Pharmacologic Agents for Weight Management: Clinical Evidence and Management Strategies

EXECUTIVE SUMMARY

Systematic Review and Policy Report

October 2023

Executive Summary

Background

The US has both the highest rate of obesity among high-income countries and the highest per capita health expenditure related to overweight and obesity in the world. Obesity has been considered a national epidemic by the Centers for Disease Control since 1999, and the most recent data show the persistence of an upward trend of adult obesity increasing from 36% in 2020 to 41% in 2021. Obesity was recognized as a disease by the American Medical Association in 2013 and is clinically defined as a body mass index (BMI) of 30 mg/kg^2 and higher in adults (overweight defined as a BMI greater than 25 but under 30); a BMI in the 95th percentile or higher for age and sex is classified as obese in youth ages 2 to 20 years. Excess body fat and increasing weight are positively correlated with morbidity and all-cause mortality. Obesity is a complex disease caused by a variety of factors including genetic, environmental, and societal components. Prevalence of obesity is greater among low-income individuals, and racial and ethnic disparities in the US are notable. With Medicaid covering mostly low-income individuals, people covered by Medicaid are 27% more likely to be obese compared to those with commercial insurance.

Lifestyle behavioral modifications continue to be the first line of treatment for obesity, although they are mostly ineffective for long-term weight loss. Research has illuminated the biological basis for obesity, advancing medical treatments in bariatric surgery and pharmacotherapy. Currently, 6 drugs are approved by the US Food and Drug Administration (FDA) for chronic weight loss management. Cost is a major barrier to chronic weight management medications. Insurance coverage historically has been mixed for weight management drugs. Broadly, state Medicaid programs are required to cover FDA-approved outpatient drugs that have a rebate agreement on file with the US Department of Health and Human Services. Federal law explicitly excludes several drugs and drug classes from mandatory coverage by Medicaid programs, including drugs for weight loss, sexual dysfunction, cosmetic use, hair growth, and infertility.

Medicaid administrators are interested in learning about the clinical evidence for chronic weight management drugs, including longer-term effects and cost-effectiveness; the clinical criteria Medicaid programs use when determining the appropriate populations for weight management drugs; and the appropriate use of these chronic weight management drugs in the obesity treatment pathway.

PICOS and Key Questions

This report focuses on select drugs for weight management in individuals of any age with primary overweight or obesity. We identified published and ongoing randomized controlled trials (RCTs), nonrandomized studies (with greater limits), and economic studies that reported the effectiveness (e.g., changes in body weight, weight-related comorbidities, quality of life [QoL]), harms (e.g., adverse events [AEs], withdrawals due to AEs), and cost-effectiveness of FDA-approved pharmacological agents, select pipeline drugs (tirzepatide), and off-label treatments (i.e., glucagon-like peptide-1 [GLP-1] agonists) for chronic weight management. Eligible comparators included another active treatment, standard of care including lifestyle interventions, and surgery or other medical devices, and placebo.

Methods

Published and ongoing trials for the evidence and economic review were identified through searching bibliographic databases (e.g., Ovid MEDLINE) through February 3, 2023; scanning reference lists of relevant systematic reviews; and searching several other websites. Effectiveness and harms literature was limited by geography (countries assessed as very high human development according to the United Nations' Human Development Index) and study duration (at least 1 year except for setmelanotide, and for studies in pediatric and type 1 diabetes [T1DM] populations); key limitations for economic studies were US data only and published within the past 5 years. We assessed the risk of bias (RoB) of eligible studies using standard instruments adapted from national and international quality standards. We rated the certainty of evidence (CoE) for 4 outcome categories for drugs with identified evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. Where appropriate, statistical tests for differences (two-tailed Mantel-Haenzel chi-square) were calculated using OpenEpi and RevMan software. We combined data for meta-analyses of major outcomes with sufficient published data using RevMan 5.4. Throughout the report, statistical significance is implied when effects are reported as significant, or significantly different.

Core policy sources (e.g., FDA) and DuckDuckGo were also searched for policy and management strategy key questions, and 4 state Medicaid officials and 3 subject matter experts were interviewed.

Key Findings

Effectiveness and Harms Findings

We identified 36 studies in 47 publications for effectiveness and harms key questions:

- Liraglutide: 13 RCTs in 17 publications, 11 in adults and 2 in youth (all are vs. placebo)
- Semaglutide: 7 RCTs in 8 publications, 6 in adults and 1 in youth (all are vs. placebo)
- Semaglutide: 1 RCT in adults (vs. liraglutide)
- Tirzepatide: 1 RCT in adults (vs. placebo)
- Exenatide: 1 RCT in adults (vs. glibenclamide) and 2 in youth (vs. placebo)
- Naltrexone-bupropion: 5 RCTs in 6 publications in adults (4 vs. placebo and 1 vs. usual care)
- Phentermine-topiramate: 3 RCTs in 6 publications, 2 in adults and 1 in youth (all vs. placebo)
- Setmelanotide: 1 RCT with single-arm extension in 2 publications (vs. placebo) and 2 single-arm studies in 3 publications

No eligible trials for effectiveness and harms were identified for dulaglutide and lixisenatide.

All included studies for all drugs were funded by industry, and most authors had important conflicts of interest. Funding industry sponsors were involved in the design, data analysis, and report writing for many of the included published studies, and some authors held patents or stock options with the company providing the medications and funding the study.

Adults

Weight

- All included drugs were effective at reducing body weight respective to studied comparators (placebo, glibenclamide, or usual care).

- Tirzepatide, semaglutide, and phentermine-topiramate achieved clinically meaningful levels of at least 5% loss of body weight compared to placebo at 15.4% (1 RCT for tirzepatide, N = 2,539; moderate CoE), 11.6% (7 RCTs for semaglutide, N = 4,997; low CoE), and 8.6% (2 RCTs for phentermine-topiramate, N = 3,513; low CoE). Compared to glibenclamide, exenatide achieved a mean of 12.7 kg weight loss (1 RCT, N = 128; moderate CoE); a calculation of percent change in body weight suggests this difference was clinically meaningful.
- Liraglutide (7 RCTs, N = 5,864; low CoE) and naltrexone-bupropion (4 RCTs, N = 4,122; low CoE) achieved smaller, but statistically significant, reductions in percent body weight loss of less than 5%, compared to placebo.
- In the single head-to-head trial, semaglutide resulted in a clinically meaningful difference in weight loss of 9.4% compared to liraglutide (N = 253; low CoE) and participants who received semaglutide were nearly 3 times more likely to achieve at least 10% weight loss (low CoE).

- Table ES-1 presents the probabilities that individuals exposed to the drug achieved at least 5% and 10% weight loss, compared to individuals who received placebo (as risk ratio [RR]); drugs with the highest probabilities are listed first. We did not identify any eligible studies reporting this outcome for exenatide.

Table ES-1. Risk Ratio for 5% and 10% Weight Loss in Adults Compared With Placebo

With ≥ 5% Weight Loss vs. Placebo				With ≥ 10% Weight Loss vs. Placebo			
Drug	No. RCTs	N	Risk Ratio	Drug	No. RCTs	N	Risk Ratio
PhenTop	2	3,444	3.5 (95% CI, 2.9 to 4.1)	PhenTop	2	3,444	6.1 (95% CI, 5.1 to 7.4)
Tirzepatide	1	2,539	2.6 (95% CI, 2.3 to 2.9)	**Semaglutide**	7	4,727	4.7 (95% CI, 3.5 to 6.3)
Semaglutide	6	4,786	2.3 (95% CI, 1.9 to 2.8)	Tirzepatide	1	2,539	4.1 (95% CI, 3.5 to 4.8)
NalBup	4	3,710	2.3 (95% CI, 1.7 to 3.2)	NalBup	4	3,035	3.1 (95% CI, 2.1 to 4.7)
Liraglutide	7	5,817	2.0 (95% CI, 1.6 to 2.6)	Liraglutide	8	6,012	2.7 (95% CI, 2.0 to 3.5)
Key.	*Moderate CoE*	*Low CoE*					

Abbreviations. CI: confidence interval; CoE: certainty of evidence; NalBup: naltrexone-bupropion; PhenTop: phentermine-topiramate.

Indirect Measures for Comorbidity Risk Factors

Systolic Blood Pressure

- Only tirzepatide demonstrated a clinically meaningful reduction in systolic blood pressure (SBP) of at least 5 mmHg compared to placebo (-6.2 mmHg; 1 RCT, N = 2,539; low CoE).
- In general, liraglutide (10 RCTs, N = 6,125; moderate CoE), semaglutide (7 RCTs, N = 4,997; low CoE), and phentermine-topiramate (2 RCTs, N = 3,513; moderate CoE) achieved small but statistically significant decreases in SBP compared to placebo of less than 5 mmHg; there was no difference in the head-to-head trial of semaglutide and liraglutide (N = 253; very low CoE).

- Use of naltrexone-bupropion resulted in a small but significant *increase* in SBP over 52 weeks compared to placebo; this effect was not unexpected and improved with weight loss over time (3 RCTs, N = 3,447; low CoE).
- Change in SBP was not measured in the study of exenatide in adults.

Low-Density Lipoprotein Cholesterol

- None of the drugs reduced low-density lipoprotein (LDL) cholesterol by clinically meaningful levels of at least 1 mmol/L (about 36 mg/dL) compared to placebo.
- In general, liraglutide (8 RCTs, N = 5,701; moderate CoE), semaglutide (5 RCTs, 2,221; low CoE), tirzepatide (1 RCT, N = 2,539; moderate CoE), naltrexone-bupropion (4 RCTs, N = 4,122; low CoE), and phentermine-topiramate (2 RCTs, N = 3,513; moderate CoE) achieved small, but statistically significant, decreases in LDL cholesterol compared to placebo, but not at clinically meaningful levels.
- There was no difference in change in LDL cholesterol in the head-to-head trial of semaglutide and liraglutide (N = 253; very low CoE).
- Change in LDL cholesterol was not measured in the study of exenatide in adults.

Hemoglobin A1c

- Tirzepatide demonstrated clinically meaningful improvements (by at least 0.3%) in hemoglobin A1c (HbA1c) compared to placebo in people without type 2 diabetes (T2DM) by 0.4% (1 RCT, N = 2,539; moderate CoE).
- In general, liraglutide (8 RCTs, N = 5,955; low CoE), semaglutide (7 RCTs, N = 4,997; low CoE), and naltrexone-bupropion (1 RCT, N = 424; very low CoE) reduced HbA1c levels by clinically meaningful levels, mostly in populations with elevated baseline levels and people with T2DM.
- In general, change in percent HbA1c was statistically lower with phentermine-topiramate compared with placebo (1 RCT, N = 2,487; moderate CoE), but the pooled effect did not reach a clinically meaningful difference of at least 0.3% in people with mostly normal baseline HbA1c levels; the small difference between semaglutide and liraglutide was also not at clinically meaningful levels in the single head-to-head study (N = 253; low CoE).
- There was no difference in change in percent HbA1c between exenatide and glibenclamide (N = 128; low CoE).

Quality of Life

- QoL was measured in studies of liraglutide (6 RCTs, N = 5,509; low CoE), semaglutide (5 RCTs, N = 4,481; low CoE), tirzepatide (1 RCT, N = 1,909; moderate CoE), and naltrexone-bupropion (3 RCTs, N = 4,031; low CoE) in adults; overall, these drugs statistically improved physical functioning QoL compared to placebo, but likely not at clinically meaningful levels.

Safety

Withdrawals Due to Adverse Events

- Compared with placebo, all drugs resulted in significantly greater withdrawals due to AEs:
  - Liraglutide: RR, 2.20 (11 RCTs, N = 6,480; moderate CoE)
  - Semaglutide: RR, 1.81 (7 RCTs, N = 4,995; moderate CoE)
  - Tirzepatide: RR, 2.21 (1 RCT, N = 2,539; moderate CoE)
  - Naltrexone-bupropion: RR, 1.92 (4 RCTs, N = 4,481; moderate CoE)

- Phentermine-topiramate: RR, 1.88 (2 RCTs, N = 3,713; moderate CoE)

In the single head-to-head study, liraglutide was associated with nearly 4 times the risk of withdrawal due to an AE compared with semaglutide (N = 253; very low CoE).

There was no difference in withdrawals due to AEs of exenatide compared with glibenclamide (1 RCT, N = 128; low CoE).

Very high drop-out rates in the studies of naltrexone-bupropion (range across 5 RCTs, 50% to 63%) and phentermine-topiramate (range across 3 RCTs, 54% to 62%) should also be considered when assessing safety and tolerability; explanations were mostly vague with broad categories for reasons of withdrawal (e.g., "lost to follow-up," "withdrew consent," "drug non-compliance").

Adverse and Serious Adverse Events

In general, there were more AEs compared to placebo for all drugs. All common AEs occurred more frequently with the drug than with placebo, and they included:

- Liraglutide, semaglutide, and tirzepatide: nausea, diarrhea, constipation, and vomiting
- Naltrexone-bupropion: nausea, constipation, headaches, dizziness, and dry mouth
- Phentermine-topiramate: paresthesia (i.e., tingling or burning sensation of the skin), dry mouth, constipation, disordered taste, insomnia, and dizziness
- Exenatide compared to glibenclamide: more nausea, diarrhea and vomiting with exenatide; more hypoglycemia with glibenclamide

Overall, there were few serious adverse events (SAEs) across studies, and they were generally poorly described. However, in general, SAEs, occurred slightly more often with medication compared with placebo, and those attributed to the drug were often conditions triggered by rapid weight loss, such as issues with the hepatobiliary systems (e.g., cholecystitis, cholelithiasis).

Deaths

Deaths were rare and either not further described or reported as not considered related to the study drug.

Change in Medication Use

In general, net use of oral medications prescribed to improve blood pressure, cholesterol levels, and blood glucose levels decreased in all studies measuring these outcomes. Change in insulin use was measured for liraglutide in 1 RCT in people with T2DM and in 3 RCTs in people with T1DM; total insulin units used per day was lower with liraglutide than with placebo across studies, but whether the difference was statistically significant depended on diabetes type or dose of liraglutide used.

Youth

We identified studies in youth for liraglutide (10 to 17 years), semaglutide (adolescents only), exenatide (10 to 18 years), and phentermine-topiramate (adolescents only).

Weight

All drugs were effective at reducing body weight respectively compared to placebo in youth:

- Semaglutide achieved clinically meaningful decreases in BMI z/standard deviation (SD) scores (at least 0.2 SDs) and percent BMI (at least 5%) compared to placebo:

    - BMI z/SD scores: -1.0 points (1 RCT, N = 201; moderate CoE)
    - BMI, %: -16.7% (1 RCT, N = 201; moderate CoE)
- The single study of phentermine-topiramate in adolescents did not measure BMI z/SD scores, but it measured percent BMI and found clinically meaningful improvements compared to placebo:
    - BMI, %: -9.7% (1 RCT, N = 223; low CoE)
- Liraglutide achieved significant improvements in in BMI z/SD scores and in percent BMI in 1 study, but at borderline levels of important differences across both measures:
    - BMI z/SD scores: -0.21 (2 RCTs, N = 386; low CoE)
    - BMI, %: -4.64% (1 RCT, N = 251; low CoE)
- Exenatide achieved a small and significant (but not clinically meaningful) decrease in change in BMI z/SD scores (1 RCT, N = 44; very low CoE) compared to placebo in 1 study at 24 weeks, but no difference in percent BMI (1 RCT, N = 66; very low CoE) in another study at 52 weeks.

Only 1 study in adolescents reported the proportion who achieved at least 5% and 10% weight loss. The probability of adolescents who received semaglutide and achieved at least:

- 5% weight loss was 4.1 times that of those who received placebo (N = 201; moderate CoE)
- 10% weight loss was 7.7 times that of those who received placebo (N = 201; moderate CoE)

Indirect Measures for Comorbidity Risk Factors

Systolic Blood Pressure

- Only liraglutide demonstrated a reduction in SBP at the level for statistical significance in youth, compared to placebo, but not at a clinically meaningful levels of at least 5 mmHg (*P* = .04; 1 RCT, N = 386; moderate CoE).
- There was no difference in SBP compared to placebo in youth for semaglutide (1 RCT, N = 201; moderate CoE), exenatide (2 RCTs, N = 110; low CoE), and phentermine-topiramate (1 RCT; N = 223; low CoE).

Low-Density Lipoprotein Cholesterol

- Only semaglutide demonstrated an overall significant reduction in LDL cholesterol compared to placebo in youth, but the difference is likely not clinically meaningful (1 RCT, N = 201; moderate CoE).
- There was no difference in change in LDL cholesterol compared to placebo in youth for liraglutide (2 RCTs, N = 386; moderate CoE).
- Exenatide demonstrated a small (and not clinically meaningful), but statistically significant, reduction in change in LDL cholesterol compared to placebo over 24 weeks in 1 RCT (N = 44), while in another RCT (N = 66), there was no difference in maintenance of reduced LDL cholesterol at 52 weeks in after a weight loss of at least 5% during a 4-week run-in period.
- LDL cholesterol was not reported in the study for phentermine-topiramate.

Hemoglobin A1c

- Only semaglutide demonstrated a clinically meaningful reduction in percent HbA1c compared to placebo in adolescents with normal mean levels at baseline (4% of population with T2DM; mean difference [MD], -0.3%; 1 RCT, N = 201; low CoE).

- There was no overall difference in percent change in HbA1c from placebo for liraglutide in youth (although it may depend on diabetes status; 2 RCTs, N = 386; very low CoE), and for exenatide (1 RCT, N = 66; low CoE).
- Change in HbA1c was not measured in the study of phentermine-topiramate in youth.

Quality of Life

- In youth, QoL was measured in studies of liraglutide (1 RCT, N = 251; moderate CoE) and exenatide (1 RCT, N = 66; very low CoE); overall, there was no difference in QoL survey scores compared to placebo.

Safety

Withdrawals Due to Adverse Events

- There were no significant differences in withdrawals due to AEs compared to placebo for all drug interventions in youth. Overall, there were few AEs that led to withdrawal across the different medications (32 across all studies and groups [N = 386]). Our CoE was rated as very low for liraglutide, exenatide, and phentermine-topiramate and low CoE for semaglutide.

Adverse and Serious Adverse Events

- For liraglutide (2 RCTs, N = 386) and exenatide (2 RCTs, N = 110), more youth experienced AEs when compared with placebo.
- For semaglutide (1 RCT, N = 200), slightly fewer adolescents experienced AEs when compared with placebo.
- In general for phentermine-topiramate (1 RCT, N = 223), there was no difference in AEs compared to placebo.

There were very few SAEs reported across all studies for all drugs, and most were assessed as not related to the study drug. One individual experienced a bile duct stone within 1 week after study completion with phentermine-topiramate.

The most frequent AEs with liraglutide, semaglutide, and exenatide were nausea, diarrhea, vomiting, constipation, and abdominal pain; in the 1 RCT of phentermine-topiramate, nervous system disorders (e.g., headaches) and gastrointestinal disorders (e.g., nausea, abdominal pain) were reported as more frequent AEs, but all were relatively equally dispersed across medication and placebo groups.

Deaths

No deaths were reported in any studies in youth.

Setmelanotide for Monogenic Obesity

Setmelanotide acts on the melanocortin-4 receptors for the treatment of severe obesity caused by a mutation or deficiency of a single gene, also known as monogenic obesity.

Weight

- In monogenic obesity conditions, setmelanotide demonstrated weight loss from baseline levels in general, but it appears to be more effective for weight loss for some genetic mutations studied than others (1 RCT and 2 single-arm studies, N = 69; very low CoE):
    - In a 14-week RCT, participants with Bardet-Biedl syndrome (BBS) alone achieved statistically greater loss of percent body weight compared to placebo (MD, -3.4%; *P* = .002), but when the analysis included participants with Alström syndrome (an indication not included in the approval by the FDA), the result was not statistically different (*P* = .052).
    - In 2 single-arm studies in people with BBS, there were notable differences in percent body weight lost from baseline over 52 weeks; about 7% lost in 1 study (N = 31) and over 16% lost in the other (N = 7).
    - In 1 publication with 2 single-arm studies, people with the proopiomelanocortin (POMC) variant lost more body weight from baseline with setmelanotide than did those with the leptin receptor (LEPR) variant after 52 weeks of treatment (-25.6% with POMC [N = 9]; -12.5% with LEPR [N = 7]).

Indirect Measures for Comorbidity Risk Factors

Only single-arm data were reported for these measures; all outcomes were rated as very low CoE.

Systolic Blood Pressure

There were no differences in SBP from baseline with setmelanotide for any genetic variant studied (BBS, Alström syndrome, and POMC or LEPR variants; 3 studies, N = 69; very low CoE).

Low-Density Lipoprotein Cholesterol

In general, there was no difference in LDL cholesterol levels from baseline with setmelanotide at 1 year; however, the difference may depend on the specific genetic condition (3 studies, N = 69; very low CoE). Participants with the LEPR variant achieved statistically significant reductions in LDL cholesterol from baseline after 52 weeks of treatment with setmelanotide, but not at clinically meaningful levels (MD, −10.0, *P* = .04; 1 RCT, N = 11); there were no differences from baseline for people with the LEPR variant, BBS, or Alström syndrome.

Hemoglobin A1c

There were no differences in percent HbA1c from baseline with setmelanotide for people with POMC or LEPR variants (1 study, N = 21; very low CoE); no other studies measured this outcome.

Quality of Life

QoL was measured in people with BBS and the POMC or LEPR variant in single-arm studies only.

All mean scores improved from baseline with setmelanotide, and all were reported as clinically meaningful improvements (2 studies, N = 59; very low CoE); statistical tests for difference from baseline were not reported, and some individuals did not demonstrate improved QoL in these studies with very small sample sizes.

Safety

Withdrawals Due to Adverse Events

- In the 14-week RCT, there was no difference in withdrawals due to AEs from placebo in people with BBS or Alström syndrome (1 study, N = 38; very low CoE).
- There was only 1 other withdrawal due to an AE across the 2 single-arm trials; grade 1 hypereosinophilia in a participant with a LEPR genetic variant was considered as possibly related to setmelanotide and resolved following discontinuation.

Adverse and Serious Adverse Events

- In the 1 RCT, there were similar rates of AEs experienced by setmelanotide and placebo groups (94.7% each) at 14 weeks.
- Nearly all of the 69 participants who received setmelanotide in the 3 trials experienced at least 1 AE, and most were reported as generally mild and transient.
- Nine SAEs were reported across all single-arm studies for setmelanotide, and none were considered related to treatment.
- In addition to nausea and vomiting, one notable common side effect of setmelanotide is hyperpigmentation, or discoloration, of the skin; the majority of participants experienced this side effect.

Deaths

The 1 death reported across all 3 studies was considered unrelated to the study drug.

Off-Treatment Outcomes

We found only limited information on the pattern of weight change after stopping treatment with liraglutide, semaglutide, and setmelanotide; we did not identify any off-treatment information for other drugs of interest.

- More weight was regained after discontinuation of liraglutide compared to the discontinuation of the placebo in adults and adolescents, but weight did not reach baseline levels within the duration of the off-treatment phases (4 RCTs, with off-treatment phases of 12 to 26 weeks)
- Adults who stopped semaglutide regained more weight compared to those switched to placebo after 20 weeks on semaglutide and those who stopped placebo (2 RCTs, with off-treatment phases of 48 to 52 weeks); about a third of weight was regained irrespective of ongoing diet and exercise background therapy.
    - This pattern of weight regain was similar in adolescents after 7 weeks off treatment.
- Weight regain after stopping setmelanotide also was demonstrated in people with POMC or LEPR genetic variants.

Ongoing Studies

We identified 42 RCTs and 5 nonrandomized ongoing studies for liraglutide, semaglutide, tirzepatide, naltrexone-bupropion, phentermine-topiramate, and setmelanotide. Study sizes range from 12 to 17,500 and are enrolling individuals aged 2 years and older. Of the 31 studies that provide eligibility details related to diabetes status, 17 (55%) explicitly exclude individuals with T1DM or T2DM, while the remainder accept participants with diabetes; only 3 studies are exclusively enrolling individuals with T2DM. No ongoing studies for exenatide, dulaglutide, or lixisenatide were identified.

Cost-Effectiveness Findings

Eight eligible cost-effectiveness studies were identified for this report and consistently ranked phentermine-topiramate most favorably with the lowest cost per quality-adjusted life year (QALY) gained, followed by naltrexone-bupropion, tirzepatide, semaglutide (2.4 mg, weekly), and liraglutide (3 mg, daily) in terms of cost-effectiveness, respectively. The studies that evaluated cost-effectiveness of phentermine-topiramate relative to usual care indicated that it is likely a cost-effective intervention with cost-effectiveness ratios (CERs) consistently below the conventional cost-effectiveness threshold of $100,000 per QALY regardless of the time horizon and other modeling choices in these studies. The CER estimates for naltrexone-bupropion, while higher than the CERs for phentermine-topiramate in all studies that included a comparison between these two interventions, may still potentially be within the cost-effective range for higher willingness-to-pay (WTP) thresholds of $150,000 and $200,000 per QALY. The findings for cost-effectiveness of semaglutide relative to usual care were mixed, with one study indicating that it was cost-effective at $150,000 WTP threshold 82% of the time and another study suggesting that it was cost-effective at $150,000 WTP threshold only 1% of the time. Finally, the CER estimates for liraglutide were consistently greater than $400,000 per QALY, above any conventional WTP threshold for cost-effectiveness.

Although all economic studies included in our review considered costs from a health care payer perspective in the US, there were significant structural and methodological differences across these studies, particularly on model time horizon, treatment duration, post-treatment weight regain, and adjustment of costs and utilities for treatment harms and AEs and weight-related complications and comorbidities.

Policy Findings

We interviewed staff from 4 state Medicaid programs that cover weight management drugs and reviewed the coverage policies of those programs and 3 non-Medicaid payers, along with policy sources on coverage.

- Payers are taking varying approaches to coverage, with some adding coverage (notably, federal employees gaining coverage) while others are cutting coverage.
- The specific drugs covered also vary from payer to payer. Some Medicaid programs cover weight management drugs that are not the focus of this report (e.g., benzphetamine and phendimetrazine).
- Payers also are working to limit off-label use of diabetes medications such as tirzepatide (Mounjaro) for weight management.
- Even among Medicaid programs that have opted to cover weight management drugs for years, coverage decisions are shifting because of the high costs of newer weight management drugs and diabetes drugs.

Among payers who cover weight management drugs, prior authorization (PA) requirements are common, though not universal.

- Prior authorization criteria typically follow the FDA-approved indications for use of the drugs. Initial PA criteria for Saxenda (liraglutide), Wegovy (semaglutide), Contrave (bupropion and naltrexone), and Qsymia (phentermine and topiramate) usually require that the patient either has obesity or has both overweight (BMI of 27 or greater) and weight-related comorbidities.

- For patients with overweight, payers vary in the strictness of their requirements regarding comorbidities or risk factors.
- Reauthorization criteria commonly require achieving and maintaining specified weight loss and sometimes also require toleration of maintenance doses, which are typically the highest FDA-approved dosage of GLP-1s.
- Some state Medicaid programs receive supplemental rebates by adding weight management drugs to their preferred drug lists, but doing so may limit the PA criteria they can set for those drugs.

Although a full review of clinical practice guidelines and their methodologies was out of scope for this report, recommendations from 4 recent guidelines are summarized as follows:

- Guidelines on obesity treatment have evolved rapidly in light of FDA approvals of new drugs and use of weight management drugs in adolescent populations.
- The US Preventive Services Task Force is working on recommendations for weight management interventions for children and adults, which includes review of pharmacotherapy, but it is unclear when the recommendations will be published.

According to the subject matter experts we interviewed, individualized assessment should be used to formulate treatment plans for patients with obesity.

- Obesity is a complex, chronic disease, and the evidence base needed to tailor treatment options to individuals' needs has not yet developed.
- Because of individual genetic factors (which have yet to be identified), individuals may respond much more strongly to one medication than another, and the individual's history, health conditions, and preferences should factor into the care plan.

Our key informants described that, ideally, a multidisciplinary care team would treat patients with obesity.

- As with other chronic conditions, specialists would work with patients with greater complexity, and primary care would manage patients with less complexity.
- Access to obesity specialists, however, is very limited, and the population with obesity is far greater than the capacity of the limited number of providers trained to care for it.
- Medical education on obesity care would need to become standardized and widespread to fill that gap and to decrease stigmatization of people with obesity.

Costs and supply shortages of weight management drugs diminish access. Over time, costs may decline as oral forms of GLP-1s become available, new medications are approved, and older drugs become available in generic forms. However, it is unclear when that might occur.

State Considerations Overview

This is a difficult time for state Medicaid programs to make coverage decisions on weight management drugs; the evidence base is rapidly evolving and some significant questions about future costs and cost-effectiveness remain unanswerable at this time. Conflicting demands may arise between members who want to access these medications and drug makers lobbying for coverage, on the one hand, and budget conscious policymakers and managed care plans, on the other.

As state Medicaid programs navigate decisions about coverage, important considerations arise related to state plan design, utilization management tools, and value-based purchasing approaches. State Medicaid programs that carve pharmacy benefits or specific drug classes out of managed care may have a larger lever for negotiating rebates from drug makers. Programs with pharmacy benefits covered under managed care will need to work with their managed care organizations to address the effect on coverage on capitation rates.

State Medicaid programs also can use utilization management tools, including PA and reauthorization criteria, quantity limits, step therapy, and cost sharing to manage these medications. Managed care organizations may be required to align their drug coverage benefit with the state's fee-for-service program. State Medicaid agencies also can explore ways to negotiate with drug makers for rebates (including supplemental rebates for drugs on the preferred drug list), joint procurements with other state agencies (e.g., state employee health insurance), and multistate purchasing pools.

Coverage decisions about weight management drugs may be considered in conjunction with related benefits, such as obesity prevention programs that support nutrition and physical activity, particularly for children.

Conclusions

Overall, the medications reviewed in this report are associated with varying levels of weight loss; however, their effect on cardiovascular risk factors is less certain, with sometimes only small changes in outcomes. Use of the medications also appears to be commonly associated with adverse effects, such as nausea, constipation, and other symptoms, depending on the specific drug.

Cost-effectiveness varies by medication, with phentermine-topiramate consistently ranked most favorably with the lowest cost per QALY gained and CER estimates for liraglutide being consistently greater than $400,000 per QALY, above any conventional WTP threshold for cost-effectiveness.

State Medicaid agencies may need to use a range of strategies, such as state plan design, utilization management tools, and value-based purchasing agreements, when covering weight management medications. As state Medicaid programs consider coverage of weight management drugs, they may want to review related benefits at the same time. Especially for children and adolescents, there may be opportunities to promote obesity prevention through support for nutrition and physical activity. Preventive interventions will require multisector collaboration with public health, education, and housing to reduce obesogenic pressures. For people who already have overweight or obesity, coverage considerations could include improving access to intensive behavioral interventions and considering coverage of and improved access to bariatric surgery.

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