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# Drug Effectiveness Review Project Summary Report – Pharmacologic Agents for Weight Management

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**Plain Language Summary:**

- Medicines can help people lose weight. The Food and Drug Administration has approved medicines be prescribed along with increased physical activity and diets to promote healthy eating and decrease calories.
- Medicines studied for weight loss include semaglutide, liraglutide, tirzepatide, exenatide, orlistat, setmelanotide, combination phentermine and topiramate (phen/top), and combination naltrexone and bupropion. Compared to a sugar pill (placebo), medicines had 11 to 26.4 pounds of weight loss in people that were overweight or obese. Semaglutide, liraglutide and phen/top also decreased weight in children and young adults (ages 10-18 years).
- Side effects that commonly occur with weight loss drugs include nausea, diarrhea and vomiting.
- Several organizations make recommendations for weight management:
    - The National Institute for Health and Care Excellence recommends liraglutide and semaglutide for patients who are overweight with other medical conditions or are obese. Patients must also be willing to participate in healthy eating and exercise programs.
    - The Veterans Administration/Department of Defense suggests that liraglutide, naltrexone/bupropion, orlistat, and the combination product phentermine and topiramate can be considered as options for people that need to lose weight because these medicines caused more weight loss compared to placebo.
    - The American Diabetes Association recommends that people with type 2 diabetes be treated with medicines such as semaglutide and tirzepatide because they lower blood sugar levels and also cause weight loss.
    - The American Pediatric Association recommends diet and exercise for children and adolescents that are overweight. Medicines to lower weight may be an option in children 12 years and older.
- Semaglutide studies show that cardiovascular deaths, such as heart attacks and strokes, are reduced by 1.5% in some people that have heart disease and are overweight.
- The Oregon Health Plan does not currently pay for weight loss medicines for most members. The Drug Research and Management Group recommends that the Oregon Health Authority (OHA) evaluate the costs of medicines used for weight loss and secure funds before paying for these medicines.

**Purpose of the Review:**

Drugs for weight management are currently an optional benefit for Medicaid programs and are not covered for most members. Coverage under the Early Periodic Screening and Treatment (EPSDT) program can be considered with individual review for members who are less than 21 years of age. The purpose of this review is to evaluate effectiveness, safety, and comparative evidence for weight management agents to assist evaluation of coverage by the Oregon Health

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Authority. This review will describe populations for which weight management agents have been studied, available comparative evidence of clinical efficacy and safety between agents, and coverage recommendations from various guidelines.

**Current Status of PDL Class:**
Drugs used for weight loss are currently not covered by Oregon Medicaid and are exempt from the requirement for coverage under Federal Law. Coverage under the Early Periodic Screening and Treatment (EPSDT) program can be considered with individual review for members who are less than 21 years of age. See **Appendix** 1 for drugs with indications for weight management.

**Research Questions:**
1. What is the evidence for efficacy and harms for the use of weight loss therapies in adults, children and adolescents for important outcomes such as weight loss, weight-related comorbidity benefits (e.g., HbA1c, cardiovascular benefits), and durability of weight loss?
2. Are there subgroups of people that would specifically benefit or be harmed by weight management therapies (e.g. BMI, comorbidities)?

**Conclusions:**
- The 2023 report on weight management by the Drug Effectiveness Review Project (DERP) was the primary evidence source for this review. The DERP Reports are not clinical guidelines but provide comparative clinical effectiveness between efficacy and harms of medications used for weight management. Evidence presented in the DERP Reports serve as a high-quality evidence. Primary literature included in the DERP Report are summarized below. The DERP Report considered youth participants as those 10 to 18 years. Eight high-quality guidelines, one new drug approval, and 5 randomized controlled trial (RCTs) were identified with a supplemental literature search through January 8, 2024.
- Drugs approved by the Food and Drug Administration (FDA) for weight loss include liraglutide, semaglutide, tirzepatide, bupropion/naltrexone and phentermine/topiramate. Background therapy with diet and exercise or intensive behavioral therapy is recommended for all agents.[1]
- Outcomes evaluated by the Drug Effectiveness Review Project (DERP) included weight loss, CV risk factors (e.g., systolic blood pressure, low density lipoprotein [LDL] levels and hemoglobin A1c [HbA1c]).
- Weight loss
    - Clinically meaningful weight loss (e.g., ≥5% decrease in BMI compared to placebo) in adults was demonstrated with tirzepatide (ARR 53%/NNT 2; moderate quality of evidence), semaglutide (ARR 49%/NNT 2; low quality of evidence), liraglutide (ARR 33%/NNT 3; low quality evidence) and phentermine-topiramate (ARR 47%/NNT 2) low quality of evidence) when compared to placebo.[1]
    - There was moderate quality of evidence that exenatide caused more weight loss compared to glyburide in adults with T2DM who are overweight.[1]
    - Liraglutide and naltrexone-bupropion, compared to placebo, demonstrated statistically significant reductions in body weight in adults; however, changes were not considered clinically meaningful.[1]
    - Tirzepatide, at 5 mg, 10 mg or 15 mg SC weekly, resulted in a greater reduction in BMI compared to placebo at 72 weeks (-15% to -20.9% vs. -3.1% for placebo; moderate quality evidence).[2]
    - In people with T2DM and obesity, tirzepatide 10 mg and 15 mg weekly reduced weight by -12.8% to -14.7% compared to -3.2% with placebo over 18 months (moderate strength evidence).[3];
    - In adult patients who had lost 5% or more of body weight with lifestyle modifications, tirzepatide 10 mg or 15 mg SQ weekly, was more effective than placebo at reducing weight and the percentage of patients achieving 5% or more weight loss at 72 weeks, based on moderate quality evidence.[4]

- Evidence for weight loss drugs studied by DERP in youth (ages 10-18) were identified for liraglutide, semaglutide, exenatide, phentermine-topiramate and setmelanotide.[1] All therapies studied demonstrated clinically significant weight loss in youth with the exception of exenatide. The evidence for semaglutide demonstrated the most weight loss with a reduction of -16.7% in BMI based on moderate evidence.[1]

- CV risk factors
  - Beneficial effect of weight management therapies on CV risk factors (e.g., blood pressure, LDL levels and HbA1c) was not consistently demonstrated.[1]
  - Changes in indirect outcomes (e.g., LDL levels and systolic blood pressure [SBP]) were decreased statistically, but not clinically, more than placebo in adult patients treated with liraglutide, semaglutide and phen/top.[1] There were statistically and clinically significant decreases in HbA1c in adult patients that were overweight or obese treated with semaglutide, liraglutide, and naltrexone-bupropion. Studies demonstrating HbA1c reductions enrolled patients with T2DM.[1]
  - In youth 10 to 18 years of age, only semaglutide produced clinically significant changes for reduction in HbA1c levels compared to placebo.[1]
- Morbidity and mortality
  - Conclusive benefit on reduction in morbidity (e.g., prevention or improvement in weight related co-morbidities) and mortality has not been established due to lack of long-term evidence.
  - There is moderate strength of evidence that semaglutide reduces the risk of death from CV causes, nonfatal myocardial infarction (MI) or nonfatal stroke, compared to placebo, in adults with CV disease and who are overweight(e.g., a BMI of least 30 $kg/m^2$ or at least 27 $kg/m^2$ with bodyweight-related complications and comorbidities, without T2DM).[5] Sixty-seven people would need to be treated for 3.3 years to prevent one CV event (absolute risk reduction [ARR] 1.5%/number needed to treat [NNT] 67).[5] Seventeen percent of patients discontinued semaglutide due to adverse events compared to 8% of patients taking placebo ($p<0.001$) (mean duration of follow-up was 39 months).
- Safety
  - Withdrawals due to adverse events (AE) were higher than placebo in patients treated with liraglutide (RR 2.20), semaglutide (RR 1.81) , phen/top (1.88) and bupropion/naltrexone (1.92).[1] Common AE experienced with liraglutide, semaglutide, tirzepatide, and exenatide were gastrointestinal (e.g., nausea, diarrhea). Phen/top is associated with dizziness, insomnia, dry mouth and increased heart rate. Adverse reactions experienced with naltrexone/bupropion are nausea, constipation, insomnia and vomiting. Naltrexone/bupropion should not be used in those with uncontrolled hypertension (HTN) or chronic opioid use.
  - There is moderate strength of evidence that patients who continued on treatment, after a 36 week open-label lead-in period followed by a 52-week, double-blind, placebo-controlled trial, maintained larger weight loss reductions compared to placebo.[6] Two-percent of patients discontinued treatment due to adverse reactions related to tirzepatide compared to 1% of placebo treated patients. The lead-in period likely contributed to the low rates of discontinuations.[63] In an 18 month study of tirzepatide in people with T2DM and obesity, discontinuation rates were 9% to 14% in patients treated with tirzepatide compared to 15% for placebo.[3]
- Guideline recommendations
  - The National Institute for Health and Care Excellence (NICE) recommend semaglutide and liraglutide for weight management in adults who meet specific criteria based on BMI and comorbidities (e.g., based on recommendations from 2023 and 2020, respectively.[7,8] Pharmacotherapy should be taken in conjunction with a weight management behavioral lifestyle program. Naltrexone/bupropion is not recommended for weight management by NICE.[7–9]
  - A 2020 Veterans Administration (VA)/Department of Defense (DOD) guideline found moderate quality evidence that liraglutide, naltrexone/bupropion, orlistat, and phen/top caused more weight reduction than placebo. The VA/DOD suggests pharmacotherapy, with lifestyle

modifications, for adults who are overweight or obese and meet clinical criteria (e.g., BMI specifications and weight related comorbidities) (weak recommendation).[10]
    - The Canadian Agency for Drugs and Technologies in Health (CADTH) reviewed semaglutide for weight management in 2022, prior to the release of evidence demonstrating CV benefits of semaglutide in select populations.[11] They recommended against use of semaglutide for weight management.
    - The Institute for Clinical and Economic Review (ICER) evaluated drugs approved for weight management (e.g., semaglutide, liraglutide, phen/top, and bupropion/naltrexone) compared to lifestyle interventions in 2022.[12] The evidence is graded by assessing the certainty and magnitude of benefit. Recommendations are rated from "A" (superior – high certainty of a substantial net health benefit) to "I" (insufficient – level of certainty in the evidence is low).[13] Semaglutide and liraglutide were given a B+ and B rating for evidence of comparative effectiveness to lifestyle modifications, respectively. Phen/top and bupropion/naltrexone received a C++ and C+ rating, respectively.[12]
    - In guidance from 2024, The American Diabetes Association (ADA) strongly recommends that adults who are overweight or obese with type 2 diabetes mellitus (T2DM) be treated with a glucagon-like peptide-1 receptor agonist (GLP-1 RA) or glucose-dependent insulinotropic polypeptide receptor agonist (GIP RA). Recommendations were to use drugs with evidence of the largest weight reduction, such as semaglutide and tirzepatide.[14]
    - The American Pediatric Association (APA) recommends intensive health and behavior modifications for children and adolescents who are overweight (BMI $\geq 85^{th}$ to $<95^{th}$ percentile for age and sex), obese (BMI $\geq 95^{th}$ percentile) and severely obese (BMI $\geq$120% of the $95^{th}$ percentile) in guidance released in 2023.[15] APA recommends offering pharmacotherapy to those children who are obese, in addition to lifestyle changes, in those 12 and older based on level B evidence.[15]
- Tirzepatide received FDA approval in November of 2023 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of 30 $kg/m^2$ or greater (obesity) or 27 $kg/m^2$ or greater (overweight) with at least one weight-related condition (e.g., hypertension, dyslipidemia, T2DM, obstructive sleep apnea or CV disease).[16]
- There is a lack of evidence on weight changes upon discontinuation of therapy, optimal duration of use and conclusive benefit on weight related comorbidities (e.g., SBP changes, LDL changes and reduction in adverse CV outcomes). All medications were studied in conjunction with lifestyle modification programs. Studies are limited by a higher number of female participants and high attrition rates in most medication management trials.

**Recommendations:**

- Recommend the Oregon Health Authority (OHA) perform a budgetary analysis and identify a funding plan before opening up coverage for weight management drugs. Draft prior authorization (PA) criteria for adults will be presented to the committee to inform future steps.
- Recommend implementation of PA criteria for members who qualify for coverage under the Early Periodic Screening Diagnostic and Treatment (EPSDT) Program.
- Weight management pharmacotherapy should be used in conjunction with diet and lifestyle modifications (e.g., reduction in daily calorie of approximately 500 kcals, and physical activity of at least 150 minutes weekly).
- Recommend the OHA evaluate and establish clinically appropriate minimum standards for required lifestyle modification.

**Methods:**

The October 2023 drug class report on Pharmacological Agents for Weight Management: Clinical Evidence and Management Strategies by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

**DERP Summary Findings:**

A recent report from DERP evaluated the risks and benefits of the use of pharmacotherapy to assist in weight management.[1] Lifestyle modifications are recommended first line for weight loss, but often individuals who are overweight require assistance in obtaining and maintaining long term weight loss. Six drugs are FDA approved for chronic weight loss management. The DERP report focuses on drugs used for management of weight loss for adults and children who are overweight (BMI of 25 to up to 30 kg/m$^2$) or obese (BMI of 30 kg/m$^2$ or greater). FDA approved drugs for weight management were included in the review.[1] Studies had to be at least 12 months in duration to be included, with the exception of studies enrolling pediatrics and people with type 1 diabetes mellitus (T1DM), which needed to be 6 months or longer. There were no restrictions on study length for setmelanotide. Forty-four studies were identified from a literature search through February 2023, 36 of which were used to evaluate effectiveness and harms (**Table 1**).[1] All studies had conflicts of interest with funding provided by industry. Comparators included lifestyle modifications, active treatment comparisons, surgery or other interventional procedure or devices. Studies that met inclusion criteria included comparators to placebo, liraglutide, glyburide and usual care.[1]

**Table 1. Therapies for Weight Loss Included in the DERP Review**[1]

| Drugs | Dose | Studies Included in the DERP Report | FDA Approved Indication in Adults | FDA Approved for Weight Loss in Youth |
|---|---|---|---|---|
| **GLP-1 RAs** | | | | |
| Liraglutide (SAXENDA) | 0.6, 1.2, 1.8, 2.4 or 3.0 mg SC daily | 14 | Weight Loss | Ages 12 and older |
| Semaglutide (WEGOVY) | 0.25, 0.5, 1.0, 1.7 or 2.4 mg SC weekly | 8 | Weight Loss | Ages 12 and older |
| Dulaglutide (TRULICITY) | 0.75, 1.5, 3.0 or 4.5 mg SC weekly† | 0 | T2DM | Not studied; approved for youth for T2DM who are 10 years of age and older |
| Exenatide (BYETTA AND BYDUREON BCISE) | BYETTA: 5 or 10 mcg SC twice daily<br>BYDUREON BECISE: 2 mg SC weekly | 3 | T2DM | Off-label; approved for youth for T2DM who are 10 years of age and older |
| Liraglutide (VICTOZA) | 0.6, 1.2 or 1.8 mg SC daily | 0 | T2DM | Off-label; approved for youth for T2DM who are 10 years of age and older |
| Lixisenatide (ADLYXIN) | 10 or 20 mcg SC daily | 0 | T2DM | Not studied; not approved for use in youth for T2DM |
| Semaglutide (OZEMPIC AND RYBELSUS) | OZEMPIC: 0.25, 0.5, 1.0 or 2.0 mg SC weekly<br>RYBELSUS: 3, 7 or 14 mg orally daily | 0 | T2DM | Off-label; not approved for use in youth for T2DM |
| **GLP-1 RAs and GIP RA** | | | | |

| | | | | |
|---|---|---|---|---|
| Tirzepatide (ZEPBOUND)* | 2.5, 5.0, 7.5, 10.0, 12.5 or 15 mg SC weekly | 0 | Weight Loss | Not studied; not approved for use in youth for T2DM |
| Tirzepatide (MOUNJARO) | 2.5, 5.0, 7.5, 10.0, 12.5 or 15 mg SC weekly | 1 | T2DM | Not studied; not approved for use in youth for T2DM |
| **Misc. Agents** | | | | |
| Naltrexone-bupropion (CONTRAVE) | 4 tablets (32 mg + 360 mg) orally daily (available as 8 mg/90 mg tablets) | 5 | Weight Loss | Not studied |
| Phentermine-topiramate (QSYMIA) | 4 capsules (15 mg + 92 mg) orally daily (available as 3.75 mg/23 mg, 7.5/ 46 mg, 11.25 mg/69 mg, 15 mg/92 mg) | 3 | Weight Loss | Ages 12 and older |
| Setmelanotide (IMCIVREE) | 3.0 mg SC daily | 1 | Weight Loss – for obesity caused by genetic conditions | Ages 6 and older |
| Orlistat (XENICAL, ALLI) | XENICAL: 120 mg orally three times daily<br>ALLI: 60 mg orally up to 3 times daily | 0 | Weight Loss | Not studied |
| Key: * Not included in DERP due to approval on 11/8/23 for weight loss. Included in table for completeness. † Not commonly used clinically due to undesirable adverse effects leading to high discontinuation rates. | | | | |
| Abbreviations: GIP RA = glucose-dependent insulinotropic polypeptide receptor agonist; GLP-1 RA = glucagon-like peptide-1 receptor agonist; SC = subcutaneous; T2DM = type 2 diabetes mellitus. | | | | |

Outcomes of interest evaluated in the report include body weight changes, proportion with a 5% or more weight loss, CV outcomes (e.g., stroke and MI), changes in related comorbidities (e.g., blood pressure, T2D), health related quality of life, mortality and adverse events.[1] In children and adolescents the conversion of BMI percentiles to z-scores are used for assessing longitudinal change in adiposity in youth with obesity.[15] The z-score is a statistical measure that describes a value to a population mean derived from the CDC Growth charts. The BMI expressed as a percentage (e.g., BMI percentile above the 95$^{th}$ percentile for the age and sex) is also another option for categorizing adiposity in youth. Minimal clinically important differences (MCID) for important outcomes are presented in **Table 2**.[1] Clinically meaningful changes related to therapy help to interpret efficacy findings; however, they should be interpreted in the context of patient population and other study variables.

**Table 2. Weight Loss Outcomes and Associated Minimal Clinically Important Differences**[1]

| Outcome | MCID |
|---|---|
| Percent change in body weight | 5% or more weight loss |
| Body Mass Index (BMI) z or standard deviation score (SD)* (BMI z/SD score)<br>- Measure of relative weight adjusted according to references standards for the age of the child (2 to 20 years) and sex<br>- Scores quantify a measurement's distance from the mean; often converted to percentiles | 0.15 to 0.25 or more units |
| Percent change in BMI | 5% or more loss of BMI |

| | |
|---|---|
| Systolic blood pressure | 5 mmHg or more reduction has been shown to reduce major CV events by 10% |
| Low-density lipoprotein (LDL) cholesterol | 1 mmol/L (40 mg/dL) decrease associated with 23% to 25% reduction in major CV events.<br>Goal of statin therapy is 50% or more reduction in LDL cholesterol |
| Hemoglobin A1c (HbA1c) | 0.3% to 0.4% |
| Impact of Weight on Quality of Life-Lite survey (IWQoL-Lite)<br>• 20-item self-report survey of 20 items to assess obesity-specific QoL I adults<br>• Scores range from 0-100 with higher scores indicating better quality of life | Increases of 7.7 to 12 points of total score |
| SF-36 Physical Function Score<br>• Scores range from 0-100 with higher scores indicating better quality of life | 3.8 points or more for obesity health-related QoL |
| Pediatric quality of life inventory (PedsQL) | 4.4 points or more for health-related QoL |
| Key: * Measurement of relative weight adjusted according to reference standards for child age (2 to 20 years) adjusted for sex; scores correspond to growth chart percentiles. | |
| Abbreviations: CV = cardiovascular; MCID = minimal clinically important difference; QoL = quality of life | |

All drugs studied were compared to placebo except for 2 trials evaluating semaglutide versus liraglutide and exenatide versus glyburide. Liraglutide, semaglutide, exenatide and phentermine-topiramate were studied in youth.[1]

LIRAGLUTIDE

**Adults**

Liraglutide was studied in 11 RCTs versus placebo and 1 RCT versus semaglutide in adult patients.[1] Trials included patients with and without diabetes. Three RCTs included patients with T2DM and 3 trials were studied in patients with T1DM. Two RCTs studied weight loss maintenance in those individuals who had lost at least 5% body weight during a run-in period using diet and exercise.[1] Doses of liraglutide studied for weight loss were 3.0 mg daily and 1.8 mg daily. Most of the studies also offered diet and exercise or intensive behavioral therapy as background treatment. Study duration were from 24 to 68 weeks. Three trials enrolled participants with a BMI of 25 kg/m$^2$ or greater, 4 studies evaluated a BMI of 27 kg/m$^2$ or greater, 4 enrolled people with a BMI of 30 kg/m$^2$ (3 studies also allowed participants with a BMI of 27 kg/m$^2$ if comorbidities) and one trial included participants with a BMI of 32 kg/m$^2$ to 43 kg/m$^2$. Participants had a mean age of mid to late 40's and baseline BMI of 35-40 kg/m$^2$. Twelve of the studies had moderate risk of bias and the remaining 2 had high risk of bias.[1]

Liraglutide use was associated with more weight loss than placebo (**Table 3**). There was heterogeneity across the trials, so variations in results were probably not due to chance alone. Enrollment of differing population, such as diabetes, could influence heterogeneity levels. One trial, not include in the assessment of evidence, followed participants for 160 weeks. Weight loss was maintained out to 3 years, -5.4% at 56 weeks and -4.2% at 160 weeks.[1]

Liraglutide use demonstrated favorable findings on comorbidity outcomes. There is moderate strength of evidence that liraglutide reduced systolic blood pressure (SBP) (mean difference [MD] -2.89 mmHg; 95% confidence interval [CI], -3.54 to -2.24; p<0.001); however, this difference did not a achieve thresholds for a clinically meaningful change.[1] Changes in LDL cholesterol were greater for liraglutide compared to placebo but were not clinically meaningful (standardized mean difference [SMD] -0.12 mmol/L; 95% CI, -0.17 to -0.06; p<0.001) (moderate quality of evidence). There was low quality evidence that changes in hemoglobin A1c (HbA1c) were reduced more with liraglutide compared to placebo (MD -0.33%; 95% CI, -0.44 to -0.21; p<0.001) by a clinically meaningful amount (in people with and without diabetes).[1] No difference in HbA1c was demonstrated between liraglutide and placebo in those with T1DM. There was low quality of evidence that quality of life may have slightly improved with liraglutide compared to placebo. Liraglutide use caused more withdrawals due to AEs compared to placebo that was not dose dependent (relative risk [RR] 2.20; 95% CI, 1.75 to 2.76; p<0.001) (moderate strength of evidence).[1] The most common AEs were nausea, constipation, diarrhea and vomiting in those taking liraglutide. Gallbladder issues (e.g., cholecystitis, cholelithiasis) occurred more often in those treated with liraglutide compared to placebo.

**Table 3. Weight Outcomes for Liraglutide in Adults**[1]

| Outcomes | Results | Strength of Evidence | Comments |
|---|---|---|---|
| General study characteristics:<br>- BMI ≥25 kg/m$^2$ (3 studies)<br>- BMI ≥ 27 kg/m$^2$ (4 studies)<br>- BMI of 30 kg/m$^2$ (4 studies; 3 studies also allowed participants with a BMI of 27 kg/m$^2$ if comorbidities)<br>- BMI of 32 kg/m$^2$ to 43 kg/m$^2$ (1 study)<br>- Diabetes excluded (2), T1DM included (3), T2DM (3)<br>- liraglutide 1.8 mg daily (0.6 mg weekly to until target), liraglutide 3.0 mg daily<br>- Trials lasted 56-172 weeks | | | |
| Change in BMI %<br>(7 RCTs; n=5,864) | MD -4.61% (95% CI, -5.44 to -3.78; p<0.001) | Low | Percent change in body weight were not clinically meaningful with liraglutide treatment but are statistically significant (5% or more reduction is considered clinically meaningful). |
| Change in Body Weight<br>(8 RCTs; n=4,777) | MD -5.58 kg (95% CI, -7.63 to -2.41; p<0.001) | Moderate | Patients taking liraglutide lost more weight compared to placebo. |
| Change in BMI<br>(5 RCTs; n=5,129) | MD -1.82 kg/m$^2$ (95% CI, -1.95 to -1.68; p<0.001) | Low | BMI was reduced with liraglutide compared to placebo. |
| Proportion with ≥ 5% weight loss<br>(7 RCTs; n=5,817) | RR 2.04 (95% CI, 1.61 to 2.57; p<0.001) | Low | Liraglutide treated patients were more likely to lose more body weight compared to placebo. |
| Proportion with ≥ 10% weight loss<br>(8 RCTs; n=6,012) | RR 2.66 (95% CI, 2.00 to 3.53; p<0.001) | Moderate | Liraglutide treated patients were more likely to lose more body weight compared to placebo. |
| Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinically trial; RR = relative risk | | | |

**Youth**

Liraglutide was studied in 2 RCTs for weight loss use in youth (**Table 4**).[1] One study enrolled youth with HbA1c levels over 7% (all had T2DM and were on metformin) and the other study included youth with an average normal HbA1c (5.3%) and approximately 30% had prediabetes or T2DM. Youth had to have a BMI of at least the 85$^{th}$ percentile in one study and 95$^{th}$ percentile or more in the second study.[1] The study durations lasted from 52-56 weeks and doses were 1.8 mg weekly in one study and 3.0 mg weekly in the second study. Compared to placebo, liraglutide resulted in a potentially clinically meaningful change in BMI z/SD score, according to some estimates.[1] Other weight outcomes were not clinically meaningful. There was moderate evidence of no difference in LDL cholesterol measurements between liraglutide and placebo. There was a small, statistically significant, but not clinically meaningful change, at 52 weeks in in systolic blood pressure (MD -2.06; 95% CI, -4.06 to -0.05; P=0.04) between liraglutide and placebo (moderate evidence).[1] There was no difference in change in HbA1c between liraglutide and placebo (very low evidence; p=0.29). Moderate quality of evidence found no difference between liraglutide and placebo in quality of life. Withdrawals due to adverse events were not different between groups based on very low evidence. In both studies, liraglutide was associated with an increased risk of AEs and severe adverse events (SAEs) when compared to placebo; however the differences were not considered statistically significant (strength of evidence was not provided).[1] In the 5 studies that evaluated medication use, people randomized to liraglutide were less likely to require of medications for hypertension, lipids and diabetes (when applicable) compared to placebo.

**Table 4. Weight Outcomes for Liraglutide in Youth**[1]

| Outcomes | Results | Strength of Evidence | Comments |
|---|---|---|---|
| <u>General study characteristics:</u><br>- BMI of 85$^{th}$ percentile or more in one study and 95$^{th}$ percentile in the second study<br>- Diabetes (1 study)<br>- Portion with prediabetes or diabetes (1 study)<br>- Ages: 10-17, 12-18 | | | |
| Changes in BMI z/SD score<br>(2 RCTs; n=386) | MD -0.21 SDs (95% CI, -0.31 to -0.11; p<0.001) | Low | Clinically meaningful decreases with liraglutide according to some estimates. Clinically meaningful effect is cited as a change in SD of -0.15 or -0.25. |
| Change in BMI %<br>(1 RCT; n=251) | MD -4.64% (95% CI, -7.12 to -2.16; p<0.001) | Low | Results of liraglutide treatment are not clinically meaningful by a small margin. |
| Change in Body Weight<br>(1 RCT; n=251) | MD -5.02% (95% CI, -7.63 to -2.41; p<0.001) | Moderate | Growth and height development can influence weight changes in youth so results aren't clinically meaningful. |
| Change in BMI<br>(1 RCT; n=251) | MD -1.58 kg/m$^2$ (95% CI, -2.47 to -0.69; p<0.001) | Moderate | Unlikely to be clinically meaningful. |
| Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinically trial; SD = standard deviation | | | |

<u>SEMAGLUTIDE</u>

**Adults**

Semaglutide was studied in 7 placebo-controlled trials and one active treatment trial which compared semaglutide to liraglutide in adult patients who were overweight or obese.[1] One trial enrolled diabetic patients exclusively, one allowed enrollment for people with or without T2DM, and the other trials excluded those with T2DM. All trials offered diet and exercise or behavioral counseling therapy as background therapy. Trial durations were 68 weeks for 6 trials and 104 weeks for one trial. Five trials enrolled patients with a BMI of at least 30 kg/m$^2$ or those with a BMI of 27 kg/m$^2$ and at least one comorbidity.[1] One trial required participants to have a BMI of at least 27 kg/m$^2$. One trial included those with a BMI of at least 27 kg/m$^2$ plus at least 2 comorbidities or a BMI of 35 kg/m$^2$ plus at least 1 comorbidity.[1] Majority of trials enrolled patients in their mid 40's to early 50's with baseline BMIs around 38 kg/m$^2$. Trials were considered to have a moderate risk of bias due to conflicts of interests. Enrollment of participants with differing baseline characteristics (e.g., diabetes) caused heterogeneity across the included studies.[1]

Semaglutide was associated with favorable results for all weight loss outcomes (e.g., change in BMI and body weight) in which decreases met the threshold for being clinically meaningful (**Table 5**). In the trial, enrolling people with T2DM, the treatment effect was less when compared to the trials studied in participants without diabetes (change in body weight compared to placebo, MD -6.22% for patients with diabetes versus -12.53% for those without diabetes). Reasons for the difference between study results are not entirely clear, and additional studies are needed to clarify these results. The one trial which studied patients out to 104 weeks found percent change in body weight increased slightly from week 52 to 104 in both the semaglutide and placebo group, but not back to baseline in either group.[1] There was low quality evidence that semaglutide treatment resulted in a decrease in SBP and LDL cholesterol more than placebo, but by a magnitude which did not meet established thresholds for clinically meaningful differences (low quality of evidence). Low quality evidence found semaglutide decreased HbA1c more than placebo, which was statistically and clinically meaningful (MD -0.43%; 95% CI, -0.55 to -0.30; p<0.001).[1] The evidence for the decrease in HbA1c mostly came from 2 trials which enrolled participants with T2DM (all participants had T2DM in the first trial and 25% had T2DM in the second trial). Changes in quality of life were not significantly different between semaglutide and placebo.[1] There was moderate quality evidence for more withdrawals due to AE in those treated with semaglutide compared to placebo (RR 1.81; 95% CI, 1.34 to 2.44; p<0.001). The most common AEs were nausea, constipation, diarrhea and vomiting. Evidence for changes in medication use were considered exploratory and were small subpopulations of study participants.

One study evaluated the comparison of semaglutide 2.4 mg to liraglutide 3.0 mg and placebo (n=253) enrolling participants without diabetes.[1] An open-label study design comparison was used for the semaglutide versus liraglutide comparison. For this reason, the trial was considered to be at moderate risk of bias. Semaglutide was found to be superior to liraglutide for weight outcomes based on low quality of evidence. A decrease in body weight percentage was higher with semaglutide compared to liraglutide (MD -9.40%; 95% CI, -11.82 to -6.98; p<0.001) and body weight (MD -8.50 kg; 95% CI, -11.19 to -5.81; p<0.001).[1] Those participants treated with semaglutide were more likely to lose at least 10% more body weight compared to liraglutide (RR 2.77; 95% CI, 1.99 to 3.85; p<0.001).[1] Changes between semaglutide and liraglutide were not statistically different for the outcomes of SBP and LDL cholesterol. Participants randomized to semaglutide had lower HbA1c compared to liraglutide, but differences were not clinically significant (MD -0.2%; 95% CI, -0.2 to -0.1; p-value not reported).[1] About 34-35% of people in each group had prediabetes. There was very low quality evidence that semaglutide participants withdrew from the trial due to AEs less frequently than those randomized to liragutide.[1] Gastrointestinal AEs were common in both groups.

**Table 5. Weight Outcomes for Semaglutide in Adults**[1]

| Outcomes | Results | Strength of Evidence | Comments |
|---|---|---|---|
| General study characteristics:<br>- BMI of 27 kg/m$^2$ and those with 2 or more comorbidities or a BMI of 35 kg/m$^2$ and 1 or more comorbidity (1 study)<br>- BMI $\geq$ 27 kg/m$^2$ (1 study) | | | |

| | | | |
|---|---|---|---|
| - BMI of 30 kg/m$^2$ or BMI of 27 kg/m$^2$ if comorbidities (5 studies)<br>- Those with and without T2DM<br>- Doses Studied**:** Semaglutide 2.4 mg SC weekly (initiated at 0.25 mg and increased every 4 weeks to target dose)<br>- Trials lasted 52-120 weeks | | | |
| Change in BMI %<br>(7 RCTs; n=4,997) | MD -11.59% (95% CI, -14.09 to -9.09; p<0.001) | Low | Percent change in body weight were clinically meaningful with semaglutide treatment (5% or more reduction is considered clinically meaningful). Downgraded for significant heterogeneity between studies. |
| Change in Body Weight<br>(6 RCTs; n=4,190) | MD -12.00 kg (95% CI, -13.32 to -10.68; p<0.001) | Moderate | Patients taking semaglutide lost more weight compared to placebo. |
| Change in BMI<br>(5 RCTs; n=3,979) | MD -4.25 kg/m$^2$ (95% CI, -4.75 to -3.76; p<0.001) | Moderate | BMI was reduced with semaglutide compared to placebo. |
| Proportion with ≥ 5% weight loss<br>(6 RCTs; n=4,786) | RR 2.34 (95% CI, 1.93 to 2.83; p<0.001)<br>ARR 49% /NNT 2 | Low | Patients treated with semaglutide were more likely to lose more body weight compared to placebo. |
| Proportion with ≥ 10% weight loss<br>(7 RCTs; n=4,727) | RR 4.70 (95% CI, 3.53 to 6.26; p<0.001)<br>ARR 54% / NNT 2 | Low | Patients treated with semaglutide were more likely to lose more body weight compared to placebo. |
| Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinical trial; SD = standard deviation | | | |

**Youth**

The use of semaglutide 2.4 mg was compared to placebo in one trial in youth over 68 weeks (**Table 6**).[1] About 4% of participants had diabetes and participants could be taking metformin (percent not reported). Thirteen percent of patients had HTN. Diet and exercise counseling was also provided. Youth had to have a BMI of at least the 95$^{th}$ percentile for their sex and age or the 85$^{th}$ percentile plus at least one comorbidities to be included.[1] Semaglutide demonstrated significant differences in all weight outcomes, clinically and statistically. There is moderate evidence that the reductions in systolic blood pressure were not significantly different from placebo. Semaglutide caused significant reductions in LDL cholesterol compared to placebo (MD -6.08%; 95% CI, -11.90 to -1.70; p=0.009) (moderate evidence).[1] Clinically meaningful decreases (0.3% or more) in HbA1c were demonstrated with semaglutide versus placebo (MD -0.30%; 95% CI, -0.35 to -0.25; p<0.001). There was no difference in withdrawals due to AEs between semaglutide or placebo. Gastrointestinal AEs (e.g., nausea, diarrhea, vomiting, and abdominal pain) were more common with those taking semaglutide.

**Table 6. Weight Outcomes for Semaglutide in Youth**[1]

| Outcomes | Results | Strength of Evidence | Comments |
|---|---|---|---|
| General study characteristics:<br>- BMI of ≥95$^{th}$ percentile or ≥85$^{th}$ percentile plus at least one comorbidity<br>- Diabetes (4%) | | | |

| | | | |
|---|---|---|---|
| Changes in BMI z/SD score<br>(1 RCT; n=201) | MD -01.00 SDs (95% CI, -1.30 to -0.70; p<0.001) | Moderate | Clinically meaningful decreases in weight with semaglutide |
| Change in BMI %<br>(1 RCT; n=201) | MD -16.70% (95% CI, -20.25 to -13.15; p<0.001) | Moderate | Clinically meaningful reductions in BMI % with semaglutide (5% or more reduction is considered clinically meaningful) |
| Change in Body Weight<br>(1 RCT; n=201) | MD -17.40% (95% CI, -21.10 to -13.70; p<0.001) | Moderate | Growth and height development can influence weight changes in youth so results aren't clinically meaningful |
| Proportion with ≥ 5% weight loss<br>(1 RCT; n=201) | RR 4.09 (95% CI, 2.37 to 7.06; p<0.001) | Moderate | Semaglutide caused more weight loss than placebo |
| Proportion with ≥ 10% weight loss<br>(1 RCT; n=201) | RR 7.67 (95% CI, 3.27 to 17.96; p<0.001) | Moderate | Semaglutide caused more weight loss than placebo |
| Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinically trial; SD = standard deviation | | | |

**EXENATIDE**

**Adults**

Exenatide was studied in one RCT active treatment comparison to glyburide in adult patients.[1] In the active treatment trial exenatide 20 mcg daily was compared to oral 15 mg daily of glyburide. Patients (n=128) had T2DM, with HbA1c >8%, and were also taking background metformin. Lifestyle modifications of diet and exercise were used in conjunction with pharmacotherapy. To be eligible, patients had to have a BMI between 25 and 30 kg/m$^2$.[1] The trial lasted 52 weeks. It was considered to have high risk of bias because it was single-blind and lacked detail on methodology. Only changes in body weight and BMI were studied. There were no statistically significant differences in HbA1c levels or withdrawals due to AEs between the two groups. Cardiovascular outcomes were not reported.

**Table 7. Weight Outcomes for Exenatide in Adults**[1]

| Outcomes | Results | Strength of Evidence | Comments |
|---|---|---|---|
| General study characteristics:<br>- BMI of ≥25 to <30 kg/m$^2$<br>- Diabetes (100%)<br>- Trial lasted 52 weeks | | | |
| Change in Body Weight<br>(1 RCT; n=128) | MD -12.70 kg (95% CI, -15.60 to -9.80; p<0.001) | Moderate | Patients on exenatide lost more weight compared to glyburide, which could be clinically meaningful. |
| Change in BMI<br>(1 RCT; n=128) | MD -4.10 kg/m$^2$ (95% CI, -4.59 to -3.61; p<0.001) | Moderate | BMI was reduced with exenatide compared to glyburide. |
| Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinically trial; SD = standard deviation | | | |

**Youth**

Exenatide was studied in 2 trials enrolling youth (**Table 8**).[1] Both studies enrolled individuals without diabetes and compared exenatide 2.0 mg weekly to placebo. One trial lasted 52 weeks and one trial lasted 24 weeks. One study enrolled individuals who had severe obesity (BMI 1.2, or greater, times 95$^{th}$ percentile or 35 kg/m$^2$ or greater), and the second trial enrolled those with a BMI of 30 kg/m$^2$ or greater.[1] There was no difference in SBP or HbA1c between exenatide and placebo (low quality of evidence). Changes in LDL cholesterol levels were mixed. One study demonstrated a small, statistically significant reduction in LDL cholesterol with exenatide compared to placebo and the other study did not (very low quality of evidence).[1] The results may be due to study design differences and differing baseline LDL cholesterol levels. No differences between exenatide and placebo were found for quality of life, based on low quality evidence. Withdrawals due to AEs occurred in only one participant taking exenatide across the 2 trials (very low quality of evidence).[1] There were more gastrointestinal AEs (e.g., nausea, diarrhea, vomiting and constipation) in those taking exenatide compared to placebo.

**Table 8. Weight Outcomes for Exenatide in Youth**[1]

| Outcomes | Results | Strength of Evidence | Comments |
|---|---|---|---|
| General study characteristics:<br>- BMI 1.2 times or greater than 95$^{th}$ percentile or 35 kg/m$^2$ or greater) (1 study)<br>- BMI of 30 kg/m$^2$ or greater (1 study)<br>- Non-diabetics | | | |
| Changes in BMI z/SD score<br>(1 RCT; n=44) | MD -0.09 SDs (95% CI, -0.18 to -0.00; p<0.05) | Very low | Differences in weight loss with exenatide were not clinically meaningful |
| Change in BMI %<br>(1 RCT; n=66) | MD -4.1% (95% CI, -8.6 to -0.5; p=0.08) | Very low | There were no statistical or clinical differences between groups |
| Percent of 95$^{th}$ BMI percentile<br>(2 RCTs; n=110) | MD -1.84% (95% CI, -3.18 to -0.49; p=0.008) | Low | Those treated with exenatide experienced significantly more weight loss than those treated with placebo but weight loss may depend on duration of treatment (longer durations may result in more weight loss) |
| Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinically trial; SD = standard deviation | | | |

**TIRZEPATIDE**

There was one RCT (n=2,539) identified for inclusion into this review. Adult participants without diabetes were randomized to tirzepatide 5.0 mg weekly, 10 mg weekly, or 15 mg SC weekly compared to placebo for 72 weeks (doses were pooled).[1] Patients were eligible for inclusion if they had a BMI of 30 kg/m$^2$ or more or had a BMI of 27 kg/m$^2$ or more plus at least one comorbidity. There was moderate evidence of a clinically meaningful difference in percent change in body weight for tirzepatide compared to placebo (MD -15.37%; 95% CI, -16.68 to -14.06; p<0.001).[1] More patients taking tirzepatide lost 5% or more of body weight compared to placebo, (88.3% versus 34.5%; RR 2.56; 95% CI, 2.30 to 2.85; p<0.001). More participants taking tirzepatide lost 10% or more of body weight compared to placebo (76.7% versus 18.8%; RR 4.08; 95% CI, 3.47 to 4.80; p<0.001; moderate quality of evidence).[1] There was a dose-related decrease in weight

loss between the different doses of tirzepatide were -15%, -19.5%, and -20.9%. Treatment discontinuation due to adverse events occurred for 2.6% of people in the placebo group compared to 4.3%, 7.1%, and 6.2% for tirzepatide 5 mg, 10 mg and 15 mg, respectively.[2] Additional study details are presented in Table 15.

**NALTREXONE-BUPROPION**

**Adults**

Five placebo-controlled studies evaluated the combination of naltrexone-bupropion in adults. Four studies used the same dose; naltrexone 32 mg and bupropion 360 mg. One study also evaluated 16/360 mg naltrexone-bupropion[1]. One trial included patients with T2DM and the other 4 trials excluded those with T2DM. Trials lasted 52-56 weeks and enrolled 242 to 1,742 patients. Three trials enrolled patients with a BMI between 30 kg/m$^2$ and 45 kg/m$^2$ or patients with a BMI between 27 and 45 kg/m$^2$ plus HTN or hyperlipidemia.[1] One trial included patients with a BMI of ≥27 kg/m$^2$ and ≤45 kg/m$^2$. The last trial included patients with a BMI of ≥27 kg/m$^2$ and HTN or hyperlipidemia. The mean ages ranged from 44-46 years and BMI of 36 kg/m$^2$ to 37 kg/m$^2$.[1]

Small, non-significant increases in SBP were demonstrated with naltrexone-bupropion (low strength of evidence).[1] LDL cholesterol was slightly improved with the use of naltrexone-bupropion compared to placebo; however, differences were small and not considered clinically meaningful (low strength of evidence). In the one study which enrolled patients with T2DM, HbA1c levels were reduced with the use of naltrexone-bupropion compared to placebo (MD -0.5%; 95% CI, -0.78 to -0.22; p<0.001), which was considered clinically significant based on low strength of evidence.[1]

**Table 9. Weight Outcomes for Naltrexone-Bupropion in Adults**[1]

| Outcomes | Results | Strength of Evidence | Comments |
|---|---|---|---|
| General study characteristics:<br>- BMI of 30 to 45 kg/m$^2$ or 27 to 45 kg/m$^2$ or greater with HTN or hyperlipidemia (3 studies)<br>- BMI of ≥27 kg/m$^2$ and ≤45 kg/m$^2$(1 study)<br>- BMI of ≥27 kg/m$^2$ and HTN or hyperlipidemia (1 study)<br>- T2DM (1 study), excluded those with T2DM (4 studies)<br>- Trials lasted 26-56 weeks | | | |
| Changes in Body Weight %<br>(4 RCTs; n=4,122) | MD -4.25% SDs (95% CI, -5.07 to -3.42; p<0.001) | Low | Statistically significant decreases in weight with naltrexone-bupropion compared to placebo but differences did not meet thresholds for clinically meaningful changes. |
| Change in Body Weight<br>(2 RCTs; n=3,023) | MD -4.49 kg (95% CI, -5.28 to -3.71; p<0.001) | Low | Statistically significant decreases in weight with naltrexone-bupropion compared to placebo but differences did not meet thresholds for clinically meaningful changes. |
| Proportion with ≥ 5% weight loss<br>(4 RCTs; n=3,710) | RR 2.31 (95% CI, 1.66 to 3.23; p<0.001)<br>ARR 29%/NNT 4 | Low | Patients treated with naltrexone-bupropion lost more weight than placebo. |
| Proportion with ≥ 10% weight loss<br>(4 RCTs; n=3,035) | RR 3.12 (95% CI, 2.07 to 4.68; p<0.001)<br>ARR 19.5%/NNT 5 | Low | Patients treated with naltrexone-bupropion lost more weight than placebo. |

Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinically trial; SD = standard deviation; T2DM = type 2 diabetes mellitus

**PHENTERAMINE-TOPIRAMATE**

**Adults**

The use of phen/top in adults was studied in 2 RCTs lasting 56 weeks.[1] The dose was phen/top 15/92 mg daily compared to placebo in both trials in conjunction with lifestyle modifications. Each trial also studied a lower dose, phen/top 3.75/23 mg daily and phen/top 7.5/46 mg daily. The trials enrolled participants with and without diabetes. One study included participants with a BMI of 27 kg/m$^2$ to 45 kg/m$^2$ and at least 2 comorbidities; the second study enrolled those with a BMI of 35 kg/m$^2$ or greater.[1] Change in BMI was not reported in the studies. Studies had a high risk of bias due to lack of details on methods, conflicts of interest, high attrition, and variable discontinuation rates. The mean ages for participants in the trials were 42 to 45 years old. Baseline BMI ranged from 36 kg/m$^2$ to 42 kg/m$^2$.

Evidence from 2 RCTs demonstrated that phen/top was statistically and clinically more effective at reducing weight compared to placebo based on moderate quality of evidence (**Table 10**). There was moderate quality evidence that there were not clinically meaningful reductions in SBP, LDL or HbA1c. Withdrawal rates were significantly higher in those randomized to phen/top compared to placebo in trials lasting 1 year.

**Table 10. Weight Outcomes for Phentermine/Topiramate in Adults**[1]

| Outcomes | Results | Strength of Evidence | Comments |
|---|---|---|---|
| **General study characteristics:**<br>- BMI of 27 kg/m$^2$ to 45 kg/m$^2$ and at least 2 comorbidities or those with a BMI of 35 kg/m$^2$ or greater<br>- Included those with and without diabetes<br>- Trials lasted 26 -108 weeks | | | |
| Change in body weight %<br>(2 RCTs; n=3513) | MD -8.56% (95% CI, -9.93 to -7.19; p<0.001) | Low | Statistically and clinically meaningful reductions in body weight percent with phen/top compared to placebo. |
| Change in weight<br>(1 RCT; n= 2487) | MD -8.10 kg (95% CI, -8.86 to -7.34; p<0.001) | Moderate | Phen/top use caused more weight loss compared to placebo |
| Proportion with 5% or greater weight loss<br>(2 RCTs; n=3444) | RR 3.47 (95% CI, 2.93 to 4.11; p<0.001) | Moderate | Participants treated with phen/top were more likely to lose at least 5% body weight when compared to placebo. |
| Proportion with 10% or greater weight loss<br>(2 RCTs; n=3444) | RR 6.12 (95% CI, 5.08 to 7.38; p<0.001) | Moderate | Participants treated with phen/top were more likely to lose at least 10% body weight when compared to placebo. |
| Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; RCT = randomized clinically trial; RR = relative risk | | | |

**Youth**

Phen/top was studied for weight loss in adolescents in one RCT (**Table 11**).[1] Doses included phen/top 15/92 mg daily and phen/top 7.5/46 mg daily compared to placebo. Doses were pooled for outcome analysis. Eligible participants had to have a BMI of 95$^{th}$ percentile or greater, for sex and age. Outcomes were assessed at 56 weeks, and all participants received background diet and exercise counseling. The study was considered to have a high risk of bias due to lack of details on methods, study design, and conflicts of interest.

Phen/top resulted in statistically and clinically meaningful decreases in weight outcomes (**Table 10**).[1] There was no clinically significant differences between semaglutide and placebo based on a low quality evidence.[1] Withdrawals due to AEs were not different between phen/top and placebo (very low quality evidence).

**Table 11. Weight Outcomes for Phentermine-Topiramate in Youth**[1]

| Outcomes | Results | Strength of Evidence | Comments |
|---|---|---|---|
| General study characteristics:<br>- BMI of 95$^{th}$ percentile or greater<br>- Diabetes not reported | | | |
| Changes in BMI z/SD score | Not reported | N/A | N/A |
| Change in BMI %<br>(1 RCTs; n=223) | MD -9.70% (95% CI, -12.93 to -6.47; p<0.001) | Low | Statistically and clinically meaningful reductions in percent of BMI with phen/top (5% or more reduction is considered clinically meaningful) |
| Change in BMI (kg/m$^2$)<br>(1 RCTs; n=223) | MD -4.83 kg/m$^2$ (95% CI, -5.86 to -3.79; p<0.001) | Low | Phen/top significantly reduced BMI compared to placebo |
| Abbreviations: BMI = body mass index; CI = confidence interval; MD = mean difference; N/A = not applicable; RCT = randomized clinically trial; SD = standard deviation | | | |

**SETMELANOTIDE**

Setmelantotide was studied in 3 trials, one was a RCT. Setmelanotide 3.0 mg daily was given to people with obesity caused by genetic variants.[1] Variants included in the studies were Bardet-Biedl syndrome, Alstrom syndrome, proopiomelanocortin (POMC) deficiency and leptin receptor (LEPR) deficiency. In the RCT, participants (n=69) were a mean age of 21 years and were treated for 14 weeks with either setmelanotide or placebo.[1] Placebo treated patients were transferred to setmelanotide after 14 weeks to an additional 52 weeks in an open-label study. Studies enrolled people with or without diabetes and the one RCT also included nutritional counseling. All studies were considered to have a high-risk of bias.

More weight loss was reported with setmelanotide compared to placebo in all 3 trials with percent body weight loss ranging from -5.5% to -25%. In the RCT the change in body weight percent between setmelanotide and placebo was -2.1% (95% CI, -4.6 to 0.4; p=0.052).[1] The pooled weight loss results were also not statistically significant and quality of evidence was graded as very low. There were no statistically significant differences between setmelanotide and placebo for comorbidity risk factors (very low quality evidence). Quality of life measures were higher in those taking setmelanotide compared to placebo; however, p-values

were not reported. Withdrawals due to adverse events were lower in those treated with setmelanotide compared to placebo but not they were not significant (RR 0.33; 95% CI, 0.04 to 2.93; p=0.32).[1]

**Guidelines:**

**New Guidelines:**

NICE- Liraglutide for Managing Overweight and Obesity

In 2023 NICE published guidance for the use liraglutide in the management of patients who are overweight or obese.[8] NICE recommends that if liraglutide is used then it should be used in conjunction with a reduced-calorie diet and increased physical activity. Recommendation are focused on adults that have a high risk of experiencing the adverse consequences of obesity. Adults who are candidates for liraglutide should have the following clinical criteria:[8]

- A BMI of at least 35 kg/$m^2$. Some ethnic groups are known to be at equivalent risk for consequences of obesity at a lower BMI compared to people who identify as white. These populations should have a BMI of at least 32.5 kg/$m^2$ and
- A diagnosis of non-diabetic hyperglycemia (an HbA1c of 6.0% to 6.4%) or a fasting plasma glucose of 99 mg/dl to 124.2 mg/dl and
- A high risk of CV disease based on risk factors such as HTN and dyslipidemia and
- Prescribed by a specialty multidisciplinary tier 3 weight management service. Tier 3 weight management services provide dietary, lifestyle and behavior modification with psychological support.

NICE – Semaglutide for Managing Overweight and Obesity

In March of 2023, NICE published guidance for the use of semaglutide.[7] Evidence showed that adults that use semaglutide with a supervised weight management support lose more weight than management support alone. Semaglutide was associated with more weight loss than liraglutide. Semaglutide use in adults with non-diabetic hyperglycemia, who also used lifestyle modifications, had more normalized blood glucose levels more often than lifestyle modifications alone.[7] Semaglutide has been shown to reduce the risk of CV disease.

The recommendations for semaglutide, in conjunction with a reduced-calorie diet and increased physical activity, in adults for weight management are as follows[7]:

- Maximum use of 2 years and in conjunction with a specialist weight management service providing management of overweight and obesity AND
- Presence of one weight related comorbidity AND
- A BMI of:
    - At least 35 kg/$m^2$ or
    - 30 kg/$m^2$ to 34.9 kg/$m^2$ and meet the criteria for referral to a specialist weight management services (e.g. has not been able to manage weight with education on diet, nutrition, lifestyle and behavior advice for up to 12 weeks)
    - Lower BMI thresholds are recommended for people from South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family backgrounds. Usually a reduction of 2.5 kg/$m^2$.

Reassessment of semaglutide efficacy should be performed at 6 months, and if there is less than a 5% weight loss from the initial weight, then consider discontinuing therapy.

NICE- Obesity: Identification, Assessment and Management Clinical Guideline

A 2023 publication from NICE offers updated guidance, from their original publication in 2014, on the pharmacotherapy recommendations for children and adults who are obese.[9] Diet, exercise and behavioral therapy is recommended before pharmacotherapy should be offered. If target weight loss had not been achieved, then drug treatment may be considered, along with continued counseling on diet, physical activity and behavior strategies.

Drug treatment recommendations include liraglutide, semaglutide and orlistat.[9] Naltrexone-bupropion is not recommended for weight management by NICE due to lack of long-term effectiveness data and unknowns regarding cost-effectiveness. Specific recommendations by NICE regarding the use of liraglutide and semaglutide are discussed above. NICE recommends that orlistat be an option for those with a BMI of at least 30 kg/m$^2$ or at least 28 kg/m$^2$ with associated risk factors (risk factors not specifically described).[9] Reassessment at 3 months is recommended with continuation of therapy if at least 5% of initial body weight has been lost since starting orlistat.

In children younger than 12 years of age, drug therapy for weight management is not routinely recommended by NICE.[9] Drug therapy in children 12 and younger should only be done by a pediatric specialist. Orlistat is recommended for children 12 and older if physical comorbidities (e.g., orthopedic problems or sleep apnea) are severe and drug therapy is recommended by a pediatric specialist.[9] A 6 to 12-month trial is recommended with follow-up for assessment of adverse reactions, effectiveness and adherence.

VA/DOD – Clinical Practice Guideline for the Management of Adult Overweight and Obesity

In a 2020 guideline the VA/DOD reviewed evidence for weight management including the use of pharmacotherapy.[10] Twenty-three studies were included, 5 had high risk of bias. Bias was commonly attributed to lack of details on allocation concealment. The VA/DOD strongly recommends comprehensive lifestyle interventions (CLI) that include behavioral, dietary, and physical activity aspects for adults that are overweight or obese. There is evidence for sustained weight loss with CLI in addition to improvements in obesity related conditions.

The recommendation for the use of long-term pharmacotherapy was considered weak; however, the recommendation was based on moderate quality evidence for the outcomes of weight loss and 5% to 10% weight loss compared to placebo. Treatments evaluated include: liraglutide, naltrexone/bupropion, orlistat, or phen/top (**Table 12**).[10] Patients are candidates for treatment if they have BMI of at least 30 kg/m$^2$ or have a BMI of 27 kg/m$^2$ with obesity-associated comorbidities. Pharmacotherapy should be used in conjunction with a CLI. There was a statistically significant increase in discontinuations due to adverse events, compared to placebo, for all medications studied.[15] The highest rate of discontinuations was found with liraglutide. The effect of weight management medications on cardiometabolic parameters were inconsistent.

**Table 12. Evidence for Long-term Weight Loss Medications**[10]

| Medications | Mean weight loss versus placebo | 5% or more weight loss (odds ratio) | 10% or more weight loss (odds ratio) | Discontinuations due to Adverse Events (odds ratio) |
|---|---|---|---|---|
| Phentermine/topiramate | -8.8 kg | 9.22 | 11.40 | 2.29 |
| Liraglutide | -5.24 kg | 5.54 | 4.99 | 2.95 |
| Naltrexone/bupropion | -4.95 kg | 3.96 | 4.19 | 2.64 |
| Orlistat | -2.63 kg | 2.70 | 2.42 | 1.84 |

Evidence for use of medications to maintain weight loss was also evaluated, emphasizing the importance of initial weight loss and maintenance of weight loss. Liraglutide was associated with a higher number of patients maintaining initial weight loss when compared to placebo.[15] Weight is often regained after discontinuation of weight management medications and long-term therapy is needed.[10]

There was insufficient evidence for the short-term, long-term or intermittent use of phentermine monotherapy, benzphetamine, diethylpropion, or phendimetrazine based on low quality evidence. The recommendation was neither in support or against the use of these therapies.

Limitations to the evidence include very specific inclusion and exclusion criteria for enrollment into the studies, particularly due to comorbidity requirements which exclude many in the general population. There was a higher rate of female participants enrolled across most the studies. Attrition was high (above 30%) in most studies. Long-term outcome data is lacking for efficacy and safety outcomes.

CADTH – Semaglutide Reimbursement Recommendation

A 2022 review from CADTH evaluated the evidence for the use of semaglutide in people who are overweight or obese.[11] The recommendation was made before the publication of the SELECT trial (**Table 15**), which found semaglutide reduced the risk of CV events more than placebo in adult patients with CV disease who are overweight or obese.[5] Evidence cited for the reasoning for the recommendation was the lack of data demonstrating preventing or reducing the risk of weight-related comorbidities (e.g., HTN, CV disease). There was also insufficient evidence for improvements in health-related quality of life with the use of semaglutide.

Therefore, semaglutide was not recommended as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of 30 kg/m2 or greater or 27 kg/m2 or greater in the presence of at least 1 weight-related comorbidity (e.g., hypertension, T2DM, dyslipidemia, or obstructive sleep apnea).[11]

ICER – Medications for Obesity Management: Effectiveness and Value

The Institute for Clinical and Economic Review (ICER) released guidance on the use of pharmacotherapy for weight management.[12] Medications FDA approved for weight management (e.g., semaglutide, liraglutide, phen/top, and bupropion/naltrexone), in addition to lifestyle interventions, were compared to placebo. Types of lifestyle management programs varied for the included studies, from diet and exercise counseling to intensive behavioral therapy (IBT) and meal replacement programs. Weight loss outcomes, HRQoL, weight gain and weight-related comorbidities (e.g., HbA1c, SBP, and LDL) were evaluated. Evidence of comparative clinical effectiveness was graded from highest (A) to lowest (I).

Evidence demonstrated efficacy of weight management drugs in adults without diabetes and who had obesity or overweight (BMI of 27 kg/m2 or greater) with at least one weight-related comorbidity (**Table 13**).[12] Indirect and direct evidence found semaglutide and phen/top caused greater weight loss compared to liraglutide and bupropion/naltrexone. Long-term data is lacking. All drugs were found to have higher discontinuation rates compared to placebo. There was insufficient evidence on sustained weight loss and weight regain upon medication discontinuation.

**Table 13. ICER Evidence Ratings of Weight Management Pharmacotherapy**[12]

| Pharmacotherapy | Comparator | Evidence Rating |
|---|---|---|
| Semaglutide | Lifestyle modification | B+ |
| Liraglutide | Lifestyle modification | B |

| | | |
|---|---|---|
| Phen/Top | Lifestyle modification | C++ |
| Bupropion/naltrexone | Lifestyle modification | C+ |
| Semaglutide* | Liraglutide | C+ |
| | Phentermine/topiramate | C+ |
| | Bupropion/naltrexone | C++ |
| * Based on direct and indirect comparisons | | |

ADA – Standards of Care: Recommendations for Obesity and Weight Management

In 2024 the ADA published guidance on the use of pharmacotherapy in patients with T2DM.[14] Recommendations are graded from A to E, strongly recommended to expert consensus. Management of obesity has demonstrated evidence for delaying the progression of prediabetes to diabetes. In those with T2DM, a weight reduction of 3-7% has shown to improve glucose levels and other CV risk factors.[14] A sustained weight loss of 10% or more may potentially lead to remission of T2DM and improved CV outcomes.

ADA recommends pharmacotherapy that has beneficial weight loss effects to reduce blood glucose in patients with T2DM who are overweight or obese (Grade A). Therapies with clinical meaningful weight loss are the following: GLP-1 RAs, GLP-1 RA/GIP RAs, sodium glucose cotransporter 2 (SGLT-2) inhibitors, metformin and amylin mimetics.[14] Weight neutral options include the dipeptidyl peptidase 4 (DPP-4) inhibitors, alpha-glucosidase inhibitors, central acting dopamine agonists (e.g., bromocriptine) and bile acid sequestrants. Weight gain is associated with insulin, sulfonylureas, meglitinides, and thiazolidinedione. Structured lifestyle programs, in conjunction with pharmacotherapy, are also strongly recommended (Grade A).[14]

Providers should also review patient medications to ensure concomitant medications (e.g., antipsychotics, antidepressants, steroids) are not contributing to weight gain.[14]

All therapies are associated with potential safety concerns with long term use. Phentermine/topiramate is contradicted with use of monoamine oxidase inhibitors (MOAIs) and may cause birth defects, cognitive impairment, and acute angle glaucoma.[14] Naltrexone/bupropion should not be used in those with uncontrolled hypertension and/or seizure disorders, chronic opioid therapy, acute angle glaucoma and there is a boxed warning of an increased risk of suicidal behavior in those younger than 24 years with depression.[14] The GLP-1 RAs and dual GIP RAs/GLP-1 RAs have a boxed warning of the risk of thyroid C-cell tumors in rodents. They also have a risk of pancreatitis, precautions in those with kidney disease, may cause GI disorders, cholelithiasis and gallstone-related complications. Tirzepatide may also influence concentrations of narrow therapeutic index drugs and contraceptives.[14]

The preferred treatment option in patients with T2DM and are overweight or obese is a GLP-1 RA or GLP-RA/GIP RA as they have evidence of the largest amount weight loss potential such as semaglutide or tirzepatide (Grade A).[14]

American Pediatric Association – Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents with Obesity

The APA released their first guidance on managing obesity in children and adolescents in January 2023.[15] Methodology was well described. Conflicts of interest were solicited and reported by one author. Recommendations were graded from Level A, high quality evidence, to Level D, expert opinion. An additional evidence designation of Level X was given to situations which were “validating studies cannot be performed and there is clear preponderance of benefit or harm”.

BMI is as useful evaluation measure to identify children and adolescents who are obese or overweight.3/5/2024 5:49:00 PM Evidence has demonstrated that BMI correlates well with direct measures of body fat, bioelectrical impedance, densitometry, and dual-energy x-ray absorptiometry.[15] The use of BMI may under- or over detect adiposity in specific ethnic and racial groups, as BMI does not directly measure body composition. Additionally, some children who have a high fat-free mass may be categorized as overweight or obese.[15]

Intensive health behavior and lifestyle treatment (IHBLT) is recommended for children and adolescents who are overweight or obese (**Table 14**).[15]

Drug therapy may be considered in children 8 years of age and older, in addition to IHBLT.[15] Evidence for the use of weight reduction therapies in children and adolescents included the following: metformin, exenatide, orlistat or other medications (phentermine, mixed carotenoids, topiramate, ephedrine and recombinant human growth hormone).[15] Additional therapies (e.g., setmelanotide, liraglutide, and combination phentermine/topiramate) have evidence for use that was published after the initial evidence review and are included as well. Recommendations for the use of pharmacotherapy in children and adolescents are presented below. Evidence for specific therapy recommendations were not graded.

- Metformin: can be considered as an adjunct to IHBLT in patients when other indications for metformin are present (e.g., polycystic ovary syndrome, prediabetes, prevention of weight gain when used with an atypical antipsychotic). Metformin is not FDA approved for weight loss but is approved for T2DM in patients 10 and older.[15]
- Orlistat: approved for children 12 and older for the long-term treatment of obesity.[15]
- GLP-1 RAs (semaglutide, liraglutide, dulaglutide, exenatide): exenatide is approved for use in children 10-17 years with T2DM. GLP-RAs are associated with BMI reductions of 0.9 to 1.8 U. Liraglutide was associated with a 4.5 kg weight reduction. Liraglutide and semaglutide are approved for weight loss in youth 12 and older.[15]
- Melanocortin 4 receptor (MC4R) agonist (e.g., setmelanotide): setmelanotide demonstrated weight loss of 12% to 25% in one uncontrolled study in those with rare genetic deficits.[15] Setmelanotide is approved for use in those patients 6 years and older with proopiomelanocortin (POMC) deficiency, proprotein subtilisin or kexin type 1 deficiency, and leptin receptor deficiency.[15]
- Phentermine: approved for short-course therapy, up to 3 months, in those 16 years and older.[15]
- Topiramate: approved for use in children 2 years and older for epilepsy and headache prevention. One study in children did not show benefits over placebo for weight management. Topiramate is FDA -approved in adults for binge eating disorder.[15]
- Phentermine and topiramate: evidence has demonstrated weight loss with a BMI reduction of -10.44% (phen/top 15 mg/92 mg) and -8.11% (phen/top 7.5 mg/92 mg) compared to placebo. Phen/top is approved for weight loss in adults.[15]
- Lisdexamfetamine: approved for binge eating disorder in those 18 and older. Lisdexamfetamine is approved for attention-deficit/hyperactivity disorder (ADHD) in children 6 and older. There is insufficient evidence for use in children to assist in weight management.[15]

**Table 14. Recommendations from the American Pediatric Association**[15]

| Recommendation | Grade of Recommendation |
|---|---|
| Pediatricians and other primary health care providers (PHCP) should measure height and weight, calculate BMI, and assess BMI percentile using age- and sex-specific Centers for Disease Control and Prevention growth charts or growth charts for children with severe obesity | B |

| | |
|---|---|
| (assessment interval not reported) or at least annually for all children 2 to 18 years of age to screen for overweight (BMI ≥85th percentile to <95th percentile), obesity (BMI ≥95th percentile) and severe obesity (BMI ≥120% of the 95th percentile for age and sex). | |
| Pediatricians and other PHCPs should provide or refer children 6 years and older (Grade B) and may provide or refer children 2 through 5 years of age (Grade C) with overweight (BMI ≥85th percentile to <95th percentile) and obesity (BMI ≥95th percentile) to intensive health behavior and lifestyle treatment. Health behavior and lifestyle treatment is more effective with greater contact hours; the most effective treatment includes 26 or more hours of face-to-face, family-based, multicomponent treatment over a 3 to 12-month period. | B and C |
| Pediatricians and other PHCPs should offer weight loss pharmacotherapy to adolescents 12 years and older with obesity (BMI ≥95th percentile) according to medication indications, risks, and benefits, as an adjunct to health behavior and lifestyle treatment. | B |

**New Approvals:**

Tirzepatide (ZEPBOUND):

In November 2023, tirzepatide received an FDA approved indication as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of:[16]

- 30 kg/m$^2$ or greater (obesity) or
- 27 kg/m$^2$ or greater (overweight) with the presence of at least one weight-related condition (e.g., hypertension, dyslipidemia, obstructive sleep apnea or CV disease)

Approval was based off of 2 double-blind, placebo-controlled, RCTs (SURMOUNT-1 and SURMOUNT-2).[16] The primary endpoint, mean percent change in body weight and the percentage of patients achieving a 5% or more weight reduction compared to placebo, was assessed at 72 weeks. Tirzepatide was titrated over 20 weeks to a maintenance dose of 5 mg (one study only), 10 mg or 15mg subcutaneously once weekly. Tirzepatide was used in conjunction with a reduced calorie diet (500 kcal/day deficit approximately) and physical activity of 150 min/week. Patients in SURMOUNT-1 lost more weight taking tirzepatide compared to placebo, mean difference of -11.9% to -17.8%.[16] In SURMOUNT-2, treatment with tirzepatide resulted in a mean weight loss compared to placebo of -9.6% and -11.6%. Higher doses were associated more weight reduction.

**Table 15. Randomized Clinical Trials**

| Study | Drug | Population | Primary Endpoint | Results | Comments |
|---|---|---|---|---|---|
| Aronne, et al[6] (SURMOUNT-4)<br><br>DB, PC, Phase 3, RCT | Tirzepatide 10 or 15 mg SC weekly (maximum tolerated dose)<br><br>Vs.<br><br>Placebo | Adults with a BMI of ≥30 kg/m$^2$ or ≥27 kg/m$^2$ and weight-related complication, excluding diabetes<br><br>(n=783, open-label)<br>(n=660, double-blind) | Mean percent change in weight from week 36 to week 88 who maintained a least 80% of the weight-loss during the lead-in period | Mean percent weight change:<br>Tirzepatide: -5.5%<br>Placebo: 14.0%<br>(MD -19.4%;<br>95% CI, -21.2% to -17.7%; P<0.001) | 71% women, 89.5% of patients receiving tirzepatide at 88 weeks maintained at least 80% of weight loss compared to 16.6% receiving placebo (p<0.001) |

| | | | | | |
|---|---|---|---|---|---|
| | 36 week open-label lead-in period followed by a 52-week, double-blind, placebo-controlled trial. | | | | |
| Garvey, et al[3] (SURMOUNT-2)<br><br>DB, PC, Phase 3, RCT | Tirzepatide 10 or 15 mg SC weekly (maximum tolerated dose)<br><br>Vs.<br><br>Placebo<br><br>(72 weeks duration – including a 12 to 20 weeks of dose escalation) | Adults with a BMI of $\geq$27 kg/m$^2$, with T2DM and HbA1c of 7% to 10%<br><br>(n=1514) | Co-primary endpoints of percent change in bodyweight from baseline and bodyweight reduction of 5% or higher | Least squares mean change in body weight:<br>Tirzepatide 10 mg: -12.8%<br>Tirzepatide 15 mg: -14.7%<br>Placebo: -3.2%<br><br>Tirzepatide 10 mg vs. placebo:<br>-9.6% (95% CI, -11.1% to -8.1%);<br>p<0.0001<br><br>Tirzepatide 15 mg vs. placebo:<br>-11.6% (95% CI, -13.0% to -10.1%);<br>p<0.0001<br><br>Bodyweight reduction of 5% or higher:<br>Tirzepatide 10 mg: 79%<br>Tirzepatide 15 mg: 83%<br>Placebo: 32%<br>P<0.0001<br><br>Tirzepatide 10 mg vs. placebo:<br>OR 8.3 (95% CI, 5.6 to 12.3)<br>P<0.0001<br>ARR 47% /NNT 3<br>Tirzepatide 15 mg vs. placebo:<br>OR 10.5 (95% CI, 6.8 to 16.1)<br>P<0.0001<br>ARR 51% /NNT 2 | Mean age of 54.2 years, 76% white, 51% female with a baseline BMI of 36.1 kg/m$^2$. |

| | | | | | |
|---|---|---|---|---|---|
| Jastreboff, et al[2] (SURMOUNT-1)<br><br>DB, PC, Phase 3, RCT | Tirzepatide 5*, 10 or 15 mg SC weekly (maximum tolerated dose)<br><br>Vs.<br><br>Placebo<br><br>(72 weeks duration including a 20-week dose-escalation phase)<br><br>* Tirzepatide 5 mg was analyzed as a secondary endpoint and was not part of the co-primary endpoint. | Adults with a BMI of $\geq$30 kg/m$^2$ or $\geq$27 kg/m$^2$ with at least one weight related complication (excluding diabetes)<br><br>(n=2539) | Co-primary endpoints of percent change in bodyweight from baseline and bodyweight reduction of 5% or higher | Mean change in body weight:<br>Tirzepatide 5 mg: -15.0%<br>Tirzepatide 10 mg: -19.5%<br>Tirzepatide 15 mg: -20.9%<br>Placebo: -3.1%<br><br>Tirzepatide 5 mg vs. placebo:<br>-11.9% (95% CI, -3.4% to -10.4%);<br>p<0.001<br><br>Tirzepatide 10 mg vs. placebo:<br>-16.4% (95% CI, -17.9% to -14.8%);<br>p<0.001<br><br>Tirzepatide 15 mg vs. placebo:<br>-17.8% (95% CI, -19.3% to -16.3%);<br>p<0.001<br><br>Bodyweight reduction of 5% or higher:<br>Tirzepatide 5 mg: 85%<br>Tirzepatide 10 mg: 89%%<br>Tirzepatide 15 mg: 91%<br>Placebo: 35%<br>P<0.001<br><br>Tirzepatide 5 mg vs. placebo:<br>ARR 50% / NNT 2<br>Tirzepatide 10 mg vs. placebo:<br>ARR 54% / NNT 2<br>Tirzepatide 15 mg vs. placebo:<br>ARR 56% / NNT 2 | Mean baseline BMI 38.0 kg/m$^2$, mean age of 44.9 years, 67.5% female and 70.6% white. |
| Knop, et al[17] (OASIS 1)<br><br>DB, PC, Phase 3, RCT | Semaglutide 50 mg orally<br><br>Vs.<br><br>Placebo daily | Adults with a BMI of least 30 kg/m$^2$ or at least 27 kg/m$^2$ with bodyweight-related complications and comorbidities, without T2DM | Co-primary endpoints of percent change in bodyweight from baseline and bodyweight | Mean change in bodyweight:<br>Semaglutide: -15.1%<br>Placebo: -2.4%<br>ETD -12.7% (95% CI, -14.2 to -11.3)<br>P<0.0001<br><br>Bodyweight reduction of 5% or higher: | Adults enrolled with comorbidities were most likely to have hypertension (46%) or dyslipidemia (40%). Seventy-three percent of participants were female, mean BMI was |

| | | | | | |
|---|---|---|---|---|---|
| | (17 months) | (n=667) | reduction of 5% or higher | Semaglutide: 269 (85%)<br>Placebo: 76 (26%)<br>P<0.0001<br>ARR 59%/NNT 2 | 37.5 kg/m$^2$ and average age of 50 years. |
| Lincoff, et al[5] (SELECT Trial)<br><br>DB, PC, Phase 3, RCT | Semaglutide 2.4 mg SC weekly<br><br>Vs.<br><br>Placebo<br><br>(mean exposure of 34.2 months) | Adults with CV disease, and BMI of 27 kg/m$^2$ or greater and no diabetes<br><br>(n=17604) | Composite of death from CV causes, nonfatal MI or nonfatal stroke | CV end-point event:<br>Semaglutide: 569 (6.5%)<br>Placebo: 701 (8.0%)<br><br>HR 0.80 (95% CI, 0.72 to 0.90)<br>P<0.001<br><br>ARR 1.5%/NNT 67 | Mean duration of exposure was 34.2 months, mean age was 61.6 years, 73% male, and 84% White. Mean bodyweight was a BMI of 33 kg/m$^2$. Individual components of composite endpoint were not statistically different between semaglutide and placebo. Sixty-seven people would need to be treated for approximately 34 months to prevent one CV event. |
| Wadden, et al[4] (SURMOUNT-3)<br><br>DB, PC, Phase 3, RCT | Tirzepatide 10 or 15 mg SC weekly (maximum tolerated dose)<br><br>Vs.<br><br>Placebo<br><br>(72 weeks duration) | Adults with a BMI of $\geq$30 kg/m$^2$ or $\geq$27 kg/m$^2$ with at least one weight related complication (excluding diabetes) who achieved $\geq$5.0% weight reduction in 12-week intensive lifestyle program<br><br>(n=579) | Co-primary endpoints of percent change in bodyweight from baseline and bodyweight reduction of 5% or higher | Least squares mean change in body weight:<br>Tirzepatide 10 mg and 15 mg (pooled results): -18.4%<br>Placebo: -2.5%<br><br>Tirzepatide vs. placebo:<br>-20.8% (95% CI, -23.2% to -18.5%);<br>p<0.001<br><br>Bodyweight reduction of 5% or higher:<br>Tirzepatide 10 mg and 15 mg (pooled doses): 87.5%<br>Placebo: 16.5%<br>OR 34.6 (19.2 to 62.6)<br>P<0.001<br>ARR 71% / NNT 2 | Baseline BMI was 39 kg/m$^2$, mean age of 46 years, 63% female and 86% White. |
| Abbreviations: ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; CV = cardiovascular; DB = double-blind; HbA1c = hemoglobin A1c; MD = mean difference; MI = myocardial infarction; NNT = number needed to treat; OR = odds ratio; PC = placebo-controlled; RCT = randomized controlled trials; SC = subcutaneous; T2DM = type 2 diabetes mellitus | | | | | |

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**Appendix 1:** Current Preferred Drug List

| Generic | Brand | Form | Route |
|---|---|---|---|
| benzphetamine HCl | BENZPHETAMINE HCL | TABLET | Oral |
| diethylpropion HCl | DIETHYLPROPION HCL | TABLET | Oral |
| diethylpropion HCl | DIETHYLPROPION HCL ER | TABLET ER | Oral |
| liraglutide | SAXENDA | PEN INJCTR | Subcutaneous |
| orlistat | ORLISTAT | CAPSULE | Oral |
| orlistat | XENICAL | CAPSULE | Oral |
| phendimetrazine tartrate | PHENDIMETRAZINE TARTRATE ER | CAPSULE ER | Oral |
| phendimetrazine tartrate | PHENDIMETRAZINE TARTRATE | TABLET | Oral |
| phentermine HCl | ADIPEX-P | CAPSULE | Oral |
| phentermine HCl | PHENTERMINE HCL | CAPSULE | Oral |
| phentermine HCl | ADIPEX-P | TABLET | Oral |
| phentermine HCl | LOMAIRA | TABLET | Oral |
| phentermine HCl | PHENTERMINE HCL | TABLET | Oral |
| semaglutide | WEGOVY | PEN INJCTR | Subcutaneous |
| setmelanotide acetate | IMCIVREE | VIAL | Subcutaneous |
| tirzepatide | ZEPBOUND | PEN INJCTR | Subcutaneous |
| naltrexone/bupropion | CONTRAVE | TABLETS | Oral |
| Phentermine/topiramate | QSYMIA | CAPSULES | Oral |

**Appendix 2:** Search History

Database(s): **Ovid MEDLINE(R) ALL** 1946 to January 05, 2024

Search Strategy:

| # | Searches | Results |
|---|---|---|
| 1 | Benzphetamine/ | 326 |
| 2 | diethylpropion.mp. or Diethylpropion/ | 399 |
| 3 | liraglutide.mp. or Liraglutide/ | 4247 |
| 4 | orlistat.mp. or Orlistat/ | 2408 |
| 5 | phendimetrazine.mp. | 110 |
| 6 | phentermine.mp. or Phentermine/ | 1298 |
| 7 | semaglutide.mp. | 1482 |
| 8 | setmelanotide.mp. | 99 |
| 9 | tirzepatide.mp. | 373 |
| 10 | naltrexone.mp. or Naltrexone/ | 11344 |
| 11 | bupropion.mp. or Bupropion/ | 5700 |
| 12 | phentermine.mp. or Phentermine/ | 1298 |
| 13 | topiramate.mp. or Topiramate/ | 5834 |
| 14 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 | 31140 |
| 15 | limit 14 to (english language and humans and yr="2022 -Current") | 1896 |
| 16 | limit 15 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review") | 241 |

# Weight Management Drugs for Youth

## Goal(s):

- Allow case-by-case review for members covered under the EPSDT program. Recommend semaglutide as weight reduction pharmacotherapy in patients which evidence has demonstrated efficacy, including CV benefits. (e.g. patients with a BMI ≥30 kg/m$^2$ or with a BMI of ≥27 kg/m$^2$ and comorbid conditions [e.g., diabetes mellitus, hypertension, dyslipidemia, or cardiovascular disease]).

## Length of Authorization:

- Up to 6 months

## Requires PA:

- Non-preferred drugs used for weight management.

**Table 1. Drugs FDA Approved for Weight Management**

| Drug | Adults | Pediatrics |
|---|---|---|
| Liraglutide (SAXENDA) | Yes | Yes – 12 years and older |
| Naltrexone/bupropion (CONTRAVE) | Yes | No |
| Phentermine/topiramate (QSYMIA) | Yes | Yes – 12 years and older |
| Semaglutide (WEGOVY) | Yes | Yes – 12 years and older |
| Tirzepatide (ZEPBOUND) | Yes | No |
| Setmelanotide (IMCIVREE) | Yes | Yes – 6 years and older |

## Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

**Table 2. BMI Cutoffs for Obesity by Sex and Age for Pediatric Patients Aged 12 Years and Older (CDC Criteria)**

| Age (years) | Body mass index (kg/m2) at 95% percentile | |
|---|---|---|
| | Males | Females |
| 12 | 24.2 | 25.2 |
| 12.5 | 24.7 | 25.7 |
| 13 | 25.1 | 26.3 |
| 13.5 | 25.6 | 26.8 |

| | | |
|---|---|---|
| 14 | 26.0 | 27.2 |
| 14.5 | 26.4 | 27.7 |
| 15 | 26.8 | 28.1 |
| 15.5 | 27.2 | 28.5 |
| 16 | 27.5 | 28.9 |
| 16.5 | 27.9 | 29.3 |
| 17 | 28.2 | 29.6 |
| 17.5 | 28.6 | 30 |

| **Approval Criteria** | | |
|---|---|---|
| 1. What diagnosis is being treated? | Record ICD10 code. | |
| 2. Is this a request for continuation of therapy after an initial approval by FFS? | **Yes**: Go to renewal criteria | **No:** Go to #3 |
| 3. Is this an FDA approved indication? | **Yes**: Go to #4 | **No:** Pass to RPh. Deny; medical appropriateness |
| 4. Is requested medication for a patient less than 21 years of age and 12 years of age or older? | **Yes:** Go to #5 | **No:** Deny; weight loss drugs are not covered by OHP for adults |
| 5. Is the request for setmelanotide? | **Yes**: Go to #6 | **No:** Go to #8 |
| 6. Does the patient have obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance OR does the patient have Bardet—Biedl syndrome (BBS)? | **Yes**: Go to #7 | **No:** Deny; medical appropriateness. |
| 7. Does the patient have a history of depression and/or suicidal ideation? | **Yes**: Deny; medical appropriateness. | **No:** Approve for up to 6 months. |

| Approval Criteria | | |
|---|---|---|
| 8. Does the patient have a BMI corresponding to 30 kg/m$^2$ or ≥27 kg/m$^2$ and comorbid conditions [e.g., diabetes mellitus, hypertension, dyslipidemia, or cardiovascular disease] for adults or a BMI at the 95$^{th}$ percentile or greater for age and sex (Table 2 above)? | **Yes:** Go to #9<br><br>Record baseline BMI | **No:** Deny; medical appropriateness |
| 9. Does the patient have comorbidities (e.g., hypertension, dyslipidemia, diabetes, fatty liver disease, depression, or sleep apnea)? | **Yes:** Go to #11 | **No:** Go to #10 |
| 10. Has the patient previously tried a weight loss treatment plan administered by a health care provider (e.g., diet and exercise program, nutritional counseling, and/or a calorie restricted diet) for a time period of at least 3 months within the previous 6 month timeframe*?<br><br>* See Clinical Notes Below | **Yes:** Go to #11 | **No:** Deny; medical appropriateness. Lifestyle modifications are recommended by guidelines. |
| 11. Will the patient be engaged in a weight management lifestyle modification program in addition to pharmacotherapy? | **Yes:** Approve for 6 months. Medication supply is subject to quantity limits. | **No:** Deny; medical appropriateness. All drugs approved for weight loss are indicated as an adjunct to diet and exercise. |

| Renewal Criteria | | |
|---|---|---|
| 1. Is this a request for a weight loss medication previously approved under the EPSDT program? | **Yes**: Go to #2 | **No:** Go to **Approval Criteria** above |

| Renewal Criteria | | |
|---|---|---|
| 2. Is the person requesting the medication less than 21 years of age? | **Yes:** Go to #3 | **No:** Deny; weight loss not covered by OHP |
| 3. Has the patient lost at least 1% of BMI from baseline or maintained at least a 1% BMI weight loss? | **Yes:** Go to #4 | **No:** Deny; medical appropriateness |
| 4. Is the patient continuing with a weight loss treatment plan (e.g., diet and exercise program, nutritional counseling, and/or a calorie restricted diet)? | **Yes:** Go to #5 | **No:** Deny; medical appropriateness. All drugs approved for weight loss are indicated as an adjunct to diet and exercise. |
| 5. Has the patient been adherent to therapy based on provider attestation? | **Yes:** Approve for 6 months | **No:** Deny; medical appropriateness |

*P&T/DUR Review: 4/24 (KS)*
*Implementation: TBD*

## *Clinical Notes

Adapted from the following guideline on the treatment of adolescents with obesity:

- American Academy of Pediatrics. *Pediatrics*. 2023;151(2): e2022060640. Available at: https://publications.aap.org/pediatrics/article/151/2/e2022060640/190443/Clinical-Practice-Guideline-for-the-Evaluation-and?autologincheck=redirected

Recommended Behavior Strategies

| Strategy | Description |
|---|---|
| 1. Reduction in sugar-sweetened beverages (SSBs) | Higher intake of sugar-sweetened beverages (carbonated beverages, sweetened beverages, soda, sports drinks, and fruit drinks) is associated with greater weight gain in adults and children. The American Heart Association (AHA) recommends not more than 25 g (6 tsp) each day of added sugar and not more than 1, 8-oz serving of SSB per week. The AAP |

| | |
|---|---|
| | discourages the consumption of sports drinks and energy drinks for children and adolescents. The AAP statement on fruit juice notes that it is a poor substitute for whole fruit because of its high sugar and calorie content and pediatricians should advocate for elimination of fruit juice in children with excessive weight gain. |
| 2. Choose My Plate | MyPlate is the US Department of Agriculture's (USDA) broad set of recommendations for healthy eating for Americans. These recommendations include multiple healthy diet goals: low in added sugar, low in concentrated fat, nutrient dense but not calorie dense, within an appropriate calorie range without defined calorie restriction, and with balanced protein and carbohydrate. The principles can be adapted to different food cultures. There is a surprising dearth of literature on the impact of these guidelines on health and BMI outcomes and on the most effective education practices.<br>**Available at: USDA choose my plate.gov** |
| 3. 60 minutes daily of moderate to vigorous physical activity | Aerobic exercise, especially for 60 min at a time, is associated with improved body weight in youth although its effect may be small and variable. It is also associated with better glucose metabolism profiles. High-intensity interval training in youth with obesity may improve body fat, weight, and cardiometabolic risk factors, although the effect is variable. The Physical Activity Guidelines for Americans recommends 60 min per day for children and adolescents. |
| 4. Reduction in sedentary behavior | Reduction in sedentary behavior, generally defined as reduced screen time, has consistently shown improvement in BMI measures, although impact is small. Early studies focused on reduced television, a discrete activity that is simpler than current multifunctional electronic devices. The AAP recommends no media use under age 18 month, a 1-hour limit for ages 2–5 years, and a parent- monitored plan for media use in older children, with a goal of appropriate, not- excessive use but without a defined upper limit. |
| The activities most commonly associated with positive behavior change are: parental involvement in goal setting, problem solving, social support, demonstrating desired behaviors, and home environment modifications to support positive change. | |
| Abbreviations: AAP – American Academy of Pediatrics; BMI = body mass index; oz = ounce; tsp = teaspoon; USDA = United States Department of Agriculture | |

# Weight Management Drugs for Adults

**Goal(s):**

- To provide guidance for the use of weight management therapies to ensure they are used in the most appropriate patient populations in which evidence supports efficacy and safety.

**Length of Authorization:**

- Up to 6 months

**Requires PA:**

- All drugs used for weight management.

**Table 1. Drugs FDA Approved for Weight Management**

| Drug |
|---|
| Liraglutide (SAXENDA) |
| Naltrexone/bupropion (CONTRAVE) |
| Phentermine/topiramate (QSYMIA) |
| Semaglutide (WEGOVY) |
| Tirzepatide (ZEPBOUND) |
| Setmelanotide (IMCIVREE) |

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

| **Approval Criteria** | | |
|---|---|---|
| 1. What diagnosis is being treated? | Record ICD10 code. | |
| 2. Is this a request for continuation of therapy after an initial approval? | **Yes**: Go to **Renewal Criteria** below | **No:** Go to #3 |

| Approval Criteria | | |
|---|---|---|
| 3. Is this an FDA approved indication? | **Yes**: Go to #4 | **No:** Pass to RPh. Deny; medical appropriateness |
| 4. Will the prescriber consider a change to a preferred product?<br><br>Message:<br>Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee. | **Yes:** Inform prescriber of covered alternatives in class | **No:** Go to #5 |
| 5. Is the request for setmelanotide? | **Yes**: Go to #6 | **No:** Go to #8 |
| 6. Does the patient have obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance OR the patient has Bardet-Biedl syndrome (BBS)? | **Yes**: Go to #7 | **No:** Deny; medical appropriateness. |
| 7. Does the patient have a history of depression and/or suicidal ideation? | **Yes**: Deny; medical appropriateness. | **No:** Approve for up to 6 months. |
| 8. Has the patient tried a weight loss treatment plan (e.g., diet and exercise program, nutritional counseling, and/or a calorie restricted diet), for at least 3 months duration, within the last 6 months and been unable to meet weight loss goals? | **Yes:** Go to #9 | **No:** Deny; medical appropriateness. All drugs approved for weight loss are indicated as an adjunct to diet and exercise. |
| 9. Does the patient have a BMI $\geq$30 kg/m$^2$ or a BMI of $\geq$27 kg/m$^2$ and at least one weight-related comorbid condition (e.g., type 2 diabetes mellitus, hypertension, dyslipidemia, or cardiovascular disease)? | **Yes:** Go to #10 | **No:** Deny; medical appropriateness |

| Approval Criteria | | |
|---|---|---|
| 10. Is the patient enrolled in a Medicaid approved lifestyle modification program*? | **Yes:** Approve for up to 6 months to allow for titration. Medication supply is subject to quantity limits. | **No:** Deny; medical appropriateness |
| * An approved Oregon FFS Medicaid lifestyle modification program is to be determined and should document adherence to diet modifications and physical activity requirements | | |

| Renewal Criteria | | |
|---|---|---|
| 1. Is this a request for a weight loss medication previously approved? | **Yes**: Go to #2 | **No:** Go to Approval Criteria above |
| 2. Has the patient lost at least 5% of their BMI from baseline or maintained at least a 5% BMI weight loss? | **Yes:** Go to #3 | **No:** Deny; medical appropriateness |
| 3. Is the request for continuation of therapy without a lapse in treatment? | **Yes:** Go to #5 | **No:** Go to #4 |
| 4. Is the request for an additional trial of the same or different weight loss drug within the last 2 years AND the medication is being prescribed by a specialist? | **Yes:** Go to #5 | **No:** Deny; medical appropriateness. Refer patient to a specialist to ensure appropriate weight loss management. |
| 5. Is the patient continuing with a weight loss treatment plan (e.g., diet and exercise program, nutritional counseling, and/or a calorie restricted diet) and has been adherent to drug therapy? | **Yes:** Approve for 12 months | **No:** Deny; medical appropriateness. All drugs approved for weight loss are indicated as an adjunct to diet and exercise. |

*P&T/DUR Review: 4/24 (KS)*
*Implementation:*