Effectiveness of pharmaceutical interventions on clinical outcomes in obesity

Technical Report

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Summary table

Title	Semaglutide for the treatment of overweight and obesity: A review	Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes	Screening for and Management of Obesity in Adults: U.S. Preventive Services Task Force Recommendation Statement
Authors	Bergmann et al, 2022	Rubino et al. 2022	Shi et al. 2022
Type of study	SR review of STEP trial RCTs	RCT	Meta-analysis of n = 54 RCTS
Outcome Variable	Primary outcome = % weight loss Mean weight difference in kg weight reported	Primary outcome = % weight loss Mean weight difference in kg weight reported	Primary outcome % body weight change
Treatment	2.4 mg Semaglutide weekly for 68 weeks plus standard behavioural interventions	3.0 mg Liraglutide once daily for 68 weeks, plus standard behavioural interventions	Orlistat plus lifestyle modification, duration not reported in paper
Control	Placebo	Comparator = 2.4 mg Semaglutide, and Placebo	Lifestyle modification alone or lifestyle plus placebo
Magnitude of effect (adults)	Mean body weight change== -15.83%	Mean body weight change –6.4% with liraglutide after 68 weeks, -6.8 kg mean weight loss difference	Mean body weight change = = -3.16% (-3.53, -2.78)

	-13.70kg mean weight loss difference		
Magnitude of effect (children)	n/a	n/a	n/a

Background

Obesity is a chronic disease of multifactorial aetiology which affects more than 650,000 adults worldwide (WHO, 2016). In England, about 26% of adults (16 +) live with obesity (i.e., BMI of 30 or above) and approximately 38% are overweight (Health Survey for England, 2021). Although lifestyle modification interventions (e.g. diet modification, physical activity) are the mainstay for the treatment of obesity, pharmaceutical interventions are becoming increasingly important in the clinical management of this disease.

The National Health Service (NHS) has sanctioned three specific weight loss medications—Orlistat, Liraglutide, and Semaglutide—as safe options for combating obesity in the UK. Orlistat aids weight loss by blocking the absorption of dietary fats in the digestive system whereas Semagutide and Liraglutide belong to the GLP-1 agonist category of drugs which mimic the action of the hormone glucagon-like peptide -1 to promote satiety, slow gastric emptying, and reduce food intake, aiding in weight reduction. Although there are slight variations in licensing requirements among these drugs, they are typically prescribed to individuals with a Body Mass Index (BMI) of ≥28 (more commonly ≥35) who have previously made significant but unsuccessful efforts to lose weight through lifestyle interventions such as diet modification or physical activity. A fourth drug Tirzepatide, glucose-lowering medication that stimulates both glucose-dependent insulinotropic polypeptide (GIP) and (GLP)-1 receptors, was approved for the treatment of type 2 diabetes and not obesity in the UK in 2023 and will be made available to patients at some point during 2024.

Objectives

The objective of this report is to summarise the best available evidence of the effectiveness of NHS approved pharmaceutical weight loss interventions on clinical outcomes for adults living with obesity.

Method

We used a rapid review protocol developed by Nesta to identify and synthesise the review that was reflective of the best evidence, based on (a) suitability to the research question, (b) year published and (c) quality of review as judged by Joanna Briggs Institute (JBI) critical appraisal checklist.

However, in rapidly evolving fields like pharmacological interventions for obesity, recent reviews or meta-analyses may not include the latest evidence on drug efficacy. In such cases, we rely on guidance from our Expert Advisory Group to select recent trials for the most comprehensive review of the latest evidence.

Eligibility criteria

Types of Review. To be eligible for inclusion papers were required to use a systematic review methodology (i.e., use of systematic search and inclusion strategy to identify all available studies) and include quantitative or qualitative data synthesis (e.g., meta-analysis) of multiple studies that examined the effect of drugs in weight-loss in individuals with obesity. If the search does not identify any source where a meta-analysis has been conducted, we will include reviews with narrative synthesis.

Participants: To be eligible for inclusion, reviews were required to examine the effect of surgical drug interventions in adults (>18y old) of any age with overweight or obesity.

Intervention: Medications used in obesity targeting weight management in the categories of Fat absorption reducers, appetite suppressants and glucagon-like

peptide-1 (GLP-1) agonists (Table 1.). Multicomponent interventions will only be included if they report the effects of the individual components of the intervention.

Table 1. Medications included in the search strategy.

Category/ Purpose	Medication
Reduction of fat absorption	Orlistat
	Cetilistat
Appetite suppression	Phentermine-topiramate
	Bupropion-naltrexone
	Cagrilintide (amylin analogue)
	Phentermine
	Benzphetamine
	Diethylpropion
	Phendimetrazine
	Phenylpropanolamine
	Satietin
	Sibutramine
	Phenmetrazine
	Rimonabant
Agonist of GLP1	Semaglutide
	Dulaglutide
	Tirzepatide
	Liraglutide

Comparator: Authors did not restrict inclusion by the comparator group. For reviews of randomised controlled trials, the comparator may be a placebo, no intervention, or other intervention (behavioural or pharmacological). For reviews of natural / quasi-experimental studies, a comparator group may be pre- versus post-intervention.

Outcomes. The main outcome of interest is weight change. To be eligible for inclusion, reviews must include a clinical measure of weight [e.g., mean difference in the following variables: weight, BMI, waist circumference, percentage of excess weight loss (percentage of weight lost over a BMI 25 kg/m^2)].

Information sources and article selection

The search strategy was designed to identify systematic reviews published between the year 2010 and the date of the search. Initial keywords were identified through scoping relevant papers (Rodgers et al. 2012, Kang et al. 2012, Chakhktoura et al. 2023), and reports as well as via MEDLINE using the MeSH function. A search was performed in MEDLINE and Cochrane database of systematic reviews (see Appendix 1 for search strategy) using MeSH terms and free text. Grey literature was searched using Google and Google Scholar (limited to the first 10 pages) to identify relevant reports. The search was run on May 18th, 2023.

Screening

Due to the rapid nature of the reviews, a single reviewer screened titles and abstracts and discussed any uncertainty with a second reviewer. For relevant titles/abstracts, the full text was retrieved for full-text review. One reviewer reviewed the full texts and discussed uncertainties with a second reviewer.

Assessment of methodological quality

The systematic reviews that included a quantitative synthesis of the effectiveness of pharmaceutical interventions on clinical outcomes relevant to individuals with obesity were considered for inclusion. The quality of reviews was appraised by one reviewer and verified by a second reviewer using the JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses (Appendix 2). Each study was allocated a final score out of 10.

If more than one review was identified, we selected the review that better answered our research question. If multiple reviews were identified, we selected the highest

quality and up-to-date review for data extraction. Where no single review captured the most comprehensive or up-to-date data on promising drugs or those licensed for use in the UK, we draw on evidence from reviews of individual drugs or recently published high quality RCTs.

Data extraction

The JBI Data Extraction Form for Review for Systematic Reviews and Research Syntheses (see Appendix 3) was used for data extraction for the final review to be included. Characteristics to be attached to the review report included:

- Review characteristics: author/year, objectives, participants (characteristics, total number), setting/context, interventions of interest, date range of included studies, detailed description of the included studies (number/ type/ country of origin of included studies), appraisal instrument and rating, type of review/method of analyses and outcomes.
- Results: findings of the review and comments.

Results

A total of 4,409 articles were identified through databases including PubMed and Cochrane. Grey literature searches identified an additional 38 articles. After removing duplicates (N=675), the total number of articles was 3,772, which underwent the screening phase. This led to the exclusion of 3,591 titles and 28 abstracts. Subsequently, 153 full-text articles were assessed for eligibility, of which 150 were excluded. Ultimately, 3 articles were selected.

Three systematic reviews were subjected to critical appraisal after a full-text review (Siebenhofer *et al.*, 2016, Siebenhofer *et al.*, 2021, Shi *et al.*, 2021). Since the reviews

by Siebenhofer *et al.* focused on individuals with hypertension, the findings of a review by Shi et al. (2021), were most suited to addressing our research question.

However, while Shi et al.'s (2021) review stood out as the most comprehensive review to date, it was nonetheless constrained in its ability to fully elucidate the efficacy of pharmacological treatment for obesity. This limitation stemmed from the omission of the latest data from trials of GLP-1 agonist Semaglutide from the STEP trials, whose recent findings demonstrate some of the highest efficacy among all drugs tested so far. It also omitted recent evidence from the SURPASS and SURMOUNT trials of Tirzepatide, which acts as a glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist and trialled as a weight loss medication amongst patients with obesity both with and without diabetes. Instead of reporting full findings from Shi et al we report on selected effect sizes on weight loss from their analysis supplemented by more recent published findings from STEP and SURPASS and SURMOUNT drug trials referred to above.

Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials (Shi et al. 2021)

Shi *et al.* (2021) systematically reviewed randomised controlled studies exploring the effect of weight loss drugs on body weight. They conducted a network meta-analysis, in which network nodes included all drugs within a specific drug class in order to allow indirect and direct comparisons between relative efficacy of different drugs. Cardiometabolic health outcomes and adverse events in adults with overweight and obesity were also assessed in this paper but are not discussed further here.

Which studies did the review include?

Participants**:** Adults aged 18 years and older, with overweight or obesity (BMI cut offs were not specified). Inclusion was irrespective of comorbidities.

Intervention**:** Lifestyle modification plus an approved or candidate drug for weight management, including phentermine/topiramate, GLP-1 receptor agonists, naltrexone/bupropion, orlistat, metformin, levocarnitine, SGLT2 inhibitors, and pramlintide.

Comparators: Behavioural or lifestyle modification alone with or without placebo or an alternative active drug.

Outcomes **:** A range of weight-related outcomes, of which the following was of most interest to the current research question; percentage body weight change from baseline to end of follow-up. Other outcomes not detailed here were assessed, but for the purposes of the current resort we focus on outcomes related to weight loss only.

Design**:** *n= 143 randomised* controlled trials were included in the review .

Duration: Minimum 12 weeks follow-up

What were the systematic review methods?

Statistical Analysis: The review employed network meta-analysis only, which 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. Network nodes included all drugs in a particular drug class. 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. Heterogeneity between studies was estimated using the DerSimonian-Laird random-effects model and global and local heterogeneity was evaluated with generalised Cochran's Q. The risk of bias of individual studies was assessed using the revised Cochrane risk-of-bias tool for randomised trials (ROB 2). Publication bias was explored using four methods: comparison-adjusted funnel plots, Egger's regression test, Begg's rank test, and a

method that relaxes distributional and asymptotic assumptions, in whi:ch the calculations are based solely on point estimates instead of variance estimates.

What did the review find?

This is a non-exhaustive summary of the review findings. Please see the original article for more detail missing here.

The review included RCTs for the following drugs or classes of drugs: Phentermine/Topiramate, GLP-1 receptor agonists, Naltrexone/Bupropion, Orlistat, Metformin, Levocarnitine, SGLT2 inhibitors, Pramlintide.

All investigated drugs, except levocarnitine reduced body weight with moderate certainty evidence, with phentermine-topiramate and GLP-1 receptor agonists reported to have the best effect (Table 2). A post hoc analysis suggested a GLP-1 receptor agonist was associated with the greatest reduction in percentage bodyweight and a higher likelihood of weight loss by 5% or more in patients without diabetes. Subgroup comparisons revealed that among the three GLP-1 agonists effects were largest for Semaglutide. Semaglutide was associated with a −11·41% (−12·54 to −10·27) reduction in body weight between baseline and end of follow up compared to Liraglutide which was associated with -4·68% (−5·30 to −4·06)) and Exenatide a −3·72% (−4·82 to −2·62) reduction in body weight.

Table 2. Characteristics of findings of post-hoc analysis by Shi et al. 2021 network meta-analysis on body weight outcomes by drug intervention

Intervention	No. of studies	Total sample size	Mean difference percent weight change (95% confidence interval)
Percent body weight change from baseline			
Phentermine/Topiramate	5	3407	MD -7.97 (-9.28, -6.66)

GLP-1 receptor agonists	24	11084	MD -5.76 (-6.30, -5.21)
Naltrexone/Bupropion	6	9949	MD -4.11 (-5.19, -3.02)
Orlistat	57	16964	MD -3.16 (-3.53, -2.78)
Metformin	13	3234	MD -2.50 (-3.25, -1.74)
Levocarnitine	2	512	MD -1.88 (-3.8, 0.04)
SGLT2 inhibitors	10	2076	MD -2.07 (-3.01, -1.13)
Pramlintide	2	242	MD -2.19 (-4.36, -0.03)

Bergman et al. (2023)- Semaglutide for the treatment of overweight and obesity: A review,

Regarding drugs currently available on the NHS, although Shi et al captures the most current evidence on the impact of Orlistat, more up to date evidence is available on Semaglutide, Liraglutide (both GLP-1 agonists) and Tirzpepatide (dual GLP-1/GIP receptor co-agonist).

Bergman and colleagues conducted a comprehensive review of the Semaglutide Treatment Effect in People with Obesity (STEP) clinical trial program and this review reports the most current evidence on Semaglutide. The STEP program evaluated the effectiveness of weekly injections of 2.4 mg Semaglutide in promoting weight loss among patients with a body mass index (BMI) of 30 or higher, or a BMI of 27 or higher with at least one obesity-related health issue. The review encompasses findings from six separate trials, each involving participants with or without diabetes depending on the specific trial's criteria.

In phase 1 of the study, STEP 1 (n =1961), individuals were randomly divided into two groups: one receiving once-weekly subcutaneous injections of semaglutide 2.4 mg, while the other received a comparable placebo over a period of 68 weeks. All patients also received an accompanying lifestyle intervention. For all trials except

STEP 3, lifestyle intervention = reduced calorie diet (500 kcal/day deficit relative to estimated energy expenditure) and increased physical activity (150 min/week). The Step 4 trial featured a more intensive lifestyle intervention with significantly larger calorie deficits and physical activity. After this duration, treatments, including lifestyle interventions, were stopped, and a subsequent off-treatment extension phase followed a selected subset of participants for an additional year. See table 3 for details of all six trials.

Results

Across STEP 1, 3, 4 and 8 trials, 2.4 mg semaglutide was associated with mean % body weight losses of 14.9-17.4% in individuals with overweight or obesity and without type 2 diabetes from baseline to week 68. In STEP 5, which examined longer term administration, mean weight loss was 15.2% with semaglutide 2.4 mg versus 2.6% with placebo from baseline to week 104. In STEP 2 (individuals with overweight or obesity, and type 2 diabetes), mean weight loss was 9.6% with semaglutide 2.4 mg versus 3.4% with placebo from baseline to week 68. See Table 3 for treatment differences for mean % weight loss and mean body weight loss for each trial.

Testing Semaglutide against Liraglutide

Rubino et al (2020) reported on the STEP 8 trial in which Semaglutide was trialled against Liraglutide. The trial lasted 68 weeks, and all participants also received standard behavioural interventions (diet and exercise). Participants were randomly allocated (3:1:3:1) to receive once-weekly injections of 2.4 mg semaglutide (16-week escalation; n = 126), or matching placebo, or once-daily subcutaneous liraglutide, 3.0 mg (4-week escalation; n = 127), or matching placebo.

Of the 338 participants randomised to groups, 319 (94.4%) successfully completed the trial, and 271 (80.2%) finished the treatment. The average weight change from

baseline was –15.8% with semaglutide compared to –6.4% with liraglutide (difference of –9.4 percentage points [95% CI, –12.0 to –6.8]; $p < .001$); whereas the weight change with the combined placebo group was –1.9%. The weight loss difference between the two active drugs was -6.8 kg in favour of Semaglutide.

Table 3 Step trials (description and impact on bodyweight)

	STEP 1 Weight management only	STEP 2 Weight management in T2 diabetes	STEP 3 Weight management + intensive behavioural IV	STEP 4 Sustained weight management	STEP 5 Two-year weight management	STEP 8 Semaglutide vs. liraglutide
Randomised and treatment arms	Semaglutide 2.4 mg vs. placebo 2:1 ratio	Semaglutide 2.4 mg Semaglutide 1.0 mg Placebo 1:1:1 ratio	Semaglutide 2.4 mg vs. placebo 2:1 ratio	All get semaglutide for 20 weeks. Then semaglutide 2.4 mg vs. placebo 2:1 ratio	Semaglutide 2.4 mg vs. placebo 1:1 ratio	Semaglutide 2.4 mg vs. placebo vs. liraglutide 3.0 mg vs. placebo 3:1:3:1 ratio
N	1961	1210	611	902 enrolled; 803 randomised	304	338
Population (all adult)	BMI ≥30, or BMI ≥ 27 with ≥1 comorbidity, and no diabetes	BMI 27 and type 2 ≥ diabetes, with HbA1c 7.0%b 10.0%	BMI ≥30, or BMI ≥ 27 with ≥1 comorbidity, and without diabetes	BMI ≥30, ≥ or BMI ≥ 27 with ≥1 comorbidity, and a without diabetes	BMI ≥30, or BMI ≥27 with ≥1 comorbidity, and a without diabetes	BMI ≥30, or BMI ≥27 with ≥1 comorbidity, and a without diabetes
Duration	68 weeks	68 weeks	68 weeks	68 weeks (randomised into 2 arms after 20 weeks)	104 weeks	68 weeks
% change in body weight	-12.4	2.4mg vs 1.0mg = -2.7	-10.3	-14.8	-12.6	-9.4 in favour of Semaglutide

Treatment difference		2.4 mf vs placebo = -6.2				
Weight change Treatment difference (kg)	-12.7	2.4mg vs 1.0mg = - -2.7 2.4mg vs placebo = -6.1	-10.6	-13.2	-12.9	-8.5 in favour of Semaglutide

Sinha et al. (2023): Efficacy and Safety of Tirzepatide for Type 2 Diabetes and Obesity Management

Tirzepatide is an NHS approved treatment for type 2 diabetes mellitus (T2DM), but is not currently listed as an approved drug for weight management in patients without diabetes.

Sinha et al (2023) have summarised the results of the SURMOUNT AND SURPASS trials of Tirzepatide for obesity management in patients with and without T2DM. Across seven SURPASS trials running from 40 to 104 weeks, Tirzepatide was assessed for safety and efficacy in people with T2DM. Once weekly Tirzepatide at doses of 5 to 15 mg led to reductions in body weight by between 5.4 and 12.9 kg respectively. Comparisons were against placebo and other commonly used glucose-lowering medications, including lower dosage of semaglutide 1 mg.

The SURMOUNT-1 trial assessed the efficacy of Tirzepatide for impact on weight loss in individuals BMI ≥ 30 or ≥ 27 with comorbidities [hypertension/dyslipid-emia/obstructive sleep apnoea/cardiovascular disease]. Trial duration was 72 weeks with n = 2,539 participants randomly allocated to one of 4 treatment arms (ratio 1:1:1:1). Trial participants receiving once-weekly subcutaneous Tirzepatide at doses of 5, 10, or 15 mg lost an average of 15.0%, 19.5%, and 20.9%, respectively, compared with just 3.1% in people taking placebo.

Appendix 4. Characteristics all included studies by Shi et al. 2021 meta-analysis on body weight outcomes by drug intervention

Intervention	Number of studies	Country	Total sample size	Sample size range	Age range
Percent body weight change from baseline					
Phentermine/Topiramate	5	US	3407	45-1989	42-52
GLP-1 receptor agonists	24	-	11084	-	-
Naltrexone/Bupropion	6	US	9949	148-5843	40-61
Orlistat	57	-	16964	-	-
Metformin	13	-	3234	-	-
Levocarnitine	2	Italy	512	254-258	51-54
SGLT2 inhibitors	10	-	2076	-	-
Pramlintide	2	US	242	118-124	42-27
Percent body weight reduction ≥5					
Phentermine/Topiramate	5	US	3407	45-1989	42-52
GLP-1 receptor agonists	15	-	10433	-	-
Naltrexone/Bupropion	6	US	4348	-	-
Orlistat	26	-	13751	-	-
Metformin	2	-	2198	-	-
SGLT2 inhibitors	10	-	2076	-	-
Pramlintide	2	US	242	118-124	42-47
Percent body weight reduction ≥10					
Phentermine/Topiramate	5	US	3337	45-1989	42-52
GLP-1 receptor agonists	15	-	10433	-	-
Naltrexone/Bupropion	6	US	4348	-	-
Orlistat	26	-	13751	-	-
Metformin	2	-	2198	-	-
SGLT2 inhibitors	3	-	1260	-	-
Pramlintide	2	US	242	118-124	42-47

Note: Data was extracted to match the total number of studies and total sample size according to the results presented in Table 2. The dash symbol (-) indicates that cross-referenced information did not match.