

## GUIDELINES

## AGA Clinical Practice Guideline on Pharmacological Interventions for Adults With Obesity



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**BACKGROUND & AIMS:** Pharmacological management of obesity improves outcomes and decreases the risk of obesity-related complications. This American Gastroenterological Association guideline is intended to support practitioners in decisions about pharmacological interventions for overweight and obesity. **METHODS:** A multidisciplinary panel of content experts and guideline methodologists used the Grading of Recommendations Assessment, Development and Evaluation framework to prioritize clinical questions, identify patient-centered outcomes, and conduct an evidence synthesis of the following agents: semaglutide 2.4 mg, liraglutide 3.0 mg, phentermine-topiramate extended-release (ER), naltrexone-bupropion ER, orlistat, phentermine, diethylpropion, and Gelesis100 oral superabsorbent hydrogel. The guideline panel used the evidence-to-decision framework to develop recommendations for the pharmacological management of obesity and provided implementation considerations for clinical practice. **RESULTS:** The guideline panel made 9 recommendations. The panel strongly recommended the use of pharmacotherapy in addition to lifestyle intervention in adults with overweight and obesity (body mass index  $\geq 30$  kg/m<sup>2</sup>, or  $\geq 27$  kg/m<sup>2</sup> with weight-related complications) who have an inadequate response to lifestyle interventions. The panel suggested the use of semaglutide 2.4 mg, liraglutide 3.0 mg, phentermine-topiramate ER, and naltrexone-bupropion ER (based on moderate certainty evidence), and phentermine and diethylpropion (based on low certainty evidence), for long-term management of overweight and obesity. The guideline panel suggested against the use of orlistat. The panel identified the use of Gelesis100 oral superabsorbent hydrogel as a knowledge gap. **CONCLUSIONS:** In adults with overweight and obesity who have an inadequate response to lifestyle interventions alone, long-term pharmacological therapy is recommended, with multiple effective and safe treatment options.

**Keywords:** Adiposity; Cardiovascular Risk; Insulin Resistance.

The prevalence of obesity in the United States has increased dramatically over the past few decades from 30.5% in 1999–2000 to 41.9% in 2019–2020.<sup>1,2</sup> According to the National Health and Nutrition Examination Survey, the prevalence of obesity for young adults increased from 6.2% in 1976–1980 to 33% in 2017–2018.<sup>3</sup> Childhood obesity has also become more prevalent in recent decades.<sup>4</sup> In adults, obesity-related complications, such as cardiovascular disease, stroke, type 2 diabetes mellitus (T2DM), nonalcoholic steatohepatitis, obstructive sleep apnea, osteoarthritis, and certain types of cancer (eg, colorectal cancer), have also increased, contributing to high morbidity and

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**Abbreviations used in this paper:** AGA, American Gastroenterological Association; AOM, anti-obesity medication; BMI, body mass index; C, comparison; CNS, central nervous system; COI, conflict of interest; ER, extended release; FAERS, US Food and Drug Administration Adverse Event Reporting System; FDA, US Food and Drug Administration; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HbA1c, glycated hemoglobin; I, intervention; ITT, intention to treat; LCD, low-calorie diet; LOCF, last observation carried forward; MCID, minimal clinically important difference; MD, mean difference; MID, minimal important difference; PICO, population, intervention, comparator, and outcome; RA, receptor agonist; RCT, randomized controlled trial; RR, relative risk; SAE, serious adverse event; SQ, subcutaneous; TBWL, total body weight loss; T2DM, type 2 diabetes mellitus.

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mortality. Lifestyle intervention is the foundation for management of obesity, but it has limited effectiveness and durability for most individuals.<sup>5</sup> Pharmacological therapies have been developed and approved for long-term management of obesity, with high efficacy in achieving weight loss. However, there is limited use of these agents in routine clinical care with wide practice variability, and a small number of providers are responsible for >90% of the prescriptions, partly due to lack of familiarity and limited access and insurance coverage.<sup>6</sup>

Therefore, the American Gastroenterological Association (AGA) prioritized the development of clinical guidelines informing the use of pharmacological therapies for the long-term management of obesity in adults. These guidelines will complement recent AGA Clinical Practice Guidelines on Intra-gastric Balloons in the Management of Obesity.<sup>7,8</sup>

## Objective

The purpose of these guidelines was to provide evidence-based recommendations for the pharmacological management of obesity in adults. Although the management of obesity in children is of critical importance because of the interrelated nature of excess adiposity across the lifespan, it is beyond the scope of this guideline to address the pharmacological treatment of childhood obesity.

## Target Audience

The target audience of these guidelines includes health care professionals (ie, gastroenterologists, primary care clinicians, endocrinologists, and any provider caring for patients with overweight and obesity), patients, and policy makers. These guidelines are not intended to impose a standard of care, but rather, they provide the basis for rational, informed decisions for patients and health care professionals. Statements regarding the underlying values and preferences, as well as qualifying remarks or comments accompanying each recommendation, should never be omitted when quoting or translating recommendations from these guidelines. Recommendations provide guidance for typical patients with overweight and obesity; no recommendation can include all of the unique individual circumstances that must be considered when making recommendations for individual patients. However, discussions around benefits and harms can be used for shared decision making, especially for conditional recommendations when patients' values and preferences are important to consider. These recommendations are summarized in [Table 1](#) (Executive Summary of Recommendations).

## Methods

### Overview

This document represents the official recommendations of the AGA and was developed by the AGA Clinical Guideline Committee and approved by the AGA Governing Board. These guidelines were developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE)

framework and adhere to best practices in guideline development as outlined by the National Academy of Medicine (formerly Institute of Medicine) using a process outlined previously.<sup>9</sup> Development of this guideline was fully funded by the AGA Institute without additional outside funding.

### Panel Composition and Conflict of Interest

Members of the guideline panel were selected based on their clinical and methodological expertise after undergoing a vetting process that required disclosing all conflicts of interest (COIs). The evidence synthesis team consisted of 5 members, including 2 clinicians with expertise in obesity medicine (internist: Eduardo Grunvald; gastroenterologist: Octavia Pickett-Blakely), and 3 GRADE methodologists (senior methodologist and co-chair of the guideline: Perica Davitkov; junior methodologists: Raj Shah, Apoorva Chandar). The guideline panel consisted of a gastroenterologist and hepatologist (guideline chair: Ruben Hernaez), endocrinologist focusing on obesity (Tasma Harindhanavudhi), a registered dietitian with expertise in obesity (Levi Teigan), and gastroenterologists with expertise in guideline development (Shahnaz Sultan, Siddharth Singh). A patient representative with obesity who received pharmacotherapy also participated in developing the guideline recommendations. All panel members disclosed all potential COIs. Conflicts were managed according to AGA policies, the National Academy of Medicine (formerly Institute of Medicine), and Guidelines International Network standards. The guideline chairs and guideline methodologists had no relevant or direct COIs. All COI disclosures are maintained by the AGA Office.

### Formulation of Clinical Questions and Determining Outcomes of Interest

A protocol was developed *a priori* to guide the systematic evidence review. The PICO format was used to outline the specific patient population (P), intervention (I), comparator (C), and outcome (O) for each clinical question. We focused on US Food and Drug Administration (FDA)-approved anti-obesity medications (AOMs) to treat adults with body mass index (BMI)  $\geq 27$  kg/m<sup>2</sup> who have had an inadequate response to lifestyle interventions ([Supplementary Table 1](#)). Drugs included semaglutide 2.4 mg, liraglutide 3.0 mg, phentermine-topiramate extended release (ER), naltrexone-bupropion ER, orlistat, phentermine, diethylpropion, and Gelesis100 oral superabsorbent hydrogel. Although Gelesis100 oral superabsorbent hydrogel is considered to be a device by the FDA, the panel included it as an intervention, given its ability to be used via an oral route, similar to a pill. Setmelanotide, a melanocortin-4 receptor agonist approved by the FDA in 2020 for the treatment of rare genetic causes of obesity, was not included in these guidelines, as it was outside the scope of the review.<sup>10,11</sup>

### Outcomes of Interest and Determination of Minimally Important Difference Thresholds

The panel selected desirable (benefits) and undesirable (harms) patient-important outcomes. The outcomes deemed to be critical for decision making included percent total body weight loss (%TBWL), proportion of patients achieving  $\geq 5\%$ ,

**Table 1.** American Gastroenterological Association Recommendations on Pharmacological Interventions for Management of Obesity

Recommendation	Strength of recommendation	Quality of evidence
<p>1. In adults with obesity or overweight with weight-related complications, who have had an inadequate response to lifestyle interventions, the AGA recommends adding pharmacological agents to lifestyle interventions over continuing lifestyle interventions alone.</p> <p>Implementation considerations:</p> <ul style="list-style-type: none"> <li>• AOMs generally need to be used chronically, and the selection of the medication or intervention should be based on the clinical profile and needs of the patient, including, but not limited to, comorbidities, patients' preferences, costs, and access to the therapy.</li> </ul>	Strong	Moderate
<p>2. In adults with obesity or overweight with weight-related complications, the AGA suggests using semaglutide 2.4 mg with lifestyle modifications, compared with lifestyle modifications alone.</p> <p>Implementation considerations:</p> <ul style="list-style-type: none"> <li>• Given the magnitude of net benefit, semaglutide 2.4 mg may be prioritized over other approved AOMs for the long-term treatment of obesity for most patients.</li> <li>• Semaglutide has glucoregulatory benefits and is also approved for the treatment of T2DM</li> <li>• Semaglutide may delay gastric emptying with adverse effects of nausea and vomiting. Gradual dose titration may help mitigate these adverse effects.</li> <li>• GLP-1 RAs have been associated with increased risk of pancreatitis and gallbladder disease.</li> </ul>	Conditional	Moderate
<p>3. In adults with obesity or overweight with weight-related complications, the AGA suggests using liraglutide 3.0 mg with lifestyle modifications, compared with lifestyle modifications alone.</p> <p>Implementation considerations:</p> <ul style="list-style-type: none"> <li>• Liraglutide has glucoregulatory benefits and is also approved for the treatment of T2DM</li> <li>• Liraglutide may delay gastric emptying with adverse effects of nausea and vomiting. Gradual dose titration may help mitigate these adverse effects.</li> <li>• Liraglutide has been associated with an increased risk of pancreatitis and gallbladder disease</li> </ul>	Conditional	Moderate
<p>4. In adults with obesity or overweight with weight-related complications, the AGA suggests using phentermine-topiramate ER with lifestyle modifications, compared with lifestyle modifications alone.</p> <p>Implementation considerations:</p> <ul style="list-style-type: none"> <li>• Because topiramate is effective for treating migraine headaches, phentermine-topiramate ER may be preferentially used in patients with comorbid migraines.</li> <li>• Phentermine-topiramate ER should be avoided in patients with a history of cardiovascular disease and uncontrolled hypertension.</li> <li>• Topiramate is teratogenic. Women of childbearing potential should be counseled to use effective contraception consistently.</li> <li>• Blood pressure and heart rate should be monitored periodically while taking medications with phentermine.</li> </ul>	Conditional	Moderate
<p>5. In adults with obesity or overweight with weight-related complications, the AGA suggests using naltrexone-bupropion ER with lifestyle modifications, compared with lifestyle modifications alone.</p> <p>Implementation Considerations:</p> <ul style="list-style-type: none"> <li>• Naltrexone-bupropion ER may be considered for the treatment of overweight or obesity in patients who are attempting smoking cessation, and in patients with depression.</li> <li>• Naltrexone-bupropion ER should be avoided in patients with seizure disorders and used with caution in patients at risk of seizures.</li> <li>• Naltrexone-bupropion ER should not be used concomitantly with opiate medications.</li> <li>• Blood pressure and heart rate should be monitored periodically while taking naltrexone-bupropion ER, especially in the first 12 weeks of treatment.</li> </ul>	Conditional	Moderate

Table 1. Continued

Recommendation	Strength of recommendation	Quality of evidence
<p>6. In adults with obesity or overweight with weight-related complications, AGA suggests against the use of orlistat.</p> <p><i>Comment:</i> Patients who place a high value on the potential small weight loss benefit and low value on GI adverse effects may reasonably choose treatment with orlistat.</p> <p>Implementation Considerations:</p> <ul style="list-style-type: none"> <li>• Patients using orlistat should take a multivitamin daily. Vitamins should contain fat-soluble vitamins (A, D, E, K) and should be taken 2 hours apart from orlistat.</li> </ul>	Conditional	Moderate
<p>7. In adults with obesity or overweight with weight-related complications, the AGA suggests using phentermine with lifestyle modifications, compared with lifestyle modifications alone.</p> <p>Implementation Considerations:</p> <ul style="list-style-type: none"> <li>• Phentermine monotherapy is approved by the FDA for short-term use (12 weeks). However, given the chronic nature of weight management, many practitioners use phentermine longer than 12 weeks in an off-label fashion.</li> <li>• Phentermine should be avoided in patients with a history of cardiovascular disease.</li> <li>• Blood pressure and heart rate should be monitored periodically while taking phentermine.</li> </ul>	Conditional	Low
<p>8. In adults with obesity or overweight with weight-related complications, the AGA suggests using diethylpropion with lifestyle modifications, compared with lifestyle modifications alone.</p> <p>Implementation considerations:</p> <ul style="list-style-type: none"> <li>• Diethylpropion monotherapy is approved by the FDA for short-term use (12 weeks). However, given the chronic nature of weight management, many practitioners use diethylpropion longer than 12 weeks in an off-label fashion.</li> <li>• Diethylpropion should be avoided in patients with a history of cardiovascular disease.</li> <li>• Blood pressure and heart rate should be monitored periodically while taking diethylpropion.</li> </ul>	Conditional	Low
<p>9. In adults with BMI between 25 and 40 kg/m<sup>2</sup>, the AGA recommends using Gelesis100 oral superabsorbent hydrogel only in the context of a clinical trial.</p>	No recommendation	Knowledge gap

≥10%, and ≥15% TBWL, treatment discontinuation due to adverse event, and serious adverse events (SAEs).

The evidence synthesis panel determined *a priori* that the minimal clinically important difference (MCID) for the efficacy of pharmacotherapy in the management of obesity that corresponds to important patient benefits is a mean difference (MD) of 3% TBWL between adjunctive pharmacotherapy over lifestyle interventions alone or an absolute 5% TBWL over baseline.<sup>12</sup> Given the mean of approximately 2% TBWL in placebo groups in randomized controlled trials (RCTs), the MD between adjunctive pharmacotherapy and lifestyle intervention alone of at least 3% TBWL will achieve the threshold of 5% TBWL over baseline, and was therefore used as the MCID. In a secondary analysis of a multicenter RCT on the effects of a lifestyle intervention (Look AHEAD Trial) in patients with a BMI ≥25 kg/m<sup>2</sup> and T2DM, patients who lost 2%–5% TBWL were more likely to have an improvement in blood pressure, glycemic control, and triglyceride values; the higher magnitude of weight loss was associated with greater odds of improvement.<sup>13</sup> The Center for Medicare and Medicaid Services uses a threshold of 3-kg weight loss at 6 months of intensive behavioral therapy for obesity to cover further face to face visits based on their assessment of the literature.<sup>14</sup> Lifestyle interventions alone result in modest long-term weight loss for

most individuals. A systematic review and meta-analysis of 31 RCTs assessing lifestyle vs control interventions showed a pooled estimate of 3.6-kg weight loss at 1 year and 2.5 kg at 3 years.<sup>15</sup> The US FDA uses a 5% TBWL threshold to assess the efficacy of pharmacotherapy for the long-term management of obesity.<sup>12,13,16–18</sup> For harm assessment, the guideline panel deemed the threshold of crossing 1% for absolute risks to be imprecise.<sup>19</sup>

### Search Strategy

We identified a recently published systematic review and network meta-analysis that used a comprehensive search strategy (PubMed, Embase, and Cochrane Library [CENTRAL]) from inception to March 23, 2021, for RCTs of AOMs.<sup>20</sup> We updated the search to January 1, 2022 with the help of a medical librarian for all included interventions except for phentermine, diethylpropion, and Gelesis100 oral superabsorbent hydrogel. A separate search from inception to January 1, 2022 was conducted for these 3 interventions because they were not included in the network meta-analysis. The search was limited to English language and human adults. The final strategy is available in [Supplementary Figure 1](#). References from included references and prior guidelines were searched to

identify any missing relevant studies. Furthermore, content experts aided in the identification of any ongoing studies.

### Study Selection, Data Collection, and Analysis

The systematic review and meta-analysis informing the guideline was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>21</sup> The inclusion and exclusion criteria were based on the formulated PICO questions. RCTs that assessed FDA-approved medications for obesity management in adults were assessed for inclusion. As obesity is a chronic disease, *a priori*, the panel decided to include studies that had a follow-up of at least 48 weeks. If 48-week outcomes were not available, a follow-up period of less than 1 year was included. The title and abstract of each identified reference were reviewed by 2 investigators, and disagreements were resolved by means of discussion and, if necessary, by a third member (see [Supplementary Figure 2](#) for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram). Data on the following outcomes were abstracted: baseline BMI, weight, waist circumference, age, definition of lifestyle intervention, number of participants in the intervention and comparator groups, %TBWL, weight loss (in kilograms), the proportion of participants who lost  $\geq 5\%$ ,  $\geq 10\%$ , and  $\geq 15\%$  of their body weight, SAEs, discontinuation rate due to adverse effects, and post-marketing data on SAEs from the US FDA Adverse Event Reporting System (FAERS).

We performed a meta-analysis using Review Manager (RevMan), version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), when outcomes were deemed similar enough to be pooled together. In scenarios when 3 or fewer studies were present, we used a fixed-effects model due to the instability of between-study variance; otherwise, a random-effects model was used.<sup>22,23</sup> When needed, imputations of SDs were performed using the RevMan, version 5.3, calculator. We reported categorical variables as relative risk (RR) and continuous variables as MD with 95% CIs. For dichotomous outcomes, heterogeneity was assessed using  $I^2$  statistic. We presented data in a narrative fashion when the meta-analysis was not feasible.

### Certainty of the Evidence

We assessed the risk of bias using the Cochrane Risk of Bias Tool for RCTs and the certainty of evidence across outcomes using the GRADE approach.<sup>9,24,25</sup> In this approach, evidence derived from RCT studies starts as high certainty. The certainty in the evidence conveys our confidence in the estimates of effect. Across each outcome, the evidence is graded into 4 categories (ie, high, moderate, low, or very low) ([Table 2](#)) and can be rated down for risk of bias, inconsistency, indirectness, imprecision, and publication bias. Using the GRADEpro Guideline Development Tool (<https://gradepro.org>), evidence profiles were created for each PICO question.

### Evidence to Recommendations

The evidence synthesis team convened virtually on a weekly basis to analyze, interpret, and synthesize the evidence and presented the findings to the entire guideline panel at a virtual face-to-face meeting to formulate the guideline recommendations on May 7, 2022. The evidence-to-decision

**Table 2.** Interpretation of the Certainty in Evidence of Effects Using the Grading of Recommendations Assessment, Development and Evaluation Framework

Certainty	Description
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

framework was used to formulate recommendations through consensus—this framework assesses and weighs the magnitude of and balance between the benefit and harms of interventions, patients' values and preferences, and the domains of feasibility, acceptability, and resource requirements and the impact on health equity. We also included a patient representative to assess patients' values and preferences. Cost and cost-effectiveness were important but did not drive a decision. The certainty of evidence and the strength of recommendation are provided for each clinical question. According to the GRADE approach, recommendations are labeled as "strong" and use the phrasing of "we recommend," or "conditional" and use the wording of "we suggest." The suggested interpretation per the GRADE approach of strong and conditional recommendations for patients, clinicians, and health care policy makers can be found in [Table 3](#).

### Review Process

Comments from a symposium presentation at Digestive Disease Week 2022 and a 14-day open public comment period were solicited. All comments were reviewed and addressed in an internal response document and were used to revise the guidelines as needed.

### Recommendations

An executive summary of all the recommendations is provided in [Table 1](#).

**Recommendation 1: In adults with obesity or overweight with weight-related complications, who have an inadequate response to lifestyle interventions, the AGA recommends adding pharmacological agents to lifestyle interventions over continuing lifestyle interventions alone. (Strong recommendation, moderate certainty evidence)**

**Table 3.** Interpretation of Strong and Conditional Recommendations Using the Grading of Recommendations Assessment, Development and Evaluation Framework

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients consistent with their values and preferences. Use shared decision making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

NOTE. Strong recommendations are indicated by statements that lead with “we recommend,” and conditional recommendations are indicated by statements that lead with “we suggest.”

### Implementation Considerations

- AOMs generally need to be used chronically, and the selection of the medication or intervention should be based on the clinical profile and needs of the patient, including, but not limited to, comorbidities, patients’ preferences, costs, and access to the therapy.

### Summary of the Evidence

Evidence informing the overarching recommendation for the use of pharmacotherapy in addition to lifestyle interventions is derived from RCTs. Details on the individual studies, patient selection, demographics, and lifestyle interventions are discussed under each drug separately. FDA-approved medications given simultaneously with lifestyle interventions that showed significant weight loss (defined as MD of 3% and thus, as low as 5% TBWL) were used to inform this PICO. We identified 27 RCTs in adults with obesity or overweight with weight-related complications. Mean age was approximately 40–60 years and mean BMI was approximately 32–36 kg/m<sup>2</sup>. All trials compared pharmacological treatment added to lifestyle interventions vs placebo or usual care and lifestyle interventions. They were all with long-term treatment and follow-up  $\geq$ 52 weeks. At the minimum, the lifestyle interventions generally included hypocaloric diets (500–600 kcal/d deficit) along with 150 minutes of physical activity per week. All studies reported weight loss, tolerability, and SAEs. Lifestyle interventions, which include diet (ie, reduced calorie intake), physical activity, and behavior therapy, are essential aspects of any obesity prevention or treatment program. Lifestyle modification as an intervention, however, lacks a standardized definition. Often, the structured lifestyle modification programs patients are exposed to in clinical trials do not reflect clinical practice. In the clinical setting, determining efficacy of lifestyle interventions in advance of

pharmacological treatment can encompass anything from formal comprehensive lifestyle treatment programs to patient reports of self-directed efforts.

### Benefits and Harms

Reported weight loss was substantially higher in the pharmacotherapy group and the MD ranged between 3.0% and 10.8% TBWL depending on the pharmacological agents. Treatment discontinuation due to adverse effects (ie, tolerability) and SAEs were also higher in the treatment group. Treatment discontinuation ranged from 34 per 1000 to 219 per 1000 more in the treatment group and the adverse events rate was low, ranging from 7 fewer to 27 more depending on the pharmacotherapy used.

### Certainty in Evidence of Effects

Across all included drugs for this PICO, the overall certainty in the evidence of effects was moderate (high for efficacy, moderate for SAEs) (Table 4). The certainty of evidence for all benefits (weight loss outcomes, both continuous and binary) was high. All included studies were RCTs without risk of bias. There was a concern for attrition bias in some studies, but almost all of them used intention-to-treat (ITT) analyses for categorical outcomes, and last observation carried forward (LOCF) for continuous outcomes. Furthermore, there was serious imprecision only in naltrexone-bupropion ER for %TBWL outcome because the lower confidence limit crosses the minimal important difference (MID) (3%). However, the categorical outcomes, such as 5%, 10% and 15% weight loss were all precise and, therefore, the overall certainty for benefits was high. There was moderate certainty in harms across all drugs due to small numbers of SAEs, with wide CIs that were crossing 1%, the *a priori* determined MCID threshold for harms,

**Table 4.** Evidence Profile for Supporting the Use of Pharmacologic Interventions for the Treatment of Obesity

Outcomes	No. of participants (studies), follow-up	Certainty of the evidence (GRADE)	Relative effect, RR (95% CI)	Anticipated absolute effects (risk difference with treatment)
Semaglutide 2.4 mg %TBWL	4352 (8 RCTs)	⊕⊕⊕⊕ High	—	MD 10.76% more (8.73 more to 12.8 more)
Treatment discontinuation due to adverse events	4353 (8 RCTs)	⊕⊕⊕⊕ High <sup>a</sup>	2.10 (1.54 to 2.86)	34 more per 1000 (from 17 more to 57 more)
Liraglutide 3.0 mg %TBWL	5968 (8 RCTs)	⊕⊕⊕⊕ High	—	MD 4.81% lower (5.39 lower to 4.23 lower)
Treatment discontinuation due to adverse events	6362 (10 RCTs)	⊕⊕⊕⊕ High <sup>a</sup>	2.31 (1.85 to 2.88)	91 more per 1000 (69 more to 120 more)
Phentermine-topiramate ER %TBWL	3141 (3 RCTs)	⊕⊕⊕⊕ High <sup>b</sup>	—	MD 8.45% higher (7.89 higher to 9.01 higher)
Treatment discontinuation due to adverse events	3141 (3 RCTs)	⊕⊕⊕⊕ High <sup>a,j</sup>	2.08 (1.71 to 2.52)	91 more per 1000 (from 60 more to 129 more)
Naltrexone-bupropion ER %TBWL	12659 (5 RCTs)	⊕⊕⊕⊙ Moderate <sup>c</sup>	—	MD 3.01% lower (3.54 lower to 2.47 lower)
Treatment discontinuation due to adverse events	12839 (5 RCTs)	⊕⊕⊕⊕ High <sup>d</sup>	2.39 (1.69 to 3.37)	129 more per 1000 (64 more to 219 more)

<sup>a</sup>Serious imprecision in the SAE outcome because the absolute risk crosses threshold of 1%, which was the predetermined MID threshold. Thus, the overall certainty of evidence for this pharmacotherapy was moderate.

<sup>b</sup>Low event rate leading to serious imprecision in both %TBWL  $\geq$ 15% and SAE.

<sup>c</sup>MID or clinically important threshold below which there is no clear benefit of the intervention in discussion with the guideline panel and technical review team was determined to be 3 kg (or approximately 3%). We noted serious imprecision as the lower confidence limit crosses the MID for benefit.

<sup>d</sup>Low event rate leading to serious imprecision in SAE outcome.

leading to serious imprecision. Thus, the overall certainty of evidence mostly driven by the lowest certainty in harm outcomes, was deemed to be moderate.

## Discussion

Four drugs—semaglutide 2.4 mg, liraglutide 3.0 mg, phentermine-topiramate ER and naltrexone-bupropion ER—approved for long-term use were deemed to have a moderate or large magnitude of weight loss and small or not-substantial harms, and hence a balance favoring their utilization. Furthermore, each of the 4 drugs used adjunctively with lifestyle interventions is likely to result in a high proportion of patients achieving 5% and 10% TBWL, which has a significant favorable effect on long-term health outcomes. Treatment goals should be individualized to particular complications of a patient. The cost of AOMs remains a concern for the implementation and access to these therapies, especially among more vulnerable populations. Data regarding the cost-effectiveness of anti-obesity pharmacotherapy is limited, and likely to evolve with more effective therapies.<sup>26,27</sup>

There are some general considerations when considering AOMs. They should not be used in pregnant women. In patients with T2DM treated with insulin or insulin secretagogues (eg, sulfonylureas), AOMs may increase the risk of hypoglycemia, and medication dose adjustment may be necessary because serum glucose levels could drop with weight loss and reduced caloric consumption. Similarly, for patients taking medications that can lower blood pressure, caution is advised when starting AOMs, as blood pressure can drop with weight loss. Caution is also advised when considering AOMs with certain eating disorders. They should not be used in patients with active bulimia nervosa. Patients with binge eating disorder should be monitored closely for decompensation of binge eating behaviors.

**Recommendation 2. In adults with obesity or overweight with weight-related complications, the AGA suggests using semaglutide 2.4 mg with lifestyle interventions, compared with lifestyle interventions alone. (Conditional recommendation, moderate certainty evidence)**

### Implementation Considerations

- Given the magnitude of net benefit, semaglutide 2.4 mg may be prioritized over other approved AOMs for the long-term treatment of obesity for most patients.
- Semaglutide has glucoregulatory benefits and is also approved for the treatment of T2DM.
- Semaglutide may delay gastric emptying with adverse effects of nausea and vomiting. Gradual dose titration may help mitigate these adverse effects.
- Glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) have been associated with increased risk of pancreatitis and gallbladder disease

### Summary of the Evidence

A total of 8 RCTs assessing semaglutide 2.4 mg subcutaneous (SQ) weekly dose was used to inform this PICO.<sup>28-35</sup> We excluded oral semaglutide, as it is only FDA-approved for treatment of T2DM and not for obesity. Two studies used a lower threshold for BMI inclusion of  $\geq 25$  kg/m<sup>2</sup>,<sup>29,31</sup> another  $\geq 30$  kg/m<sup>2</sup>,<sup>32</sup> and the remaining 5 studies used inclusion BMI  $\geq 27$  kg/m<sup>2</sup> with comorbid conditions or  $\geq 30$  kg/m<sup>2</sup> (Kadowaki et al<sup>30</sup> studying an East Asian population included BMI  $\geq 27$  kg/m<sup>2</sup> with 2 comorbid conditions or  $\geq 35$  kg/m<sup>2</sup> with 1 comorbidity).<sup>28,30,33-35</sup> At baseline, mean BMI in the intervention arm across studies ranged from 32.0 to 39.9 kg/m<sup>2</sup>, mean weight ranged from 86.9 to 113.2 kg, and mean waist circumference ranged from 103.8 to 119 cm. Mean age ranged from 46.0 to 59.5 years, with the majority of studies including predominately female participants. Four studies<sup>32-35</sup> included a population without T2DM, 3 studies<sup>29-31</sup> had a mixed population, and 1 study<sup>28</sup> assessed subjects with T2DM. Three studies<sup>29,31,32</sup> used 0.4 mg SQ daily, and the remaining studies used 2.4 mg SQ weekly after a protocolized dose escalation. In addition, the majority of studies incorporated lifestyle intervention of a hypocaloric diet (500-kcal daily deficit) along with 150 minutes of physical activity per week. Two studies<sup>29,31</sup> allowed for diet and exercise counseling, one<sup>29</sup> of which did not include a formal weight loss program. Wadden et al<sup>34</sup> included intensive behavioral therapy and an initial low-calorie diet (LCD).

### Benefits

Eight RCTs (2658 participants treated with semaglutide group vs 1694 participants in the placebo group) informed the outcome of %TBWL with a follow-up period ranging from 52 to 72 weeks.<sup>28-35</sup> MD %TBWL was 10.76% TBWL (95% CI, 8.73%–12.80%) in favor of the treatment group. Six RCTs reported weight loss ranging from 9.7 to 16.8 kg in the semaglutide group vs 1.5 to 6.2 kg in the placebo group (MD, 10.81 kg; 95% CI, 8.19–13.43 kg).<sup>28,30,32-35</sup> Six RCTs with 2543 participants in the semaglutide group and 1583 participants in the placebo group reported for the proportion of participants achieving percent weight loss by thresholds.<sup>28,30,32-35</sup> A pooled analysis showed 82.3% vs

30.6% for  $\geq 5\%$  TBWL (RR, 2.74; 95% CI, 2.21–3.40), 64.9% vs 12.3% for  $\geq 10\%$  TBWL (RR, 5.25; 95% CI, 3.61–7.64), and 46.1% vs 5.4% for  $\geq 15\%$  TBWL (RR, 7.82; 95% CI, 5.19–11.76) in the semaglutide group vs control group, respectively (Supplementary Figure 3A–E).

### Special Consideration for Patients With Type 2 Diabetes Mellitus

Because semaglutide was originally approved for T2DM, we also examined glycemic control of semaglutide 2.4-mg dose that was approved for the treatment of obesity. Three studies included a mixed population of individuals with and without T2DM.<sup>29-31</sup> In a phase 2, double-blind, clinical trial involving 320 participants who had biopsy-confirmed nonalcoholic steatohepatitis with and without T2DM, subjects with T2DM had a glycated hemoglobin (HbA1c) reduction of 1.15% in the semaglutide 0.4 mg SQ daily group (49 subjects) vs 0.01% in the placebo group (50 subjects).<sup>31</sup> Moreover, a phase 3, double-blind, placebo trial that examined an East Asian population with overweight/obesity and with or without T2DM, Kadowaki et al<sup>30</sup> reported 83% of participants (39 of 47) with T2DM in the semaglutide 2.4-mg cohort (baseline mean HbA1c, 8.4%) and 4% of participants (1 of 25) in the placebo group (baseline mean HbA1c, 8.1%) were able to achieve HbA1c  $\leq 6.5\%$  at week 68. Davies et al<sup>28</sup> assessed the effect of semaglutide 2.4 mg weekly in adults with overweight or obesity with T2DM and found that the MD in reduction for HbA1c was 1.2% compared with the placebo group and the MD in %TBWL in the semaglutide group (n = 404) vs placebo group (n = 403) was 6.22% (95% CI, 5.11%–7.33%), favoring the semaglutide group.

### Harms

We pooled 8 RCTs to inform harm outcomes with 2657 participants in the semaglutide group and 1696 participants in the control group<sup>28-35</sup> (Supplementary Figure 3F and G). SAEs were defined by the original studies' definition. The pooled estimate for SAEs showed a 38% higher risk of SAEs with semaglutide vs placebo (95% CI, 1.10–1.73). Selected examples of SAEs from the largest study<sup>35</sup> included reported rates of abdominal pain (intervention [I]: 3 of 1306 vs comparison [C]: 0 of 655), constipation (I: 1 of 1306 vs C: 0 of 655), diarrhea (I: 1 of 1306 vs C: 0 of 655), nausea (I: 1 of 1306 vs C: 0 of 655), vomiting (I: 4 of 1306 vs C: 0 of 655), pancreatitis (I: 2 of 1306 vs C: 0 of 655), vertigo (I: 3 of 1306 vs C: 0 of 655), cholelithiasis (I: 12 of 1306 vs C: 1 of 655), cholecystitis (I: 4 of 1306 vs C: 0 of 655), acute myocardial infarction (I: 2 of 1306 vs C: 1 of 655), gastroenteritis (I: 5 of 1306 vs C: 0 of 655), and suicidal ideation (I: 1 of 1306 vs C: 0 of 655). Treatment discontinuation due to adverse events occurred at a rate of 6.4% (170 of 2657) in the semaglutide group and 3.1% (52 of 1696) in the placebo group (RR, 2.10; 95% CI, 1.54–2.86). Of note, semaglutide is contraindicated in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2 based on animal



studies. SAEs from studies, FDA, and contraindications are summarized in [Supplementary Table 2](#).

### Certainty in Evidence of Effects

The overall certainty in the evidence of effects for semaglutide was moderate. See [Supplementary Table 3](#) for the full evidence profile. We found inconsistency among the studies for weight loss, but as the effect was in the same direction and did not cross the *a priori* MCID, we decided not to rate it down. The inconsistency can be explained by Davies et al,<sup>28</sup> including patients with T2DM, while Wilding et al<sup>35</sup> does not. The %TBWL appears to be lower in individuals who have T2DM. For the proportion of participants who achieved %TBWL threshold outcomes, we noted inconsistency, which could be explained by Wadden et al<sup>34</sup> because intensive behavioral therapy and LCD were implemented in both arms. Thus, this could minimize the difference between both arms. For the SAEs, we observed serious imprecision, as the 95% CI of the absolute risk crossed 1%.

### Discussion

GLP-1 is an endogenous incretin hormone produced by L cells within the intestinal mucosa in response to the intake of nutrients. GLP-1 receptors are expressed in multiple organs, including pancreas, gastrointestinal (GI) tract, heart, brain, kidney, lung, and thyroid. This ubiquitous expression of GLP-1 receptors could be the reason for its pleiotropic benefits for T2DM, weight loss, and cardioprotection.<sup>36</sup> GLP-1 has numerous metabolic effects, including but not limited to, glucose-dependent stimulation of insulin secretion, delayed gastric emptying, inhibition of food intake, and modulation of  $\beta$ -cell proliferation.<sup>37</sup> Semaglutide was approved for the management of obesity in 2021. Having a dose-response effect on weight loss, semaglutide was approved at doses higher than indicated for T2DM.<sup>32,38</sup> GLP-1 RAs do not have the same neuropsychiatric adverse effects as other FDA-approved drugs on the market.<sup>35,39</sup> Other benefits include inherent gluco-regulatory properties and cardioprotection in select populations.<sup>28,40</sup> At the time of publication of this guideline, results from the SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial were not yet available, but those results may help inform patients, prescribers, and payers on the cardiovascular benefits of GLP-1 RAs, specifically semaglutide, for individuals with excess adiposity and cardiovascular disease, but without T2DM.<sup>41</sup> In our evidence synthesis, semaglutide led to a large magnitude of weight loss, with a small risk of undesirable adverse effects and low risk of treatment discontinuation due to adverse events, with moderate certainty of evidence. However, the guideline panel deemed that there was uncertainty and substantial variability in individuals' values and preferences between desirable and undesirable effects. In other words, it is not clear that individuals would consistently prioritize the desired outcomes over the potential adverse effects, inconvenience of weekly SQ administration, potentially high cost, burden of monitoring, and challenges associated with insurance authorization. There is also variability in response,

with potentially inferior weight loss outcomes in people with T2DM.<sup>28,35</sup> Lastly, some patients may prefer other available nonpharmacologic therapies for the treatment of obesity. Therefore, the panel made a conditional recommendation suggesting the use of semaglutide in individuals with obesity or overweight with weight-related complications due to variability in values and preferences.

**Recommendation 3. In adults with obesity or overweight with weight-related complications, the AGA suggests using liraglutide 3.0 mg with lifestyle interventions, compared with lifestyle interventions alone. (Conditional recommendation, moderate certainty)**

### Implementation Considerations

- Liraglutide has gluco-regulatory benefits and is also approved for the treatment of T2DM.
- Liraglutide may delay gastric emptying with adverse effects of nausea and vomiting. Gradual dose titration may help mitigate these adverse effects.
- Liraglutide has been associated with an increased risk of pancreatitis and gallbladder disease.

### Summary of the Evidence

Our search identified direct comparative evidence from 11 RCTs on liraglutide for the long-term treatment of obesity with a study duration of at least 52 weeks. In 3 studies, both the liraglutide and placebo groups received adjunctive intensive lifestyle intervention composed of diet, physical activity, and behavior change counseling.<sup>42–44</sup> Most studies emphasized a hypocaloric diet with at least 500-kcal energy deficit below their individualized daily total caloric requirements, along with  $\geq 150$  min/wk of physical activity. Liraglutide or matching placebo was delivered as a daily SQ injection, starting at a dose of 0.6 mg, with weekly dose escalations until the target of 3.0 mg daily was reached. In 3 weight maintenance studies, the effect of liraglutide was studied against placebo after a variable-length run-in period, wherein participants were asked to follow a calorie-restricted diet.<sup>43,45,46</sup> For instance, in 2 studies, subjects had to lose at least 5% of their baseline body weight before randomization and were assigned to an LCD (800–1000 kcal/d for 8 weeks before randomization),<sup>45,46</sup> whereas in another study, participants had to lose  $\geq 5\%$  of their initial body weight during a variable-length (4–12 weeks) run-in period, during which time they were prescribed an LCD (1200–1400 kcal diet) before qualifying for randomization.<sup>43</sup> In SCALE (Satiety and Clinical Adiposity – Liraglutide Evidence)-Maintenance, participants lost 6.5 kg during the run-in period before randomization,<sup>43</sup> whereas in the other 2 studies they lost an average of 12.5–13.1 kg before randomization.<sup>45,46</sup>

A total of 3964 subjects were randomized to liraglutide 3.0 mg and 2498 subjects were randomized to control groups. At baseline, participants had a BMI  $\geq 30$  kg/m<sup>2</sup> or

$\geq 27$  kg/m<sup>2</sup> in the presence of weight-related complications. Baseline demographic characteristics of the population were similar across the studies, with a mean age between 43 and 59 years, predominantly female (approximately 70%) and White (>80%); mean baseline weight was between 100 and 105 kg. Two studies included individuals with T2DM, 1 of which only included participants on oral antidiabetic medications,<sup>47</sup> and in the other, patients were on basal insulin and were also allowed to be on up to 3 oral antidiabetic medications.<sup>48</sup> In another trial, participants with T2DM were only excluded if they were on antidiabetic pharmacotherapy other than metformin, but separate outcome data were not provided for those with T2DM in this RCT.<sup>46</sup>

### Benefits

Eight studies provided data on %TBWL.<sup>32,33,39,42–44,47,48</sup> Pooled analysis of these studies showed an MD of 4.81% (95% CI, 4.23%–5.39%) in favor of liraglutide. Similarly, those in the liraglutide group had a higher mean weight loss (in kilograms) compared with controls (9 studies; MD, -5.3 kg; 95% CI, -5.9 to -4.7 kg).<sup>32,33,39,42,43,45–47,49</sup> Participants treated with liraglutide were significantly more likely to achieve  $\geq 5\%$  TBWL (11 trials; RR, 2.09; 95% CI, 1.80 to 2.42),  $\geq 10\%$  TBWL (11 trials; RR, 2.67; 95% CI, 2.14 to 3.34) and  $\geq 15\%$  TBWL (6 trials; RR, 3.04; 95% CI, 2.25 to 4.12), compared with placebo.<sup>32,33,39,42–49</sup> (Supplementary Figure 4A–E).

### Special Consideration for Patients With Type 2 Diabetes Mellitus

There were only 2 studies that included patients with obesity and T2DM, namely SCALE Insulin RCT and the SCALE Diabetes RCT.<sup>47,48</sup> In the SCALE Insulin RCT, participants achieved a modest reduction in HbA1c with liraglutide compared with placebo (MD, -0.5; 95% CI, -0.8 to -0.3), although it is to be noted that a total of 24 participants who completed the trial (21 on liraglutide and 3 on placebo) were no longer using insulin at the end of the study period.<sup>48</sup> The reduction in HbA1c in the SCALE Diabetes RCT was similar (MD, -0.93; 95% CI, -1.08 to -0.78).<sup>47</sup>

### Harms

All 11 studies reported on SAEs.<sup>32,33,39,42–49</sup> There was no significant difference between liraglutide and control groups (RR, 1.22; 95% CI, 1.00–1.50). Most SAEs were not deemed to be drug-related, and they were predominantly GI-related adverse effects. GI adverse effects, particularly nausea and vomiting, were significantly more common in the liraglutide group compared with controls (Supplementary Figure 4F and G). The incidence of nausea and vomiting with liraglutide was 40% and 16%, respectively, and with placebo 14.8% and 4.3%, respectively. Extrapolating AEs reported to the FAERS, out of approximately 29,277 patients who took liraglutide 3.0 mg between 2015 and 2018,<sup>50</sup> 40 cases of acute pancreatitis (<0.1%), and 17 cases of symptomatic gallstones (<0.05%) requiring

hospitalization were reported. Ten studies reported on treatment discontinuation due to AEs.<sup>32,33,39,43–49</sup> Meta-analysis of these 10 studies showed that liraglutide was associated with a significantly higher risk of treatment discontinuation compared with controls (RR, 2.31; 95% CI, 1.85–2.88). SAEs from studies, FDA, and contraindications for liraglutide are summarized in Supplementary Table 4.

### Certainty in Evidence of Effects

The overall certainty in the evidence of effects for liraglutide 3.0 mg was moderate and was driven mainly by harms. See Supplementary Table 5 for the full evidence profile. We noted considerable attrition, up to 30% in some studies, but this was similar between intervention and control groups and all studies performed ITT analyses, thus, we did not rate it down for risk of bias. There was 1 study of concern with regard to blinding.<sup>49</sup> In this study, a list containing unblinded subject data was inadvertently sent to 3 trial sites in Europe (22 participants), but the investigators performed a sensitivity analysis for the primary outcome by excluding these 22 subjects and found that the results were not affected by their exclusion.<sup>49</sup> In addition, we performed a sensitivity analysis by excluding 3 studies using an LCD diet run in a period when participants lost significant weight before randomization.<sup>43,45,46</sup> Sensitivity analysis did not show any meaningful change in the pooled estimate of effect by excluding these studies, and hence we did not rate down for indirectness.

For the  $\geq 5\%$  TBWL outcome, there was substantial heterogeneity present in this meta-analysis ( $I^2 = 68\%$ ), but the heterogeneity was largely due to differences in magnitude and not the direction of effect estimates, and hence we did not rate it down for inconsistency. Finally, we rated for imprecision for SAEs as the 95% CI extended from no harms to clinically significant SAEs.

### Discussion

Liraglutide is another GLP-1 RA that the FDA originally approved in 2010 for the treatment of T2DM. As an antidiabetic therapy, it is available up to a dose of 1.8 mg SQ injection daily. Based on phase 3 clinical trials from the SCALE program, liraglutide was approved in 2014 for the treatment of obesity up to a dose of 3.0 mg daily, as an adjunct to lifestyle interventions. Similar to semaglutide, liraglutide at 1.8 mg has been found to reduce morbidity and mortality in people with T2DM at risk for cardiovascular disease.<sup>51</sup> The magnitude of the desirable effect of weight loss was moderate, with a small magnitude of potential harms, mostly GI adverse effects. Studies tried to mitigate GI adverse effects by means of a slow escalation of liraglutide dosing (daily 0.6 mg titrated weekly) until the target dose (3.0 mg) was reached. Nausea and vomiting were mostly transient, with most incidents occurring during the first 4–6 weeks of treatment, coinciding with dose escalation.

The guideline panel discussed the balance between weight loss and adverse effects and decided it was favorable for using liraglutide. Like semaglutide, it is not clear that

individuals would consistently prioritize the desired outcomes over the potential adverse effects, inconvenience of daily SQ administration, potentially high cost, burden of monitoring, and challenges associated with insurance authorization. There is also a variable response to therapy and potentially inferior weight loss outcomes in people with insulin resistance.<sup>39,52</sup> Lastly, some patients may prefer other nonpharmacologic therapies for treating obesity. Therefore, the panel made a conditional recommendation for the use of liraglutide in individuals with obesity or overweight with weight-related comorbidities.

### Special Clinical Considerations When Using Glucagon-Like Peptide 1 Receptor Agonists, Semaglutide and Liraglutide

To minimize risk of GI adverse effects, gradual dose titration is recommended for semaglutide and liraglutide. Semaglutide is started at 0.25 mg weekly for the first 4 weeks, followed by doses of 0.5 mg, 1.0 mg, and 1.7 mg weekly every 4 weeks at each dose, until the maintenance dose of 2.4 mg is reached after 16 weeks. For liraglutide, it is recommended to start with 0.6 mg daily for the first 7 days, followed by doses of 1.2 mg, 1.8 mg, and 2.4 mg daily every 7 days at each dose until the maintenance dose of 3.0 mg is reached after 4 weeks. Clinical judgment is recommended for adjusting the titration schedule as needed for an individual patient's response, tolerance, and adverse effects. If more than 2 consecutive doses are missed, clinical judgment is required to decide on subsequent dosing. Based on our expert opinion, resuming at the same dose can be considered if a patient has tolerated the medication well. Otherwise, prescribers should consider lowering the next dose. Restarting the titration schedule should be considered if 3 or more consecutive doses are missed. Some patients may achieve a strong response at a submaximal dose and could continue that given dose long term.

Liraglutide and semaglutide should not be used with other GLP-1 RAs or with dipeptidyl peptidase-4 inhibitors. Because GLP-1 RAs can delay gastric emptying, it may impact the absorption of some oral medications that require rapid onset of action. Caution is advised when using GLP-1 RAs in combination with insulin or insulin secretagogues (eg, sulfonylureas). Doses should be adjusted as clinically indicated and patients should be counseled and monitored for hypoglycemia. Otherwise, GLP-1 RAs stimulate insulin secretion from  $\beta$  cells in a glucose-dependent manner and thus carry a very low risk of hypoglycemia. GLP-1 RAs have been associated with thyroid C-cell tumors in rodents in dose- and treatment duration-dependent fashion.

**Recommendation 4. In adults with obesity or overweight with weight-related complications, the AGA suggests using phentermine-topiramate ER with lifestyle interventions, compared with lifestyle interventions alone. (Conditional recommendation, moderate certainty)**

### Implementation Considerations

- Because topiramate is effective for treating migraine headaches, phentermine-topiramate ER may be preferentially used in patients with comorbid migraines.
- Phentermine-topiramate ER should be avoided in patients with a history of cardiovascular disease and uncontrolled hypertension.
- Topiramate is teratogenic. Women of childbearing potential should be counseled to use effective contraception consistently.
- Blood pressure and heart rate should be monitored periodically while taking medications with phentermine.

### Summary of the Evidence

Three RCTs with a follow-up time of 52–56 weeks were included to inform this PICO.<sup>53–55</sup> Allison et al<sup>54</sup> used inclusion criteria of BMI  $\geq 35$  kg/m<sup>2</sup>, and Gadde et al<sup>55</sup> used BMI 27–45 kg/m<sup>2</sup> with 2 or more comorbidities and Garvey et al<sup>53</sup> included BMI of 27–45 kg/m<sup>2</sup> with T2DM. Gadde et al also included participants with a BMI  $\leq 27$  kg/m<sup>2</sup> if they had T2DM, comprising 17% of the study population. Mean BMI, weight, and waist circumference ranges across studies were as follows: 35.5–41.9 kg/m<sup>2</sup>, 94.9–115.1 kg, and 109–120.1 cm, respectively. Mean age ranged from 41.9 to 51 years; the majority of patients were female. All 3 studies included lifestyle counseling, most with a caloric reduction goal of 500 kcal/d.

### Benefits

Pooled analysis of 3 RCTs<sup>53–55</sup> with a total of 1580 participants in the phentermine-topiramate 15 mg/92 mg dosing group vs 1561 participants in the placebo group demonstrated an MD of 8.45% (95% CI, 7.89%–9.01%) TBWL, favoring the intervention (Supplementary Figure 5A–C). When assessing 7.5 mg/46 mg dosing, Gadde et al<sup>55</sup> reported 6.55% (95% CI, 5.66%–7.44%) TBWL in the phentermine-topiramate ER group (498 participants) compared with the control group (993 participants). We pooled the same 3 RCTs for the outcome of  $\geq 5\%$  and  $\geq 10\%$  TBWL. For the group treated with phentermine-topiramate ER 15 mg/92 mg, 67.6% of subjects achieved  $\geq 5\%$  TBWL vs 19.4% of those in the placebo arm (RR, 3.48; 95% CI, 3.13–3.87), with similar results for  $\geq 10\%$  TBWL (46.2% vs 7.3%; RR, 6.33; 95% CI, 5.26–7.61). One RCT reported TBWL  $\geq 15\%$  in 31.5% vs 3.3% of subjects treated with phentermine-topiramate ER 15 mg/92 mg and placebo, respectively (RR, 9.51; 95% CI, 5.86–15.44).<sup>54</sup>

### Special Consideration for Hypertension

The largest trial assessing phentermine-topiramate ER was designed to include only subjects with weight-related complications, including a systolic blood pressure 140–160 mm Hg (130–160 mm Hg in those with T2DM), diastolic blood pressure 90–100 mm Hg (85–100 mm Hg in those

with T2DM), or treatment with at least 2 antihypertensive medications. Both phentermine-topiramate ER treatment groups included 52% (261 of 498 and 520 of 995 in the 7.5-mg/46-mg and 15-mg/92-mg groups, respectively) of participants with hypertension. In the control group, 53% (524 of 994) had hypertension. Reduction in systolic blood pressure in the placebo group, 7.5-mg/46-mg group, and 15-mg/92-mg group was an average of 2.4 mm Hg, 4.7 mm Hg, and 5.6 mm Hg, respectively. For diastolic blood pressure, the reduction was 2.7 mm Hg, 3.4 mm Hg, and 3.8 mm Hg, respectively. Notably, there was greater discontinuation of antihypertensive agents in the treatment groups (11% [27 of 256] and 15% [76 of 514] in the 7.5-mg/46-mg and 15-mg/92-mg groups, respectively) compared with the control group (5% [24 of 516]). Adverse events due to blood pressure elevation leading to discontinuation occurred for 5 subjects in the placebo group, 2 in the 7.5/46-mg group, and 3 in the 15/92-mg group.<sup>55</sup>

For patients undergoing invasive procedures requiring general anesthesia, specific considerations and precautions may be warranted. One case report has documented perioperative hypertensive complications<sup>56</sup> and a systematic review has identified other complications, such as hypotension, bradycardia, and hyperthermia.<sup>57</sup> Because phentermine is a sympathomimetic, hyperadrenergic effects can be a potential hazard in the perioperative period. Moreover, because phentermine is also a reuptake inhibitor of norepinephrine, refractory hypotension has been reported, possibly a result of catecholamine depletion and autonomic dysfunction. It has been suggested that phentermine (and phentermine-containing medications) be discontinued at least 4 days before a procedure requiring anesthesia.<sup>57</sup>

### Harms

Three RCTs were pooled to inform treatment discontinuation due to adverse events.<sup>53–55</sup> This occurred at a rate of 17.4% (275 of 1580) in the phentermine-topiramate ER 15-mg/92-mg group and 8.5% (132 of 1561) in the control group (RR, 2.08; 95% CI, 1.71–2.52). SAEs occurred in 4.2% (67 of 1580) of participants in the phentermine-topiramate ER 15 mg/92 mg vs 3.5% (55 of 1561) in the control group (Supplementary Figure 5D and E). SAEs from studies, FDA, and contraindications for phentermine/topiramate ER are summarized in Supplementary Table 6.

### Certainty in Evidence of Effects

The overall certainty of evidence in effects for phentermine-topiramate ER 15 mg/92 mg was moderate, driven mainly by harms. See Supplementary Table 7 for the full evidence profile. There was serious risk of bias when assessing Garvey et al,<sup>53</sup> as only complete data from the first 28 weeks appeared to be reported instead of ITT outcomes, and details describing the first 28 weeks of treatment were limited. In addition, in the first 28 weeks, phentermine and topiramate were given as individual immediate-release medications rather than the ER formulation. Sensitivity analysis was performed for the above outcomes, and the effect estimates had trivial differences; thus, Garvey et al

was included in our analysis. As the effect estimates were considered more conservative, we did not rate down for risk of bias or inconsistency. For the outcome of  $\geq 15\%$  TBWL, there was a serious concern for imprecision due to the low event rate. However, for the outcomes of  $\geq 5\%$ ,  $\geq 10\%$ , and  $\%TBWL$ , there was high certainty of evidence. In addition, there was serious imprecision for the outcome of SAEs due to the low event rate and the CI showing both increase and decrease in harm.

### Discussion

In 2012, the FDA approved the combination of phentermine immediate release and topiramate extended release, as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of  $\geq 30$  kg/m<sup>2</sup> or  $\geq 27$  kg/m<sup>2</sup> in the presence of at least 1 weight-related complication, such as hypertension, T2DM, or dyslipidemia. Phentermine is a monoamine sympathomimetic with a mechanism of action that is likely mediated through the elevation of norepinephrine in the central nervous system (CNS). Recommendation 7 describes the history and clarifies common misconceptions regarding phentermine. Although 2-year data using phentermine with topiramate in the SEQUEL Trial exist,<sup>58</sup> it should be noted that the dosing of phentermine (maximum dose of 15 mg) in this combination therapy is lower than the dose usually prescribed by most clinicians as phentermine monotherapy (37.5 mg). Topiramate has been approved for the treatment of epilepsy and migraine headaches for many years. Its effect on weight loss was noted in clinical trials for seizures.<sup>59</sup> The exact mechanism of action of topiramate is unknown, but reduced energy consumption through modulation of gamma-aminobutyric acid receptors in relevant CNS structures may be involved.<sup>60,61</sup> In animals, topiramate is known to reduce energy intake, an effect that is also observed in humans.<sup>62,63</sup> Interestingly, topiramate has been shown to increase energy expenditure in rodents by means of reducing bioenergetic efficiency, but this has not been demonstrated in humans.<sup>63,64</sup> Topiramate alone is not FDA-approved as an AOM, but many prescribers use it for this purpose in an off-label fashion. Prospective, randomized, placebo-controlled trials have demonstrated its efficacy in patients with overweight and obesity, but most of them have been less than 12 months in duration.<sup>61,65–68</sup> Moreover, topiramate has been used to manage some eating disorders, although most published effects are case series or case reports.<sup>69–71</sup> Notably, zonisamide, another antiepileptic drug with pharmacologic properties similar to topiramate, is also used off-label by some health care professionals treating obesity. Although there are published short-term studies, it is not FDA-approved as an AOM.<sup>72,73</sup>

The magnitude of weight loss for phentermine-topiramate ER 15 mg/92 mg was judged to be moderate to large. Although there was a higher rate of treatment discontinuation with phentermine-topiramate ER, this was deemed to be not substantial, and SAEs were rare. Therefore, the balance between desirable and undesirable effects

was favorable for the use of phentermine-topiramate ER. Similar to other medications, there were concerns about the differences in patients' values and preferences and an increase in the burden on monitoring with pharmacotherapy (eg, blood pressure and heart rate monitoring, pregnancy tests). Taken together, the panel made a conditional recommendation for the use of phentermine-topiramate ER.

### Special Clinical Considerations

Phentermine-topiramate ER is available in capsules with doses of 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg. It is recommended to initiate treatment with the starter dose of 3.75 mg/23 mg taken once daily for 14 days, followed by a maintenance dose of 7.5 mg/46 mg daily. After 12 weeks, if the patient has not lost at least 3% of their body weight, consider discontinuation or further dose escalation, depending on tolerance, adverse effects, and patient preference. For escalating the dose, titrate up to 11.25 mg/69 mg daily for 14 days, followed by the maintenance maximum dose of 15 mg/92 mg daily. Although 7.5 mg/46 mg is considered the standard dose, our analysis demonstrated superior efficacy for the 15 mg/92 mg option, and we recommend this as the target dose, as long as the balance of benefit and risk is favorable for a given individual patient. If the patient has not lost 5% or more of their weight after 12 weeks on the maximum dose, treatment should be discontinued with dose titration by taking 1 capsule every other day for at least 1 week, then stopping, to minimize the risk of precipitating a seizure. Because of the potential benefits for patients with migraine headaches, phentermine-topiramate ER should be considered in patients with obesity and migraines.

One of the most important concerns among prescribers surrounds the cardiovascular safety of phentermine. Perceptions regarding cardiotoxicity with sympathomimetic AOMs can be categorized into 2 different pathophysiologic domains. The first, regarding serotonergic stimulation of myocardial tissues (pulmonary hypertension, valvulopathies), is addressed in Recommendation 7 for phentermine monotherapy. The second domain reflects adrenergic hemodynamic effects (eg, heart rate and blood pressure) and the potential for adverse cardiovascular outcomes. In pivotal clinical trials for phentermine-topiramate ER, blood pressure generally declined, and there was a very modest increase in heart rate, usually at higher doses.<sup>54,55,58</sup> Observational data from phentermine monotherapy do not seem to demonstrate significant increases in blood pressure or heart rate in treated individuals.<sup>74-76</sup> Currently, there are no large cardiovascular outcome trial data for long-term use of phentermine-topiramate ER. Hence, caution is advised and phentermine-topiramate ER should be avoided in patients with a history of cardiovascular disease or uncontrolled hypertension. Pivotal phase 3 trials enrolled subjects up to the age of 70 years, but there are no high-quality data to guide the use of phentermine-topiramate ER in the geriatric population. It should also be avoided in patients treated with, or within 14 days, of monoamine oxidase inhibitors. Due to concerns for arrhythmias and seizures,

medications with phentermine should not be used in patients with untreated hyperthyroidism.

Fetal exposure to topiramate during the first trimester is associated with an increased risk of oral clefts.<sup>77</sup> Female patients with child-bearing potential should be counseled on the risks of teratogenicity and consistent use of reliable contraception while using phentermine-topiramate ER. Monitoring with monthly pregnancy tests can be considered. Topiramate has carbonic anhydrase inhibitor properties and can induce metabolic acidosis and elevated urine pH with hypercalciuria and hypocitraturia.<sup>78</sup> With higher doses and prolonged exposure, there may be an increased risk of kidney stones. Caution is advised in patients with a history of significant nephrolithiasis. Consideration should be given to periodic monitoring of serum bicarbonate levels in patients treated with phentermine-topiramate ER long term.

Due to the potential for insomnia, it is recommended that phentermine-topiramate ER be taken early in the day. Other commonly reported adverse effects include cognitive impairment, constipation, dry mouth, palpitations, paresthesias, dysgeusia, and irritability.<sup>54,55,58</sup> Phentermine-topiramate ER is classified as a schedule IV-controlled substance based on concerns for abuse and dependence.

**Recommendation 5. In adults with obesity or overweight with weight-related complications, the AGA suggests using naltrexone-bupropion ER with lifestyle interventions, compared with lifestyle interventions alone. (Conditional recommendation, moderate certainty)**

### Implementation Considerations

- Naltrexone-bupropion ER may be considered for the treatment of overweight or obesity in patients who are attempting smoking cessation, and in patients with depression.
- Naltrexone-bupropion ER should be avoided in patients with seizure disorders and used with caution in patients at risk of seizures.
- Naltrexone-bupropion ER should not be used concomitantly with opiate medications.
- Blood pressure and heart rate should be monitored periodically while taking naltrexone-bupropion ER, especially in the first 12 weeks of treatment.

### Summary of the Evidence

We identified 5 RCTs comparing naltrexone-bupropion ER vs placebo for long-term treatment for obesity (all studies were with a follow-up time of 56 weeks).<sup>79-83</sup> Demographic and baseline characteristics of the population were similar across the studies. Mean age ranged between 43 and 61 years and the population was predominantly female; baseline weight was approximately 100 kg, BMI was

approximately 36 kg/m<sup>2</sup>, and waist circumference was approximately 110–120 cm. Furthermore, 3 studies included patients without T2DM and with controlled hypertension and/or dyslipidemia.<sup>81–83</sup> All of the studies encouraged a hypocaloric diet (500 kcal/d deficit) and increased physical activity by walking 30 minutes most days of the week in both the treatment and control groups, except for Wadden et al,<sup>81</sup> in which a more intensive program of diet, physical activity, and behavior therapy was applied.

### Benefits

All 5 studies<sup>79–83</sup> report on %TBWL, weight loss (in kilograms), and categorical weight loss measures, except for 1 study<sup>80</sup> that reported %TBWL only and another study<sup>79</sup> that excluded the 15% TBWL category (Supplementary Figure 6A–E). On meta-analysis, MD for %TBWL was 3.01% (95% CI, 2.47%–3.54%), favoring naltrexone-bupropion ER; corresponding MD in weight loss was 3.01 kg (95% CI, 2.62–3.39 kg). Patients treated with naltrexone-bupropion ER were significantly more likely to achieve ≥5% TBWL (4 RCTs; RR, 2.18; 95% CI, 1.41–3.37), ≥10% TBWL (4 RCTs; RR, 3.04; 95% CI, 1.80–5.14), and ≥15% TBWL (RR, 3.88; 95% CI, 2.13–7.08).

### Special Consideration for Comorbidities

**Psychiatric disorders.** All of the analyzed studies investigated psychiatric disorders, such as anxiety and depression, as comorbidities and as adverse effects. In both scenarios, there was no significant difference between the groups. At the end of the study, anxiety was reported to occur from 0.6%–5.4% for subjects in the intervention group and 0.2%–4.3% for those in the placebo group. Depression occurred in 0.1%–1.3% of participants in the intervention group and from 0.2%–1.6% for those in the placebo group.

**Type 2 diabetes mellitus and hypertension.** Two studies that included subjects with T2DM reported improvement in HbA1c favoring the treatment group (–0.6% vs –0.1% with placebo).<sup>80,81</sup> Similarly, there were modest but statistically significant increases in systolic and diastolic blood pressure in the treatment groups, most prominently observed in the first 8 weeks, with no significant differences noted by 12 weeks.

### Harms

All 5 studies reported harms on all subjects that were randomized. Discontinuation due to adverse effects, SAE outcomes, and adverse effect frequencies were reported in all studies.<sup>79–83</sup> The total number of participants included in the analysis was 6947 and 5892 for the treatment and placebo groups, respectively. There were significantly more subjects that discontinued treatment due to adverse effects in the naltrexone-bupropion ER group vs placebo (25% vs 10%; RR, 2.39; 95% CI, 1.69–3.37). The most common reasons for discontinuation of the study drug were nausea (4.6%–9.6%), vomiting (0.7%–2%), headache (0.9%–1.8%),

dizziness (0.7%–1.4%), and depression (0.2%–0.6%). There was no difference in the risk of SAEs between intervention and placebo (RR, 0.74; 95% CI, 0.53–1.03). Most reported SAEs were not typically from the investigated drug and were predominantly cardiovascular, GI, or psychiatric (Supplementary Figure 6F and G). SAEs from studies, FDA, and contraindications for naltrexone/bupropion ER are summarized in Supplementary Table 8.

### Certainty in Evidence of Effects

The overall certainty in the evidence of effects for naltrexone-bupropion ER was moderate. See Supplementary Table 9 for the full evidence profile. There was a concern for attrition bias in Apovian et al<sup>82</sup> because there was an imputation in the analysis for week 56. After re-randomization, subjects receiving a higher dose of naltrexone were excluded from the final analysis and those receiving FDA-approved doses were counted twice and "double-weighted." This was not a large number and we thought it would not impact the pooled estimate. Also, most studies used ITT analysis to deal with attrition bias, and the total original number was used as the LOCF. However, Hollander et al<sup>79</sup> reported only a modified ITT analysis and excluded the subjects who discontinued the drug within the first 4 weeks. The majority of these discontinuations were due to adverse effects. We explored this in sensitivity analysis and there was no difference between the results. Thus, we decided not to rate down for risk of bias. Although statistical heterogeneity was high for most pooled estimates, all of the studies showed clear benefit or harm, so we did not rate down for inconsistency. The lower 95% confidence limit for %TBWL (and weight loss in kilograms) crossed the MCID of 3% (or 3 kg); hence, evidence was rated down for imprecision. Similarly, wide CIs and small event numbers for SAEs were noted, leading to serious imprecision. Lastly, the results of Wadden et al<sup>81</sup> were inconsistent with the other studies. This was most likely due to the intense behavior co-intervention that may have led to a ceiling effect. Therefore, we performed a sensitivity analysis to explore, which did not show significantly different results and thus we did not rate down for inconsistency.

### Discussion

The FDA approved the combination of naltrexone, an opioid antagonist, and bupropion, a dopamine and norepinephrine reuptake inhibitor class of antidepressant, in 2014 as an adjunctive therapy to lifestyle interventions for chronic weight management in adults with BMI ≥30 kg/m<sup>2</sup>, or ≥27 kg/m<sup>2</sup> in the presence of at least 1 weight-related complication (eg, hypertension, T2DM, or dyslipidemia).<sup>84</sup> This combination likely has dual mechanisms of action, both by modulating hedonic eating and anorexigenic effects. The former phenomenon is likely driven by increased dopamine levels and antagonism of opioid receptors by bupropion and naltrexone, respectively, in mesolimbic structures.<sup>85–87</sup> Bupropion can cause activation of anorexigenic neurons in the hypothalamus, but β-endorphin has

auto-inhibitory activity on these cells, hence the weak anorectic effects of bupropion monotherapy.<sup>88</sup> Naltrexone, therefore, by antagonizing this inhibition, is the rationale for combining the 2 agents as an AOM.

The guideline panel deemed moderate magnitude of benefit in weight loss, whereas the magnitude of undesirable effects was judged to be small. Therefore, the balance between desirable and undesirable effects would probably favor the use of naltrexone-bupropion ER. Accounting for important uncertainty and variability about how much different individuals will value the desirable vs undesirable outcomes, moderate cost of intervention, unknown incremental net benefit, but with the convenience of oral therapy, overall, the panel made a conditional recommendation favoring the use of naltrexone-bupropion ER in individuals with obesity or overweight with weight-related complications.

### Special Clinical Considerations

Naltrexone-bupropion ER is available in tablets, each containing 8 mg of naltrexone and 90 mg of bupropion in a sustained-release formulation. The recommended titration schedule begins with 1 tablet daily in the morning, followed by weekly escalation to 1 tablet twice per day, then 2 tablets in the morning and 1 in the afternoon, until the maintenance dose of 2 tablets twice per day is reached. The second dose should not be taken late in the day to minimize the risk of insomnia. In patients with moderate to severe renal impairment, the total daily dose should be reduced by one-half (ie, 1 tablet twice per day) and avoided in end-stage renal disease. In patients with moderate to severe hepatic impairment, the total daily dose should not exceed 1 tablet daily. After 12 weeks of therapy on the maintenance dose, if the patient has not lost 5% of their total body weight, the medication should be discontinued, as they are likely a poor responder.

Because of the opioid antagonism from the naltrexone component, it should not be used in patients that require short-term or long-term opiate therapy because naltrexone-bupropion ER could reduce the efficacy of the analgesic or precipitate a withdrawal reaction, respectively. Notably, it should be discontinued before procedures that require the use of opiates. For example, gastroenterologists using fentanyl during endoscopies should consider holding naltrexone-bupropion before the procedure. Bupropion may lower the seizure threshold and naltrexone-bupropion ER should be avoided in patients with epilepsy and should be used with caution in patients with a history of seizures or with any clinical factors that may increase the risk of seizures.<sup>89</sup>

Bupropion is FDA-approved as an antidepressant. At 300 mg daily, close to the daily dose contained in bupropion-naltrexone ER, bupropion has been shown to be effective for the long-term treatment of recurrent major depression.<sup>90</sup> It is difficult to assess the effect of naltrexone-bupropion ER on depression based on large pivotal studies because they largely excluded subjects with significant

psychiatric disorders or the use of antidepressants.<sup>79,81,82</sup> Although not formally tested for its effect on mood as a primary outcome in these trials, a small open-label study in women with major depressive disorder showed significant improvement in depressive symptoms that were sustained at 24 weeks of therapy with naltrexone-bupropion ER at FDA-approved doses.<sup>91</sup> Based on these data, as well as clinical experience and plausibility, it is reasonable to prioritize naltrexone-bupropion ER for appropriate patients with depressed mood.

Bupropion is also approved by the FDA for smoking cessation.<sup>92</sup> Similar to the preceding remarks regarding pivotal clinical trials and depression, these studies were not designed to assess smoking cessation. Limited data on smoking cessation with the combination of sustained-release bupropion and naltrexone at the same doses used for obesity showed a reduction of nicotine use and mitigation of associated weight gain.<sup>93</sup> Another study investigating the addition of naltrexone to bupropion for smoking cessation demonstrated superior efficacy with the combination therapy at 7 weeks of treatment, followed by equivalent relapse at 6 months of follow-up after the intervention was terminated,<sup>94</sup> supporting the concept of chronic treatment, similar to weight management. Taken together, these studies provide support for clinical consideration in using naltrexone-bupropion ER for patients in need of weight loss and assistance with smoking cessation.

Vital signs should be monitored in patients treated with naltrexone-bupropion ER and should be avoided in patients with uncontrolled hypertension. It should also be avoided in patients treated with, or within 14 days of, monoamine oxidase inhibitors. Currently, there are no long-term cardiovascular outcome data for naltrexone-bupropion ER. An FDA-mandated cardiovascular outcome trial did not show a significant increase in events based on prespecified non-inferiority rates at planned interim analyses, but this trial was terminated early due to the publication of confidential results at the 25% interim analysis.<sup>80</sup> Although a subsequent cardiovascular outcome trial was initiated, it was terminated prematurely due to poor recruitment and inadequate statistical power.<sup>95</sup> The long-term cardiovascular safety of naltrexone-bupropion ER remains unclear. Because bupropion is also an antidepressant, patients should be observed for neuropsychiatric adverse effects, including suicidal thoughts and behaviors, especially in individuals younger than 24 years. Patients and their families should be counseled for the emergence of these reactions.

**Recommendation 6. In adults with obesity or overweight with weight-related complications, the AGA suggests against the use of orlistat. (Conditional recommendation, moderate certainty)**  
**Comment: Patients who place a high value on the potential small weight loss benefit and low value on GI adverse effects may reasonably choose treatment with orlistat.**

## Implementation Considerations

- Patients using orlistat should take a multivitamin daily. Vitamins should contain fat-soluble vitamins (A, D, E, K) and should be taken 2 hours apart from orlistat.

## Summary of the Evidence

Our search identified 28 RCTs comprising 6455 subjects treated with orlistat and 5893 treated with placebo for the long-term treatment of obesity. Studies varied in duration between 48 weeks and 4 years. Most studies encouraged a hypocaloric diet (500–800 kcal/d deficit) with particular emphasis on low-fat diet (30% energy from fats) and increased physical activity. The examined dose of orlistat was 120 mg 3 times per day with meals. The study population was mostly female (55%–85%), ages ranged between 42 and 58 years. Mean weight in the trials ranged between 95 and 112 kg, mean BMI was between 33 and 36 kg/m<sup>2</sup>, and mean waist circumference was between 105 and 115 cm. An over-the-counter formulation of orlistat available in a 60-mg dose was not examined in this systematic review and guideline, given the paucity of long-term study data using this strength of medication.

## Benefits

Fifteen RCTs comprising 16 cohorts provided data for %TBWL.<sup>96–110</sup> Meta-analysis showed that subjects on orlistat lost 2.78% (95% CI, 2.36%–3.20%) TBWL compared with placebo (Supplementary Figure 7A–D). A total of 23 RCTs with 24 cohorts reported a mean weight loss of 2.81 kg (95% CI, 2.17–3.45) with orlistat vs placebo. On meta-analysis, subjects treated with orlistat were significantly more likely to achieve ≥5% TBWL (18 RCTs; RR, 1.71; 95% CI, 1.55–1.88)<sup>49,96–102,104–107,109–114</sup> and ≥10% TBWL (15 RCTs; RR, 1.94; 95% CI, 1.70–2.22)<sup>49,96–99,101,102,104–107,109,110,113,114</sup>; but no RCT provided data on ≥15% TBWL.

## Harms

Of the RCTs examined, only 11 provided data on SAEs.<sup>49,97,103,105,106,110,111,113–116</sup> Pooled analysis found that there were no significant differences in the incidence of SAEs between orlistat and control groups (RR, 1.04; 95% CI, 0.81–1.33). Meta-analysis of 20 RCTs demonstrated that subjects on orlistat had a higher incidence of treatment discontinuation due to adverse effects compared with controls (RR, 1.51; 95% CI, 1.22–1.89).<sup>49,96–107,109–111,113,115–117</sup> Most treatment discontinuations of orlistat were due to transient GI adverse effects, such as flatulence, oily spotting/stools, fecal urgency, and fecal incontinence. Meta-analysis of 12 RCTs showed that the risk of treatment discontinuations due to GI adverse effects were significantly higher with orlistat compared with controls (RR, 2.86; 95% CI, 1.91–4.30)<sup>97–102,106,109–112,116</sup> (Supplementary Figure 7E and F).

Per the FDA, there have been 12 cases of liver failure occurring in patients outside the United States on orlistat 120 mg and 1 case of liver failure in a patient on orlistat 60

mg in the United States between April 1999 and August 2009, of an estimated 40 million patients who have used these medications. Although a causal association has not been established, the FDA has added a label warning about the potential for serious liver injury due to orlistat.<sup>118</sup> SAEs from studies, FDA, and contraindications for orlistat are summarized in Supplementary Table 10.

## Certainty in Evidence of Effects

The overall certainty of evidence in the effects of orlistat was moderate. See Supplementary Table 11 for the full evidence profile. We rated down the certainty of evidence for imprecision for the 2 continuous outcomes, namely weight loss (in kilograms) and %TBWL, as the 95% CI for the pooled effect size for both of these outcomes included the MID. Although there was significant attrition (25%–56%) seen in most studies, it was usually not disproportionate among groups and studies used ITT analyses with LOCF, hence the evidence synthesis team opted not to rate down the certainty of evidence for risk of bias. The quality of evidence for ≥5% TBWL and ≥10% TBWL outcomes were both rated as high, despite substantial heterogeneity ( $I^2 = 73%$  and  $I^2 = 46%$ , respectively), as the inconsistency was driven largely by the magnitude and not the direction of the effect estimates. In terms of SAEs, we rated down for imprecision because the 95% CI extended from no harms to clinically significant SAEs based on *a priori* criteria.

## Discussion

Orlistat, a locally acting, irreversible inhibitor of GI lipase, was approved in 1999 by the FDA for the treatment of obesity. The drug is indicated for the treatment of obesity in conjunction with a reduced-calorie diet.<sup>119</sup> Orlistat exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine residue site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to hydrolyze approximately 30% of ingested dietary fat from triglycerides into absorbable free fatty acids and monoglycerides. The undigested triglycerides are not absorbed, resulting in a caloric deficit and subsequent weight loss.

In our evidence-to-decision framework, weight loss with orlistat was thought to be of a small magnitude (2.78% TBWL). In contrast, the magnitude of the harms was judged to be moderate because the treatment discontinuation rate due to adverse events was significantly higher in the orlistat group and were also considered to be very bothersome. Thus, the balance between desirable and undesirable effects would probably not favor the use of orlistat. The panel recognized that different individuals may value the weight loss and adverse effects differently. Furthermore, compared with some of the newer agents, the cost of orlistat is lower, making it attractive for some patients and, because orlistat is not a centrally acting agent, some individuals may favor the low potential for neuropsychiatric adverse effects. Altogether, the guideline panel made a conditional recommendation against the use of orlistat for individuals with obesity or overweight with weight-related complications.



However, the panel recognized that a small but meaningful minority of patients who place a higher value on the modest amount of weight loss and lower value on the possibility of GI adverse effects may reasonably choose treatment with orlistat.

### Special Clinical Considerations

Orlistat is available in 60-mg (over the counter) or 120-mg (prescription) capsules. Taking 1 capsule during or within 1 hour after meals is recommended as an adjunct to a calorie-reduced diet and physical activity. The corresponding dose can be omitted if a meal is very low in fat. Because the mechanism of action involves fat malabsorption, patients are at risk of deficiencies of fat-soluble vitamins, and it is recommended to supplement with a daily multivitamin to be taken at least 2 hours apart from orlistat. Certain medications, such as cyclosporine, levothyroxine, and warfarin, may require longer intervals between doses of orlistat and may require closer monitoring. Patients with chronic malabsorption from conditions such as chronic diarrhea, celiac disease, inflammatory bowel disease, or a history of bariatric surgery, may not be ideal candidates for long-term orlistat therapy. Weight loss with orlistat may be associated with a small risk of cholelithiasis.

**Recommendation 7. In adults with obesity or overweight with weight-related complications, the AGA suggests using phentermine with lifestyle interventions, compared with lifestyle interventions alone. (Conditional recommendation, low certainty)**

### Implementation Considerations

- Phentermine monotherapy is approved by the FDA for short-term use (12 weeks). However, given the chronic nature of weight management, many practitioners use phentermine longer than 12 weeks in an off-label fashion.
- Phentermine should be avoided in patients with a history of cardiovascular disease.
- Blood pressure and heart rate should be monitored periodically when taking phentermine.

### Summary of the Evidence

We identified 8 short-term RCTs comparing phentermine vs placebo for the treatment of obesity<sup>120-127</sup> and there were no studies with long-term treatment for >52 weeks. All identified studies with short-term treatment used phentermine doses between 15 and 37.5 mg daily vs placebo for 12 weeks, except 2 studies<sup>120,122</sup> that used phentermine 15 mg daily for 26-28 weeks. Almost all studies included subjects with BMI  $\geq 30$  kg/m<sup>2</sup>, except for the studies from the Asia-Pacific region, which used BMI  $\geq 25$  kg/m<sup>2</sup>. All studies either included subjects without major

metabolic comorbidities or with well-controlled comorbidities: hypertension by taking antihypertensive treatment except MAO inhibitors (systolic blood pressure <140 mm Hg and diastolic pressure <90 mm Hg); dyslipidemia, mostly included subjects that had controlled lipids with lifestyle modifications; and diabetes if HbA1c <7.5%. Demographics and baseline characteristics of the population were similar across the studies. Mean age ranged between 34 and 46 years, population was predominantly female, baseline weight was 80-110 kg, and BMI was 29-38 kg/m<sup>2</sup>. All of the studies encouraged lifestyle interventions that were either a hypocaloric diet (500-kcal/d deficit) and increased physical activity by walking 30 minutes most days of the week, in addition to the study medication, or hypocaloric diet with total 1200-1800 kcal/d along with increased physical activity, except 1 study,<sup>123</sup> which included a commercial weight loss program as the lifestyle intervention.

### Benefits

Seven<sup>120-123,125-127</sup> of 8 studies reported weight loss (in kilograms) as a continuous outcome, and 3 studies<sup>120,122,123</sup> reported on %TBWL. Furthermore, 5 studies<sup>120-122,125,127</sup> reported on the 5% and 10% TBWL thresholds, but no studies reported on 15% TBWL (Supplementary Figure 8A-D). On meta-analysis, phentermine-treated subjects (n = 205) lost 3.63% (95% CI, 2.97-4.29) TBWL vs placebo (n = 202) in favor of phentermine, and 4.74 kg (95% CI, 3.75-5.73). Subjects treated with phentermine were significantly more likely to achieve  $\geq 5\%$  TBWL (RR, 4.12; 95% CI, 3.04-5.59) and  $\geq 10\%$  TBWL (RR, 5.10; 95% CI, 3.02-8.61).

### Harms

Seven<sup>120-126</sup> of 8 studies reported on discontinuation due to adverse effect outcomes and five<sup>120-123,125</sup> of 8 reported on SAE outcomes (Supplementary Figure 8E and F). The total number of subjects included in the analysis was 1274 in the phentermine group and 730 in the placebo group. More subjects discontinued the treatment because of adverse effects in the treatment group compared with placebo (20% vs 10%; RR, 1.73; 95% CI, 1.36-2.19). The most common reasons for discontinuation of the study drug were insomnia, irritability, anxiety, headache, nausea, and increase in blood pressure and heart rate. None of the studies described clear definitions for SAEs. Patients in the phentermine group experienced higher rate of SAEs, although this was not statistically significant (4% vs 1%; RR, 2.44; 95% CI, 0.6-10.03). Given the small sample size and adverse effects event rate, we evaluated FAERS reporting as indirect evidence because this database only reports harms without any denominator, for which we used a large cohort study using claims data from commercial health insurance in the United States.<sup>50</sup> In the FAERS database, the rate of SAEs was significantly lower, <1 in 1000. SAEs from studies, FDA, and contraindications for phentermine are summarized in Supplementary Table 12.

### Certainty in Evidence of Effects

The overall certainty in the evidence of effects of phentermine was low. See [Supplementary Table 13](#) for the full evidence profile. Although there was a concern for attrition bias, attrition rates were very similar between the 2 groups. Thus, we did not rate down for risk of bias. In addition, some smaller and older studies did not use blinding, but because these studies did not contribute much to the overall pooled estimate, we were not concerned about serious risk of bias across the pool of evidence. In addition, for the continuous outcome (%TBWL), the lower confidence limit crossed the predetermined threshold of 3 kg or approximately 3% MID, for benefit; thus, we rated down for imprecision. Similarly, wide CIs and small event numbers for SAEs were noted, leading to serious imprecision. Moreover, there was a serious inconsistency among the studies in the weight loss (in kilograms) outcome because some studies showed clear benefits with lower CIs above the MID, and other studies failed to show clear clinical benefit as the point estimate and the lower CI were below the MID. Serious inconsistency was considered in the  $\geq 10\%$  TBWL outcome and was possibly due to different intervention duration and follow-up time. Therefore, we performed a sensitivity analysis to explore this and confirmed that the inconsistency is likely due to the difference in intervention duration. Lastly, there was serious indirectness detected in all of the outcomes because of the intervention duration. Our PICO question is weight loss treatment for chronic management, which we determined *a priori* to be at least 48 weeks. However, the available data are generally in the 3- to 6-month range. The overall certainty of evidence supporting the use of phentermine is low.

### Discussion

Phentermine has remained the most commonly prescribed AOM in the United States.<sup>128,129</sup> Nevertheless, many health care professionals fear using phentermine due to its history associated with fenfluramine. Popular in the 1990s, phentermine with fenfluramine, commonly known as “fen-phen,” was prescribed to millions of patients in the United States.<sup>130</sup> In 1997, the first report of valvular heart disease and pulmonary hypertension associated with this combination drug was published.<sup>131</sup> Phentermine’s therapeutic effect is mediated through increased levels of norepinephrine in the CNS, and fenfluramine is thought to increase central serotonin levels, hence exerting their anorexigenic effects synergistically in relevant brain structures. It was initially thought that valvulopathies associated with fenfluramine were also a result of increased serotonin levels in cardiac tissues, but studies later demonstrated that fenfluramine metabolites activated serotonin receptors directly with more affinity than serotonin itself.<sup>132</sup> The serotonin receptor, 5-hydroxytryptamine type 2B, is prominent in human cardiovascular tissue and may be responsible for the cardiotoxicity seen with fenfluramine-phentermine.<sup>133</sup> A prospective analysis of patients with primary pulmonary

hypertension in North America implicated fenfluramine, but not phentermine, as a risk factor.<sup>134</sup>

Using the evidence-to-decision framework, the panel examined the evidence for the magnitude of phentermine’s desirable and undesirable effects in individuals with BMI  $\geq 30$  kg/m<sup>2</sup> or  $\geq 27$  kg/m<sup>2</sup> and weight-related complications. Obesity is a chronic condition that warrants long-term management and phentermine’s trials were only 3–6 months in duration, hence the low certainty of evidence for the recommendation, given that data on long-term use for phentermine monotherapy are lacking (note that phentermine at 7.5–15 mg is approved for long-term use when combined with topiramate in the FDA-approved ER combination). The desirable effect was thought to be of moderate magnitude. The cumulative treatment discontinuation rate due to adverse events was much higher in the phentermine group compared with the control group, mainly because of significant CNS effects (eg, insomnia, irritability); however, SAEs were rare. Altogether the panel judged that the undesirable effects from phentermine were frequent but not serious and, therefore, the balance between desirable and undesirable effects would probably favor the use of phentermine. The panel also examined uncertainty and variability regarding how much different individuals will value desirable and undesirable effects. The long-term safety of phentermine monotherapy is uncertain, although, as noted previously, it has been studied up to 2 years in phase 3 clinical trials when combined with topiramate in ER formulation. There are some observational studies that may be informative regarding long-term safety. One retrospective observational study in approximately 270 patients treated with phentermine continuously for an average of 7 years did not show worsening of hemodynamic measures, such as blood pressure or heart rate, compared with a group that lost weight without AOMs.<sup>76</sup> Another study using a retrospective review of electronic health record data in nearly 14,000 patients showed superior weight loss and no increased cardiovascular events with long-term use compared with short-term treatment.<sup>75</sup> Due to the lack of high-quality data for the efficacy and safety of long-term monotherapy, the panel made a conditional recommendation for the use of phentermine for individuals with obesity or overweight with weight-related complications. It should be noted, however, that because of the current understanding of obesity as a chronic metabolic disease and the biological realities of weight regulation, many experienced clinicians use phentermine for longer than 3 months in off-label fashion.<sup>135</sup> Prescribers are advised to confirm with their respective state licensure authorities regarding local laws and regulations. It is advised that, if a health care professional deems the benefits of long-term use are warranted, they document the specific benefits, tolerance, and adverse effects, and that the patient is advised regarding off-label use and limited data supporting this approach. Phentermine is classified as a schedule IV-controlled substance based on concerns for abuse and dependence.

### Special Clinical Considerations

Phentermine is available in capsules at doses of 15 mg, 30 mg, and 37.5 mg, and in tablet formulation at 8 mg and 37.5 mg. The recommended dosage is to be taken once daily up to 37.5 mg, preferably earlier in the day to minimize risk of insomnia. In 2016, phentermine 8 mg was approved in the United States for dosing up to 3 times per day, approximately 30 minutes before meals. These tablets are scored so that dosing can be achieved as low as 4 mg. Some have used these low doses on an “as needed basis” before situations with a high risk of hedonic food consumption (expert opinion).

One of the most important concerns among prescribers surrounds the cardiovascular safety of phentermine. Perceptions regarding cardiotoxicity with sympathomimetic AOMs can be categorized into 2 different pathophysiologic domains. The first relates to serotonergic stimulation of myocardial tissues (ie, pulmonary hypertension and valvulopathies), which was addressed above. The second domain reflects adrenergic hemodynamic effects (eg, heart rate and blood pressure) and potential adverse cardiovascular outcomes. In pivotal clinical trials for phentermine-topiramate ER, blood pressure generally declined, and there was a very small increase in heart rate, usually at higher doses.<sup>54,55,58</sup> Observational data from phentermine monotherapy do not show significant increases in blood pressure or heart rate in treated individuals.<sup>74-76</sup> Readers are directed to Recommendation 4 (phentermine-topiramate ER) for remarks surrounding the management of phentermine before procedures requiring general anesthesia. Currently, there are no large cardiovascular outcome trial data for long-term use of phentermine-topiramate ER or phentermine monotherapy. Caution is therefore advised, and it should be avoided in patients with a history of cardiovascular disease or uncontrolled hypertension. Phase 3 clinical trials for phentermine-topiramate ER enrolled subjects up to the age of 70 years, but there are no high-quality data to guide the use of phentermine-based therapies in the geriatric population. It should be avoided in patients treated with, or within 14 days of, monoamine oxidase inhibitors. Due to concerns for arrhythmias and seizures, phentermine should not be used in patients with untreated hyperthyroidism. Commonly reported adverse effects included constipation, dry mouth, palpitations, insomnia, and irritability.<sup>135</sup>

**Recommendation 8. In adults with obesity or overweight and weight-related complications, the AGA suggests using diethylpropion with lifestyle interventions, compared with lifestyle interventions alone. (Conditional recommendation, low certainty)**

### Implementation Considerations

- Diethylpropion monotherapy is approved by the FDA for short-term use (12 weeks). However, given the chronic nature of weight management, many practitioners use

diethylpropion longer than 12 weeks in an off-label fashion.

- Diethylpropion should be avoided in patients with a history of cardiovascular disease.
- Blood pressure and heart rate should be monitored periodically while taking diethylpropion.

### Summary of the Evidence

We identified 6 RCTs<sup>136-141</sup> comparing diethylpropion vs placebo for the treatment of obesity. There was only 1 study<sup>138</sup> with long-term treatment and follow-up more than 52 weeks, 2 studies<sup>136,139</sup> used diethylpropion for 24 weeks, and 3 RCTs<sup>137,140,141</sup> used diethylpropion for 12 weeks. Older studies did not report on the BMI as an inclusion criterion, but 3 newer studies<sup>136,138,139</sup> included subjects with BMI more  $\geq 30$  kg/m<sup>2</sup>. None of the studies included subjects with T2DM or dyslipidemia, and some studies included patients with hypertension (blood pressure  $< 160/100$  mm Hg).

Demographic and baseline characteristics of the population were similar across the studies. Mean age ranged between 34 and 38 years, the population was predominantly female, with baseline weight approximately 80–95 kg, and BMI approximately 34 kg/m<sup>2</sup>. Lastly, all the studies encouraged lifestyle interventions that included increased physical activity and hypocaloric diets with either a goal deficit of 500–600 kcal/d or a target range of 1000–1200 kcal/d.

### Benefits

All 6 studies<sup>136-141</sup> reported on weight loss (in kilograms) as a continuous outcome, and four<sup>136,138,141</sup> of them reported on %TBWL (Supplementary Figure 9A–D). Furthermore, 3 studies<sup>136,138,139</sup> reported categorical weight loss of  $\geq 5\%$  and  $\geq 10\%$  TBWL, but not  $\geq 15\%$  TBWL. In pooled quantitative meta-analysis for %TBWL outcomes, 119 subjects received diethylpropion and 108 received placebo. MD for %TBWL was 5.36% (95% CI, 3.50%–7.23%) in favor of diethylpropion. Similarly, diethylpropion-treated subjects experienced greater absolute weight loss (MD, 4.74 kg; 95% CI, 3.08–6.40 kg). Patients treated with diethylpropion were significantly more likely to achieve  $\geq 5\%$  TBWL (RR, 3.51; 95% CI, 1.50–8.18) and  $\geq 10\%$  TBWL (RR, 14.48; 95% CI, 5.13–40.87) compared with placebo.

### Harms

Five<sup>136,138,141</sup> of 6 studies reported on harms, but only on discontinuation due to adverse events (Supplementary Figure 9E). There was no significant difference in the risk of treatment discontinuation in the treatment group (5% vs 3%; RR, 1.37; 95% CI, 0.51–3.66). The most common reasons for discontinuation were insomnia, irritability, or anxiety. There were no SAEs reported in any of the studies. When exploring the FAERS database, the rate of SAEs was significantly lower, similar to that of phentermine, occurring  $< 1$  in 1000.<sup>50,142</sup>

### Certainty in Evidence of Effects

The overall certainty in evidence of effects for diethylpropion was low. See [Supplementary Table 14](#) for the full evidence profile. There was some concern for serious risk of bias because most of the older studies did not perform ITT analyses using LOCF for continuous outcomes. Benefits data were derived from the subjects who completed the study, and this probably introduced bias and overestimated the effect of the intervention. In addition, it is unclear how the randomization and allocation were conducted in most of the studies. Thus, we decided to rate down once for risk of bias for continuous outcomes. Furthermore, as discussed before, MCID was determined to be 3 kg (or approximately 3%). For the categorical outcome of absolute weight loss (in kilograms), there was serious inconsistency because some studies showed clear benefits with lower CIs being above the MCID, and other studies failed to show clear clinical benefit as the point estimate and the lower CI were below the MCID. Almost all of the outcomes were imprecise due to the small sample size and very small number of events. Lastly, we found serious indirectness in all of the outcomes because of the intervention duration. Our PICO question is weight loss outcomes with long-term therapy, which was determined *a priori* to have a minimum treatment duration of 48 weeks. However, the available data are mostly 3–6 months in duration. In summary, the certainty of the evidence for benefits is low, as determined by the highest certainty among benefits. Likewise, certainty for harms was also low. Hence the overall certainty of evidence supporting the use of diethylpropion therapy was low.

### Discussion

The FDA approved diethylpropion in 1959 for the treatment of obesity adjunctively with caloric restriction and increased physical activity.<sup>143</sup> It is approved for short-term use in patients that have not responded adequately to lifestyle interventions alone. Similar to other sympathomimetic amines, it has potential for CNS stimulation, but it is chemically modified to limit these symptoms as well as other adrenergic effects.<sup>132</sup> Like other amphetamine derivative AOMs, diethylpropion was approved by the FDA when obesity was considered a curable condition, a concept that has since been proven wrong. Given that obesity is a chronic condition that warrants long-term management, and trials were conducted for only 3–12 months, the evidence for the recommendation was deemed low due to lack of long-term data. The desirable effect was thought to be of moderate magnitude. The panel judged that the undesirable effects from diethylpropion were infrequent, not serious and, therefore, the balance between desirable and undesirable effects would probably favor the use of diethylpropion. Overall, the panel made a conditional recommendation for the use of diethylpropion in individuals with obesity or overweight with weight-related complications.

Like phentermine and other amphetamine derivatives, there was concern in the literature regarding the risk of pulmonary hypertension with diethylpropion exposure. Although a case-control study suggested a higher incidence

of pulmonary hypertension associated with diethylpropion use, most of the affected patients also used other anorectics, including fenfluramine.<sup>144</sup> Similar to phentermine, there are concerns regarding stimulant properties, cardiotoxicity, and potential for abuse and dependence. However, a chemical modification of the active molecule results in less potential for CNS stimulation and blood pressure elevation.<sup>132</sup>

Diethylpropion is classified as a schedule IV-controlled substance based on concerns for abuse and dependence. Many prescribers who use AOMs off-label use diethylpropion longer than 12 weeks as well.<sup>145</sup>

### Special Clinical Considerations

Diethylpropion is available in doses of 25-mg immediate-release tablets or 75-mg ER tablets, to use 3 times per day before meals or once daily in the morning, respectively.

Due to concerns for arrhythmias and seizures, diethylpropion should not be used in patients with untreated hyperthyroidism. Commonly reported adverse effects included constipation, dry mouth, insomnia, headache, and irritability.<sup>136</sup> Because it is also a sympathomimetic, prescribers are directed to Recommendation 4 (phentermine-topiramate ER) for remarks on the management of diethylpropion before procedures requiring general anesthesia.

**Recommendation 9. In adults with BMI between 25 and 40 kg/m<sup>2</sup>, the AGA recommends using Gelesis100 oral superabsorbent hydrogel only in the context of a clinical trial. (Knowledge gap)**

### Summary of the Evidence

One multicenter, double-blind RCT with 24 weeks of follow-up was found to inform this PICO and recommendation.<sup>146</sup> Similar in both the treatment and placebo groups, mean BMI, weight, waist circumference, and age were 33.5 kg/m<sup>2</sup>, 97.6 kg, 108.3 cm, and 48 years, respectively. Lifestyle intervention for both groups included a recommended energy deficit of 300 kcal/d and moderate intensity physical activity daily.

### Benefits

A total of 223 participants in the intervention group vs 213 in the control group informed this recommendation. MD for %TBWL was 2.02% (95% CI, 0.96%–3.08%) favoring Gelesis100. A greater proportion of subjects were able to achieve  $\geq 5\%$  TBWL (58.3% vs 42.3%; RR, 1.38; 95% CI, 1.14–1.67) and  $\geq 10\%$  TBWL (27.4% vs 15%; RR, 1.82; 95% CI, 1.24–2.67) with intervention.

### Harms

Treatment discontinuation rate was similar in the intervention vs placebo arms (3.6% vs 3.3%; RR, 1.09; 95% CI, 0.40–2.96). Only 1 SAE was reported in the control group.

### Certainty in Evidence of Effects

The overall certainty in the evidence of effects for Gelesis100 oral superabsorbent hydrogel was low. See [Supplementary Table 15](#) for the full evidence profile. We found very serious imprecision for the harm outcomes due mainly to low event rate and CI crossing unity. Dichotomous weight loss outcomes were found to have serious imprecision due to a low event rate. Moreover, we noted very serious imprecision for the outcome of %TBWL, as the pooled estimate did not meet the predetermined MCID threshold of 3% and wide CIs.

### Discussion

In contrast to the pharmacological agents examined in this review, FDA identifies Gelesis100 oral superabsorbent hydrogel as a device similar to ingestible balloons that are delivered in the form of a “pill.” Gelesis100 is a capsule containing hyperabsorbent hydrogel spheres (made of modified cellulose and citric acid) that, once ingested, create a transient space occupying 3-dimensional matrix (composed of cellulose, citric acid, water, and food material) in the stomach, compared with FDA-approved intragastric balloons, which remain in the stomach until removal. The 3-dimensional matrix passes through the luminal GI tract until reaching the colon, where it is degraded. The water component of the matrix is reabsorbed, and other components are excreted in the stool. The mechanism of action is enhanced satiety and reduced caloric intake resulting from increased gastric volume generated from the 3-dimensional matrix. Gelesis100 oral superabsorbent hydrogel is approved for weight management in adults with overweight and obesity with a BMI of 25–40 kg/m<sup>2</sup>, in conjunction with a calorie-reduced diet and physical activity. The recommended dosing is 3 capsules (2.25 g/dose) with water before both lunch and dinner.<sup>147</sup>

The panel was not able to make a recommendation for the use of Gelesis100 oral superabsorbent hydrogel in adults with BMI between 25 and 40 kg/m<sup>2</sup> with only a single RCT informing low certainty evidence. The study showed that subjects had a small amount of weight loss over 24 weeks.<sup>146</sup> One interesting finding was that subjects with evidence of insulin resistance (prediabetes or T2DM) seemed to have a more robust response to treatment compared with those with normoglycemia at baseline. Because this observation is contrary to most studies, with other interventions showing inferior weight loss in individuals with T2DM, it merits further confirmation and investigation. Due to paucity of data, the panel recommended using this adjunct therapy for treating obesity only in the context of a randomized clinical trial.

### Limitations and Evidence Gaps

Effective pharmacological interventions for obesity have historically been challenging to achieve. The reasons are complex and include both behavioral and biological factors, which are difficult to separate from each other. Physiologically, metabolic adaptations in response to energy deficits

and weight reduction defend against sustained fat mass loss. In the CNS, there are redundant pathways that seem to favor a state of anabolic and orexigenic activity. Hence, efforts to develop pharmaceutical agents that can overcome these strong neurobiological defenses, while limiting adverse effects, has proven to be somewhat elusive. Our evidence synthesis found that, even with the best available therapies, TBWL (in addition to lifestyle intervention) is, on average, 15%. Although these results are fairly impressive, bridging the gap between evidence-based expectations and patients' desired weight loss outcomes remains a major challenge. Foster et al<sup>148</sup> reported that patients may consider success only if the magnitude of their weight loss approaches that of bariatric surgery. Prescribers will therefore not only need to have an understanding of these realities, but also be prepared to properly counsel patients to maintain adherence to various treatments, including pharmacotherapy. Health care professionals should help the patient focus on health-related improvements and quality of life benefits, rather than the absolute number on the scale ([Table 5](#)).

Currently, there is a scarcity of data addressing whether the use of AOMs has any effect on health care disparities and/or equity. However, it is expected that in the current sociodemographic landscape, AOM use may widen this gap. First, obesity rates are higher in non-White patients (40.7% in non-Hispanic Blacks and 35.2% in Hispanic adults),<sup>149</sup> which usually correlates with lower socioeconomic status. Several authors have addressed that in the treatment of patients with obesity, researchers need to identify and overcome several barriers to implementing therapy for obesity in these minorities.<sup>150,151</sup> For example, data from a large Midwestern, academic health center-based pediatric weight management clinic showed that in 1725 children (mean age, 11.5 years), the incidence rate ratio for prescriptions was lower among Hispanic and Latino compared with non-Hispanic White youth at 1 year (incident rate ratio,

**Table 5.** Key Evidence Gaps in the Pharmacological Management of Obesity

Key evidence gaps
Impact of pharmacological interventions for obesity on long-term patient important outcomes, besides weight loss, such as cardiovascular events, cancer risk, mortality, and other weight-related complications
Comparative effectiveness and tolerability of different pharmacological interventions, as well as in comparison with nonpharmacological interventions (such as endoscopic bariatric and metabolic interventions and bariatric surgery)
Personalization of pharmacological interventions for the management of obesity based on patient and disease characteristics
Role of combining pharmacological interventions with other nonpharmacological interventions, either as adjunctive therapy, or sequentially
Approaches to alleviating health care disparities in the pharmacological management of obesity

0.70; 95% CI, 0.49–1.00;  $P = .047$ ), and the use of interpreters was independently associated with increased frequency of AOM prescriptions.<sup>152</sup> Because of cost, variable insurance coverage, inconsistent acceptance of some health care professionals to treat obesity as a biologic disease, and racial and minority disparities, many individuals who may benefit from treatment may never have the opportunity to receive adequate therapy. Burdensome insurance authorization requirements and visits to monitor for adverse effects may further dissuade some from using these agents. Finally, the participants in the randomized clinical trials reported in this AGA guideline are predominantly non-Hispanic White patients. Future randomized clinical trials addressing the use of AOMs should include a higher proportion of other ethnic groups to assess whether the response to AOM therapy is universal and to further support reimbursement from insurance companies to curb the obesity pandemic.<sup>153</sup>

As obesity is both a disease and a risk factor for other chronic illnesses, it is paramount to continue to assess the effect of weight loss using pharmacological interventions on important outcomes, such as cardiovascular events, nonalcoholic fatty liver disease, mortality, and cancer incidence and treatment response, among others. Although weight and BMI are the measures patients and clinicians use to assess efficacy in the clinical setting, important benefits for health risks, longevity, quality of life, and cost-effectiveness are critical measures with current and emerging treatments. The Look AHEAD trial revealed that intense lifestyle intervention may not be enough to reduce the risk of adverse cardiovascular outcomes.<sup>154</sup> Results of the SELECT Trial will further inform prescribers, patients, and payers regarding cardiovascular benefits of greater weight loss from semaglutide 2.4 mg.<sup>155</sup> Given the challenges of conducting large long-term RCTs to assess important health outcomes, these knowledge gaps will need to be filled by a combination of RCTs, well-designed observational studies, and real-world data.

Likewise, because of a lack of comparative data, prescribers are left to choose among available pharmacological therapies with limited guidance on hierarchical decision making. Head-to-head trials with AOMs are limited to the comparison of liraglutide vs semaglutide.<sup>33</sup> A systematic review suggested superiority of phentermine-topiramate and liraglutide 3.0 mg over other AOMs, but this was before the emergence of more effective therapies now and in the pipelines.<sup>156</sup> Moreover, given the variability in response to any weight loss intervention, establishing response to a given AOM for an individual patient has largely required a trial-and-error approach. Other clinical factors, such as comorbidities, contraindications, historical response, cost, patient preference, and potential drug–drug interactions, are currently the most important contributors to decision making. Phenotype matching to specific agents or class of drugs has shown some promising results.<sup>157</sup> More research is needed to better understand whether and how pharmacogenomic predictors may further enhance weight loss effects beyond current strategies.<sup>158</sup>

Other approaches to optimize weight loss and health outcomes involves combining therapeutic agents and

modalities, similar to other conditions, such as cancer, diabetes, or cardiovascular disease. Like other chronic illnesses commonly encountered in the clinic, such as T2DM or hypertension, it would seem logical that a combination of different AOMs may be effective for optimizing outcomes. Although this practice is not uncommon among obesity medicine specialists, the literature is extremely scarce with respect to guidance for the general practitioner beyond the formulated FDA-approved options of phentermine-topiramate ER and naltrexone-bupropion ER.<sup>159,160</sup>

Another common practice is the use of AOMs in patients who have had suboptimal results after bariatric and metabolic surgery. Studies have demonstrated effectiveness for orlistat, phentermine-topiramate ER, topiramate (off-label use), phentermine, naltrexone-bupropion ER, and liraglutide.<sup>161</sup> To date, no large, prospective, long-term RCT has been performed with any AOM specifically in a population with a history of bariatric surgery. There are minimal data on the weight loss effect of combining AOMs with intragastric balloons and other endoscopic bariatric and metabolic therapies. Using liraglutide adjunctively with intragastric balloons may enhance weight loss, but the analyses performed had study designs with a high risk for bias.<sup>162,163</sup> More research is needed to assess the combination of AOMs and various endoscopic bariatric procedures, especially in the era of more effective pharmacotherapy.

Finally, the present review evaluated current FDA-approved AOMs. At the time of publication, tirzepatide, a novel co-agonist of GLP-1 and glucose-dependent insulinotropic polypeptide receptors, was recently approved for the treatment of T2DM, with mean weight loss results of 5.5 kg more than semaglutide 1.0 mg at 40 weeks of treatment in subjects with T2DM.<sup>164</sup> Although not yet approved for the treatment of obesity, results from a phase 3 clinical trial in participants without T2DM, at the highest dose of tirzepatide 15 mg weekly, demonstrated mean weight loss of 21% after 72 weeks of treatment, and nearly 40% of subjects on treatment at the maximum dose demonstrated  $\geq 25\%$  TBWL.<sup>165</sup>

### What Do Other Guidelines Say?

The present guidelines are similar to recommendations on the management of overweight and obesity published previously. Naturally, given the rapid advances in this field, particularly with anti-obesity pharmacotherapy, this report bridges some gaps in the contemporary literature. “Guidelines for Managing Overweight and Obesity in Adults,” supported by the National Heart, Lung, and Blood Institute, published in 2013 by The Obesity Society with the American College of Cardiology/American Heart Association Task Force on Practice Guidelines addressed lifestyle intervention and bariatric surgery, without much guidance for use of AOMs, due to the fact that most of the newer FDA-approved medications had not come to market yet.<sup>166</sup> In 2018, the US Preventive Services Task Force published its most recent Recommendation Statement, “Behavioral Weight Loss Interventions to Prevent Obesity-Related Morbidity and

Mortality in Adults,” but focused on guidance for intense lifestyle interventions.<sup>167</sup> In 2013, the American Academy of Family Physicians published a document titled “Diagnosis and Management of Obesity,” which touched on the use of the most recent agents at that time, phentermine-topiramate ER and lorcaserin, which has since been withdrawn from the market.<sup>168</sup> Naltrexone-bupropion ER and GLP-1 RAs had not yet been approved for obesity. Likewise, over the past decade, the American Association of Clinical Endocrinologists and American College of Endocrinology, the Obesity Medicine Association, Endocrine Society, and Obesity Canada with The Canadian Association of Bariatric Physicians and Surgeons, have all provided guidance to health care professionals for many aspects of obesity care, including pharmacotherapy.<sup>169–171</sup> The AGA now further advances evidence-based recommendations with this rigorous guideline on currently available AOMs to help the millions of people with obesity and its complications.

## Plans for Updating This Guideline

Guidelines are living products. To remain useful, they need to be updated regularly as new information accumulates. This document will be updated when major new research is published. The need for update will be determined no later than summer of 2025 and, if appropriate, we will provide rapid guidance updates to incorporate updated recommendations as new evidence, without duplicating or creating a new comprehensive guideline.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org), and at <https://doi.org/10.1053/j.gastro.2022.08.045>.

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**Conflicts of interest**

The authors disclose no conflicts.