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REVIEW

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Pharmacotherapy in obesity: a systematic review and meta-analysis of randomized controlled trials of anti-obesity drugs

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ABSTRACT

Introduction: Obesity poses a significant increase in morbidity and mortality and thus five anti-obesity drugs have been approved currently by US FDA. Several phase 3 trials have shown a significant improvement in cardio-metabolic profile including significant weight reduction with these agents compared to placebo.

Areas covered: We systematically searched the database of PubMed, Embase, The Cochrane Library and The ClinicalTrials.gov up to 30 September 2019 and retrieved all the randomized controlled trials (RCTs) that were conducted with these five drugs for ≥1 year and explicitly reported their efficacy versus placebo. Subsequently, we have conducted the meta-analysis to primarily study the effect of these anti-obesity drugs on weight reduction. We additionally reviewed the effect of these drugs on other cardio-metabolic parameters including key adverse events.

Expert opinion: This meta-analysis finds a significant reduction in body weight with orlistat (N = 10,435; Δ −3.07 Kg, 95% CI, −3.76 to −2.37), phentermine plus topiramate (N = 2985; Δ −9.77 Kg; 95% CI, −11.73 to −7.81), lorcaserin (N = 16,856; Δ −3.08 Kg; 95% CI, −3.49 to −2.66), naltrexone plus bupropion (N = 3239; Δ −4.39 Kg; 95% CI, −5.05 to −3.72) and liraglutide (N = 4978; Δ −5.25 Kg; 95% CI, −6.17 to −4.32), compared to placebo (all $p < 0.00001$).

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KEYWORDS
Obesity; anti-obesity drugs; orlistat; lorcaserin; phentermine plus topiramate; naltrexone plus bupropion; liraglutide 3.0 mg

1. Introduction

Obesity has been an issue of concern since ancient times. There is a documentation in writings of ancient Greece, Egypt, and India, mentioning obesity as an obstacle to good health and long life. Sushruta, an ancient Indian physician considered obesity to be a 'disease' in circa 600 B.C. [1]. In June 2014, American Medical Association declared obesity (BMI [Body Mass Index] ≥30) as a 'disease' in its 'Resolution 420' and recommended interventions for obesity treatment and prevention. Emerging data clearly indicate that obesity is a burgeoning problem and it has already reached an epidemic proportion worldwide with nearly 1.9 billion overweight and 650 million obese adults according to WHO [2]. Non-Communicable Disease (NCD) risk factors collaborators reported a staggering rise in obesity even in the developing countries [3].

Although obesity has been closely linked with the development and progression of other co-existing complications that include type 2 diabetes, hypertension, dyslipidemia, coronary artery disease, stroke, heart failure, osteoarthritis, obstructive sleep apnea, malignancy and an increase in all-cause death; a modest weight loss of 5–10% has shown to be associated with a significant improvement in these conditions [4].

In 2007, FDA laid down certain conditions to qualify an agent to be an effective anti-obesity drug. The conditions set forth required at least one of the following criteria to be met after 1 year of treatment: a) 'Mean' efficacy criterion: the difference in mean weight loss between the active product and the placebo-treated groups should be ≥5% and the difference must be statistically significant or, b) 'Categorical' efficacy criterion: the proportion of subjects loosing ≥5% of baseline body weight in the active-product group should be ≥35%, which is approximately double the proportion in the placebo-treated group, and the difference between groups should be statistically significant [5].

Although lifestyle modification (LSM) is the gold standard way to tackle this menace, a wide range of anti-obesity drugs has been developed in the past few decades for supplementation. Drug therapy has been recommended along with LSM, in people with BMI ≥30 Kg/m2 or ≥27 Kg/m2 with at least one weight-related comorbidities, such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease or sleep apnea [6]. Pharmacotherapy has also been considered for people who have not had satisfactory benefits with LSM or, have difficulty to maintain initial weight loss accrued through LSM or, where LSM is difficult to follow and maintain as in chronic medical diseases.

Currently, only five anti-obesity drugs such as orlistat, lorcaserin, phentermine plus topiramate, naltrexone plus bupropion and liraglutide (3.0 mg) have been approved by FDA for long-term use (>12 weeks). Table 1 summarizes their current status, dosing and mechanism of action. Orlistat was the first

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Supplemental data for this article can be accessed here.

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Article highlights

- Obesity poses a major public health risk, as it is frequently associated with significant increase in morbidity and mortality.
- Currently, five anti-obesity drugs have been approved by US FDA for long-term use. The weight lowering potential of these five anti-obesity drugs appears to be in following descending orders – phentermine/topiramate > liraglutide 3.0 mg > naltrexone/bupropion > lorcaserin = orlistat.
- The ease of dosing and better tolerability put lorcaserin and orlistat at a better position, compared to others, nonetheless, the weight lowering potential of both these agents are modest at its best and definitely lesser than other approved anti-obesity drugs. Additionally, non-responders to orlistat and lorcaserin are comparatively higher than others. No cardio-vascular outcome trial (CVOT) is available till date for orlistat; however, lorcaserin has demonstrated CV safety in CAMELLIA-TIMI 61, against placebo. Therefore, lorcaserin should be the preferred agent in people with established cardiovascular disease or high CV risk.
- While phentermine/topiramate has shown most robust reduction in body weight compared to other anti-obesity agents, increased neuropsychiatric adverse events require strict pharmacovigilance. Increased fetal toxicity (oral clefts) with topiramate also limits its use in female of reproductive age and need risk evaluation and mitigation strategy (REMS).
- Naltrexone/bupropion and liraglutide 3.0 mg have shown a moderate effect on body weight reduction. While the former increases systolic blood pressure (SBP) and heart rate (HR), the latter reduces SBP, but increases HR. The CV safety of naltrexone/bupropion is still unknown as their CVOT, the LIGHT study was unblinded prematurely, by the sponsors. Liraglutide 1.8 mg has shown significant reduction in CV outcome including reduction in CV death in LEADER trial in patients with type 2 diabetes and high CV risk, however, this benefit could not be entirely extrapolated to liraglutide 3.0 mg use in subjects with obesity without type 2 diabetes and a high CV risk. Nevertheless, liraglutide 3.0 mg should be the preferred agent in obese type 2 diabetes subjects.

drug approved for long-term use by USFDA in 1999, and several phase 3/4 trials of orlistat of ≥1 year have been conducted till date [7–23]. The short- and long-term effect of other four newer drugs (approved in last decade) on body weight reduction has been summarized in Table 2 [24–45].

Our primary aim is to systematically review the studies of these 5 anti-obesity drugs conducted for ≥12 months against placebo, and meta-analyze its efficacy on weight reduction. Additionally, we aim to elaborate on the cardio-metabolic effects and the key adverse events with these five drugs and present a comparative perspective.

2. Aims and objectives

2.1. Study design

This study has been conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [46]. However, this study has not been registered in the International Prospective Register of Systematic Reviews (PROSPERO).

2.2. Eligibility criteria, comparison arms and outcomes

Inclusion criteria for this study are all adults (older than 18 years) who have obesity, with or without type 2 diabetes and who have been subjected to either orlistat or phentermine plus topiramate or lorcaserin or naltrexone plus bupropion or liraglutide (3.0 mg) versus placebo for at least 1-year duration. The primary outcome is efficacy, i.e. reduction in body weight (in kilograms) compared to placebo at the end of 1 year.

2.3. Type of studies

We have only included phase 3/4 RCTs conducted with these five drugs versus placebo that have been conducted for ≥1 year. Other RCTs that have been conducted for less than 1 year, retrospective or prospective observational cohort studies, cross-sectional studies, and case-control studies, have been excluded from this meta-analysis.

2.4. Search strategy

We have conducted a comprehensive systematic search of the following databases from their inception to 30 September 2019, including PubMed, Scopus, The Central Cochrane library and The ClinicalTrials.gov. Relevant keywords and their combinations have been applied in the search strategy restricted to the English language. All potentially eligible studies have been considered for review.

2.5. Selection of studies, data collection process, assessment of methodological quality

The abstracts of all the records that met our predefined inclusion criteria were screened by all the authors, and studies that entirely fulfilled our inclusion criteria, were retrieved with their supplementary appendix, for further analysis. Any ambiguity during the study selection has been resolved by mutual discussions and consensus. A detailed PRISMA flow-diagram for the process of inclusion and exclusion for selecting key studies that has been used in this meta-analysis is depicted in supplementary Figure S1.

Assessment of bias for the methodological quality of included RCTs was evaluated by all the authors using The Cochrane tool based on seven domains that include – random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias [47]. Any discrepancy that arose has been met through consensus. Supplementary Table S1 depicts the risk of bias, assessed by using The Cochrane tool.

2.6. Data synthesis and statistical analysis

The Comprehensive Meta-Analysis (CMA) software Version 3, Biostat Inc. Englewood, NJ, USA, has been used to calculate all the statistical analysis. We have pooled the mean differences and the standard deviation and/or 95% confidence intervals (CI) for the effect of continuous outcomes across the trials wherever applicable, based on intention-to-treat analysis, last observation carried forward (ITT-LOCF). Results have been synthesized using inverse variance-weighted averages of logarithmic risk ratio and random-effects analysis. Heterogeneity has been measured using Higgins I^2 and Cochrane Q statistic [48]. Heterogeneity was considered low if I^2 was ≤25% or

Table 1. Current status of anti-obesity drugs for the long term uses (>12 weeks).

Drugs	Year approved	Dosing schedule	Mechanism of action	Cost (in US $)	Special notes
Orlistat	1999	Oral. 120 mg TID with or within 1 hour of meals. If weight loss is ≥5% at 12-weeks, continue it, otherwise stop it.	Inhibits fat absorption. Meals should have at least 30% of fat for orlistat to work.	≈530	Also approved for pediatric obesity at lower dosage. Lower dose (60 mg) available in US, even without prescription since 2007. No CVOT trial available.
Phentermine + Topiramate	2012	Oral. Starting dose of 3.75/23 mg once daily in morning for 2 weeks → after 2 weeks increase the dose to 7.5/46 mg (recommended dose) → continue it for 12 weeks → if weight loss is not at least 3% from baseline at 12 weeks → stop or escalate the dose to 11.25/69 mg for 2 weeks → and then a maximum dose of 15/92 mg → evaluate the weight loss at additional 12-weeks, if it is ≥5% continue it or else, stop it gradually after tapering off the dose every other day by 1 week to avoid seizure precipitation.	Phentermine reduces appetite while topiramate increases (?) energy expenditure.	≈199	Marketed under REMS to reduce risks of teratogenicity. Decrease in SBP but increase in HR. No CVOT currently available. AQLAIM, the proposed CVOT trial with phentermine/topiramate is currently under progress.
Lorcaserin	2012	Oral. 10 mg BID or 20 mg ER OD. If weight loss is ≥5% at 12-weeks, continue it, otherwise stop it.	Reduces energy intake	≈212	Marketing delayed due to Drug Enforcement Administration. CAMELLIA-TIMI 61, a CVOT conducted with lorcaserin found non-inferiority to placebo. Thus, lorcaserin is CV safe.
Naltrexone + Bupropion	2014	Oral. Starting dose is 1 tab of 8/90 mg per day in morning for 1 week → increase dose to 1 tab BID (16/180 mg per day) for next 1 week → in third week escalate the dose to 2 tab in morning and 1 tab in evening (24/270 mg per day) → in fourth week switch to maximal dose of 2 tab BID (total dose 32/360 mg per day). Continue the drug for 12 weeks, if weight loss ≥5% → continue, or else stop without tapering the dose. Avoid the drug with fatty meals to prevent seizure.	Reduces appetite	≈212	Increase in SBP and HR. The Light Study, a CVOT of naltrexone/bupropion remains inconclusive, owing to premature unblinding of data.
Liraglutide (3.0 mg)	2014	Injectable. Start with 0.6 mg once daily and increase dose weekly to 1.2, 1.4, 2.4 and 3.0 mg. If weight loss is ≥5% at 12-weeks, continue it, otherwise stop it.	Increased satiety and delayed gastric emptying	≈1095	Lower dose (0.6–1.8 mg) approved for T2DM. The LEADER trial, a CVOT conducted with liraglutide 1.8 mg in subjects with T2DM with high CV risk showed benefit.

OD – once daily, BID – twice daily, TID – thrice daily, ER – extended release, CV – cardiovascular, CVOT – cardiovascular outcome trial, T2DM – type 2 diabetes, SBP – systolic blood pressure, HR – heart rate, REMS – risk evaluation and mitigation strategy.

Table 2. Results (ITT-LOCF data) from randomized placebo-controlled trials conducted with highest-licensed dose of recently approved anti-obesity drugs (except orlistat).

First author/trial eponyms	N	Study criteria	Active arm (max. licensed dose/day)	Studies duration (weeks)	Δ PBO-subtracted weight loss (Kg)	% weight loss (drug vs PBO)	Δ PBO-subtracted weight loss (%)	% of patients with ≥5% weight loss (drug vs PBO)	% of patients with ≥10% weight loss (drug vs PBO)	Ref.
Lorcaserin										
Smith et al	234	BMI 30–45 Kg/m2	10 mg BID	12	2.9	NR	NR	31.2 vs 2.3[c]	0	[24]
TULIP	57	BMI 27–45 Kg/m2	10 mg BID	8	1.6	NR	NR	NR	NR	[25]
BLOOM[a]	3182	BMI 30–45 Kg/m2 or BMI 27–45 Kg/m2 if at least one comorbidity	10 mg BID	104	3.6	5.8 vs 2.2	**3.6**	47.5 vs 20.3	22.6 vs 7.7	[26]
BLOSSOM[a]	4008	BMI 30–45 Kg/m2 or BMI 27–29.9 Kg/m2 if comorbidity	10 mg BID	52	2.9	5.8 vs 2.8	**3.0**	47.2 vs 25	22.6 vs 9.7	[27]
BLOOM-DM[a]	604	DM with BMI 27–45 Kg/m2	10 mg BID	52	3.1	4.5 vs 1.5	**3.0**	37.5 vs 16.1	16.3 vs 4.4	[28]
CAMELLIA[a]	12,000	BMI ≥27 Kg/m2 with or without established CVD	10 mg BID	Median (3.3 Yrs.)	2.8	4.2 vs 1.4	**2.8**	38.7 vs 17.4	14.6 vs 4.8	[29]
Phentermine plus Topiramate										
EQUIP	1267	BMI ≥35 Kg/m2	15/92 mg	56	10.8	10.9 vs 1.6	**9.3**	66.7 vs 17.3	47.2 vs 7.4	[30]
CONQUER	2487	BMI ≥27 and ≤45 Kg/m2 ± comorbidities	15/92 mg	56	8.8	12.4 vs 1.6	**10.8**	70.0 vs 21.0	48.0 vs 7.0	[31]
SEQUEL (Ext. of CONQUER)	676	Same as CONQUER	15/92 mg	104	8.8	10.5 vs 1.8	**8.7**	79.3 vs 30.0	53.9 vs 11.5	[32]
Winslow et al	45	BMI 30–40 kg/m2 with moderate/severe OSA + AHI ≥ 15	15/92 mg	28	6.1	10.3 vs 4.2	**6.1**	72.7 vs 47.8	54.5 vs 13.0	[33]
EQUATE	756	Non-diabetic, BMI ≥35 Kg/m2	15/92 mg	28	7.4	9.2 vs 1.7	**7.5**	66.0 vs 15.5	40.8 vs 6.8	[34]
Naltrexone plus Bupropion										
COR-I	1742	BMI 30–45 Kg/m2 or BMI 27–45 Kg/m2 with HTN or dyslipidemia	32/360 mg	56	4.7	6.1 vs 1.3	**4.8**	48.0 vs 16.0	25.0 vs 7.0	[35]
COR-II	1496	BMI 30–45 Kg/m2 or BMI 27–45 Kg/m2 with HTN or dyslipidemia	32/360 mg	56	4.9	6.4 vs 1.2	**5.2**	50.5 vs 17.1	28.3 vs 5.7	[36]
COR-BMOD	793	BMI 30-45 Kg/m2 or BMI 27–45 Kg/m2 with HTN or dyslipidemia	32/360 mg	56	4.1	9.3 vs 5.1	**4.2**	66.4 vs 42.5	41.5 vs 20.2	[37]
COR-DM	505	DM with BMI ≥ 27 to ≤ 45 Kg/m2	32/360 mg	56	3.4	5.0 vs 1.8	**3.2**	44.5 vs 18.9	18.5 vs 5.7	[38]
LIGHT	8910	BMI 27–50 Kg/m2 with high CV risk	32/360 mg	121	2.7	3.6 vs 1.1	**2.5**	NR	NR	[39]
Liraglutide										
Astrup et al	564	Non-diabetic, BMI 30–40 Kg/m2	3.0 mg	20	4.4	7.4 vs 2.9	**4.5**	76.1 vs 29.6	28.3 vs 2.0	[40]
Astrup et al[a] 2-Year Ext.	398	Non-diabetic, BMI 30–40 Kg/m2	3.0 mg	104	5.8	8.0 vs 2.1	**5.9**	73.0 vs 28.0	37.0 vs 10.0	[41]
SCALE-Maintenance	422	BMI ≥30 or BMI ≥27 Kg/m2with comorbidities	3.0 mg	56	5.9	6.2 vs 0.2	**6.1**	50.5 vs 21.8	26.1 vs 6.3	[42]
SCALE- Obesity and Pre-diabetes	3731	Non-diabetic, BMI ≥30 or ≥27 Kg/m2 with dyslidemia or HTN	3.0 mg	56	5.6	8.0 vs 2.6	**5.4**	63.2 vs 27.1	33.1 vs 10.6	[43]
SCALE-DM	846	DM plus BMI ≥27 Kg/m2	3.0 mg	56	4.0	6.0 vs 2.0	**4.0**	54.3 vs 21.4	25.2 vs 6.7	[44]
SCALE- Sleep Apnea	359	Non-diabetic with obesity and moderate/severe AHI ≥15	3.0 mg	32	4.9	5.7 vs 1.6	**4.2**	46.3 vs 18.5	23.4 vs 1.7	[45]

[a] At 1 year; [a] – data at 1 year, [c] – completers analysis, PBO – placebo, BID – twice daily, BMI – body mass index, DM – diabetes mellitus, CVD – cardiovascular disease, max. – maximum, vs- versus, NR – not reported, HTN – hypertension, Ext – extension, AHI – apnea-hypopnea index, IIT-LOCF – intention-to-treat analysis last observation carried forward.

moderate (I^2 >25 to <75%) or high (I^2≥75%). All the p values reported here are two-sided and a p value of <0.05 is to be considered statistically significant. This study has evaluated potential publication bias by funnel plots using 'Trim and Fill' adjustment, rank correlation test and Egger's test through the CMA software Version 3, Biostat Inc. Englewood, NJ, USA (Supplementary Figure S2, S3, S4, S5).

3. Results: effect on body weight reduction

This meta-analysis (using random effects model, based on heterogeneity) found a significant reduction in body weight with orlistat (N = 10,435; Δ −3.07 Kg, 95% CI, −3.76 to −2.37), lorcaserin (N = 16,856; Δ −3.08 Kg; 95% CI, −3.49 to −2.66), phentermine plus topiramate (N = 2985; Δ −9.77 Kg; 95% CI, −11.73 to −7.81), naltrexone plus bupropion (N = 3239; Δ −4.39 Kg; 95% CI, −5.05 to −3.72) and liraglutide (N = 4978; Δ −5.25 Kg; 95% CI, −6.17 to −4.32), compared to placebo (all p < 0.00001; Figures 1–5, respectively). Since the funnel plot found no publication bias with lorcaserin (Supplementary Figure S3) and liraglutide (Supplementary Figure S5) studies, Duval and Tweedie's Trim and Fill imputed point estimates and 95% CI, are similar to random effects model for both. However, after adjustments of publication bias in orlistat (Supplementary Figure S2) and naltrexone/bupropion (Supplementary Figure S4) studies, Duval and Tweedie's Trim and Fill imputed point estimates have been found to be −3.28 Kg (−3.97, −2.59) and −4.81 Kg (−5.56 to −4.07), respectively. Since only two studies have been conducted for ≥1 year for phentermine plus topiramate, no funnel plot for publication bias could be made.

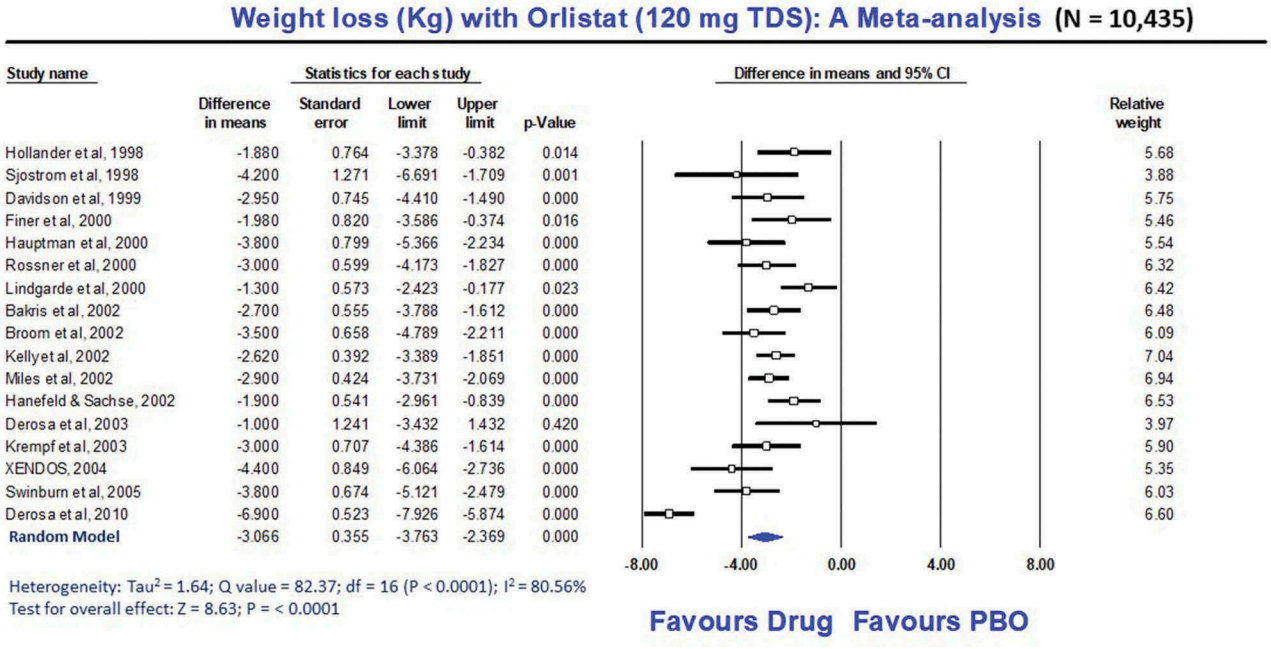


Figure 1. Weight loss with orlistat in RCT: A meta-analysis.

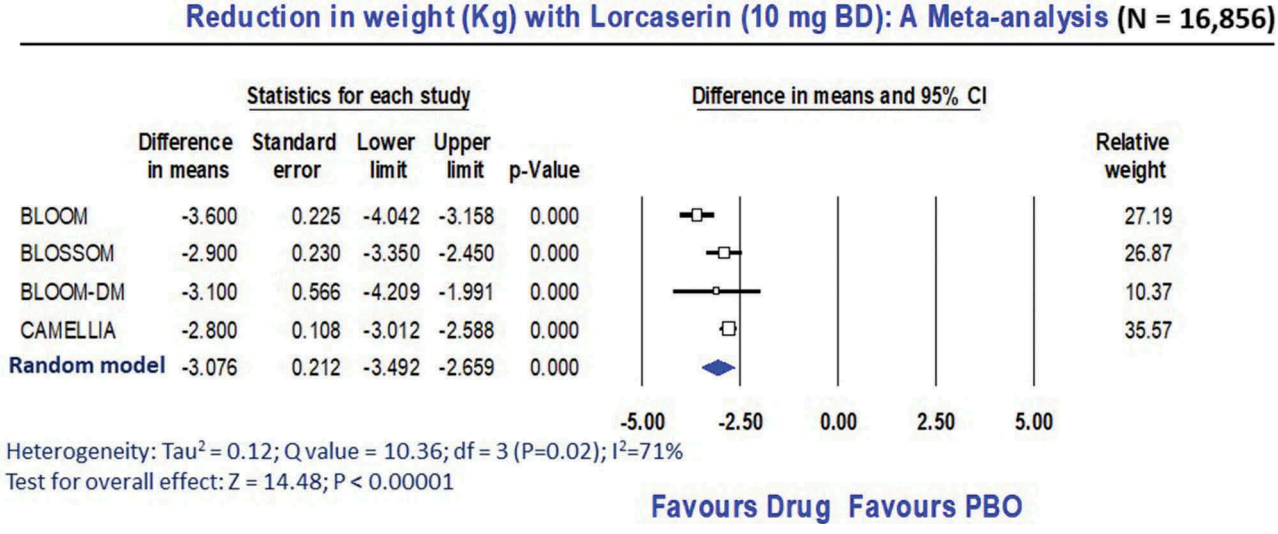


Figure 2. Weight loss with lorcaserin in RCT: A meta-analysis.

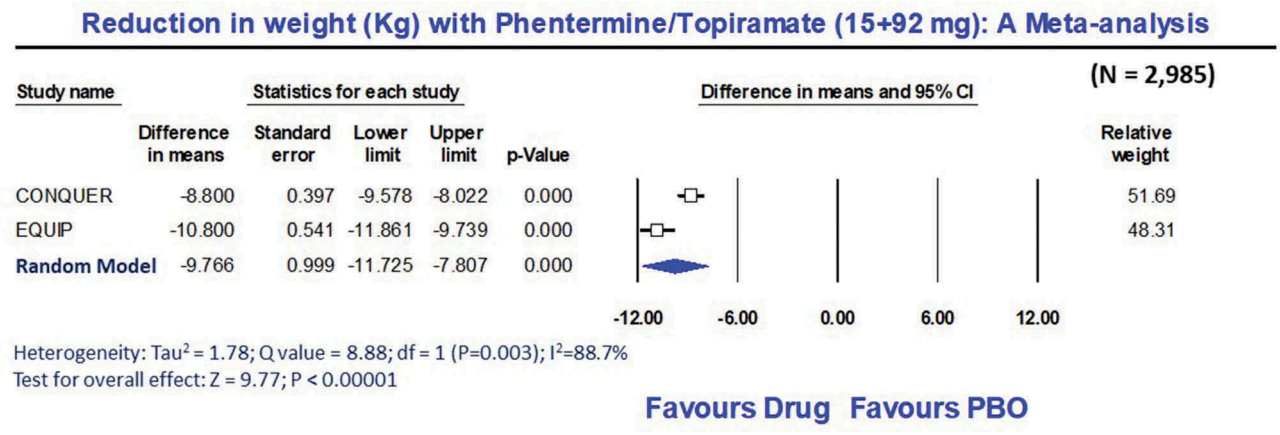


Figure 3. Weight loss with phentermine/topiramate in RCT: A meta-analysis.

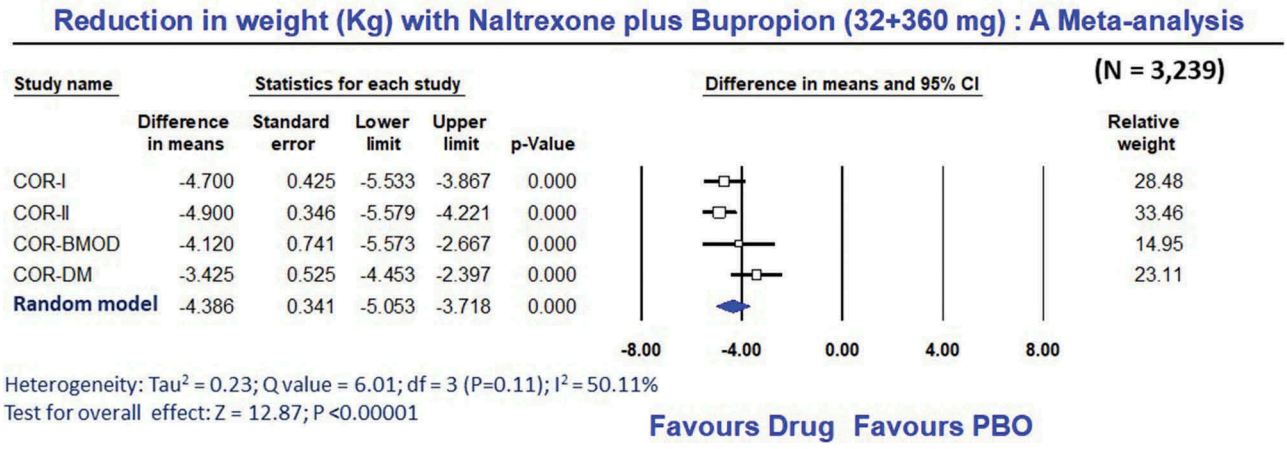


Figure 4. Weight loss with naltrexone/bupropion in RCT: A meta-analysis.

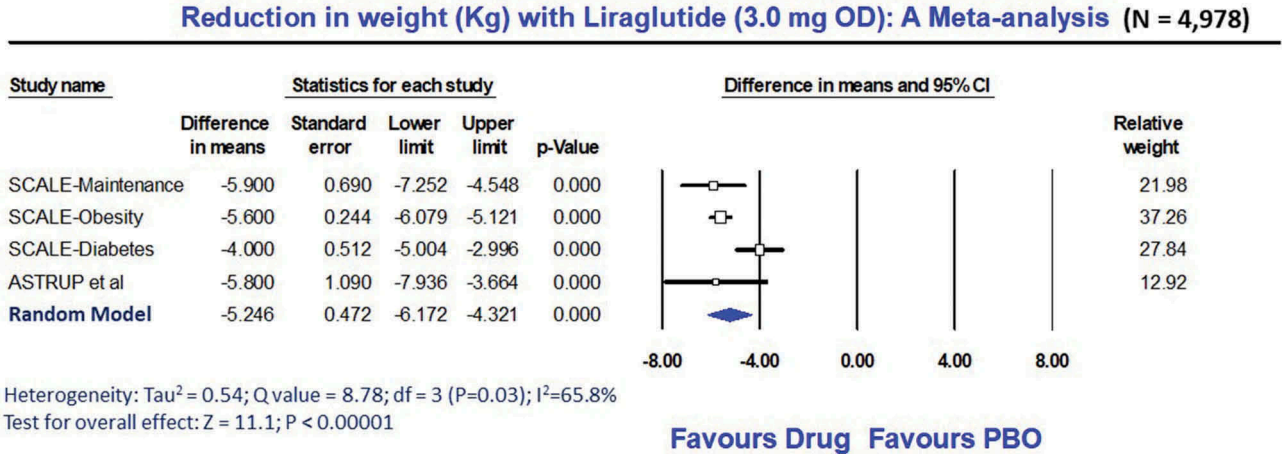


Figure 5. Weight loss with liraglutide in RCT: A meta-analysis.

Although, there were no head-to-head trials amongst these five drugs, we found that weight reduction abilities of these drugs in descending order are: phentermine plus topiramate > liraglutide (3.0 mg) > naltrexone plus bupropion > lorcaserin = orlistat, based on individual studies and their meta-analysis.

3.1. Strength and limitations

As with any other meta-analysis, this study also acknowledges its strength and limitations. Strength includes the rigorous approach of systematically review of data from only randomized studies that were conducted for

a reasonable time period (at least 12 months). To our knowledge, this would be the first meta-analysis to determine the efficacy of all currently approved anti-obesity drugs put together. We have additionally analyzed other cardiometabolic effects of these five approved anti-obesity drugs, including key adverse events and attempted to put a comprehensive perspective. The limitations include, applying aggregate instead of individual patient data, very high attrition rates across the trials, and a significant heterogeneity across the studies that may limit any conclusion. Other limitation includes the non-evaluation through the grading of recommendations assessment, development and evaluation (GRADE) approach.

3.2. Cautions in interpretation

While this meta-analysis found a significant reduction in body weight with all these drugs, there were a certain proportion of patients who seemed to be non-responders to these drugs [49]. Moreover, some regain in the weight was also observed after 1 year [50]. Furthermore, FDA recommends discontinuation of these drugs, if at least 5% of weight loss is not achieved after the initial 12 weeks of therapy.

4. Effects of anti-obesity drugs on other cardio-metabolic parameters

4.1. Glycemic effect

In the meta-analysis of five trials (N = 1678) conducted in subjects with type 2 diabetes, orlistat was found to reduce the HbA1c by Δ −0.4% and fasting plasma glucose (FPG) by Δ −18 mg/dl [51]. Significantly, lesser number of subject progressed to frank diabetes from impaired glucose tolerance (IGT) in orlistat versus placebo group (3.0% vs. 7.6%; p = 0.04), in pooled analysis of the two studies [52]. The XENDOS (Xenical in the Prevention of Diabetes in Obese Subjects), a 4-year, double-blind, placebo-controlled randomized study which included subjects with both normal glucose tolerance (NGT) and IGT, demonstrated an appreciable 37.3% reduction of incident diabetes, compared to placebo (HR, 0.63; 95% CI 0.46 to 0.86) [21].

The BLOOM-DM study (Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus) conducted in patients with type 2 diabetes with obesity, demonstrated a significant decrease in HbA1c and FPG with lorcaserin, compared to placebo (Δ −0.5% and −15.5 mg/dl; both p < 0.001). Moreover, a significantly higher percentage of the patients achieved a target HbA1c of either ≤7% (50.4 vs 26.3%; p < 0.001) or ≤6.5% (23.9 vs 8.6%; p < 0.001) with lorcaserin compared to placebo, respectively [28]. Furthermore, use of lorcaserin was associated with 19% reduced risk of incident diabetes (HR, 0.81; 95% CI, 0.66–0.99) in subjects with pre-diabetes, and 21% increased chance of remission from diabetes (HR, 1.21; 95% CI, 1.07–1.36) in subjects with type 2 diabetes at baseline, as demonstrated in the CAMELLIA TIMI 61 (Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients – Thrombolysis in Myocardial Infarction 61), against placebo [53].

While a decrease in HbA1c of Δ −0.1% to −0.2% was observed in subjects without diabetes, a significant Δ −0.4% decrease in HbA1c versus placebo was seen in people with diabetes, on phentermine plus topiramate [30–34]. Additionally, either a significant reduction in dose or a significant decrease in need for other diabetic agents was observed while on phentermine plus topiramate. Moreover, the CONQUER study demonstrated a 53% reduction in the development of diabetes (HR, 0.47; 95% CI, 0.25–0.88) in 84% of subjects without type 2 diabetes at baseline, during the 56 weeks of trial period. Further extension of the CONQUER study named the SEQUEL trial, also showed a 78.7% reduction in developing incidental diabetes in patients with pre-diabetes or metabolic syndrome [54].

The change in HbA1c ranged from 0 to −0.5% in the COR (Contrave Obesity Research) trials with naltrexone plus bupropion. While the COR-I study showed a significant decrease of FPG, COR-Diabetes study showed significant reduction in HbA1c at 1-year (Δ – 0.5%; p < 0.001) [35,38]. No data with regard to the remission rate of diabetes or its prevention, currently exist with naltrexone plus bupropion.

The phase 3 LEAD (Liraglutide Effect and Action in Diabetes) studies (dose up to 1.8 mg) have already demonstrated a significant effect of liraglutide in reducing HbA1c ranging from Δ −0.33% to −1.85% in patients with type 2 diabetes. In the SCALE-DM study, liraglutide 3.0 mg significantly reduced the HbA1c (Δ −1.0%) in people with diabetes, compared to placebo. Moreover, 69% and 57% of patients with diabetes achieved the target HbA1c of <7% or ≤6.5%, respectively, with liraglutide 3.0 mg, compared to 27% and 15% with placebo [44]. The SCALE trials additionally show an HbA1c reduction of −0.2% to −0.9% with liraglutide 3.0 mg in subjects without diabetes, compared to the placebo [42,43].

4.2. Effect on lipids

Orlistat has shown an overall reduction in lipids parameters. Meta-analysis of 13 studies have found a small but significant reduction in total cholesterol (TC) by −12 mg/dl, and low-density-lipoprotein-cholesterol (LDL-C) by −10 mg/dl with orlistat versus placebo. Additionally, a non-significant reduction in triglyceride (TG) and high-density-lipoprotein-cholesterol (HDL-C) has been also observed (−3 and −1 mg/dl, respectively) with orlistat against placebo [7–23,51].

Lorcaserin has shown a small but significant reduction in TG ranging from −5 to −12 mg/dl consistently across all phase 3 trials as well as in the CAMELLIA-TIMI 61 [26–29]. However, a reduction in TC by −2 to −3 mg/dl was observed only in CAMELLIA-TMI 61 and BLOOM trial, respectively, and a small reduction in LDL-C by −1.2 mg/dl was only observed in CAMELLIA-TIMI 61. Interestingly, a small but consistent increase (ranging from +0.5 to +2 mg/dl) in the HDL-C was also observed across all the phase 3/4 trials, except the BLOOM. Additionally, a significant decrease (p < 0.001) in ApoB was also seen with lorcaserin against placebo in the BLOSSOM (Behavioral Modification and Lorcaserin Second Study for Obesity Management) trial [27].

Similarly, phentermine plus topiramate reduced TG (−17 to −24 mg/dl) and also increased HDL-C (+2 to +4 mg/dl);

however, no effect on LDL-C (−4 to +6 mg/dl) was observed across the phase 3 trials against the placebo [30,31].

The overall favorable effect on lipid profile was also demonstrated with naltrexone plus bupropion. A small but significant decrease in TG and LDL-C by −11 to −15 mg/dl and −1 to −4 mg/dl, respectively, as well as, a small increase in HDL-C by +3 to +5 mg/dl was also observed with naltrexone plus bupropion, against the placebo [35–38].

Liraglutide 3.0 mg throughout the SCALE (Satiety and Clinical Adiposity – Liraglutide Evidence in Nondiabetic and Diabetic Individuals) program demonstrated a consistent reduction in the TG (−10 to −25 mg/dl) but no significant improvement in the LDL-C (−4 to +3 mg/dl) or the HDL-C (neutral to +3 mg/dl) observed against the placebo [42–44]. Comparatively larger TG reduction with liraglutide was in expected lines from an agent that improves glycemic control.

4.3. Effects on Systolic Blood Pressure (SBP) and Heart Rate (HR)

A small but significant reduction in SBP (−1.5 to −2.0 mm Hg) was observed with orlistat, against placebo in a pooled meta-analysis, while no effect on the heart rate was noticed [51].

Lorcaserin reduced SBP by −1.0 mm Hg in the BLOOM and the CAMELLIA-TIMI 61 but no similar effect observed in other phase 3 trials [26–29]. Although no change in HR was observed with lorcaserin, a reduction of −1 to −2 beat per minute was observed in the BLOOM-DM and the CAMELLIA-TIMI 61 [28,29].

Interestingly, phentermine plus topiramate decreased SBP by −1.1 to −3.8 mm Hg, the increase in HR by +0.3 to +1.8 beats per min was also observed against placebo [30–32,34]. This increase in HR is consistent with the known sympathomimetic effects of phentermine.

In the COR trials, there was an increase in both SBP (+1.1 to +2.6 mm Hg) and HR (+0.8 to +1.1 beats per min) with naltrexone plus bupropion, compared to the placebo [35]. These unfavorable effects were likely to be due to the bupropion effect on dopamine and the norepinephrine. Thus, the effects of naltrexone plus bupropion on SBP and HR were largely unfavorable.

While the liraglutide SCALE program demonstrated a small but significant decrease in SBP ranging from −2.6 to −3.1 mm Hg, a consistent small increase in HR (+0.6 to +3.5 beats per min) was also observed simultaneously when compared to placebo [42–44].

4.4. Effects on inflammatory markers

Effects of anti-obesity drug on improving the inflammatory markers have been largely inconsistent. Although reduction in weight has generally been associated with decrease in both tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) levels, only TNF-alpha levels were significantly lower ($p < 0.05$) in orlistat arm compared to the placebo, at 1 year. Similarly, a significant decrease in high-sensitivity C-reactive protein (hs-CRP) and fibrinogen ($p < 0.001$ and $p = 0.001$, respectively) was observed with lorcaserin against placebo in the BLOOM, although no difference in hs-CRP was observed in the BLOOM-DM trial with subjects with diabetes.

Phentermine plus topiramate showed a significant increase in adiponectin in the CONQUER (+1.75 mg/ml) trial that was maintained in the 2-year extension SEQUEL trial. However, a significant reduction in hs-CRP of 1.7 mg/l was only observed in CONQUER but not in the SEQUEL trial.

Naltrexone plus bupropion showed a significant reduction in hs-CRP of 12.3% and 20.5% in COR-I and COR-II, respectively, against placebo, although no significant changes in hs-CRP were observed in the COR-BMOD and the COR-Diabetes study.

Liraglutide effect on the inflammatory markers was even more interesting. While no significant change in leptin, adiponectin, TNF-alpha, and IL-6 level was observed, plasma levels of the visfatin (insulin-mimetic hormone) and resistin (insulin desensitizer) was significantly higher in liraglutide-treated obese patients with type 2 diabetes. Ironically, another study found a decreased level of adiponectin (insulin sensitizer) and an increased level of the inflammatory protein pentraxin-3, after 6 months of liraglutide treatment. However, a significant decrease in levels of hs-CRP, urinary isoprostanes, platelet P-selectin, and serum endothelial adhesion markers was seen with liraglutide treatment in obese women with polycystic ovarian syndrome. Furthermore, a significant decrease in hsCRP, increases in fibrinogen and no change in adiponectin was observed in the SCALE Diabetes study with liraglutide 3.0 mg.

4.5. Effects on cardiovascular outcome and micro-vascular complications

Orlistat has not undergone any cardiovascular outcome trial (CVOT) and thus the direct effect on CV risk is largely unknown. The CAMELLIA-TIMI 61 was a large (N = 12,000; DM – 56%, Pre-diabetes – 36%; median duration – 3.3 years) CVOT, conducted with lorcaserin and has demonstrated a non-inferiority against placebo (hazard ratio [HR], 0.99; 95% CI, 0.85 to 1.14; $P < 0.001$ for noninferiority) on the composite of 3P-MACE (three point-major adverse cardiovascular events that include CV death, non-fatal myocardial infarction, or non-fatal stroke) in patients with high CV risk (≈75% had established CV disease), after a median follow-up of 3.3 years [29]. Additionally, lorcaserin significantly reduced the micro-vascular complications (HR, 0.79; 95% CI, 0.69 to 0.92; $P = 0.001$) primarily by reducing micro-albuminuria (HR, 0.77; 95% CI, 0.66 to 0.90; $P = 0.001$). Furthermore, analysis of CAMELLIA showed a significant reduction (HR, 0.87; 95% CI, 0.79 to 0.96; $P = 0.006$) in the composite of renal outcomes (new or worsening persistent micro- or macroalbuminuria, new or worsening chronic kidney disease, doubling of serum creatinine, end-stage renal disease, renal transplant or renal death) [55].

The CV outcomes with phentermine plus topiramate are currently unknown. Recently, a retrospective cohort study from US insurance-based data of MarketScan did not find any significant increase in MACE with phentermine/topiramate users versus non-users. However, the number of events in this study is too small to claim any CV safety [56]. Nevertheless,

AQCLAIM, the CVOT of phentermine plus topiramate is currently being conducted that may finally enlighten the CV safety of this class of drug.

Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects With Cardiovascular Risk Factors (The LIGHT Study) was started earlier in 2012 and published in 2016. While the 25% interim analysis of 3P-MACE in the Light study demonstrated an HR of 0.59 with 95% CI of 0.39 to 0.90, the 50% interim analysis found an HR of 0.88 with 95% CI, 0.57 to 1.34 [39]. Obviously, due to early unblinding and termination of the study, no conclusion with regards to CV safety of naltrexone plus bupropion can be made at this point of time.

Liraglutide underwent a CVOT named LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) and has shown a significant reduction in 3P-MACE (HR, 0.87; 95% CI, 0.78 to 0.97; p = 0.01 for superiority), and CV-death (HR, 0.78; 95% CI, 0.66 to 0.93; p = 0.07), however, this was conducted in people with type 2 diabetes, with high CV risk with or without obesity, and used liraglutide 1.8 mg [57]. Moreover, the benefit in CV outcome with liraglutide primarily exists in patients with established CV disease. Thus, it is not fully clear that liraglutide 3.0 mg can have a similar CV benefit in obese subjects, in the absence of high CV risk or established CV disease. Table 3 schematically depicts the comparative composite cardio-metabolic effect of five anti-obesity drugs.

5. Side effects and cautions

The most common side effects (incidence ≥5% or rate 1.5 times more than placebo) with orlistat were gastrointestinal (GI) side effects (diarrhea, oily spotting, steatorrhea, fecal incontinence). Increased incidence of oxalate stones and cases of acute hepatic injury has also been reported with orlistat. Deficiency of the fat-soluble vitamins and beta carotene on long-term use has also been documented and it is pragmatic to supplement these vitamins, 2 h before or after orlistat administration [58].

Nausea, headache, and dizziness were the most common and consistent side effects observed with lorcaserin in all RCTs. No significant increase in FDA-defined valvulopathy, depression and suicidal risk was observed with lorcaserin in any of phase 3/4 studies, unlike other nonselective serotonin receptor agonists [26–29]. Interestingly, a meta-analysis by DiNicolantonio and colleague (based on 3 RCTs) reported a significant increase in the FDA-defined moderate or greater MR (RR 1.88; 95% CI, 1.02 to 3.47; P = 0.04) and depression (RR 1.89; 95% CI, 1.04 to 3.44; P = 0.04) with lorcaserin [59]. The medical review by FDA (based on 3 RCTs) found an increased risk of FDA-defined moderate or greater MR (RR 1.95; 95% CI, 1.05 to 3.59; P = not reported) mITT-LOCF analysis data, but not in completers group analysis. However, no significant increase in the FDA-defined valvulopathy (RR 1.16; 95% CI, 0.81 to 1.67, P = not reported) or the FDA-defined mild or greater AR (RR 0.89; 95% CI, 0.56 to 1.42; P = not reported) was observed with lorcaserin [60]. Lorcaserin should not be used concomitantly with other selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors so as to avoid hyper-serotonergic/neurolept-malignant syndrome [61].

The most common side effects (incidence ≥5% or rate 1.5 times more than placebo) observed with phentermine and topiramate are paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth. Other adverse events to be noted include increase in heart rate, creatinine, mood and sleep disorders (depression, anxiety, and insomnia), cognitive impairments, suicidal ideations, acute myopia, exacerbation of secondary angle-closure glaucoma, metabolic acidosis and oxalate stone formation, that needs a strict pharmacovigilance. Significant increase in fetal toxicity (oral clefts) due to topiramate component mandates negative pregnancy test and further monitoring, in female of reproductive age, before the use of this drug. This is the reason as to why phentermine and topiramate is available through a limited program under risk evaluation and mitigation strategy (REMS). These drugs cannot be used during or within 14 days of taking monoamine-oxidase (MAO) inhibitors [62].

The most common adverse events observed with naltrexone plus bupropion include nausea, vomiting, constipation or diarrhea, dry mouth, dizziness, and insomnia. Other adverse events of importance include increase in SBP, HR, depression, suicidal ideations, seizures, exacerbation of angle-closure glaucoma and hepatic dysfunction that need close monitoring. Like phentermine plus topiramate, these drugs cannot be used during or within 14 days of taking MAO inhibitors [63].

GI side effects and increase in lipase are most commonly observed events noted with liraglutide 3.0 mg. Increase in gall

Table 3. Cardio-metabolic effect of the five approved anti-obesity drugs for long-term use.

Drugs	Weight	SBP	Heart rate	Effect on lipids	Effect on glucose	CV safety	DM prevention	Ref.
Orlistat	↓	**N↓**	**N**	**N↓**	**N↓**	**Not known**	↓ **(XENDOS Trial)**	[7–23,51]
Lorcaserin	↓	**N↓**	**N↓**	**N↓**	**N↓**	**CV neutral (CAMELLIA-TIMI 61 Trial)**	↓ **(CAMELLIA-TIMI 61 Trial)**	[24–29]
Phentermine + Topiramate	↓↓↓	**N↓**	**N↑**	**N↓**	**N↓**	**Not known (AQLAIM Trial ongoing)**	↓ **(CONQUER Trial)**	[30–34]
Naltrexone + Bupropion	↓	↑	↑	**N↓**	**N↓**	**Not known (LIGHT Trial unblinded)**	-	[35–39]
Liraglutide(3.0 mg)	↓↓	↓↓	↑	**N↓**	↓↓	**↓ CV risk (LEADER Trial)**	↓ **(SCALE PRE-DIABETES Trial)**	[40–44]

N – no change, ↓ – modest decrease, ↓↓ – moderate decrease, ↓↓↓ – robust decrease, ↑ – modest increase, CV – cardiovascular, Ref. – references.

Table 4. Important side effect profile of the five approved anti-obesity drugs for long-term use.

Drugs	G.I. S/E	GBP Dysf.	Hepatic injury	Oxalate stones	Depression	Suicidal tendency	Effect on cognition	Possible VHD	Narrow angle glaucoma	REMS req.	Drop-out rate	Ref.
Orlistat	↑↑	-	±	↑	-	-	-	-	-	-	↑↑	[7–23,51]
Lorcaserin	±	-	-	-	±	±	-	±	-	-	↑	[24–29]
Phentermine + Topiramate	±	-	-	↑	↑	↑	↓	-	↑	++	↑↑	[30–34]
Naltrexone + Bupropion	±	-	±	-	↑	↑	±	-	↑	-	↑↑	[35–39]
Liraglutide3.0 mg	↑↑	↑	-	-	-	-	-	-	-	-	↑↑	[40–44]

±: possible increase, -: no effect, ↑: modest increase, ↑↑: moderate increase, ++: need serious attention, G.I. S/E: gastro-intestinal side effect, GBP Dysf: gall bladder pancreatic dysfunction, VHD: valvular heart disease, REMS: risk evaluation and mitigation strategy, req: required, Ref: references.

bladder-related events such as cholelithiasis and cholecystitis were also noted with liraglutide 3.0 mg in SCALE program. Increase in HR is consistently seen with liraglutide both in LEADER and SCALE programs. Liraglutide is contraindicated in patients with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 [64]. Table 4 depicts the schematic comparative side effect profile of five anti-obesity drugs.

6. Expert opinion

With regards to quantum of weight reduction, it is clearly apparent from the available evidence (Table 1), that amongst the five anti-obesity drugs, only phentermine plus topiramate have fulfilled both the 'mean efficacy' (placebo subtracted ≥5% weight loss, at 1 year) and 'categorical efficacy' (≥35% patients with ≥5% weight loss in active arm) criteria of anti-obesity drugs across all the phase 3 trials, as mandated by the USFDA in 2007. Next is liraglutide 3.0 mg, where three (Astrup et al., SCALE-Maintenance and SCALE-Obesity and Pre-diabetes) out of total four RCTs, fulfilled both the 'mean efficacy' and 'categorical efficacy' criteria. Only one study (COR-II) of naltrexone plus bupropion fulfilled both the 'mean' and 'categorical' efficacy criteria, while none of the phase 3/4 studies of lorcaserin and orlistat fulfilled both the criteria. To note, all the five classes of drugs fulfilled the 'categorical' efficacy criterion, one of the reasons for the approval as an anti-obesity drugs for long-term use.

With regards to adverse events, both phentermine plus topiramate and naltrexone plus bupropion presumably have higher neuro-psychiatric manifestation and the use of former is limited under REMS. Moreover, both drugs increase HR and naltrexone plus bupropion also increase SBP, that might limit their use in obese patients with high CV risks in the absence of proven cardiovascular safety. The dose-escalation and tapering also appear to be cumbersome for both these class of drugs.

While orlistat has been in use for almost two decades and the only drug currently approved in adolescent, the non-responders to this drug are also very high. Moreover, the most frequent lingering GI side effects with orlistat also limit its widespread use, apart from cost-effectiveness.

Lorcaserin seems to have the most reasonably acceptable profile in terms of ease of oral dosing, side effects, cardiovascular safety, and overall cost, compared to others. However, weight reduction is just modest at its best and very similar to orlistat. Furthermore, non-responders to lorcaserin also appear to be reasonably high. A 12-week pilot study suggested only 28% of patients showing ≥5% weight loss to lorcaserin.

Liraglutide 3.0 mg has reasonably acceptable side effect profile, excellent glycemic effect, and anticipated cardiovascular benefit, but injectable approach, moderate weight loss and prohibitive cost, may limit its widespread use.

Collectively, available data points toward a significant role of anti-obesity drugs in improving body weight and other clusters of metabolic syndromes.

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