Medications for obesity management: Effectiveness and value

A summary from the Institute for Clinical and Economic Review's New England Comparative Effectiveness Public Advisory Council

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Obesity is a common chronic disease that increases the risk of many other health conditions affecting morbidity and mortality, such as diabetes and heart disease.[1,2] Social stigma can make individuals with obesity feel judged, shamed, and ostracized.[3] Often starting in childhood, obesity can also affect educational development, social interactions, relationships, and work.[4,5]

Obesity is most commonly assessed using the body mass index (BMI, weight in kg/height in m^2).[6,7] More than two-thirds of adults in the United States are overweight (BMI ≥ 25) or obese (BMI ≥ 30), with the highest prevalence among non-Hispanic Black women, and over half the US population is projected to be obese by 2030.[8,9] The direct medical costs of obesity are estimated to be $260 billion in the United States[10] and are even higher if one includes the indirect costs of lower wages, greater work loss, and disability.[11,12]

Treatments promoting weight loss are broadly intended to prevent, treat, or reverse the complications of obesity, including its impact on quality of life.[13-15] Observational studies support an association between weight loss and reductions in mortality.[16] Given that treating obesity can improve health, screening adults for obesity is recommended by the US Preventive Services Task Force.[17]

Initial treatment recommendations include lifestyle interventions, such as healthy nutrition, increased physical activity, and behavioral modifications,[18,19] but weight loss is usually modest, and most people regain weight over time. Since most people do not achieve the desired weight loss with lifestyle modification, medications and surgical interventions are often considered. Bariatric surgery decreases weight and weight-related complications,[20,21] but the invasive nature of surgery and its small risk of causing serious adverse events leads to a significant ongoing unmet need for pharmacological treatment options.

We evaluated medications approved by the US Food and Drug Administration (FDA) for weight loss, including recently approved single agents liraglutide (Saxenda, Novo Nordisk) and semaglutide (Wegovy, Novo Nordisk), as well as the combination drugs phentermine/topiramate (Qysmia, Vivus) and bupropion/naltrexone (Contrave, Currax Pharmaceuticals) (Table 1). Semaglutide and liraglutide are glucagon-like peptide-1 (GLP-1) receptor agonists that are also approved for diabetes mellitus and given by subcutaneous injection, whereas phentermine/topiramate and bupropion/naltrexone are combination oral agents that work via other mechanisms. Other promising therapies (eg, tirzepatide) are still under investigation and were therefore not included in the scope of this review.

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TABLE 1 Medications for Obesity Management Reviewed

Intervention	Mechanism of action	Delivery route	Prescribing information
Semaglutide	GLP-1 receptor agonist	Subcutaneous	2.4 mg once weekly
Liraglutide	GLP-1 receptor agonist	Subcutaneous	3 mg once daily
Phentermine/topiramate	Sympathomimetic amine/GABA receptor modulation	Oral	7.5-15 mg/46-92 mg daily
Bupropion/naltrexone	Opioid antagonist/NE and DA inhibitor	Oral	32 mg/360 mg daily

DA = dopamine; GABA = γ-aminobutyric acid; GLP-1 = glucagon-like peptide-1; NE = norepinephrine.

TABLE 2 Network Meta-Analysis Results on Weight Loss Outcomes: Medications for Obesity Management vs Placebo

	Percent weight loss from baseline at 1 year	≥5% Weight loss	≥10% Weight loss
	Mean difference (95% CrI)	Odds ratio (95% CrI)	
Semaglutide	–13.7 (–12.6 to –15.1)	17.3 (8.9-38.3)	22.4 (13.6-36.2)
Liraglutide	–9.1 (–7.1 to –11)	8.6 (3.3-22.0)	8.8 (4.7-18.1)
Phentermine/topiramate	–5.0 (–3.9 to –6.1)	4.3 (2.5-6.7)	4.2 (2.6-5.7)
Bupropion/naltrexone	–4.6 (–3.0 to –6.0)	4.3 (1.7-10.2)	3.6 (2.0-6.8)

CrI = credible interval.

Summary of Findings

We evaluated the evidence on the effectiveness and safety of these drugs among adults with a BMI of at least 30 kg/m^2 or a BMI of at least 27 kg/m^2 with at least 1 weight-related comorbid condition (such as hypertension or dyslipidemia). There were 5 randomized controlled trials (RCTs) of semaglutide, including 1 with liraglutide as a comparator,[22-26] 6 RCTs of liraglutide,[27-32] 3 RCTs of phentermine/topiramate,[33-35] and 4 RCTs of bupropion/naltrexone that met our inclusion criteria.[36-39] These RCTs were placebo controlled with patients receiving either standard lifestyle modification or lifestyle modification with intensive behavior therapy.[24,31,32,36] Primary weight loss outcomes included the percentage of weight loss from the baseline and the proportion of participants achieving 5% or 10% body weight loss. Outcomes were assessed 1 year after treatment initiation, with the dose escalation periods ranging from 4 to 16 weeks. We focused on outcomes among patients without preexisting diabetes mellitus because we have previously performed a review of semaglutide and liraglutide for diabetes mellitus, and the most important competitive question is how all of these drugs compare among patients without diabetes.[40]

RCT evidence demonstrates that semaglutide, liraglutide, phentermine/topiramate, and bupropion/naltrexone all reduce body weight compared with placebo when added to standard lifestyle modification. In the 1 head-to-head trial, semaglutide achieved greater weight loss than liraglutide.[26] None of these drugs have assessed long-term outcomes in adults without preexisting diabetes mellitus, and thus there is uncertainty around long-term benefits, such as cardiovascular morbidity and mortality.

We conducted a network meta-analysis (NMA) using a baseline risk-adjusted random effects model to perform indirect comparisons across all drugs of their impact on weight loss and other short-term outcomes. These results are shown in Table 2. Indirect mean and categorical weight loss comparisons show that semaglutide (13.7%) and phentermine/topiramate (9.1%) achieve a greater percentage average weight loss than liraglutide (5.0%) and bupropion/naltrexone (4.6%). RCT results also showed that semaglutide and liraglutide improve blood glucose and blood pressure levels compared with usual care, but how they compare with phentermine/topiramate and bupropion/naltrexone is less certain.

Adverse events in the RCTs were common among all interventions, but few serious harms were noted. All interventions had greater discontinuation because of adverse events than placebo in an NMA, although semaglutide appears to have lower rates of discontinuation than the other drugs.

Limitations of the Clinical Evidence

A lack of direct comparisons among the medications and differences among the trials regarding their size, patient characteristics, concomitant lifestyle interventions, outcomes assessed, and duration of follow-up contribute to indirect analyses having more uncertainty. Because the chronic management of obesity is likely to require lifelong pharmacotherapy for most people, the lack of long-term follow-up reduces certainty

TABLE 3 Incremental Cost-Effectiveness Ratios for the Base Case

Treatment	Comparator	Cost per QALY gained, $	Cost per evLY gained, $
Semaglutide	Lifestyle modification	237,000	234,000
Liraglutide	Lifestyle modification	483,000	473,000
Phentermine/topiramate	Lifestyle modification	8,000	7,000
Bupropion/naltrexone	Lifestyle modification	123,000	121,000
Semaglutide	Liraglutide	31,000	31,000
	Phentermine/topiramate	469,000	465,000
	Bupropion/naltrexone	275,000	272,000

evLY = equal value life-year; QALY = quality-adjusted life-year.

in long-term efficacy, harms, and potential off-target benefits, such as a decrease in cardiovascular events with GLP-1 agonists, as seen in the treatment of diabetes. In addition, for all interventions, there is uncertainty about whether weight regain occurs over time despite continued therapy.

Long-Term Cost-Effectiveness

We evaluated the cost-effectiveness of semaglutide, liraglutide, phentermine/topiramate, and bupropion/naltrexone plus lifestyle modification compared with standard lifestyle modification alone for weight reduction among patients without preexisting diabetes. A Markov model with a US health care sector perspective was developed to compare the cost and quality-adjusted life-years gained across the 5 weight management strategies. Using Framingham equations, the average BMI reduction with therapy was the primary input and the key predictive factor to calculate the differences in cardiovascular comorbidity.[41] The impact of weight loss on glucose control was used to predict the risk of progression to diabetes mellitus.[42] The model was also developed to try to reflect the broader effects of weight reduction on quality of life. Costs and outcomes were discounted at an annual rate of 3% over a lifetime horizon. Full details on the Institute for Clinical and Economic Review (ICER)'s cost-effectiveness analysis and model are available on ICER's website at https://icer.org/wp-content/uploads/2022/03/ICER_Obesity_Final_Evidence_Report_and_Meeting_Summary_102022.pdf.

At the current price net of rebates, the incremental cost-effectiveness ratio for semaglutide and liraglutide exceeded the commonly accepted thresholds (Table 3). In contrast, branded phentermine/topiramate was cost-effective, primarily because of its lower price. Branded bupropion/naltrexone was cost-effective at higher thresholds only. When prescribed as combinations of their generic components, phentermine/topiramate appeared cost-saving, whereas bupropion/naltrexone was cost-effective.

Limitations of the Cost-Effectiveness Model

Results from 1-year clinical trials were extrapolated to estimate lifetime treatment benefits, with assumptions of continued adherence and treatment effectiveness. The model may not include the full potential impact of weight loss, as the impact of treatment on some conditions related to obesity was purposefully excluded because of concern over the double counting of weight loss benefits. The risk equations used for estimating the effects of weight loss on cardiovascular and diabetes outcomes were derived from observational studies and may have introduced unknown bias into the model's predictions. The model also did not specifically address outcomes in subpopulations with larger potential benefits, such as women of childbearing age or underserved populations, because the analysis was limited by the available evidence.

Policy Discussion

The New England Comparative Effectiveness Public Advisory Council (CEPAC) convened on September 16, 2022, to publicly deliberate on the clinical effectiveness and cost-effectiveness of medications for obesity management. The New England CEPAC is an independent appraisal committee composed of medical evidence experts, including practicing clinicians, methodologists, and leaders in patient engagement and advocacy. Their deliberations included input from clinical experts and patient representatives with obesity expertise and formal comments from a manufacturer and the public.

Following the discussion, the CEPAC members deliberated on key questions raised by the ICER's report. Based on the evidence in the clinical trials and the input received during the meeting, a majority of the panel voted that the evidence was adequate, demonstrating a net health benefit vs lifestyle management alone for semaglutide (15-0), liraglutide (15-0), phentermine/topiramate (14-1),

TABLE 4 Votes on Other Contextual Considerations

Contextual considerations	Very low priority	Low priority	Average priority	High priority	Very high priority
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability	10	1	2	1	1
Magnitude of the lifetime impact on individual patients of the condition being treated	0	0	3	7	5

TABLE 5 Votes on Other Benefits or Disadvantages

Potential other benefits or disadvantages	Major negative effect	Minor negative effect	No difference	Minor positive effect	Major positive effect
Patients' ability to achieve major life goals related to education, work, or family life	0	0	0	**10**	5
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life	0	0	6	**9**	0
Society's goal of reducing health inequities	0	0	4	**6**	5

Bolded values represent the highest number of votes.

and bupropion/naltrexone (10-5). A majority of the panel also felt the evidence was adequate to demonstrate the superiority of semaglutide compared with all other treatment options: liraglutide (14-1), phentermine/topiramate (10-5), and bupropion/naltrexone (10-5).

The New England CEPAC votes on "potential other benefits" and "contextual considerations" as part of a process intended to signal to policymakers whether there are important considerations when making judgments about the long-term value for money not adequately captured in the analyses of clinical effectiveness and/or cost-effectiveness. As shown in Tables 4 and 5, a majority of the panel voted that treatments for obesity should receive high or very high priority given the magnitude of the lifetime burden of the condition, and a majority believed that semaglutide's impact on weight loss provides either a minor or a major positive effect on patients' broader ability to meet their life goals.

The culminating vote of the CEPAC panel, intended to reflect its integration of the relevant elements of the value assessment framework, was on the "long-term value for money." For semaglutide, the panel members voted that its long-term value for money at its current pricing is low (11/15 votes) or intermediate (4/15 votes).

The meeting concluded with a policy roundtable that included 2 patient advocates, 2 clinical experts, and 2 representatives of the payer perspective. Manufacturers declined to participate in the policy roundtable. Participants discussed how best to apply the evidence and additional considerations to clinical practice and pricing and insurance coverage policies. The full set of policy recommendations can be found in the Final Evidence Report on the ICER website. The key policy recommendations are as follows:

RECOMMENDATION 1

All stakeholders have an important role to play in ensuring that people living with obesity have access to effective medications as a core benefit of health care insurance coverage in ways that do not exacerbate health care inequities.

RECOMMENDATION 2

Manufacturers should set prices that will foster affordability and good access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. Medication pricing at launch should also be moderated until additional evidence is generated to demonstrate long-term safety and reductions in adverse cardiovascular outcomes.

RECOMMENDATION 3

The following are some considerations for prior authorizations:

Patient Eligibility. Weight and age criteria are likely to follow the FDA label, so payers should have efficient mechanisms for clinicians that seek coverage exceptions for

patients with serious unmet needs near the cutoff for weight and age. For patients receiving therapy and switching insurance, payers should have mechanisms to prevent coverage gaps while undergoing an exception process to regain coverage.

Clinical Eligibility. Medication trials required prior lifestyle modification with an inadequate response. Given the evidence that lifestyle modification is usually ineffective, requiring enrollment in a lifestyle program or prior lack of success should be eliminated and replaced with clinician attestation that individuals are provided diet and activity guidance.

Duration of Coverage and Renewal Criteria. The initial duration of coverage should permit enough time to allow individuals to demonstrate a response to the recommended dose of medication (at least 6 months and a 5% durable reduction in weight).

RECOMMENDATION 4

Payers may consider step therapy with less expensive or off-label medications but should permit choosing from multiple options, including combination therapy. Payers should only use step therapy when they have designed it with adequate flexibility to meet the needs of diverse individuals and when the implementation can meet high standards of transparency and efficiency.

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