Archivos de Bronconeumología xxx (xxxx) xxx–xxx

Sociedad Española de Neumología y Cirugía Torácica SEPAR

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Bronconeumología

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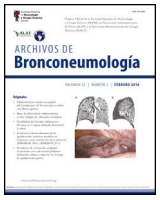

Editorial

Impact of Glucagon-Like Peptide-1 Analogues in the Treatment of Obstructive Sleep Apnoea: A Pro/Con Debate

Glucagon-like peptide-1 (GLP-1) is a 30-amino acid peptide hormone[1] mainly produced by the L-cells of the small intestine in answer to nutrient absorption. GLP-1 acts aslant binding to the GLP-1 receptor (GLP-1R) expressed in several tissues, as pancreas, brain, heart, and gastrointestinal region.[1,2] GLP-1 augments insulin secretion from pancreatic beta cells, prevents glucagon liberation by alpha cells, decelerates gastric emptying inhibiting the vagal nerve and endorses satiety. Consequently, GLP-1 is a crucial regulator of glucose metabolism and appetite.

GLP-1 receptor agonists (GLP-1RA) have been principally employed to treat type 2 diabetes and obesity. GLP-1RAs comprise exenatide, liraglutide, dulaglutide, semaglutide and tirzepatide. The last concurrently acts in two incretin receptors, the glucose dependent insulinotropic polypeptide receptor (GIPR) and GLP-1R, causing higher glycaemic and weight reductions.[2] GLP-1RA expand glycaemic control, favour weight loss, and cardiovascular and neurologic protections[2–5] (Fig. 1). Adverse effects embrace gastrointestinal disorders as nausea, vomiting, diarrhoea and constipation.[2–5]

This article, in a pro and con format, comments results from randomized controlled trials (RCT) published with GLP-1RAs in obesity-related from moderate to severe obstructive sleep apnoea (OSA) patients (Table 1).

Pro and Con Position

The advent of glucagon-like peptide-1 receptor agonists (GLP-1 RAs), in particular tirzepatide[6] represents a paradigm shift in the treatment of obesity-related OSA. These agents provide an effective pharmacological option that bridges the gap between lifestyle interventions and invasive surgical procedures for obesity treatment. The international consensus document on obstructive sleep apnoea[7] already includes weight loss as the first line treatment in obese OSA patients. This position statement advocates the use of GLP-1 RAs in patients with obesity and OSA based on their significant efficacy in weight loss, metabolic improvements and direct impact on OSA severity.

Historically, the OSA treatment landscape has lacked an effective pharmacological option to address the underlying aetiology of obesity. Although lifestyle modification remains the cornerstone of obesity treatment, long-term adherence is notoriously poor and weight loss is often insufficient to achieve significant improvements in OSA severity. Bariatric surgery, although highly effective, is invasive, associated with significant complications and not universally accessible. This led to predominantly treating OSA patients with long life CPAP treatment.

GLP-1 RA offer a novel interim treatment by inducing substantial weight loss through appetite suppression, delayed gastric emptying and improved insulin sensitivity. Clinical trials, including the SURMOUNT-OSA study,[6] have shown that tirzepatide leads to an average 17.7–19.6% reduction in body weight over 52 weeks. In patients with moderate to severe OSA, reductions in AHI correlated strongly with weight loss. The SURMOUNT-OSA study resulted in a estimates treatment different in change in AHI of approximately 23.8 events per hour compared to placebo. Such reductions are clinically significant, reinforcing the role of GLP-1 RAs as a transformative intervention for OSA. This positions GLP-1 RAs as the first pharmacological treatment able to address both obesity and its side effects in OSA.

The potency and speed of weight loss induced by GLP-1 RAs distinguishes them from previous anti-obesity drugs. Semaglutide and tirzepatide show dose-dependent reductions in body weight, with tirzepatide achieving superior efficacy due to its dual GLP-1/GIP receptor agonism. The weight loss trajectory observed in clinical trials suggests that significant reductions in adiposity occur in the first three months of treatment, accelerating the resolution of obesity-related complications, including OSA.

Unlike CPAP, which mainly controls symptoms, GLP-1 RAs address the underlying pathophysiological mechanisms that drive OSA. By reducing visceral and pharyngeal fat deposition, these agents improve upper airway patency, reduce collapsibility and improve neuromuscular control of the airway. In addition, the weight loss achieved with GLP-1 RA therapy has been associated with improvements in systemic inflammation, insulin resistance and hypertension, further reducing the cardiovascular risk markers associated with OSA.

Notably, a subset of patients in clinical trials demonstrated complete resolution of OSA with AHI reductions below diagnostic thresholds. Although the ability to withdraw CPAP in patients already on the treatment is unknown, this fact gives us an idea of this possibility. We must not lose sight of the fact that there are patients who are intolerant to CPAP for whom this treatment would be an effective alternative, and that it could help to reduce CPAP pressure when weight loss is partial. This highlights the potential of GLP-1 RAs not only as an adjunctive therapy but also as a definitive treatment for selected patients with obesity-related OSA.

One of the main advantages of GLP-1 RAs is their favourable safety and tolerability profile. The most commonly reported adverse effects are gastrointestinal (nausea, vomiting, diarrhoea)

https://doi.org/10.1016/j.arbres.2025.03.009

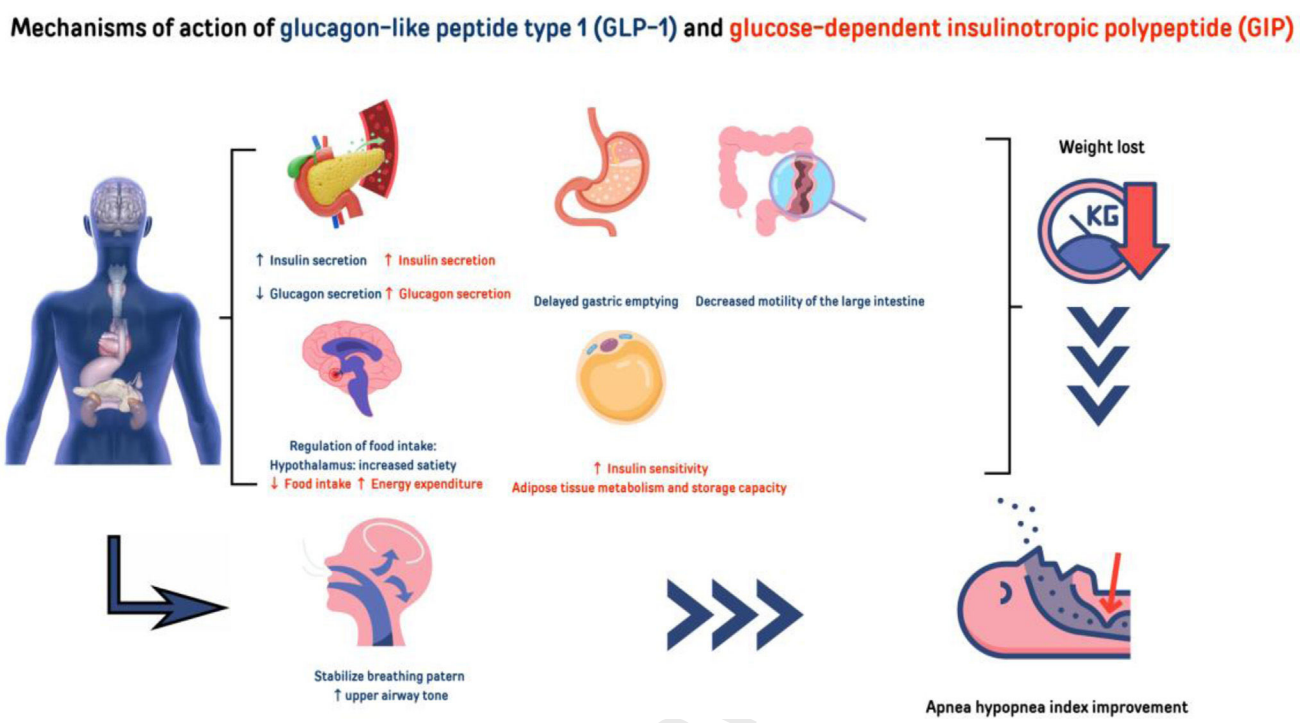

Fig. 1. Mechanisms of action of GLP-1 (blue) and GIP (red) analogues in obesity. The figure highlights the effects responsible for the improvement in obstructive sleep apnoea. (1) Mediated by weight loss: GLP1 at the level of the brain increases satiety and reduces appetite, in the pancreas it increases insulin secretion and reduces glucagon secretion, in the stomach it delays gastric emptying and reduces intestinal motility. GIP also improves insulin sensitivity and increases the metabolism of adipose tissue, increasing insulin and glucagon secretion and reducing food intake with greater energy expenditure. (2) Mediated through respiratory control: GLP-1 stabilizes the respiratory pattern through the central respiratory centre and increases upper airway tone.

and tend to resolve over time with continued use. It is important to stress that the incidence of serious adverse events is low and there is no evidence of increased cardiovascular risk; on the contrary, GLP-1 RA have been shown to have cardiovascular protective effects. These side effects are avoided by gradually increasing the dose and adjusting it to achieve the target weight loss.

Furthermore, concerns about long-term safety have been allayed by extensive clinical data from diabetes and obesity trials supporting the long-term use of these agents. Compared to other weight loss interventions, GLP-1 RAs offer a non-invasive, scalable and well-tolerated solution that reduces the reliance on CPAP and bariatric surgery for the treatment of OSA.

Regulatory approvals and clinical impact Regulatory authorities have recognized the role of GLP-1 RAs in the treatment of obesity, and their indications have been expanded to include OSA. Semaglutide and tirzepatide have been approved in several countries for the treatment of obesity, and recent data from the SURMOUNT-OSA study have confirmed their efficacy in OSA. Tirzepatide is the first GLP-1Ras approved for the FDA for OSA treatment. This regulatory support underlines the clinical importance of these agents and makes their integration into standard care pathways for patients with obesity and OSA a necessity.

Considering the effectiveness of GLP-1RAs in obese patients with moderate to severe OSA (Table 1), we wonder how it impacts in our clinical practice addressing questions based on quotidian scenarios:

Question 1. – Are GLP-1RAs an alternative treatment for obese OSA patients who receive CPAP treatment? Not yet

Two RCTs have compared CPAP treatment, with GLP-1RA alone[8] or in combination GLP-1RA + CPAP.[9] Only one[8] performed the sleep study at the end of follow-up period with CPAP in place. Consequently, another study cannot assess the efficacy of CPAP being the AHI the main outcome. In O'Donnel's study the two arms including CPAP achieved greater AHI reduction than liraglutide arm. However, O'Donnel's trial was a randomized proof-of-concept study with only around 10 patients included in each group and 12 weeks of follow-up. Besides, neither study measured the adherence to CPAP.

Current studies demonstrate a clear weight reduction with GLP-1RAs but specially with tirzepatide.[10,11] GLP-1RAs have demonstrate reduction in cardiovascular event incidence in long-term trial in obese non-diabetic patients[12,13] but they were not addressed in obesity-related OSA. A retrospective cohort study including diabetic type 2 with OSA (OSA severity and CPAP treatment were unknown) has observed greater reduction in cardiovascular events with tirzepatide than with liraglutide or semaglutide.[14] RCTs in OSA (Table 1) showed improvement in cardiovascular risk markers and in patient-centred outcomes but they had not enough follow-up periods to drive important long-term patient-centred outcomes as health resource utilization, cardiovascular event occurrence and mortality. Moreover, the cost of GPL-1RAs is high and consequently, cost or cost-effectiveness approach is crucial.

Table 1
Randomized Controlled Trials for GLP-1RA Treatments in Obesity-Related to OSA.

	Study Population	Intervention/ Control	Baseline Intervention (Mean ± SD)	Baseline Control (Mean ± SD)	Duration	Main Outcome Changes Intervention/ Control	Other/ Patient-Centred Outcomes
Liraglutide until 3.0 mg							
Blackman[b,15]	359 non-diabetic patients unwilling/unable CPAP	Liraglutide/ placebo Double blind	AHI (49.0 ± 27.5) BW (116.5 ± 23.0)	AHI (49.3 ± 27.5) BW (118.7 ± 5.4)	32 weeks	AHI: −12.2/−6.1 BW, Kg: −6.7/−1.9	Significant reduction in SBP/non-significant in ESS and HRQL.
Jiang[c,9]	90 diabetic patients on CPAP	Liraglutide+CPAP/ CPAP No blind	AHI (31.0 ± 7.3) BMI (26.5 ± 4.4)	AHI (30.1 ± 6.2) BMI (27.0 ± 2.4)	24 weeks	AHI: −4.9/0.5[a] BMI: −2.1/−0.1	Significant reduction in SBP.
O'Donnell[d,8]	30 patients	Liraglutide/ Liraglutide.+ CPAP/CPAP No blind	AHI (53 ± 20/47 ± 16) BMI 35.0 ± 3.1/34.0 ± 3.3	AHI (50 ± 21) BMI (36.0 ± 3.2)	12 weeks	AHI: −12/−45/−43 BW, kg: −6.17/−3.67/2.73	Non-significant improvement in BP.
Tirzepatide until 15 mg							
Malhotra[e,6] Trial 1	114 non-diabetic patients unwilling/ unable CPAP	Tirzepatide/placebo Double blind	AHI (52.9 ± 30.5) BW (116.7 ± 24.6)	AHI (50.1 ± 31.5) BW (112.8 ± 22.6	52 weeks	AHI: −25.3/−5.3 BW, %: −17.7/−1.6	Significant reductions in SBP/ and in PROMIS-SRI and -SD T scores.
Malhotra[e,6] Trial 2	120 non-diabetic patients using CPAP	Tirzepatide + CPAP/placebo Double blind	AHI (46.1 ± 22.4) BW (115.8 ± 21.5)	AHI (53.1 ± 30.2) BW (115.1 ± 22.7)	52 weeks	AHI: −29.3/−5.5[a] BW, %: −19.6/−2.3	Significant reductions in SBP/ and in PROMIS-SRI and -SD T scores.

Abbreviations: GLP-1RA = Glucagon-like Peptide-1 receptor agonist; OSA = obstructive sleep apnoea; SD = standard deviation; CPAP = continuous positive airway pressure; AHI = apnoea–hypopnea index; BW = body weight; SBP = systolic blood pressure; EES = Epworth sleepiness scale; HRQL = health related quality of life; BMI = body mass index (kg/m^2); BP = blood pressure; and PROMIS-SRI and -SD T = PROMIS Short Form Sleep-related Impairment 8a and PROMIS Short Form Sleep Disturbance 8b.

[a] CPAP not in place during the sleep study at the end of follow-up.

[b] Blackman et al. steered a 32-week randomized double-blind clinical trial including 359 non-diabetic obese OSA patients (AHI ≥ 15/h). Patients received either liraglutide (initial dose 0.6 mg/day, growing weekly by 0.6 mg up to 3 mg/day) or placebo, together with diet and exercise advice. Liraglutide group gets greater reduction (−12.2/h) compared with placebo group (−6.1/h), with a significant difference (95% CI, −11.0 to −1.2, $p = 0.015$).

[c] Jiang et al. drive a randomized controlled trial including diabetic type II OSA patients (AHI ≥ 15/h) on CPAP therapy. Applicants received either liraglutide (initial dose 0.6 mg/day, increasing weekly up to 1.8 mg/day) plus CPAP or CPAP alone for three months. The combination treatment significantly reduced AHI compared to CPAP alone ($p < 0.05$).

[d] O'Donnell et al. directed a 24-week proof-of-concept study comparing CPAP therapy alone, liraglutide alone (opening dose 0.6 mg/day, growing weekly p to 3 mg/day), and the combination of liraglutide and CPAP in obese OSA patients (AHI > 15/h). All arms significantly reduced AHI compared with baseline. Nevertheless, liraglutide alone was less effective compared with CPAP alone and the combination of both.

[e] Malhotra et al. conducted two randomized double-blind controlled trials in non-diabetic obese OSA patients. In the first trial, patients without CPAP treatment and in the second trial, patients on CPAP were randomized to tirzepatide (starting with 2.5 mg increasing up to 10 mg or 15 mg) or a placebo and tirzepatide + CPAP or placebo in the second trial. Patients on tirzepatide had a greater reduction in AHI than in the placebo arm in both trials.

In summary, to answer this first question is an essential direct comparison between tirzepatide (or analogous[15]) with CPAP in RCT with long-term patient-centred outcomes and cost analysis. Interestingly, the power should be enough to analyze CPAP adherence sub-groups or RCTs focused in these subgroups of patients.

Question 2. – Are GLP-1RAs an adjuvant treatment for obese OSA patients who receive CPAP treatment? Could be yes, but more studies are required

The main target for this scenario should be to decrease the cardiovascular risk principally caused by the weight drop. Two medium-term RCTs compared GLP-1RA+CPAP vs. CPAP,[8,9] but there are no long-term studies with patient-centred outcomes as reduction of cardiovascular events and mortality.

Question 3. – Are GLP-1RAs an alternative to the habitual treatment for obese OSA patients who have CPAP indication but they are unwilling or unable to receive CPAP treatment? Not yet for all

Two RCTs have compared GLP-1RAs vs. placebo in this group of patients, with liraglutide[16] or tirzepatide.[6] Tirzepatide group gathered greater improvement in AHI and weight discount than liraglutide from similar baseline values (Table 1). But, even in the tirzepatide's study, the residual AHI was close to 28 and only 42% of patients had an "acceptable" residual situation (AHI of <5 or AHI of 5–14 with ESS ≤ 10) at the end of trial.

In clinical practice for the group of patients included in question 3 we carried out a holistic treatment including diet and exercise, mandibular advancement devices (MAD) and bariatric surgery in some cases.[7] There are no RCTs comparing GLP-1RAs with this holistic approach or with some of them.

Tirzepatide's study had 48 exclusion criteria and close to 43% of patients excluded of the eligible population (alike to our 1 and 3 question/scenarios). Diabetic patient was an exclusion criterion. The proportion of diabetes type 2 in obese patients with moderate-severe AOS is not negligible. Although diabetic patients treated with GLP-1RAs may have better long-term outcomes than non-diabetic patients, the residual AHI observed with this treatment may counterbalance the potential benefit. Tirzepatide improved clinical symptoms after 52 weeks of treat-

ment compared with placebo but there are not long-term RCTs to know important outcomes as cardiovascular event reduction. Consequently, this absence of evidence and exclusions may limit the external validity and preventing the clinical applicability.

Tirzepatide is an approved treatment for obese patients with moderate-severe OSA[17,18] but in our country is uncovered by Heath Care Services. Tirzepatide's cost is only allowable to some pockets.

In summary, according to the available evidence, tirzepatide may be prescribed for patients included in question 3 if they are non-diabetic, who do not meet the remaining 48 exclusion criteria, non-subsidiary to MAD treatment, with a principal aim of treatment to improve clinical symptoms and who are willing to pay the cost of treatment for at least 4 months.[6] To overcome this minority of candidates for treatment we need long-term RCTs comparing tirzepatide, or analogous, with the habitual treatment alternative (including MAD) in this group of patients, counting diabetic and non-diabetic patients and analysing long-term patient-centred outcomes and cost.

Question 4. – Are GLP-1RAs an alternative to the habitual treatment for obese patients who have significant OSA (AHI > 15) but have not CPAP indication? Not yet

This scenario includes patients without relevant clinical symptoms or resistant hypertension that commonly receive holistic treatment (MAD included) because they maintain potential cardiovascular risk and/or non-mayor symptoms.[7] Unfortunately, there is no RCTs focused in this population despite GLP-1RAs may be an interesting treatment for weight loss.

Question 5. – Are GLP-1RAs an alternative to the habitual treatment for non-obese patients who have significant OSA (AHI > 15) but they are unwilling or unable to receive CPAP treatment? Not yet

The main GLP-1Rs effect to get reduction in the AHI is the weight loss[19] but not the only[20] because GLP-1RAs themselves may lead to AHI reduction (Fig. 1). Future studies should brighten this gap.

In conclusion, GLP-1 receptor agonists, particularly tirzepatide, represent a revolutionary advance in the treatment of obesity-associated OSA. Their unprecedented efficacy in weight loss, rapid onset of action, ability to target the primary cause of OSA and favourable safety profile position them as a viable and interesting treatment option for several patients. Given the strong evidence base and recent regulatory approvals, the integration of GLP-1 RAs into OSA treatment could be prioritized, offering patients an effective pharmacological adjuvant therapy to CPAP or an alternative to CPAP in some cases as well as to bariatric surgery.

However, up to the present time there is not long-term information about reduction of cardiovascular events or comparison with other alternative OSA treatments (i.e. MAD, bariatric surgery) in obesity-related OSA patients treated with GLP-1RAs which, jointed with the GLP-1RA costs, preventing to answer some questions based on everyday clinical scenarios limiting the clinical applicability.

Artificial Intelligence Involvement

During the preparation of this work the authors used Canva for figures development. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Funding of the Research

There is no founder relationship.

Conflict of Interest

OM served as a consultant for Resmed and Eli Lilly. No conflicts exist for JFM.

Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2025.03.009.

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