient care involving education on both pharmacological and lifestyle factors that affect weight management.

(3) *What are mechanisms underlying GLP-1 and GIP receptor agonists leading to improvement in OSA?* Although we speculate above regarding potential mechanisms, we strongly support rigorous scientific investigation to elucidate further if OSA improvement on incretin therapies is mainly a result of weight loss or if there is a direct impact on OSA pathophysiology. Such knowledge will be critical to informing the discussion about whether these agents may be comparably helpful in individuals without obesity (e.g. those with overweight).

(4) Given that most trials including SURMOUNT OSA have limited follow-up, questions remain regarding the long-term impact of GLP-1RA and dual GLP-1 and GIP receptor agonists on OSA. The SURMOUNT-4 randomized clinical trial published in JAMA strongly suggests that the discontinuation of Tirzepatide leads to regain of body weight [56]. Beyond maintaining weight loss, continued therapy is required for sustaining metabolic benefits in most individuals [57]. These data suggest the need for long-term treatment and careful follow-up on incretin therapies. Longitudinal safety data will also be helpful to inform discussions on benefits and risks of treatment. Three year follow-up from the SURMOUNT 1 study is strongly suggestive of reduced incident diabetes with Tirzepatide compared to placebo [6]. Several strategies have been proposed to maintain weight loss including ongoing GLP-1RA therapy, switching to oral agents such Orforglipron, use of skeletal muscle agents such as Bimagrumab, as well as reinforcement of lifestyle factors including healthy diet and exercise [58,59].

CONCLUSION

In summary, new data have created considerable excitement regarding pharmacotherapy for OSA [60]. The use of incretin-based therapies including GLP-1RA and dual GLP-1 and GIP receptor agonists may not just improve OSA but also associated cardiometabolic and neurocognitive sequalae. This multiorgan impact of incretin therapies may enhance overall patient well being and quality of life. We strongly support further rigorous research in this area to optimize clinical outcomes and to guide individualized treatment approaches.

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