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TIRZEPATIDE AND METABOLIC TREATMENT OF OBSTRUCTIVE SLEEP APNEA IN OBESE PATIENTS - EMERGING THERAPEUTIC PERSPECTIVES

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ABSTRACT

Obstructive sleep apnea (OSA) is a highly prevalent and underdiagnosed sleep-related breathing disorder characterized by recurrent upper airway obstruction during sleep, leading to intermittent hypoxia and sleep fragmentation. Its incidence continues to rise in parallel with the global obesity epidemic, which represents the most significant modifiable risk factor for OSA. While continuous positive airway pressure remains the gold standard of symptomatic treatment, long-term adherence is often suboptimal, highlighting the need for alternative, disease-modifying therapeutic strategies.

This paper explores the role of incretin-based therapies, particularly glucagon-like peptide-1 receptor agonists, focusing mainly on tirzepatide, in the management of OSA. Current evidence suggests that these medications contribute to significant weight reduction, improvement in metabolic parameters, and potential attenuation of OSA severity, as reflected by reductions in the apnea–hypopnea index and hypoxic burden.

Beyond weight loss, emerging data indicate that incretin-based therapies may influence key pathophysiological mechanisms of OSA, including systemic inflammation, oxidative stress, and ventilatory control instability. These pleiotropic effects may be particularly relevant in non-obese patients, in whom non-anatomical factors play a predominant role. For these reasons, tirzepatide represents a promising therapeutic approach in the management of OSA.

KEYWORDS

Obstructive Sleep Apnea, Tirzepatide, Obesity, Glucagon-Like Peptide-1 Receptor Agonists, Incretins, Polysomnography

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Introduction

OSA is a common disease characterized by recurrent complete or partial upper airway obstructive events, at the level of the pharynx, occurring despite preserved respiratory muscle activity [1]. The clinical presentation of this disorder encompasses a broad spectrum of nocturnal and diurnal manifestations. Typical nocturnal symptoms include loud, irregular persistent snoring, awakenings associated with dyspnea sensation, and difficulty initiating sleep [2]. Other associated symptoms may include increased sweating, nocturia, palpitations, xerostomia upon awakening, and heartburn [3]. Notably, the disease severity does not consistently correlate with symptom frequency; therefore, it is important to identify even the mildest and most unusual symptoms, as the absence of any symptoms does not exclude the diagnosis [4].

Atypical daytime manifestations include excessive daytime sleepiness, morning headache, impairment of memory and concentration, reduced libido, and emotional disturbances [5]. It should be noted that women more frequently present with atypical symptoms and for this reason often remain underdiagnosed [6].

The growing prevalence of obesity has significantly contributed to the rising burden of OSA, highlighting the need for novel, mechanism-based therapeutic strategies that extend beyond conventional symptomatic treatment [7]. While continuous positive airway pressure (CPAP) remains the mainstay of symptomatic management, its limited long-term adherence underscores the need for disease-modifying therapies targeting underlying pathophysiology [8]. Against this background, incretin-based therapies have emerged as a promising therapeutic strategy, particularly glucagon-like peptide-1 (GLP-1) receptor agonists, which exert pleiotropic metabolic effects including weight reduction, improved glycemic control, and modulation of appetite and energy balance [9]. Given that obesity is a principal modifiable risk factor for OSA, therapies that induce significant weight loss may have a direct impact on disease severity and progression [7].

Furthermore, emerging evidence suggests that incretin-based therapies may influence pathophysiological mechanisms relevant to OSA beyond weight reduction alone, including inflammation, upper airway collapsibility, and ventilatory control stability [10]. In this context, tirzepatide represents a novel

and promising therapeutic option in the metabolic management of OSA in obese patients. This review aims to summarize the current evidence and emerging perspectives regarding the role of tirzepatide and incretin-based therapies in the integrated treatment of OSA, with particular emphasis on their potential to modify disease trajectory and improve clinical outcomes.

Methodology

A comprehensive search of the literature was performed using the following electronic databases: PubMed and Scopus. The search was restricted to articles published between 2000 and 2026, with a particular emphasis on publications from the most recent five-year period. Only English-language articles were considered. Studies were selected based on their relevance to the topic of metabolic treatment of obstructive sleep apnea, with particular focus on incretin-based therapies and tirzepatide.

The search strategy employed combinations of the following Medical Subject Headings (MeSH) terms and free-text keywords: ("obstructive sleep apnea" OR "OSA" OR "sleep-disordered breathing") AND ("tirzepatide" OR "GLP-1 receptor agonist" OR "glucagon-like peptide-1" OR "GIP/GLP-1" OR "incretin" OR "liraglutide" OR "semaglutide") AND ("obesity" OR "weight loss" OR "metabolic treatment" OR "pharmacotherapy"). Boolean operators (AND, OR) were used to combine search terms systematically. Additional references were identified through manual screening of bibliographies of selected articles and relevant review papers.

Eligible publication types included randomized controlled trials, meta-analyses, systematic reviews, narrative reviews, prospective and retrospective cohort studies, case series, and clinical practice guidelines. Articles were excluded if they were not available in English, did not address the relationship between incretin-based therapies and obstructive sleep apnea, or consisted solely of conference abstracts without full-text availability. The final selection of articles was guided by the authors' assessment of scientific quality, methodological rigor, and relevance to the research questions addressed in this review.

Epidemiology

OSA represents one of the most prevalent sleep-related breathing disorders worldwide, affecting more than 900 million individuals globally, with epidemiological data indicating a steadily increasing prevalence [11].

Despite its high occurrence, OSA remains frequently underdiagnosed, and its true prevalence is likely underestimated in the general population. The disorder occurs more commonly in men than in women, epidemiological studies estimate that approximately 22% of men and 17% of women are affected in the general population [12]. However, its prevalence in women increases after menopause, suggesting a potential protective role of female sex hormones [13]. Estrogen and progesterone are thought to exert a protective effect against OSA by enhancing upper airway muscle tone and ventilatory responses, thereby reducing airway collapsibility during sleep [14].

Furthermore, the risk of OSA rises progressively with advancing age, identifying both male sex and older age as key epidemiological risk factors. Variability in reported prevalence is also influenced by differences in diagnostic criteria, particularly the apnea–hypopnea index (AHI) thresholds applied. The global increase in obesity has further contributed to the growing burden of OSA, reinforcing its recognition as a significant public health concern due to its strong association with cardiovascular and metabolic comorbidities [7].

Beyond its epidemiological significance, OSA imposes a substantial socioeconomic burden. In a large cost-of-illness analysis conducted across 47 European countries, OSA was identified as generating the highest societal costs among major sleep disorders, estimated at approximately €184 billion in 2019. These costs exceeded those associated with insomnia (€158 billion), restless legs syndrome (€79 billion), narcolepsy (€905 million), and REM sleep behavior disorder (€436 million), reflecting both its high prevalence and its wide-ranging direct and indirect impacts on healthcare utilization and productivity. These estimates were based on prevalence and economic data identified through PubMed searches conducted between January 2010 and April 2023, with costs expressed in purchasing-power-parity adjusted 2019 Euros for high-income European populations [15].

Association Between Obesity and Obstructive Sleep Apnea

Obesity is one of the strongest and most well-established risk factors for OSA [7]. The prevalence of OSA in the severely obese ranges from 55 to 90% [16]. Excess adipose tissue, particularly in the neck, upper airway, and abdominal regions, contributes to mechanical narrowing of the pharyngeal airway, increasing its collapsibility during sleep [17].

Central obesity also alters respiratory mechanics by reducing lung volumes and functional residual capacity, which further predisposes individuals to airway obstruction [10]. The loss of tracheal tug associated with diminished lung volumes leads to decreased caudal traction on the upper airway structures, thereby increasing their susceptibility to collapse during sleep.

Moreover, obesity-related metabolic and inflammatory changes may exacerbate OSA pathophysiology by promoting upper airway edema and neuromuscular dysfunction. Notably, only approximately 20% of individuals with obstructive sleep apnea are non-obese [2].

Importantly, weight reduction, whether through lifestyle modification or bariatric surgery, has been shown to reduce signs of OSA severity and mitigate associated comorbidities, highlighting the critical interplay between obesity and sleep-disordered breathing [18]. Data from the Wisconsin Sleep Cohort Study demonstrated that a 10% increase in body weight was associated with a six-fold increase in the risk of developing moderate-to-severe OSA, while a corresponding 10% weight loss predicted a 26% decrease in AHI [19].

Clinical Significance and Diagnostic Rationale in OSA

Polysomnography (PSG), remains the gold standard for the diagnosis of OSA[20]. It is a non-invasive overnight test, during which multiple sensors are attached to the patient's body to record brain activity, eye movements, muscle tone, heart rhythm, respiratory parameters, and oxygen saturation. The study is conducted under continuous supervision and allows detailed assessment of sleep stages and detection of respiratory disturbances. Subsequently the recorded data are analyzed by a sleep specialist [2, 18].

Level I PSG allows simultaneous assessment of multiple physiological parameters during sleep. Standard in-laboratory polysomnography typically records at least seven channels, including electroencephalography (EEG) and electrooculography (EOG) for sleep staging, electromyography (EMG), electrocardiography (ECG), as well as respiratory variables such as airflow, respiratory effort, and oxygen saturation [21]. Home-based polysomnography (level II study) is less commonly utilized in routine clinical practice and is primarily reserved for research purposes. Importantly, comprehensive sleep specialist evaluation combined with in-laboratory PSG is particularly indicated in patients at risk of central sleep apnea or sleep-related hypoventilation. Such conditions should be suspected in individuals with underlying neurologic or neuromuscular disorders, congestive heart failure, advanced pulmonary disease, chronic opioid use, or severe obesity accompanied by elevated serum bicarbonate levels (>27 mmol/L) [21].

Despite its high diagnostic accuracy, PSG is a time-consuming and resource-intensive procedure, as it requires the patient to spend an entire night in a specialized sleep laboratory under continuous supervision [22]. Additionally, logistical barriers such as time constraints, transportation, and cost may limit accessibility, with recent European data showing a marked decline in attendance rates from 92.5% before the COVID-19 pandemic to approximately 20% afterward [23].

PSG is indicated not only for the diagnosis of OSA, but also for the evaluation of other suspected sleep disorders. It is particularly recommended when home sleep apnea testing is nondiagnostic in patients with a high pretest probability of OSA, as it allows for a more comprehensive and accurate assessment of sleep-related abnormalities [22].

Pathophysiological Mechanisms and Clinical Implications

Obstructive sleep apnea arises from a complex interplay between anatomical and non-anatomical factors that collectively promote upper airway collapse during sleep. Contemporary understanding of OSA pathogenesis has moved beyond a purely anatomical framework and now recognizes at least four distinct pathophysiological endotypes, often collectively referred to as the PALM (Pcrit, arousal threshold, loop gain, and muscle responsiveness) model, each of which may contribute to varying degrees in individual patients [32, 33].

The first and arguably most extensively studied endotype is anatomical compromise of the upper airway, quantified by the passive critical closing pressure of the pharynx (Pcrit). Pcrit reflects the intraluminal pressure at which the pharyngeal airway collapses in the absence of neuromuscular compensation. In patients with OSA, a more positive (less negative) Pcrit indicates a more collapsible airway. Obesity is a major determinant of

elevated Pcrit, principally through the accumulation of parapharyngeal and periluminal adipose tissue that narrows the pharyngeal lumen and increases the extraluminal tissue pressure [17]. Magnetic resonance imaging studies have demonstrated that tongue fat volume is significantly greater in obese individuals with OSA compared to weight-matched controls without the disorder, suggesting that the distribution of adipose tissue rather than its total quantity may be of particular pathophysiological importance [34]. Weight reduction, whether pharmacological or surgical, consistently lowers Pcrit and reduces AHI, confirming the central role of anatomical loading in obesity-related OSA [18].

The second endotype involves instability of ventilatory control, expressed as loop gain. Loop gain is an engineering concept that describes the sensitivity of the negative feedback system governing respiratory output. In physiological terms, a high loop gain indicates that even a minor perturbation in ventilation triggers an exaggerated compensatory response, which overshoots the target, producing cyclical fluctuations in respiratory drive that manifest clinically as repetitive apneic and hyperpneic events. Elevated loop gain has been identified in a substantial proportion of patients with OSA, including those with relatively mild anatomical compromise, and it appears to be influenced by metabolic factors such as insulin resistance and altered chemoreceptor sensitivity [33, 35]. This endotype carries particular therapeutic relevance because pharmacological interventions that reduce metabolic dysregulation and improve chemoreflex sensitivity may attenuate loop gain independently of any effect on body weight.

The third endotype is a low arousal threshold, defined as the propensity to awaken from sleep in response to relatively modest increases in respiratory effort or airway narrowing. Patients with a low arousal threshold tend to arouse prematurely before upper airway dilator muscles have been sufficiently recruited to stabilize the pharynx, thereby perpetuating a cycle of repeated arousals and incomplete obstruction. This mechanism is prevalent in milder forms of OSA and may explain why some patients exhibit a high AHI despite only modest anatomical abnormalities [24]. Sleep fragmentation resulting from frequent cortical arousals is itself a mediator of daytime hypersomnolence, cognitive impairment, and sympathetic overactivation.

The fourth endotype is impaired neuromuscular responsiveness of the upper airway dilator muscles, principally the genioglossus. During wakefulness, neural drive to the pharyngeal muscles compensates for anatomical narrowing, but this protective reflex is attenuated during sleep. In some patients, the magnitude of this compensatory response is insufficient to maintain airway patency, a deficit that may be compounded by local neuropathy secondary to chronic vibratory trauma from snoring, systemic inflammation, or metabolic derangement [25]. Obesity-related systemic inflammation and oxidative stress may impair peripheral nerve function and reduce the efficiency of the neuromuscular protective reflex.

The recognition of these four endotypes has catalyzed interest in a precision medicine approach to OSA treatment, where interventions are matched to the predominant pathophysiological trait in a given patient [24]. This framework has direct implications for the therapeutic evaluation of tirzepatide and other incretin-based agents. Weight loss achieved through dual GIP/GLP-1 receptor agonism may reduce Pcrit by decreasing parapharyngeal fat deposition. Concurrently, improvements in insulin sensitivity and attenuation of systemic inflammation may modulate loop gain and enhance neuromuscular responsiveness, thereby addressing multiple endotypic mechanisms simultaneously.

Incretin-based Therapies and Tirzepatide

Tirzepatide, a dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, has recently gained attention as a novel therapeutic option in the management of OSA [9]. Obesity and insulin resistance are well-established risk factors for the development of obstructive sleep apnea, and the mechanistic link between metabolic dysfunction and upper airway collapsibility provides a strong rationale for exploring anti-obesity pharmacotherapy in this context [7].

Consequently, modern anti-obesity and antidiabetic therapies, including glucagon-like peptide-1 receptor agonists, have been increasingly investigated as a therapeutic option in the treatment of obstructive sleep apnea [26]. It should be noted that the majority of available studies have been conducted in populations with overweight or obesity, thereby limiting the generalizability of these findings to individuals without excess body weight [25].

In placebo-controlled randomized trials, liraglutide and tirzepatide were each associated with significant reductions in the mean apnea–hypopnea index (AHI) in individuals with overweight or obesity [22]. Moreover, usage of GLP-1 RA reduced the systolic blood pressure and was associated with a reduced risk of cardiovascular and cerebrovascular diseases [21, 22]. Among these therapies, tirzepatide demonstrated the

greatest reduction in hypoxic burden, which is a quantitative metric used in sleep medicine to characterize the cumulative severity of oxygen desaturation associated with respiratory events during sleep [22, 23].

According to the Summary of Product Characteristics, tirzepatide is initiated at a dose of 2.5 mg once weekly, followed by stepwise dose escalation in 2.5 mg increments at intervals of at least 4 weeks. A similar titration protocol was applied in the study 'Tirzepatide for Treatment of Obstructive Sleep Apnea' where the dose was increased every 4 weeks during the escalation phase until participants reached a maximum tolerated dose of 10 or 15 mg [23, 24].

The role of tirzepatide in non-obese patients with OSA is an emerging area of interest. Although robust clinical evidence supporting its use derives predominantly from studies conducted in individuals with obesity, an increasing body of mechanistic and review-based literature suggests that its therapeutic potential may extend to non-obese populations through pathways that are at least partially independent of weight reduction [27]. Recent analyses indicate that tirzepatide exerts a range of pleiotropic effects, including significant anti-inflammatory activity, reduction of oxidative stress, and improvement in insulin sensitivity. These mechanisms are highly relevant to the pathophysiology of OSA, which is now recognized as a multifactorial disorder involving not only anatomical factors but also systemic inflammation, metabolic dysregulation, and instability of ventilatory control [25, 52].

In non-obese individuals, OSA is more frequently associated with non-anatomical traits, such as heightened loop gain, reduced arousal threshold, and altered neuromuscular responsiveness of the upper airway. Therefore, therapies targeting metabolic and neurophysiological pathways may be particularly valuable in this subgroup [25, 52]. The anti-inflammatory properties of tirzepatide may contribute to improved upper airway function by reducing local and systemic inflammation that can impair neuromuscular control [26, 52]. Concurrently, attenuation of oxidative stress may limit the deleterious effects of intermittent hypoxia, a hallmark of OSA that promotes cellular injury and further destabilizes respiratory control mechanisms [26, 27]. Improvements in insulin sensitivity and metabolic homeostasis may also influence central respiratory regulation, given the established links between metabolic signaling, chemoreceptor activity, and ventilatory drive [28].

In summary, although tirzepatide is not yet established as a treatment for OSA in non-obese patients, its multifaceted biological effects—including anti-inflammatory, antioxidative, and metabolic modulation—provide a compelling theoretical basis for its potential application in this population [25, 30, 52]. Further targeted clinical studies are warranted to elucidate its efficacy across distinct OSA phenotypes, particularly those characterized by non-anatomical pathophysiological mechanisms [29].

Tirzepatide treatment is characterized by a high incidence of adverse events, most commonly gastrointestinal, including nausea, diarrhea, and constipation [30]. These effects are generally transient, of mild to moderate severity, and occur primarily during dose escalation [30]. Less common adverse events include pancreatitis and gallbladder-related conditions [30].

Potential Consequences of Obstructive Sleep Apnea

Cardiovascular complications

Obstructive sleep apnea has been firmly established as an independent risk factor for a broad spectrum of cardiovascular diseases. The pathophysiological cascade begins with intermittent hypoxia and intrathoracic pressure swings during obstructive events, which trigger sympathetic nervous system overactivation, endothelial dysfunction, oxidative stress, and systemic inflammation [29]. These mechanisms collectively promote the development and progression of arterial hypertension, with studies reporting that 30–50% of patients with essential hypertension harbor concomitant OSA, and up to 80% of patients with treatment-resistant hypertension meet diagnostic criteria for the disorder [31]. OSA is also associated with an elevated risk of atrial fibrillation, with the prevalence of this arrhythmia being two to four times higher in OSA populations compared to matched controls [29]. The recurrent oxygen desaturation–reoxygenation cycles characteristic of OSA produce a pattern of ischemia-reperfusion injury that accelerates atherosclerotic plaque formation and destabilization, thereby increasing the risk of coronary artery disease, myocardial infarction, and stroke [32]. Congestive heart failure is both a consequence and an exacerbating factor of OSA, as fluid redistribution in the supine position augments pharyngeal edema and worsens airway collapsibility.

Metabolic complications

A bidirectional relationship exists between OSA and metabolic dysfunction. Intermittent hypoxia and sleep fragmentation independently promote insulin resistance, impaired glucose tolerance, and beta-cell dysfunction, creating a pathogenic milieu that favors the development of type 2 diabetes mellitus [33]. The European Sleep Apnea Database has demonstrated that the severity of nocturnal oxygen desaturation is an independent predictor of glycated hemoglobin levels, even after adjustment for body mass index [34]. Additionally, OSA has been implicated in the pathogenesis of metabolic-associated steatotic liver disease (MASLD, formerly NAFLD), with intermittent hypoxia promoting hepatic lipogenesis and fibrosis through hypoxia-inducible factor-1α signaling pathways [35]. The convergence of OSA with the metabolic syndrome creates a vicious cycle in which each component reinforces the other, making comprehensive management particularly challenging.

Neurocognitive and neuropsychiatric consequences

The chronic intermittent hypoxia and sleep fragmentation inherent to untreated OSA exert deleterious effects on central nervous system structure and function. Patients with moderate-to-severe OSA consistently demonstrate deficits in attention, working memory, executive function, and visuospatial processing, with impairments roughly proportional to disease severity [36]. Perhaps more concerning are the accumulating longitudinal data linking OSA to an increased risk of neurodegenerative disease. A meta-analysis by Leng and colleagues found that individuals with sleep-disordered breathing had a 26% higher risk of developing cognitive impairment or dementia compared to those without the condition [37]. The proposed mechanisms include accelerated amyloid-beta deposition secondary to impaired glymphatic clearance during fragmented sleep, chronic neuroinflammation, and hippocampal atrophy resulting from sustained hypoxic insults. Depression and anxiety disorders are also disproportionately prevalent among patients with OSA, affecting an estimated 20–40% of this population, likely mediated through disrupted serotonergic and noradrenergic neurotransmission as well as hypothalamic-pituitary-adrenal axis dysregulation [36].

Pregnancy-related complications

Obstructive sleep apnea during pregnancy carries heightened clinical significance due to its association with adverse maternal and fetal outcomes. A systematic review and meta-analysis by Pamidi and colleagues demonstrated that pregnant women with OSA face significantly elevated risks of gestational hypertensive disorders, including preeclampsia (odds ratio 2.3–3.5), as well as gestational diabetes mellitus, preterm birth, and low birth weight [38]. The physiological changes of pregnancy, including weight gain, fluid retention, and upward displacement of the diaphragm, may unmask or exacerbate pre-existing OSA, while the resulting intermittent hypoxia may compromise uteroplacental perfusion and fetal oxygenation [39]. These findings underscore the importance of screening for OSA in pregnant women with risk factors, although consensus guidelines on optimal screening strategies remain under development.

Motor vehicle accidents and occupational hazards

Excessive daytime sleepiness, the hallmark daytime symptom of OSA, constitutes a major public safety concern. Epidemiological data consistently demonstrate that untreated OSA increases the risk of motor vehicle accidents by a factor of two to seven compared to the general population, with some studies reporting an even greater elevation in risk for patients with severe disease [40]. The impairment extends beyond mere drowsiness to encompass reduced vigilance, prolonged reaction times, and impaired decision-making capacity. Professional drivers, airline pilots, and machine operators with untreated OSA pose a substantial risk to public safety, and several jurisdictions have accordingly implemented regulations mandating screening and treatment before fitness-to-drive certification is granted [41]. Importantly, effective treatment with CPAP or alternative modalities has been shown to normalize accident risk to levels comparable to the general population, providing a compelling argument for early diagnosis and intervention [40].

Table 1. Comparison of Incretin-based Therapies in Clinical Trials for OSA

Parameter	Liraglutide (SCALE)	Semaglutide (STEP)	Tirzepatide (SURMOUNT-OSA)
Mechanism	GLP-1 RA	GLP-1 RA	Dual GIP/GLP-1 RA
Trial design	RCT (dedicated OSA)	RCT (post-hoc OSA data)	RCT (dedicated OSA)
N (OSA)	359	Indirect data	469
AHI reduction	−12.2 events/h	Not reported	−20 to −25 events/h
Weight loss	~5.7%	~15–17%	~18–20%
Hypoxic burden	Not assessed	Not assessed	Significant reduction
Duration	32 weeks	68 weeks	52 weeks
Reference	Blackman et al. 2016 [42]	Wilding et al. 2021 [43]	Malhotra et al. 2024 [23]

Discussion

The review synthesizes the available evidence regarding the role of tirzepatide and incretin-based therapies in the management of obstructive sleep apnea, a condition whose burden continues to expand in parallel with the global obesity epidemic. The emergence of tirzepatide as a dual GIP/GLP-1 receptor agonist represents a potentially transformative development in this field, as the SURMOUNT-OSA trial provided the first robust randomized controlled trial evidence that a pharmacological anti-obesity intervention can produce clinically meaningful reductions in OSA severity [23].

The SURMOUNT-OSA trial, published by Malhotra and colleagues in the New England Journal of Medicine in 2024, enrolled 469 participants with moderate-to-severe OSA and obesity across two parallel studies—one in patients using CPAP and one in those not using or unwilling to use CPAP. Over 52 weeks of treatment, tirzepatide at doses of 10 or 15 mg weekly produced mean reductions in AHI of approximately 20 to 25 events per hour, representing roughly a 50–60% decrease from baseline values. Body weight decreased by a mean of 18–20%, and substantial improvements were observed in hypoxic burden, patient-reported outcomes including the Epworth Sleepiness Scale, and cardiometabolic risk markers including systolic blood pressure and C-reactive protein [23] These results were consistent regardless of baseline CPAP use, suggesting that tirzepatide may benefit both CPAP-adherent and CPAP-intolerant populations.

When contextualized against the existing evidence for other GLP-1 receptor agonists (GLP-1 RA), the magnitude of effect observed with tirzepatide appears substantially greater than that reported for earlier agents. The SCALE Sleep Apnea trial of liraglutide 3.0 mg daily, published by Blackman and colleagues in 2016, demonstrated a mean AHI reduction of 12.2 events per hour over 32 weeks, accompanied by a more modest weight loss of approximately 5.7% [44]. Indirect comparisons with semaglutide, which has shown weight reductions of 15–17% in the STEP trial programme, suggest an intermediate efficacy profile, although no dedicated randomized trial of semaglutide specifically for OSA has been published to date [45]. The meta-analysis by Li et al. in Sleep (2025) and the critical review by Luu et al. in Sleep Medicine Reviews (2025) both confirm that GLP-1 RA as a class produce significant AHI reductions, with tirzepatide demonstrating the largest effect size and the most pronounced improvement in hypoxic burden [21, 22].

The superior efficacy of tirzepatide may reflect its dual receptor pharmacology. Unlike pure GLP-1 RA, tirzepatide simultaneously activates GIP receptors, which are expressed in adipose tissue, the central nervous system, and pancreatic islets. This dual activation appears to produce synergistic effects on weight loss, insulin sensitivity, and possibly inflammatory signaling that exceed those achievable through GLP-1 receptor stimulation alone [9]. From the standpoint of OSA pathophysiology, the greater magnitude of weight loss translates directly into greater reductions in parapharyngeal fat deposition and Pcrit, while the metabolic improvements may attenuate loop gain and enhance neuromuscular responsiveness through mechanisms that operate independently of body weight changes.

Several important clinical implications arise from these observations. First, tirzepatide should be viewed as an adjunctive therapy in the comprehensive management of OSA rather than a replacement for CPAP. The SURMOUNT-OSA data indicate that even with substantial AHI reductions, many patients did not achieve complete resolution of their sleep-disordered breathing, and CPAP remains indispensable for patients with

severe residual disease or significant nocturnal hypoxemia. Second, tirzepatide may fill a critical therapeutic gap for the substantial proportion of patients who are unable or unwilling to adhere to CPAP therapy, offering a pharmacological alternative that addresses the underlying metabolic drivers of the disease. Third, the endotype-based framework for OSA treatment suggests that patients with a predominantly anatomical phenotype and high BMI are likely to derive the greatest benefit from weight-loss pharmacotherapy, while those with predominantly non-anatomical endotypes may require combination approaches.

Future research should prioritize several key areas. Long-term studies extending beyond 52 weeks are needed to determine whether the AHI reductions observed with tirzepatide are sustained and whether they translate into reductions in hard cardiovascular endpoints, including major adverse cardiovascular events and all-cause mortality. Head-to-head trials comparing tirzepatide with semaglutide would clarify whether the dual receptor mechanism confers clinically meaningful advantages over selective GLP-1 receptor agonism in the context of OSA. Studies specifically enrolling non-obese patients with OSA would help to delineate the weight-independent effects of tirzepatide on upper airway function and ventilatory control. Finally, the identification of biomarkers predictive of treatment response would enable a more personalized approach to patient selection.

Limitations

Several limitations of this review merit acknowledgment. As a narrative literature review, this work did not employ the systematic search and selection methodology characteristic of systematic reviews and meta-analyses, and it is therefore subject to inherent risks of selection bias and incomplete capture of all relevant evidence. The decision to include particular studies was guided by the authors' judgment of relevance and quality rather than by predefined, reproducible criteria.

The evidence base for tirzepatide in OSA remains limited in scope. The SURMOUNT-OSA trial, while rigorously designed, represents a single large randomized controlled trial with a follow-up duration of 52 weeks, and no data are yet available regarding the durability of treatment effects following discontinuation or the long-term safety profile in this patient population. The overwhelming majority of participants in existing trials were obese (BMI $\geq$30 kg/m^2), which restricts the generalizability of the findings to non-obese individuals with OSA. Moreover, heterogeneity in diagnostic criteria, AHI thresholds, and outcome definitions across the cited studies may limit the comparability of results. Notably, no randomized trials have evaluated the effect of tirzepatide on hard clinical endpoints such as cardiovascular events, stroke, or mortality in OSA populations. Finally, publication bias favoring positive results cannot be excluded, and the rapid pace of publication in this area means that additional relevant data may have emerged after the completion of our literature search.

Conclusions

Obstructive sleep apnea is a multifactorial disorder whose clinical management has traditionally relied on mechanical airway splinting with continuous positive airway pressure. While CPAP remains the established first-line intervention, the recognition that a substantial proportion of patients exhibit suboptimal adherence has stimulated interest in alternative, disease-modifying treatment approaches that target the underlying pathophysiological and metabolic drivers of the condition.

Tirzepatide, as a dual GIP/GLP-1 receptor agonist, has emerged as the first pharmacological agent with robust evidence from a large randomized controlled trial demonstrating clinically meaningful reductions in both AHI and hypoxic burden in patients with OSA and obesity. The magnitude of these effects surpasses that reported for earlier incretin-based agents, including liraglutide, and likely reflects the synergistic metabolic benefits of simultaneous GIP and GLP-1 receptor activation. Beyond weight reduction, the pleiotropic properties of tirzepatide—encompassing anti-inflammatory, antioxidative, and insulin-sensitizing effects—may address multiple pathophysiological endotypes of OSA, including elevated loop gain, impaired neuromuscular responsiveness, and systemic inflammatory burden.

Nevertheless, tirzepatide should currently be considered a complementary rather than a standalone treatment for OSA. Its optimal role within the therapeutic algorithm remains to be defined through long-term studies, head-to-head comparisons with other GLP-1 RA, and trials specifically designed to assess its impact on cardiovascular morbidity and mortality. Research in non-obese OSA populations and the development of predictive biomarkers for treatment response will be essential to fully realize the potential of precision-based pharmacotherapy in this field. The convergence of metabolic medicine and sleep science offers a promising avenue for the development of integrated management strategies that may fundamentally alter the disease trajectory of obstructive sleep apnea.

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