Medications for Obesity Management

Draft Background and Scope

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Background

Obesity is an increasingly common chronic condition that is associated with increased risk of chronic diseases such as diabetes, cancer, and heart disease as well as death.[1] Individuals who are overweight or those with obesity face considerable social stigma that can make them feel judged, shamed, and ostracized, and can affect interactions with family, friends, and even health professionals.[2] Because obesity often starts in childhood, the stigma can affect social interactions, educational development, relationships, and work throughout life.[3]

Obesity is defined as abnormal or excessive fat accumulation that presents a risk to a person's health.[4] Body mass index (BMI, weight in kilograms/height in meters^2) is commonly used to assess for obesity because it is easy to reliably measure and correlates with body fat measurements.[3,5] More than two-thirds of the United States (US) population is overweight (BMI ≥25) or has obesity (BMI ≥30). The prevalence of obesity among adults has increased over time and was 40-45% in 2017-2018.[6] Among children and adolescents, the prevalence of obesity is almost 20%.[7] The total number of adults who were overweight was estimated at 79 million and those with obesity was estimated at 70 million in 2015 with half of the US population projected to have obesity by 2030.[8,9] Though obesity does not significantly vary by age, there are important disparities by race/ethnic status with the prevalence higher for Hispanic adults and highest among non-Hispanic Black women.[7,10] Given the prevalence of obesity and its impact on health, the costs of obesity are staggering, estimated to be $260 billion in the US.[11] The financial impact of obesity on individuals includes not only direct medical costs but also indirect costs of lower wages and greater work loss and disability.[12,13]

There are many factors that contribute to developing obesity including increasing recognition of complex genetic factors associated with the body's mechanisms that control energy balance.[14,15] The goal of therapy for obesity is to broadly prevent, treat, or reverse its complications, including its impact on quality of life.[16,17] Treatments to promote weight loss are intended to prevent the health risks associated with obesity (e.g., diabetes, hypertension, heart disease) and ultimately improve quality of life and longevity. Observational studies support an association between weight loss and reductions in mortality.[5] Initial treatments focus on lifestyle interventions that variably combine

diet, exercise, and behavioral modifications. Though helpful for some, weight loss is usually modest and regaining weight over time occurs in the vast majority of individuals. Earlier generation medications and dietary supplements also had modest effects on weight loss, and some were also found to pose significant health risks. The introduction of surgical procedures to promote weight loss demonstrated that for severe obesity, significant weight loss was possible and was associated with decreased weight-related complications.[18]

For individuals who have not achieved desired weight loss with lifestyle changes, there are multiple pharmacotherapy options that are indicated to promote weight loss and prevent complications of obesity. Pharmacotherapy is often considered first-line before more invasive weight loss techniques are considered (e.g., bariatric surgery). Currently approved medications by the US Food and Drug Administration (FDA) include the single agents: phentermine (1959), orlistat (Xenical®, H2 Pharma, 2007), liraglutide (Saxenda®, Novo Nordisk, 2014), and semaglutide (Wegovy®, Novo Nordisk, June 2021), and the combination drugs: phentermine/topiramate (Qysmia®, Vivus, 2012) and naltrexone/bupropion (Contrave®, Currax Pharmaceuticals, 2014). Liraglutide and semaglutide are glucagon-like peptide-1 (GLP-1) peptides that are approved for diabetes due their effect in stimulating insulin production. Their weight loss effect is mediated by decreasing appetite. Both are given by injection under the skin with liraglutide administered daily and semaglutide weekly. Semaglutide appears to promote greater weight loss than other FDA-approved medications and, as a result, has engendered interest among patients and providers.

The other FDA-approved medications are administered by mouth and taken daily. Because orlistat results in modest weight loss and causes intestinal side effects, it is less commonly used for initial medication management. Phentermine is approved for short-term use (less than 12 weeks). A combination of phentermine and fenfluramine (Fen-Phen) was withdrawn in 1997 due to heart problems. Phentermine is currently available in combination with topiramate. The combination of naltrexone and bupropion works in the brain to decrease hunger. Since bupropion, naltrexone, and topiramate are available as single agents, clinicians may also use them “off label” alone and in combination for weight loss.

Practical issues in using medications for weight loss are potential side effects, durability of treatment effect, and concerns about insurance coverage and pre-authorization. Consequently, there is a need to understand the comparative benefits and costs of the newer branded medications for individuals interested in weight loss after not achieving their goals with initial lifestyle modification.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patients, patient advocacy organizations, consumer advocates, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders. A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of medications for obesity management.

Initial comments from patients and patient advocacy groups emphasized that obesity is a serious condition that has important health consequences affecting both physical and mental well-being. There was also broad recognition that the social stigma associated with obesity can begin at a young age and affect an individual throughout their life. This stigma and bias directed at individuals with obesity can also lead to behaviors that make self-care harder and may impact one's willingness to engage with health care providers in weight loss and managing the consequences of obesity.

We also heard that there are diverse perspectives about obesity that broadly reflect the many individuals with obesity and the variety of underlying factors that contribute to obesity and its management. Though many individuals with obesity are interested in weight loss, the cycle of weight loss and gain, the many "fad" diets that offer unrealistic expectations, and the cost of treatments that are often not covered by health insurance all impact perceptions about weight loss. We heard some advocate more for efforts focused on managing the medical issues associated with obesity, especially for those individuals who have suffered through failed treatments, weight cycling, and the psychological harms associated with such prior experiences. Even among those more interested in weight-neutral treatment efforts, there was recognition that more can be done in the health care system to reduce the stigma of obesity and better support individuals interested in weight loss treatment.

From clinical specialists, researchers, and manufacturers, we also heard that there is a need for new therapeutic options for individuals with obesity who are interested in weight loss treatments, particularly individuals who have not responded to lifestyle treatments or who responded but then regained weight lost over time. Clinical specialists emphasized that no one treatment is a panacea, and this reflects the various underlying mechanisms that contribute to obesity as well as the benefits and harms associated with all therapies. Given the wide variety of treatments available for those interested in weight loss treatment, they supported our focus on medical therapies for those who have not responded to lifestyle interventions and are interested in additional treatments. Though surgical and other device interventions may be considered alongside medical therapies, clinicians felt that many individuals had preferences that made direct comparison of medical and non-medical therapies less important. This also reflected increased interest in medical therapies

that have been demonstrated to provide weight loss that is becoming comparable to bariatric surgery. Clinicians also reported that they commonly used medications approved in combination products for weight loss as single medications in an off-label manner. This reflected that they often saw this as minimizing side effects when starting treatment and being less costly for patients given the higher costs of approved medications that are often not covered by insurers. The net effect is that many patients end up on a combination of medications, but not always using the approved combination products. There was also recognition that the addition of medications such as the GLP-1 peptides represents a step forward in the magnitude of weight loss achieved, but they do not work for everyone, and the weight loss achieved is still less than that seen for bariatric surgery. Finally, it is acknowledged that medications will often require chronic use to maintain the weight loss achieved, but there was concern about the safety of long-term use and the willingness of individuals to remain on therapy for many years, especially if it requires considerable out-of-pocket costs to the individual.

Report Aim

This project will evaluate the health and economic outcomes of FDA-approved pharmacotherapies for individuals with obesity who are interested in weight loss treatment. The ICER Value Framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms—including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs—are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for the review is adults with a BMI ≥30kg/m^2 or ≥27kg/m^2 with at least one weight-related comorbid condition (such as hypertension, type 2 diabetes, obstructive sleep apnea, or hyperlipidemia) who are actively seeking medical management for weight loss. Data permitting, we intend to examine the following patient subgroups, including but not limited to:

- BMI categories: 25-29.9, 30-34.9, 35-39.9, or greater than 40 kg/m^2
- Pre-diabetes or diabetes.

Interventions

The full list of interventions is as follows:

- Semaglutide
- Liraglutide
- Bupropion and naltrexone in combination
- Phentermine and topiramate in combination.

Comparators

We intend to compare each intervention to placebo and/or lifestyle modification. Data permitting, we will also compare the interventions to one another.

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Quality of life and functional status
    - Anxiety and depression
    - Body image
    - Long-term health outcomes such as cardiovascular disease, cancer, and mortality
    - Weight loss (as measured by % weight loss, BMI, etc.)
    - Weight re-gain
    - Adverse events including:
        - Side effects
        - Psychological harm
        - Serious adverse events

- Other Outcomes
    - Metabolic profile, such as LDL (low-density lipoprotein), hemoglobin A1C, and blood pressure
    - Weight cycling
    - Waist circumference
    - Progression from pre-diabetes to diabetes or pre-hypertensive to hypertensive
    - Withdrawal or dose reduction in concomitant medications for weight-related comorbidities
    - Subsequent surgical interventions for weight loss
    - Discontinuation due to adverse events

Timing

Evidence on intervention effectiveness will be derived from studies of at least 12 weeks duration and evidence on harms from studies of any duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the US.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration*
Acuity of need for treatment of individual patients based on the severity of the condition being treated
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

Potential Other Benefit or Disadvantage*
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients' ability to manage and sustain treatment given the complexity of regimen
Society's goal of reducing health inequities
Other (as relevant)

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the 10-year and lifetime cost effectiveness of the treatments of interest relative to placebo or lifestyle modification. The model structure will be based in part on a literature review of prior published models of the proportional changes in weight, BMI, and impact on weight-related comorbidities. The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of change in weight, BMI, and comorbidities on the loss of productivity is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per quality-adjusted life year (QALY), and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained.

The target population will consist of adults who are overweight or have obesity and are interested in weight loss and meet eligibility criteria for medication treatment. Data permitting, the model will consist of health states marked by diabetes, cardiovascular comorbidities, and death as the absorbing health state. Other weight-related complications, such as osteoarthritis, obstructive sleep apnea, or cancer will be considered as potential health states included in the model. The final structure of the model will undergo review for face validity by clinical experts and patient leaders. Onset of each comorbidity and complication will be subject to changes in BMI and diabetes. A cohort of patients will transition between states during predetermined cycles (of one year) over a 10-year time horizon, a typical time horizon observed in previous model-based economic outcome assessments for weight management. In addition, cost effectiveness will be estimated for a lifetime horizon until death.

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using network meta-analysis or meta-analysis if sufficient data suitable for quantitative synthesis exist. If such data are not available, clinical trial data will be used directly to estimate treatment effectiveness. Preference will be given to modeling health effects directly measured in clinical trials or cohort studies.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events, and direct medical costs. Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events and for non-health-state-based treatment or weight-related complications. The model will include direct medical costs, including

but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis, data permitting. The health outcome of each intervention will be evaluated in terms of weight and BMI reduction, presence of diabetes and other comorbid conditions, life years gained, QALYs gained, and equal value of life years gained (evLY). Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the incremental cost per QALY, cost per evLY, and cost per life year gained. An efficiency frontier will be developed to guide which pairwise comparisons should be reported. In scenario analyses, we will simulate clinically plausible treatment modalities and BMI trajectories, including shorter and longer duration of treatment, and long-term weight regain.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. If warranted by clinical and real-world evidence, a shorter time horizon may be considered. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER Value Framework). These services are ones that would not be directly affected by semaglutide, liraglutide, bupropion and/or naltrexone, and phentermine and/or topiramate, such as need for obstructive sleep apnea treatment, as these services will be captured in the economic model. Rather, we are seeking services used in the current management of obesity beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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