Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials

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Summary

Background Pharmacotherapy provides an option for adults with overweight and obesity to reduce their bodyweight if lifestyle modifications fail. We summarised the latest evidence for the benefits and harms of weight-lowering drugs.

Methods This systematic review and network meta-analysis included searches of PubMed, Embase, and Cochrane Library (CENTRAL) from inception to March 23, 2021, for randomised controlled trials of weight-lowering drugs in adults with overweight and obesity. We performed frequentist random-effect network meta-analyses to summarise the evidence and applied the Grading of Recommendations Assessment, Development, and Evaluation frameworks to rate the certainty of evidence, calculate the absolute effects, categorise interventions, and present the findings. The study was registered with PROSPERO, CRD 42021245678.

Findings 14 605 citations were identified by our search, of which 143 eligible trials enrolled 49 810 participants. Except for levocarnitine, all drugs lowered bodyweight compared with lifestyle modification alone; all subsequent numbers refer to comparisons with lifestyle modification. High to moderate certainty evidence established phentermine–topiramate as the most effective in lowering weight (odds ratio [OR] of ≥5% weight reduction 8·02, 95% CI 5·24 to 12·27; mean difference [MD] of percentage bodyweight change −7·97, 95% CI −9·28 to −6·66) followed by GLP-1 receptor agonists (OR 6·33, 95% CI 5·00 to 8·00; MD −5·76, 95% CI −6·30 to −5·21). Naltrexone–bupropion (OR 2·69, 95% CI 2·11 to 3·43), phentermine–topiramate (2·40, 1·69 to 3·42), GLP-1 receptor agonists (2·17, 1·71 to 2·77), and orlistat (1·72, 1·44 to 2·05) were associated with increased adverse events leading to drug discontinuation. In a post-hoc analysis, semaglutide, a GLP-1 receptor agonist, showed substantially larger benefits than other drugs with a similar risk of adverse events as other drugs for both likelihood of weight loss of 5% or more (OR 9·82, 95% CI 7·09 to 13·61) and percentage bodyweight change (MD −11·41, 95% CI −12·54 to −10·27).

Interpretation In adults with overweight and obesity, phentermine–topiramate and GLP-1 receptor agonists proved the best drugs in reducing weight; of the GLP-1 agonists, semaglutide might be the most effective.

Funding 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University.

Introduction

Overweight and obesity are global health problems[1] and contribute to multiple health problems, including type 2 diabetes, cardiovascular disease, depression, and malignancy.[2,3] Lifestyle modification might improve quality of life and health outcomes,[3,4] but only 61% of individuals with overweight and obesity complete lifestyle programmes.[5] Although bariatric surgery, including the Roux-en-Y gastric bypass, provides long-term protection against complications in people with very high body-mass index (BMI),[6] many people might be reluctant to undergo what they perceive as a major surgery.[7] Pharmacotherapy is an important alternative or adjunct therapy for weight loss, in addition to lifestyle modification and bariatric surgery.[2,8]

The 2016 American Association of Clinical Endocrinology guideline evaluated the five medications (orlistat, lorcaserin, naltrexone–bupropion, liraglutide, and phentermine–topiramate) currently approved for chronic management of obesity in adults.[2] However, in 2020, the US Food and Drug Administration requested the withdrawal of lorcaserin because of an increased risk of cancer.[9] In 2021, four trials were published for semaglutide, a novel weekly GLP-1 receptor agonist, with results that appear practice-changing.[10–13] Moreover, evidence exists regarding the use of other anti-diabetic drugs, including SGLT2 inhibitors, metformin, and pramlintide, for management of obesity.[8] We undertook a systematic review and network meta-analysis to assess the weight-lowering effects and safety of drugs, provided in addition to lifestyle modification, for the management of bodyweight in adults with overweight and obesity.

Lancet 2022; 399: 259–69

Published **Online** December 8, 2021 https://doi.org/10.1016/S0140-6736(21)01640-8

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Research in context

Evidence before this study

Regulatory authorities have approved a small number of medications for weight management in adults with overweight and obesity. New evidence has emerged for other agents, including semaglutide, a GLP-1 receptor agonist. The relative merits of existing and new drugs remain unclear.

Added value of this study

This network meta-analysis, including all randomised controlled trials (RCTs) addressing the efficacy of both approved and candidate drugs for weight management in adults with overweight and obesity, allowed direct and indirect comparisons between treatments in 49 810 participants in 143 RCTs. Our structured evidence summary provides absolute estimates of effects and certainty of evidence across treatment options. The findings should facilitate optimal evidence-informed decision making for people and clinicians regarding pharmacological interventions for weight reduction.

Implications of all the available evidence

In our analysis, phentermine–topiramate and GLP-1 receptor agonists proved the most effective in reducing weight. Semaglutide proved the most effective of the GLP-1 receptor agonists and showed larger effects than any other drug. Phentermine–topiramate and naltrexone–bupropion resulted in the highest risk of adverse events leading to discontinuation.

Methods

Study design

This systematic review and network meta-analysis was performed as part of the West China Recommendation project and a collaboration with the non-profit MAGIC (Making GRADE [Grading of Recommendations Assessment, Development, and Evaluation] the Irresistible Choice) Evidence Ecosystem Foundation. A nationwide multidisciplinary panel consisting of endocrinologists, primary care physicians, a dietitian, a geriatrician, a gastrointestinal surgeon, a nurse, a pharmacist, and methodologists formulated the clinical question and provided input into the study protocol. They sought evaluation of drugs for adults with overweight and obesity who sought help for weight loss. The results will inform the group's guideline recommendation. We registered our study on PROSPERO (CRD 42021245678) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and PRISMA-2020 guidelines and the extension statement for network meta-analysis (PRISMA-NMA).[14,15]

Search strategy and selection criteria

We searched PubMed, Embase (using the OVID platform), and the Cochrane Library (CENTRAL) from inception to March 23, 2021. To supplement the identified citations, we searched ClinicalTrials.gov and the reference lists of key reviews and meta-analyses. Searches included terms relating to weight loss, investigated drugs, and randomised controlled trials (RCTs; appendix pp 7–14). Duplicate records were removed with R (version 3.6.1). Teams of paired reviewers independently used EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) and Zotero 5.0 (Corporation for Digital Scholarship, Vienna, VA, USA) to first screen titles and abstracts and then full-text manuscripts, and extracted data on study identifiers, study design and setting, participant characteristics at baseline, intervention, and outcomes. Discrepancies were resolved by discussion or, if necessary, by third party adjudication.

See **Online** for appendix

Eligible RCTs enrolled adults with overweight or obesity regardless of the comorbidity of the weight-related complications. These RCTs compared lifestyle modification and a candidate weight-lowering drug with lifestyle modification alone with or without placebo or an alternative active drug; reported absolute or percentage weight change from baseline or pretreatment and post-treatment absolute bodyweight or any type of quality-of-life score; and had a treatment duration of 12 weeks or more (chosen as the shortest duration in which the drugs are most likely to result in important weight reduction) with no limit set on maximum duration. We excluded trials for these reasons: with a crossover design; investigating any type of drug combination except for one-pill combinations (ie, phentermine–topiramate and bupropion–naltrexone); systematically recruiting individuals with psychological conditions, such as schizophrenia, depression, and eating disorders; including pregnant participants or those with a normal bodyweight; and trials published in a language other than English.

Data analysis

The guideline panel judged the following outcomes as crucial: percentage bodyweight change from baseline to end of follow-up, the proportion of participants reducing their bodyweight by 5% or more, and the proportion of participants reporting adverse events leading to treatment discontinuation, weight regain after treatment discontinuation, and change in quality-of-life score. The panel judged the following outcomes as important but not crucial: total number of gastrointestinal events, number of severe gastrointestinal events, change in body image score, and change in depression and anxiety symptom scores. They judged the following outcomes of less importance: change in absolute bodyweight from baseline to end of follow-up, and change in glycated haemoglobin (HbA_{1c}), LDL cholesterol, and systolic blood pressure (appendix pp 16–17). As recommended by a peer reviewer, we added an exploratory outcome regarding the

proportion of participants reducing their bodyweight by 10% or more. Outcome data were extracted preferentially from study-reported modified results or original intention-to-treat results with last observations carried forward imputation, if reported. Alternatively, we extracted per-protocol results with or without an imputation and did not restrict the imputation methods. If reported, we prioritised adjusted mean via regression (usually least-square mean). We chose the following measures of effect: odds ratios for individual-based binary outcomes, such as the proportion of people reducing their bodyweight by 5% or more; incidence rate ratios for event-based binary outcomes, such as gastrointestinal events in which people can have more than one event; mean differences for changes in percentage and absolute bodyweight; and standardised mean differences using Hedges' method for changes in quality-of-life score, body image, and depression and anxiety symptom scores. When authors of these RCTs did not report the absolute or percentage bodyweight change, we estimated this from the reported data (appendix pp 18–19).

Network meta-analysis was performed with the frequentist model with a graph-theoretical method by R package netmeta. The estimator was based on weighted least-square regression with the Moore–Penrose pseudoinverse method.[16] The DerSimonian–Laird random-effects model was used to estimate the variance in heterogeneity between studies.[17] Network nodes included all drugs in a particular drug class. Because results suggested semaglutide might have a larger effect than other GLP-1 receptor agonists, we conducted a post-hoc analysis using each GLP-1 receptor agonist as a separate node in the analysis. Forest plots and league tables of the relative treatment effects were used to visualise comparisons of network estimations. Interventions were ranked according to P score with the interpretation of the mean extent of certainty that one treatment was better than another.[18] Global and local statistical heterogeneity was assessed with generalised Cochran's Q.[19] We compared distributions of characteristics across study arms grouped by drugs to assess the transitivity assumption of indirect comparisons. Local inconsistency of direct and indirect results was assessed with the node-splitting method for all comparison loops and indirect results were derived from direct and network results by the back-calculation method.[20,21] We performed prespecified subgroup analyses for the following baseline variables: obesity severity category (overweight *vs* mild obesity *vs* moderate-to-severe obesity), with a predefined hypothesis of larger relative effect in the moderate-to-severe obesity group; and diabetes status (with diabetes *vs* without diabetes), with a predefined hypothesis of larger effect in the diabetes group (appendix p 20). We assessed the credibility of subgroup effects with the ICEMAN tool.[22]

The methods of multiple sensitivity analyses and publication bias assessments are detailed in the appendix (pp 21–23). Two researchers (YWa and SX) independently assessed the risk of bias of individual studies using ROB 2, a revised Cochrane risk-of-bias tool for randomised trials, with discrepancies resolved by a third researcher (QS; appendix p 24).[23]

The GRADE approach provided the framework for rating the certainty of the evidence of each paired comparison as high, moderate, low, or very low.[24,25] The absolute effects of the drug treatments were calculated with baseline risk and the pooled relative effects compared with lifestyle modification alone (appendix p 25). For categorical outcomes, the lifestyle modification alone study arms across the studies with a follow-up duration of 1 year or more from the random-effect meta-analysis provided baseline risk estimates. For continuous outcomes, we applied the pooled single means across these studies.

To classify interventions in categories from among the best to among the worst according to the magnitude of effects and evidence certainty, we adapted a recently published GRADE approach.[26] In particular, we used a minimally contextualised approach to network meta-analysis, meaning that our focus was on judging certainty in whether interventions caused differences greater than those of minimal importance to patients (referred to as minimal important differences [MIDs]).[27,28] The key comparator for these judgements was lifestyle modification alone. Adopting estimates in literature, we judged the MID for percentage bodyweight change as 5%; the number of people losing weight by 5% or more (266 more per 1000 person-years) and 10% or more (106 more per 1000 person-years) as twice the proportion reaching the target with lifestyle modification alone;[29,30] 12 points for the Impact of Weight on Quality of Life; 2·7 points for the Patient Health Questionnaire; 0·5% for HbA_{1c}; 0·26 mmol/L for LDL cholesterol; and 5 mm Hg for systolic blood pressure (appendix pp 26–27).[31,32]

For benefit outcomes, we categorised drugs on the basis of whether the point estimate of effect size was greater or less than the MID, and whether the 95% CI overlapped that threshold. With this approach, drugs that were categorised as among the best showed point estimates larger than the MID with 95% CI not overlapping the MID. Drugs that were categorised as among the worst showed point estimates and entire 95% CI less than the MID. Using this system, we differentiated between drugs for which evidence was high or moderate certainty from those in which the evidence was low or very low certainty. For harm outcomes, we categorised drugs on the basis of the comparisons with other drugs and evidence certainty. Further details of GRADE ratings of certainty are available (appendix pp 28–29).

Role of the funding source

The funder had no role in study design, data collection, analysis, and interpretation, or writing of the manuscript and the decision to submit.

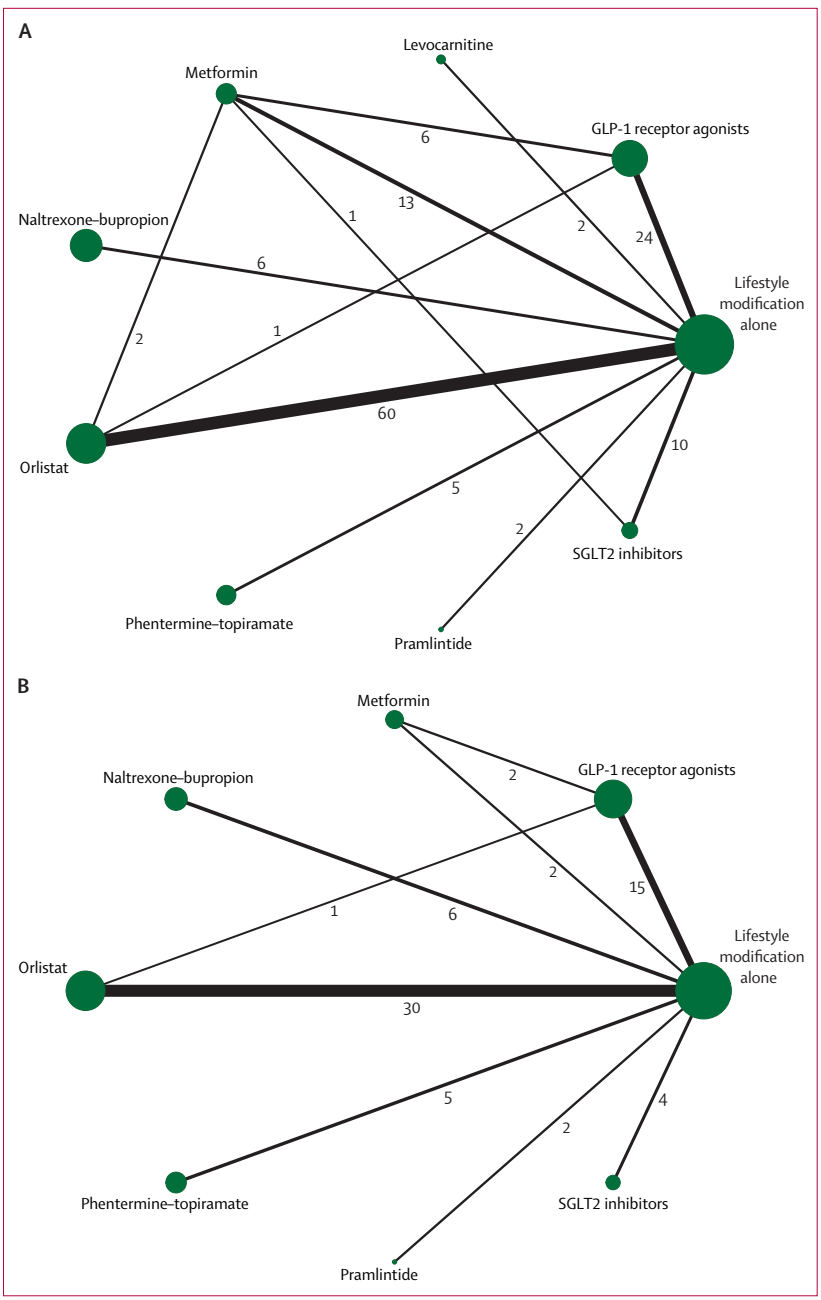


Figure 1: **Network plots of available direct comparisons**
Percentage change in bodyweight from baseline (A) and participants with bodyweight reduction of 5% or more (B). Each node (solid circle) stands for a weight-lowering drug or lifestyle modification only. The size of the nodes is proportional to the number of participants (ie, sample size) involving the specific treatment intervention. The solid lines link treatments with direct comparison with the thickness proportional to the number of trials.

Results

Of 14 605 citations identified, the team assessed 538 full manuscripts for eligibility of which 143 unique RCTs, which included 49 810 adults in total, proved eligible (appendix pp 31–74). Among the participants, the median age was 47 (IQR 43–54) years, the median female proportion was 75% (54–89), median baseline BMI was 35·3 (33·1–36·8) kg/m², and median length of follow-up was 24 (24–52) weeks (appendix p 31). A high risk of bias occurred predominantly in the domains of deviations from the intended interventions and missing outcome data (appendix pp 75–98). A high risk of bias in the domain of measurement of outcome was identified for adverse events. Heterogeneity, intransitivity, and inconsistency of the network meta-analysis were also evaluated (appendix pp 150–169). Figure 1 shows the network plots for percentage bodyweight change from baseline and participants with a bodyweight reduction of 5% or more. All other network plots are in the appendix (pp 99–107). Figure 2 shows the league tables for the network estimates of all comparisons (appendix pp 132–137). The results of post-hoc analyses are presented in the appendix (pp 239–346). Also presented in the appendix are the summary of findings tables (pp 108–124) and the minimally contextualised frameworks (pp 125–131). Figure 3 presents the categorisation of interventions from among the best to among the worst—when compared with lifestyle modification alone—for the four key benefit and two key harm outcomes, and the magnitude of effect relative to lifestyle modification alone, and the certainty of the evidence. Figure 3 also presents estimates of effect from the post-hoc analysis treating each of the three GLP-1 agonists as separate drugs. The subgroup and sensitivity analyses are presented in the appendix (pp 347–427). All sensitivity analyses proved consistent with the primary results.

For the outcome of percentage bodyweight change from baseline, all drugs except levocarnitine reduced bodyweight, with phentermine–topiramate and GLP-1 receptor agonists proving among the best (point estimates and 95% CI were greater than MID and not overlapping the MID, moderate certainty evidence; figure 3). All drugs except pramlintide were associated with a greater proportion of participants reducing their bodyweight by 5% or more compared with lifestyle modification alone. All drugs except metformin, SGLT2 inhibitors, and pramlintide led to a higher proportion of participants reducing their weight by 10% or more. Phentermine–topiramate, GLP-1 receptor agonists, and naltrexone–bupropion proved among the most effective in bodyweight reduction by 5% or more and 10% or more (high certainty evidence; figure 3).

Lifestyle modification alone resulted in 266 people per 1000 person-years reducing their weight by 5% or more and 106 people per 1000 person-years reducing their weight by 10% or more (figure 4). Treatment with phentermine–topiramate, GLP-1 receptor agonists, and naltrexone–bupropion more than doubled people losing weight by 5% or more and 10% or more (high certainty; figure 4). Subgroup analyses (appendix pp 375–376) showed that GLP-1 receptor agonists were associated with a greater reduction in percentage bodyweight and a higher likelihood of weight loss by 5% or more in people

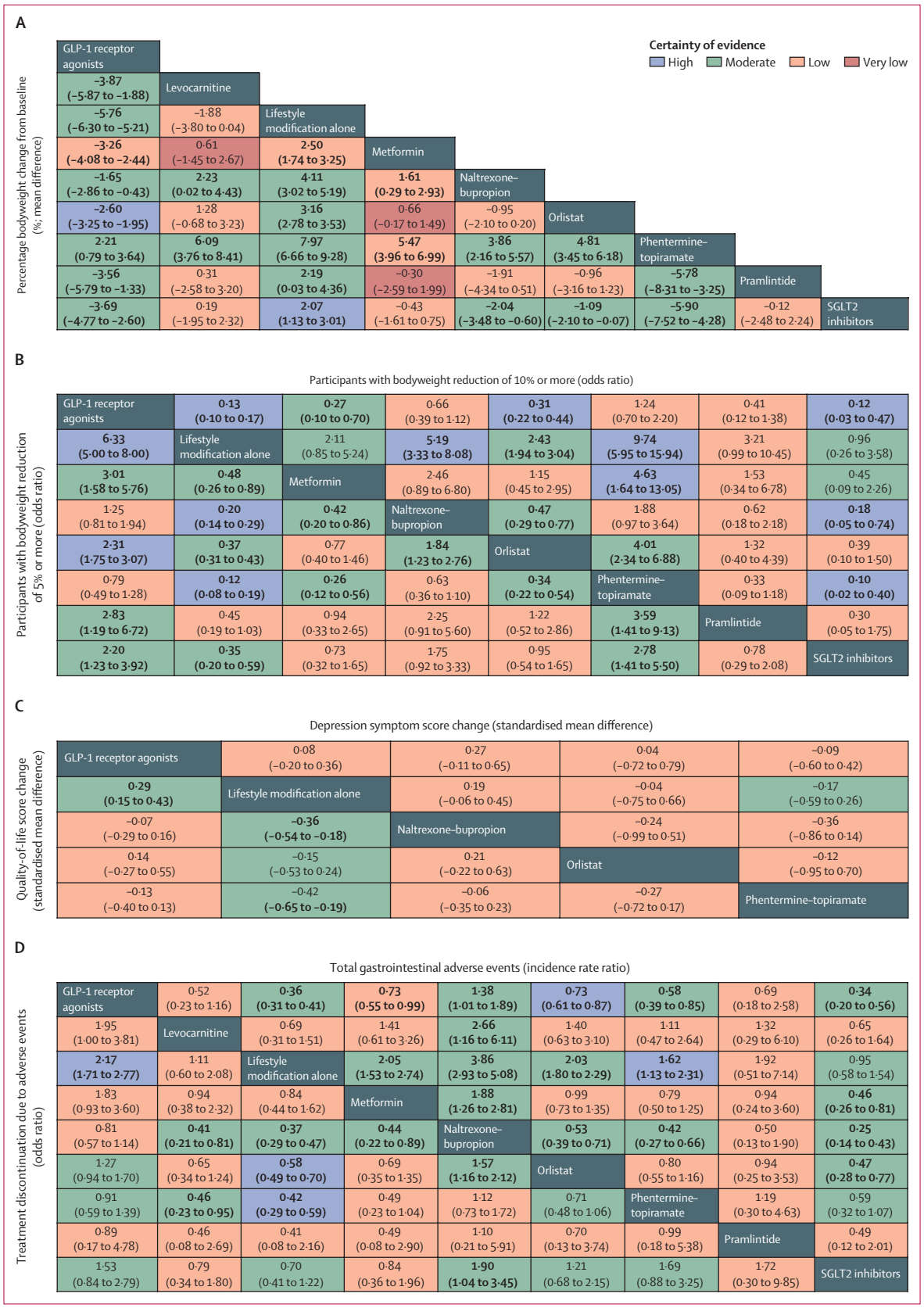


Figure 2: **League tables of outcome analyses**
(A) Percentage change in bodyweight from baseline (lower left). (B) Participants with bodyweight reduction of 5% or more (lower left) and participants with bodyweight reduction of 10% or more (upper right). (C) Quality-of-life (lower left) and depression symptom score (upper right). (D) Treatment discontinuation due to any adverse event (lower left) and total gastrointestinal adverse events (upper right). The league tables show the relative effects of each weight-lowering drug and lifestyle modification only (the treatment on the column to the treatment of the row). The relative effects are measured as a mean difference for percentage bodyweight change, odds ratios for participants with bodyweight reduction of 5% or more and 10% or more, and treatment discontinuation, and standardised mean differences for quality-of-life and depression symptom score, along with 95% CIs. Bold indicates statistical significance. The colour of each cell indicates the certainty of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation. All tables list the treatments in alphabetical order.

	Benefit outcomes		Harm outcomes	
	High or moderate certainty evidence	Low or very low certainty evidence	High or moderate certainty evidence	Low or very low certainty evidence
Among the best	Definitely better than lifestyle modification alone	May be better than lifestyle modification alone	No more harmful than lifestyle modification alone	No more harmful than lifestyle modification alone
Intermediate—possibly better	Possibly better than lifestyle modification alone	Might be better than lifestyle modification alone	More harmful than lifestyle modification alone, but no worse than other interventions	More harmful than lifestyle modification alone, but no worse than other interventions
Intermediate—possibly worse	Possibly no better than lifestyle modification alone	Might be no better than lifestyle modification alone		
Among the worst	Definitely no better than lifestyle modification alone	May be no better than lifestyle modification alone	More harmful than lifestyle modification alone and some other interventions	More harmful than lifestyle modification alone and some other interventions

	Benefit outcomes					Harm outcomes	
	Percentage bodyweight change from baseline, MD (95%)	Participants with bodyweight reduction ≥5%, OR (95% CI)	Participants with bodyweight reduction ≥10%, OR (95% CI)	Quality-of-life score, SMD (95% CI)	Depression symptom score, SMD (95% CI)	Discontinuation due to any adverse event, OR (95% CI)	Total gastrointestinal adverse events, IRR (95% CI)
Phentermine–topiramate	**−7·97 (−9·28 to −6·66)**	**8·02 (5·24 to 12·27)**	**9·74 (5·95 to 15·94)**	**0·42 (0·19 to 0·65)**	−0·17 (−0·59 to 0·26)	**2·40 (1·69 to 3·42)**	**1·62 (1·13 to 2·31)**
GLP-1 receptor agonists	**−5·76 (−6·30 to −5·21)**	**6·33 (5·00 to 8·00)**	**7·83 (5·89 to 10·40)**	**0·29 (0·15 to 0·43)**	−0·08 (−0·36 to 0·20)	**2·17 (1·71 to 2·77)**	**2·79 (2·42 to 3·23)**
Naltrexone–bupropion	**−4·11 (−5·19 to −3·02)**	**5·04 (3·50 to 7·27)**	**5·19 (3·33 to 8·08)**	**0·36 (0·18 to 0·54)**	0·19 (−0·06 to 0·45)	**2·69 (2·11 to 3·43)**	**3·86 (2·93 to 5·08)**
Orlistat	**−3·16 (−3·53 to −2·78)**	**2·73 (2·32 to 3·22)**	**2·43 (1·94 to 3·04)**	0·15 (−0·24 to 0·53)	−0·04 (−0·75 to 0·66)	**1·72 (1·44 to 2·05)**	**2·03 (1·80 to 2·29)**
Metformin	**−2·50 (−3·25 to −1·74)**	**2·10 (1·13 to 3·91)**	2·11 (0·85 to 5·24)	..	..	1·19 (0·62 to 2·28)	**2·05 (1·53 to 2·74)**
SGLT2 inhibitors	**−2·07 (−3·01 to −1·13)**	**2·88 (1·69 to 4·90)**	0·96 (0·26 to 3·58)	..	..	1·42 (0·82 to 2·46)	0·95 (0·58 to 1·54)
Pramlintide	**−2·19 (−4·36 to −0·03)**	2·24 (0·97 to 5·14)	3·21 (0·99 to 10·45)	..	..	2·43 (0·46 to 12·79)	1·92 (0·51 to 7·14)
Levocarnitine	−1·88 (−3·80 to 0·04)	..	..	..	..	1·11 (0·60 to 2·08)	1·45 (0·66 to 3·19)
Drug effect for GLP-1 receptor agonists							
Semaglutide	**−11·41 (−12·54 to −10·27)**	**9·82 (7·09 to 13·61)**	**13·32 (9·94 to 17·83)**	**0·27 (0·08 to 0·46)**	..	**1·99 (1·35 to 2·92)**	**2·79 (2·14 to 3·64)**
Liraglutide	**−4·68 (−5·30 to −4·06)**	**4·91 (3·78 to 6·38)**	**4·80 (3·60 to 6·41)**	**0·32 (0·08 to 0·56)**	−0·08 (−0·36 to 0·20)	**2·45 (1·80 to 3·33)**	**3·10 (2·59 to 3·71)**
Exenatide	**−3·72 (−4·82 to −2·62)**	**2·86 (1·27 to 6·47)**	**3·12 (1·17 to 8·32)**	..	..	1·50 (0·66 to 3·44)	**1·72 (1·19 to 2·50)**

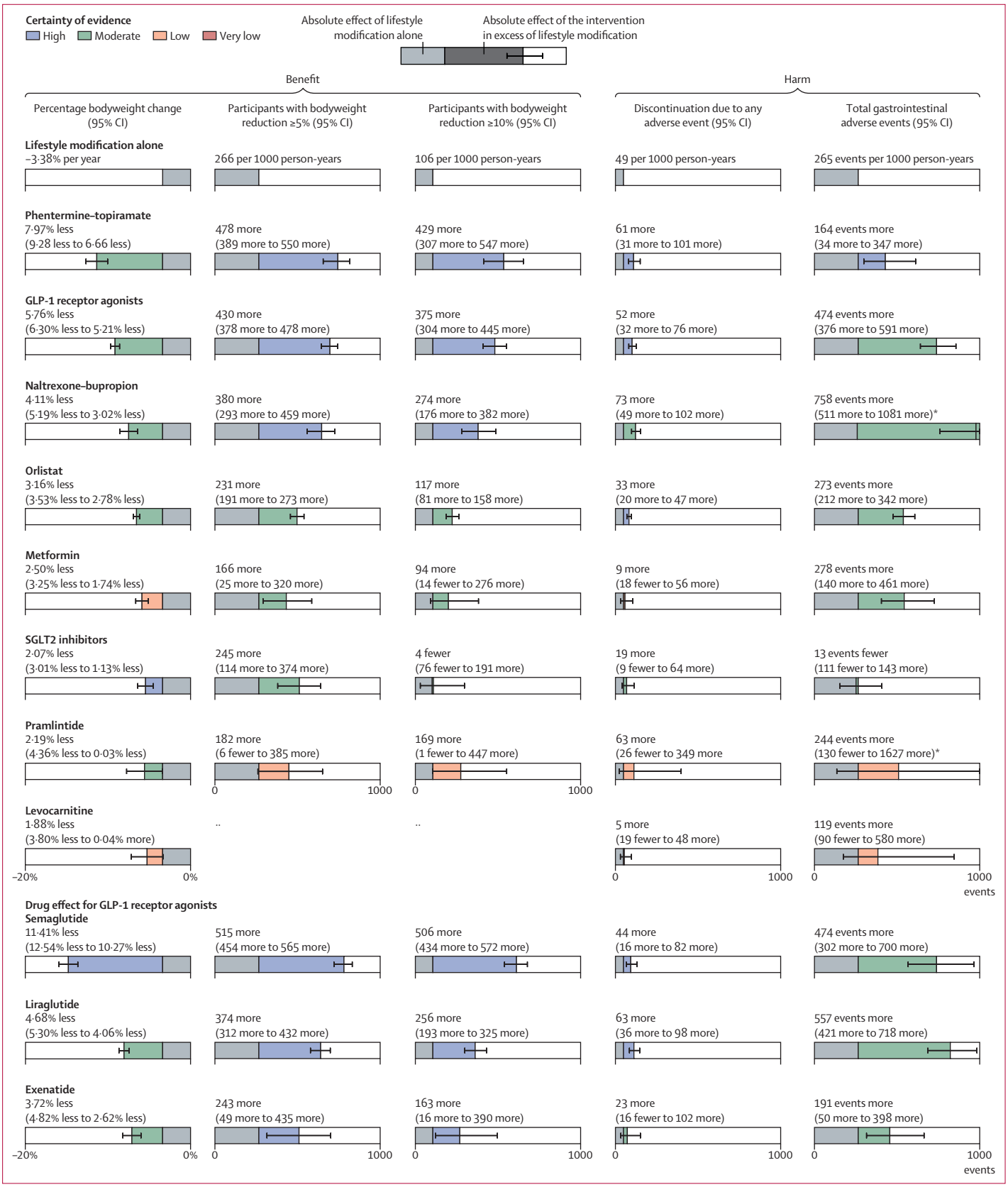
Figure 3: **Summary of relative effects of weight-lowering drugs on benefit and harm outcomes**

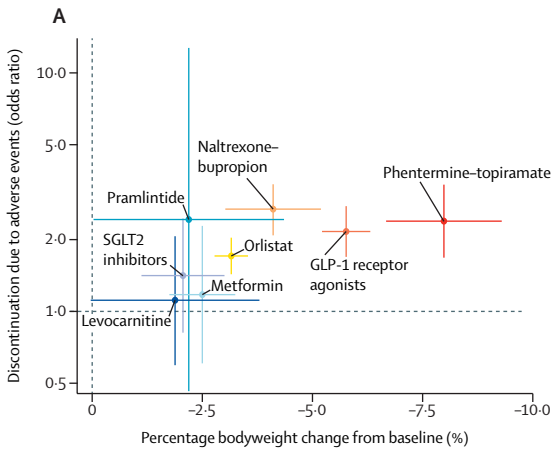
The certainty of evidence was rated by the Grading of Recommendations Assessment, Development, and Evaluation criteria, including imprecision; we rated down for imprecision only when the 95% CI crossed null effect. We categorised the drugs and rated our certainty of the benefit outcome in one of two ways: whether the intervention was clearly better or worse than lifestyle modification alone (the mean effect size exceeding or less than the MID and the 95% CI not crossing the MID threshold); or possibly better or worse than the lifestyle modification alone (the point estimate greater or less than the MID and the 95% CI crossing the threshold). We categorised the drugs by the statistical significance in comparisons of intervention of the harm outcomes. The best, intermediate, and worst categories show whether the effect is clinically important or not, whereas the certainty of evidence shows whether the effect is trustworthy or not. Bold text represents statistical significance. MD=mean difference. MID=minimal important difference. OR=odds ratio. IRR=incidence rate ratio. SMD=standardised mean difference.

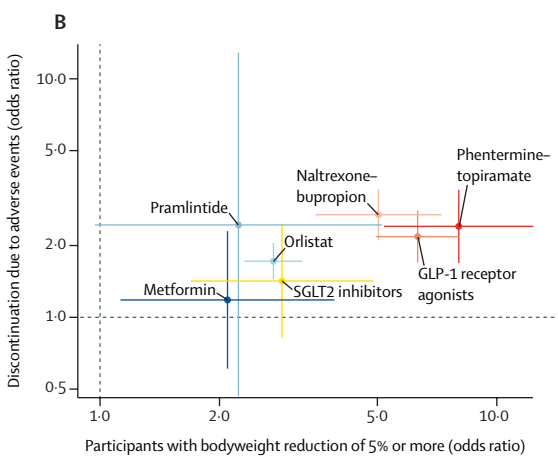
without diabetes compared with lifestyle modification alone but with low credibility because of inconsistency across studies and between-trial comparisons-based effect modification, and disagreement with our predefined hypothesis. No other subgroup effects were identified. In the analysis of absolute weight change among 122 studies with 42 148 adults, similar results to those of percentage weight change were observed. We did not identify any evidence for weight regain after treatment discontinuation; however, only three studies provided data of the weight changes both at the end of treatment and follow-up (12 weeks extension) and none of the three reported the bodyweight change from the end of drug treatment to the end of follow-up with associated estimates of variability.

Figure 4: **Summary of absolute effects of weight-lowering drugs on benefit and harm outcomes**

Effect of lifestyle modification alone was estimated from the placebo arms within the original studies with at least 1 year follow-up duration via a random-effect meta-analysis of single means, proportions, or rates. This pooled effect represents how much bodyweight a person with overweight or obesity can expect to lose through lifestyle modification alone. *The upper bounds of confidence intervals are truncated in the bar plots due to space.


Certainty of evidence
High
Moderate
Low
Very low
Absolute effect of lifestyle modification alone
Absolute effect of the intervention in excess of lifestyle modification
Benefit
Harm
Percentage bodyweight change (95% CI)
Participants with bodyweight reduction ≥5% (95% CI)
Participants with bodyweight reduction ≥10% (95% CI)
Discontinuation due to any adverse event (95% CI)
Total gastrointestinal adverse events (95% CI)
Lifestyle modification alone
−3·38% per year
266 per 1000 person-years
106 per 1000 person-years
49 per 1000 person-years
265 events per 1000 person-years
Phentermine–topiramate
7·97% less (9·28 less to 6·66 less)
478 more (389 more to 550 more)
429 more (307 more to 547 more)
61 more (31 more to 101 more)
164 events more (34 more to 347 more)
GLP-1 receptor agonists
5·76% less (6·30% less to 5·21% less)
430 more (378 more to 478 more)
375 more (304 more to 445 more)
52 more (32 more to 76 more)
474 events more (376 more to 591 more)
Naltrexone–bupropion
4·11% less (5·19% less to 3·02% less)
380 more (293 more to 459 more)
274 more (176 more to 382 more)
73 more (49 more to 102 more)
758 events more (511 more to 1081 more)*
Orlistat
3·16% less (3·53% less to 2·78% less)
231 more (191 more to 273 more)
117 more (81 more to 158 more)
33 more (20 more to 47 more)
273 events more (212 more to 342 more)
Metformin
2·50% less (3·25% less to 1·74% less)
166 more (25 more to 320 more)
94 more (14 fewer to 276 more)
9 more (18 fewer to 56 more)
278 events more (140 more to 461 more)
SGLT2 inhibitors
2·07% less (3·01% less to 1·13% less)
245 more (114 more to 374 more)
4 fewer (76 fewer to 191 more)
19 more (9 fewer to 64 more)
13 events fewer (111 fewer to 143 more)
Pramlintide
2·19% less (4·36% less to 0·03% less)
182 more (6 fewer to 385 more)
169 more (1 fewer to 447 more)
63 more (26 fewer to 349 more
244 events more (130 fewer to 1627 more)*
Levocarnitine
1·88% less (3·80% less to 0·04% more)
..
..
5 more (19 fewer to 48 more)
119 events more (90 fewer to 580 more)
−20%
0%
0
1000
events
Drug effect for GLP-1 receptor agonists
Semaglutide
11·41% less (12·54% less to 10·27% less)
515 more (454 more to 565 more)
506 more (434 more to 572 more)
44 more (16 more to 82 more)
474 events more (302 more to 700 more)
Liraglutide
4·68% less (5·30% less to 4·06% less)
374 more (312 more to 432 more)
256 more (193 more to 325 more)
63 more (36 more to 98 more)
557 events more (421 more to 718 more)
Exenatide
3·72% less (4·82% less to 2·62% less)
243 more (49 more to 435 more)
163 more (16 more to 390 more)
23 more (16 fewer to 102 more)
191 events more (50 more to 398 more)
−20%
0%
0
1000
events





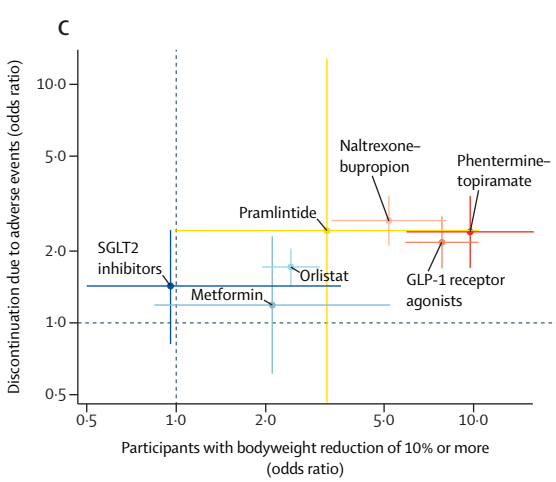


Figure 5: **Two-dimensional graphs of efficacy versus safety of weight-lowering drugs**
(A) Percentage change in bodyweight from baseline versus discontinuation due to adverse events. (B) Bodyweight reduction of 5% or more versus discontinuation due to adverse events. (C) Bodyweight reduction of 10% or more versus discontinuation due to adverse events. Effect sizes for drugs are represented by coloured nodes, with bars representing the corresponding 95% CIs.

We included 15 trials with 15 742 adults in the analyses of quality-of-life scores and seven trials with 2498 participants in the analysis of depression symptom score. The nodes of the network included phentermine–topiramate, naltrexone–bupropion, GLP-1 receptor agonists, orlistat, and lifestyle modification alone (appendix pp 99–107). Except for orlistat, all three of these drugs improved quality of life (moderate certainty evidence; figures 2B, 3). The pooled results did not identify a statistically significant improvement of depression symptom scores by adding the investigated drugs to lifestyle modification alone (moderate to low certainty). However, one trial suggested a statistically significant increase in depression symptom score in people receiving naltrexone–bupropion;[33] although, this result might not be important from the perspective of patients due to the very small effect.[34] The study team failed to identify evidence addressing body image or anxiety symptom scores.

Discontinuations due to any adverse events were investigated in 114 studies involving 44 824 participants, and discontinuations due to any reported gastrointestinal events were investigated in 98 studies involving 43 582 participants. Phentermine–topiramate, naltrexone–bupropion, GLP-1 receptor agonists, and orlistat were associated with increased risks of any adverse event leading to treatment discontinuation (figure 2D). Naltrexone–bupropion and phentermine–topiramate were among the worst (high to moderate certainty evidence), followed by GLP-1 receptor agonists and orlistat with intermediate risk of harm (high certainty evidence; figure 3). Lifestyle modification alone resulted in 49 people per 1000 person-years discontinuing their treatment due to adverse events (figure 4). The four interventions led to 73 (phentermine–topiramate), 61 (naltrexone–bupropion), 52 (GLP-1 receptor agonists), and 33 (orlistat) more people in treatment discontinuation (figure 5). For total gastrointestinal events, treatment with naltrexone–bupropion, GLP-1 receptor agonists, metformin, and orlistat were among the worst risk of harm with moderate certainty evidence (figure 3). Lifestyle modification alone resulted in 265 total gastrointestinal events per 1000 person-years (figure 4). Naltrexone–bupropion was associated with 758 events more per 1000 person-years, followed by GLP-1 receptor agonists (474 events), metformin (278 events), orlistat (273 events), and phentermine–topiramate (164 events; figure 4). 35 studies reported severe gastrointestinal events, with no significant differences observed for any drug compared with lifestyle modification alone.

In post-hoc analyses (figures 3, 4; appendix pp 247–58), semaglutide was associated with the largest percentage weight loss and the greatest likelihood of losing weight by 5% or more and 10% or more with high certainty evidence and contributed to 515 and 506 more people per 1000 person-years than lifestyle modification alone, and performed better than liraglutide and exenatide.

Semaglutide led 44 more people per 1000 person-years to discontinue the drug, a result similar to liraglutide and exenatide.

We pooled 51 trials with 15 714 adults to estimate the drug effects on change in HbA_{1c}, 76 trials with 22 756 to estimate the drug effects on change in LDL cholesterol, and 57 trials with 30 186 adults to estimate the drug effects on change in systolic blood pressure (appendix pp 99–192). GLP-1 receptor agonists reduced HbA_{1c} significantly compared with lifestyle modification alone and exceeded the MID threshold of 0·5% with low certainty, whereas orlistat reduced LDL cholesterol significantly compared with lifestyle modification alone and exceeded the MID of 0·26 mmol/L with very low certainty evidence. GLP-1 receptor agonists and phentermine–topiramate resulted in the largest reductions in systolic blood pressure with statistically significant differences that did not exceed the MID threshold of 5 mm Hg.

Discussion

This network meta-analysis involving 143 studies that enrolled 49 810 participants provided high to moderate certainty evidence that phentermine–topiramate and GLP-1 receptor agonists (and in particular semaglutide) are among the most effective agents for reducing weight in patients with obesity, with reductions in bodyweight by 6–11% (figure 3). These drugs showed some benefits on quality of life but with a relatively small magnitude of uncertain importance. We did not identify the effects of the drugs on depression with only low certainty evidence available. Evidence regarding HbA_{1c}, LDL cholesterol, and systolic blood pressure was of low to very low certainty, failing to provide compelling evidence of benefit.

Strengths of our review include the most comprehensive synthesis of evidence to date on benefits and harms of drug therapies for adults with overweight or obesity, capturing all recent publications. By involving a nationwide multidisciplinary guideline panel in defining the clinical questions, subgroup analyses, and selecting patient-important outcomes, the review also ensured relevance for clinical practice. We used state-of-the-art approaches to categorise and present the findings using GRADE frameworks.

Limitations of our review include the absence of individual patient data pooling, which particularly reduced the precision of synthesis for subgroup effects. Although the variance of missing percentage weight change from baseline was estimated in some of the included trials, thus introducing uncertainty in the confidence intervals, sensitivity analyses confirmed the robustness of using these estimated values. Studies varied in population characteristics and duration of follow-up. However, our sensitivity analyses showed no important differences in results across follow-up durations, baseline BMI, and comorbid diabetes.

Our findings regarding the weight-lowering effects of the approved drugs in the current analysis are consistent with those from a previous network meta-analysis[35] in which all drugs were associated with higher odds of weight loss by 5% or more. All drugs investigated in both systematic reviews were associated with an increased risk of discontinuation due to adverse events. Our study included additional drug candidates and further evaluated the absolute benefit and harm. Our results on laboratory outcomes are consistent with a previous meta-analysis that explored the effect of weight-loss drugs on cardiometabolic risk profiles.[36] In that study, liraglutide, orlistat, and phentermine–topiramate were among the highest for lowering HbA_{1c}, LDL cholesterol, and systolic blood pressure. Our findings are in line, but we only highlighted the drugs lowering the metabolic parameters exceeding the MID with statistical significance.

Phentermine–topiramate represents a well established weight-lowering treatment that is approved for this indication only in the USA.[8] Our post-hoc analysis supports the use of semaglutide as a new therapeutic option for weight management, given the superior weight-lowering effects and intermediate risk of adverse events leading to treatment discontinuation. The suggested dose of semaglutide for weight loss is 2·4 mg per week, which is notably higher than the suggested dose of 1·0 mg per week for the treatment of type 2 diabetes.[11] The large effect of semaglutide might be attributable to its once-weekly administration, which greatly improves treatment compliance.[10] However, other once-weekly GLP-1 receptor agonists, such as dulaglutide and once-weekly exenatide, did not show similar effects in absolute weight reduction.[37,38] People living with overweight and obesity might be hesitant to initiate treatment with GLP-1 receptor agonists due to their subcutaneous injection route of administration,[39] and this drug class is also associated with an increased risk of gastrointestinal adverse events, including diarrhoea, nausea, vomiting, constipation, and abdominal pain.[8] Although some clinicians link these adverse effects to a reduction in food intake that assists the weight loss,[40] shared decision making might be helpful by fully informing patients of the benefits and harms of the weight-lowering drugs.[8,41]

Orlistat is widely used for weight loss worldwide, but possibly ranks no better than lifestyle modification alone in our study. Nevertheless, orlistat reduces LDL cholesterol exceeding the MID, which might favour its use in those with hyperlipidaemia. Metformin and SGLT2 inhibitors have been evaluated as weight-lowering candidates because of their effects on weight in people with diabetes.[8] However, in the present analysis, the weight-lowering effects of these drugs proved less than the MID threshold weight loss. Furthermore, metformin is associated with gastrointestinal adverse events and SGLT2 inhibitors increase the risk of genital infection and ketoacidosis.[42,43]

In conclusion, phentermine–topiramate and GLP-1 receptor agonists proved among the best for weight-lowering effects in adults with overweight and obesity as an adjunct to lifestyle modification. Semaglutide, in a post-hoc analysis, showed appreciably greater weight loss than the other investigated drugs. Phentermine–topiramate and naltrexone–bupropion result in the most adverse events. The moderate or high certainty evidence for most comparisons mandates the confident application of these findings as guides for clinical practice.

Contributors

QS, YWa, SL, QH, JL, HT, POV, and GG conceived and designed the study. QS, YWa, ZJ, SZhu, CW, FQ, YWu, XZo, and ZC screened and selected the articles. ZC, YS, KN, SZha, XZo, XZh, ZQ, YL, and KC extracted the data. QS, YWa, and SX assessed the risk of bias. QS analysed the data. LG and FS supervised the data analyses. QS and YWa rated the certainty of evidence. QS, SL, QH, HT, GG, and POV interpreted the data. QS, SL, GG, and POV drafted the manuscript. QS, SL, GG, POV, LG, FS, LL, JY, and YH contributed to revising the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

SL received grants from the Sichuan Science and Technology Program (grant numbers 2019YFS0305 and 2019YFH0150). All other authors declare no competing interests.

Data sharing

The analytic dataset is available on request by contacting the corresponding author.

Acknowledgments

This study was supported by West China Hospital of Sichuan University (1.3.5 Project for Disciplines of Excellence, grant numbers ZYGD18022 and 2020HXF011). We thank the guideline panel members of West China Rapid Recommendation for Weight-lowering Pharmacotherapy in Adults for forming and reviewing the protocol of this study and their perceptive recommendations: Yan Bi, Jinhan He, Wen Hu, Ming Liu, Shuangqing Li, Shuyi Liu, Xin Liao, Xuejun Li, Yao Li, Li Yuan, Qi Pan, Dong Wei, Xinling Wang, Yang Xiao, Yan Yang, Guixiang Zhang, Jian Zhou, Qiu Zhang, Yanhua Zhu, Zhiming Zhu.

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