Obesity

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Joint TOS/OMA/OAC Expert Guidance Statement on the Pharmacological Management of United States Adults With Overweight or Obesity Using the GRADE Approach

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ABSTRACT

Background: Obesity affects over 40% of US adults, with severe obesity on the rise. Despite recognition of obesity as a chronic disease, it remains underdiagnosed and undertreated. Access to evidence-based obesity treatment is limited, leading to increased obesity severity and related complications. Barriers to obesity treatment include socioeconomic disparities, limited clinician training, stigma, and restrictive or absent reimbursement policies. FDA-approved obesity medications offer significant health benefits, prompting the need for updated, evidence-based guidance.

Methods: The Obesity Society (TOS), the Obesity Medicine Association (OMA), and the Obesity Action Coalition (OAC) convened a multidisciplinary panel, including patient representatives and obesity care providers, to develop a guidance statement using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Systematic evidence synthesis was conducted via Epistemonikos databases, with outcomes prioritized for clinical relevance, including weight reduction, quality of life, adverse events, and improvements in obesity complications. Recommendations were developed through consensus workshops and graded as strong or conditional based on evidence certainty, benefits, harms, equity, and feasibility using the GRADE Evidence-to-Decision framework.

Results: The panel issued recommendations on FDA-approved obesity medications including orlistat, bupropion-naltrexone, phentermine, phentermine-topiramate, liraglutide, semaglutide, tirzepatide, and setmelanotide. Strong recommendations were made for bupropion-naltrexone, semaglutide, tirzepatide, and setmelanotide, with moderate-certainty evidence. Conditional recommendations were made for other agents and specific obesity complications (obstructive sleep apnea, heart failure with preserved ejection fraction, metabolic dysfunction-associated steatotic liver disease/metabolic dysfunction-associated steatohepatitis, osteoarthritis, major adverse cardiovascular events, and type 2 diabetes). Continuing obesity medications during weight maintenance received a strong recommendation.

Lydia Alexander and Jonathan Q. Purnell are co-first authors.

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Conclusion: Obesity is a chronic, often progressive, disease requiring comprehensive, long-term, and person-centered care. Effective obesity medications exist but remain underutilized due to systemic barriers. Expanding access, reducing stigma, and ensuring equitable coverage are essential to translating scientific advances into population health gains. Future priorities include access and integration of comprehensive obesity care in the primary care setting, improving affordability, addressing research gaps, conducting head-to-head trials, and updating guidance as evidence evolves.

1 | Background

According to the latest Centers for Disease Control and Prevention report, 40.3% of US adults live with obesity based on body mass index (BMI). While overall obesity prevalence has stabilized since 2013–2014, severe obesity has continued to increase from 7.7% to 9.7% in the past decade [1]. Clinical documentation lags far behind these numbers: fewer than one-third of individuals with BMI-defined obesity receive a diagnosis [2]. This rate is only slightly higher in those with severe obesity [2]. Historically, access to evidence-based treatments has been very low; only ~1.6% of eligible adults received any treatment, and even fewer received a prescription for an obesity medication [3].

Currently, insurance companies can choose not to offer coverage for obesity office visits and evidence-based treatments, even though coverage in the US for pre-existing conditions is required by the Affordable Care Act of 2014. And, even if this were not a barrier, social determinants of health, including lower income, education, and lack of insurance coverage, further impede access to evidence-based obesity care, particularly for newer medications. Higher socioeconomic status and education increase odds of treatment. Other barriers to adequate care provision include limited clinician training, low referral rates to specialists, underuse of interventions due to healthcare providers' knowledge gaps and pervasive stigma, and restrictive reimbursement policies and practices [4, 5].

Earlier US obesity guidelines include the 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults [6], 2015 Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline [7], and 2016 American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines For Medical Care of Patients with Obesity [8]. Since then, the Food and Drug Administration (FDA) has approved several newer and highly effective obesity medications that improve weight outcomes and quality of life while reducing complications—with more in the pipeline—making updated US obesity pharmacotherapy guidance urgently needed.

The purpose of this guidance statement is to provide evidence-based recommendations on pharmacological management of US adults with overweight or obesity. Its primary goals are to review, appraise, and support implementation of evidence to maximize benefits, including weight reduction and maintenance of lost weight, improved health outcomes, and quality of life, while minimizing harms including adverse drug reactions, treatment burden, and access inequality. Through improved provider and patient education and application of evidence-based recommendations and guidance, the authors' aim is to support collaborative decision-making that promotes effective, safe, person-centered care—while calling attention to widespread disparities in access to many of these medications.

2 | Methods

2.1 | Organization, Panel Composition, Planning, and Coordination

The Obesity Society (TOS), the Obesity Medicine Association (OMA), and the Obesity Action Coalition (OAC), all US-based nonprofit associations, convened a guidance panel ($n = 8$) including clinical experts from diverse specialties in academic and community settings and two representatives with lived experience. The group was co-chaired by two obesity medicine physicians (L.A., J.Q.P.). Work was coordinated by TOS, OMA, OAC, and CPG Direct, a collaboration between Epistemonikos Foundation (C.Á.-O., F.N., and A.M.R.-G), a health research methodology nonprofit, and Replica Communications (B.H., X.R.S.), a strategic research and knowledge mobilization firm.

The evidence team conducted systematic syntheses, defined methods, prepared materials, and facilitated discussions. Panel work was carried out via online tools (Google Forms, https://new-ietd.epistemonikos.org/) and virtual meetings (Zoom).

2.2 | Funding and Conflicts of Interest

Funding was provided by TOS, OMA, and OAC. Co-authors from CPG Direct (C.Á.-O., F.N., A.M.R.-G., B.H., X.R.S) supported coordination of the guidance development process (methodology, evidence synthesis, project support, and writing) but did not participate in the selection of questions or discussions to determine recommendations.

Conflicts of interest were managed per International Committee of Medical Journal Editors (ICMJE) policies and Guidelines International Network recommendations [9]. All participants disclosed financial and nonfinancial interests via ICMJE forms prior to voting on the iEtD platform and participating in the online panel discussions. No panel members, co-chairs, or evidence synthesis team members reported conflicts precluding participation. Recusal procedures were established; members with significant and direct financial conflicts, including employment or equity ownership related to products under consideration, could discuss evidence but not judge or vote on recommendations. Using this benchmark, no recusals were made.

2.3 | Formulating Clinical Questions and Outcomes of Interest

The panel identified 15 key questions on pharmacological management of obesity through a structured prioritization process (survey and online discussions), which are summarized in Table 1.

Study Importance

- Key messages for patients
  - Obesity is not a failure of willpower: it is a chronic medical condition with safe and effective treatments beyond lifestyle alone.
  - Weight reduction is part of the goal for obesity treatment. Medications to treat the disease of obesity (called "obesity medications") are available that can improve quality of life and facilitate management of obesity-related complications in addition to achieving meaningful weight reduction with long-term weight maintenance.
- Key messages for health care providers
  - Obesity is a chronic, often progressive disease requiring sustained and comprehensive treatment.
  - Obesity medications are safe and effective when used long-term. Discontinuing comprehensive obesity care including obesity medications without cause (e.g., side effects, pregnancy) can result from inadequate understanding of obesity as a chronic disease, often leading to treatment failure and exacerbating bias and stigma directed at the patients themselves.
  - Quality of life, management of obesity complications, and long-term weight maintenance are as important as initial weight reduction.
  - Obesity care should be collaborative, individualized, accessible, and stigma-free.
- Key messages for policy makers
  - Obesity is a chronic, often progressive disease requiring sustained and comprehensive treatment, including obesity medications.
  - Obesity medications should no longer be considered an "adjunct" to lifestyle but can be implemented simultaneously with lifestyle improvements, like treating other chronic diseases such as diabetes and hypertension.
  - Long-term pharmacotherapy interventions are safe, effective, and essential to preventing disease progression and associated complications at the population level.
  - Policies must prioritize access and equity to ensure that advances in obesity treatments, including obesity medications, benefit all populations, including those disproportionately affected by obesity and related complications.

Questions were selected for relevance to common clinical scenarios, management uncertainty, new evidence, practice variability, and potential patient benefit. Each question was framed using the PICO format (population, intervention, comparator, outcomes).

Note: When evidence was examined that considered both glucagon-like peptide-1 (GLP-1) receptor agonists (semaglutide, liraglutide) and the current dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist (tirzepatide; GIP/GLP-1), the umbrella term GLP-1 (+) is used.

In line with recent developments in the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (Box 1), the evidence synthesis team established referential decision thresholds to assess the magnitude of benefits and harms, as well as the certainty of those effects [10]. To do this, generic threshold indices, derived from a large sample of decision-makers across various clinical contexts [10], were adjusted using disutilities for relevant outcomes. When available, utility values were retrieved from the literature. In cases where utilities were not reported, the methods team applied a scale to categorize the magnitude of effects. This approach allowed for the development of outcome-specific thresholds to distinguish between trivial, small, moderate, and large effects for each of the critical outcomes prioritized by the guidance development group. When utilities for specific outcomes were not reported in the literature through a literature review, documentation obtained from the process of multiple guidelines, expert consultation, and internal discussion, Epistemonikos has developed a set of thresholds used to inform the panelists during the discussion of these recommendations (Table 2). These thresholds were assigned according to the relative importance of the outcomes prioritized by the experts and used to determine the effect size according to the results in absolute terms of the evidence synthesis.

The panel also selected outcomes of interest for each clinical question a priori, following a structured approach. Briefly, the panel began by generating a comprehensive list of potential outcomes, then rated each according to its relative importance for decision-making, using the GRADE methodology. Both desirable (benefits) and undesirable (harms) patient-important outcomes were considered. Outcomes deemed critical for decision-making across all clinical questions included percent total body weight loss (%TBWL), the proportion of patients achieving $\geq 5\%$, $\geq 10\%$, and $\geq 15\%$ TBWL, and serious adverse events (SAEs). SAEs were extracted as defined and reported by the included primary studies. Distinct from other clinical practice guidelines for obesity, the panel agreed to explicitly equate potential patient quality-of-life outcomes on par with other traditional clinical outcomes such as major adverse cardiovascular events (MACE) and mortality in determining the final recommendations in order to more accurately reflect the importance of and commitment to person-centered outcomes.

The outcomes are presented according to the panel's prioritization, with all-cause mortality, cardiovascular mortality, MACE, and health-related quality of life identified as critical and ranked above weight reduction. Outcomes within both categories are weighted equally, so the sequence does not alter their importance. In cases where the evidence for all-cause mortality, cardiovascular mortality, and MACE was sufficiently strong, the panel used that as the primary basis for determining certainty and the strength of recommendations, allowing the recommendations to be framed as strong rather than conditional. Because quality of life was deemed equally critical alongside the other outcomes, its evidence was considered with equal weight, which strengthened the overall certainty of the evidence for several medications. The panel's prioritization of critical and important outcomes is summarized in Table 3.

TABLE 1 | PICO (population, intervention, comparator, outcomes) formatted questions formulated and prioritized.

Q1	In adults 18 years of age or older with overweight and at least one complication or obesity, should orlistat be used compared to placebo?
Q2	In adults 18 years of age or older with overweight and at least one complication or obesity, should bupropion-naltrexone be used compared to placebo?
Q3	In adults 18 years of age or older with overweight and at least one complication or obesity, should phentermine be used compared to placebo?
Q4	In adults 18 years of age or older with overweight and at least one complication or obesity, should phentermine-topiramate be used compared to placebo?
Q5	In adults 18 years of age or older with overweight and at least one complication or obesity, should liraglutide be used compared to placebo?
Q6	In adults 18 years of age or older with overweight and at least one complication or obesity, should semaglutide be used compared to placebo intervention?
Q7	In adults 18 years of age or older with overweight and at least one complication or obesity, should tirzepatide be used compared to placebo?
Q8	In adults 18 years of age or older, should setmelanotide be used compared to usual care for approved monogenic obesity syndromes (e.g., risk alleles for leptin receptor [LEPR], proopiomelanocortin [POMC], proprotein convertase subtilisin/kexin type 1 [PCSK1], Bardet–Biedl syndrome [BBS])?
Q9	In adults 18 years of age or older with overweight or obesity who are engaged in medical obesity treatment (obesity medication) and are in the weight maintenance phase, should obesity medication interventions be used compared to no obesity medication intervention?
Q10	In adults 18 years of age or older with overweight or obesity and obstructive sleep apnea, should glucagon-like peptide-1 (GLP-1) (+) agonists be used compared to placebo?
Q11	In adults 18 years of age or older with overweight or obesity and heart failure with preserved ejection fraction (HFpEF), should glucagon-like peptide-1 (GLP-1) (+) agonists be used compared to placebo?
Q12	In adults 18 years of age or older with overweight or obesity and metabolic dysfunction-associated steatotic liver disease (MASLD) or metabolic dysfunction-associated steatohepatitis (MASH), should glucagon-like peptide-1 (GLP-1) (+) agonists be used compared to placebo?
Q13	In adults 18 years of age or older with overweight or obesity and osteoarthritis, should glucagon-like peptide-1 (GLP-1) (+) agonists be used compared to placebo?
Q14	In adults 18 years of age or older with overweight or obesity and a history of myocardial infarction, stroke, or symptomatic peripheral vascular disease, is semaglutide better than placebo in reducing major adverse cardiovascular events (myocardial infarction, stroke, and death from myocardial infarction)?
Q15	In adults 18 years of age or older with overweight or obesity and type 2 diabetes, should FDA-approved obesity medications be used compared to placebo?

2.4 | Evidence Review

The Epistemonikos Foundation methods team conducted an evidence synthesis process on the effects of interventions, the importance of outcomes, resource use, and considerations of equity, acceptability, and feasibility of treatment alternatives. Eligibility criteria were defined for the components of each prioritized question. Systematic reviews and randomized trials that met the inclusion criteria for each question were included to inform the intervention effects criteria.

A search for systematic reviews was conducted through the Epistemonikos database until May 29, 2025. The Epistemonikos database is a comprehensive database of systematic reviews relevant to health decision-making that is maintained by screening multiple sources of information to identify systematic reviews and their included primary studies, including the Cochrane Database of Systematic Reviews, Pubmed/MEDLINE, Embase, CINAHL, PsycINFO, LILACS, DARE, HTA database, Campbell database, JBI database of systematic reviews and implementation reports, and EPPI Centre evidence library [11]. No date or language restrictions were applied. To identify primary studies not included in the reviews, additional searches of randomized controlled trials (RCTs) were performed in the Epistemonikos Database of Trials (ED-Trials) (https://trials.epistemonikos.org/). The ED-Trials is built and maintained through automated and manual searches across several sources, including electronic databases, preprint repositories, trial registries, and other relevant sources. The search strategies used for each clinical question are available in online Supporting Information: Supplementary Data. Duplicate records from the searches were identified by an automated process through the Epistemonikos database.

BOX 1 | Understanding GRADE Methodology.

GRADE (Grading of Recommendations Assessment, Development and Evaluation) is the most commonly used development tool for clinical practice guidelines globally. It rates the certainty of evidence and the strength of recommendations, focusing on the *overall body of evidence for each outcome*, not the outcomes or merits of individual studies.
Certainty reflects confidence that the true effect lies within a clinically important range as defined according to two key concepts:

1. Decision thresholds that represent clinically meaningful treatment effect cutoffs: trivial, small, moderate, or large benefit or harm.
2. Target of certainty representing the treatment effect range that can confidently be assessed as true.

The certainty assessment follows four steps:

1. Define the clinically important cutoffs.
2. Identify a range the results suggest is a true treatment effect, which becomes the target.
3. Assess factors that could make results misleading, such as risk of bias, inconsistency, indirectness, imprecision, and publication bias.
4. Adjust certainty only if these concerns could plausibly shift the effect across an important cutoff. Certainty may be raised only if the observed effect is unlikely to be due to bias or confounding.

Based on this process, certainty is assigned on of the following ratings:

- High: The true effect is very close to the estimate.
- Moderate: The effect is probably close, but a meaningful difference is possible.
- Low: The effect may be quite different.
- Very low: There is little confidence in the estimate.

Randomized trials start as high certainty but can be downgraded during the assessment process, even large studies. Panels also consider benefit magnitude, condition severity, patient values, safety, and resource use. GRADE supports clinical decisions by clarifying whether benefits are large enough to justify harms or burdens (e.g., cost, adverse effects, long-term treatment), making trade-offs explicit and patient-specific when benefits are small.

To move from evidence to recommendations, GRADE uses Evidence-to-Decision (EtD) frameworks, which systematically consider evidence certainty, benefits and harms, patient values, resources, equity, and feasibility. Findings are summarized in standardized Summary of Findings tables showing outcomes, relative and absolute effects, confidence intervals (CI), and certainty ratings.
Based on this structured assessment, panels issue strong or conditional recommendations. GRADE's strength lies in its explicit, transparent, and broadly applicable approach to evaluating evidence and guiding decisions across health care contexts. For a more detailed overview of GRADE, see online Supporting Information: Appendix 1.

For example, if data are limited to a single trial or population, the conditional recommendation of "low certainty" does not imply a lack of confidence in the single trial or clinical benefit. Rather, it reflects that the available evidence comes primarily from one large, high-quality study and has not yet been replicated across diverse settings. In this case, the panel would use GRADE's structured approach to remain transparent about the evidentiary strength while still supporting the intervention's use.

TABLE 2 | Thresholds for the minimal important difference according to their relative importance.

Relative importance of the outcome (RIO)		Large effect	Moderate effect	Small effect	Trivial effect
5	Critical	50 per 1000[a]	25 per 1000	10 per 1000	< 10 per 1000
4		100 per 1000	50 per 1000	25 per 1000	< 25 per 1000
3	Important but not critical	200 per 1000	100 per 1000	50 per 1000	< 50 per 1000
2	Surrogate outcomes	300 per 1000	200 per 1000	100 per 1000	< 100 per 1000
1		400 per 1000	300 per 1000	200 per 1000	< 200 per 1000

[a]Referential decision thresholds for classifying the magnitude of absolute effects according to the relative importance of the outcome (RIO). Values are expressed as absolute risk differences per 1000 participants over the study follow-up period (i.e., not per year). For each RIO level (5 = critical, 4 = important, 3 = important but not critical, 2 = surrogate outcomes), absolute effects are categorized as large, moderate, small, or trivial according to the ranges shown. These thresholds were developed a priori, informed by GRADE guidance and consensus among the panel, and were used within the GRADE Evidence-to-Decision framework to support panel judgments about the magnitude of desirable and undesirable effects.

TABLE 3 | Prioritization of outcomes.

Outcomes	Descriptions	Rate the outcome based on clinical importance	Is this outcome important for patients?
All-cause mortality	The rate of death from any cause in a given population over a specified time.	Critical	5
Cardiovascular mortality	The rate of death specifically due to cardiovascular diseases, including myocardial infarction (MI) and strokes.	Critical	5
Major adverse cardiovascular events	Composite of serious heart-related outcomes, typically including MI, stroke, and cardiovascular death.	Critical	5
Health-related quality of life	Subjective measure of how health status affects an individual's ability to live a fulfilling life, often captured through standardized questionnaires.	Critical	4
Diabetes risk reduction	Impact on the likelihood of developing type 2 diabetes.	Critical	4
Weight maintenance	Stability of weight loss over time	Critical	4
Weight regain	Extent of weight gain recurrence after initial loss.	Critical	4
Changes in measures of obstructive sleep apnea severity	Changes in apnea events and symptoms, relevant due to strong links between obesity and sleep apnea.	Critical	4
Changes in measures of heart failure with preserved ejection fraction severity	Impact of obesity treatments on this heart condition common in people with obesity.	Critical	4
KCCQ-CSS	Score reflecting heart failure symptoms, for patients with obesity and heart disease.	Critical	4
Changes in measures of osteoarthritis severity	Changes in pain and function in weight-bearing joints.	Critical	4
Body weight	Measured in kilograms or pounds to assess weight loss or gain.	Important	3
Cardiometabolic risk factor	Measures like blood pressure, lipids, and glucose that are linked to obesity and cardiovascular diseases	Important	3
Improvements in cardiometabolic outcomes	Combined or individual improvement in these risk factors.	Important	3
Exercise function	Capacity for physical activity, a key marker of health and fitness.	Important	3
Changes in measures of metabolic dysfunction-associated steatotic liver disease (MASLD) or metabolic dysfunction-associated steatohepatitis (MASH).	Measures of liver fat, inflammation, and/or fibrosis reflecting the metabolic burden of obesity.	Important	3

Relative importance of the outcome (RIO): 1 (less important)–5 (very important).

Evidence was screened by independent peer reviewers in two stages (title and abstract, full text) using the SK screening software (https://www.skplatform.org/) developed by the Epistemonikos Foundation. Data extraction and risk of bias assessment were performed by two reviewers using standardized forms. The RoB-2 tool was used to assess the risk of bias of randomized trials [12].

The effects findings were synthesized quantitatively (i.e., through meta-analysis) or narratively, depending on the availability,

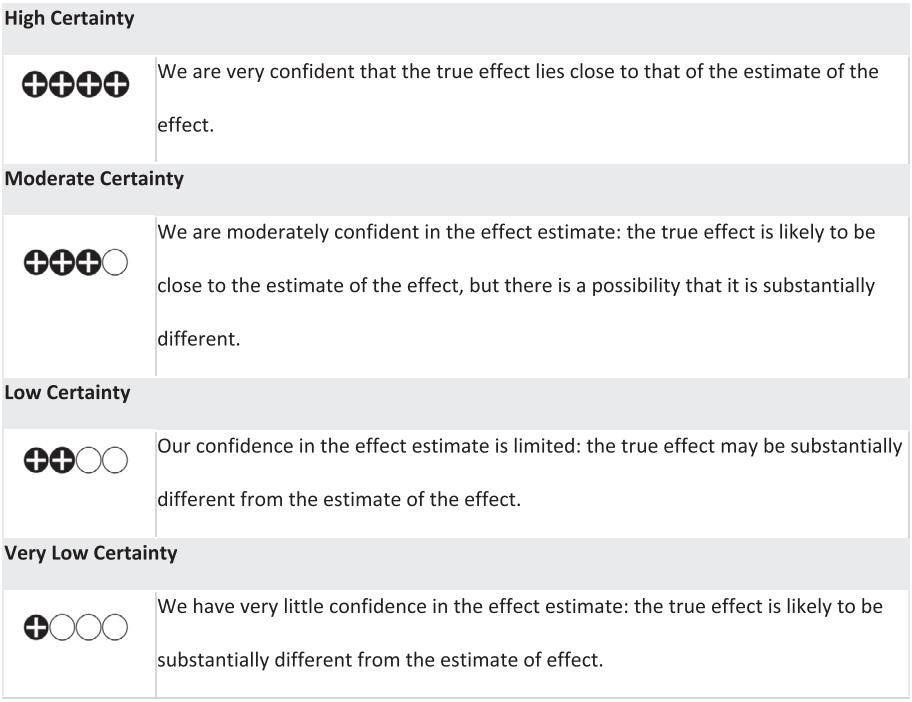

FIGURE 1 | Evidence certainty.

completeness, and comparability of the data. An independent methods team assessed the certainty of the evidence for each critical and important outcome and provided this prespecified assessment to the panel before the formulation of recommendations. Certainty of the evidence was evaluated using the GRADE approach, which considers not only the study design but also five key domains: risk of bias, inconsistency (unexplained heterogeneity of results), indirectness (applicability of the population, intervention, comparator, or outcomes), imprecision (width of confidence intervals [CI] and optimal information size), and publication bias. RCTs typically start as high-certainty evidence; the rating can be downgraded by one or two levels when there are serious or very serious concerns in one or more GRADE domains [13–15]. All judgments were made independently by at least two reviewers, with disagreements resolved through discussion and, when needed, consultation with a third reviewer. The final certainty rating for each outcome was categorized into four standard GRADE levels—very low, low, moderate, and high [13–15]—and, in this report, these categories are represented by symbols, as described in Figure 1.

Each sponsoring organization reviewed and approved the recommendations prior to submission for peer review, ensuring consistency with the missions and standards of the participating organizations.

The results of the synthesis of the effects were integrated in the Evidence-to-Decision (EtD) tables through Summary of Findings tables following the GRADE EtD framework [16]. For each question, EtD tables were created through the interactive EtD (iEtD) platform (https://new-ietd.epistemonikos.org/).

To inform the criteria of importance of the outcomes, resource use, and considerations of equity, acceptability, and feasibility, we searched for systematic reviews or primary studies of utility studies, economic evaluations, and qualitative studies, respectively.

2.5 | Development of Recommendations

To develop the clinical recommendations, five online workshops were held from June to August 2025. For each recommendation, the panel took a population perspective and came to consensus on the following: the certainty of the evidence, the balance of benefits and harms of the compared management options, and the assumptions about the values and preferences associated with the decision. The panel also explicitly took into account the extent of resource use associated with alternative management options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or, in rare instances, by voting (a 70% majority was required for making recommendations), based on the balance of all desirable and undesirable consequences. After making judgments for each criterion, the panelists voted on the direction and strength of each recommendation. This entire process was conducted using the iEtD platform. The final guidance, including recommendations, was reviewed and approved by all members of the panel.

2.6 | Interpretation of Strong and Conditional Recommendations

The recommendations are labeled as either “strong” or “conditional” according to the GRADE approach. The words “the guidance panel recommends” are used for strong recommendations, and “the guidance panel suggests” for conditional recommendations. Figure 2 provides GRADE's interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers.

	"Recommends…"	"Recommends against…"	"Suggests…"	"Suggests against…"
				
	Interpretation of Strong Recommendations		**Interpretation of Conditional Recommendations**	
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.		Most individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.	
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.		Different choices will be appropriate for individual patients; clinicians must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.	
Policymakers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guidance could be used as a quality criterion or performance indicator.		Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess if decision making is appropriate.	
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.		The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.	

FIGURE 2 | Interpretation of strong and conditional recommendations (adapted from GRADE).

3 | FDA-Approved Medications for Use in Adults With Obesity

This guidance statement focuses on the FDA-approved obesity medications for adults with BMI ≥27 kg/m^2 with at least one complication or BMI ≥30 kg/m^2. The medications considered included orlistat, bupropion-naltrexone, phentermine, phentermine-topiramate, liraglutide, semaglutide, and tirzepatide. While some of the included obesity medications had an approved generic form, only studies of the non-generic formulations were considered in the analysis. All should be used in conjunction with a healthy lifestyle.

Results for each medication provide a narrative description of the Summary of Findings tables found in online Supporting Information: Supplementary Data. The list of included studies and references in the review for each research question is available in online Supporting Information: Appendix 2. All reported outcomes are presented as comparisons with placebo.

3.1 | Orlistat

Orlistat is a gastrointestinal lipase inhibitor approved as a prescription obesity medication in 1999 that blocks enzymatic breakdown of dietary triglycerides within the intestinal lumen, resulting in reduced fat absorption. It is administered orally as a capsule or tablet and became available over-the-counter in 2007.

In adults with overweight or obesity:

- Body weight: Orlistat may be associated with a small reduction in body weight (mean difference 3.38 kg less; 95% CI from 3.42 to 3.35 kg less; low certainty; 44 studies, n = 9262).
- Health-related quality of life: Orlistat may lead to a trivial increase in health-related quality of life (mean difference 3.15 points higher; 95% CI 0.02 to 6.27 higher; very low certainty; 1 study, n = 339).
- Serious adverse events: Orlistat may result in a trivial increase in serious adverse events (risk difference about 2 more per 1000; 95% CI 14 fewer to 26 more; low certainty; 15 studies, n = 3394).

3.2 | Bupropion-Naltrexone

Bupropion-naltrexone is a centrally acting combination therapy that targets hypothalamic appetite pathways. Bupropion enhances pro-opiomelanocortin (POMC) activity, while naltrexone mitigates endogenous auto-regulatory mu-opioid receptor-mediated feedback inhibition, collectively improving appetite control. Approved as an obesity medication in 2014, it is administered orally as a fixed-dose combination tablet.

In adults with overweight or obesity:

- Body weight: Naltrexone plus bupropion may be associated with a small reduction in body weight (mean difference 3.27 kg lower; 95% CI 3.49–3.05 kg lower; low certainty; 4 studies, n = 9410), corresponding to about a small increase in percentage weight loss (mean difference 5.42 percentage points more weight loss; 95% CI 5.00–6.00 more; low certainty; 7 studies, n = 3655).
- Weight loss ≥5%: Naltrexone plus bupropion may be associated with a large increase in the proportion achieving ≥5% weight loss (risk difference 350 more per 1000; 95% CI 227–508 more; very low certainty; 7 studies, n = 5435).
- Weight loss ≥10%: Naltrexone plus bupropion may be associated with a moderate increase in the proportion achieving ≥10% weight loss (risk difference 172 more per 1000; 95% CI 111–253 more; very low certainty; 7 studies, n = 5558).
- Serious adverse events: Naltrexone plus bupropion may be associated with a small increase in serious adverse events (risk difference about 15 more per 1000; 95% CI 7–24 more; low certainty; 9 studies, n = 22,612).
- Cardiovascular death: Naltrexone plus bupropion probably leads to a small reduction in cardiovascular death (risk difference about 4 fewer per 1000; 95% CI 0.8–5.5 fewer; moderate certainty; 1 study, n = 8905).
- Health-related quality of life: Naltrexone plus bupropion probably leads to a small improvement in health-related quality of life (mean difference 3.82 points higher; 95% CI 3.06–4.59 higher; moderate certainty; 5 studies, n = 3425).

3.3 | Phentermine

Phentermine enhances norepinephrine and dopamine signaling in the hypothalamus, leading to improved appetite control. It is administered orally as a tablet or capsule. It was first approved as an obesity medication in 1959. At that time, due to a lack of understanding of the biology and chronic nature of the disease of obesity, it was only FDA approved for short-term use (typically 12 weeks or less). As the longest generically available obesity medication, it is considered cost-effective but lacks the robust supportive safety and outcomes data from RCTs as compared to other obesity medications. Nevertheless, with support from recent real-world cohort analyses, it is commonly used off label for the long-term treatment of obesity.

In adults with overweight or obesity:

- Body weight: Phentermine probably causes a small reduction in body weight percentage (mean difference 3.30 percentage points lower; 95% CI 3.31 to 3.29 lower; moderate certainty; 3 RCTs, n = 249).
- Weight loss ≥5%: Phentermine may be associated with a large increase in the proportion achieving ≥5% weight loss (absolute increase 493 more per 1000; 95% CI 101 to 1283 more per 1000; low certainty; 4 RCTs, n = 528).
- Weight loss ≥10%: Phentermine may be associated with a moderate increase in the proportion achieving ≥10% weight loss (absolute increase 236 more per 1000; 95% CI 9 fewer to 1705 more per 1000; very low certainty; 2 RCTs, n = 383).

- Severe psychiatric adverse events: The evidence for severe psychiatric adverse events was reported in one trial with 28-week follow-up, with no intervention-related severe psychiatric events reported (very low certainty; 1 RCT, $n = 326$).

3.4 | Phentermine-Topiramate

This combination adding topiramate to phentermine was approved as an obesity medication in 2012 and is administered as a single, oral, extended-release capsule. Topiramate is both a weak carbonic anhydrase inhibitor and blocks voltage-gated sodium channels, mechanisms that likely led to its initial indication for seizure disorders. Its action to additively improve appetite control likely involves alterations in central GABAergic neuronal signaling.

In adults with overweight or obesity:

- Body weight: Phentermine/topiramate probably leads to a small reduction in body weight, by about 4.6 kg (mean difference 4.59 kg lower; 95% CI 4.68 to 4.50 lower; low certainty; 4 RCTs, $n = 2376$).
- Weight loss ≥ 5%: Phentermine/topiramate may be associated with a large increase in the proportion achieving ≥ 5% weight loss (absolute increase 265–569 more per 1000; low certainty; 5 RCTs, $n = 2478$).
- Weight loss ≥ 10%: Phentermine/topiramate probably leads to a large increase in the proportion achieving ≥ 10% weight loss (absolute increase 248–432 more per 1000; moderate certainty; 4 RCTs, $n = 2433$).
- Weight loss ≥ 15%: Phentermine/topiramate may also be associated with a moderate increase in the proportion achieving ≥ 15% weight loss (absolute increase about 161 more per 1000; 95% CI 112 to 354 more per 1000; low certainty; 2 RCTs, $n = 1905$).
- Serious adverse events: Serious adverse events resulted in a small increase with phentermine/topiramate (about 9 more per 1000; 95% CI 9 fewer to 40 more per 1000; low certainty; 4 RCTs, $n = 1267$).
- Health-related quality of life: Phentermine/topiramate resulted in a trivial change in health-related quality of life (overall SF-36 at 28 weeks; low certainty; 1 RCT).

3.5 | Liraglutide

Liraglutide is a GLP-1 receptor agonist that improves appetite control by binding peripheral and central (hypothalamic) receptors, independent of its incretin effect on pancreatic islet cells or its effects on gastrointestinal motility. It was FDA approved to treat obesity in 2014 and is administered subcutaneously once daily.

In adults with overweight or obesity:

- Weight loss ≥ 5%: Liraglutide may be associated with a large increase in the proportion achieving ≥ 5% weight loss (about 282 more per 1000; 95% CI 19 to –393 more; high certainty; 7 studies, $n = 5239$).
- Weight loss ≥ 10%: Liraglutide may be associated with a moderate increase in the proportion achieving ≥ 10% weight loss (about 186 more per 1000; 95% CI 65 to 397 more; low certainty; 7 studies, $n = 5239$).
- Weight loss ≥ 15%: Liraglutide may result in a small increase in the proportion achieving ≥ 15% weight loss (about 61 fewer per 1000; 95% CI 137 fewer to 134 more; very low certainty; 1 study, $n = 98$).
- Weight loss ≥ 20%: Liraglutide may result in a trivial difference in the proportion achieving ≥ 20% weight loss (about 0 fewer per 1000; 95% CI 1 fewer to 226 more; very low certainty; 1 study, $n = 98$).
- Serious adverse events: Liraglutide probably results in a small increase in serious adverse events (about 10 more per 1000; 95% CI 1 fewer to 24 more; moderate certainty; 12 studies, $n = 5618$).
- Health-related quality of life: Liraglutide may result in a small increase in health-related quality of life, including general health (mean difference 4.50 points lower; 95% CI 13.44 lower to 4.44 higher; low certainty; 1 study, $n = 98$) and physical functioning (mean difference 6.10 points lower; 95% CI 13.78 lower to 1.58 higher; low certainty; 1 study, $n = 98$).
- Mortality: No deaths were reported in the included studies (95% CI not estimable; very low certainty; 3 studies, $n = 312$).

3.6 | Semaglutide

Semaglutide is a GLP-1 receptor agonist that improves appetite control by binding peripheral and central (hypothalamic) receptors, independent of its incretin effect on pancreatic islet cells or its effects on gastrointestinal motility. It was FDA approved to treat obesity in 2021 and is administered subcutaneously once weekly.

In adults with overweight or obesity:

- Body weight (kg): Semaglutide probably results in a large reduction in body weight, by about 12.3 kg on average (mean difference 12.27 kg lower; 95% CI 12.77 to 12.62 lower; moderate certainty; 7 studies, $n = 4051$),
- Body weight (%): Semaglutide probably results in a large reduction in body weight, corresponding to an 8.6 percentage topoint greater loss in body weight (mean difference 8.61 percentage points lower; 95% CI 8.84 to 8.37 lower; low certainty; 2 studies, $n = 15{,}225$).
- Weight loss ≥ 5%: Semaglutide probably results in a large increase in the proportion achieving ≥ 5% weight loss (about 534 more per 1000; 95% CI 437 to 643 more; moderate certainty; 5 studies, $n = 3499$).
- Weight loss ≥ 10%: Semaglutide probably results in a large increase in the proportion achieving ≥ 10% weight loss (about 532 more per 1000; 95% CI 414 to 676 more; moderate certainty; 6 studies, $n = 3499$).

- Weight loss≥15%: Semaglutide probably results in a large increase in the proportion achieving ≥15% weight loss (about 402 more per 1000; 95% CI 287 to 402 more; moderate certainty; 5 studies, $n = 3179$).
- Weight loss ≥20%: Semaglutide may result in a small increase in the proportion achieving ≥20% weight loss (about 332 more per 1000; 95% CI 160 to 673 more; low certainty; 5 studies, $n = 3179$).
- Cardiovascular death: Semaglutide may result in a small reduction in cardiovascular death (about 4 fewer per 1000; 95% CI 9 fewer to 0.4 more; low certainty; 1 study, $n = 17{,}604$).
- Mortality: Semaglutide probably results in a small reduction in all-cause mortality (about 8 fewer per 1000; 95% CI 13 fewer to 3 fewer; moderate certainty; 9 studies, $n = 21{,}730$).
- Serious adverse events: Semaglutide probably results in a small increase in serious adverse events (about 15 more per 1000; 95% CI 41 fewer to 82 more; moderate certainty; 9 studies, $n = 22{,}236$).
- Health-related quality of life: Semaglutide probably leads to a small increase in health-related quality of life (mean difference 0.05 points higher; 95% CI 0.03 to 0.06 higher; moderate certainty; 6 studies, $n = 3348$).

3.7 | Tirzepatide

Tirzepatide is a dual GIP/GLP-1 receptor agonist. The mechanistic role of GIP receptor activation remains uncertain but, as a GLP-1 receptor agonist, it improves appetite control by binding peripheral and central (hypothalamic) receptors, independent of its incretin effect on pancreatic islet cells or its effects on gastrointestinal motility. It was FDA approved to treat obesity in 2023 and is administered subcutaneously once weekly.

In adults with overweight or obesity:

- Body weight (%): Tirzepatide probably results in a large reduction in body weight percentage (mean difference 11.92 percentage points lower; 95% CI 11.98 to 11.85 lower; high certainty; 5 studies, $n = 2525$).
- Weight loss ≥5%: Tirzepatide may be associated with a large increase in the proportion achieving ≥5% weight loss (about 870 more per 1000; 95% CI 308 to 1923 more; low certainty; 5 studies, $n = 4176$).
- Weight loss ≥10%: Tirzepatide may be associated with a large increase in the proportion achieving ≥10% weight loss (about 1144 more per 1000; 95% CI 411 to 2776 more; low certainty; 5 studies, $n = 4176$).
- Weight loss ≥15%: Tirzepatide may be associated with a large increase in the proportion achieving ≥15% weight loss (about 1199 more per 1000; 95% CI 416 to 3198 more; low certainty; 5 studies, $n = 4176$).
- Serious adverse events: Tirzepatide probably results in a small decrease in serious adverse events (about 2 fewer per 1000; 95% CI 14 fewer to 13 more; moderate certainty; 7 studies, $n = 4870$).
- Health-related quality of life: Tirzepatide probably leads to a small improvement in health-related quality of life (mean difference 6.39 points higher; 95% CI 6.21 to 6.57 higher; moderate certainty; 6 studies, $n = 4198$).

3.8 | Setmelanotide

Setmelanotide is a melanocortin-4 receptor (MC4R) agonist that restores signaling within the leptin-melanocortin pathway, which is critical for appetite regulation and energy balance. It is administered subcutaneously once daily. It was FDA approved in 2020 to treat patients with severe obesity due to confirmed genetic risk alleles in the MC4R pathway, including POMC, PCSK1, or LEPR genes; its approval was expanded in 2022 to treat those with Bardet–Biedl syndrome (BBS).

In patients with these genetic traits:

- Body weight: Setmelanotide may be associated with a small reduction in body weight overall (mean difference 3.89 kg lower; 95% CI 5.82 to 1.96 lower; low certainty; 2 studies, $n = 49$), with better weight loss responses in patients with POMC or PCSK1 mutations and those with BBS and more limited responses in patients with LEPR mutations.
- Serious adverse events: Setmelanotide may result in a trivial reduction in serious adverse events (about 19 fewer per 1000; 95% CI 29 fewer to 96 more; very low certainty; 2 studies, $n = 87$).
- Mortality: No deaths were reported in the selected study (95% CI not estimable; very low certainty; 1 study, $n = 49$).

4 | Role of Obesity Medications in the Weight Maintenance Phase

Recent studies have reported outcomes of patients with obesity initially assigned to an obesity medication for at least 1 year who were then re-randomized to active drug or placebo with continued follow-up of weight loss maintenance.

In these patients, continued treatment with an obesity medication:

- Body weight: Results in a large reduction in body weight, of about 16 kg more than stopping treatment (mean difference 16.38 kg lower; 95% CI 17.41 to 15.36 lower; high certainty; 2 studies, $n = 1473$).
- Serious adverse events: Probably results in a small increase (about 10 more per 1000; 95% CI 9 fewer to 42 more; moderate certainty; 2 studies, $n = 1473$).
- Mortality: Probably results in a small reduction in mortality (about 1 fewer death per 1000; 95% CI 3 fewer to 13 more; moderate certainty; 2 studies, $n = 1473$).

- Health-related quality of life: Results in a small improvement in health-related quality of life, including:
- **SF-36 v2:**
  - Role-physical: mean difference +1.00 (95% CI +0.15 to +1.85; high certainty; 1 study, $n = 670$).
  - Role-emotional: mean difference +1.80 (95% CI +0.67 to +2.93; high certainty; 1 study, $n = 670$).
  - Mental health: mean difference +2.45 (95% CI +1.72 to +3.18; high certainty; 2 studies, $n = 1473$).
  - Physical component summary: mean difference +1.50 (95% CI +0.78 to +2.22; high certainty; 1 study, $n = 803$).
- **Obesity-specific IWQOL-Lite-CT:**
  - Physical function composite: mean difference +9.40 (95% CI +6.86 to +11.94; high certainty; 1 study, $n = 670$).

Additional considerations for all obesity medications can be found in online Supporting Information: Appendix 3.

5 | Role of Obesity Medications in the Prevention and Management of Obesity Complications

Obesity—particularly abdominal and visceral adiposity—is a major risk factor for chronic diseases, driving morbidity and mortality. Visceral fat promotes insulin resistance, inflammation, and metabolic dysregulation, elevating the risk of type 2 diabetes [17, 18], hypertension [19], cardiovascular diseases [20], obstructive sleep apnea (OSA) [21], osteoarthritis [22], and metabolic dysfunction–associated steatotic liver disease (MASLD) or steatohepatitis (MASH) [23]. These links underscore obesity as a treatment target for chronic disease burden.

Mounting evidence paints a wider picture of the utility of obesity medications in treating these complications of obesity, and as such several related clinical questions were posed by the panel. Given the focus of this guidance review on medications FDA approved for the treatment of overweight and obesity, evidence considered in this section was restricted to studies that primarily included these populations. For example, even though GLP-1 (+) medications have been used for nearly 20 years to treat type 2 diabetes, only those studies that selected patients with overweight or obesity in their inclusion criteria were considered here for analysis. The panel acknowledges that many other significant outcomes studies using GLP-1 (+) medications have been published, including oral formulations and in subpopulations with chronic kidney disease, that included populations of patients not living with overweight or obesity. Many of these have been included in guidelines by endocrine and diabetes associations, and the panel encourages providers to consider all results when counseling their patients regarding health care decisions.

5.1 | Obstructive Sleep Apnea (OSA)

In adults with overweight or obesity and OSA:

- Apnea-hypopnea index (severity of OSA): GLP-1 (+) treatment probably reduces the apnea-hypopnea index (about 10 events per hour, meaning fewer breathing interruptions during sleep; mean difference 9.70 points lower; 95% CI 12.10 to 7.30 lower; moderate-certainty evidence; 3 studies, $n = 747$).
- Serious adverse events: GLP-1 (+) treatment may result in a trivial reduction in serious adverse events (about 9 fewer events per 1000; 95% CI 29 fewer to 36 more per 1000; low-certainty evidence; 2 studies, $n = 812$).
- Weight change (%): GLP-1 (+) treatment probably results in a large reduction in percentage weight loss, of about 17 percentage points more body weight lost compared with control

  (mean difference 16.74 percentage points lower; 95% CI 18.11 to 15.36 lower; moderate-certainty evidence; 1 study, $n = 469$).

5.2 | Heart Failure With Preserved Ejection Fraction (HFpEF)

In adults with overweight or obesity and HFpEF:

- Composite heart failure outcome: GLP-1 receptor agonists probably result in a small reduction in composite heart failure events (about 7 fewer per 1000; 95% CI 12 fewer to 1 fewer; high certainty; 1 study, $n = 17{,}604$).
- Heart failure hospitalization: GLP-1 receptor agonists probably result in a small reduction in heart failure requiring hospitalization (about 3 fewer per 1000; 95% CI 5 fewer to 1 more; moderate certainty; 1 study, $n = 17{,}604$).
- Cardiovascular death: GLP-1 receptor agonists probably result in a small reduction in cardiovascular death (about 4 fewer per 1000; 95% CI 8 fewer to 1 more; moderate certainty; 3 studies, $n = 18{,}864$).
- All-cause mortality: GLP-1 receptor agonists probably lead to a small reduction in all-cause mortality (about 8 fewer per 1000; 95% CI 14 fewer to 3 fewer; high certainty; 3 studies, $n = 18{,}864$).
- Serious adverse events: GLP-1 receptor agonists probably result in a small reduction of serious adverse events (110 fewer per 1000; 95% CI 223 fewer to 95 more; very low certainty; 2 studies, $n = 18{,}133$).
- Body weight: GLP-1 receptor agonists probably lead to a large reduction in body weight percentage (mean difference 8.73 percentage points lower; 95% CI 9.00 to 8.50 lower; moderate certainty; 3 studies, $n = 16{,}071$).
- Weight loss $\geq 20\%$: GLP-1 receptor agonists result in a small increase in the proportion achieving $\geq 20\%$ body weight reduction (about 232 more per 1000; 95% CI 29 to 1684 more; very low certainty; 1 study, $n = 529$).
- Health-related quality of life: GLP-1 receptor agonists probably lead to a small improvement in health-related quality of life (mean difference 1.67 points higher; 95% CI 1.29 to 2.05 higher; high certainty; 2 studies, $n = 13{,}906$).

5.3 | Metabolic Dysfunction-Associated Steatotic Liver Disease and Steatohepatitis

The authors note that earlier studies commonly used the term nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), whereas updated nomenclature has shifted to metabolic dysfunction-associated steatotic liver disease (MASLD) and steatohepatitis (MASH). These conditions can be thought of as a continuum starting with fatty liver (MASLD) and progressing in a subset of individuals to include hepatic tissue inflammation, hepatocellular damage, and fibrosis. In this review, we include studies reporting outcomes for reduction in fatty liver and MASH, retaining the terminology reported in the original studies when describing their findings, while otherwise using the current terminology where appropriate. It should be noted that the GLP-1 receptor agonist semaglutide currently has FDA approval only for the treatment of MASH.

In adults with overweight or obesity and MASLD/MASH:

- Resolution of fatty liver/MASH: GLP-1 treatment may result in a large increase in resolution of fatty liver/MASH (about 323 more per 1000; 95% CI 106 to 713 more; very low certainty; 3 studies, $n = 290$).
- Body weight (kg): GLP-1 treatment probably results in a moderate reduction in body weight (mean difference 7.11 kg lower; 95% CI 8.30 to 5.80 lower; moderate certainty; 4 studies, $n = 438$).
- Body weight percentage: GLP-1 treatment probably results in a small reduction in body weight percentage (mean difference 4.80 percentage points lower; 95% CI 7.41 to 2.19 lower; low certainty; 1 study, $n = 45$).
- Weight loss $\geq 5\%$: GLP-1 treatment may result in a large increase in the proportion achieving $\geq 5\%$ weight loss (about 419 more per 1000; 95% CI 214 to 729 more; low certainty; 2 studies, $n = 390$).
- Weight loss $\geq 10\%$: GLP-1 treatment may result in a large increase in the proportion achieving $\geq 10\%$ weight loss (about 296 more per 1000; 95% CI 73 to 1063 more; very low certainty; 2 studies, $n = 390$).
- Serious adverse events: GLP-1 treatment may result in little to no effect in serious adverse events (about 41 more per 1000; 95% CI 25 fewer to 160 more; very low certainty; 3 studies, $n = 442$).
- Health-related quality of life: GLP-1 treatment may lead to a small improvement in quality of life (mean difference 2.49 points higher; 95% CI 0.62 to 4.34 higher; low certainty; 2 studies, $n = 339$).

5.4 | Osteoarthritis

In adults with overweight or obesity and osteoarthritis:

- Overall osteoarthritis symptoms (WOMAC total, 0–96): GLP-1 treatment may result in a moderate reduction of overall symptoms, with about 8 points lower on the WOMAC total score (mean difference −8.16 points; 95% CI −11.90 to −4.40; very low certainty; 2 studies, $n = 560$).
- Pain (WOMAC pain score): GLP-1 treatment probably reduces pain scores, with fewer people having a pain outcome (about 274 fewer per 1000 with an unfavorable outcome; 95% CI 128 fewer to 467 fewer per 1000; moderate certainty; 1 study, $n = 362$).
- Weight loss $\geq 5\%$: GLP-1 treatment probably results in a large increase in the proportion achieving at least 5% weight loss (about 415 more per 1000; 95% CI 231 to 670 more; moderate certainty; 2 studies, $n = 529$).
- Weight loss $\geq 10\%$: GLP-1 treatment probably results in a large increase in the proportion achieving at least 10% weight loss (about 309 more per 1000; 95% CI 32 to 1208 more; low certainty; 2 studies, $n = 529$).
- Weight loss $\geq 15\%$: GLP-1 treatment probably results in a large increase in the proportion achieving at least 15% weight loss (about 278 more per 1000; 95% CI 127 to 500 more; moderate certainty; 1 study, $n = 373$).
- Serious adverse events: GLP-1 treatment probably results in a small increase in serious adverse events, with a slight increase (about 46 more per 1000; 95% CI 18 fewer to 136 more; moderate certainty; 2 studies, $n = 560$).

5.5 | Myocardial Infarction, Stroke, or Symptomatic Peripheral Vascular Disease

In adults with overweight or obesity and established cardiovascular disease, treatment with semaglutide:

- Major adverse cardiovascular events (MACE): Probably results in a small reduction in MACE (16 fewer patients per 1000; 95% CI from 22 to 9 less; high certainty; 1 study, $n = 17{,}591$).
- Cardiovascular death: Probably results in a small reduction in cardiovascular death (4 fewer patients per 1000; 95% CI from 9 to 0 less; low certainty; 1 study, $n = 17{,}604$).
- Composite heart failure outcome: Probably results in a small reduction in heart failure events (about 7 fewer patients per 1000; 95% CI 12 fewer to 1 fewer; moderate certainty; 1 study, $n = 17{,}604$).
- All-cause mortality: Probably results in a small reduction in all-cause mortality

  (9 fewer patients per 1000; 95% CI 15 fewer to 3 fewer; moderate certainty; 1 study, $n = 17{,}604$).
- Serious adverse events: Probably results in a trivial or small reduction of serious adverse events (30 fewer patients per 1000; 95% CI 43 to 16 less; very low certainty; 1 study, $n = 17{,}604$).
- Body weight (% change): Probably results in a large percentage of weight loss, with about 9 percentage points more body weight lost than control (mean difference −8.52 percentage points; 95% CI 8.75 to 8.28 less; moderate certainty; 1 study, $n = 14{,}852$)

- Health-related quality of life (0–100 scale): Probably leads to a small improvement in health-related quality of life (mean difference 1.61 points; 95% CI from 1.23 to 1.98 more; moderate certainty; 1 study, $n = 13{,}906$).

5.6 | Type 2 Diabetes

Outcomes data for type 2 diabetes were considered for the group of obesity medications in aggregate. The panel acknowledges that drugs in the GLP-1 (+) category demonstrate superiority for glycemic control (hemoglobin A1c), MACE, and mortality.

In adults with overweight or obesity and type 2 diabetes:

- Mean weight change (kg): Obesity medications may result in a trivial reduction in body weight (mean difference 0.21 kg lower; 95% CI 0.27 to 0.14 lower; low certainty; 10 studies, $n = 4024$).
- Body weight percentage change: Obesity medications may result in a small reduction in body weight percentage (mean difference 2.67 percentage points lower; 95% CI 3.00 to 2.58 lower; low certainty; 13 studies, $n = 5322$).
- Weight loss ≥ 5%: Obesity medications probably result in a large increase in the proportion achieving ≥ 5% weight loss (about 329 more per 1000; 95% CI 237 to 439 more; moderate certainty; 9 studies, $n = 4355$).
- Weight loss ≥ 10%: Obesity medications probably result in a large increase in the proportion achieving ≥ 10% weight loss (about 208 more per 1000; 95% CI 137 to 305 more; moderate certainty; 8 studies, $n = 3991$).
- Weight loss ≥ 15%: Obesity medications probably result in a large increase in the proportion achieving ≥ 15% weight loss (about 315 more per 1000; 95% CI 127 to 726 more; moderate certainty; 2 studies, $n = 1693$).
- Mortality: Obesity medications may result in a trivial reduction in mortality events (about 0 more per 1000; 95% CI 1 fewer to 4 more; low certainty; 5 studies, $n = 2497$).
- Serious adverse events: Obesity medications may result in a small increase in serious adverse events (about 4 more per 1000; 95% CI 11 fewer to 23 more; low certainty; 8 studies, $n = 3838$).
- Health-related quality of life (physical health/functioning): Obesity medications may lead to a small improvement in physical health/functioning (mean difference 1.65 points higher; 95% CI 1.01 to 2.29 higher; low certainty; 3 studies, $n = 1947$).

Additional considerations for obesity medications for prevention and management of obesity complications can be found in online Supporting Information: Appendix 4.

6 | Recommendations

Recommendations are summarized in Table 4. As with any chronic disease management strategy, all pharmacotherapy recommendations and suggestions for the treatment of overweight and obesity are intended to be implemented alongside lifestyle/behavioral interventions to reflect the evidence base. These recommendations are not presented in a prioritized manner and are therefore not numbered. Specific recommendations for the use of obesity medications for patients with overweight or obesity should include shared decision-making that is person-centric. Important outcomes to be considered include initial weight, achieved weight with medication(s), tolerability, cost and availability, number and severity of obesity-related complications, and degree of response of the complication(s) to the obesity medication intervention.

The list of included studies in the review for each research question is available in online Supporting Information: Appendix 2.

Recommendation strength reflects the certainty of evidence and the balance of benefits and harms, not direct comparative efficacy across agents; for details on the evidence synthesis and grading process, refer to Section 2.4.

7 | Discussion

Obesity medications vary widely in terms of clinical efficacy, safety, accessibility, and economic cost. Established agents such as phentermine, orlistat, and liraglutide offer options supported by long-term clinical use, favorable safety profiles, and moderate effects on weight reduction, though tolerability issues can limit adherence; however, the current pricing of liraglutide may not represent a low-cost alternative despite its generic availability. Combination products such as phentermine-topiramate provide more substantial weight reduction benefits at moderate cost, yet access remains inconsistent due to insurance non- or restricted coverage and regulatory constraints. Similarly, the combination of bupropion/naltrexone offers moderate efficacy with an oral route of administration, though gastrointestinal and neuropsychiatric side effects can limit tolerability and adherence. In contrast, newer therapies, including GLP-1 receptor agonists such as semaglutide and the GLP-1/GIP receptor dual agonist tirzepatide, demonstrate robust efficacy with clinically meaningful weight reduction and quality-of-life improvements but are often limited in clinical care due to strong restrictions in insurance coverage and costs. These agents also show evidence for benefit for specific obesity-related conditions, including OSA, HFpEF, MASH, cardiovascular diseases, and osteoarthritis.

Despite newer, effective treatments, many clinicians remain skeptical, underscoring the need for better guidance and education on current obesity medication options. A recent qualitative study of primary care practitioners in the US found that newer obesity medications improved outcomes for many patients, but clinicians and patients faced safety concerns that included side effects, uncertainty about long-term use, and risks linked to compounded products. These issues shaped how providers prescribed these medications and how patients accessed and used them [24].

This guidance statement is the first step in improving obesity care and is intended to summarize the current highest-level evidence base, clinical expertise, and patient perspectives. A

TABLE 4 | Recommendations of pharmacotherapy for obesity.

Recommendation	Recommendation strength / Certainty of the evidence
TOS, OMA, and OAC suggest using **orlstat** in adults aged 18 years or older with overweight or obesity (conditional recommendation for the intervention; low certainty of the evidence).	Recommendation strength Conditional Certainty of the evidence ⊕⊕◯◯Low
TOS, OMA, and OAC recommend using **bupropion-naltrexone** in adults aged 18 years or older with overweight or obesity (strong recommendation for the intervention; moderate certainty of the evidence).	Recommendation strength Strong Certainty of the evidence ⊕⊕⊕◯ Moderate
TOS, OMA, and OAC suggest using **phentermine** for 3 months or more in adults aged 18 years or older with overweight or obesity (conditional recommendation for the intervention; low certainty of the evidence). Remarks: Phentermine is FDA approved for short-term use (e.g., 3 months), and long-term use is considered off-label, which may be subject to state-specific regulations.	Recommendation strength Conditional Certainty of the evidence ⊕⊕◯◯ Low
TOS, OMA, and OAC suggest using **phentermine-topiramate** in adults aged 18 years or older with overweight or obesity (conditional recommendation for the intervention; low certainty of the evidence).	Recommendation strength Conditional Certainty of the evidence ⊕⊕◯◯ Low
TOS, OMA, and OAC suggest using **liraglutide** in adults aged 18 years or older with overweight or obesity (conditional recommendation for the intervention; low certainty of the evidence).	Recommendation strength Conditional Certainty of the evidence ⊕⊕◯◯ Low
TOS, OMA, and OAC recommend using **semaglutide** in adults aged 18 years or older with overweight or obesity (strong recommendation for the intervention; moderate certainty of the evidence).	Recommendation strength Strong Certainty of the evidence ⊕⊕⊕◯ Moderate
TOS, OMA, and OAC recommend using **tirzepatide** in adults aged 18 years or older with overweight or obesity (strong recommendation for the intervention; moderate certainty of the evidence).	Recommendation strength Strong Certainty of the evidence ⊕⊕⊕◯ Moderate
TOS, OMA, and OAC recommend using **setmelanotide** in adults aged 18 years or older with monogenic obesity syndromes (e.g., risk alleles for LEPR, POMC, PCSK1, and BBS) (strong recommendation for the intervention; moderate certainty of the evidence).	Recommendation strength Strong Certainty of the evidence ⊕⊕⊕◯ Moderate
TOS, OMA, and OAC recommend **continuing obesity medications** in adults undergoing medical obesity treatment during the weight maintenance phase, compared with not continuing obesity medications (strong recommendation; moderate certainty of the evidence).	Recommendation strength Strong Certainty of the evidence ⊕⊕⊕◯ Moderate
TOS, OMA, and OAC suggest using GLP-1 receptor agonists or GLP-1/GIP receptor dual agonists in adults aged 18 years or older with **obstructive sleep apnea (OSA)** (conditional recommendation for the intervention; low certainty of the evidence). Remarks: Evidence examined included trials using liraglutide or tirzepatide; tirzepatide is FDA approved for moderate-to-severe OSA.	Recommendation strength Conditional Certainty of the evidence ⊕⊕◯◯ Low

(Continues)

TABLE 4 | (Continued)

Recommendation TOS, OMA, and OAC suggest using GLP-1 receptor agonists or GLP-1/GIP receptor dual agonists in adults aged 18 years or older with **heart failure with preserved ejection fraction (HFpEF)** (conditional recommendation for the intervention; low certainty of the evidence). Remarks: Evidence examined included trials using semaglutide or tirzepatide, in which treatment of HFpEF is considered off-label use.	Recommendation strength Conditional Certainty of the evidence ⊕⊕◯◯ Low
Recommendation TOS, OMA, and OAC suggest using GLP-1 receptor agonists or GLP-1/GIP receptor dual agonists in adults aged 18 years or older **to reduce liver fat and treat metabolic dysfunction-associated steatohepatitis (MASH)** (conditional recommendation for the intervention; low certainty of the evidence). Remarks: Semaglutide is not FDA approved for treatment of MASLD without MASH.	Recommendation strength Conditional Certainty of the evidence ⊕⊕◯◯ Low
Recommendation TOS, OMA, and OAC suggest using GLP-1 receptor agonists compared to lifestyle interventions/placebo in adults aged 18 years or older with **osteoarthritis** (conditional recommendation for the intervention; low certainty of the evidence).	Recommendation strength Conditional Certainty of the evidence ⊕⊕◯◯ Low
Recommendation TOS, OMA, and OAC suggest using semaglutide in adults aged 18 years or older with a history of myocardial infarction, stroke, or symptomatic **peripheral vascular disease** (conditional recommendation for the intervention; low certainty of the evidence).	Recommendation strength Conditional Certainty of the evidence ⊕⊕◯◯ Low
Recommendation TOS, OMA, and OAC suggest using FDA-approved obesity medications in adults aged 18 years or older with **type 2 diabetes** (conditional recommendation for the intervention; low certainty of the evidence). Remarks: Certainty of evidence and recommendation strength were notably affected by heterogeneity across drug classes and trials and do not preclude FDA approvals for certain drug classes (e.g., GLP-1 (+)) or standards of care for type 2 diabetes.	Recommendation strength Conditional Certainty of the evidence ⊕⊕◯◯ Low

second phase needs to involve guidance statement dissemination and implementation strategies that will include lower-level evidence (e.g., non-randomized studies, retrospective analysis, case studies, expert opinion). TOS, OMA, and OAC are committed to developing guidance implementation strategies and tools (e.g., clinical decision aids, education programs for health care professionals, patient education materials, policy briefs) that serve the needs of patients, clinicians, and policy makers.

When used appropriately, acceptability of obesity medications is generally high among patients and clinicians, particularly for oral agents and once-weekly injectable formulations [25, 26], but feasibility is frequently constrained by affordability and system-level barriers to chronic comprehensive obesity care [27]. In the few studies with access to adequate information, cost-effectiveness analyses indicate that, while obesity medication treatment is generally more efficient than no treatment, overall value is highly sensitive to drug pricing and availability, treatment duration, and patient subgroup [28]. As indicated here later, the economics of obesity medication coverage is rapidly evolving and has been identified as a leading study outcome for future research.

8 | Priorities for Policy

Equity remains a central concern in the implementation of obesity pharmacotherapy. Access is often restricted by inconsistent insurance coverage, high out-of-pocket costs, and additional regulatory or logistical requirements such as controlled dispensing or ongoing monitoring. Most US private health insurers limit or deny coverage for obesity medications, even though the Affordable Care Act of 2014 prohibits exclusion of pre-existing conditions, forcing many patients to pay out-of-pocket [29], including seeking drugs through compounding pharmacies. Historically, coverage for obesity medications was limited—only ~11% of marketplace plans offered any coverage in 2018. While coverage has expanded modestly since then, it remains inconsistent across payers and states. Medicare generally excludes obesity medications unless the medication has a separate FDA-approved indication such as diabetes, prior myocardial infarction or stroke, OSA, or MASH, and Medicaid coverage is inconsistent across states [30].

These barriers to medication access disproportionately exclude patients with fewer financial resources, thereby risking an increase in disparities despite the overall potential of these medications to

reduce obesity-related complications [31] and improve quality of life. Variable insurance coverage, which can frequently change based on formulary updates from payers or pharmacy benefits managers (PBMs), impedes patient care and public health efforts to fully understand the costs and benefits of long-term medical weight management. Currently, resources needed to support medical weight management are considered substantial due to obfuscated health care costs, high list prices [32], and administrative burden, with Medicare part D requiring 100% of GLP-1 receptor agonist prescriptions to undergo prior authorization [33]. A single-payer's commitment to access, such as the recently announced plans for Medicare and Medicaid to begin coveringobesity medications [34], would provide the impetus, information, and investment needed to deliver effective responses to the obesity epidemic. Such coverage expansions could also generate critical data regarding cost-effectiveness, resource requirements, and feasibility, as current evidence acquisition is hampered by these very barriers.

At the same time, the availability of non-compounded, lower-cost, and generic formulations offers opportunities to improve equity by expanding access to underserved populations. Generic medications should be priced substantially lower than branded products, perhaps via a transparent cost-plus or reference pricing model, as cost feasibility often determines whether patients choose medical treatment at all. Ensuring sustainable, affordable, and equitable access to these therapies will be essential for realizing their full public health potential.

Weight reduction represents the initial phase of obesity treatment, but sustained weight reduction is essential to preserve achieved health benefits. Maintaining weight reduction confers ongoing health advantages valued by both patients and clinicians, including reductions in cardiovascular disease risk, improvements in conditions such as HFpEF and osteoarthritis, and broader gains in appetite regulation, energy metabolism, psychosocial well-being, quality of life, and functional status. Recent international initiatives have emphasized broader, patient-centered outcomes such as quality of life, mobility, and psychosocial well-being, yet these are seldom measured in RCTs [35–37]. The evidence base is therefore limited, particularly regarding the independence of these outcomes from weight reduction, underscoring the need for longer-term and more comprehensive evaluation of obesity treatments.

9 | Priorities for Research

Despite growing evidence supporting the use of obesity medications in appropriate patients, major research gaps remain. Most trials are 4 years or less in duration, requiring extrapolation on safety, durability of weight reduction, and sustained effects beyond 4 years on quality of life, function, and mortality. Head-to-head trials comparing newer agents (e.g., semaglutide, tirzepatide) with each other and lower-cost therapies (e.g., phentermine, orlistat, bupropion-naltrexone) are few or lacking, limiting treatment selection and cost-effectiveness modeling. For rare genetic syndromes, evidence is confined to small populations and short-term outcomes, underscoring the need for larger multicenter trials and registries to assess efficacy, safety, and cost—challenges common across rare diseases.

Research addressing patient-centered and health system outcomes is also critical. Clinical trials should include quality of life, function, and treatment satisfaction alongside weight and metabolic endpoints. It is becoming increasingly apparent that quality of life for patients living with overweight and obesity extends beyond just physical and mental functioning, but also includes normalizing appetite control (what many refer to as reducing "food noise" to appropriate hunger and fullness signals that allow normal life functioning) as well as adequately dealing with internal and external weight stigma when transitioning from a higher to lower body weight.

Although exercise function was considered an important outcome for both clinicians and patients, it was not included as an outcome in the studies reviewed and therefore could not be considered by the panel. Given that exercise function, as measured by capacity for physical activity, is a key marker of health and fitness and influences other health outcomes and quality of life, the panel identified this as an important research priority. The panel emphasized that future pharmacotherapy studies for obesity management should include exercise function as a core outcome.

Future studies must enroll more diverse populations, including those with multimorbidity, lower socioeconomic status, and historically marginalized racial and ethnic groups. Robust economic evaluations inclusive of obesity complications such as HEpEF, liver disease, osteoarthritis, and OSA are needed to inform payer and policy decisions. Real world evidence is needed to examine access, or lack thereof, on health equity. Implementation research should also test strategies to improve access, manage long-term therapy, and integrate obesity medications into routine obesity care while addressing affordability and equity.

Three initially formulated PICO questions were ultimately excluded from formal recommendation development due to insufficient evidence, though each highlights important gaps and priorities for future research. First, regarding the use of intensive behavioral therapy (IBT) alongside GLP-1 (+), no direct evidence was identified to demonstrate a significant additive benefit. Nevertheless, some insurers require patients to engage in weekly IBT as a condition for obesity medication coverage, raising concerns about equity, access, and stigma in obesity care. Policies should cover lifestyle counseling (such as consultations with registered dietitians/nutritionists or exercise physiologists) along with obesity medications, rather than requiring IBT first, since the evidence for these medications comes from trials that included general lifestyle interventions with these offerings, not IBT specifically. Second, the question of whether structured physical activity interventions (exercise) provide additional benefit over self-directed activity or usual care in adults engaged in medical obesity treatment yielded only two trials (one with orlistat and one with liraglutide). These studies suggested that structured exercise may improve body composition despite no additional effect on total weight reduction; however, the evidence base is lacking to gauge efficacy. Third, for protein intake-guided nutritional interventions compared with unguided intake intended to minimize loss of lean mass relative to fat mass during obesity pharmacotherapy interventions, no direct evidence was identified despite a focused search. Together, these excluded questions emphasize the paucity of high-quality

evidence and underscore the need for future studies to inform clinical practice and policy.

10 | Conclusion

It is the hope of the three organizations supporting this guidance statement to provide updates as new evidence emerges, so that health care providers, policy makers, and patients can make informed obesity care decisions rooted in the latest science. However, even the best science and breakthrough treatments will remain ineffectual at the population level so long as access to obesity medications and other obesity treatments and supports remains elusive due to allowed insurance exclusion, high costs, inequitable and non-evidence-based barriers within approval and reimbursement pathways, obesity stigma, and a lack of education among stakeholders, patients, and prescribers alike.

Future efforts should continue advancing obesity medication options, while also implementing comprehensive and integrated obesity care pathways, reducing obesity stigma, expanding access and coverage, and updating clinical guidance to ensure equitable, outcomes-driven treatment across populations. TOS, OMA, and OAC are committed to continue developing future guidance for health care professionals that extends beyond pharmacotherapy, through collaboration and by building on existing clinical practice guidance to ensure comprehensive, evidence-informed obesity care.

Key Takeaway Clinical Messages:

- Obesity is a chronic, often progressive, disease requiring sustained and comprehensive treatment. Obesity medications are safe and effective when used long-term.
- Quality of life, management of obesity complications, and long-term weight maintenance are as important as initial weight reduction.
- Obesity care should be collaborative, individualized, accessible, and stigma-free.

Author Contributions

Methodological support and evidence synthesis were conducted by C.Á.-O, F.N., and A.M.R.-G. L.A., J.Q.P., K.B., M.-A.C., A.G., D.B.H., M.L., and J.N. voted on and finalized PICO questions and recommendations. X.R.S., B.H., and C.Á.-O. wrote the first draft and subsequent revisions. L.A., J.Q.P., K.B., M.-A.C., A.G., D.B.H., M.L., and J.N. all reviewed, edited, and approved the final submission and publication. X.R.S. and B.H. supported the guidance statement development process.

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Declaration of Artificial Intelligence (AI)

This project used the Epistemonikos SK Platform (https://www.skplatform.org/), whose AI/ML features supported search strategy development, screening prioritization, data extraction, risk-of-bias assessment, and evidence synthesis. All outputs were reviewed by the Epistemonikos methods team for accuracy. Other than the aforementioned features, no AI tools were used for data analysis, interpretation, or content generation. The authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Conflicts of Interest

L.A. reports consulting fees from Novo Nordisk, Eli Lilly, Amgen; payment or honoraria from Eli Lilly, OMA, TOS, ASMBS, ACLM; meetings/travel support from OMA, ASMBS, TOS, ACLM; participation on advisory board for Novo Nordisk; leadership or fiduciary role for OMA; stock/stock options from Enara Health; advisor to AMGA Obesity QuIC Program. J.Q.P. reports grants from NIH; consulting fees from Novo Nordisk, Regeneron, Boehringer Ingelheim, Zealand Pharmaceuticals; payment or honoraria from TOS; meetings/travel support from TOS; participation on advisory board for NIH Metformin in Alzheimer Dementia Prevention. K.B. reports consulting fees from Novo Nordisk, Boehringer Ingelheim, Eli Lilly, Currax; payment or honoraria from Vivus, Abbott, Eli Lilly, Currax; participation on advisory board for Novo Nordisk, Boehringer Ingelheim, Vivus; leadership or fiduciary role for OMA, Illinois Obesity Society, PAs in Obesity Medicine; ownership, Gaining Health. M.-A.C. reports grants or contracts from NIH, Blue Cross Blue Shield of South Carolina Foundation, American College of Diabetology, Novartis, Amgen, Ionis, Kaneka, Cleerly; consulting fees from Astra Zeneca, Enveda, Keros, Rivus, Wave, Zyversa; participation on advisory boards for Biophytis, Eli Lilly, Novo Nordisk; payment or honoraria from TOS, Endocrine Society, Translational Medicine Academy, AACE, Medical Education Resources, MCE Conferences, Continuing Education Company; meetings/travel support from TOS, the Endocrine Society, AACE; participation on data safety monitoring board for Advarra; leadership or fiduciary role with TOS. A.G. reports consulting fees from Epitomee; payment or honoraria from Novo Nordisk, Acella, Currax, Lilly; participation on advisory board for Novo Nordisk, Acella, Currax, Lilly, Boehringer Ingelheim, WW; leadership or fiduciary role with TOS. D.B.H. reports consulting fees from Amgen, Zealand, AstraZeneca, Lilly, Novo Nordisk, Boehringer Ingelheim; payment or honoraria from TOS, OMA, Haymarket CME, Harvard Blackburn Course; meetings/travel support from TOS, OMA, Haymarket CME, Lilly, Novo Nordisk, World Obesity Federation, ADA; participation on advisory board for Novo Nordisk, Lilly, Amgen, AstraZeneca, Zealand; medical writing support from Lilly, Novo Nordisk. M.L. reports participation on advisory boards for Novo Nordisk, Eli Lilly, Boehringer Ingelheim. J.N. reports employment from OAC. C.Á.-O. reports employment with Epistemonikos, which received remuneration for the methodology work, and payment or honoraria from the School of Dentistry, Clínica Alemana–Universidad del Desarrollo. F.N. reports employment with Epistemonikos, which received remuneration for the methodology work. A.M.R.-G. reports employment with Epistemonikos, which received remuneration for the methodology work. B.H. reports consulting fees from TOS, OMA related to the guidance statement; consulting fees from European Association for the Study of Obesity, European Council for People Living with Obesity, Sociedad Mexicana de Nutrición y Endocrinología, Obesity Canada, International Federation for the Surgery of Obesity; meetings/travel support from Bias 180, European Association for the Study of Obesity; leadership or fiduciary role with Bias180, Replica

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Data Availability Statement

The data that supports the findings of this study are available in the online Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix 1:** Understanding GRADE Methodology. **Appendix 2:** Included Studies Summaries: Obesity Medications and Complications of Obesity. **Appendix 3:** Additional Considerations for Obesity Medications. **Appendix 4:** Additional Considerations for Obesity Medications in Prevention and Management of Obesity Complications. **Data S1:** Supplementary Data.