Efficacy and Safety of Glucagon Like Peptide-1 Receptor Agonism Based Therapies in Obstructive Sleep Apnoea: A Systematic Review and Meta-Analysis

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Abstract

Introduction: The exponential increase in obesity is responsible for the increased prevalence of obstructive sleep apnoea (OSA). Weight loss is critical to improvement in OSA. Glucagon-like peptide-1 receptor (GLP1R) agonism-based therapies (GLP1RA-BT) have been associated with significant weight loss. Several randomized controlled trials have been published evaluating the use of GLP1RA-BT on OSA. However, the literature review revealed that no systematic review and meta-analysis (SRM) has been published evaluating the efficacy and safety of GLP1RA-BT in OSA. **Methods:** Electronic databases were searched for studies documenting the use of GLP1RA-BT in OSA. The primary outcome was to evaluate the impact on the apnea–hypopnea index (AHI). Secondary outcomes were to evaluate the impact on percent change in AHI, Epworth Sleepiness Score, body weight, blood pressure, and side-effect profile. **Results:** From initially screened 59 articles, data from 4 articles having 5 different randomized cohorts (937 patients) were analysed in this SRM. Use of GLP1RA-BT was associated with a significant reduction in AHI [MD-12.50 events/ hour (95% CI:−17.33 – -7.67); $P < 0.001$; I^2=95%], percent-reduction in AHI [MD-52.17% (95% CI: -64.49 – -39.85); $P < 0.001$; $I^2 = 0\%$], percent-reduction in body-weight [MD-12.46% (95% CI:-22.54 – -2.39); $P < 0.001$; $I^2 = 99\%$] and systolic blood-pressure [MD -4.59 mm of Hg (95% CI:-6.61 – -2.58); P < 0.001; $I^2 = 67\%$]. The considerable heterogeneity was because of greater improvement in outcomes withtirzepatide compared to liraglutide. The occurrence of nausea [RR4.23 (95% CI: 2.73–6.55); $P < 0.001$; $I^2 = 0\%$], vomiting [RR4.22 (95% CI: 2.12–8.41); $P < 0.001$; $I^2 = 0\%$], diarrhoea [RR2.81 (95% CI: 1.84–4.31); $P < 0.001$; $I^2 = 0\%$], and constipation [RR4.51 (95% CI: 2.47–8.26); $P < 0.001$; $I^2 = 0\%$] were significantly higher with GLP1RA-BT compared to placebo. **Conclusion:** This SRM provides encouraging data on the use of GLP1RA-BT in improving different respiratory aspects of OSA and reducing body weight and blood pressure.

Keywords: Glucagon-like peptide-1 receptor, liraglutide, obesity, sleep apnoea, tirzepatide

Introduction

Obstructive sleep apnoea (OSA) is a common under-recognized complication of metabolic syndrome (MetS) and has been linked to increased daytime sleepiness, accidents, hypertension, cardiovascular events, and all-cause mortality.[1,2] OSA is a major non-communicable disease pandemic globally (1 billion people affected), with a prevalence exceeding 50% in some countries.[3] China is believed to be most affected followed by USA, Brazil, and India.[3] Continuous positive airway pressure (CPAP) has been the treatment of choice with adherence ranging from 60 to 70%.[1] The increased prevalence of obesity is primarily responsible for the increase in OSA.[4] Weight loss has been shown to improve different aspects of OSA. Apart from

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CPAP, guidelines have routinely suggested substantial weight loss as an effective treatment for OSA.[4]

The newer glucagon-like peptide-1 receptor (GLP1R) agonism-based therapies like GLP1R agonists (high dose liraglutide, semaglutide) and twincretins like tirzepatide have documented 5-20% weight loss, which was not possible with previous weight-loss medications like orlistat.[5,6] Such substantial weight loss has been linked to improvement in several aspects of MetS like diabetes remission, improvement in hypertension, improvement in steatotic liver disease, and reduction in cardiovascular events.[7,8] Several randomized controlled trials (RCTs) have been published evaluating the impact of GLP1R agonism-based therapies on OSA.[9,10] However, a literature review revealed that no dedicated systematic review and meta-analysis (SRM) has been published evaluating the efficacy and safety of GLP1 agonism-based therapies in OSA. Hence this SRM aimed to evaluate the efficacy and safety of GLP1R agonism-based therapies in OSA.

Materials and Methods

The SRM was carried out according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[11] The predefined protocol has been registered in PROSPERO having Registration number CRD42024561429. All randomized controlled trials (RCTs), cohort studies, and case-control studies published till June 2024 were considered for this SRM. This SRM has been reported by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[11] Since ethical approval already exists for the individual studies included in the meta-analysis, no separate approval was required for this study.

The PICOS criteria were used to screen and select the studies for this meta-analysis with patients (P) being people living with OSA; intervention (*I*) being the use of GLP1R agonism-based therapies (liraglutide, semaglutide, tirzepatide and any other medication of this class) for managing OSA; control (C) being patients either on placebo or any other approved treatment for OSA; outcomes (O) being evaluated were change in the apnoea–hypopnea index (AHI, the number of apnoeas and hypopneas during an hour of sleep), percent change in AHI, the percentage of participants with an AHI of less than 5 events per hour or with an AHI of 5 to 14 events per hour and a score of 10 or less on the Epworth Sleepiness Scale (ESS; range, 0 to 24, with higher scores indicating greater daytime sleepiness), percent change in body weight, blood pressure, and side-effects profile.

The primary outcome of this SRM was to evaluate the impact of GLP1R agonism-based therapies on AHI. The secondary outcomes of this SRM were to evaluate the percentage change in AHI from baseline, participants with an AHI of less than 5 events per hour or with an AHI of 5 to 14 events per hour and a score of 10 or less on ESS, percent change in body-weight, blood pressure, and side-effects profile. Analysis of the outcomes was done based on whether the control group received an active comparator – labeled here as the active control group (ACG) or a placebo/no treatment for OSA – labeled as the passive control group (PCG).

Search method for identification of studies

A detailed electronic database of Medline (Via PubMed), Embase (via Ovid SP), Cochrane Central Register of controlled trials (CENTRAL) (for trials only), ctri.nic.in, clinicaltrials.gov, global health, and Google Scholar were searched using a Boolean search strategy: (glucagon-like peptide-1 receptor*) AND (sleep apnoea). Alternative searches were done separately by replacing the term "glucagon-like peptide-1 receptor" with GLP1R agonist, exenatide, liraglutide, dulaglutide, lixisenatide, semaglutide, tirzepatide and cotadutide.

Data extraction and study selection

Data extraction was carried out independently by two authors using standard data extraction forms. In cases where more than one publication of a single study group was found, results were grouped and relevant data from each report were used in the analyses. Data on the primary and secondary outcomes as stated above was extracted. All disagreements were resolved by the third and fourth authors.

Assessment of risk of bias in included studies

Two authors independently assessed the risk of bias in RCTs using the risk of bias assessment tool in Review Manager (Revman) Web (The Cochrane Collaboration, Oxford, UK 2023) software. We looked for adequate sequence generation (selection bias). We looked for if the allocation was adequately concealed (selection bias) or not. We also looked for whether the knowledge of the allocated interventions was adequately prevented during the study or not. Participants and personnel (performance bias) blinding was specifically looked for, and so was the blinding of the outcome assessors (detection bias). We looked for whether the incomplete outcome data issue was adequately addressed or not (attrition bias). We looked for whether the study was free of suggestion of selective outcome reporting (reporting bias). Lastly, we also looked for whether the study was free of other problems that could put it at risk of bias.

Measures of treatment effect

For continuous variables, the outcomes were expressed as mean differences (MD). Conventional units were used for analysis, and all studies reporting results in SI units were converted to conventional units for analysis. For dichotomous outcomes, results were expressed as risk ratios (RR) with 95% confidence intervals (CI).

Assessment of heterogeneity

Heterogeneity was initially assessed by studying the forest plot generated for the primary and secondary outcomes of this study. Subsequently, heterogeneity was analyzed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test.[12] The interpretation of I^2 values is as follows: 0–40%: might not be important (low heterogeneity); 40–60%: may represent moderate heterogeneity; 60–90%: may represent substantial

heterogeneity; 90–100%: considerable heterogeneity (high heterogeneity). Sensitivity analysis was done for all the major outcomes analyzed in this SRM.[13,14]

Data synthesis

Data was pooled as a random effect model for the analysis of primary and secondary outcomes. The outcomes were expressed as 95% confidence intervals (95%CI). Forrest plots were plotted with the left side of the graph favoring GLP1R agonism-based therapies and the right side of the graph favoring control. The Review Manager (RevMan) computer program, version 7.2.0 (The Cochrane Collaboration, 2024. Available at revman.cochrane.org) was used for comparing mean difference (MD) or risk ratios (RR) of the different primary and secondary outcomes. $P < 0.05$ was considered statistically significant.

Results

The initial literature search revealed 59 articles. Six duplicates were removed. After review of the title and the abstracts of the 53 articles, the search was down to 7 articles, which were reviewed in detail for inclusion in this SRM. Finally, data from 4 publications that fulfilled all the criteria were analyzed in this SRM (937 patients; Table 1).[9,10,15,16] The details have been elaborated in Supplementary Figure 1. In the study by Jiang *et al.*,[10] patients receiving liraglutide (1.8 mg/day) were compared to those not receiving liraglutide with regards to improvement in OSA. It was an open-labeled RCT, and both the study and the control group received CPAP.[10] In the study by Blackman *et al.,*[9] patients with moderate-to-severe OSA not on CPAP (unable or unwilling) and receiving liraglutide 3 mg/day were compared to those receiving placebo with regards to improvement in OSA. In the publication by Malhotra *et al.,*[15] there were 2 sub-trials. In the first RCT, tirzepatide was compared to a placebo for changes in OSA in patients who had received no treatment. The results of this cohort of patients have been presented here as Malhotra 2024a.[15] In the second RCT, tirzepatide was compared to a placebo for changes in OSA in patients who were already on CPAP and continued CPAP for the duration of the study. The results of this cohort of patients have been presented here as Malhotra 2024b.[15] The RCT by O'Donnell *et al.*[16] compared GLP1RA liraglutide to CPAP with regards to improvement in different parameters of OSA, hence the results of this study have been presented separately under the ACG. The details of the patients evaluated in the different RCTs have been elaborated in Table 1.

Risk of bias in the included studies

The risk of bias of all the 5 different study cohorts analyzed in this SRM has been elaborated in Supplementary Figure 2a and b. Random sequence generation (selection bias), attrition bias, and reporting bias were found to be low risk in all the study cohorts (100%) [Supplementary Figure 2a and b]. Allocation concealment, performance bias, and detection bias were found to be at low risk in 60% of the study cohorts [Supplementary Figure 2a and b]. Another bias which looks at pharmaceutical industry funding and the presence of one or more authors from the pharmaceutical industry was found to be at low risk in 40% of the study cohort [Supplementary Figure 2a and b].

Effect of GLP1R agonism-based therapies on primary and secondary outcomes compared to placebo

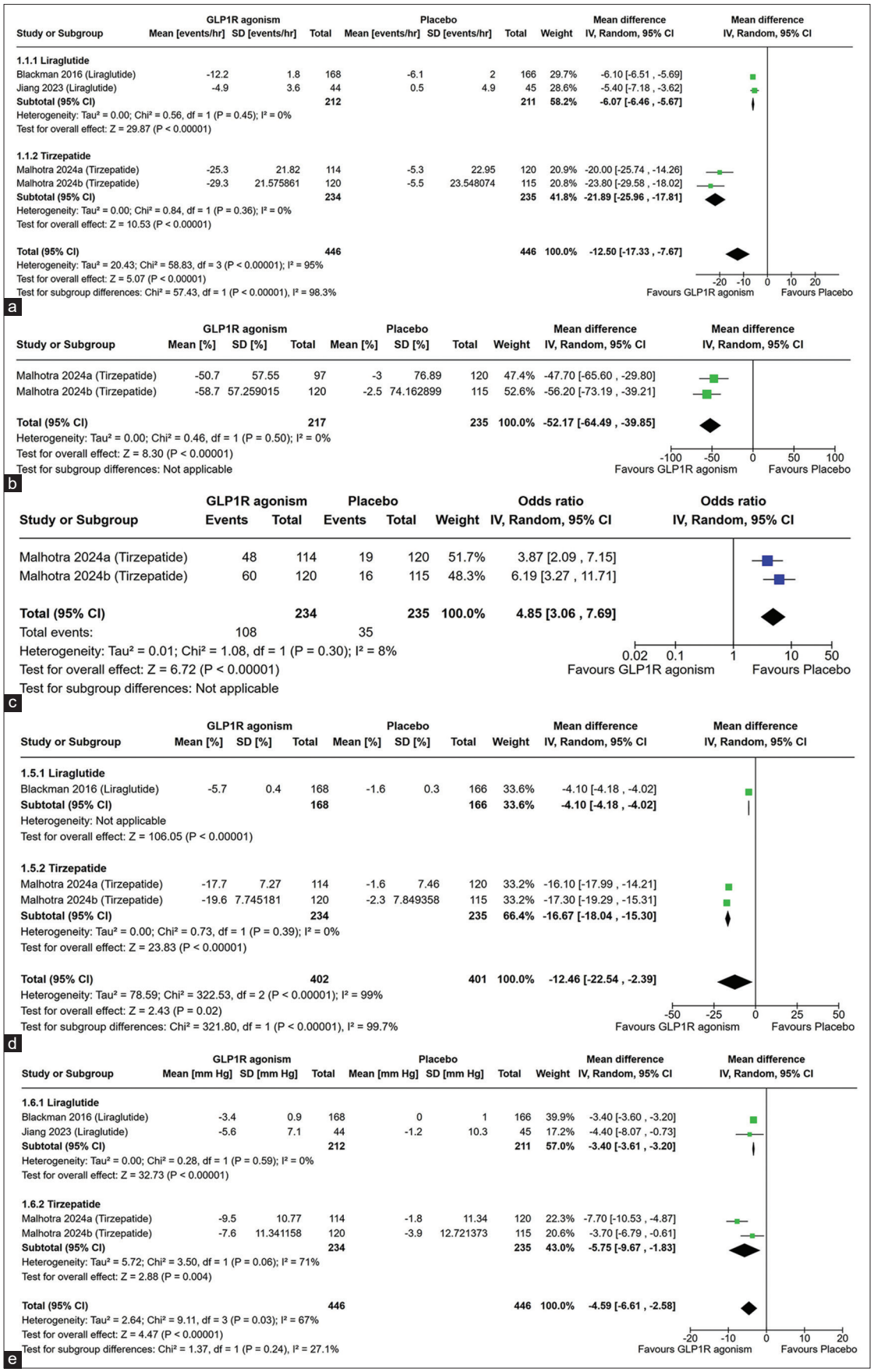
Apnoea–hypopnea index

Data from 4 different cohorts of patients (892 patients) were analyzed to find out the impact of GLP1R agonism-based therapies on AHI as compared to the placebo/passive control group (PCG). Individuals treated with GLP1R agonism-based therapies had significantly lower AHI as compared to PCG [MD -12.50 events/hour (95% CI: -17.33 – -7.67); $P < 0.001$; $I^2 = 95\%$ considerable heterogeneity); Figure 1a]. The considerable heterogeneity is because of the difference in outcomes between liraglutide and tirzepatide. Sub-group analysis revealed that AHI reduction was significantly better with tirzepatide [MD -21.89 events/hour (95% CI: -25.96 – -17.81); $P < 0.001$; $I^2 = 0\%$ (low heterogeneity); Figure 1a] as compared to liraglutide [MD -6.07 events/hour (95% CI: -6.46 – -5.67); $P < 0.001$; $I^2 = 0\%$ (low heterogeneity); Figure 1a].

Table 1: Characteristics of patients evaluated in different randomized controlled trials analyzed in this systematic review and meta-analysis

Study (Duration)		Age (years)	Male (%)	Body weight (kg)	BMI (kg/m^2)	AHI-events/hr	Severe AHI ≥30 events/hr (%)	SBP (mm Hg)	DBP (mm Hg)
Malhotra 2024a[15] (52 weeks) USA	Tirzepatide *n*=114	47.3±11	68.4%	116.7±24.6	39.7±7.3	52.9±30.5	64.9%	128.4±12.2	83.7±8.9
	Placebo *n*=120	48.4±11.9	65.8%	112.8±22.6	38.6±6.7	50.1±31.5	61.3%	130.3±10.7	84.0±8.6
Malhotra 2024b[15] (52 weeks) USA	Tirzepatide *n*=120	50.8±10.7	72.5%	115.8±215	38.6±6.1	46.1±22.4	70.6&	130.5±14.3	83.2±8.2
	Placebo *n*=115	52.7±11.3	72.2%	115.1±22.7	38.7±6.0	53.1±30.2	65.8%	130.5±12.8	80.5±8.6
Donnell 2023[16] (24 weeks) (Ireland)	Liraglutide *n*=10	50±9	80%	-	35.0±3.1	53±20	100% of both groups had AHI ≥15 events/hr	126±13	76±9
	CPAP *n*=10	51±8	90%		36.0±3.2	50±21		119±10	72±6
Jiang 2023[10] (12 weeks) China	Liraglutide *n*=44	55.7±7.4	34%	--	26.5±4.4	31.0±7.3	100% of both groups had AHI ≥15 events/hr	130.4±11.9	75.0±8.8
	Placebo *n*=45	54.8±5.5	29%		27.0±2.4	30.1±6.22		132.2±13.0	74.4±9.3
Blackman 2016[9] (32 weeks) USA	Liraglutide *n*=180	48.6±9.9	71.7%	-	38.9±6.4	49.0±27.5	66.7%	-	-
	Placebo *n*=179	48.4±9.5	72.1%		39.4±7.4	49.3±27.5	67.6%		

AHI: Apnoea–Hypopnea Index; BMI: Body mass index; DBP: Diastolic blood pressure; and SBP: Systolic blood pressure



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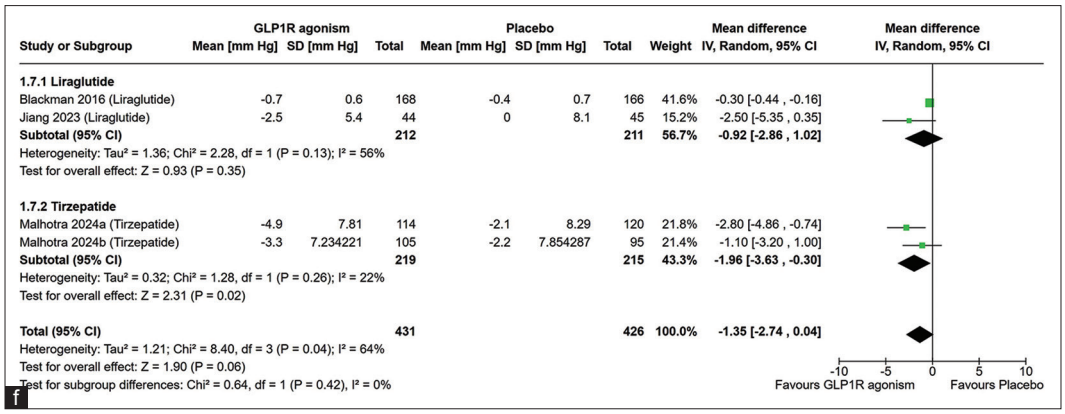


Figure 1: Forest plot highlighting the impact of glucagon like peptide-1 receptor (GLP1R) agonism based therapies as compared to placebo on (a) Apnoea- Hypopnea Index (AHI); (b) percent change in AHI from baseline; (c) Percentage of participants with an AHI of less than 5 events per hour or with an AHI of 5 to 14 events per hour and a score of 10 or less on ESS; (d) Percent change in weight; (e) Change in systolic blood pressure (SBP); (f) Change in diastolic blood pressure (DBP)

Data from 2 different cohorts of patients (452 patients) were analyzed to find the impact of tirzepatide on the percent change in AHI from baseline. Individuals treated with tirzepatide had a significantly greater percent reduction in AHI as compared to PCG [MD -52.17% (95% CI: -64.49 – -39.85); $P < 0.001$; $I^2 = 0\%$ (low heterogeneity); Figure 1b]. Data from 2 different cohorts of patients (452 patients) were analyzed to find the impact of tirzepatide on the percentage of participants with an AHI of less than 5 events per hour or with an AHI of 5–14 events per hour and a score of 10 or less on ESS. A significantly greater percentage of patients could achieve this target as compared to PCG [MD 4.85% (95% CI: 3.06 – 7.69); $P < 0.001$; $I^2 = 8\%$ (low heterogeneity); Figure 1c].

Body weight

Data from 3 different cohorts of patients (803 patients) were analyzed to find the impact of GLP1R agonism-based therapies on percent change in body weight. Patients on GLP1R agonism-based therapies had a significantly greater percent reduction in body weight from baseline as compared to PCG [MD -12.46% (95% CI: -22.54 – -2.39); $P < 0.001$; $I^2 = 99\%$ (considerable heterogeneity); Figure 1d]. The considerable heterogeneity is because of the difference in the weight-loss outcomes between liraglutide and tirzepatide. Sub-group analysis revealed that percent reduction in body weight was significantly better with tirzepatide [MD -16.67% (95% CI: -18.04 – -15.30); $P < 0.001$; $I^2 = 0\%$ (low heterogeneity); Figure 1d] as compared to liraglutide [MD -4.10% (95% CI: -4.18 – -4.02); $P < 0.001$; Figure 1d].

Blood pressure

Data from 4 different cohorts of patients (892 patients) were analyzed to find out the impact of GLP1R agonism-based therapies on systolic blood pressure (SBP) and diastolic blood pressure (DBP) as compared to PCG. Patients on GLP1R agonism-based therapies had a significantly greater reduction in SBP [MD -4.59 mm of Hg (95% CI: -6.61 – -2.58); $P < 0.001$; $I^2 = 67\%$ (moderate heterogeneity); Figure 1e] and a reduction DBP, which approached statistical significance [MD -1.35% (95% CI: -2.74 – 0.04); $P < 0.001$; $I^2 = 64\%$ (moderate heterogeneity); Figure 1e] as compared to PCG. The moderate heterogeneity is because of the differences in BP reduction between tirzepatide and liraglutide. Tirzepatide had a significantly greater reduction in both SBP and DBP as compared to liraglutide [Figure 1d and e]. Liraglutide use was associated with a significant reduction in only SBP and not DBP [Figure 1d-f].

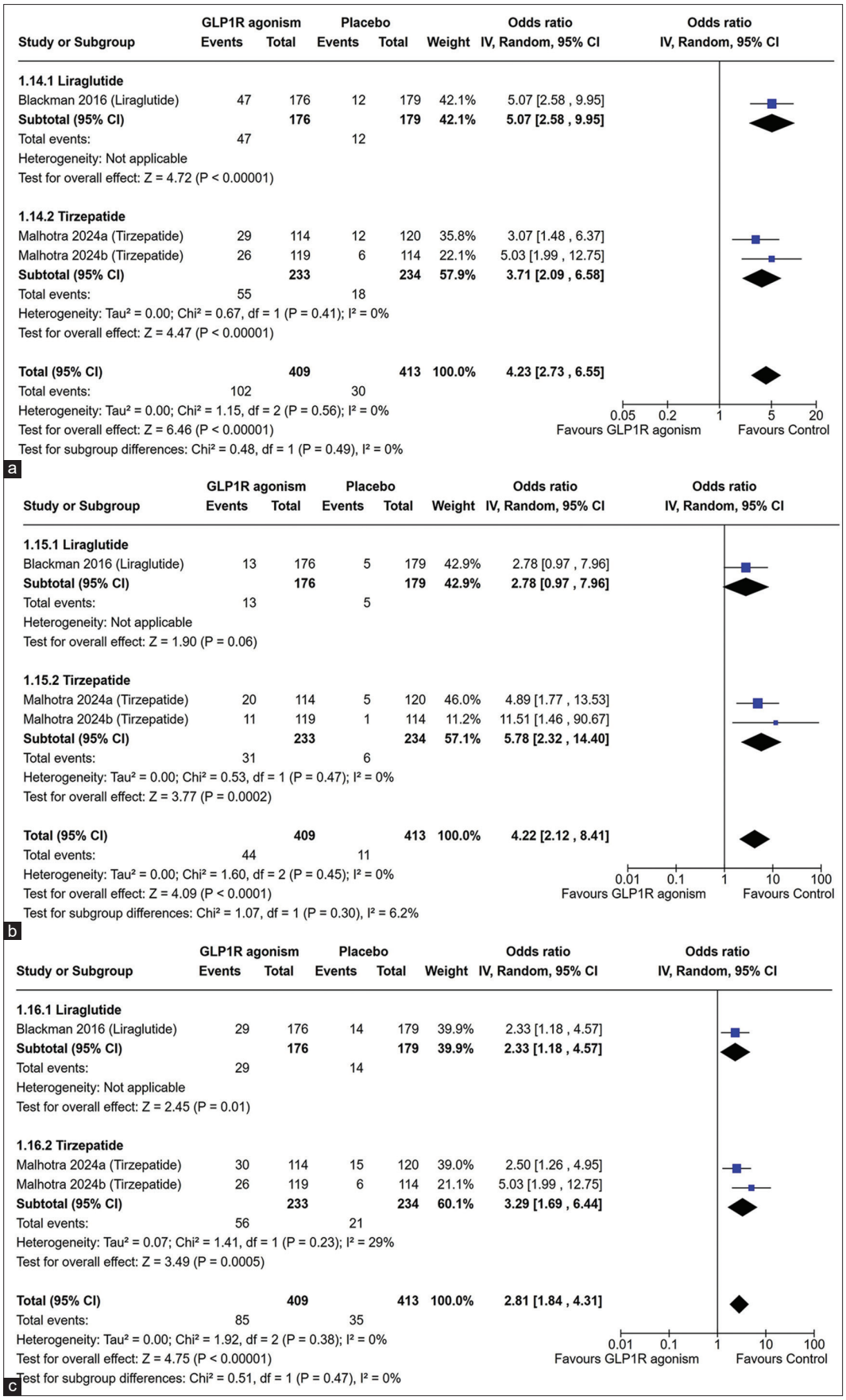
Adverse events

Data from 3 different cohorts of patients (822 patients) were analyzed to find the impact of GLP1R agonism-based therapies on the occurrence of nausea, vomiting, diarrhea, and constipation. The occurrence of nausea [RR 4.23 (95% CI: 2.73 – 6.55); $P < 0.001$; $I^2 = 0\%$ (low heterogeneity); Figure 2a], vomiting [RR 4.22 (95% CI: 2.12 – 8.41); $P < 0.001$; $I^2 = 0\%$ (low heterogeneity); Figure 2b], diarrhea [RR 2.81 (95% CI: 1.84 – 4.31); $P < 0.001$; $I^2 = 0\%$ (low heterogeneity); Figure 2c] and constipation [RR 4.51 (95% CI: 2.47 – 8.26); $P < 0.001$; $I^2 = 0\%$ (low heterogeneity); Figure 2d] were significantly higher with the use of GLP1R agonism based therapies as compared to PCG, with no difference in outcomes between liraglutide and tirzepatide.

Data from 2 different cohorts of patients (467 patients) were analyzed to find the impact of tirzepatide on the occurrence of depression/suicidal tendencies and severe hypoglycemia. The occurrence of depression/suicidal tendencies [RR 0.76 (95% CI: 0.07 – 7.96); $P = 0.82$; $I^2 = 33\%$ (low heterogeneity); Figure 2e] and severe hypoglycaemia [RR 0.33 (95% CI: 0.03 – 3.21); $P = 0.32$; $I^2 = 0\%$ (low heterogeneity); Figure 2f] were similar in patients on tirzepatide as compared to those on placebo (PCG).

Effect of GLP1R agonism-based therapies on primary and secondary outcomes compared to CPAP (ACG)

Data from one study (O'Donnell *et al.*[16]; n = 20) was analyzed to evaluate the impact of liraglutide as compared



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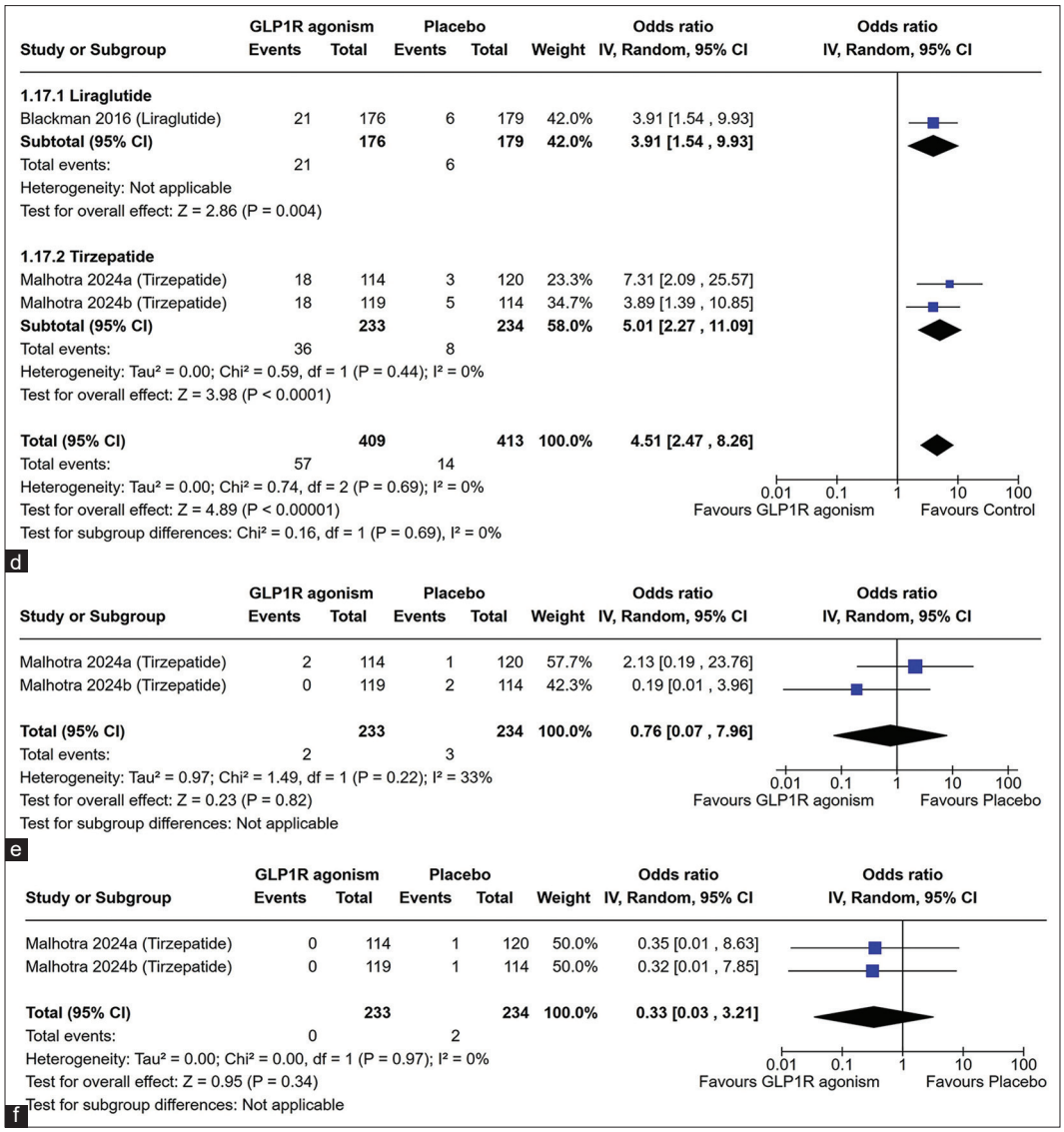

Figure 2: Forest plot highlighting the impact of glucagon like peptide-1 receptor (GLP1R) agonism based therapies as compared to placebo on the occurrence of (a) nausea; (b) Vomiting; (c) Diarrhoea; (d) Constipation; (e) Depression or suicidal tendencies; (f) Severe hypoglycaemia

to CPAP on the different outcomes (16). Liraglutide was inferior to CPAP in improvement in AHI [MD 33.04 events/hour (95% CI: 19.74 – 46.26); $P < 0.001$]. Liraglutide was superior to CPAP with regards to percent reduction in body weight [MD -8.90% (95% CI: -12.5 – 46.26); $P < 0.001$]. The reduction in SBP [MD -6.08 mm of Hg (95% CI: -12.66 – 0.50); $P = 0.07$] and DBP [MD -2.10 mm of Hg (95% CI: -6.77 – 2.57); $P = 0.38$] was higher with liraglutide as compared to CPAP, but statistically not significant.

Discussion

This SRM shows that GLPR agonism-based therapies are effective in improving outcomes in people living with OSA. GLP1R agonism-based therapies like liraglutide (GLP1 receptor agonist) and tirzepatide (a twincretin, dual GLP1 receptor and glucose-dependent insulinotropic peptide (GIP) agonist) use was associated with a significant reduction in absolute as well as percent change from baseline in the apnoea–hypopnea index (AHI). These benefits were more apparent with tirzepatide as compared to liraglutide. Percent reduction in body weight was significantly higher with GLP1 receptor agonism-based therapies as compared to placebo. The percent reduction in body weight was more with tirzepatide as compared to liraglutide. Hence, it may be said that the greater quantum of body weight reduction with tripeptide followed by liraglutide may explain the greater quantum of improvement in OSA, and other associated parameters like blood pressure. The improvement in AHI and reduction in body weight and blood pressure were associated with increased occurrence of gastrointestinal side-effects (nausea, vomiting, diarrhea, and constipation) as has been previously documented with this class of medication.[5,6] The gastrointestinal side effects can be explained by the mechanism of action of these medications which include decreasing gastric emptying and central satiety effects.[7]

The single study that compared GLP1R agonism-based therapies to CPAP with regards to improvement in OSA and metabolic parameters showed that though CPAP was better than liraglutide with regards to improvement in OSA parameters, liraglutide continued to be better than CPAP with regards to reduction in body weight and blood pressure (metabolic syndrome (MetS parameters). It must be realized that GLP1R agonism-based therapies are never meant to replace CPAP, which continues to be the treatment of choice for the management of OSA.

The majority of the patients included in these studies presented with moderate to severe OSA, characterized by high AHI scores and significant co-morbidities such as obesity and T2DM. This baseline profile is critical as it reflects the real-world scenario where OSA often coexists with metabolic dysfunction, complicating treatment approaches. GLP1 receptor agonism-based therapies address the core issue of obesity. Weight loss with the use of GLP1R agonism-based therapies results in an improvement in the different components of MetS, which include OSA. The significant reductions in AHI, BMI, and SBP observed in patients treated with GLP-1R agonism-based therapies suggest that these therapies can effectively address the multifaceted aspects of moderate to severe OSA, making them a valuable addition to existing OSA management strategies. The relationship between OSA and cardiovascular (CV) risk is well-established, with untreated OSA contributing to increased incidences of hypertension, coronary artery disease, heart failure, and stroke.[17] Improvement in these risk factors with GLP-1R agonists not only improves OSA-related outcomes but also positively impact the CV burden.

The advent of newer gut peptide-based therapies with greater and more durable weight loss like tirzepatide, orforglipron, cagrisema, retatrutide opens the possibility of their use in OSA.[5,18] These medications have been tried in people with obesity without diabetes, showing effective weight loss without hypoglycemia. Hence, further studies in larger cohorts of patients with OSA and obesity is warranted to determine the durability of these medicines in not only causing weight loss in these patients with OSA but also reducing the severity of OSA and the need for CPAP therapy. To date, only bariatric surgery (metabolic surgery) has been shown to cause >15–20% weight loss, which not only leads to improvement in OSA but also a durable remission of OSA over many years.[19,20] Whether GLP1R agonism-based therapies can lead to remission of OSA as has been seen in people with obesity or diabesity who lost more than 15% of body weight remains to be determined.

There are several limitations of this SRM. This includes the analysis of data from different GLP1R agonism-based therapies together. This SRM highlights the current paucity of work in this area and intends to promote more active research on the role of GLP1R agonism-based therapies on different aspects of OSA.

To conclude, it may be said that this first SRM evaluating the impact of GLP1R agonism-based therapies provides us with encouraging data on improvement in different respiratory aspects of OSA along with a reduction in body weight and blood pressure.

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None.

Authors' contribution

The study was conceptualized and planned by DD, RJ and NR. Literature search was done by LN, AKH, RJ and MS. Data extraction and entry was done by NR, MS AND AKH. Data analysis was done by DD, MS and LN. All authors contributed equally to the writing of the manuscript.

The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

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Conflicts of interest

There are no conflicts of interest.

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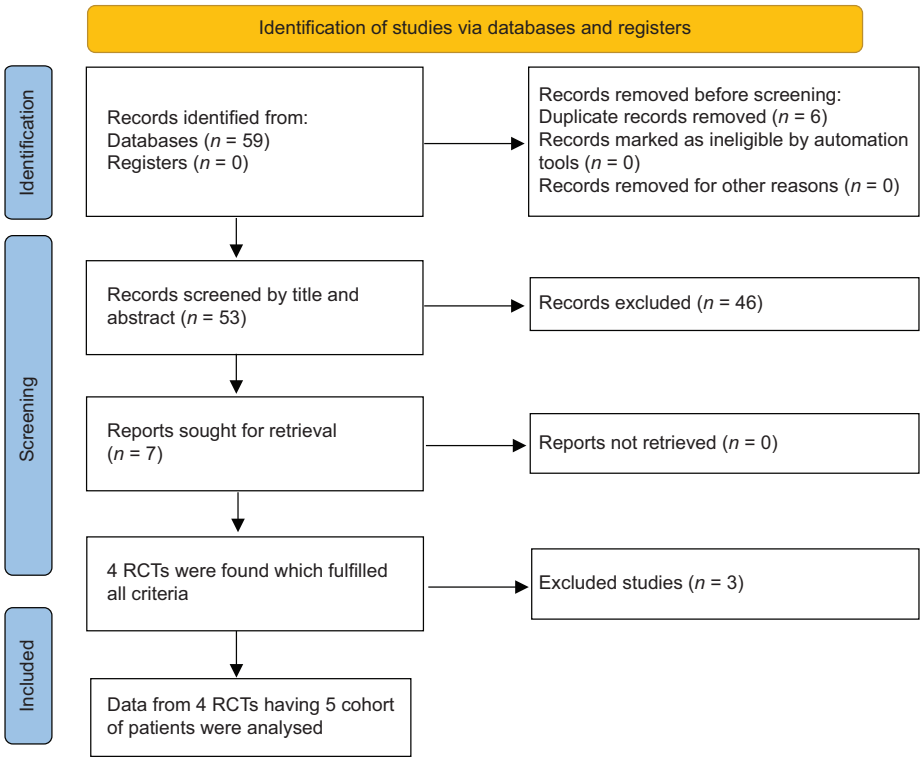
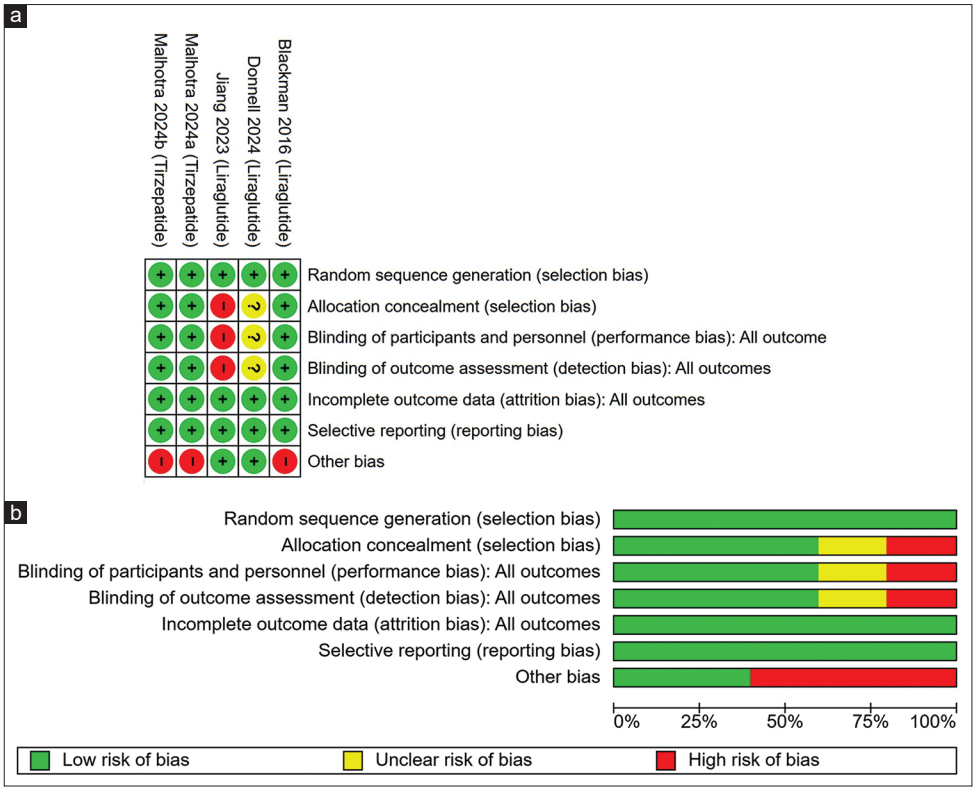


Supplementary Figure 1: Flowchart elaborating on the study retrieval and inclusion in this systematic review and meta-analysis



Supplementary Figure 2: (a) Risk of bias summary; (b) Risk of bias graph