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WEIGHT MANAGEMENT MEDICATIONS APPROVED FOR TREATING OVERWEIGHT AND OBESITY

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ABBREVIATIONS

AACE	American Association of Clinical Endocrinology
AAP	American Academy of Pediatrics
ACE	American College of Endocrinology
ADA	American Diabetes Association
AEs	adverse events
AGA	American Gastroenterological Association
BMI	body mass index
CNS	central nervous system
CV	cardiovascular
CYP	cytochrome P450 enzyme
DDP-4	dipeptidyl peptidase-4
ER	extended release
ES	Endocrine Society
FDA	US Food and Drug Administration
GI	gastrointestinal
GLP-1	glucagon-like peptide 1
HbA1c	glycated hemoglobin
IR	Immediate release
MACE	major adverse cardiovascular events
MEN 2	Multiple Endocrine Neoplasia Syndrome Type 2
MD	mean difference
MTC	medullary thyroid carcinoma
OSA	obstructive sleep apnea
PA	prior authorization
RA	receptor agonist
RCT	randomized controlled trial
SubQ	subcutaneous
T2DM	type 2 diabetes mellitus
TBWL	total body weight loss
VHA/DoD	US Veterans Health Administration and Department of Defense
WC	waist circumference
WRCs	weight-related complications
WMPs	weight-management pharmacotherapies

1.0 INTRODUCTION

Obesity has long been considered a chronic medical condition by a number of health-oriented organizations (eg, the National Institutes of Health, American Medical Association, American Association of Clinical Epidemiology, Obesity Society, Obesity Medicine Association, American College of Endocrinology, American Association of Clinical Endocrinologists, World Health Organization, European Medicines Agency).[1-8] In the US, obesity has increased in prevalence over the past couple decades, recently estimated to affect 42% of US adults and 20% of the pediatric population.[9] In parallel with this trend, weight-related complications (WRCs) have also increased in prevalence,[10-12] stemming from the prothrombotic, pro-inflammatory, angiogenic, diabetogenic, and biomechanical effects of excess adiposity.[13-16]

To reduce the risk of morbidity and mortality associated with excess adiposity/WRCs, clinical guidelines have long recommended lifestyle therapy/modification (with dietary, physical activity, and behavior modification approaches) for overweight/obesity in both adults and children. However many patients are unable to engage in such programs or are unable to achieve or sustain meaningful weight reduction and/or maintenance goals with lifestyle intervention alone.[10,17] With the growing number of approved weight-management pharmacotherapies (WMPs) that have become available over the years, updated guidelines offer evidence-based recommendations to guide therapy decision-making.

This report reviews WMPs and guideline recommendations for WMP use in the management of overweight/obesity. Two groups of US Food and Drug Administration (FDA)-approved WMPs reviewed in this report are (1) *early-approved* WMPs, approved prior to 1980 for short-term weight management (ie, benzphetamine, diethylpropion, phendimetrazine, phentermine); and (2) *newer* WMPs, approved more recently than the previous group and indicated for long-term weight management (ie, liraglutide 3.0 mg, semaglutide 2.4 mg, orlistat, naloxone/bupropion ER, and phentermine/topiramate ER). In general, these products are approved for adults with obesity (ie, initial BMI ≥30 kg/m^2), or overweight (ie, BMI ≥27 kg/m^2) in the presence of at least one WRC (eg, managed hypertension, type 2 diabetes [T2DM], or dyslipidemia). Several agents also have pediatric-specific indications for weight management (ie, liraglutide, semaglutide, and phentermine/topiramate ER), while others have indications unspecified to age but are recommended to be avoided in patients below 12 years of age (as with orlistat) or below 17 years of age (as with benzphetamine, diethylpropion, phendimetrazine, and phentermine). Regardless of the group, all approved WMPs are indicated as adjunctive therapy to lifestyle modification (eg, increased physical activity and reduced calorie diet).

In this report, the term, weight-management pharmacotherapies (WMPs), will refer specifically to the WMP formulations with active ingredients listed in **Table 1**. The following topics are beyond the scope of this report: setmelanotide, approved for patients 6 years of age and older with certain rare genetic disorders of obesity,[18] and medical devices for the management of obesity (eg, Plenity). Additionally, this review does not include amphetamine sulfate (Evekeo), which has an indication for *short-term* treatment of obesity but is a schedule II substance, immediate-release formulation with considerable risk of abuse.[19] Since current US guidelines do not include this particular product as a recommended option for weight management and long-term evidence for its use is not established, we view its risks to outweigh potential benefits for obesity given the many other options now on the market, particularly with long-term evidence and/or lower or no risk of abuse.

Table 1. Active Ingredients FDA-approved for Weight Management

Agents Approved for Short-term Treatment		Agents Approved for Long-term Treatment (>12 weeks)	
benzphetamine	Approved prior to 1980	liraglutide	Approved 2014
diethylpropion		semaglutide	2021
phendimetrazine		naltrexone/bupropion	2014
phentermine		orlistat	1999
		phentermine/topiramate	2012

2.0 METHODS

The following websites were searched (during January 2023) for recent US clinical guidelines, from 2016 onward, addressing pharmacotherapy for obesity:

- American Gastroenterological Association (AGA): https://gastro.org/clinical-guidance/
- American Academy of Pediatrics (AAP): https://publications.aap.org/collection/523/Clinical-Practice-Guidelines
- The American Diabetes Association (ADA) Standards of Care: (https://professional.diabetes.org/content-page/practice-guidelines-resources/)
- American Thoracic Society: https://www.thoracic.org/statements/
- American College of Cardiology: www.acc.org/guidelines
- American Association of Clinical Endocrinology (AACE): https://pro.aace.com/disease-state-resources/diabetes/guidelines
- American Heart Association: https://professional.heart.org/en/guidelines-and-statements/guidelines-and-statements-search
- The Trip database: https://www.tripdatabase.com/Home

A supplemental search for recent US guidelines (2017 through March 2023) was performed in Ovid Medline using key word phrases* for guidelines and obesity. Other information included in the report is from references cited by guidelines, from reviews identified during the literature search for the 2023 Utah Medicaid Weight Management Pharmacotherapy P&T report, or from ClinicalTrials.gov.

Professional prescribing information (ie, package inserts) was obtained from the drug sponsor's website dedicated to the product or from DAILYMED (https://dailymed.nlm.nih.gov/) for products without a dedicated website.

* Search string executed: ((obes* or weight) and (treatment* or management* or pharmaco* or therap*)).ti. and (position statement* or policy statement* or practice parameter* or best practice* or guideline* or CPG or CPGs or standards* or consensus* or recommendat* or (care adj2 (standard* or pathway* or map* or plan*)) or (algorithm* adj2 (pharmacotherap* or therap* or treatment* or intervention*))).ti,pt.

3.0 DISEASE OVERVIEW

Overweight and obesity are terms used to describe high weights for a given height, which are generally associated with elevated risk of adiposopathy or WRCs. Obesity emerges and is often perpetuated by an interplay of factors beyond personal choice, including genetic, psychologic, socioeconomic, and environmental factors.[20] Obesity is more common with lower economic status, related to disproportionate socioeconomic challenges and insufficient resources.[†20] Adipose tissue is recognized as an endocrine organ because it excretes hormones, some that contribute to the development/worsening of weight-related medical diseases (eg, tumor necrosis factor α, interleukin-6, plasminogen activator inhibitor 1, vascular endothelial growth factor).[13,21,22] Moreover, pathophysiologic mechanisms have been observed to counteract weight loss (eg, changes in leptin, ghrelin, and other hormones that increase appetite)[4,21,23]—a reason why patients often regain weight after stopping weight-loss interventions. Obesity is considered a chronic disease that may require lifelong management,[24] as "The natural course of obesity across the lifespan is characterized by responses to treatment and relapse when treatment ends" (page 47).[20]

In adults, overweight and obesity (ie, excess adiposity) increases the risk of developing many serious chronic diseases such as heart disease, stroke, T2DM, dyslipidemia, nonalcoholic steatohepatitis, obstructive sleep apnea (OSA), osteoarthritis/degenerative joint disease, gastroesophageal reflux disease, and a number of cancers (eg, colorectal cancer, breast cancer[25]).[10,11,24] Along with the increased incidence of obesity over the past couple decades, the incidence of WRCs has also increased.[10,11,26] According to the American Thoracic Society (ATS), obesity contributes to dramatic changes in lung health and the development of disease;[27] obesity is a major risk factor for the development of asthma, acute respiratory distress syndrome (ARDS), pulmonary hypertension, and sleep-disordered breathing. Obesity with metabolic syndrome is associated with decreased lung capacity reserve and chronic low-grade systemic inflammation that is thought to drive impaired pulmonary immune response and complications from infection.[27,28] For instance, persons with obesity have higher risk of severe illness from COVID infection.[28]

The prevalence of obesity in US adults is estimated to be 41.9%, based on data from 2017–2020, and nearly 10% of US adults have severe obesity[‡].[9] In US children and adolescents (age 2-19), obesity is estimated to affect 19.7% (14.7 million), based on data from 2017–2020.[9,29] The pediatric population with obesity is also at increased risk for serious short- and long-term health conditions, including cardiovascular disease, hypertension, dyslipidemia, T2DM, nonalcoholic fatty liver disease (NAFLD), and depression.[20,30-33]

Guidelines recommend assessing patients (pediatric and adult) with obesity or overweight for WRCs.[4,20] Rather than avoiding discussions regarding the health risks of obesity, and thus perpetuating barriers to evidence-based care, the American Academy of Pediatrics (AAP) highlights approaches to facilitate a

[†] Refer to the 2023 American Pediatric Academy guideline on Obesity treatment for information further information regarding risk factors and social determinants of health that can influence the development of obesity (eg, obesogenic environment, under-resourced conditions, neighborhood/community influences, home behaviors, psychosocial stressors and adversity, genetic, and comorbid conditions).

[‡] Obesity is defined as a body mass index (BMI) of 30 kg/m^2 or greater, and severe obesity defined as a BMI of 40kg/m^2 or greater.

more comfortable conversation about weight such as asking permission to discuss weight and health implications, avoiding blame, and using non-labeling language and words perceived as more neutral by parents/patient.[20]

3.1 Adiposity Assessment

Clinical guidelines recommend screening for obesity/overweight (ie, excess adiposity) by measuring body mass index[§] (BMI) while taking into account other clinical factors (eg, age, gender, ethnicity, fluid status, musculature composition), as BMI is the most practical approach for adiposity screening on a population level.[4,34] BMI classifications for overweight, obesity, and severe obesity for adults (age ≥ 20 years) are as follows[3,35**]:

- overweight (BMI of 25.0 – 29.9 kg/m^2)
- obesity (BMI of ≥30.0 kg/m^2)
    - severe obesity (BMI≥40 kg/m^2)

The 2016 American Association of Clinical Endocrinology/American College of Endocrinology (AACE/ACE) guideline recommended that adiposity risk assessment should include measuring waist circumference (WC) in patients with a BMI <35 kg/m^2.[4] The guideline describes that "In many populations, a waist circumference cutoff point of ≥94 cm in men and ≥80 cm in women should be considered at risk and consistent with abdominal obesity; in the United States (US) and Canada, cutoff points that can be used to indicate increased risk are ≥102 cm for men and ≥88 cm for women (Grade A; BEL 2, upgraded due to high relevance)" (page 13).[4] The 2020 US Veterans Health Administration and Department of Defense (VHA/DoD) guideline recommends using the latter threshold of ≥88 cm [≥35 in] for women and ≥102 cm [≥40 in] for men, since these are associated with increased cardiometabolic risk.[24] Other measures such as waist-to-hip ratio may also be useful in assessing abdominal obesity, especially among those with smaller body frames.[24] Although there are other methods to estimate adiposity that can be incorporated if accessible to the provider/patient (eg, skin-fold caliper measurement, hydrodensitometry, dual-energy X-ray absorptiometry, magnetic resonance imaging, and bioelectrical impedance), most of these are not readily available or not practiced in clinical settings and may be of limited clinical utility due to non-validated cutoff points.[4,34]

The assessment of BMI in children is interpreted using age- and sex-specific percentiles. According to the American Academy of Pediatrics (AAP) guideline for the management of obesity, childhood overweight and obesity definitions (for ages 2 to 19 years) are determined according to the Centers for Disease Control and Prevention (CDC) growth charts: overweight and obesity are BMIs of above the 85th and 95th percentiles for age and sex, respectively. In older adolescents, the adult cutoff for obesity (BMI≥30 kg/m^2) may be used.[20] Severe obesity in children is a BMI ≥120% above the 95th percentile (ie, approximately the 99th percentile), or a BMI ≥35 kg/m^2, whichever is lower based on age and sex.[20] Slightly different cutoff points may be used by other organizations.

To further determine the possible health burden of elevated BMI in an individual, other weight-related diseases and markers of disease progression should be assessed.[4,20]

[§] BMI = weight (kg)/[height (m) squared]

[**] Other BMI categories may be considered depending on race, ethnicity or menopausal status. Among some Asian populations, a BMI of 23–27.5 kg/m^2 may be classified as overweight and ≥27.5 kg/m^2, as obese.

3.1.1 Weight-related Diseases or Complications

The AACE/ACE 2016 guideline recommends that all patients with overweight or obesity should be screened/evaluated regularly for weight-related complications (WRCs) caused or exacerbated by excess adiposity, as follows[4]:

- Prediabetes, T2DM, and metabolic syndrome by assessing WC, fasting glucose, hemoglobin A1c (HbA1c), blood pressure, and lipid panel
- Dyslipidemia
- Hypertension/prehypertension
- Cardiovascular (CV) disease and risk of CV mortality
- Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis
- Obstructive sleep apnea
- Asthma/reactive airway disease
- Osteoarthritis
- Gastroesophageal reflux disease
- Depression
- Urinary stress incontinence
- Polycystic ovary syndrome (for premenopausal females)
- Female infertility or male hypogonadism

The guideline recommended that patients with either a) excess adiposity (ie, BMI ≥25kg/m^2; or BMI ≥23kg/m^2 for certain ethnicities [South Asian, Southeast Asian, and East Asian adults]), and/or b) weight-related disease or complications to be considered as candidates for weight-management interventions.[4]

Performing age-appropriate screening for WRCs (eg, dyslipidemia, diabetes, hyperglycemia, hypertension, nonalcoholic fatty liver disease) in pediatric patients with overweight or obesity is also recommended by the AAP.[20] Children with early-onset (before age 5) severe obesity should be screened for genetic causes of obesity, despite genetic obesity syndromes being relatively rare, representing fewer than 10% of severe pediatric obesity cases.[36]

3.1.2 Disease Severity

The ACCE/ACE 2016 guideline stages the severity of the patient's condition according to BMI ***and*** whether WRCs are present, as well as the severity of the WRC.[4]

- **Overweight Stage 0**: *No WRCs present* but with overweight (ie, BMI 25.0-29.9, or 23.0-24.9 in certain ethnic groups)
- **Obesity Stage 0**: *No WRCs present* but with obesity (ie, BMI ≥30.0, or ≥25.0 in certain ethnic groups)
- **Obesity Stage 1**: One or more mild to moderate WRCs with BMI ≥25.0 (or ≥23.0 in certain ethnic groups)
- **Obesity Stage 2**: At least one severe WRC with BMI ≥25.0 (or ≥23.0 in certain ethnic groups)

4.0 PHARMACOTHERAPIES FOR OBESITY MANAGEMENT

Products that were approved prior to 1980 (benzphetamine, diethylpropion, phendimetrazine, phentermine) were FDA-approved for short-term weight management; others, approved more recently, are indicated for long-term weight management (liraglutide 3.0 mg, semaglutide 2.4 mg, orlistat, naloxone/bupropion ER, and phentermine/topiramate ER).[37-50] Regardless of the agent, WMPs are approved *as adjunctive therapy* to lifestyle modification (eg, dietary changes [ie, reduced caloric intake] and increased physical activity).[37-50] The glucagon-like peptide 1 (GLP-1) receptor agonists (RAs), (liraglutide and semaglutide) are subcutaneously administered, whereas others are available as oral dosage forms. All products are approved for adults with initial BMI ≥30 kg/m^2 (obesity), and the majority are also approved for adults with initial BMI ≥27 kg/m^2 (overweight) in the presence of at least one WRC (eg, hypertension, T2DM, or dyslipidemia). A handful of products have specific indications for the pediatric population ≥12 years of age (ie, liraglutide 3.0 mg, semaglutide 2.4 mg, phentermine/topiramate ER). The package insert for liraglutide, however, points out that the Saxenda (liraglutide 2.4 to 3.0 mg) dosage form has not been studied in children with T2DM (although Victoza [liraglutide] 1.8 mg has). Other agents have an indication that does not specify an age group, yet recommends against use below a certain age in other parts of the package insert (eg, recommended against use in patients <12 years of age for orlistat, and <17 years of age for benzphetamine, diethylpropion, phendimetrazine, and phentermine).[37-50] Naltrexone/bupropion ER is specifically indicated in adults only.[44]

The GLP-1 RAs are administered subcutaneously on a daily (liraglutide) or weekly (semaglutide) basis, while other OMs are orally administered on a daily to thrice daily basis. The GLP-1 RAs are gradually up-titrated to the maintenance dose to minimize GI adverse effects.

- Liraglutide is started at 0.6 mg daily and the dose increased every 7 days as tolerated until reaching the maintenance dose of 3.0 mg daily after 4 to 5 weeks.[45]
- Semaglutide is started at 0.25 mg once weekly and the dose increased every 4 weeks as tolerated, until reaching the maintenance dose of 2.4 mg once weekly after 16 to 20 weeks.[46]
- Naltrexone/bupropion ER is titrated to the maintenance dose over at least 4 weeks.[44]
- Phentermine/topiramate ER is titrated over 4 to 16 weeks (depending on the final maintenance dose): it is initiated at 3.75 mg/23 mg once daily for 14 days, then increased to 7.5 mg/46 mg once daily. If needed after 12 weeks of 7.5 mg/46 mg once daily, the dose may be increased to 11.25mg/69 mg once daily for 14 days, followed by an increase to 15 mg/92 mg once daily.[40]

Dose titration is not required for the products indicated for short-term use or orlistat but may be considered for benzphetamine.[51]

Table 2 summarizes available dosage forms, FDA-approved indications, and dosing information for weight management products.

Table 2. Weight Management Agents, Approved Indications and Usual Dosage

Active Ingredient Formulations	Labeled Indication	Route & Usual Maintenance Dose	Titration at initiation
Agents Approved for Short-Term Treatment (<12 weeks)			
Benzphetamine hydrochloride[38] **Generic** Tablet: 50 mg	Indicated for short-term (a few weeks) treatment (as an adjunct to caloric restriction) in the management of exogenous obesity for patients with an initial BMI ≥30 kg/m^2, and who have not responded to diet and/or exercise alone; should be used as monotherapy only	**Oral:** 25 mg to 50 mg **daily to TID**, avoiding late afternoon ingestion *Pediatrics*: not recommended for pediatric patients <17 years of age since safety/efficacy is not established in this population *RI/HI:* No dose-adjustment mentioned	Initiate with daily dosing and increase to TID depending on patient response
Diethylpropion[37,47] **Generics** Tablet: 25 mg ER Tablet (24 hour):75 mg	Indicated for short-term (a few weeks) treatment (as an adjunct to caloric restriction) in the management of exogenous obesity for patients with an initial BMI ≥30kg/m^2, and who have not responded to diet and/or exercise alone; should be used as monotherapy only	**Oral** • **IR**: 25 mg **TID**, before meals and in midevening to overcome night hunger, if desired • **ER**: 75 mg **daily** *Pediatrics*: not recommended for pediatric patients <17 years of age since safety/efficacy is not established in this population *RI/HI*: No dose adjustments included. Accumulation may occur with renal impairment.	None
Phendimetrazine tartrate[39,50] **Generics** Tablet: 35 mg ER capsule: 105 mg	Both IR and ER formulations are indicated for short-term treatment (a few weeks) of exogenous obesity, as an adjunct to caloric restriction, in patients who have not responded to diet/exercise alone. • The IR formulation is indicated for patients with an initial BMI ≥30kg/m^2; for use as monotherapy only • The ER formulation is indicated for patients with an initial BMI ≥30 kg/m^2, or ≥27 kg/m^2	**Oral** • **IR**: 35 mg **BID to TID** before meals; use the lowest effective dosage for adequate response • **ER**: 105 mg daily before breakfast *Pediatrics*: not recommended for pediatric patients <17 years of age since safety/efficacy is not established in this population *RI/HI:* No dose adjustments included. Accumulation may occur with renal impairment.	None

Abbreviations: BID; twice daily; BMI, body mass index: ER, extended release; ESRD, end-stage renal disease; GI, gastrointestinal; HI, hepatic impairment; HTN, hypertension; IR, immediate release; RI, renal impairment; SubQ, subcutaneous; T2DM, type 2 diabetes mellitus; TID, three times daily

Table 2. Weight Management Agents, Approved Indications and Usual Dosage

	in the presence of other weight-related risk factors; for use as monotherapy only		
Phentermine hydrochloride[42,43,48,49] **Adipex-P** Capsules and tablets: 37.5 mg **Generics** Capsules: 15 mg, 30 mg, 37.5 mg Tablet: 37.5 mg **Lomaira** Oral Tablet: 8mg	Indicated for short-term (a few weeks) treatment (as an adjunct to exercise, behavioral modification, and caloric restriction) in the management of exogenous obesity for patients with an initial BMI ≥30 kg/m^2, or ≥27 kg/m^2 in the presence of other risk factors (eg, controlled hypertension, diabetes, hyperlipidemia); should be used as monotherapy only	**Oral:** 8 mg **TID**; or 15 mg to 37.5 mg **daily** Use the lowest effective dose for adequate response. *Pediatrics*: not recommended in patients <17 years of age (Adipex and generics). Not recommended for chronic obesity in pediatric patients (Lomaira). Safety and effectiveness in pediatric patients have not been established (all products) *RI/HI:* No dose-adjustment mentioned	None
Agents Approved for Long-Term Treatment			
Orlistat[41] **Xenical** Capsule: 120 mg **Generic** Capsule: 120 mg	Indicated for a. obesity management (ie, weight loss and weight maintenance) as adjunct to a reduced-calorie diet b. to reduce the risk for weight regain after prior weight loss Intended for patients with BMI ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of other risk factors (eg, HTN, diabetes, dyslipidemia)	**Oral:** 120 mg **TID** *Pediatrics*: Safety and effectiveness in pediatric patients <12 years of age have not been established *RI/HI:* No dose-adjustment mentioned	None
Liraglutide[45] **Saxenda** Pre-filled pen: 6 mg/mL (3 mL total)	Indicated for chronic weight management, as an adjunct to a reduced-calorie diet and increased physical activity, for the following patients: • **Adults** with initial BMI ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of at least one weight-	**SubQ**: 3 mg **daily** for adults; 2.4 mg to 3 mg daily for pediatric patients Evaluate response in adults 16 weeks after initiation and in pediatric patients 12 weeks after initiation; discontinue the medication if baseline body weight has not reduced by at least 4% in	Titrate over 5 weeks from 0.6 to 3 mg daily dose to minimize GI side effects; may delay dose escalation for

Abbreviations: BID; twice daily; BMI, body mass index: ER, extended release; ESRD, end-stage renal disease; GI, gastrointestinal; HI, hepatic impairment; HTN, hypertension; IR, immediate release; RI, renal impairment; SubQ, subcutaneous; T2DM, type 2 diabetes mellitus; TID, three times daily

Table 2. Weight Management Agents, Approved Indications and Usual Dosage

	related comorbid condition (eg, HTN, T2DM, or dyslipidemia) • **Pediatric patients ≥ 12 years** of age with body weight above 60 kg and initial BMI corresponding to ≥ 30 kg/m^2 for adults by international cut-offs	adults, or at least 1% in pediatric patients. Discontinue medication if the adult patient cannot tolerate the 3 mg dose or if the pediatric patient cannot tolerate at least 2.4 mg dose. *RI/HI:* No dosage adjustment mentioned. There is limited treatment experience with mild to severe RI or HI; administer with caution.	about 1 week if needed
Semaglutide[46] **Wegovy** Pre-filled, single-dose pens: 0.25 mg/0.5 mL 0.5 mg/0.5 mL 1 mg/0.5 mL 1.7 mg/0.75 mL 2.4 mg/0.75 mL	Indicated for chronic weight management, as an adjunct to a reduced-calorie diet and increased physical activity, for the following patients: • **Adults** with initial BMI ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of at least one weight-related comorbid condition (eg, HTN, T2DM, or dyslipidemia) • **Pediatric patients ≥ 12 years** of age with initial BMI at the 95th percentile or greater for age and sex	**SubQ**: 2.4 mg **once weekly** for adults; 1.7 mg to 2.4 mg once weekly for pediatric patients If 2.4 mg/week is not tolerated, decrease to 1.7 mg/week for 4 weeks, then escalate after 4 weeks; discontinue if the adult patient cannot tolerate the 2.4 mg dosage, or if the pediatric patient cannot tolerate the 1.7 mg dosage. *RI/HI:* No dosage adjustment recommended.	Titrate over 17 weeks from 0.25 to 2.4 mg weekly dose. If patient dose not tolerate dose, may delay dose escalation for 4 weeks, or may temporarily decrease the dosage for 4 weeks.
Naltrexone/ bupropion ER[44] **Contrave** ER tablet: 8 mg/90 mg	Indicated for chronic weight management, as an adjunct to a reduced-calorie diet and increased physical activity, for the following patients: • **Adults** with initial BMI ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of at least one weight-related comorbid condition (eg, HTN, T2DM, or dyslipidemia)	**Oral**, adults: 16 mg/180 mg **BID** Evaluate response after 12 weeks on the maintenance dosage; discontinue if at least 5% of baseline body weight loss has not been achieved. *Pediatrics*: Safety and effectiveness in pediatric patients have not been established *RI/HI:* Reduce dose for moderate to severe RI or moderate HI (max 2 tablets daily). Not recommended for ESRD or severe HI. CYP2B6 inhibitors: reduce dose (max 2 tablets daily)	Start with 1 tablet daily; titrate to target dose (2 tablets BID) with weekly adjustments over 4 weeks

Abbreviations: BID; twice daily; BMI, body mass index: ER, extended release; ESRD, end-stage renal disease; GI, gastrointestinal; HI, hepatic impairment; HTN, hypertension; IR, immediate release; RI, renal impairment; SubQ, subcutaneous; T2DM, type 2 diabetes mellitus; TID, three times daily

Table 2. Weight Management Agents, Approved Indications and Usual Dosage

Phentermine/ topiramate ER[40] **Qsymia** ER capsules: 3.75 mg/23 mg 7.5 mg/46 mg 11.25 mg/69 mg 15 mg/92 mg	Indicated for chronic weight management, as an adjunct to a reduced-calorie diet and increased physical activity, for the following patients: • **Adults** with initial BMI ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of at least one weight-related comorbid condition (eg, HTN, T2DM, or dyslipidemia) • **Pediatric patients ≥12 years** of age with initial BMI at the 95th percentile or greater for age and sex	**Oral**, adult and pediatric: 7.5 mg/46 mg to 15 mg/92 mg **daily** in the morning. Consider a lower dose for pediatrics if rate of weight loss exceeds 2 pounds/week. If after 12 weeks on the max dose of 15 mg/92 mg, there is not a loss for adults of 5% body weight or 5% BMI for pediatric patients, taper off the medication *RI/HI:* Reduce dose for moderate to severe RI or moderate HI (max 7.5/46 mg daily). Avoid use for ESRD on dialysis or severe HI.	Start 3.75/23mg daily and escalate after 14 days to 7.5/46 mg daily Evaluate response after 12 weeks. Escalate dose to 15/92 mg over 14 week titration if adult patient has not lost at least 3% of baseline body weight or if pediatric patient has not lost at least 3% of baseline BMI

Abbreviations: BID; twice daily; BMI, body mass index: ER, extended release; ESRD, end-stage renal disease; GI, gastrointestinal; HI, hepatic impairment; HTN, hypertension; IR, immediate release; RI, renal impairment; SubQ, subcutaneous; T2DM, type 2 diabetes mellitus; TID, three times daily

4.1 Mechanism of Action

The four early-approved WMPs are pharmacologically classified as sympathomimetic anorexiants (benzphetamine, diethylpropion, phendimetrazine, and phentermine). The 5 newer WMPs have a range of pharmacological mechanisms as summarized in following bullets. With the exception of orlistat, which reduces intestinal fat absorption, the WMPs have actions at the central nervous system (CNS) that enhance satiety and/or decrease hunger, leading to reduced caloric intake.[4,10,52]

- Lipase inhibitor: orlistat
  - Orlistat reduces intestinal fat absorption by inhibiting the ability of lipase to hydrolyze dietary fat in the stomach lumen and small intestine. This prevents the breakdown of triglycerides into an absorbable form resulting in reduced caloric intake.[41]
- GLP-1 receptor agonists: liraglutide, semaglutide
  - GLP-1 RAs are thought to regulate (ie, decrease) appetite via GLP-1 receptors in the brain. GLP-1 RAs also slow gastric emptying.[53] Ultimately, GLP-1 RA therapy decreases food/caloric intake and body weight. In a glucose-dependent manner, GLP-1 RAs increase insulin secretion and decrease inappropriate glucagon secretion, thus, are also effective for treating T2DM.[45] Moreover, in patients with T2DM, liraglutide and semaglutide have proven cardiovascular protective effects (eg, decrease major adverse cardiovascular events [MACE] outcomes).[54] Preliminary evidence (eg, in vitro studies and preclinical models) and exploratory analysis from clinical trials suggest GLP-1RAs have anti-inflammatory properties.[55,56]
  - Due to the dose-dependent effect on weight loss, the approved dose (subcutaneous) is larger for the weight management formulations of liraglutide (Saxenda) and semaglutide (Wegovy) compared to the T2DM formulations (Victoza and Ozempic), respectively.
- Anorexiant, CNS stimulant, sympathomimetic amines: benzphetamine, diethylpropion, phendimetrazine, phentermine
  - The exact mechanism of action that leads to weight loss with sympathomimetic amines is unclear, but it is thought to involve the elevation of norepinephrine in the CNS.[10] These agents have pharmacologic activities similar to amphetamine and are commonly referred to as “anorectics” or “anorexigenics,” although it is not established that their efficacy is driven by reducing hunger.[42,43,47,49-51,57-59]
- Anorexiant, carbonic anhydrase inhibitor, antiseizure agent: topiramate
  - The exact mechanism of action of topiramate for weight management is unknown, but appetite suppression and enhanced satiety observed with topiramate treatment may be mediated by modulating gamma-aminobutyric acid receptors, inhibition of AMPA/kainite excitatory glutamate receptors, and/or inhibition of carbonic anhydrase in the CNS.[40] Topiramate monotherapy is also approved to treat seizure disorders and prevent migraine headaches.[10]
- Anorexiant, dopamine/norepinephrine-reuptake inhibitor, antidepressant: bupropion; and opioid receptor antagonist: naltrexone
  - Naltrexone/bupropion is thought to decrease appetite by acting on the hypothalamus (appetite regulatory center) and the mesolimbic dopamine circuit (reward system) the brain.[44] Naltrexone may inhibit beta-endorphin auto-inhibitory activity at anorexigenic neurons in the hypothalamus; bupropion is thought to weakly modulate the anorexigenic neurons, but is augmented with naltrexone activity.[10] At higher doses than the dose used with the naltrexone/bupropion ER

product, bupropion monotherapy is approved to treat depression and seasonal affective disorders, and as an aid for smoking cessation.[10]

5.0 GUIDELINE RECOMMENDATIONS FOR PHARMACOTHERPAY

Goals of weight-management interventions are to prevent (or slow the progression) or improve WRCs through maintained weight reduction.[4,10,60] The American Heart Association (AHA) and American College of Cardiology (ACC) recommend weight loss to lessen ASCVD risk in persons with overweight or obesity.[10,11,20,34] The rationale for including *'adiposcentric treatment'* is to target the major contributor of WRC development and persistence, rather than treating the WRC symptoms alone.[61] Although evidence for the long-term effect of weight management pharmacotherapies on important weight-associated outcomes (eg, incidence of cardiovascular disease, nonalcoholic fatty liver disease, mortality, cancer) is still early in development (eg, based on observational evidence, or limited to certain populations or T2DM dosage forms), several RCTs are active or planned.[10] For example, phase 3 studies for semaglutide 2.4 mg are ongoing for WRC outcomes related to osteoarthritis, non-alcoholic fatty liver disease, prediabetes, heart failure, and chronic kidney disease (NCT05064735, NCT04822181, NCT05040971, NCT04916470, NCT03819153).[62] Additionally, we are aware of a published study for liraglutide 3.0 mg for OSA-related outcomes in patients with obesity (see Section 7.1).[63]

Recent practice guidelines consider achievement of ≥5% weight loss from baseline to be a meaningful target for weight management interventions, since it is correlated with clinically significant improvements in cardiometabolic parameters.[10,34,64,65] Greater weight-loss targets exceeding ≥5% may be pursued depending on the intended WRC for improvement;[4] benefits tend to increase with greater weight loss from baseline (eg, ≥10%), including improvement or resolution of some WRCs.[4,10,34,65,66] The benefits of weight loss in patients with pre-diabetes and obesity can prevent the development of Type 2 diabetes (T2DM), or in patients with recently diagnosed T2DM, can lead to remission of T2DM.[67-69]

5.1 Adult Population

Generally, guidelines recommend comprehensive lifestyle interventions (including calorie restriction and increased physical activity) to support weight loss.[11] Although lifestyle therapy is a cornerstone of treatment, because sufficient weight loss is difficult to attain[70] and sustain, pharmacotherapy and metabolic surgery have a place in therapy, as they produce greater and more sustained weight loss compared with lifestyle modifications alone.[71]

Recent guidelines addressing pharmacotherapy to support weight loss/maintenance for the adult population with obesity or overweight (with or without WRCs) include those by the American Gastroenterological Association (AGA 2022), US Veterans Health Administration and Department of Defense (VHA/DoD 2020), and the American Association of Clinical Endocrinologists with the American College of Endocrinology (AACE/ACE 2016). Other guidelines for adults with particular WRCs (eg, T2DM, obstructive sleep apnea, etc.) will be reviewed in later sections.

The **2022 AGA guideline** strongly recommends adding pharmacological agents to lifestyle interventions for adults *with inadequate response* to lifestyle interventions alone for the treatment of obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with a WRC. Authors highlight that chronic pharmacotherapy is generally required for long-term weight management, and the choice of therapy should be based on the individual's clinical profile/needs (eg, comorbidities, contraindications, drug-drug interactions,

historical response, likelihood of adherence, preferences, costs, and access). The following agents are supported by moderate quality of evidence (semaglutide, liraglutide, phentermine/topiramate ER, naltrexone/bupropion ER). Authors note that, of these agents, semaglutide can be prioritized due to its large effect magnitude and favorable safety profile. Older agents (phentermine and diethylpropion) are supported by low quality of evidence. Authors recommend against the use of orlistat for *most* patients since it has a low effect magnitude (based on a conditional recommendation). The AGA guideline further describes that "…given the variability in response to any weight loss intervention, establishing response to a given AOM [antiobesity medication] for an individual patient has largely required a trial-and-error approach," (AGA, page 1219).[10]

Based on the meta-analysis of placebo-controlled RCTs conducted as part of the AGA guideline, agents were considered to have a **low** effect magnitude (orlistat), **moderate** effect magnitude (liraglutide 3.0 mg, naltrexone/bupropion ER, phentermine/topiramate ER, phentermine, diethylpropion), and/or **large** effect magnitude (semaglutide 2.4 mg, phentermine/topiramate ER) for weight management when used adjunctively with lifestyle intervention. However, the certainty in the evidence was low for phentermine and diethylpropion (due to limited long-term evidence) compared to moderate certainty with the other agents. The safety profile of these agents was considered "*small or not-substantial harms"*.[10] A summary of the meta-analysis effect estimates reported in the AGA guideline are include in Table 1 of **Appendix A**. Authors outline the following gaps in available evidence for pharmacotherapy:

- long-term patient important outcomes (eg, cardiovascular events, cancer risk, mortality, fatty-liver disease, and other weight-related complications) related to OM therapy
- comparative effectiveness and tolerability between WMPs or between WMPs versus surgical or device approaches. However, authors acknowledge the head-to-head trial of liraglutide vs. semaglutide (by Rubino et al)[72]
- evidence regarding combined therapies/interventions

Similar to the 2022 AGA guideline, the **2020 VHA/DoD guideline** supports considering long-term pharmacotherapy, as an adjunct to comprehensive lifestyle intervention (CLI) for the treatment of adults with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with weight-related comorbidity.[24] In contrast to the AGA guideline, the VHA/DoD guideline recommends use of only the agents approved for long-term treatment, and deemed that there was insufficient evidence to recommend for or against the use of the old sympathomimetics (phentermine monotherapy, benzphetamine, diethylpropion, or phendimetrazine) for short-term, long-term, or intermittent weight management.[24] Authors note lacking evidence to guide decisions for exactly when to initiate pharmacotherapy in conjunction with CLI (ie, how long patients should be on lifestyle interventions without meeting goals before adding pharmacotherapy).[24] Nonetheless, authors consider a goal of 5% to 10% weight loss at month 6 with CLI as a reasonable intermediate goal, with the shorter-term goal of 0.5 – 2.0 pounds loss per week (which is possible with a caloric deficit of 500 – 1,000 kcal/day). If patients are not meeting such goals, barriers to behavior change should be addressed along with consideration for intensifying the treatment approach (eg, increasing the intensity or frequency of the CLI, adding pharmacotherapy for weight loss, or bariatric surgery consultation).[24]

In general, the **2016 AACE/ACE guideline** encourages prevention of progressive weight gain for patients who meet the BMI threshold for overweight or obesity (ie, 25-29.9 for overweight; ≥ 30 for obesity, or ≥23 for obesity in certain ethnicities).[4] If weight-related complications (WRC) are present, weight loss

targets between ≥5% to ≥15% are suggested according to the specific WRC and patient-specific clinical goals (eg, prevention of T2DM, HbA1c reduction, lower BP, inflammation/fibrosis reduction, intrahepatocellular lipid reduction, reduced symptomatology of WRC manifestations, etc.). Similar to other guidelines, comprehensive lifestyle modification (eg, healthy meal planning and reduced caloric intake, physical activity, and behavioral intervention) is recommended for patients with overweight/obesity. According to the guideline algorithm, weight loss medication can be considered in the following scenarios:[4]

a) When BMI is ≥30 but WRCs are not evident (eg, Obesity Stage 0): weight loss medication can be considered if lifestyle therapy is insufficient to prevent progressive weight gain
b) When BMI is ≥27 and 1 or more mild to moderate WRCs are present (eg, Obesity Stage 1): weight loss medication can be initiated concurrently with lifestyle therapy, or initiated after lifestyle therapy alone is insufficient to achieve weight loss target
c) When BMI is ≥27 and at least 1 severe WRC is present (eg, Obesity Stage 2): weight loss medication should be considered for initial treatment along with concurrent lifestyle therapy.

The AACE/ACE guideline provided drug preferences according to individual co-morbidities (eg, cardiovascular disease, hypertension, kidney disease, hepatic disease, psychiatric disease, eating disorders, seizure disorder or risk, etc.); refer to Table 3.[4] Notably, the recommendations are with respect to the newer WMPs only. Authors describe that there is insufficient evidence to recommend short-term pharmacotherapy (ie, no data showing that short-term treatment leads to long-term health benefits), considering that obesity should be treated as a chronic condition. The recommendations regarding which agent to avoid in the presence of particular disease states (or which agents to use with extra caution) generally correspond to labeled drug warnings/precautions/contraindications.[4]

Table 3 consolidates pharmacotherapy recommendations among recent clinical guidelines (by the AGA, VHA/DoD and AACE/ACE) for the management of overweight/obesity in the general adult population.

Table 3. US Guideline Recommendations for Weight Management Pharmacotherapy in the General Adult Population

2022 AGA Clinical Practice Guideline on Pharmacological Interventions for Adults With Obesity[10]
• "…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 .." (page 1199)[10] • Authors performed a systematic review for randomized controlled trials of anti-obesity medications versus lifestyle intervention alone (plus placebo) to inform the development of recommendations. Benzphetamine and phendimetrazine were not included in this guideline; the reason is not clear. • *Interpretation of Strong and Conditional recommendation:* o **Strong**: Most patients should receive the intervention. The recommendation can be implemented into policy or performance measure in most situations. Most patients (but a small portion would not) want the recommended treatment o **Conditional**: Different choices will be appropriate for individual patients. The majority of patients (but many would not) want the recommended treatment. Policy-making will require debate and involvement of stakeholders.

Table 3. US Guideline Recommendations for Weight Management Pharmacotherapy in the General Adult Population

- *Quality of evidence (QOE) ratings[73]:*
  - **Moderate**: moderate confidence in the estimate of effect supporting the recommendation (ie, the estimate is likely a close to the true effect, but there is a possibility it is substantially different)
  - **Low**: limited confidence in the effect: the true effect may be substantially different than estimated
- Adding pharmacological agents to lifestyle interventions is **strongly recommended** (based on moderate QOE) over continuing lifestyle interventions alone in adults with obesity or overweight with weight-related complications (WRC) **and** inadequate response to lifestyle interventions.
  - Implementation considerations: Medication generally needs to be used chronically, and should be based on the individual clinical profile/ needs of the patient (eg, comorbidities, preferences, costs, and access).

A. The following mediations plus lifestyle modification are **conditionally recommended, based on moderate QOE,** for adults with obesity or overweight with WRC, compared to using lifestyle intervention alone

a) **Semaglutide 2.4 mg** (moderate QOE)
   - Implementation considerations: Due to the magnitude of effect with semaglutide 2.4 mg, it may be prioritized over other agents for long-term treatment of obesity for most patients. Semaglutide is also approved for T2DM due to its glucoregulatory benefits. It should be gradually up-titrated to minimize GI side effects. GLP-1 RAs as a class are associated with increased risk of pancreatitis and gallbladder disease.

b) **Liraglutide 3.0 mg** (moderate QOE)
   - Implementation considerations: liraglutide is also approved for T2DM due to its glucoregulatory benefits. Use gradual up-titrated to minimize GI side effects monitor for pancreatitis/gallbladder adverse effects.

c) **Phentermine/topiramate ER**
   - Implementation considerations: phentermine-topiramate may be preferentially used in patients with comorbid migraines since topiramate is effective for this indication. Avoid phentermine in patients with a history of cardiovascular disease and uncontrolled hypertension. Women of childbearing potential should be counseled to use effective contraception while using this medication since topiramate is teratogenic. Employ regular monitoring of blood pressure and heart rate with the use of phentermine.

d) **Naltrexone/bupropion ER**
   - Implementation considerations: this product can be beneficial for patients attempting smoking cessation, and in patients with comorbid depression; however, should be avoided in cases with history of seizure disorders and used with caution in those at risk of seizure, and in combination with opioids. Employ regular monitoring of blood pressure and heart rate with the use of this medication.

B. The following medications plus lifestyle modification are **conditionally recommended, based on low QOE,** for adults with obesity or overweight with WRC, compared to using lifestyle intervention alone

a) **phentermine**
   - The guideline notes that the 8 mg tablet formulation is scored and that a 4 mg dose has been used on an "as needed basis" for scenarios where there is a high likelihood of hedonic food consumption (intermittent use based on expert opinion).

b) **diethylpropion**
   - Implementation considerations: Phentermine and diethylpropion are approved for short-term use but are commonly used long-term (off-label) given the chronic nature/needs of weight management. Avoid these agents in patients with a history of cardiovascular disease and uncontrolled hypertension. Employ regular monitoring of blood pressure and heart rate while on either of these agents.

Table 3. US Guideline Recommendations for Weight Management Pharmacotherapy in the General Adult Population

• Use or **orlistat** is recommended <u>against</u> due to the small weight loss benefit and GI adverse effects; however, patients who place value on the drug profile may reasonably chose treatment with orlistat (conditional recommendation, moderate LOE) o Implementation considerations: Patients using orlistat should take a multivitamin daily (2 hours apart from orlistat) containing fat-soluble vitamins (A, D, E, K). **C.** The AGA advises reserving use of Gelesis 100 (Plenity) oral superabsorbent hydrogel only in the context of a clinical trial for adults with BMI between 25 and 40 kg/m^2 due to low quality of evidence (No recommendation, knowledge gap
2020 VHA/DoD Guideline for the Management of Adult Overweight and Obesity[34]
• Treatment should be decided using a shared decision making approach between the patient and provider to individualize treatment plans and goals based on patient needs, ability, values, and preferences • Authors suggest offering liraglutide, naltrexone/bupropion, orlistat, or phentermine/topiramate, as an adjunct to comprehensive lifestyle intervention, for long-term weight loss in patients with a BMI ≥30 kg/m^2, or BMI≥27 kg/m^2 and obesity-associated conditions (weak recommendation) o Note that semaglutide was not yet approved for obesity at the time of writing the guideline • Authors deemed that evidence was insufficient to recommend for or against phentermine monotherapy, benzphetamine, diethylpropion, or phendimetrazine, for short-term, long-term, or intermittent management of overweight or obesity.
2016 AACE/ACE Guideline for Medical Care of Patients with Obesity[4]
• Note that this guideline was published prior to the approval (2021) of semaglutide. Although the guideline included lorcaserin, this agent has been discontinued so recommendations regarding its use are not included for this table. • Best evidence level (BEL) meaning: BEL 1, RCT evidence or meta-analysis of RCTs Grade meanings: o Grade A: Strong recommendation o Grade B: Intermediate recommendation o Grade D: Not evidence based • Pharmacotherapy for obesity should be used as an adjunct to lifestyle therapy (Grade A; BEL 1). • Pharmacotherapy add-on treatment (to lifestyle therapy) produces greater weight loss and maintenance versus lifestyle therapy alone (Grade A; BEL 1). • Medication-assisted weight loss (plus lifestyle therapy) employing the long-term agents (eg, phentermine/topiramate ER, liraglutide 3 mg, or orlistat) should be considered for those at risk for T2DM; when a 10% weight loss goal is desired. (Grade A; BEL 1). • Initial pharmacotherapy plus lifestyle therapy can be initiated together and considered for patients with weight-related complications that can be potentially modified by weight loss (Grade A; BEL 1). o Offer pharmacotherapy for chronic treatment when potential benefits outweigh the risks (Grade A; BEL 1). ▪ Short-term treatment (3 to 6 months) with pharmacotherapy has not been shown to produce longer-term health benefits and cannot be generally recommended based on scientific evidence (Grade B; BEL 1, downgraded due to evidence gaps) o When deciding on pharmacotherapy, the following factors should be considered: differences in efficacy, side effects, and warnings; and the presence of weight-related complications and medical history. o Combination medication regimens are recommended in a manner approved by the FDA (Grade A; BEL 1) or when there is sufficient safety and efficacy data available to support and informed judgment regarding a positive benefit-to-risk ratio (Grade D).

Table 3. US Guideline Recommendations for Weight Management Pharmacotherapy in the General Adult Population

- It is recommended that patients with obesity have access to all approved medications to allow for optimization of pharmacotherapy according patient-specific factors and needs. (Grade D).

Individualization of Weight Loss Pharmacotherapy According to Co-morbidities

Kidney Disease

- **Avoid** weight-loss medication with end-stage renal failure, with the exception of orlistat and liraglutide 3 mg which may be used with a high level of caution (Grade B; BEL 2).
- **Avoid** naltrexone/bupropion ER and phentermine/topiramate ER in severe renal impairment (<30 mL/min); do not exceed 8 mg/90 mg twice per day in moderate renal impairment (Grade B; BEL 2).
- Do not exceed a daily dose of phentermine/topiramate ER 7.5 mg/46 mg in the presence of moderate renal impairment (Grade B; BEL 2).
- All other weight-loss medications can be used, but with caution, in patients with mild (50 to 79 mL/min) and moderate (30 to 49 mL/min) renal impairment.
- **Avoid** orlistat in patients with, or at risk of, oxalate nephropathy (Grade C; BEL 3).
- Discontinue the GLP-1 receptor agonist, liraglutide 3 mg if volume depletion develops as a result of GI side effects (Grade B; BEL 2).

Nephrolithiasis

- Naltrexone ER/bupropion ER and liraglutide 3 mg are preferred agents in cases with a history, or at risk, of nephrolithiasis (Grade D); use phentermine/topiramate ER and orlistat with caution (Grade A; BEL 1).

Hepatic impairment

- Use weight-loss medications with caution in the presence of hepatic impairment and avoid such agents in severe hepatic impairment (Child-Pugh score >9) (Grade C; BEL 3); consider dose adjustments for moderate hepatic impairment (eg, maximum recommended dose for naltrexone ER/bupropion ER, 1 tablet (8 mg/90 mg); and for phentermine/topiramate ER, 7.5 mg/46 mg daily) (Grade D).
- "Clinicians should maintain a high index of suspicion for cholelithiasis in patients undergoing weight-loss therapy, regardless of the treatment modality…"(page 25); in high-risk patients, liraglutide 3 mg should be used with caution. Preventive measures for cholelithiasis include a slower rate of weight loss, an increase in dietary fat, or administration of ursodeoxycholic acid (Grade A; BEL 1).

Hypertension

- In patients with hypertension, orlistat, phentermine/topiramate ER, and liraglutide 3 mg are preferred weight-loss medications (Grade B; BEL 1, downgraded due to evidence gaps).
- Monitor heart rate during treatment with liraglutide and phentermine/topiramate ER (Grade A; BEL 1).
- Naltrexone ER/bupropion ER should be last-line because it cannot be expected to reduce blood pressure, and is contraindicated in uncontrolled hypertension (Grade B; BEL 1, downgraded due to evidence gaps).

Cardiovascular disease and cardiac arrhythmia

- In the presence of atherosclerotic cardiovascular disease, orlistat is a preferred agent (Grade A; BEL 1); liraglutide 3 mg, phentermine/topiramate ER, and naltrexone ER/bupropion ER can be used with caution but heart rate and blood pressure should be monitored (Grade A; BEL 1).
- Orlistat is a preferred agents for patients with a history or risk of cardiac arrhythmia (Grade B; BEL 1, downgraded due to evidence gaps); use naltrexone ER/bupropion ER, liraglutide 3 mg, and phentermine/topiramate ER cautiously (as secondary options) and monitor heart rate and rhythm (Grade A; BEL 1).

Depression

- Monitor patients on weight-loss therapy for mood disorders, depression, and suicidal ideation (Grade A; BEL 2, upgraded due to high relevance).
- For patients with depression, orlistat, liraglutide 3 mg, and phentermine/topiramate ER can be used ongoing at initiation doses (3.75 mg/23 mg) or low-dose(7.5 mg/46 mg) (Grade A; BEL 1).

Table 3. US Guideline Recommendations for Weight Management Pharmacotherapy in the General Adult Population

- Use naltrexone ER/bupropion ER cautiously (or avoid use) if the patient is taking medications for depression (Grade A;BEL 1).

Anxiety

- Use the high-end dose (15 mg/92 mg) of phentermine/topiramate ER with caution in patients with obesity and anxiety disorders (Grade A; BEL 1).

Psychotic disorders

- Metformin may be beneficial for modest weight loss and metabolic improvement in those on antipsychotic medications (Grade A; BEL 1).
- Weight-loss medication should be use with caution in patients with psychotic disorders due to insufficient current evidence in this population (Grade D).

Eating disorders including binge eating disorder

- Candidates for weight-loss therapy should be screened for binge eating disorder and night eating syndrome (Grade B; BEL 3, upgraded due to high relevance)
  - Treatment for confirmed cases of binge eating disorder should include structured behavioral/lifestyle program in conjunction with cognitive behavioral therapy or other psychological interventions (Grade A; BEL 1).
  - For cases of night eating syndrome, treatment may include structured lifestyle therapy and/or selective serotonin reuptake inhibitor (Grade B; BEL 1, downgraded due to evidence gaps).
- Options for patients with overweight or obesity and binge eating disorder, include orlistat or approved agent containing topiramate or bupropion, as adjunct to structured lifestyle therapy, cognitive behavioral therapy, and/or other psychological interventions (Grade A; BEL 1).

Glaucoma

- Liraglutide 3 mg and orlistat are preferred weight-loss agents for those with history, or at risk of, glaucoma (Grade B; BEL 2). **Avoid** phentermine/topiramate ER in patients with glaucoma, and use naltrexone ER/bupropion ER with caution (Grade C; BEL 2, downgraded due to evidence gaps).

Seizure disorder

- Phentermine/topiramate, liraglutide, and orlistat are preferred weight-loss agents in those with a history, or at risk, of seizure/epilepsy (Grade B; BEL 1, downgraded due to evidence gaps). **Avoid** naltrexone ER/bupropion ER in this population.

Pancreatitis

- Obesity is associated with pancreatitis; patients with obesity should be monitored for signs/symptoms (Grade A; BEL 1). Pancreatitis signs/symptoms should also be monitored while taking glyburide, orlistat, or incretin-based therapies (GLP-1 RAs or DPP4is)(Grade C; BEL 3).
- Glyburide, orlistat, and incretin-based therapies should be withheld in cases of prior or current pancreatitis (Grade D).

Opioid use

- Avoid naltrexone ER/bupropion ER when chronic opioid therapy is required; consider phentermine/topiramate ER, liraglutide 3 mg, and orlistat instead (Grade B; BEL 1, downgraded due to evidence gaps).

Women of reproductive potential

- Avoid the use of weight-loss medications during pregnancy (Grade A; BEL 2, upgraded due to high relevance), and in women who are lactating and breast-feeding (Grade D).
- Use weight-loss medications in conjunction with appropriate contraception in women of reproductive potential (Grade A; BEL 1).

Table 3. US Guideline Recommendations for Weight Management Pharmacotherapy in the General Adult Population

Elderly, ≥65 years of age

- Elderly candidates being considered for weight-loss therapy should be evaluated for osteopenia and sarcopenia (Grade B; BEL 2), and if initiated, weight-loss medication should be used with extra caution in elderly patients since evidence in this population is limited (Grade A; BEL 1)

Addiction/alcoholism

- Avoid naltrexone ER/bupropion ER, which can lower the seizure threshold, in patients with alcohol abuse and/or withdrawal (contraindicated during alcohol withdrawal); consider using orlistat or liraglutide 3 mg in patients with obesity and alcohol addiction or other addictions (Grade A; BEL 1).

Post-bariatric surgery

- "Patients that have regained excess weight (≥25% of the lost weight), have not responded to intensive lifestyle intervention, and are not candidates for reoperation may be considered for treatment with liraglutide (1.8 to 3.0 mg) or phentermine/topiramate ER; the safety and efficacy of other weight-loss medications have not been assessed in these patients (Grade D; BEL 3, downgraded due to evidence gaps)" (page 29).

Abbreviations: AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; AGA, American Gastrological Association; BMI, body mass index; DPP4is, dipeptidyl peptidase 4 inhibitors; GI, gastrointestinal; ER, extended release; GLP-1 RAs, glucagon-like peptide 1 receptor agonist; QOE, quality of evidence; T2DM, type 2 diabetes mellitus; US, United States; VHA/DoD, US Veterans Health Administration and Department of Defense; WRC, weight-related complications

5.2 Adults with Prediabetes or with T2DM

Obesity substantially increases the risk for developing type 2 diabetes.[4,74] Strong evidence shows that obesity management can delay the progression from prediabetes to T2DM, according to the ADA 2023 Standards of Care guideline.[75] For every kilogram of weight loss, an additional 16% reduction in the risk of T2DM progression was observed over 3.2 years.[76,77] Weight loss between 3–7% (of baseline weight) improves glycemia and intermediate cardiovascular risk factors, while greater, sustained reduction of body weight by 10% leads to reduced need for glucose-lowering medications, possible remission of type 2 diabetes, and long-term cardiovascular and mortality benefits.[68,74,78]

Patients with overweight/obesity at high risk of developing T2DM[††], should be recommended to an intensive lifestyle behavior change program to achieve and maintain weight reduction of at least 7%, according to the 2023 ADA guideline.[77] Authors suggest considering weight management pharmacotherapy, in general, to support person-centered care goals.[75] Weight-loss pharmacotherapy is considered as an effective option, as an adjunct to nutrition, physical activity, and behavioral counseling, for patients with T2DM and a BMI ≥27 kg/m^2. Furthermore, agents including orlistat, phentermine/topiramate ER, liraglutide, semaglutide, and tirzepatide (a GLP-1 approved for T2DM and in study for obesity) have been shown to decrease the incidence of developing T2DM in RCTs, "…to various degrees in those with prediabetes...,"[77] (ADA, page S44). Table 4 summarizes recommendations related to WMP from the 2023 ADA Standards of Care guideline for diabetes.

[††] A risk calculator for the development of T2DM is available at (https://diabetes.org/diabetes/risk-test) or (https://www.cdc.gov/diabetes/prevention/about-prediabetes.html). Patients at particularly high risk of progression to diabetes are those with a BMI>35 kg/m^2, higher glucose levels (fasting plasma glucose 110–125 mg/dL, 2-h post-challenge glucose 173–199 mg/dL, and HbA1c ≥6.0%), or with a history of gestational diabetes.[76]

Although not specific to the GLP-1 RA weight-management formulations, the American Association of Clinical Endocrinology and American Association for the Study of Liver Diseases (2022), also recommends GLP-1 RAs for the treatment of patients with T2DM and nonalcoholic fatty liver disease.[12]

Table 4. 2023 ADA Guideline Recommendations on Weight Management Pharmacotherapy in Adults with T2DM

Prevention or Delay of T2DM and Associated Comorbidities Chapter 3, Standards of Care[77]
• Use intensive lifestyle behavior change program for adults with overweight/ obesity at high risk of type 2 diabetes, "…as typified by the Diabetes Prevention Program…," to achieve/ maintain 7% weight loss (incorporate a healthy reduced-calorie diet and >150 min/week of moderate intensity physical activity). (Grade A) o The guideline recommends that diabetes prevention programs should be reimbursed by third-party payers, and that access barriers should be improved • Pharmacotherapy for weight management may be considered to support therapy goals. (Grade B)
Obesity and Weight Management for the Prevention and Treatment of T2DM Chapter 8, Standards of Care[79]
• Obesity pharmacotherapy, as an adjunct to nutrition, physical activity, and behavioral counseling, is effective for those with T2DM and BMI ≥27 kg/m^2; However, potential benefits and risks should be considered with the patient. (Grade A) • Obesity pharmacotherapy should be considered for discontinuation if at least 5% of weight loss is not achieved after 3 months of use or if there are safety/tolerability issues. Alternative medications or treatment approaches can be considered. (Grade A) • The ADA guideline did not make a recommendation regarding the oral hydrogel medical device (Plenity) which is taken before meals to expand/occupy gastric space with the goal of decreasing food intake. The effect compared to placebo was described as relatively small. • Metabolic surgery (ie, bariatric surgery) is a recommended option for T2DM in patients with a BMI ≥40 kg/m^2 (or BMI ≥37.5 kg/m^2 in Asian American individuals) or with a BMI 35.0–39.9 kg/m^2 (or 32.5–37.4 kg/m^2 in Asian American individuals) and insufficient weight loss/durability and improvement of comorbidities with nonsurgical methods. (Grade A) • Metabolic surgery may be considered to treat T2DM in patients with a BMI 30.0–34.9 kg/m^2 (27.5–32.4 kg/m^2 in Asian American individuals) who have insufficient weight loss/durability and improvement of comorbidities with nonsurgical methods. (Grade A)

Grade A: encompasses evidence from well-conducted randomized controlled trials that are adequately powered, or compelling non-experimental evidence; Grade B: involves evidence from well-conducted cohort studies or case-controlled studies

Abbreviations: ADA, American Diabetes Association; BMI, body mass index; T2DM, type 2 diabetes mellitus

5.3 Adults with Sleep-dependent Breathing Disorders

The **American Thoracic Society (ATS)** describes that the association between weight gain and the development and worsening of obstructive sleep apnea (OSA) is well established.[80] Overall, the ATS recommends considering obesity pharmacotherapies for patients with OSA and a BMI ≥27 kg/m^2 who have not achieved weight loss targets despite participation in a comprehensive lifestyle weight-loss program. Authors further specify that this recommendation is meant for patients without active

contraindications or active cardiovascular disease; and the recommendation overall is based on very low certainty in the estimated effects due to few studies in the population with OSA, and theoretical concerns with agents that can increase heart rate and myocardial oxygen demand such as phentermine/topiramate and naltrexone/bupropion. Authors described 2 RCTs, 1 each for liraglutide 3.0mg and phentermine/topiramate ER, with results showing that these treatments in combination with diet and exercise improved sleep quality and OSA severity.[80] Furthermore, liraglutide and semaglutide (in T2DM formulations) have proven cardioprotective benefits in patients with T2DM (ie, reduction in major cardiovascular events).[54,80]

Obesity hypoventilation syndrome (OHS) is considered the most severe form of obesity-induced respiratory dysfunction.[81] OHS is defined as the combination of obesity (BMI ≥30 kg/m^2) complicated by sleep-disordered breathing (SDB) and daytime hypercapnia (awake resting PaCO2 >45 mmHg at sea level), after excluding other hypoventilation causes. About 90% of patients with OHS also have OSA and the remaining 10% experience non-obstructive hypoventilation during sleep. While positive airway pressure can be used to manage the respiratory complication, it does not treat the underlying cause (obesity), so OHS morbidity and mortality remains high. Thus, the American Thoracic Society suggested, in their 2018 guideline, using weight-loss interventions (ie, pharmacotherapy or bariatric surgery) to achieve/sustain weight reduction of 25–30% (of actual body weight) in order to achieve resolution of hypoventilation (*conditional recommendation, very low level of certainty in the evidence*). There is uncertainty in the evidence, however, since studies have yet to assess OHS as an outcome of weight-loss interventions.[81]

5.4 Osteoarthritis

The American College of Rheumatology guideline (2019) for the management of knee and hip osteoarthritis (OA) recommended ≥5% of body weight loss for patients with obesity and OA of the hip or knee in order to improve symptoms and/or physical function. Moreover, authors highlighted a dose-response relationship of increased benefits related to greater ranges of weight loss (5–10%, 10–20%, and >20% of body weight). However, authors do not go as far as providing specific guidance regarding weight-loss pharmacotherapies.[82]

5.5 Pregnancy

Guidelines recommend avoiding WMPs during pregnancy, including 2021 guidance from the American College of Obstetricians and Gynecologists (ACOG).[4,10,83] Weight loss *before* pregnancy should be encouraged for women with overweight/obesity, and behavior/dietary interventions are the ideal approaches for addressing adverse effects/associations of excess weight on pregnancy outcomes.[83]

Phentermine/topiramate ER is contraindicated during pregnancy because first-trimester fetal exposure to topiramate is associated with an increased risk of oral clefts, and weight loss does not present a clear clinical benefit during pregnancy, based on epidemiological data in humans.[40] Pregnancy testing to rule out pregnancy prior to initiating phentermine/topiramate ER is recommended, and monthly testing thereafter while on therapy. Patients with child-bearing potential should use effective contraception and be counseled on the risks of teratogenicity with this medication.[40]

Other weight loss medications are also labeled with a contraindication for use in pregnancy (as with orlistat, liraglutide, phentermine, benzphetamine, and phendimetrazine) or a warning (as with

naltrexone/bupropion, semaglutide, and diethylpropion), with the stated rationale in some package inserts being that weight loss does not offer a clear benefit during pregnancy and may result in fetal harm[37-43,45-50,57]; and animal studies identified increased adverse embryofetal developmental outcomes with liraglutide and semaglutide.[45,46]

6.0 PEDIATRIC PATIENTS

Recent guidelines by the American Academy of Pediatrics (AAP; 2023) and the Endocrine Society (ES; 2017) foremost recommend/advocate for lifestyle interventions to manage children/adolescents with overweight or obesity.[84,85] Moreover, the AAP published guidance on counseling and motivational interviewing (for lifestyle modification) in the primary care setting over several editions of the guideline handbook, *Bright Futures*.[84] Both *Bright Futures* and the AAP's 2023 comprehensive guideline recommend that primary-care providers offer or refer children/adolescents with overweight or obesity to dietary and physical activity counseling;[20,84] the recommendation in favor of intensive health behavior and lifestyle treatment is graded B for patients 6 years and older, and graded C for children 2 to 5 years of age (in the 2023 AAP guideline).[20] Intensive lifestyle therapy incorporating dietary, physical activity, behavioral and psychological interventions is the cornerstone to management of pediatric obesity,[36] and may be the only recommended intervention depending on the patient's age and disease severity.[20] Both the ES and AAP encourage using formal intensive lifestyle programs when accessible.[20,36] Efficacy of lifestyle intervention is generally increased with greater contact hours. Contact hours (face-to-face) of 26 or more, administered as family-based multicomponent treatment (eg, behavior, physical activity, and nutrition counseling) over 3 to 12 months, has been shown to be more effective over approaches with fewer contact hours.[20]

In addition to addressing lifestyle factors and interventions, guidelines included evidence-based recommendations regarding the pharmacotherapies that have been approved for obesity in the pediatric population. Weight-management pharmacotherapy as an adjunct to behavior/lifestyle treatment (and according to approved indications, and weighing risks vs. benefits) is recommended to be offered (ie, *should* be offered) to adolescents 12 years and older with obesity (BMI ≥95th percentile; key action statement, Grade B) according to the AAP guideline.[20] The rationale for including pharmacotherapy as an option was to fill a treatment gap where patients require additional treatment beyond intensive health behavior lifestyle therapy to manage their obesity: "In particular, children with more immediate and life-threatening comorbidities, those who are older, and those affected by more severe obesity may require additional therapeutic options," (page 60).[20] AAP authors also suggest that pharmacotherapy *may* be offered to children 8-11 years of age with obesity (according to medication indications, risks, and benefits; as an adjunct to behavior/lifestyle treatment; and considering that the evidence is rapidly evolving), but the expert-opinion statement for this age range is not rated as a key action statement since evidence was too limited.[20] Additionally, formal graded recommendations regarding the particular agent for use or preference for certain agents are not provided in the AAP guideline.

The ES recommended considering adjunctive pharmacotherapy for children or adolescents (unspecific to exact age) with obesity *after* failure of intensive lifestyle therapy due to the limited evidence for pharmacotherapies at the time of writing the guideline.[36] At the time of drafting the ES guideline, only orlistat was FDA-approved for children ≥ 12 years, and according to guideline authors, other products may have been indicated for treatment of adolescents ≥ 16 years (eg, sympathomimetics).[36] Neither the

ES nor the AAP recommended weight management pharmacotherapy for children/adolescents who are *overweight* but not obese.[20,36] The ES specifically recommended against adjunctive pharmacotherapy for patients who are *overweight* and <16 years old other than as part of a clinical trial.[36]

As in adults, treatment of pediatric obesity is often needed long-term since discontinuation usually leads to a regain of weight.[20,36] Compelling evidence supports improvements in WRC with weight loss among pediatric patients.[20,36] Thus, pediatric obesity should be treated with the goal of losing weight, preventing additional weight gain, and improving WRCs.[20] However, the AAP does acknowledge the following evidence gaps related to pharmacotherapy and the need for more research:

- Optimal duration of treatment; evidence regarding long-term outcomes is very limited.
- Evaluation of intervention on quality of life and mental health
- Treatment outcomes based on stratification by age, degree of obesity, and social determinants of health

Table 5 summarizes the AAP and ES guideline recommendations regarding pharmacotherapy for obesity in the pediatric population.

Table 5. Recent Guideline Recommendations for Weight Management Pharmacotherapy for Pediatric Patients

2023 American Academy of Pediatrics[20]
• Intensive health behavior and lifestyle treatment is recommended for children 2 through 5 years of age (Grade C) and 6 years and older (Grade B) with overweight (BMI ≥85th percentile to <95th percentile) and obesity (BMI ≥95th percentile). • **Weight-loss pharmacotherapy** as an adjunct to behavior/lifestyle treatment (and according to approved indications, risk, and benefits) should be offered to adolescents 12 years and older with obesity (BMI ≥95th percentile) (Grade B) o Guideline does not give agent-specific graded recommendations. Pharmacotherapies with some pediatric evidence mentioned by the guideline include: orlistat, liraglutide, phentermine (FDA-approved for age ≥ 16), and phentermine/topiramate ER • Weight-loss pharmacotherapy as an adjunct to behavior/lifestyle treatment (and according to approved indications, risk, and benefits) may be offered to children 8-11 years of age with obesity (non-graded expert opinion) • Metformin may have modest weight loss effect (eg, <5%, or 1 BMI unit) but the effect magnitude appears inconsistent across various populations, including the pediatric population. The AAP states that, "Given the modest and inconsistent effectiveness, metformin may be considered as an adjunct to intensive health behavior and lifestyle treatment and when other indications for use of metformin are present."[20] • Referral to specialty centers (ie, comprehensive multidisciplinary pediatric metabolic and bariatric surgery centers) for consideration of metabolic/ bariatric surgery is recommended for adolescents 13 years and older with severe obesity (BMI ≥120% of the 95th percentile for age and sex) (Grade C) • Considering the treatment barriers that patients face, the guideline committee strongly encourages supporting public-health policies and coverage for comprehensive obesity prevention, evaluation, and treatment, including efforts to help expand access to treatment programs and address resource/access disparities.

2017 Endocrine Society Guideline[85]

• Intensive lifestyle modifications (including diet, physical activity and behavioral) that are family-centered and age- and culture-appropriate are recommended to reduce BMI (Strong; Moderate QOE)
  o Recommended physical activity includes a minimum of 20 minutes of moderate or higher intensity activity with a goal of 60 minutes daily (Strong; Low QOE)
  o Additional lifestyle recommendations address familial communication interventions and psychosocial interventions when psychosocial contributors are suspected
• **Pharmacotherapy** is suggested for **children/adolescents with obesity** only after an intensive formal lifestyle program does not achieve desired outcomes (eg, reduce weight, improve comorbidities) (Weak; Very low QoE)
  o No formal age recommendation was provided; however, it was noted that some FDA-approved therapies for adults that may be indicated for age ≥ 16 years. Authors discouraged off-label prescribing of weight loss pharmacotherapies for ages <16 due to scant evidence. However, they acknowledged the benefits/risks should be weighed against potential harms of pediatric obesity.
  o At the time of drafting this guideline, only orlistat was FDA-approved for children ages 12-16 old; guideline authors cited its limited efficacy and high discontinuation rates as barriers to widespread clinical use.
• Discontinuation of pharmacotherapy is recommended if unable to achieve desired weight loss (ie, >4% BMI/BMI *z* score) after 12 weeks of the maximum pharmacotherapy dose (Weak; Very low QoE)
• Pharmacotherapy for children/adolescents <16 years old who are overweight (NOT obese) is only recommended as part of a clinical trial (Strong; Very low QoE)
• Pharmacotherapy (FDA-approved agents for obesity) should be administered adjunctively with intensive lifestyle changes (of the highest available intensity) by experienced clinicians (Weak; Very low QoE)
• Bariatric surgery is recommended only for adolescents (Tanner stage 4/5 with near adult height) with BMI ≥ 35 kg/m^2 in the presence of serious comorbidities or ≥ 40 kg/m^2 regardless of comorbidities despite an intensive formal lifestyle program (±pharmacotherapy) with demonstrated familial competence and patient adherence. Care at a pediatric bariatric surgery center of excellence is recommended when accessible. (Weak; Low QoE)

AAP Grades: Grade B, evidence from trials with minor limitations, multiple consistence observational studies, or extrapolations from higher level evidence (ie, consistent well-designed and conducted trials, or meta-analyses); Grade C: single or few observational studies (or with inconsistent findings or major limitations) or extrapolations from level B or level C studies

ES Evidence Ratings: Used the GRADE approach,[86,87] which considers the study design and evidence quality, consistency and directness to assign a strength of recommendation (Strong or Weak). Strong recommendations are intended for most patients on average whereas weak recommendations depend on an individual's preferences and circumstances. No statement of the type of evidence required for a given QoE rating was provided.

Abbreviations: AAP, American Academy of Pediatrics; BMI, body mass index; ES, Endocrine Society; QOE, quality of evidence

6.1.1 Pediatric Patients with T2DM

According to the ADA Standards of Care 2023 guideline, metformin is generally the initial therapy in T2DM for those who are metabolically stable (HbA1c< 8.5% and asymptomatic).[88] A GLP-1 RA approved for pediatric patients is recommended in children/adolescents 10 years or older if metformin (with or without long-acting insulin) is insufficient for glycemic control. When choosing antidiabetic medications, the ADA suggests weighing the effects on weight. Comprehensive lifestyle programs, integrated with diabetes management and based on a chronic care model, should be implemented to achieve a 7–10%

decrease in excess weight for pediatric patients with overweight/obesity and T2DM. Generally speaking, only FDA-approved medications approved for pediatrics are recommended for the management type 2 diabetes in youth.[88]

- With the exception of Contrave (naltrexone/bupropion ER), each of the reviewed weight-loss formulations is indicated for *chronic* weight management is approved for pediatric patients ≥12 years of age (Saxenda [liraglutide], Wegovy [semaglutide], Xenical [orlistat], Qsymia [phentermine/topiramate]). As for the agents approved for short term use (benzphetamine, diethylpropion, phentermine, phendimetrazine), package inserts (ie, labeled prescribing information) recommends against use in patients *under* 17 years of age.

The ADA recommends considering metabolic surgery for adolescents with T2DM, severe obesity (BMI >35 kg/m^2), and elevated HbA1c and/or serious comorbidities despite attempts to implement lifestyle and pharmacologic interventions.[88]

7.0 OTHER POTENTIAL BENEFITS OF WEIGHT-MANAGEMENT PHARMACOTHERAPY

7.1 Obstructive Sleep Apnea (OSA)

There is at least one published RCT that assessed OSA-related outcomes when using liraglutide 3.0 mg to treat obesity as an adjunct to diet and exercise.[63] The double-blind RCT included 359 patients without diabetes but with obesity and moderate to severe OSA who were unwilling/unable to use continuous positive airway pressure therapy. At the primary endpoint (32 weeks), greater weight loss and mean reduction in the apnea hypoxia index [AHI] were achieved with liraglutide compared to placebo (mean apneic event treatment difference: -6.1, 95% CI -11.0 to -1.2). The post-hoc assessment showed a significant association between the degree of weight loss and improvement in OSA-related end points (eg, AHI, oxygen saturation, sleep architecture and total scores on Epworth Sleepiness Scale).[63]

7.2 Physical Function

A 2023 systematic review meta-analysis of RCTs found that weight loss pharmacotherapy (based on studies with liraglutide 3.0 mg, semaglutide 2.4 mg, naltrexone/bupropion, and phentermine/topiramate; 14 RCTs total) was associated with improved physical function and effects generally consistent across therapies. Commonly used measures included The Short-Form 36-Item Questionnaire (SF-36) and the physical function component of the Impact of Weight on Quality Of Life-Lite (IWQOL-Lite) tool.[89]

7.3 Pharmacy Compendia Off-label Uses

Three of the reviewed weight loss products have non-FDA uses (ie, off-label uses) indexed in Micromedex as an "effective" or "possibly effective," as shown in **Table 6**.

Table 6. Off-label Uses Indexed in Micromedex for Weight Management Agents[90]

Agent	Off-label Use	Evidence Rating[a]
Liraglutide	• Non-alcoholic fatty liver (0.6 to 3 mg/day)	*Effective (Category A)*
Semaglutide	• Nonalcoholic steatohepatitis (0.05 to 0.4 mg/day)	*Evidence favors efficacy (Category B)*
Orlistat	• Hyperlipidemia • Diabetes mellitus, prophylaxis • Coronary arteriosclerosis, prophylaxis	*Evidence favors efficacy (Category B), for all*

Abbreviations: LOE, level of evidence; RCTs, randomized controlled trials

[a] Non-FDA uses were extracted that were at least rated as "effective" or "evidence favors efficacy"

Micromedex Category

- *A: strength of evidence is based on meta-analyses of RCTs with similar effect sizes, or based on large and well-performed RCTs.*
- *B: strength of evidence is based on data from nonrandomized studies or meta-analyses of RCTs with either incongruent effect estimates, small populations, or significant methodological flaws..*

8.0 ADDITIONAL PLACE IN THERAPY AND SAFTEY CONSIDERATIONS

The general approach for initial selection of WMPs for the treatment of indicated patients is based on considering patient values and preferences, comorbidities, drug interactions, potential adverse event risks, and access to the therapy. Beyond these considerations, a trial and error approach may be taken to find an effective regimen for the patient. The AGA recommends for the selection of the medication to be individually tailored based to the patient's clinical profile.[10] Moreover, there is interest in the field to determine predictors of response in order to better tailor the choice of therapy at treatment initiation to achieve greater response rates.

Considering the pathophysiological/etiological heterogeneity of obesity, researchers have trialed a phenotypic-classification approach to tailor therapy as follows: hungry-brain phenotype (ie, abnormal satiation; assigned to receive phentermine/topiramate), emotional hunger (assigned to naltrexone/bupropion), hungry gut (abnormal satiety; received liraglutide 3.0 mg), and slow burn (decreased metabolic rate; received phentermine). In this prospective study (non-randomized), compared to the group receiving non-phenotype guided treatment, the phenotype-guided approach was associated with a 1.75-fold greater weight reduction, and significantly more patients achieved >10% weight loss at 1 year.[91] In addition to the pros and cons described below, practitioners may consider patient phenotypes in the initial selection of treatment. The AGA guideline described that while phenotype-guided treatment has shown some early promising results, more research is needed.[10]

Refer to **Tables 7 and 8** for details about contraindications, and select warnings or precautions from product labeling for the newer WMPs and early-approved WMPs, respectively. See Table 1 of Appendix B for drug-drug interactions and Table 2 of Appendix B for common adverse events consolidated from package inserts.

Although warnings for possible hypoglycemia and hypotension are not labeled across all WMPs, the AGA describes that these are potential risks with any weight-loss intervention due to the secondary effects of weight loss itself (ie, normalization of blood pressure and glycemic control). Because blood pressure and glucose levels an can drop (ie, become more normalized) with weight loss and reduced high calorie consumption, dosage needs for antihyperglycemic and antihypertensive medications may be reduced, and therefore dose adjustment required.[10]

8.1 GLP-1 RAs, Liraglutide and Semaglutide

8.1.1 Pros

Semaglutide and liraglutide are considered to have a large or moderate magnitude of effect for weight loss/management, respectively.[10] In addition**,** GLP-1 RAs have glucose regulating effects and can serve as part of T2DM antihyperglycemic therapy.[10] GLP-1 RA weight loss therapy is associated with improvements in blood pressure and lipid levels (eg, LDL, HDL, and triglycerides).[52,92,93] GLP-1 RAs are not known to cause cognitive impairment (as with phentermine/topiramate[94]), nephrolithiasis (possible risk with orlistat and phentermine/topiramate[41,94]), or worsening of glaucoma (as with phentermine/topiramate[94]). Additionally, GLP-1 RAs are not controlled substances with abuse potential. Regarding administration, semaglutide has the advantage of once weekly dosing as opposed to daily (or multi-daily) dosing required with all other WMPs including liraglutide.

Semaglutide (as Ozempic 2mg/week) and liraglutide (as Victoza 1.8 mg/day) have also demonstrated cardiovascular benefits in patients with T2DM with established CV disease or at high CV event risk.[10,54] Additionally, a few studies with T2DM formulations of liraglutide and semaglutide also suggest renoprotective effects with these agents.[95] A cardiovascular-outcomes phase 3 study is active for semaglutide 2.4 mg/week (Wegovy) in patients with obesity but without T2DM (NCT03574597, estimated study completion date in September 2023).[96] In a meta-analysis of RCTs (9 trials with 11,430 patients) in adults with overweight or obesity and without diabetes, treatment with GLP-1 RAs (liraglutide and semaglutide), versus placebo, was found to reduce the incidence of CV events (8.7% vs. 11.2% patient event) and significantly reduce CV event risk (RR = 0.81, CI 0.70-0.92; p = .001).[97] Investigations on outcomes for weight-related comorbidities such as osteoarthritis, non-alcoholic fatty liver disease, prediabetes, heart failure, and chronic kidney disease are also ongoing in phase 3 studies for semaglutide (NCT05064735, NCT04822181, NCT05040971, NCT04916470, NCT03819153).[62]

8.1.2 Cons

Gastrointestinal (GI)-related side-effects are common with GLP-1 RAs including nausea, vomiting, diarrhea, and constipation, which can limit tolerability and predispose patients to dehydration and kidney injury.[45,46] However, gradual titration schedules can help minimize GI side effects. Other common AEs (eg, occurring in 10% or more of treated patients in clinical trials), aside from GI side effects included headache and fatigue for semaglutide; and injection site reactions, headache, and hypoglycemia (in patients with T2DM) for liraglutide. Dose adjustment of insulin or insulin secretagogues in patients with

T2DM should be considered when adding a GLP-1 RA since the additive glucose lowering effect of GLP-1 RA arises the potential for hypoglycemia.[45,46] Both liraglutide and semaglutide are administered subcutaneously, which may be a deterrent for some patients who may prefer oral dosing.

Labeled warnings for the rare but serious adverse events for GLP-1 RAs include thyroid C-cell tumors demonstrated in animal models (contraindication with personal/family history of medullary thyroid carcinoma [MTC] or Multiple Endocrine Neoplasia syndrome type 2 [MEN 2]), the potential for pancreatitis (causality is unclear); severe hypersensitivity reactions; acute kidney injury; acute gallbladder events (eg, cholelithiasis or cholecystitis); suicidal ideation/behavior (causality is unclear), and possible heart rate increase. Liraglutide is contraindicated during pregnancy, and use of semaglutide is not advised during pregnancy.[45,46] Refer to Table 7 for an exhaustive list of warnings and contraindications.

Regarding choletlithias, guideline authors describe that this is an adverse event associated with rapid weight loss; thus, a risk while engaging in any weight-loss therapy, "…regardless of the treatment modality…" (page 25).[4] However, certain agents may be more closely tied with this adverse event such as GLP-1 RAs. A recommended approach for preventing cholelithiasis especially in high-risk patients (eg, those with weight loss >25% of body weight or at a rate of >1.5 kg per week, fasting or very low-fat calorie diet, and elevated triglycerides) is to proceed therapy at a slower rate of weight loss. Ensuring dietary intake of fat and administering ursodeoxycholic acid are also suggested preventative approaches.[4]

8.2 Phentermine/Topiramate ER

8.2.1 Pros

Topiramate, as the mono-ingredient formulation, is approved for migraine prophylaxis; thus, the phentermine/topiramate formation may be preferable in patients with obesity and comorbid migraine disorder.[10] The AACE/ACE guideline also highlights that approved agents containing topiramate (or bupropion and orlistat) are favorable for overweight/obesity with concomitant binge eating disorder.[4] Topiramate has been used off-label for adults with binge eating disorder; though, antidepressants or lisdexamfetamine are typically considered first for binge eating disorder in adults according to a 2023 American Psychiatric Association guideline.[98] The AACE/ACE guideline also highlights that this formulation may be beneficial with comorbid hypertension as the agent is generally associated with lowering blood pressure in the long-term.[4,99] Phentermine/topiramate ER was considered (by the AGA guideline) to have a moderate to large effect magnitude for weight reduction.[10]

8.2.2 Cons

Common adverse effects of phentermine/topiramate ER in adults include paresthesia, dizziness, cognitive impairment, and insomnia, which can interfere with concentration/productivity (ie, in academic and employment settings) and activities of daily living.[40] In children, common adverse events in clinical trials were depression, dizziness, nausea, pyrexia, and arthralgia. Phentermine can increase heart rate so should be avoided with unstable cardiac or cerebrovascular disease, and/or hyperthyroidism (contraindicated). The *potential* risks of long-term use in patients with cardiovascular risk factors is unclear but caution is advised to avoid the medication if possible since there are plausible risks (eg, serotonin stimulation, increased heart rate and blood pressure, possible risk for pulmonary

hypertension, and valvulopathies).[10,40] Nonetheless, several clinical studies did include patients with cardiovascular risk factors such as T2DM with controlled hypertension and/or dyslipidemia.[10,100]

Since topiramate is a teratogen, patients of childbearing potential taking this medication are advised to use reliable birth control. A negative pregnancy test is also recommended before its initiation and monthly while on therapy in such patients.[40]

Because physical dependence can develop while on taking phentermine/topiramate ER, the medication should not be suddenly discontinued.[40] Abrupt discontinuation of topiramate is associated with seizures as a withdrawal effect (even in patients without history of epilepsy); and abrupt discontinuation of phentermine is associated with extreme fatigue and mental depression. This combination agent should be slowly off-titrated (eg, 1 capsule every other day for at least 1 week before stopping) in order to minimize the risk of precipitating severe adverse events. Similar to the early-approved WMPs, phentermine/topiramate ER is a controlled substance with abuse potential (classified as schedule 4 controlled substance) due to the phentermine component. The package insert describes that "Phentermine is related chemically and pharmacologically to amphetamines."[40] Thus, the patient's risk for abuse should be considered prior to initial and re-prescribing this medication (as with sympathomimetic amines in general).[40]

Labeled warnings for other rare but serious adverse events not previously mentioned for phentermine/topiramate ER include the following (refer to Table 7 for an exhaustive list): suicidal behavior/ideation with antiepileptics, possible ophthalmic AEs (contraindicated with glaucoma), decrease in renal function, possible slowing of growth (in height), and increased risk of kidney stones, and hypokalemia.[40]

8.3 Naltrexone/Bupropion ER

8.3.1 Pros

The AGA guideline highlights that naltrexone/bupropion ER may be prioritized for patients with comorbid depression since bupropion is an antidepressant.[10] The suggestion is based on expert experience, plausibility, and a small single arm, open-label study that showed improved depression outcomes and reduced body weight after 24 weeks of therapy in women with overweight/obesity with major depressive disorder.[10,101] This combination may also be preferable for patients attempting smoking cessation as there is some evidence supporting the use of the active ingredients for this purpose.[10] Similar to GLP-1 RAs, naltrexone/bupropion may be preferable for patients at risk of kidney stone development, and is not a controlled substance with abuse potential (as are WMPs containing sympathomimetics).[10] Naltrexone/bupropion ER was considered (by the AGA guideline) to have a moderate effect magnitude for weight reduction.[10]

8.3.2 Cons

Because naltrexone is an opioid antagonist, this agent should not be used in patients who require or are anticipated to require opioid therapy for pain management (contraindicated in patients on chronic opioid therapy).[44] Due to the potential of bupropion to lower the seizure threshold, this medication is contraindicated in patients with seizure disorder.[44] Use should proceed with caution in patients with clinical risk factors for seizure (eg, dehydration, hyponatremia, hypoxia, hypoglycemia, concomitant use

with other seizure-threshold lowering agents [eg, antipsychotics, tricyclic antidepressants, and systemic steroids; excessive use of alcohol, sedatives, or stimulants]). Bupropion is contraindicated in patients with current or prior diagnosis of anorexia nervosa or bulimia, or those undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs. Administration with high-fat meals should be avoided since this significantly increases drug exposure to both agents. Additionally, exposure to naltrexone/bupropion can be affected by inhibitors/inducers of cytochrome P450 enzyme (CYP) 2B6 and substrates of CYP2D6 (see Table B2 of Appendix B).[44]

Common adverse events occurring in 10% or more of naltrexone/bupropion-treated patients in clinical trials included nausea, constipation, vomiting, dizziness, insomnia, and dry mouth.[44] Labeled warnings for other rare but serious adverse events not previously mentioned include the following (refer to Table 7 for a more exhaustive list)): black box warning for increased risk for worsening suicidal thoughts and behaviors during bupropion treatment in patients with major depression, case reports of neuropsychiatric events during treatment with bupropion for smoking cessation, may increase blood pressure and heart rate (contraindicated with uncontrolled hypertension), hepatotoxicity, precipitation of mania, glaucoma attacks, and potential hypoglycemic risk in patients on antidiabetic therapy with T2DM. Labeling highlights that the effect of naltrexone/bupropion on cardiovascular outcomes has not been established.[44] Nonetheless, we are aware of 2 meta-analyses (published 2021) that reviewed adverse event data from naltrexone/bupropion ER clinical studies and found no signal of increased cardiovascular event risk with this therapy so far.[102,103]

8.4 Orlistat

8.4.1 Pros

Orlistat may be preferable in the following scenarios[4] based on the AACE/ACE guideline; other preferable options for the respective scenario are also indicated in parentheses:

a. In patients with hypertension (along with phentermine/topiramate ER, and the approved GLP-1 RA, liraglutide 3 mg, at that time)
b. In the presence of atherosclerotic cardiovascular disease. However, newer evidence suggests GLP-1 RAs have cardiovascular benefits (based on studies in T2DM at the T2DM dosages), thus may be highly favorable in this scenario.[54,104]
c. In patients with history or risk of cardiac arrhythmia
d. For patients with depression (along with naltrexone/bupropion ER[10])
e. In the presence of binge eating disorder (along with agents containing topiramate or bupropion)
f. For patients with history or at risk of glaucoma (along with GLP-1 RAs)
g. For patients with risk of seizure including alcohol abuse (along with phentermine/topiramate, and liraglutide)

Additionally, orlistat is not a controlled substances with abuse potential.

8.4.2 Cons

Orlistat was considered (by the AGA guideline) to have a low effect magnitude for weight reduction making for an unfavorable benefit vs. risk profile for most people considering its high GI side effect burden.[10] Common adverse effects include fecal urgency and incontinency, flatulence with discharge,

and increased defecation and fatty/oily stool limit tolerability. Orlistat has the potential for interactions with many drugs (refer to Table B2 of Appendix B), and interferes with vitamin absorption.[4,10,41] Thus, patients should be counseled to take a multivitamin containing fat soluble vitamins while on this medication. Orlistat is contraindicated in patients with chronic malabsorption syndrome and during pregnancy. Labeled warnings for rare but serious adverse events include hepatotoxicity, nephrotoxicity related to possible oxalate accumulation, and possible cholelithiasis (contraindicated in patients with cholestasis).[41]

8.5 Sympathomimetic Amines

8.5.1 Cons

Sympathomimetic amines are structurally and pharmacologically similar to amphetamines. Prolonged use is associated with the development of physical dependence. Longer-term use of these agents may have limited utility since tolerance to their effects commonly develops. These agents have potential for abuse thus are classified as Schedule 3 or 4 controlled substances (3, phendimetrazine and benzphetamine; 4, phentermine and diethylpropion).[37-39,42,43,47-50,57]

Adverse reactions for sympathomimetic amines include cardiovascular reactions (eg, palpitation, tachycardia, increased blood pressure), CNS reactions (overstimulation, insomnia, anxiety, tremor, dizziness, dysphoria, headache), gastrointestinal reactions (eg, dry mouth, diarrhea, and constipation), and endocrine side effects (libido changes);[105] however, the incidence rates of these are not included in the product labeling.[37-39,42,43,47-50,57] Labeled contraindications include overt cardiovascular disease[‡‡], risk for increased sensitivity to sympathomimetic effects (eg, hyperthyroidism, glaucoma, agitated condition), and a history of drug abuse. Key warnings include increased risk for pulmonary hypertension, regurgitant cardiac valvopathies, and impaired ability to engage in hazardous tasks.[37-39,42,43,47-50,57] According to the AGA guideline, pulmonary hypertension and valvopathy risks associated with this drug class seem to be primarily driven by fenfluramine, a discontinued drug that was commonly used in combination with phentermine and that binds strongly to serotonin receptors in cardiac tissue, potentially causing cardiotoxicity.[10] Notably, warnings for pulmonary hypertension and valvopathies are not carried over to labeling for the newer combination product with phentermine (ie, phentermine/topiramate ER).[40] Diethylpropion, which is structurally similar to bupropion, carries a precaution for increased seizures in at-risk patients.[37,47,106]

[‡‡] The following examples of contraindicated cardiovascular diseases are as follows, per agent: coronary artery disease, stroke, arrhythmias, congestive heart failure, and uncontrolled hypertension labeled as contraindicated for phentermine and phendimetrazine; pulmonary hypertension contraindicated for phendimetrazine and diethylpropion; advanced arteriosclerosis, and severe hypertension contraindicated for diethylpropion; and advanced arteriosclerosis, symptomatic cardiovascular disease, and moderate to severe hypertension contraindicated for benzphetamine.

Table 7. Approved Long-term Agents: Contraindications, Warnings, or Precautions[40,41,44-46]

GLP-1 RA Drug-class Warnings

Liraglutide (Saxenda) & Semaglutide (Wegovy)

Contraindications

- Personal/family history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Hypersensitivity to the product or components.

Warnings or Precautions

Thyroid C-cell tumors **[black box warning]:** risk has been demonstrated in animal models at clinically relevant exposures of liraglutide and semaglutide.

Acute pancreatitis: Cases of pancreatitis have been reported with GLP-1 RAs. Pancreatitis occurred in a few cases in both the experimental and control arms of clinical trials; events were numerically higher in the GLP-1 RA arms, but occurred in <1% of treated patients.

Acute gallbladder disease**:** Acute gallbladder events (eg, cholelithiasis or cholecystitis) have been reported in clinical trials with these agents. Gallbladder studies should be employed if cholelithiasis is suspected.

Renal impairment and acute kidney injury (AKI)*:* GLP-1 RAs may cause severe GI adverse reactions manifesting as nausea, vomiting, and/or diarrhea, which can lead to dehydration and acute kidney injury (AKI) if not adequately managed. AKI and worsening of chronic renal failure have been reported in patients on GLP-1 RAs, including liraglutide and semaglutide; some AKI events occurred in patients without known underlying renal disease. Cautionary measures should be employed (ie renal function monitoring) in patients with renal impairment.

Hypoglycemia potential with concomitant use of insulin or insulin secretagogues (eg, sulfonylurea); inform patients of the risks and consider dose modifications. The package insert of liraglutide also highlights that hypoglycemia can occur in patients without T2DM, as occurred in a few pediatric cases in clinical trials.

Heart rate increase: GLP-1 RA treatment was associated with elevations in resting heart rate. Patients should be monitored at regular intervals and the medication should be discontinued in those with sustained elevated resting heart rate while taking either of these medications.

Hypersensitivity reactions: Cases of serious hypersensitivity reactions (eg, anaphylactic reactions and angioedema) have been reported with the use of liraglutide and semaglutide.

Suicidal behavior and Ideation were reported in 10 patients treated with liraglutide 3.0 mg in clinical trials (compared 2 in the control arm). Despite that a causal relationship is unclear, a warning is labeled for both liraglutide and semaglutide to monitor for depression or suicidal thoughts and discontinue treatment if symptoms develop.

Additional Contraindication for Liraglutide (Saxenda)

Pregnancy*:* there is a risk of fetal harm, and weight loss is not recommended during pregnancy

Additional Warning for Semaglutide (Wegovy)

Diabetic retinopathy*:* Temporary worsening and complications of diabetic retinopathy are associated with rapid improvement of glycemic control. In some clinical trials including patients with T2DM, there were numerically more cases of diabetic retinopathy complications in the semaglutide treatment vs. control arm. Patients receiving GLP-1 RAs with a history of diabetic retinopathy should be monitored for retinopathy progression.

Table 7. Approved Long-term Agents: Contraindications, Warnings, or Precautions[40,41,44-46]

Phentermine/Topiramate ER*[40] *(Qsymia)
Contraindications
• Pregnancy • Glaucoma • Hyperthyroidism • Concurrent use of MAIO or within 14 days of stopping an MAOI • Known hypersensitivity to any component of the product or idiosyncrasy to sympathomimetic amines
Warnings or Precautions
Embryo-fetal toxicity: This product is **contraindicated** during pregnancy because first trimester fetal exposure to topiramate is associated with an increased risk of oral clefts, and weight loss does not present a clear clinical benefit during pregnancy.[40] In patients with childbearing potential, a negative pregnancy test is recommended before therapy initiation and monthly during therapy; these patients should also use effective contraception. A risk Evaluation and Mitigation Strategy (REMS) program is in place for this agent the limits distribution to certified pharmacies only. ***Increased heart rate*** is possible, as a result of taking this medication but the clinical significance is unclear. Heart rate should be monitored regularly, especially in those with cardiac or cerebrovascular disease. This agent is not recommended in the presence of unstable cardiac or cerebrovascular disease. ***Suicidal behavior and ideation***: Antiepileptics such as topiramate increase the risk of suicidal ideation/behavior. Patients should be monitored for depression or suicidal thoughts. The package insert recommends to avoid use of this product in patients with a history of suicidal attempts or active suicidal ideation. ***Possible ophthalmic adverse reactions****:* cases of acute myopia, secondary angle closure glaucoma (in pediatric and adult patients), and visual field defects have been reported with the use of topiramate. Discontinue the medication if symptoms (eg, decreased visual acuity and/or ocular pain) develop. ***Mood and sleep disorders*** (eg, depression, anxiety, insomnia) are associated with the use of phentermine/topiramate. If significant or persistent mood or sleep disturbances occur, consider dose reduction and/or discontinuation. ***Cognitive impairment*** (eg, impaired concentration, speech, memory) is a potential adverse effect associated with this medication. Moreover, concomitant use of CNS depressants can potentiate CNS depression, cognitive impairments, and other adverse effects (eg, drowsiness, impaired coordination). Patients should be cautioned to not operate automobiles or hazardous machinery until they are reasonably certain that the medication does not adversely affect their operating ability. ***Slowing growth in height***: Consider dose reduction or discontinuation if pediatric growth (in height) is slower than expected. This medication was associated with reduced gain in height per year in obese pediatric patients 12-17 years of age. ***Metabolic acidosis***: Measure electrolytes such as serum bicarbonate prior to and during treatment. ***Decrease in renal function***: monitor kidney function before and during treatment. ***Risk of hypoglycemia:*** weight loss can increase hypoglycemia risk in patients on antidiabetic therapy. Consider changes/dose reduction to the antihyperglycemic regimen if hypoglycemia occurs. ***Risk of hypotension with concomitant antihypertensives***: weight loss may increase the risk of hypotension. Monitor blood pressure before and during treatment ***Risk of seizures with abrupt discontinuation***: abrupt withdrawal of topiramate may precipitate seizures, including in patients without a history of seizures ***Increased risk of kidney stones, hypokalemia, oligohidrosis, hyperthermia, and serious skin reactions*** due to the topiramate component.

Table 7. Approved Long-term Agents: Contraindications, Warnings, or Precautions[40,41,44-46]

Orlistat[41] **(Xenical)**
Contraindications
• Pregnancy • Chronic malabsorption syndrome • Cholestasis • Hypersensitivity to orlistat or other product components
Warnings or Precautions
Potential for DDIs with many drugs and vitamins*:** Decreased effectiveness or plasma levels of multiple drugs (cyclosporine, levothyroxine, amiodarone, anti-seizure drugs, antiretroviral drugs) or increased effectiveness of warfarin and antihyperglycemic medications have occurred when used with orlistat. During orlistat treatment, monitor for changes in effectiveness, and separate administration of cyclosporine and levothyroxine from orlistat. Orlistat also interferes with vitamin absorption; patients taking orlistat should take a multivitamin containing fat soluble vitamins and administer the vitamin at least 2 hours before or after orlistat. ***Liver injury events (eg, hepatocellular necrosis, acute hepatic failure) including events leading to death have been reported during the postmarketing period. Patients should monitor for symptoms of liver dysfunction during orlistat treatment; discontinue orlistat if liver toxicity is suspected and check the patient's liver function. ***Oxalate nephrolithiasis and oxalate nephropathy with renal failure*** have been reported during treatment with orlistat. Renal function should be monitoring during orlistat treatment in patients at elevated risk of oxalate nephropathy (eg, baseline renal impairment, patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis). Discontinue orlistat if this condition develops. ***Cholelithiasis***: There is an increased risk of cholelithiasis with weight loss; a slightly higher rate of cholelithiasis occurred with orlistat (2.9%) compared to placebo (1.8%) in clinical trials. ***Other*:** Prescribers should rule out treatable causes of obesity (eg, hypothyroidism) before starting orlistat. Additionally, gastrointestinal AEs increase when orlistat is given with a high fat (>30% of total calories) diet. Patients should divide daily fat intake across daily meals.
Naltrexone/Bupropion ER[107] **(Contrave)**
Contraindications
• Uncontrolled hypertension • Factors increasing seizure risk: seizure disorders; eating disorders; patients rapidly stopping alcohol, benzodiazepine, barbiturate, and anti-seizure drugs • Use of other bupropion products • Chronic opioid use • Use within 14 days of taking an MAOI • Allergy to Contrave, Contrave components, or other product ingredients
Warnings or Precautions
Suicidal behavior and ideation [black box warning]: All patients with MDD, but especially children and young adults, are at increased risk for worsening suicidal thoughts and behaviors during bupropion treatment. Suicidal ideation was rarely reported (0.2%) in Contrave clinical trials among adults. Monitor at-risk patients for changes in thoughts or behaviors during treatment and prescribe the lowest number of tablets needed per prescription to reduce overdose risk.

Table 7. Approved Long-term Agents: Contraindications, Warnings, or Precautions[40,41,44-46]

Neuropsychiatric adverse events and suicide risk during smoking cessation: Serious neuropsychiatric events (eg, depression, mania, psychosis, agitation, aggression, suicide attempts) occurred among patients with or without pre-existing mental health conditions when using bupropion for smoking cessation. Depression and suicidal events with an unknown causal relationship to naltrexone treatment have been reported. Stop the medication and seek medical care immediately if these symptoms develop.

***Seizures*:** There is a dose-related increased risk for seizures with bupropion. Do not administer Contrave to patients at increased risk for seizures (see contraindications), and administer cautiously to patients with factors that may lower the seizure threshold (eg, history or head trauma, stroke, brain tumors, metabolic disorders, patients receiving hypoglycemic medications, use of other medications that lower the seizure threshold). Use Contrave as directed (ie, do not exceed 360 mg bupropion daily) and avoid administering Contrave with high-fat meals.

Patients receiving opioids should avoid Contrave since naltrexone use can precipitate opioid withdrawal. Before starting Contrave, patients should be opioid free for 7-10 days with short-acting opioids or longer (eg, 2 weeks) with long-acting opioids (eg, buprenorphine, methadone).

Increases in blood pressure and heart rate may occur during Contrave treatment in patients with or without hypertension at baseline. Monitor these parameters before initiation and during treatment with Contrave. Patients that might be more sensitive to changes in these parameters (eg, patients with heart failure or serious arrythmias or recent myocardial infection) were excluded from pivotal clinical trials.

Allergic reactions (eg, urticaria, angioedema, dyspnea) occurred in bupropion clinical trials and additional hypersensitivity events (eg, Stevens Johnson syndrome, anaphylactic shock) have occurred after marketing. Delayed hypersensitivity reactions resembling serum sickness have also been reported with bupropion. Monitor for these symptoms during use of Contrave.

Hepatotoxicity (eg, clinically significant toxicity and asymptomatic hepatic transaminase elevations) have occurred during naltrexone use especially in patients with risk factors for liver toxicity. Monitor for symptoms and discontinue Contrave for signs/symptoms of acute hepatitis.

***Mania*:** Bupropion use may precipitate (hypo)mania. Screen patients for a personal or family history of bipolar disorder before starting Contrave.

Angle-closure glaucoma attacks may be triggered by bupropion in patients with narrow angles without a patent iridectomy.

Potential hypoglycemic risk in patients with T2DM taking antidiabetic medications: Due to weight loss, patients with T2DM taking hypoglycemic medications may be at increased risk for hypoglycemia during Contrave treatment. Monitor blood glucose before and during Contrave therapy. Reductions in the dose of antihyperglycemic medication may be considered.

Abbreviations: GLP-1 RA, glucagon-like peptide-1; MAOI, monoamine oxidase inhibitor; MDD, major depression disorder; T2DM, type 2 diabetes mellitus;

Table 8. Approved Short-term Agents: Contraindications, Warnings or Precautions[37-39,42,43,47-50]

Sympathomimetic Amines Drug-class Warnings

(Benzphetamine, Diethylpropion, Phendimetrazine, Phentermine)

Contraindications

- Cardiovascular disease (eg, CAD, stroke, arrhythmia, heart failure, uncontrolled hypertension)
- Concurrently or within 14 days of MAOI usage (risk for hypertensive crisis)
- Hyperthyroidism
- Glaucoma
- Agitated states
- Drug abuse history
- Known hypersensitivity or idiosyncratic reaction to drugs of this class

Warnings or Precautions (noted specifically for select products)

Avoid co-administration with other weight loss agents (including prescriptions, OTCs, herbals or serotonergic agents for weight loss) because efficacy and safety as combined weight loss therapy is not established.

Primary pulmonary hypertension (PPH)**:** Rare cases of PPH associated with diethylpropion or phentermine monotherapy and more cases with phentermine in combination with discontinued drugs (fenfluramine or dexfenfluramine) have been reported. A case-control study found a 23-fold increased risk of PH among patients using anorectic agents (including phendimetrazine, diethylpropion) when using these agents for more than 3 months. Monitor for unexplained dyspnea, angina pectoris, syncope, or lower extremity edema, and discontinue treatment if such symptoms develop. It is unknown whether there is increased risk of pulmonary hypertension with repeated courses of therapy; package inserts note that the possible risk cannot be ruled out.

Valvular heart disease: Cardiac mitral, aortic and/or tricuspid valve diseases have occurred in patients without a history of valvular disease taking anorectic agents (eg, with fenfluramine and dexfenfluramine, or rare cases with phentermine or diethylpropion alone). Longer length of use, co-use of anorectic agents, and use of higher than recommended doses may increase risk. Use is not recommended in patients with known vascular heart disease or heart murmur (phendimetrazine, benzphetamine, diethylpropion). Continue treatment beyond 4 weeks only if there is a satisfactory response (eg, at least 4 pounds weight loss) (phendimetrazine, benzphetamine, diethylpropion).

Discontinue treatment if tolerance develops: Tolerance to weight-loss effects of these drugs may develop. Do not increase the dose above the recommended dose if tolerance occurs; the drug should be discontinued.

Caution in patients with hypertension: Use of these agents may increase blood pressure; exercise caution even in patients with mild hypertension. Not recommended for severely hypertensive patients or patients with other cardiovascular diseases (benzphetamine, diethylpropion).

Impaired ability to engage in hazardous tasks: May impair ability to safety operate machinery or drive; advise patients to exercise caution.

Abuse and physical dependence risk; and extreme fatigue and depression with abrupt discontinuation: these agent have some structural and pharmacologic properties similar to stimulants that have been abused (eg, amphetamines). Consider the potential for abuse when weighing the benefits versus risks of treatment. *Prescribe the lowest needed dose and amount at one time to mitigate overdosage.*

There is a risk of withdrawal symptoms upon abrupt cessation after prolonged use; extreme fatigue and depression have been reported after abrupt discontinuation of high dosages.

Use with alcohol can lead to adverse effects (phentermine, phendimetrazine, diethylpropion).

Table 8. Approved Short-term Agents: Contraindications, Warnings or Precautions[37-39,42,43,47-50]

Additional for Phentermine
Contraindications
• Pregnancy (may cause fetal harm) or nursing
Warnings or Precautions
Hypoglycemic DM medication dose reductions: Reductions in insulin or oral hypoglycemic medications may be needed when used with this medication.
Additional for Benzphetamine
Contraindications
• Concurrent use with CNS stimulants • Pregnancy (may cause fetal harm)
Warnings or Precautions
Psychological disturbances: These events have occurred in patients taking anorectic agents and undergoing a restricted diet. ***Use not recommended if another anorectic agent has been used in the past year*** ***Insulin co-use:*** The needed insulin dose may be altered when used with benzphetamine along with restricted caloric intake.
Additional for Phendimetrazine
Contraindications
• Concurrent use with CNS stimulants or anorectic agents • Pregnancy (may cause fetal harm) or nursing • Pulmonary hypertension
Warnings or Precautions (noted specifically for a particular formulation).
Use not recommended if another anorectic agent has been used in the past year ***Co-use may decrease hypotensive effect of guanethidine*** ***Yellow tablets may contain tartrazine*** **(FD&C Yellow No. 5)** which can rarely cause allergic reactions in susceptible patients. (Phendimetrazine IR tablet only) ***Hypoglycemic DM medication co-use*****:** The needed dose for these DM medications may be altered when used with phendimetrazine. (Phendimetrazine ER capsule only)
Additional for Diethylpropion
Contraindications
• Concurrent use with anorectic agents • Pulmonary hypertension
Warnings or Precautions
Use not recommended if another anorectic agent has been used in the past year ***Toxic psychosis and hallucinations*****:** Rare hallucinations and some cases of toxic psychosis have occurred, primarily after using higher dosages including doses exceeding the recommended amount. Psychosis reverted after discontinuation of diethylpropion. ***Seizure risk in patients with a seizure disorder*****:** Use may increase the frequency of seizures in susceptible patients; monitor at-risk patients carefully. Adjusting the diethylpropion dose or discontinuation may be necessary.

[a] *Labeled contraindications, warnings or precautions specifically listed in prescribing information for each active ingredient are listed together first, followed by information specific to one or more (but not all) other active ingredients.*

Abbreviations: DM, diabetes mellitus; CAD, coronary artery disease; MAOI, monoamine oxidase inhibitor; OTC, over-the-counter; PPH, primary pulmonary hypertension; SSRI, selective serotonin reuptake inhibitor;

8.6 Drug Combinations

Product information for the newer WMPs, with the exception of orlistat, highlight that the safety and effectiveness of combining multiple weight loss drugs has not been established. Labeling for the early-approved WMPs recommends their use as monotherapy, and with the exception of phentermine, recommends against their initiation within 1 year of another anorectic agent.[37,38,47,50] The rationale for the latter recommendation is not provided. Liraglutide (Saxenda) and semaglutide (Wegovy) should not be combined with other GLP-1 RAs, such as those approved for the treatment of T2DM.[45,46] Naltrexone/bupropion ER should not be used with other bupropion-containing agents to prevent supratherapeutic bupropion doses.[44] We are aware of related information regarding other pertinent drug combinations:

a. Naltrexone/bupropion ER (NB) has been studied in combination with incretin therapies, GLP-1 RAs (*at dosages used for T2DM*) and DPP-4 inhibitors, in patients with T2DM in the LIGHT RCT. A post-hoc assessment of this trial observed greater improvements in weight loss with NB combined with an incretin therapy (either GLP-1 RA or DPP-4 inhibitor) vs. combination with placebo. Adverse events (mainly gastrointestinal, musculoskeletal, headache, and tremor) were slightly higher in the NB/incretin combination groups versus NB/placebo; yet, the frequency of most adverse events were low, occurring in 3% or less of treated patients, with the exception of nausea (occurring in 7-9%).[108]

b. Authors of a post-hoc assessment evaluating the impact of naltrexone/bupropion ER in combination with antidepressants in a subset of patients on antidepressants from a large RCT concluded that the combination was generally well-tolerated and naltrexone/bupropion ER was effective in promoting weight loss regardless of antidepressant use.[109]

c. A double-blind RCT assessed the combination regimen of phentermine 37.5 mg once daily and orlistat 120 mg three times daily vs. matched dose phentermine/placebo in patients with obesity or overweight. At week 12, greater changes in endothelium-dependent vasodilation (primary endpoint) were achieved with orlistat/phentermine vs. placebo/phentermine. Both treatment groups similarly lost about 6 kg of weight from baseline, but mean changes in total and non-high-density lipoprotein cholesterol were significantly greater in the orlistat/phentermine group than in the placebo/phentermine group. Adverse events were similar between treatment groups (ie, $p>0.05$ for the incidence rate differences).[110]

9.0 CONSIDERATIONS FOR PRIOR AUTHORIZATION (PA) CRITERIA

In order to prevent the use of weight-loss agents in non-indicated patients among the Medicaid population, the following prior authorization (PA) criteria (and/or educational notes) may be considered for implementation:

1. *Age restriction based on the labeled indications*
   a. The following bullets summarize the age for use according to product labels; may refer to Table 2 for fuller wording of FDA-approved indications:
      i. ≥ 12 years of age for liraglutide 3.0 mg, orlistat, semaglutide 2.4 mg, and phentermine/topiramate ER
      ii. ≥ 17 years of age for benzphetamine, diethylpropion, phendimetrazine, phentermine; the particular brand of phentermine, Lomaira, is not recommended for chronic treatment of pediatric patients.
      iii. ≥ 18 years of age for naltrexone/bupropion ER

2. ***Initial** BMI consistent with the labeled indication (plus requirement for presence of at least 1 weight-related comorbidity for BMI 27 to 29)*
   a. The newer weight-management pharmacotherapies (WMPs), in addition to a subset of the early-approved WMPs (phentermine and phendimetrazine ER), are approved for **adults** with an initial BMI ≥30 kg/m^2, or ≥27 kg/m^2 in the presence of at least one weight-related complication (WRC). For **pediatric patients**, indicated BMIs vary per product as follows: liraglutide 3.0 mg is indicated for pediatric patients weighing **> 60 kg** and with an initial BMI corresponding to ≥ 30 kg/m^2 for adults by international cut-offs; semaglutide 2.4 mg and phentermine/topiramate ER are indicated for pediatric patients with an initial BMI at the 95th percentile or greater for age and sex.[37-50]
   b. Benzphetamine, diethylpropion, and phendimetrazine IR are approved for the management of exogenous obesity in patients with an initial BMI ≥30 kg/m^2 *who have not responded to diet and exercise alone.*[37,38,47]
   c. If a BMI requirement is included on the PA form, we suggest phrasing of the criterion to include '***initial*** BMI', so as to not inadvertently cause responders with improved BMI to discontinue therapy at reauthorization.
      i. Weight management treatment, particularly with the approved long-term agents, is intended for long-term use. Improvement of BMI is not itself a reason to discontinue therapy because therapy is generally required to maintain weight loss.

3. *Attestation that the patient intends to engage in lifestyle modification*, considering that obesity medications are approved and recommended as an adjunct to lifestyle modification (eg, reduced calorie diet, increased physical activity).

4. *Attestation that the prescriber has performed the following laboratory assessments prior to initiating **phentermine/topiramate ER** (or may include as an educational note on the PA form):*
   a. Blood chemistry including bicarbonate, creatinine, and potassium in all patients; glucose in patients with T2DM; and pregnancy test in patients with childbearing potential.
      i. Infrequent cases of hyperchloremic, non-anion gap, metabolic acidosis have been reported with this medication. Predisposing factors to metabolic acidosis include renal disease, severe

respiratory disorders, status epilepticus, diarrhea, surgery, ketogenic diet, and carbonic anhydrase inhibitors (avoid concomitant use if possible, or closely monitor).[40]

ii. Because topiramate is a teratogen, the labeling advises that patients of childbearing potential should use reliable birth control, and have a negative pregnancy test before its initiation and on a monthly basis while on therapy.[40]

5. *Attestation that the prescriber has performed the following counseling for certain medications (or may include as an educational note):*

a. If prescribing **orlistat**, the patient should be instructed to

i. Take a multivitamin (2 hours before or after taking orlistat) that contains fat-soluble vitamins to help ensure adequate nutrition. Orlistat reduces absorption of some fat-soluble vitamins and beta-carotene.[41]

ii. Orlistat should be used in conjunction with a diet of ~30% of total daily calories from fat, spread over 3 daily meals; consuming fat calories exceeding this amount is associated with increased adverse effects. The orlistat dose may be skipped if a meal does not contain fat.[41]

b. If prescribing **phentermine/topiramate ER** or **naltrexone/bupropion ER**, the patient should be instructed to

i. Take the phentermine/topiramate ER in the morning to prevent possible insomnia in the evening at bedtime.[40]

ii. Avoid taking the second dose of naltrexone/bupropion ER late in the day since this can precipitate insomnia.[10]

iii. Avoid taking naltrexone/bupropion ER with a high fat meal since this increases exposure significantly.[10]

6. *Consider including an educational note to inform prescribers/patients of the following:*

a. Naltrexone/bupropion ER and the sympathomimetic amine weight-loss therapies may result in a false positive urine drug screen for amphetamine.[44,105,111]

7. *Attestation that the prescriber has reviewed the labeled contraindications to the prescribed therapy, and concluded that the contraindications do not preclude treating this patient*

Additional Considerations

8. *Whether to step-through diet/exercise alone before initiating pharmacotherapy*:

a. Consider that the labeled indications of the newer WMPs do not require patients to first fail lifestyle modification alone before starting the medication. A subset of the early-approved WMPs (benzphetamine, diethylpropion, and phendimetrazine ER) are labeled differently, with the indication specifically for patients with obesity who have not responded to diet and/or exercise alone.[37-50]

b. Guidelines differ regarding whether adult patients should first fail lifestyle modification alone.

i. The 2022 AGA guideline is the only recent guideline to recommended pharmacotherapy ***after*** an inadequate response to diet/exercise alone, for indicated adult patients.[10]

ii. The 2023 ADA Standards of Care guideline (Chapter 8) does not address whether pharmacotherapy must be withheld until having failure of lifestyle therapy first.[79]
iii. The 2020 VHA/DoD guideline did not find sufficient evidence to make a recommendation regarding the optimal time to initiate pharmacotherapy (ie, whether to withhold therapy, regardless of disease severity, until after a failure of lifestyle therapy).[34]
iv. The 2016 AACE/ACE guideline considers the presence of WRCs as a factor for deciding when to start pharmacotherapy; the guideline recommends that *pharmacotherapy*/lifestyle modification can be stated as initial therapy (ie, without having to first fail lifestyle modification alone) in patients with Stage 1 or 2 obesity (with WRC), as defined by the AACE/ACE below:[4]
    - Obesity Stage 1 is defined as a BMI ≥27 with 1 or more mild to moderate WRCs present. According to the guideline, pharmacotherapy may be initiated concurrently with lifestyle therapy as initial therapy, or initiated after lifestyle therapy alone is insufficient to achieve weight loss target.
    - Obesity Stage 2 is defined as a BMI≥27 with at least 1 severe WRC present. Weight loss medication should be considered for initial treatment along with concurrent lifestyle therapy according to the guideline.

    If obesity (BMI is ≥30) is present but WRCs are not evident (ie, Obesity Stage 0) the guideline recommends that pharmacotherapy can be considered *after* lifestyle therapy alone is insufficient.[4]

v. The most recent pediatric guideline (2023 AAP) does not specify whether pharmacotherapy should be withheld until after a trial/failure of lifestyle therapy in indicated patients.[20] However, the older guideline by the Endocrine Society (2017) written prior to the approval of several medications with pediatric-specific indications, recommended considering adjunctive pharmacotherapy *after* failure of intensive lifestyle therapy.[36]

9. *Need for long-term treatment*; *limited information regarding early-approved WMPs*:

Obesity and weight-related conditions are now understood to be chronic conditions that require long-term management. Similar to the expected return of hypertension upon the discontinuation of antihypertensive medication, weight regain over time is expected to occur in most patients upon discontinuing obesity therapy. Nonetheless, while the newer WMPs are approved for chronic weight management, the early-approved medications are approved for short-term treatment only.

a. Diethylpropion and phentermine monotherapy as adjuncts to lifestyle interventions are *conditionally* recommended based on low-quality evidence by the AGA;[10] phendimetrazine and benzphetamine were not addressed by the AGA 2022 guideline. While short-term RCT evidence (eg, up to 12 weeks) is primarily available for early-approved WMPs, there was 1 RCT for phentermine monotherapy for up to 28 weeks, 2 RCTs for diethylpropion for 24 weeks, and 1 RCT for diethylpropion for up to 52 weeks.[10] The VHA/DoD and AACE/ACE guidelines considered that evidence was insufficient to recommend *short-term use* of pharmacotherapy. The VHA/DoD did not provide a recommendation for or against use of the sympathomimetic amines for short-term, long-term, or intermittent weight management;[24] and the AACE/ACE stated that they could not recommend short-term use of weight-loss medications.[4] The 2 guidelines for the management of pediatric patients (2023 AAP and 2017 ES) do not make drug-specific recommendations but in

general approach obesity as a chronic condition that should be treated with long-term care strategies, which may include pharmacotherapy in indicated patients.[20,85]

10. Drug combinations:

a. Liraglutide (Saxenda) and semaglutide (Wegovy) should not be combined with other GLP-1 RAs, such as those approved for the treatment of T2DM.[45,46] However, considerations may be made for initial overlap of prescription day's-supply when patients are transitioning between therapies.

b. Weight management pharmacotherapies should not be combined with other products with the same active ingredient (eg, bupropion monotherapy with naltrexone/bupropion), nor should products from the same medication class be used together (eg, 2 sympathomimetic amines like diethylpropion and phentermine).[37-50]

c. Consider that the efficacy/safety of combining various formulations approved for weight loss/maintenance has not been established. However, this does not necessarily preclude the appropriate use of **non-**GLP-1 based weight loss therapies with lower-dose GLP-1 RA formulations approved for the treatment of T2DM.

i. Product information for newer WMPs, with the exception of orlistat, highlights that the safety and effectiveness of combining multiple weight loss drugs have not been established.[37-50]

ii. Labeling for the early-approved WMPs advises that they are to be used as monotherapy only. Additionally, with the exception of phentermine, product information recommends against their initiation within 1 year of another anorectic agent;[37,38,47,50] however, the rationale is not provided. Phentermine labeling has a warning to avoid its combination with other serotonergic agents, including selective serotonin reuptake inhibitors.[48]
We are aware of at least 1 short-term study using a combined regimen with orlistat and phentermine.[110]

11. *Labeled maintenance dose and weight-loss targets:*

a. With the exception of orlistat, labeling for the newer WMPs recommends discontinuation if either certain dosages are not tolerated or if the patient does not meet certain weight loss targets as summarized below. Nonetheless, there may be clinical scenarios in which lower dosages may be favored, or slower weight loss may occur (eg, due to interruptions in therapy) based on the patient's individual circumstances. A labeled stopping rule based on response at a certain week was not included for semaglutide since the data did not support such rule.[112] In a trial designed to evaluate a stopping rule for semaglutide, many non-responders at week 20 (ie, those with less than 5% weight reduction) were still able to benefit by week 68, achieving ≥5% weight loss, and considerably more compared to the placebo comparison group (52% vs. 12%). The FDA-review document for semaglutide comments that stopping rules for previously approved drugs (ie, Qsymia, Contrave, and Saxenda) were not based on prospective trials designed to evaluate the predictive value of their stopping rules, but rather were determined from a post-hoc review of data.[112]

i. Semaglutide labeling advises discontinuation of the medication if the adult patient cannot tolerate the high-end dose of 2.4 mg weekly, or if the pediatric patient cannot tolerate the 1.7 mg dose. Note that titration to the maintenance dose may take at least 20 weeks, being that a temporary decrease in dose or delay in dose escalation for 4 weeks is permitted.[46]

ii. Liraglutide labeling advises discontinuation if an adult patient has not reached 4% of baseline body weight by 16 weeks after initiation, or if a pediatric patient has not lost 1% of baseline

body weight after 12 weeks on the maintenance dose, since "…it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment."[45] Discontinuation of the medication is also recommended if the adult patient cannot tolerate the high-end dose (3 mg daily) or if the pediatric patient cannot tolerate the 2.4 mg dose. It may take at least 5 weeks to titrate to the maintenance dose, as a temporary delay in dose escalation for 1 week is permitted.[45]

iii. Labeling for phentermine/topiramate ER advises to discontinue the medication if after 12 weeks on the max dose (15 mg/92 mg) if there is not a weight loss for adults of at least 5% body weight, or at least a 5% BMI loss for pediatric patients. Note that the medication *should be tapered off* rather than abruptly discontinued; and patients may take at least 16 weeks to titrate up to the 15 mg/92 mg dose. Nonetheless, not all patients require the highest dose to attain the weight loss target, and a dose of 7.5 mg/46 mg should not be exceeded, per product information, in patients with moderate to severe renal impairment, or with moderate hepatic impairment.

iv. Labeling for naltrexone/bupropion ER advises to evaluate response after 12 weeks on the maintenance dosage and to discontinue if at least 5% of baseline body weight loss has not been achieved. Titration may take approximately 4 weeks.[44]

b. If restrictions are made on the PA form regarding meeting certain weight loss targets and/or maintenance dosages, consider having an area for the provider to express patient-specific scenarios (eg, interruption in therapy) or reasons for which their clinical judgement favors a lower dosage (and/or slower rate of weight loss).

i. We are aware of an expert consensus statement and an expert opinion paper for managing GI-side effects of GLP-1 RAs.[113,114] GI side effects related to GLP-1 RAs are described to typically be transient, starting during the dose-escalation phase and resolving around the time the maintenance dose is reached. GI adverse event rates with GLP-1 RAs (semaglutide and liraglutide) were generally higher in obesity trials compared to T2DM trials since higher doses were used for the obesity trials.[114] Authors advise considering slower dose-escalation approaches (compared to that in package inserts) for patients with GI side effects during the escalation phase when initiating GLP-1 RA therapy. Consideration of lower doses is also recommended for patients unable to tolerate the standard maintenance dose if other options are insufficient (eg, hydration/dietary intervention, *short-term* symptomatic treatment with pharmacotherapy). [113,114]

ii. *Depression:* The 2016 AACE/ACE guideline notes that patients with depression may consider using phentermine/topiramate ER at lower dosages than the usual maintenance dosage (eg, using initiation doses as the ongoing maintenance dose), considering the dose-dependent increase in the incidence of depression observed in phentermine/topiramate ER trials.[40]

iii. Unexpected or planned interruptions in treatment may also be considered as a potential reason to extend the time frame for a weight-loss target.

10.0 SUMMARY

Obesity develops and is often perpetuated by an interplay of factors beyond personal choice including genetic, psychologic, socioeconomic, and environmental contributors.[20] Weight-related complications (WRCs) of obesity stem from the prothrombotic, pro-inflammatory, angiogenic, diabetogenic, and biomechanical effects of excess adiposity.[13-16] The AACE/ACE recommends for patients with overweight or obesity to be screened regularly for WRCs. WRCs caused or exacerbated by excess adiposity include T2DM, dyslipidemia, hypertension, cardiovascular (CV) disease/mortality, nonalcoholic fatty liver disease, obstructive sleep apnea, osteoarthritis, gastroesophageal reflux disease, depression, polycystic ovary syndrome, among others.[4] Obesity is considered a chronic medical condition. But of course, screening and management of obesity should be reserved to those who are receptive to such discussions/approaches (ie, patients who have given permission to the provider to discuss risks related to their weight and intervention options); guidelines generally advise a shared-decision making approach with the patient/caregiver for choosing therapy.[4,20,24] Moreover, experts recommend population-level efforts to help prevent obesity and its associated disease burdens.[60,115,116]

Benefits of weight reduction among people with obesity may include, but are not limited to, improvements in cardiometabolic comorbidities, reduced risk for premature death and incidence of certain cancers, and improvements in quality of life.[3,4] Weight reduction of ≥5% is a common goal since it is correlated with clinically significant improvements in cardiometabolic parameters; but, benefits tend to increase with greater weight loss from baseline (eg, ≥10%), including improvement or resolution of some WRCs.[10,34,65,66] Foremost, clinical guidelines recommend lifestyle modifications (caloric deficit, physical activity, and behavior modifications) to achieve weight-related goals. However, authors acknowledge that many patients are unable to achieve or maintain weight goals with lifestyle intervention alone— thus, creating a place-in-therapy for the option of pharmacotherapy especially in the presence of WRCs.

Weight-management pharmacotherapies (WMPs) are intended for adjunctive use with lifestyle modifications (eg, increased physical activity, reduced calorie diet). WMPs are approved for adults with initial obesity (ie, BMI ≥30 kg/m^2), and most are additionally approved for overweight (BMI ≥27 kg/m^2) in the presence of at least one WRC.[37-50] Early-approved agents (phentermine, diethylpropion, phendimetrazine, and benzphetamine) are controlled substances and were approved for short-term use. Products approved for long-term weight management include oral formulations with orlistat, phentermine/topiramate ER (also a controlled substance), or naltrexone/bupropion ER; and 2 subcutaneous GLP-1 RAs, liraglutide 3.0 mg and semaglutide 2.4 mg. Several agents have specific pediatric indications for obesity (liraglutide, semaglutide, and phentermine/topiramate; each approved for children ≥ 12 years of age); labeling for others recommends against use in patients <12 years of age (as with orlistat), or <17 years of age (as with the early-approved agents).[37-50]

The 2023 AAP guideline continues to recommend that providers offer or refer pediatric patients with overweight or obesity to intensive health behavior and lifestyle treatment.[20] Lifestyle interventions are also recommended for adults with overweight or obesity. Because a strong evidence-base to support delaying pharmacotherapy is lacking, guidelines differ regarding whether patients should first fail lifestyle modification alone (refer to Section 9.0, Item 8.b.).

Guidelines recommend consideration of WMPs, adjunctive to lifestyle modification, for adults with obesity (BMI ≥ 30 kg/m^2) or overweight (BMI ≥ 27 kg/m^2) with a WRC;[10,117,118] and for pediatric patients with obesity (BMI ≥ 95th percentile).[20,36] The AAP provided specific age thresholds for which pharmacotherapy could be considered as an option: for adolescents ≥12 years old (grade B), and possibly for children 8-11 years old (non-graded statement) with obesity in some circumstances.[20] While agents approved for long-term use are generally considered as options across guidelines, guidelines differ with respect to using the early-approved agents approved for short-term treatment (refer to Section 9.0, Item 9.a.).

Section 8.0 summarizes the pros/cons of each WMP according to the effect magnitude for weight reduction, potential indications aside from weight reduction, and the safety profile. Prior authorization (PA) criteria are proposed in Section 9.0, taking into account the labeled BMI and age for use according to the FDA-approved indication. Provider attestation or educational notes may also be considered for incorporation into the PA form to help ensure certain laboratory screening or counseling has been completed upon starting certain therapies.

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11.0 APPENDIX A – META-ANALYSIS EFFECT ESTIMATES

Table A1. 2022 AGA Meta-analysis Effect Estimates for Weight Management Agents[10]

Agents	Key Results[a]
Liraglutide 3.0 mg daily	*Moderate magnitude of effect for weight loss* MD %TBWL: 4.81% (95% CI, 4.23%, 5.39%) in favor of liraglutide MD kg-weight loss: 5.3 kg (95% CI, 4.7 kg, 5.9 kg) in favor of liraglutide Informed by 9 studies with follow-up of at least 52 weeks; study populations were with or without T2DM, or were a mixed population Notably a few studies required patients to lose at least 5% of TBWL before randomization.
Semaglutide 2.4 mg weekly	*Large magnitude of effect for weight loss* MD %TBWL: 10.76% (95% CI, 8.73%, 12.80%) in favor of semaglutide MD kg-weight loss: 10.81 kg; (95% CI, 8.19, 13.43 kg) in favor of semaglutide Informed by 8 RCTs with follow-up ranging from 52 to 72 weeks; study populations were with or without T2DM, or were a mixed population.
naltrexone/ bupropion ER vs. placebo	*Moderate magnitude of effect for weight loss* MD %TBWL: 3.01% (95% CI, 2.47%, 3.54%) in favor of naltrexone/bupropion MD kg-weight loss: 3.01% (95% CI, 2.62%, 3.39%,) in favor of naltrexone/bupropion Informed by 5 RCTs with follow-up of 56 weeks: study populations were with or without T2DM, or were a mixed population.
Orlistat vs. placebo	*Small magnitude of effect for weight loss* MD %TBWL: 2.78% (95% CI, 2.36%, 3.20%) in favor of orlistat MD kg-weight loss: 2.81% (95% CI, 2.17%, 3.45%) in favor of orlistat Informed by 15 RCTs with follow-up between 48 weeks to 4 years.
phentermine/ topiramate ER vs. placebo	*Moderate to large magnitude of effect for weight loss* 15 mg/92 mg dose result: MD %TBWL: 8.45% (95% CI, 7.89%, 9.01%) in favor of phentermine/topiramate 7.5 mg/46 mg dose result: MD %TBWL: 6.55% (95% CI, 5.66%, 7.44%) in favor of phentermine/topiramate Informed by 3 RCTs with follow-up of 52 to 56 weeks; one trial included a mix of patients with and without T2DM

Table A1. 2022 AGA Meta-analysis Effect Estimates for Weight Management Agents[10]

Phentermine vs. placebo	*Moderate magnitude of effect for weight loss* MD %TBWL: -3.36% (95% CI, -4.29%, -2.97%) in favor of phentermine MD kg-weight loss: -4.74% (95% CI, -5.73%, -3.75%) in favor of phentermine Informed by 8 RCTs with follow-up of 12-28 weeks. Studies included patients with well-controlled diabetes.
Diethylpropion vs. placebo	*Moderate magnitude of effect for weight loss* MD %TBWL: -5.36% (95% CI, -7.23%, -3.50%) in favor of diethylpropion MD kg-weight loss: -4.74% (95% CI, -6.40%, -3.08%) in favor of diethylpropion Informed by 6 RCTs; 1 RCT had follow-up out to 52 weeks, and others had 24 or 12 weeks of follow-up. None included patients with T2DM.

[a] *Supportive clinical trials for the approval of the anti-obesity medications studied these therapy as an adjunct to lifestyle modifications (eg, 500–600 kcal/d deficit, 150 minutes of physical activity per week, +/- behavior therapy)*

Abbreviations: CI, confidence interval; MD, mean difference; RCTs, randomized controlled trials; T2DM, type 2 diabetes mellitus; TBWL, total body weight loss

12.0 APPENDIX B –ADVERSE EVENTS AND DRUG INTERACTIONS

Table B1. Weight Management Agents: Common Adverse Events from Package Inserts

Active Ingredient	Common[a] Adverse Events from Clinical Trials
Agents Approved for Short-term Treatment	
Diethylpropion[47,58]	Select AEs (AE frequency in clinical trials is not reported): • *CV reactions*: tachycardia, arrhythmia, increased BP, palpitations • *CNS reactions*: nervousness, *restlessness*, dizziness, insomnia, anxiety, euphoria, drowsiness, headache, overstimulation, dyskinesia, tremor • *GI reactions*: vomiting, diarrhea, dry mouth, nausea, unpleasant taste • *Allergic reactions*: rash, urticaria, erythema, ecchymosis • *Endocrine reactions*: impotence, libido changes, gynecomastia, menstrual changes • *Hematopoietic reactions*: bone marrow depression, leukopenia, agranulocytosis
Phentermine hydrochloride[42,43,48,49,57]	Select AEs (AE frequency in clinical trials is not reported): • *CV reactions*: palpitation, tachycardia, increased BP, ischemic events, valvular disease/PH • *CNS reactions:* overstimulation, restlessness, insomnia, euphoria, dysphoria, tremor, headache, psychosis • *GI reactions:* dry mouth, diarrhea, constipation, unpleasant taste • *Allergic reactions:* urticaria • *Endocrine reactions:* impotence, libido changes
Phendimetrazine tartrate[50,59]	Select AEs (AE frequency in clinical trials is not reported): • *CV reactions*: tachycardia, arrhythmia, increased BP, palpitations; labeling for the ER capsule only: ischemic events, valvular disease/PH • *CNS reactions*: agitation, overstimulation, insomnia, flushing, tremor, dizziness, headache, blurred vision, psychosis • *GI reactions*: diarrhea, dry mouth, nausea, constipation, stomach pain • *Genitourinary reactions*: increased urinary frequency, dysuria, libido changes
Benzphetamine[51]	Select AEs (AE frequency in clinical trials is not reported): • *CV reactions*: palpitation, tachycardia, increased BP • *CNS reactions*: overstimulation, restlessness, dizziness, insomnia, tremor, sweating, headache • *GI reactions*: dry mouth, nausea, diarrhea, unpleasant taste • *Allergic reactions*: urticaria, skin reactions • *Endocrine reactions*: libido changes
Agents Approved for Long-Term Treatment (>12 weeks)	
Orlistat[41]	AEs among **≥5%** of patients and at least 2x the placebo rates, among **adults** over 1 year follow-up: • Oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, fecal incontinence Usually, GI adverse events usually resolve within 1 month of treatment *Pediatric patients* 12-16 years old: similar types and frequency of AE vs adults

Table B1. Weight Management Agents: Common Adverse Events from Package Inserts

Liraglutide[45]	AEs among **≥5**% of patients and at least 2x the placebo rates, among **adults** over a median of 56 week trial: • Nausea, diarrhea, constipation, vomiting, dyspepsia, increased lipase Hypoglycemia rates were increased compared to placebo in patients with T2D. AEs among ≥5% of patients and at least 2x the placebo rates, among **pediatrics ≥ 12 years** over 56 weeks follow-up: • Nausea, vomiting, hypoglycemia, gastroenteritis, dizziness Hypoglycemia rates were increased versus placebo despite not enrolling patients with T2D, but no hypoglycemic events were severe.
Semaglutide[46]	AEs among **≥5%** of patients and at least 2x the placebo rates, among **adults** for up to 75 weeks (including 7 weeks without treatment): • Nausea, vomiting, constipation, abdominal pain, fatigue, dyspepsia, hypoglycemia (T2D patients only), increased amylase and lipase AEs among **≥5%** of patients and at least 2x the placebo rates, among **pediatrics ≥ 12 years** over a 68 week trial: • Nausea, vomiting, abdominal pain, dizziness, gastroenteritis, constipation, increased amylase and lipase
Naltrexone/ bupropion ER[107]	AEs among **≥5%** of patients and at least 2x the placebo rates, among **adults** over up to a 56 week trial: • Nausea, constipation, vomiting, dizziness, insomnia, dry mouth
Phentermine/ topiramate ER[40]	AEs among **≥5%** of patients (for at least 1 phentermine/topiramate ER dose arm) and at least 2x the placebo rates among **adults** over 1 year follow-up: • Paresthesia, dry mouth, constipation, dysgeusia, dizziness, influenza, persistent decreased sodium bicarbonate below NR, increased SCr ≥ 0.3 mg/dL Among common AEs, the incidence of paresthesia, dry mouth, constipation, dysgeusia, dizziness tended to be dose-related (increasing incidence with increasing dose) AEs among **≥2%** of patients (for at least 1 phentermine/topiramate ER dose arm) and at least 2x the placebo rates among **pediatrics ≥ 12 years** over a 56-week trial: • Depression, pyrexia, dizziness, arthralgia, paresthesia, anxiety, upper abdominal pain, ear infection, musculoskeletal chest pain, influenza, ligament sprain, increased SCr ≥ 0.3 mg/dL

[a] AEs occurring at least at the frequency reported for each drug. For short-term agents, the incidence of events was not reported. Selected events were listed unless specifically described as rare or infrequent.

Abbreviations: AE, adverse events; BP, blood pressure; CNS, central nervous system; CV, cardiovascular; ER, extended-release; GI, gastrointestinal; NR, normal range; PH, pulmonary hypertension; SCr, serum creatinine; T2D, type 2 diabetes mellitus; x, times

Table B2. Potential Drug-Drug Interactions and Metabolism Information from Package Inserts[37-50,57]

	Interacting Medication (effect and/or recommended action from PI)	Metabolism/ CYP450 Effect
Agents Approved for Short-term Treatment		
Interactions in common for sympathomimetic agents	• **MAOIs**: concomitant use is contraindicated; separate administration by at least 14 days • **Antidiabetic drugs including insulin**: needs for these drugs may be altered; dosage adjustments may be needed	
Additional for Diethylpropion[37,47]	• **Anorectic agents** (eg, other sympathetic amines for weight loss): concomitant use is contraindicated due to risk for cardiac problems • **General anesthetics:** increased risk for arrhythmias • **Anti-HYPOtensive drugs** (eg, vasopressors): co-use may have additive pressor effects • **Select anti-HYPERtensive drugs** (eg, guanethidine, α-methyldopa): co-use may decrease anti-hypertensive effectiveness • **Phenothiazines**: co-use may decrease diethylpropion effectiveness • **Alcohol**: co-use may increase the risk for CNS depression	Extensive metabolism by dealkylation and reduction to active metabolites. Any interaction(s) with CYPs not reported.
Additional for Phentermine hydrochloride[42,43,48,49,57]	• **Alcohol**: co-use increases the risk for adverse events • **Adrenergic neuron blocking drugs**: co-use may decrease the anti-hypertensive effect of these drugs	No information provided by PI
Additional for Phendimetrazine tartrate[39,50]		Metabolized to ≥ 2 metabolites with unknown activity. Any interaction(s) with CYPs not reported.
Additional for Benzphetamine[38]	• **Anorectic agents** (eg, other sympathetic amines for weight loss): concomitant use is contraindicated due to risk for cardiac problems • **CNS stimulants**: do NOT use with benzphetamine • **Tricyclic antidepressants**: co-use may increase TCA effect • **Urinary alkalinizing agents**: co-use may increase levels of benzphetamine • **Urinary acidifying agents**: co-use may decrease levels of benzphetamine	No information provided by PI
Agents Approved for Long-Term Treatment (>12 weeks)		
Orlistat[41]	• **Amiodarone:** orlistat may slightly reduce systemic exposure to amiodarone • **Cyclosporine:** separate administration advised • **Levothyroxine**: monitor for thyroid function changes • **Warfarin**: monitor for anticoagulation status changes • **Antiepileptic drugs**: monitor for changes in seizure severity or frequency • **Antiretroviral drugs**: monitor for changes in HIV RNA levels • **Fat-soluble vitamins**: administer a multivitamin	Metabolized within GI wall to inactive metabolites
Liraglutide[45]	• **Orally administered medications:** delays gastric emptying; monitor for effect on other drugs • **Hypoglycemic drugs**: hypoglycemic risk increased	Catabolism similar to large proteins. Interactions with CYPs not expected.
Semaglutide[46]		Proteolytic cleavage

Table B2. Potential Drug-Drug Interactions and Metabolism Information from Package Inserts[37-50,57]

Naltrexone/ bupropion ER[107]	• **MAOIs**: concomitant use is contraindicated; separate administration by at least 14 days • **Opioids**: decreased opioid effectiveness and may precipitate withdrawal; wait at least 7-10 days after chronic opioid use • **CYP2D6 substrates** : co-use may substantially increase exposure; co-administer cautiously and use the lowest effective dose of substrates • **Digoxin:** may decrease DIG levels; monitor DIG plasma levels • **CYP2B6 inhibitors** : may increase BUP exposure; administer a max 2 tablets of NAL/BUP daily) • **CYP2B6 inducers**: may reduce BUP effectiveness; avoid co-use with *ritonavir, lopinavir, efavirenz* • **Seizure threshold-lowering drugs:** use cautiously, use with other BUP drugs contraindicated; start with the lowest NAL/BUP dose and titrate slowly • **Dopaminergic drugs – levodopa, amantadine** :may precipitate CNS toxicity – monitor and co-use cautiously • **Alcohol:** possible neuropsychiatric events or reduced alcohol tolerance; avoid or minimize use with alcohol	Naltrexone undergoes non-CYP metabolism to an active metabolite. Bupropion is a substrate for CYP2B6 and inhibitor of **CYP2D6**. Bupropion is metabolized to 3 active metabolites.
Phentermine/ topiramate ER[40]	• **MAOIs**: concomitant use is contraindicated; separate administration by at least 14 days • **Oral contraceptives:** co-use may lead to irregular bleeding • **CNS depressants:** co-use may potentiate CNS adverse events; may consider PHEN-TOP ER dose reduction for significant cognitive dysfunction • **Non-potassium sparing diuretics:** co-use may increase potassium-wasting; monitoring potassium during treatment • **Antiepileptic drugs:** co-use with phenytoin or carbamazepine may decrease TOP levels and co-use with VPA is associated with hyperammonemia ± encephalopathy – check ammonia levels in patients with symptoms of those disorders • **Carbonic anhydrase inhibitors:** AVOID co-use due to risk of metabolic acidosis; monitor for metabolic acidosis if used together • **Pioglitazone:** due to possible decreased pioglitazone levels, consider increased glycemic monitoring during co-use • **Amitriptyline:** may increase amitriptyline levels, adjust dose of that drug as needed during co-use	Neither PHEN nor TOP ER undergo extensive metabolism. PHEN is a minor substrate of CYP3A4.

Abbreviations: BUP, bupropion; CNS, central nervous system; CYP or CYP450, cytochrome P450 enzyme; Dig, digoxin; ER, extended-release; GI, gastrointestinal; IR, immediate release; MAOI, monoamine oxidase inhibitor;; PHEN, phentermine; PI, package insert; TCA, tricyclic antidepressants; TOP, topiramate; VPA, valproic acid