COLLEGE OF PHARMACY
UNIVERSITY OF UTAH

L. S. SKAGGS PHARMACY INSTITUTE

UTAH MEDICAID P&T REPORT
MAY 2023

PRESCRIPTION MEDICATIONS FOR WEIGHT MANAGEMENT

Benzphetamine
Diethylpropion
Liraglutide (Saxenda)
Naltrexone/bupropion ER (Contrave)
Orlistat (Xenical)
Phendimetrazine tartrate
Phentermine hydrochloride (Adipex-P, Lomaira)
Phentermine/topiramate ER (Qsymia)
Semaglutide (Wegovy)

Report finalized: April 2023
Report presented: May 2023

Drug Regimen Review Center
Lauren Heath, PharmD, MS, BCACP, Clinical Pharmacist
Valerie Gonzales, PharmD, Clinical Pharmacist
Monet Luloh, PharmD, Clinical Pharmacist
Kristin Knippenberg, MFA, Administrator and Editor
Joanne LaFleur, PharmD, MSPH, Director and Associate Professor

University of Utah College of Pharmacy, Drug Regimen Review Center

CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

AACE	American Association of Clinical Endocrinologists
AAP	American Academy of Pediatrics
ACE	American College of Endocrinology
AEs	adverse events
AGA	American Gastroenterological Association
BMI	body mass index
CNS	central nervous system
CS	controlled substance
CVD	cardiovascular disease
CYP	cytochrome P450 enzyme
DoD	US Department of Defense
ER	extended release
ES	Endocrine Society
FDA	US Food and Drug Administration
FDC	Fixed-dose combination
GI	gastrointestinal
GLP-1 RA	glucagon-like peptide 1 receptor agonist
HbA1c	glycated hemoglobin
IR	immediate release
LIR	liraglutide
MA	meta-analysis
MD	mean difference
PHEN	phentermine
PI	package insert or prescribing information
RA	receptor agonist
RCT	randomized controlled trial
SAE	serious adverse event
SEM	Semaglutide
SR	systematic review
SubQ	subcutaneous
T2DM	type 2 diabetes mellitus
TBWL	total body weight loss
TOP	topiramate
VA	Veteran Affairs
WRC	weight-related complication

EXECUTIVE SUMMARY

Background

Obesity is a chronic health condition of excess adiposity affecting many US children, adolescents, and adults.[4-8] Body mass index (BMI) is a practical population-level tool to screen for excess body fat,[5] and to identify people at risk for weight-related complications (WRCs).[9-12] Weight-associated health conditions contribute to increased disability and premature mortality among adults with obesity.[13] An increased risk for chronic conditions (eg, type 2 diabetes mellitus [T2DM], hypertension) also affects children with obesity.[12] Because obesity contributors are multifactorial, including both individual and systemic factors, policy makers should consider addressing structural, social, and economic contributors to obesity, in addition to facilitating evidence-based treatments for individuals.[14,15]

Treatments for overweight and obesity aim to facilitate weight loss to improve or prevent WRCs.[16] Options for treating overweight or obesity include lifestyle changes (eg, reduced caloric intake, exercise, behavioral changes), pharmacotherapy, and/or metabolic or bariatric surgery.[16-20] Although lifestyle therapy is a cornerstone of treatment, pharmacotherapy and metabolic surgery have a place in therapy for some patients, as they produce greater and more sustained weight loss compared with lifestyle modifications alone.[16,21]

We reviewed 9 products approved by the US Food and Drug Administration (FDA) for indications related to weight loss and/or management, most of which enhance satiety and/or decrease hunger leading to reduced caloric intake.[16,22] The reviewed agents can be put into two groups based on their FDA-approved duration for use: short-term (ie, a few weeks) or long-term. Short-term agents are mono-ingredient sympathomimetic amines,[23-32] including benzphetamine, diethylpropion, phendimetrazine, and phentermine monotherapy (Adipex-P, Lomaira). More recently approved agents are for long-term weight management: the glucagon-like peptide 1 receptor agonists (GLP-1 RAs), liraglutide 3.0 mg (Saxenda) and semaglutide 2.4 mg (Wegovy); lipase inhibitor, orlistat (Xenical); fixed-dose combination (FDC) opioid receptor antagonist and dopamine/norepinephrine reuptake-inhibitor, naltrexone/bupropion extended-release [ER] (Contrave); and FDC sympathomimetic amine and antiseizure agent, phentermine/topiramate ER (Qsymia).[33-37] The GLP-1 RAs are administered subcutaneously on a daily (liraglutide) or weekly (semaglutide) basis,[34,35] while the others are orally administered on a once daily to thrice daily basis.[23-33,36,37] Sympathomimetic amine-containing products are either schedule 3 or 4 controlled substances, depending on the agent.[23-32,36]

All included products are approved *as adjunctive therapy* to lifestyle modification.[23-38] Additionally, all are approved for people with obesity (eg, initial BMI ≥ 30 kg/m^2),[23-37] and the majority are also approved for adults with overweight (initial BMI ≥27 kg/m^2 up to <30 kg/m^2) in the presence of at least one WRC (eg, hypertension, T2DM, or dyslipidemia).[28-37] Agents only approved for obesity treatment include diethylpropion, phendimetrazine immediate-release (IR) tablets, and benzphetamine.[23-27,37] Products specifically indicated for pediatrics ≥ 12 years of age with obesity (ie, BMI ≥ 95th percentile for matched age and sex, or ≥ 30 kg/m^2) are liraglutide 3.0 mg, semaglutide 2.4 mg, and phentermine/topiramate ER;[34-36] others have a general indication not specific to an age group, but recommend against use below a certain age (eg, <12 years of age for orlistat, and <17 years of age for short-term products).[23-33] Naltrexone/bupropion ER is specifically indicated in adults only.[37]

US Guideline Recommendations for Weight Management Pharmacotherapy

US guidelines with pharmacotherapy recommendations to support weight loss for the general adult population include those by the American Gastroenterological Association (AGA; 2022),[22] US Veterans Health Administration and Department of Defense (VA/DoD; 2020),[17] and the American Association of Clinical Endocrinologists with the American College of Endocrinology (AACE/ACE; 2016).[16] US guidelines providing pediatric-specific recommendations include those by the American Academy of Pediatrics (AAP; 2023)[18] and the Endocrine Society (ES; 2017).[20] Generally, guidelines emphasize individualizing selection of pharmacotherapies for indicated children and adults, taking into consideration the risks versus benefits.[16-18,22]

For adults, *adjunctive* weight management pharmacotherapy may be considered for patients with obesity (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2) with a WRC.[16,17,22] Guidelines favor long-term treatment.[16,17,22] Short-term treatment (with any pharmacotherapy) is recommended against by the AACE/ACE,[16] and the VA/DoD is neither for or against use of the short-term agents.[17] In contrast, the AGA conditionally recommended treatment with diethylpropion or phentermine (the AGA did not address phendimetrazine or benzphetamine) based on low-quality evidence, noting that some providers may prescribe them for long-term use off-label in clinical practice.[22] Treatment with long-term agents liraglutide, naltrexone/bupropion ER, and phentermine/topiramate ER is recommended by all guidelines;[16,17,22] and semaglutide is recommended by the AGA, which is the only guideline that addressed its use.[22] Orlistat treatment is also recommended by the AACE/ACE and VA/DoD,[16,17] whereas the AGA *conditionally* recommended against its use due to having the lowest magnitude of benefit, which for some patients, may not outweigh potential AEs.[22] Semaglutide was considered to offer the largest magnitude of benefit on average, and thus may be a preferred therapy for many patients.[22]

For pediatric patients, guidelines recommend weight management pharmacotherapy *as an adjunct* to behavior/lifestyle treatment for children/adolescents with obesity (BMI ≥ 95th percentile).[18,20] Only the AAP provided specific age thresholds, considering pharmacotherapy an option for adolescents ≥12 years old (grade B), and possibly for children 8-11 years old (non-graded statement) in some circumstances.[18] Neither the AAP nor the ES prefer a specific weight loss agent for indicated pediatric patients.[18,20]

Direct Comparative Evidence

We reviewed randomized controlled trials (RCTs) comparing weight management agents to one another (head-to-head [H-H]) for the treatment of overweight or obesity. Six trials (5 RCTs and 1 RCT extension) were included. No H-H trials were found for benzphetamine, phendimetrazine, or naltrexone/bupropion ER, nor for patients under 18 years old. Except for 2 trials which also enrolled patients with overweight,[1,39] all included trials enrolled adults with obesity (BMI ≥ 30 kg/m^2) and without diabetes.

Semaglutide [SEM] subQ 2.4 mg weekly or 0.05-0.4 mg daily versus liraglutide [LIR] subQ 3.0 mg daily, with lifestyle co-interventions: Two open-label RCTs compared SEM to LIR for treatment of adults with obesity,[40] or obesity or overweight (BMI ≥ 27 kg/m^2) with ≥ 1 WRC.[1] In both trials, SEM (2.4 mg weekly or approximately equivalent daily doses) demonstrated superiority* to LIR for percent weight loss from

* Only the phase 3 trial (using semaglutide 2.4 mg weekly) formally tested for superiority of semaglutide to liraglutide. The second phase 2 trial did not adjust for multiple statistical comparisons.

baseline to 52 or 68 weeks (primary endpoint). At week 68, the proportion of patients losing ≥10% of baseline body weight favored SEM 2.4 mg (70.7%) over LIR 3.0 (25.6%).[1] The most frequent adverse effects (AEs) with both SEM 2.4 mg and LIR 3.0 mg were gastrointestinal (GI), with nausea being most common. AEs leading to treatment discontinuation occurred numerically more frequently with LIR (12.6%) versus SEM (3.2%). However, discontinuation rates could have been affected by the trial design; patients intolerant to SEM 2.4 mg were allowed to continue with 1.7 mg, whereas patients intolerant to LIR 3.0 mg were required to restart dose-titration or discontinue treatment (which is consistent with the product labeling).[1,35]

LIR subQ 1.2-3.0 mg daily versus orlistat [ORL] orally 120 mg three times daily, with lifestyle co-interventions including a low-fat diet: One open-label RCT (20 weeks)[41] and an extension study (63% of initial patients continued as randomized to year 1, and placebo-treated patients switched to LIR from year 1 to year 2)[42] compared LIR to ORL for treatment of obesity. Weight loss at 20 weeks was significantly greater with LIR treatment compared to ORL (primary endpoint); the proportion of patients with ≥10% weight loss from baseline also favored LIR (28.3%) to ORL (9.3%).[41] Cumulative weight loss after 1 and 2 years of follow-up also favored LIR.[42] During the 20-week RCT, AEs leading to treatment discontinuation were slightly more frequent with LIR (5.4%) compared to ORL (3.2%). LIR use was associated with vomiting and nausea, whereas ORL use was associated with diarrhea.[41] At 1 year follow-up, total non-serious psychiatric AEs (eg, insomnia, depressed mood, anxiety) occurred numerically more frequently with LIR (12.9%) versus ORL (5.3%).[42]

Phentermine [PHEN] 7.5-15 mg orally versus PHEN/topiramate [TOP] ER 7.5/46-15/92 mg orally daily, with lifestyle co-interventions: One double-blinded 6-month RCT demonstrated the superiority of combined treatment with PHEN/TOP to equivalent doses of PHEN monotherapy for treatment of obesity (primary endpoint). The proportion of patients with ≥10% weight loss at 28 weeks was significantly greater with PHEN/TOP 15/92 mg (40.8%) than PHEN 15 mg (20.8%). A numerically greater incidence of TOP-associated AEs (eg, paresthesia, dysgeusia, impaired attention) occurred with PHEN/TOP treatment compared to PHEN monotherapy.[43]

PHEN ER 30 mg orally daily versus diethylpropion ER [DIEP] 75 mg daily combined with caloric restriction: One smaller RCT (n=99) compared PHEN to DIEP among patients with unclear overweight or obesity status (patients exceeded their "desired" weight by ≥20%), demonstrating significantly greater mean weight loss at 12 weeks with PHEN (–18.2 pounds) versus DIEP (–13.8 pounds). Mean weight loss with DIEP tended to plateau between 8-12 weeks, unlike PHEN. Generally, similar AEs occurred with both treatments; AEs reported slightly more frequently with DIEP were dry mouth and dizziness, whereas more frequent AEs with PHEN were drowsiness and constipation.[39]

Safety and Warnings/Precautions

The safety profile varies by agent, with products in the same drug class having similar profiles. Select contraindications, warnings/precautions, or safety considerations for their use are noted below. Notably, all agents have potential drug-drug interactions (DDIs); key DDIs are summarized below (see Section 10 of the report for details).

Sympathomimetic amines (short-acting agents): These products are contraindicated in patients who may be sensitive to sympathomimetic effects (eg, severe or uncontrolled cardiovascular disease, hyperthyroidism, glaucoma, agitated states), among people with a history of drug abuse, and in patients with recent or current use of monoamine oxidase inhibitors (MAOIs). Key warnings for use of these agents include avoiding co-use with similar drugs, and possible increased risk for pulmonary hypertension and regurgitant cardiac valvopathies. Diethylpropion carries a unique warning for seizure risk.[24,27] Renal dose adjustments may be required.[23-32]

GLP-1 RAs (semaglutide and liraglutide): GLP-1 RAs are contraindicated among people with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Key warnings for GLP-1 RAs include an increased risk for acute pancreatitis, gallbladder disease, and kidney injury, especially in patients with severe GI AEs. Additionally, these products carry warnings for hypersensitivity reactions and suicidal behavior (rarely observed in liraglutide trials).[34,35] Semaglutide carries a warning for diabetic retinopathy onset or worsening.[34] Because of the glucose-lowering effects of GLP-1 RAs, lower dosages of concomitant antihyperglycemic medications may be needed to prevent hypoglycemia. DDIs with orally administered drugs may occur due to slowed gastric emptying.[34,35]

Orlistat: Orlistat is contraindicated in patients with chronic malabsorption syndrome or cholestasis.[33] Orlistat is minimally absorbed systemically[33]; and thus may carry comparatively less neuropsychiatric risk than other weight management agents.[22] Key warnings are liver injury, oxalate nephrolithiasis and oxalate nephropathy with renal failure, and cholelithiasis. Owing to lipase inhibition, multivitamin supplementation should be provided during treatment with orlistat. Orlistat may also interact with multiple narrow therapeutic index medications (eg, amiodarone, cyclosporine, warfarin). [33]

Naltrexone/bupropion ER and Phentermine/topiramate ER: Labeling for both products notes that their effect on major cardiovascular risks (eg, mortality) has not been established.[36,37] Both of these products require renal dose adjustments, and should be avoided in patients with severe hepatic impairment.[36,37]

Naltrexone/bupropion ER carries a **black box warning** for the risk of suicidal ideation. Contraindications for use include uncontrolled hypertension, risk factors for seizures, chronic opioid use, and recent or current MAOI use. Other warnings include the risks for hypersensitivity reactions, hepatotoxicity, mania, and angle-closure glaucoma attacks. Naltrexone/buprenorphine ER is the only agent with considerable CYP-related interactions (via CYP2D6 and CYP2B6).[37]

Phentermine/topiramate ER is contraindicated in patients with glaucoma, hyperthyroidism, or recent or current MAOI use. Additionally, it is contraindicated during pregnancy due to an increased risk of oral clefts; a negative pregnancy test result is recommended before and during treatment. Phentermine/topiramate carries warnings for multiple neuropsychiatric risks, ophthalmic adverse effects, increased heart rate, serious skin reactions, metabolic acidosis, kidney stones, and hypokalemia. In children 12-17 years old, the product may slow growth.[36]

Summary and Recommendations

Guidelines recommend pharmacotherapy as an adjunct to lifestyle therapy for the treatment of adults with overweight (BMI ≥ 27 kg/m^2) and ≥ 1 WRC, or adults and children (≥12 years, or possibly 8-11 years) with obesity (BMI ≥ 30 kg/m^2 or 95th percentile for children). Since long-term treatment may be needed

to sustain weight loss, treatments with evidence for long-term use are favored by some adult guidelines. Selection of pharmacotherapy should be individualized for indicated adult and pediatric patients.

The Utah Medicaid P&T Committee may consider the following:

Recommend that at least 1 weight management product FDA-approved for long-term use in adults and children ≥ 12 years old be preferred on the Utah Medicaid Preferred Drug List (PDL). The recommendation could be satisfied by one product or separate products (eg, one product for adults, and another for children; or the same product preferred for adults and children).

a) Guidelines generally support having long-term pharmacotherapy as a treatment option (adjunctive to lifestyle modifications) for *indicated* patients to achieve/maintain weight loss goals in the effort to lessen WRC risk/burden. There is little clinical trial data to support long-term treatment with the mono-ingredient sympathomimetic amines approved for short-term use (phentermine, diethylpropion, phendimetrazine, benzphetamine).

b) In adults, there may be differences in efficacy among the weight management therapies, with semaglutide being the most effective therapy and orlistat being the least effective therapy, based on indirect comparison. The AGA ranked the magnitude of benefit of therapies compared to placebo, using primarily short-term (<6 months) studies for phentermine and diethylpropion and longer studies for the remaining agents: semaglutide was considered to have the largest benefit and orlistat to have the smallest benefit on average. AGA considered each therapy to have a favorable safety profile relative to benefits, except for orlistat.[22] Our review of H-H RCTs found direct comparative evidence showing that semaglutide was more effective for weight reduction than liraglutide and liraglutide was more effective than orlistat; other direct comparisons between long-term agents are lacking.

    i) Despite efficacy differences, the P&T committee may consider recommending that at least 1 agent be preferred instead of recommending for or against specific product(s) to ensure recommendations are flexible to future changes (eg, new products to market, or new safety or efficacy data for current products).

c) Long-term weight management agents with an FDA indication and/or data supporting treatment of obesity in children ≥ 12 years are phentermine/topiramate ER, liraglutide (Saxenda), semaglutide (Wegovy), and orlistat.

1.0 INTRODUCTION

Obesity is a chronic health condition of excess adiposity affecting many US children, adolescents, and adults.[4-8] Almost one-third of Utah adults are obese, and nearly two-thirds are obese or overweight,[15] as measured by body mass index (BMI), a common surrogate measure for excess adiposity. In most populations, adult BMI thresholds of ≥25 kg/m^2 and ≥ 30 kg/m^2 define overweight and obesity, respectively.[5] BMI is also considered an efficient population-level tool for identifying people at risk for weight-related complications (WRCs).[9-12] Weight-associated health conditions (eg, type 2 diabetes mellitus [T2DM], cardiovascular disease, non-alcoholic fatty liver disease, some cancers) contribute to increased disability and premature mortality among adults with obesity.[13] Treatments for overweight and obesity that facilitate weight loss aim to improve or prevent WRCs.[16] Options for treating overweight or obesity include lifestyle changes (eg, reduced caloric intake, exercise, behavioral changes), pharmacotherapy, and/or metabolic or bariatric surgery.[16-20] Since weight regain following weight loss is common, changes (ie, interventions) made during weight loss often need to be continued indefinitely for purposes of weight-loss maintenance.[44]

Table 1 shows an overview of the 9 US Food and Drug Administration (FDA)-approved single/combination ingredients for weight loss or weight loss maintenance reviewed by this report, including an overview of indicated populations for their use, defined by BMI, or BMI in the presence of ≥1 WRCs. All weight management products are indicated for use in combination with lifestyle modifications.[23-37,45-47]

Throughout this report, we refer to these products as weight management medications and group them based on their FDA-approved durations for use. Agents approved for short-term treatment (eg, <12 weeks) entered the market between 1959 and 1975 and include diethylpropion, phentermine hydrochloride, phendimetrazine tartrate, and benzphetamine.[28,48-50] These oral products are all controlled substances that are not recommended for patients younger than 17 years.[23,24,26-28,30-32]

More recently, products have been approved for long-term or chronic use. Oral products for chronic use include orlistat (Xenical, approved 1999),[33] and combination products, phentermine/topiramate ER (Qsymia, approved 2012)[36] and naltrexone/bupropion ER (Contrave, approved 2014).[37] Subcutaneous products for chronic use include glucagon-like peptide-1 receptor agonists (GLP-1 RAs) liraglutide (Saxenda, approved 2014) and semaglutide (Wegovy, approved 2021).[34,35] Of these long-term agents, only phentermine/topiramate ER is a controlled substance.[36] Indications for pediatric use (age ≥ 12) followed initial approval for adults for liraglutide, semaglutide, and phentermine/topiramate ER.[34-36]

The **objective** of this report is to evaluate the comparative efficacy and safety of FDA-approved prescription medications for weight loss or weight maintenance (agents in Table 1) to assist the Utah Medicaid Pharmacy and Therapeutics (P&T) Committee in making recommendations. To meet this objective, this report addresses recent US guideline recommendations for weight management pharmacotherapies and summarizes indications and safety information from prescribing information and head-to-head randomized controlled trial (RCT) evidence for these therapies.

Table 1. Overview of Included Short-term and Long-term Prescription Agents for Weight Management

Active Ingredient (Initial US Approval Year)[a] **Brand Name(s)**	**Indicated Population**	**Route of Administration**	**Dosing Frequency**	**FDA-indicated or Recommended Age for Use**	**Controlled Substance**
Agents Approved for Short-term Treatment					
Diethylpropion[24,27] (1959)[49]	BMI ≥ 30	Oral	Daily (ER) or 3 times daily (IR)	Use is not recommended for patients under 17 years old	C4
Phentermine hydrochloride[28-32] (1959)[28] Adipex-P, Lomaira	BMI ≥ 30, or ≥ 27 with WRC[b]	Oral	Daily or 3 times daily (Lomaira)		C4
Phendimetrazine tartrate[23,26] (1975)[50]		Oral	Daily (ER) or 2 to 3 times daily (IR)		C3
Benzphetamine[25] (1960)[48]	BMI ≥ 30	Oral	Daily to 3 times daily		C3
Agents Approved for Long-Term Treatment					
Orlistat[33](1999)[c] Xenical	BMI ≥ 30, or ≥ 27 with WRC[e]	Oral	Three times daily	Use not established for <12 years	Not CS
Liraglutide[35] (2014)[d] Saxenda		SubQ	Daily	Indicated for age ≥12 years	Not CS
Semaglutide[34] (2021)[d] Wegovy		SubQ	Once weekly	Indicated for age ≥12 years	Not CS
Naltrexone/bupropion ER[37] (2014) Contrave		Oral	Twice daily	Use not established for age <18 years	Not CS
Phentermine/topiramate ER[36] (2012) Qsymia		Oral	Daily	Indicated for age ≥12 years	C4

[a] *Approximate year of approval of first product with that active ingredient indicated for weight management*

[b] *The indication for phendimetrazine varies by formulation; the IR tablets are only for exogenous obesity.*

[c] *A lower dose formulation of orlistat (Alli) for weight loss is available over-the-counter*

[d] *Liraglutide (Victoza) and semaglutide (Ozempic, Rybelsus) are also approved as other strengths and/or formulations for treatment of type 2 diabetes mellitus. These products were FDA-approved earlier than the weight-management products (Victoza: 2010; Ozempic: 2017; Rybelsus: 2019).*

[e] *See **Appendix A** for pediatric-specific indications for liraglutide, semaglutide, and phentermine/topiramate ER*

Abbreviations: BMI, body mass index in kg/m²; C or CS, controlled substance; ER, extended release; FDA, U.S. Food and Drug Administration; IR, immediate release; SubQ, subcutaneous; U.S., United States; WRC, weight-related complication (eg, hypertension, type 2 diabetes, dyslipidemia)

Historically, weight management pharmacotherapy has not been covered by Utah Medicaid.[51] As of April 2023, no weight management products are included on the Utah Medicaid Prescription Drug List (PDL). While some other formulations with similar active ingredients are preferred on the PDL (ie, liraglutide [as Victoza], bupropion, naltrexone [multiple mono-ingredient formulations], and topiramate), these dosage forms differ from those approved for weight management.[52] Notably, the prefilled injectable pens of semaglutide (Ozempic) and liraglutide (Victoza) approved for treating T2DM deliver a maximal dose below that of the formulations specifically approved for weight management[45,46]; the formulations for treating overweight or obesity are indicated for people with or without T2DM.[34,35]

Weight management products considered outside the scope of this report include those for rare diseases (ie, setmelanotide [Imcivree]), available over-the-counter (OTC; eg, low-dose orlistat [Alli]),[53] medical devices (eg, Plenity), and investigational products. Additionally, this review does not address amphetamine sulfate (Evekeo), which is FDA-indicated for the short-term treatment of exogenous obesity.[54] Evekeo was excluded from this report since it is a schedule 2 controlled substance,[54] and current US guidelines do not consider it a weight management treatment option.[16-18,20,22] Only 1 US guideline mentioned amphetamine treatment for obesity, considering it to be an off-label use with serious risks for abuse and adverse effects.[17] Setmelanotide is a subcutaneous injection FDA-approved for chronic weight management in adults or children ages ≥ 6 years old with specific rare genetic causes of obesity.[38] An oral medical device (Plenity) is approved as an adjunct weight management aid for adults with a BMI of 25 to 40 kg/m^2.[55] Another GLP-1 RA approved for T2DM[47] is under study for treating overweight or obesity: tirzepatide (Mounjaro). Phase 3 trial results demonstrated a significant weight loss benefit for tirzepatide (5 mg, 10 mg, or 15 mg subQ once weekly) versus placebo in adults with obesity or overweight without diabetes[56]; tirzepatide may gain approval for treating these conditions as soon as 2023.[57]

2.0 METHODS

Three bibliographic databases (Embase, Ovid-Medline, and Epistemonikos) were queried for comparative evidence using combinations of controlled vocabulary (as applicable) and keyword phrases. Ovid-Medline and Epistemonikos were searched for systematic reviews (SRs) of randomized controlled trials (RCTs) of weight-loss pharmacotherapies published from 2021 to present (January-February 2023). An additional search in Epistemonikos targeting only SRs of RCTs of short-term pharmacotherapies was performed without date restriction. For Ovid-Medline, a broadened form of a SR filter developed by McMaster University was applied;[58] and, in Epistemonikos, the website-embedded filter for SRs was used. To supplement the SR searches, additional systematic literature searches of Embase and Ovid-Medline for RCTs were performed, limiting the results to 2021 onward (for all agents except for liraglutide or semaglutide) or 2022 onward (for liraglutide and semaglutide only), and using RCT filters.[59] The search date restriction for RCTs was selected based on the span of RCTs reported among pertinent SRs.[3,60-62] Because the broadest SR targeting pediatric patients did not search for all agents (short-term agents other than phentermine and semaglutide were excluded),[61] there is a chance that trials for those excluded agents published before 2021-2022 were missed by our search. Despite this, we perceive it to be unlikely that there are direct comparative RCTs in pediatric patients for the short-term agents missed by the SR. Details of the bibliographic database search strategies are available in **Appendix B.**

The following websites were also queried for additional information:

- Product labeling (ie, package inserts) was obtained from the Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/) or National Library of Medicine DailyMed (https://dailymed.nlm.nih.gov/dailymed/) websites.
- The compendia UpToDate (https://www.uptodate.com) and the Trip Database (https://www.tripdatabase.com/) were queried for clinical practice guidelines addressing weight management pharmacotherapies.
- Websites from the American Academy of Pediatrics (AAP), American Diabetes Association (ADA), Endocrine Society (ES), American Gastroenterological Association (AGA), and American Association of Clinical Endocrinology (AACE) were searched for recent (2016-2023) US guidelines providing weight management pharmacotherapy recommendations.

2.1 Screening of Bibliographic Database Searches

References from bibliographic database searches were imported into screening software (Covidence; Veritas Health Innovation, Australia). Titles and abstracts were screened independently and in duplicate to identify studies meeting our eligibility criteria, with any conflicts resolved by consensus. Full texts for references receiving 2 inclusion votes during title/abstract screening were retrieved and reviewed for inclusion by the lead author. Reference lists for full-text articles screened and clinical practice guidelines included, were manually reviewed to identify additional relevant comparative evidence.

2.2 Comparative Evidence Inclusion and Exclusion Criteria

To supplement information from clinical practice guidelines and prescribing information, we searched for direct head-to-head comparisons of weight management agents. SRs of RCTs with head-to-head efficacy or safety comparisons between two or more medications in Table 1 being used to treat overweight or obesity were eligible for inclusion.

Excluded references met one or more of the following criteria:

- Review articles that did not use methodology consistent with SRs.
- Comparisons were only to placebo or active comparisons not addressed by this report. For combination products (eg, phentermine/topiramate ER), evidence must have used the combination product not the single ingredients in combination.
- Network meta-analyses (MA) including only indirect comparisons.
- Studies of products using doses differing from the target maintenance dose or dose range for treating overweight or obesity (eg, liraglutide or semaglutide RCTs using doses lower than those for weight management and primarily studied for their glycemic effects in patients with T2DM).
- Review articles duplicating studies already included by another SR or RCT.
- Studies of the following designs: observational, pharmacokinetic or pharmacodynamic, cost-effectiveness analyses, study protocols, and post-hoc analyses of trials.

3.0 DISEASE OVERVIEW

Obesity is a chronic condition of excess adiposity recognized as a disease by multiple US organizations (eg, American Medical Association, American Association of Clinical Epidemiology, The Obesity Society, and Obesity Medicine Association).[9,63,64] A complex interplay of genetic, environmental (eg, stress, sedentary behavior), psychological, and medical factors cumulatively cause central and peripheral neurohormonal weight-regulatory pathway dysfunction, leading to increased body fat mass.[10] Increased body fat contributes to health complications. Excess caloric intake in susceptible individuals can lead to adiposopathy (ie, pathogenic adipose tissue), triggering impaired endocrine and immune responses which contribute to developing weight-associated comorbidities.[9]

The prevalence of overweight or obesity among US adults and children increased over the past decades.[6-8] Over the period of 2017 to 2020, an estimated 41.9% of US adults and 19.7% of children (ages 2 to 19 years) were obese.[65] In Utah during 2021, the percentage of adults with obesity, or overweight or obese were 30.9% and 64.2%%, respectively.[15] Utah is among US states with the largest percent increase in the adult obesity rate (15%+) between 2016 and 2021.[15] There are disparities in obesity rates by race/ethnicity, income level and educational attainment, and geographical home dwelling. Obesity rates tend to be higher among people with lower educational attainment and income levels, Black or Latino race or ethnicity, and people living in rural areas.[15] Increased weight is often persistent: after 4 years, fewer than 10% of middle-aged adults with overweight or obesity reach a normal weight,[66] and obesity persisted to adulthood among 86% of sampled adolescents.[4]

Increased body weight is associated with adverse health consequences in adults including increased risk for T2DM, nonalcoholic fatty liver disease, cardiovascular disease, multiple cancers, joint damage, and depression.[10,11] Weight-associated health conditions contribute to increased disability and premature mortality among adults with obesity.[13] An increased risk for chronic conditions (eg, depression, T2DM, hypertension) also affects children with obesity.[12] Furthermore, people with obesity experience weight-related stigma and discrimination, including from healthcare professionals,[14] contributing to impaired social, educational, and health outcomes.[15]

Since contributors to obesity are multifactorial, including both individual and systemic factors, it is recommended that policy makers address structural, social, and economic contributors to obesity in addition to facilitating evidence-based treatments for individuals.[14,15]

3.1 Measurement and Classification of Overweight or Obesity

Increased body fat mass and distribution of fat to certain locations (eg, abdomen) are associated with increased health complications.[9] There are limited accessible, non-invasive methods for directly measuring body fat mass.[67,68] Indirect methods are commonly used to identify individuals at risk for adverse health complications associated with excess body fat mass. BMI is the most common surrogate measure, and at the population level, it correlates well with body fat and health risks. However, BMI does not differentiate between mass types (ie, muscle or bone versus fat) and it is a less reliable estimate of body fat mass among individuals with increased or decreased non-fat mass.[9,67] The US Department of Human Services and Center for Disease Control classify BMI as a *screening* tool for overweight or obesity.[67] Among people of Asian descent, body fat percentage tends to be higher at a given BMI compared to White populations, and an increased risk for some WRC starts at a lower BMI.

Thus, lower BMI thresholds for overweight and obesity may be more useful in screening Asian populations.[69]

BMI is calculated by dividing an individual's weight in kilograms by height in meters squared. Adult (age ≥ 20 years) BMI classifications of overweight and obesity are described below[5,9]†:

- Overweight (sometimes called pre-obesity): 25.0 ≤ BMI ≤ 29.9 kg/m^2
- Obese: ≥ 30.0 kg/m^2
  - Class I obesity: 30 to <35 kg/m^2
  - Class II obesity: 35 to <40 kg/m^2
  - Class III obesity (sometimes called severe obesity): ≥ 40 kg/m^2

BMI is also an accepted screening tool for adiposity in children and adolescents.[18,20] Childhood and adolescent overweight and obesity BMI categories are determined from growth charts, comparing a child's BMI to other children of the same age and sex.[68] For children under 2 years old, sex-specific weight-to-length at or exceeding the 97th percentile using World Health Organization (WHO) growth charts indicates obesity.[20] Overweight or obesity BMI categories[65] for children or adolescents ages 2 to 19 years old, calculated using CDC growth charts,[20] are the following:

- Overweight: 85th percentile ≤ BMI < 95th percentile
- Obese: ≥ 95th percentile, or an absolute BMI ≥ 30 kg/m^2 (whichever value is lower)
  - Severe obesity (per the American Heart Association, for age 2 or older)[68]: BMI ≥ 120% percentile or an absolute BMI ≥ 35 kg/m^2 (whichever value is lower)

Adiposity may also be classified by body fat percentage, measured by dual x-ray absorptiometry (DXA), or by measures of abdominal obesity (eg, waist circumference, visceral or android fat). Compared to BMI, body fat percentage or android fat in adults may be a better predictor of adiposity complications. In adults, abdominal obesity (measured by waist circumference) is defined as ≥40 inches in men ≥ 35 inches in women[17] (with lower thresholds for Asian populations).[9] A waist circumference ≥ 90th percentile in children 10-16 years old (and potentially children 6-10 years old) is part of the diagnosis of metabolic syndrome per the International Diabetes Federation.[20] The VA/DoD recommends considering waist circumference measurement for adults with an overweight BMI.[17] Although most patients with adiposity may benefit from multiple methods of measurement, waist circumference may be useful for identifying adults with a BMI <35 kg/m^2 at greatest risk for metabolic complications, and body fat percentage may be useful for patients with low or high muscle mass.[9]

Generally, assessment of other factors (eg, body fat distribution, family history, lifestyle) is recommended for those who have screened as obese/overweight to gain a holistic picture of weight-related cardiometabolic risk.[15]

3.2 Overview of Obesity Treatment Options and Outcomes

Benefits of weight loss among people with obesity include, but are not limited to, improvements in cardiometabolic comorbidities, reduced risk for premature death and incidence of certain cancers, and

† 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.

improvements in quality of life.[9] Intentional weight loss of ≥ 5% is a common goal since it is correlated with clinically significant improvements in cardiometabolic parameters.[22,70-72] Weight loss benefits tend to increase with greater weight loss (eg, ≥10%), including improvement or resolution of some WRC.[70]

Recent adult clinical practice guidelines for overweight or obesity consider achieving weight loss of at least ≥5% from baseline to be a meaningful for weight management pharmacotherapies.[17,22,73] A weight loss goal exceeding ≥5% may be selected depending on treatment goals (eg, improvement in weight-related comorbidities requiring greater weight loss). Nevertheless, 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, or cancer) is limited.[22]

Weight loss and weight loss maintenance are challenging for most individuals. During weight loss, maladaptive physiologic responses promote weight regain.[44,73] To sustain weight loss, individuals must indefinitely reduce caloric intake and/or increase energy expenditure.[73] Unfortunately, with lifestyle changes alone, weight regain within 12 months of weight loss is common.[44] Weight regain following pharmacotherapy discontinuation is also common.[16] Thus, chronic treatment, potentially including long-term pharmacotherapy, is needed to maintain weight loss.

Treatment options for overweight and obesity include lifestyle (eg, dietary and exercise), behavioral, surgical, and pharmacologic interventions.[17] Lifestyle and behavioral changes are recommended for all patients with overweight or obesity.[16,17,22] For adults, dietary changes usually target a caloric deficit (eg, 500-750 kcal daily), while exercise therapy often targets aerobic exercise for >150 minutes/week with resistance training 2-3 times per week. Behavioral interventions are multi-faceted, ranging from goal-setting to psychological counseling, among other options.[16] Surgical interventions (eg, metabolic or bariatric surgery) are also options for patients with obesity, particularly for patients with severe obesity and/or WRCs of obesity.[16,18,19] Both surgical and pharmacologic interventions are typically recommended as adjuncts to comprehensive lifestyle changes (ie, combining behavioral, dietary and physical activity).[16-18]

4.0 WEIGHT MANAGEMENT PHARMACOTHERAPIES

4.1 Indications, Dosing, and Formulations

We reviewed 9 products approved for indications related to weight loss and/or management. The first products to market (benzphetamine, diethylpropion, phendimetrazine, and phentermine monotherapy) were FDA-approved for short-term weight management[23-32]; more recently approved agents are for long-term weight management (liraglutide 3.0 mg, semaglutide 2.4 mg, orlistat, naltrexone/bupropion ER, phentermine/topiramate ER).[33-37] All products are approved *as adjunctive therapy* to lifestyle modification (reduced caloric intake and increased physical activity).[23-38] Diethylpropion, phendimetrazine, and benzphetamine are indicated for adjunctive treatment after failure of lifestyle agents alone,[23-27] whereas labeling for other products does not specify starting after trial of lifestyle changes.[28-37]

All products are approved for treatment of obesity (eg, initial BMI ≥30 kg/m^2),[23-37] and the majority are also approved for treatment of overweight (initial BMI ≥27 kg/m^2) in the presence of at least one weight-related comorbid condition (eg, hypertension, T2DM, or dyslipidemia).[28-37] Agents only approved

for obesity treatment include diethylpropion, phendimetrazine IR tablets (unlike the ER capsules), and benzphetamine.[23-27] A handful of products have specific indications for the pediatric patients with obesity (liraglutide 3.0 mg, semaglutide 2.4 mg, phentermine/topiramate ER), for patients ≥ 12 years of age.[34-36] Others have an indication not specific to an age group, but recommend against use below a certain age in other parts of the package insert (eg, <12 years of age for orlistat, and <17 years of age for short-term products).[23-33] Naltrexone/bupropion ER is specifically indicated in adults only.[37]

The GLP-1 RAs are administered subcutaneously on a daily (liraglutide) or weekly (semaglutide) basis,[34,35] while the other weight-management medications are orally administered on a once daily to thrice daily basis.[23-33,36,37] Among the oral agents for chronic use, only orlistat is administered three times daily (with fat-containing meals) whereas other agents are administered twice daily (naltrexone/bupropion ER) or daily (phentermine/topiramate ER).[33,36,37] Except for benzphetamine which is only formulated as a tablet for daily to three times daily use,[25] short-term use products are available as formulations for daily (ER or higher-dose formulations),[24,26,28-31] and multiple times daily (IR or lower-dose formulations) use.[23,27,32] Phentermine may be uniquely available as an oral disintegrating tablet[‡],[29] in addition to standard capsules or tablets[23,28,30-32] like the other oral products.[24-27,33,36,37]

The GLP-1 RAs are gradually up-titrated to the maintenance dose to minimize GI adverse effects.[34,35] 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 weeks.[35] 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 weeks.[34] Both fixed-dose combination products, naltrexone/bupropion ER and phentermine/topiramate ER, should be titrated to the maintenance dose over at least 4 weeks.[36,37] Dose titration is not required for the products indicated for short-term use,[23,24,26-32] or orlistat,[33] but may be considered for benzphetamine.[25] Labeling for most products indicated for chronic use recommend assessing response to therapy (eg, achieving weight loss of a certain magnitude by 12 weeks), and discontinuing therapy with insufficient response.[35-37] GLP-1 RAs should be discontinued if the recommended maintenance dose is not tolerated despite appropriate titration.[34,35]

Before initiating phentermine/topiramate ER, it is recommended that patients complete a pregnancy test (when indicated) and blood chemistry panel due to risks associated with topiramate. A negative pregnancy test should be verified monthly during treatment.[36]

Appendix A summarizes available dosage forms, FDA-approved indications, maintenance dosing and administration, and titration instructions for the reviewed weight management products.

4.2 Mechanism of Action

Four active ingredients are pharmacologically classified as sympathomimetic amine anorexiants (benzphetamine, diethylpropion, phendimetrazine, and phentermine).[23-25,28] The remaining 6 active ingredients are classified as GLP-1 RAs (liraglutide and semaglutide),[34,35] opioid receptor antagonist (naltrexone),[37] dopamine/norepinephrine-reuptake inhibitor (bupropion),[37] miscellaneous anorexiant (topiramate),[36] and gastrointestinal lipase inhibitor (orlistat).[33] These active ingredients have a range of pharmacologic mechanisms for weight management as summarized in the following bullets. With the

[‡] It is unclear if ODT phentermine is currently available as there are conflicting reports from multiple sources.

exception of orlistat, which reduces intestinal fat absorption to decrease caloric intake, weight management agents are thought to have actions at the central nervous system (CNS) that enhance satiety and/or decrease hunger, leading to reduced caloric intake.[16,22]

- Anorexiant, CNS stimulant, sympathomimetic amine: benzphetamine, diethylpropion, phendimetrazine, phentermine
    - The exact mechanism that leads to weight loss with treatment is unclear but it is thought to involve the elevation of norepinephrine in the CNS.[22] 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.[23-27,29-32]
- 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.[33]
- 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.[74] Ultimately, GLP-1 RA therapy decreases food/caloric intake.[34,35] In a glucose-dependent manner, GLP-1 RAs increase insulin secretion and decrease inappropriate glucagon secretion, and thus, are effective for T2DM.[75] Moreover, liraglutide and semaglutide have proven cardiovascular protective effects (eg, decrease major adverse cardiovascular events [MACE] outcomes) in patients with T2DM.[9,76,77]
- 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.[36] Topiramate monotherapy is also approved to treat seizure disorders and prevent migraine headaches.[22]
- 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.[37] Naltrexone may inhibit beta-endorphin auto-inhibitory activity at anorexigenic neurons in the hypothalamus; and bupropion is thought to weakly modulate the anorexigenic neurons, but is augmented with naltrexone activity.[22] At higher doses than the dose in the naltrexone/bupropion ER product, bupropion monotherapy is approved to treat depression and seasonal affective disorder, and as an aid for smoking cessation.[22]

5.0 GUIDELINE RECOMMENDATIONS FOR PHARMACOTHERAPY

5.1 General Adult Population

Recent guidelines providing guidance on pharmacotherapy to support weight loss for the general adult population include those by the American Gastroenterological Association (AGA; 2022),[22] US Veterans

Health Administration and Department of Defense (VA/DoD; 2020),[17] and the American Association of Clinical Endocrinologists with the American College of Endocrinology (AACE/ACE; 2016).[16] Only the 2022 AGA guideline addresses use of semaglutide as the other guidelines predated its FDA approval. Evidence for all other weight management pharmacotherapies were considered for recommendations by each guideline,[16,17] except for benzphetamine and phendimetrazine, which were not addressed by the AGA guideline only.[22]

Treatment Approach

Generally, guidelines recommend comprehensive lifestyle interventions (including calorie restriction and increased physical activity) to support weight loss.[16,17,78] Although lifestyle therapy is a cornerstone of treatment, because sufficient weight loss is difficult to attain[79] 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.[16,21] Goals of treatment are to improve patient health by prevention or improvement of WRC through weight loss.[16]

Pharmacotherapy, as an adjunct to lifestyle therapy, is recommended for adults with obesity (BMI ≥ 30 kg/m^2) or overweight (BMI ≥ 27 kg/m^2) with a weight-related complication (WRC).[16,17,22] Examples of WRC either caused or exacerbated by overweight or obesity are: hyperglycemia or T2DM, dyslipidemia, hypertension, cardiovascular disease (CVD), nonalcoholic fatty liver disease, polycystic ovary syndrome (PCOS), female infertility, male hypogonadism, obstructive sleep apnea (OSA), asthma/reactive airway disease, osteoarthritis (OA), urinary stress incontinence, gastroesophageal reflux disease (GERD), and depression.[16] Each guideline recommended pharmacotherapy to be combined with lifestyle therapy.[16,17,22] All guidelines recommend long-term treatment since obesity is chronic condition. Treatment should be individualized based on each medications relative benefits and risks given a patient's comorbidities and concerns.[16,17,22]

Recent guidelines slightly differ with respect to recommendations for *when* to initiate pharmacotherapy. The VA/DoD considered there to be a lack of evidence for when to start pharmacotherapy.[17] Whereas, the AGA strongly recommended adding pharmacotherapy *after* an inadequate response to lifestyle intervention alone (compared to continuing lifestyle intervention only).[22] The AACE/ACE approached obesity treatment using a chronic disease model addressing diagnosis and prevention of WRCs; when to initiate pharmacotherapy depends on obesity severity.[16] According to the AACE/ACE treatment algorithm,[16] pharmacotherapy may be initiated according to the following scenarios:

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

The reviewed guidelines slightly differ with respect to *which* pharmacotherapies were explicitly recommended. Although the AACE/ACE guideline implies recommending certain long-term therapies, it was noted that "Medications may not be explicitly recommended if there are not data available for use

in the specified clinical setting, even though weight loss associated with these medications may produce clinical benefits" (page 25).[16] Refer to the sections below for additional information about recommended pharmacotherapies.

Pharmacotherapies Approved for Long-term Use

Generally, guidelines equally recommend liraglutide, naltrexone/bupropion ER, or phentermine/topiramate ER for long-term adjunctive pharmacotherapy.[16,17,22] In contrast to the AACE/ACE and VA/DoD which similarly recommend orlistat relative to the aforementioned therapies,[16,17] orlistat is recommended against for most patients by the AGA due to a smaller magnitude of effect and moderate magnitude of harms.[22] However, the AGA's recommendation against orlistat is *conditional*, acknowledging that orlistat therapy may be preferred by some patients.[22] Only the AGA addressed semaglutide use, noting that semaglutide treatment might be preferred over other options for many patients because it has the largest magnitude of benefit. According to a MA by the AGA, ranking for the magnitude of weight-loss benefit for the long-term agents as follows: semaglutide (large) ≥ phentermine/topiramate (moderate-to-large) ≥ liraglutide and naltrexone/bupropion ER (moderate) > orlistat (small). AGA considered each therapy to have a favorable safety profile relative to benefits, except for orlistat.[22]

Despite differences in the efficacy magnitude in clinical trials, all guidelines recommend an individualized approach to selecting among these therapies based the individual's clinical profile/needs.[16,17,22] The AACE/ACE guideline provided drug preferences according to co-morbidities (eg, CVD, hypertension, kidney disease, hepatic disease, psychiatric disease, eating disorders, seizure risk, etc.).[16] Refer to **Appendix C** for details on preferred therapies per comorbidity. Factors leading to selection of a particular therapy may include relative efficacy, route of administration, adverse event profile, demonstrated benefit for a comorbidity, or cost.[16] Avoidance of particular medications generally aligns with warnings or precautions for their use.

Pharmacotherapies Approved for Short-term Use

Guidelines approached recommendations for pharmacotherapies approved for short-term use (ie, phentermine, diethylpropion, phendimetrazine, benzphetamine) differently:

- While the 2016 AACE/ACE acknowledged the efficacy of these therapies versus placebo for short-term (generally <12 weeks) weight loss, since obesity is a chronic condition and there is a lack of evidence for long-term benefits from short-term weight loss, short-term use of pharmacotherapies (ie, 3-6 months) was generally not recommended by them. The AACE/ACE does not list specific treatments for this recommendation, so we interpret it as generally not recommending short-term use of *any* pharmacotherapies (ie, including therapies for long-term use).[16]
- The literature search for the VA/DoD guideline found little evidence for use of benzphetamine, diethylpropion, phendimetrazine, or phentermine monotherapy; thus, they considered there to be insufficient evidence for use of these treatments in any capacity (short-term, long-term, or intermittent use). Officially, the VA/DoD recommendation is they are neither for nor against use of these therapies.[17]
- In contrast, diethylpropion and phentermine monotherapy as adjuncts to lifestyle interventions are *conditionally* recommended based on low-quality evidence by the AGA. Both treatments were

considered to result in moderate weight loss compared to placebo. While RCT evidence is primarily for use of these treatments for up to 12 weeks (there was 1 study for use of phentermine monotherapy for up to 28 weeks and diethylpropion for up to 52 weeks), guideline authors felt practitioners often use these therapies off-label for long-term use. Evidence for long-term use of these therapies is limited (although phentermine 15 mg has been studied long-term with topiramate ER), so long-term use should be limited to cases where the potential benefits outweigh the risks. The AGA considered phentermine and diethylpropion to carry similar risks (ie, cardiotoxicity, CNS toxicity, and abuse risk); although it was noted for diethylpropion that "…a chemical modification of the active molecule results in less potential for CNS stimulation and blood pressure elevation" (page 1217).[22] Phendimetrazine and benzphetamine were not addressed by the AGA 2022 guideline.[22]

Table 2 summarizes pharmacotherapy recommendation among recent clinical guidelines for the management of overweight or obesity in the general adult population.

5.2 Adults with Prediabetes or Type 2 Diabetes Mellitus

Obesity substantially increases the risk for developing T2DM.[16,80] Strong evidence shows that obesity management can delay the progression from prediabetes to T2DM per the ADA 2023 Standards of Care guideline.[81] 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.[80]

Weight-loss pharmacotherapy is considered 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, weight loss pharmacotherapies including orlistat, phentermine/topiramate, liraglutide, semaglutide, and tirzepatide have been shown to decrease the incidence of developing T2DM in RCTs, "…to various degrees in those with prediabetes…"[82] (page S44). Weight management pharmacotherapies may be discontinued if at least 5% weight loss is not achieved by 3 months, or for safety/intolerability issues.[83]

Overweight and obesity treatment guidelines non-specific to diabetes (ie, AGA, VA/DoD, AACE/ACE) do not prefer a particular weight loss pharmacotherapy in patients with T2DM.[16,17,22] Both semaglutide and liraglutide exert glucoregulatory effects and are approved for the treatment of T2DM at lower doses than those for weight loss. Weight-loss doses of semaglutide significantly reduced A1c in patients with T2DM compared to placebo; however, the percent total body weight loss is potentially less in patients with T2DM versus those without T2DM. Similarly, for liraglutide, robustness of weight loss may be less in patients with insulin resistance on average.[22] While the weight loss effect magnitude for semaglutide 2.4 mg and liraglutide >1.8 mg is significantly less in patients with T2DM versus without T2DM, both medications demonstrated significantly higher proportions of patients with T2DM achieving ≥5% weight loss (or more) versus placebo. The magnitude of weight loss with semaglutide may be higher than with liraglutide in patients with T2DM, based on indirect comparisons.[84]

Table 2. Guideline Recommendations for Weight Management Pharmacotherapy in the General Adult Population

2022 AGA Clinical Practice Guideline on Pharmacological Interventions for Adults With Obesity[22]

General:
• "…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)[22]
• 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:
  ○ **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
  ○ **Conditional**: Different choices will be appropriate for individual patients. Most patients (but many would not) want the recommended treatment. Policymaking will require debate and involvement of stakeholders.
• Quality of evidence (QOE) ratings[85]:
  ○ **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**
  ○ 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**
  ○ Implementation considerations: liraglutide is also approved for T2DM due to its glucoregulatory benefits. Gradually up-titrate to minimize GI side effects monitor for pancreatitis/gallbladder adverse effects.
c) **Phentermine/topiramate ER**

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; VA/DoD, US Veterans Health Administration and Department of Defense; WRC, weight-related complications

Table 2. Guideline Recommendations for Weight Management Pharmacotherapy in the General Adult Population

○ 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** 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. c) **Use** or **orlistat** is recommended against 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) ○ Implementation considerations: Patients using orlistat should take a multivitamin daily (2 hours apart from orlistat) containing fat-soluble vitamins (A, D, E, K).
2020 VA/DoD Guideline for the Management of Adult Overweight and Obesity[17]
• 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) ○ 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. • *Weight loss maintenance:* Authors found evidence of sustained weight loss (eg, maintenance of ≥5-10% weight loss after initial weight loss in 1-2 year follow-up) for liraglutide, orlistat, and phentermine/topiramate; there was a lack of evidence of weight loss maintenance for naltrexone/bupropion (Non-graded due to insufficient evidence to form an official recommendation).

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; VA/DoD, US Veterans Health Administration and Department of Defense; WRC, weight-related complications

Table 2. Guideline Recommendations for Weight Management Pharmacotherapy in the General Adult Population

2016 AACE/ACE Guideline for Medical Care of Patients with Obesity[16]

• Note that this guideline was published prior to the approval of semaglutide. Although the guideline included lorcaserin, this agent has been discontinued so recommendations regarding its use are not included here.
• The target population (adult vs pediatric) is not specified by this guideline; however, most pharmacotherapy evidence was for adults, so recommendations from this guideline are addressed in the adult section of this report.
• Best evidence level (BEL) meaning: BEL 1, RCT evidence or meta-analysis of RCTs. Grade meanings:
  ○ Grade A: Strong recommendation
  ○ Grade B: Intermediate recommendation
  ○ Grade D: Not evidence based
• Anti-obesity pharmacotherapy 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).
• Initial pharmacotherapy plus lifestyle therapy can be initiated together and considered in patients with weight-related complications that can be potentially modified by weight loss (Grade A; BEL 1).
  ○ 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)
  ○ 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.
  ○ 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).
  ○ It is recommended that patients with obesity have access to all approved medications to allow for optimization of pharmacotherapy according to patient-specific factors and needs. (Grade D).
Individualization of Weight Loss Pharmacotherapy According to Co-morbidities
The AACE/ACE recommended particular medications (orlistat, liraglutide, naltrexone/bupropion ER, or phentermine/topiramate ER) by disease state. Each medication was preferred for 1+ unique comorbidity. Refer **to Appendix C** for details.

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; VA/DoD, US Veterans Health Administration and Department of Defense; WRC, weight-related complications

5.3 Pediatric Population

Recent guidelines providing guidance on pharmacotherapy to support weight loss for the general pediatric population include those by the American Academy of Pediatrics (AAP; 2023) and the Endocrine Society (ES; 2017). Both guidelines took the approach of giving general pharmacotherapy recommendations lacking specificity for certain products. At the time of drafting the ES guideline, only orlistat was FDA-approved for children ≥ 12 years, and according to guideline authors, some other products approved for adults may have been indicated for treatment of adolescents ≥ 16 years (eg, sympathomimetics).[20]

Pediatric obesity is a chronic condition requiring long-term treatment.[18,20] Recognizing overweight and obesity along with performing age-appropriate screening for WRC (eg, dyslipidemia, hyperglycemia, hypertension, nonalcoholic fatty liver disease) is recommended by the AAP.[18] Children with early onset (before age 5) severe obesity and features of genetic obesity conditions should be screened for genetic causes of obesity; genetic obesity syndromes are relatively rare, representing fewer than 10% of pediatric severe obesity cases.[20] Compelling evidence supports improvements in WRC with weight loss among pediatric patients.[18,20] Thus, pediatric obesity should be treated with the goal of losing weight, preventing additional weight gain, and improving WRC.[18]

Like adults, treatment options for pediatric obesity include lifestyle therapies, pharmacotherapy, and metabolic/bariatric surgery. Intensive lifestyle therapy incorporating dietary, physical activity, behavioral and psychological interventions is the cornerstone to management of pediatric obesity,[20] and may be the only recommended intervention depending on the patient's age and disease severity.[18] Both the ES and AAP encourage using formal intensive lifestyle programs when accessible.[18,20] The AAP recommends offering or referring children/adolescents with overweight and obesity to dietary and physical activity counseling; 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.[18] Longitudinal intensive lifestyle programs typically address multiple contributors to weight gain (ie, behavior, diet, activity) with high intensity (eg, ≥ 26 hours).[18] Family dynamics should also be considered as part of lifestyle management[18]; while intensive lifestyle changes significantly reduced BMI by 1.5 kg/m^2 on average in a MA, the benefits were no longer significant when patient's families were not involved.[20]

Weight-loss pharmacotherapy *as an adjunct* to behavior/lifestyle treatment is recommended as an option for children/adolescents with obesity (BMI ≥ 95th percentile).[18,20] The ES recommends only considering adjunctive pharmacotherapy after failure of intensive lifestyle therapy due to the limited evidence for weight management pharmacotherapies at the time of writing the guideline.[20] While the AAP provided pharmacotherapy recommendations for specific age groups, the ES was less specific. Adjunctive pharmacotherapy is recommended by the AAP for adolescents ≥12 years (grade B) with obesity and may be considered for children 8-11 years old with obesity (non-graded); the expert-opinion statement for the latter age range was not rated as a key action statement due to the limited evidence.[18] Neither the ES nor the AAP recommend weight management pharmacotherapy for children/adolescents *who are overweight* but not obese[18,20]; the ES specifically recommended against adjunctive pharmacotherapy for patients who are overweight and <16 years old other than as part of a clinical trial.[20]

Neither guideline prefers a specific weight loss pharmacotherapy for indicated patients. Medications for treatment of obesity should be used in accordance with their indications and with consideration to the risks and benefits of use.[18,20]

Table 3 summarizes pharmacotherapy recommendations among recent clinical guidelines for the management of overweight or obesity in the general pediatric population.

Table 3. Recent Guideline Recommendations on Weight Management Pharmacotherapy for Pediatric Patients

2023 American Academy of Pediatrics [18]

Target: management of overweight or obesity in children and adolescents ≥ 2 years
• 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).
• 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.
Weight-loss pharmacotherapy recommendations
• **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)
• **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)
  • 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), phentermine/topiramate ER

2017 Endocrine Society Guideline[20]
Target: identification and management of overweight or obesity in children and adolescents • 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) • Dietary changes consistent with AAP and US Department of Agriculture guidelines are recommended (eg, reducing consumption of highly processed foods and foods with high sugar content; education on portion sizes and changing eating behavior such as grazing or eating due to loneliness) (Ungraded good practice) • 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) • Additional lifestyle recommendations address familial communication interventions and psychosocial interventions when psychosocial contributors are suspected. • 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]) with

Table 3. Recent Guideline Recommendations on Weight Management Pharmacotherapy for Pediatric Patients

extreme obesity and comorbidities that persist despite an intensive formal lifestyle program (± pharmacotherapy), and with demonstrated familial competence and patient adherence. Care at a pediatric bariatric surgery center of excellence is recommended when accessible. (Weak; Low QoE)
Weight-loss Pharmacotherapy recommendations 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. • **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)   • 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. • 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) • Discontinuation of pharmacotherapies is recommended if the patient does not achieve desired weight loss (ie, >4% BMI/BMI *z* score) after 12 weeks of the maximum pharmacotherapy dose (Weak; Very low QoE)

AAP Grades: Grade B, evidence from trials with minor limitations, multiple consistent 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;

6.0 DIRECT COMPARATIVE EFFICACY AND SAFETY EVIDENCE

Our search identified 950 records, of which 642 were screened in duplicate during title/abstract screening, and 50 of those were selected for full-text screening. Overall, 6 trials with head-to-head (H-H) comparisons of weight management agents were included. Refer to **Appendix D Figure 1** for a flow diagram showing identification, screening, and inclusion/exclusion of studies, including reasons for exclusion during full-text screening. See **Appendix E** for citations of excluded references.

The following is an overview of the 6 included trials (5 RCTs and 1 RCT extension) with H-H comparisons:

- All trials were conducted in adults who were at least 18 years old at enrollment. Two screened SRs focused on weight loss pharmacotherapies for children or adolescents, finding a lack of H-H trials meeting their inclusion criteria.[61,88] However, since the broadest of these SRs did not address all

short-term agents (other than phentermine) or semaglutide,[61] there is a chance that H-H trials for those excluded agents were missed by our search.

- Most trials enrolled patients with obesity (BMI ≥30 kg/m^2) without diabetes. Exceptions were the STEP-8 trial (semaglutide vs liraglutide) which also included patients with an overweight BMI (≥27 kg/m^2) with ≥1 weight-related comorbidity,[1] and phentermine vs diethylpropion trial that included patients with a baseline weight ≥20% higher than their *desired* weight.[39]
- Weight management agents included in at least 1 H-H trial are semaglutide, liraglutide, orlistat, phentermine, phentermine/topiramate ER, and diethylpropion. No H-H trials were found for benzphetamine, phendimetrazine, or naltrexone/bupropion ER.
- Comparisons among long-term treatment agents included semaglutide versus liraglutide (2 RCTs) and liraglutide versus orlistat (1 RCT and 1 RCT extension). Among short-term agents, phentermine was compared to diethylpropion (1 RCT). The remaining trial compared phentermine to phentermine/topiramate ER to assess the benefit of combination treatment versus monotherapy for short-term follow-up (28 weeks).[43]
- Pharmacotherapies were studied as an adjunct to lifestyle interventions in each trial.
- Median duration of follow-up was 40 weeks (range: 12 weeks [phentermine vs diethylpropion] to 2 years [liraglutide vs orlistat extension trial]).

6.1 Semaglutide versus Liraglutide

Two RCTs (**STEP-8**[1] and **O'Neil 2018**[40]) compared weight-management doses (ie, doses exceeding those for treatment of diabetes)[§] of subcutaneous (subQ) semaglutide to subQ liraglutide, with matching subQ placebo, as an adjunct to caloric restriction and exercise in obese or overweight adult patients without diabetes. Owing to differences in the titration time for semaglutide and liraglutide, both trials blinded patients and providers to active treatment and the corresponding matching placebo, but were open-label with respect to which agent they were allocated to receive (ie, semaglutide or liraglutide).[1,40] The phase 3b STEP-8 trial initiated patients on semaglutide 0.25 mg weekly, escalating the dose every 4 weeks to the target dose of 2.4 mg once weekly (or 1.7 mg once weekly if 2.4 mg was not tolerated).[1] In contrast, the phase 2 trial (O'Neill 2018) included 5 semaglutide doses (0.05 mg to 0.4 mg daily); the lowest dose remained constant whereas the other doses were titrated to the target dose by 0.05 mg every 4 weeks or every 2 weeks for the standard and fast titration arms, respectively.[40] In both trials, liraglutide was initiated at 0.6 mg daily and titrated by 0.6 mg weekly over 4 weeks to 3.0 mg daily. Both trials continued treatment for at least 1 year, including the titration period; the duration of the STEP-8 trial was 68 weeks and the duration of the O'Neil 2018 trial was 52 weeks. The primary outcome for each trial was the average percent change in body weight from baseline to study completion.[1,40]

Both trials enrolled adults with obesity (BMI ≥ 30 kg/m^2) without diabetes, with a stable body weight in the prior 90 days, and failure of at least 1 prior weight loss attempt.[1,40] Additionally, the STEP-8 trial enrolled patients with a BMI ≥ 27 kg/m^2 and at least 1 weight-related comorbidity (eg, hypertension, dyslipidemia, obstructive sleep apnea, CVD).[1] Excluded patients in both trials were patients treated with

[§] Only the Rubino 2022 trial used the FDA-approved semaglutide (2.4 mg subQ weekly) weight-management dose. The second trial (O'Neil 2018) included daily subQ semaglutide doses considered similar to or exceeding the weekly semaglutide dose (eg, 0.4 mg subQ daily). Both trials used weight management doses of liraglutide 3.0 mg subQ daily.

another weight loss drug within 90 days of enrollment, with severe or uncontrolled comorbidities including thyroid conditions, with severe psychiatric conditions or major depressive disorder (in past 2 years), or with other conditions presenting a safety issue with GLP-1 RAs (eg, C-cell thyroid tumors, pancreatitis).[89,90]

Both trials enrolled patients with similar demographics; additionally, treatment arms in each trial were relatively balanced with respect to age, sex, race, baseline body weight, and baseline comorbidities or cardiometabolic parameters. The mean age for each trial was the upper 40s (49 years STEP-8 and 47 years O'Neil) and included primarily White (74% STEP-8 and 73% O'Neil) women (78% STEP-8 and 65% O'Neil). The mean baseline BMI was 37.5 kg/m^2 and 39.3 kg/m^2 for the STEP-8 and O'Neill 2018 trials, respectively.[1,40] In the STEP-8 trial, the proportion of patients with a BMI <30 kg/m^2 for the semaglutide, liraglutide, and pooled placebo arms was 7.1%, 8.7%, and 4.7%, respectively.[1]

Refer to **Table 4** for an overview of each trials design, interventions, and outcome measures.

Table 4. Overview of Semaglutide Versus Liraglutide Comparative RCTs

Study Name	STEP-8 (Rubino 2022)[1] NCT04074161	O'Neil 2018[89] NCT02452711
Study design	Phase 3b, 68-week DB/OL-RCT[a] Multicenter at 19 US sites, 2019-2021	Phase 2, 52-week, dose-ranging, DB/OL-RCT[a] Multi-country at European, Australian, and North American sites (21 US), 2015-2016
Population	Adults (≥18) with BMI ≥ 30 or ≥ 27 with ≥1 comorbidity (treated or untreated) without diabetes	Adults (≥18) with BMI ≥ 30 without diabetes or endocrine disorder-related weight gain (eg, Cushing's Syndrome)
Semaglutide subQ[b]	Semaglutide 2.4 mg weekly (n=136) • 1.7 mg weekly allowed if 2.4 mg weekly not tolerated (86.2% of completers received 2.4 mg)	Semaglutide 0.05 mg daily (n=103) Semaglutide 0.1 mg daily (n=102) Semaglutide 0.2 mg daily (n=103) Semaglutide 0.3 mg daily-ST (n=103) Semaglutide 0.4 mg daily-ST (n=102) Semaglutide 0.3 mg-FT (n=102) Semaglutide 0.4 mg-FT (n=103)
Liraglutide subQ	Liraglutide 3 mg subQ daily (n=127) • Patients intolerant to liraglutide 3 mg could restart titration	Liraglutide 3 mg daily (n=103)
Placebo subQ	Matched pooled placebo (n=85)[a]	Matched pooled placebo (n=136)
Co-Interventions	HCP counseling every 4-6 wks, recommending: • Diet: 500 kcal/d deficit • Exercise: ≥ 150 min/wk	HCP counseling every 4 wks, recommending: • Diet: 500 kcal/d deficit until reaching BMI ≤ 22 • Exercise: ≥ 150 min/wk
Primary Outcome	Percent change in BW from BL to week 68	Percent change in BW from BL to week 52

Table 4. Overview of Semaglutide Versus Liraglutide Comparative RCTs

Study Name	STEP-8 (Rubino 2022)[1] NCT04074161	O'Neil 2018[89] NCT02452711
Secondary Outcome Each outcome was assessed from BL to end of the trial (ie, week 68 or 52)	"Confirmatory": • Proportion or patients reaching percent WL change from BL of ≥: 10%, 15%, 20% "Supportive": • Change in other BW measures (eg, absolute BW, waist circumference) • Change in cardiometabolic surrogate markers (eg, A1c, BP, lipids, CRP) • Permanent trial cessation	• Proportion or patients reaching percent WL change from BL of ≥: 5%, 10% • Change in other BW measures (eg, waist circumference, waist-hip ratio, BMI) • Change in cardiometabolic surrogate markers (eg, A1c, BP, lipids) • Change in SF-36 (US participants only), BP or lipid-lowering medications • Nutrition counselling compliance • WL from BL of ≥15% or ≥20% (post-hoc)

[a] *Two placebo groups matched to either the semaglutide or liraglutide group (pooled for analysis). Double-blinding was for treatment vs the matched placebo group; the trial was OL with respect to semaglutide/semaglutide-placebo vs liraglutide/liraglutide-placebo.*

[b] *Daily doses of semaglutide 0.4 mg subQ daily is "equivalent" to semaglutide 2.8 mg subQ weekly per Rubino 2022[1]*

Abbreviations: BL, baseline; BMI, body mass index in kg/m^2; BP, blood pressure; BW, body weight; CRP, C-reactive protein; DB, double-blind; FT, fast titration (escalation every 2 weeks); OL, open-label (no blinding); n, number of participants; RCT, randomized controlled trial; SF-36, Short Form Health Survey questionnaire; ST, standard titration (escalation every 4 weeks); US, United States; WL, weight loss;

In the STEP-8 trial, patients treated with weekly semaglutide achieved a higher mean percent change in body weight from baseline to week 68 compared to daily liraglutide. Additionally, a higher proportion of patients lost a clinically significant proportion of weight of 10%, 15% and 20% from baseline to week 68 with weekly semaglutide compared to daily liraglutide. Similar results were observed with other analyses of the primary outcome (eg, the estimand evaluating taking the drugs as intended and sensitivity analyses).[1] O'Neil et al found similar results to the STEP-8 trial, demonstrating greater weight loss with higher daily semaglutide dosages (0.2, 0.3, 0.4 mg) versus daily liraglutide.[40] However, only the STEP-8 trial formally evaluated the superiority of semaglutide to liraglutide for weight loss.[1] All comparisons between semaglutide and liraglutide from the O'Neil et al trial were unadjusted for multiple statistical comparisons.[40] Refer to **Table 5** for a summary of the primary and secondary weight loss outcomes from each trial.

Improvements in other body weight (eg, waist circumference) or cardiometabolic parameters (eg, blood pressure, lipids, glycemic indices) from baseline to the end of treatment occurred with both liraglutide and semaglutide (at most daily doses and 2.4 mg weekly).[1,40] Statistical comparisons between liraglutide and semaglutide for changes in these secondary measures were not reported by O'Neil 2018.[40] In the phase 3 STEP-8 trial, significantly greater reductions in absolute body weight, waist circumference, diastolic blood pressure, total cholesterol, very low-density lipoprotein, triglycerides, hemoglobin A1c, and C-reactive protein from baseline to end of treatment were observed with weekly semaglutide compared to daily liraglutide.[1]

Table 5. Primary and Select Secondary Weight Loss Outcomes from Semaglutide vs Liraglutide Trials

	Pooled Placebo	LIR 3.0 mg daily	SEM 2.4 mg weekly	SEM 0.4 mg dailya
STEP-8 phase 3b RCT: semaglutide 2.4 mg subQ weekly vs liraglutide 3 mg subQ daily vs placebo[b,1]				
Mean BW % change from baseline to week 68	–1.9	–6.4	–15.8	--
Difference from liraglutide (95% CI)‡	--	--	–9.4 (–12.0 to –6.8)*	--
Difference from placebo (95% CI)	--	–4.5 (–7.3 to –1.7)	–13.9 (–12.0 to –6.8)	--
% patients achieving weight loss ≥10% at week 68	15.4	25.6	70.9	--
% patients achieving weight loss ≥15% at week 68	6.4	12.0	55.6	--
% patients achieving weight loss ≥20% at week 68	2.6	6.0	38.5	--
O'Neil 2018 phase 2 RCT: semaglutide 0.05-0.4 mg subQ daily vs liraglutide 3 mg subQ daily vs placebo[c,40]				
Mean BW % change from baseline to week 52	–2.3	–8.3	--	–14.0
Difference from liraglutide (95% CI)	--	--	--	–6.08 (–8.41 to –3.75)***
Difference from placebo (95% CI)‡	--	–5.47 (–7.68 to –3.27)**	--	–11.55 (–13.74 to –9.36)**
% patients achieving weight loss ≥ 5% at week 52	23	66**	--	83**
% patients achieving weight loss ≥10% at week 52	10	34**	--	65**

**P<0.001 vs liraglutide; **P<0.0001 vs placebo; ***P<0.0001 vs liraglutide, unadjusted for multiple comparisons*

***‡** denotes the primary group for statistical comparison to semaglutide*

[a] The standard titration semaglutide arm except for the comparison to liraglutide which is for the semaglutide 0.4 mg FT

[b] Results from the "treatment policy" estimand, which was the primary estimand measuring the effect of treatment among all patients randomized regardless of adherence or stopping the study treatment for a rescue intervention.

[c] Primary outcome results from the "in-trial" estimated which included patients as randomized according to the intention-to-treat principle. The proportion of patients achieving a weight loss threshold is estimated with logistic regression.

Abbreviations: BW, body weight; CI, confidence interval; FT, fast titration (every 2 weeks); LIR, liraglutide; RCT, randomized controlled trial; SEM, semaglutide; subQ, subcutaneous;

6.1.1 Comparative Safety

Serious adverse events (SAEs) and selected other adverse events (AEs) among all randomized participants in the STEP-8 trial are summarized in **Table 6**. The most common AEs among both semaglutide (SEM) and liraglutide (LIR) arms were gastrointestinal related, with nausea being the most common (SEM: 61% vs LIR: 59%). Some gastrointestinal AEs were numerically more frequent with SEM versus LIR (constipation, diarrhea, vomiting, belching) whereas infections, psychiatric disorders (primarily insomnia) and injection reactions occurred numerically more frequently with LIR. AEs leading to treatment discontinuation occurred numerically more frequently with LIR versus SEM.[1]

Table 6. Serious Adverse Events and Select Adverse Events from the STEP-8 Clinical Trial[a,1]

	LIR 3.0 mg daily	SEM2.4 mg weekly	Pooled Placebo
	Number of participants (%)		
Fatal AEs	0	0	0
SAEs	14 (11%)	10 (7.9%)	6 (7.1%)
AEs leading to treatment discontinuation	16 (12.6%)	4 (3.2%)	3 (3.5%)
AEs ≥ 10% in one or more arms and with ≥5% difference between active treatment arms			
Constipation	40 (31.5%)	49 (38.9%)	20 (23.5%)
Diarrhea	23 (18.1%)	35 (27.8%)	22 (25.9%)
Vomiting	26 (20.5%)	32 (25.4%)	5 (5.9%)
Belching	5 (3.9%)	17 (13.5%)	4 (4.7%)
URTI	19 (15.0%)	9 (7.1%)	18 (21.2%)
Arthralgia	14 (11.0%)	8 (6.3%)	7 (8.2%)
Influenza	14 (11.0%)	5 (4.0%)	6 (7.1%)
Psychiatric disorders[b]	19 (15.0%)	7 (5.6%)	9 (10.6%)
Injection site reactions	14 (11.0%)	0	5 (5.9%)

[a] Data from all randomized participants. Includes events during treatment with any dose within prior 49 days.

[b] The nature of all the psychiatric events was not reported. Authors describe that differences in the rate of these events between the semaglutide and liraglutide arms were primarily driven by higher insomnia rates with liraglutide.

Abbreviations: AE, adverse events; LIR, liraglutide; SAE, serious adverse events; SEM, semaglutide; URTI, upper respiratory tract infection

Acute pancreatitis occurred in 1 (0.8%) LIR-treated patient and no SEM-treated patients. The rate of malignant neoplasms was the same in both active treatment arms (2.4%, including basal cell carcinoma, renal cell carcinoma, and breast cancers) versus 1.2% with placebo.[1]

6.2 Liraglutide versus Orlistat

The randomized, open-label/double-blinded trial** by **Astrup et al 2009** compared multiple doses of liraglutide subQ daily to orlistat or placebo (matched to liraglutide) as an adjunct to caloric restriction and physical activity among obese adults.[41] Treatment arms included placebo (n=98), orlistat (n=95), or liraglutide, at a daily dose of 1.2 mg (n=95), 1.8 (n=90), 2.4 mg (n=93), or 3.0 mg (n=93). Liraglutide was initiated at 0.6 mg daily and titrated to the target dose over 2-4 weeks, while orlistat was administered as 120 mg capsules three times daily with each meal. Co-interventions for all trial patients included a 500 kcal/day caloric deficit (from a low-fat [~30% fat] diet) and physical activity. The primary endpoint was the mean change in body weight from randomization to week 20 (encompassing the dose-titration period and 16 week liraglutide maintenance dose period) in the intention-to-treat (ITT) population.[41] **Astrup et al 2012** reported long-term follow of the Astrup 2009 trial including follow-up 1 year (phase 1) and 2 years (phase 2) after randomization in the Astrup 2009 trial. During phase 1, participants continued as randomized, with 63% completing this phase. After 1 year, for phase 2, patients who received any dose of liraglutide or placebo during phase 1 switched to liraglutide 2.4 mg daily followed by 3.0 mg daily (at week 70-96 due to a protocol change) until year 2 (47.5% of those randomized at the start of phase 2 completed phase 2).[42]

Enrolled patients were adults (ages 18-65 years) from multiple sites in Europe with obesity (BMI 30-40 kg/m^2), a stable body weight in the prior 90 days, and without diabetes. Key exclusion criteria were drug-induced obesity, treatment with approved weight loss medication (within the prior 3 months), prior weight loss surgery, and major medical conditions. Of note, mental health conditions were not a criterion for exclusion.[41]

Overall, the majority of the initial 20-week trial participants were women (~75%) with a mean age of about 45 years and a baseline mean BMI of about 35. Approximately 30% of participants had abnormal glucose tolerance in the pre-diabetic range, and between 1-6% (varying by study arm) of patients had impaired glucose tolerance in the diabetic range (the positive test occurred after screening). The study arms were generally well-balanced with respect to sex, age, bodyweight and BMI, waist circumference, blood pressure, and lipid values at baseline. Numerically more patients in the placebo arm had metabolic syndrome (33%) versus other arms (eg, orlistat: 24%, or liraglutide 2.4 mg: 23%). At screening, slight numeric differences in the proportion of patients receiving hypertensive (17% vs 12%) or cholesterol-lowering medications (2% vs 8%) was observed between the orlistat and liraglutide arms, respectively.[41]

Both orlistat and liraglutide (1.2-3.0 mg) led to more weight loss at 20 weeks compared to placebo (but only placebo comparisons to liraglutide were tested for superiority, with all liraglutide doses demonstrating superiority). Participants receiving the highest doses of liraglutide (2.4 mg and 3.0 mg) loss significantly more weight at week 20 than participants receiving orlistat. Similarly, a significantly greater proportion of patients receiving liraglutide 3.0 mg achieved a ≥5% weight loss from randomization to week 20 compared to orlistat.[41] The 2-year extension study (Astrup 2012) assessed comparative weight loss persistence at 1 year (liraglutide vs placebo and orlistat, phase 1) and 2 years (liraglutide [including participants initially randomized to placebo] vs orlistat, phase 2) in the subset of

**The Astrup 2009 trial was blinded with respect to liraglutide versus placebo, but not for liraglutide versus orlistat due to differences in the route of administration.

patients enrolled in the extension study. Weight loss at 20 weeks was generally maintained for each study arm to year 1, with cumulative weight loss in the liraglutide 3.0 mg arm significantly exceeding the orlistat arm. After 2 years, cumulative weight loss from randomization (ie, start of the 20-week trial) was numerically less than at 20 weeks or 1 year for both the liraglutide and orlistat arms. But total weight loss remained significantly greater for liraglutide-treated patients compared to orlistat-treated patients; yet, the 2-year results may have been biased (particularly for the mean weight loss outcome) in favor of liraglutide due to untreated patients being added to that group but not the orlistat group for phase 2.[42]

Refer to **Table 7** for details of the primary weight loss outcomes from the Astrup 2009 and 2012 studies.

Table 7. Primary and Select Secondary Weight Loss Outcomes from Orlistat vs Liraglutide Trials

	Placebo	LIR 3.0 mg subQ daily[a]	ORL 120 mg PO TID
Astrup 2009 RCT[b, 41] (NCT00422058)			
Mean BW (kg) change from randomization to **week 20**	–2.8	–7.2	–4.1
Mean difference from orlistat (95% CI)	--	–4.4 (–6.0 to –2.9)*	--
Mean difference from placebo (95% CI)‡	--	–3.0 (–4.5 to –1.4)*	--
% patients achieving weight loss ≥5% at week 20	29.6%	76.1%*	44.2%
% patients achieving weight loss ≥10% at week 20	2.0%	28.3%	9.5%
Astrup 2012: long-term extension study to Astrup 2009 [c, 42]			
Mean BW (kg) change from randomization to **1 year**	–2.0	–7.8**	–3.9
% patients achieving weight loss ≥ 5% at **1 year**	28%	73%***	44%
% patients achieving weight loss ≥10% at **1 year**	10%	37%***	14%
Mean BW (kg) change from randomization to **2 years**	--	–5.3[†]	–2.3
% patients achieving weight loss ≥ 5% at **2 years**	--	52%[†]	29%
% patients achieving weight loss ≥10% at **2 years**	--	26%[f]	16%

**P<0.0001 vs placebo or ORL; **P=0.02 vs placebo and P=0.03 vs ORL; ***P≤0.001 vs placebo and P<0.001 vs ORL.*

[†]P<0.001 vs ORL; f P=0.04 vs ORL

[‡] denotes the primary group for statistical comparison to liraglutide (comparison to orlistat was a 'secondary objective'). The primary efficacy objective of the extension trial was to assess weight-loss durability.

[a] For the extension trial, this arm included participants initially started on placebo or any dose of liraglutide. After 1 year, participants were switched to liraglutide 2.4 mg daily (until 70-96 weeks) and increased to liraglutide 3.0 mg until year 2.

[b] Analysis of the ITT population. Comparatively greater weight loss occurred in patients completed the trial as planned.

[c] Analyzed for the modified ITT population (randomized patients receiving at least 1 drug dose and reporting at least 1 post-randomization weight) using a last-observation-carried forward analysis.

Abbreviations: BW, body weight; CI, confidence interval; ITT, intention-to-treat; LIR, liraglutide; kg, kilograms; ORL, orlistat; PO, orally; RCT, randomized controlled trial; subQ, subcutaneous; TID, three times daily; Vs, versus.

Several secondary outcomes from the primary trial (Astrup 2009) also favored liraglutide to orlistat. The decrease in the proportion of patients with metabolic syndrome was numerically greater for liraglutide 2.4-3.0 mg arms (>60%) versus orlistat (13%). Changes in glycemic parameters (ie, probability of having a normal glucose tolerance, fasting plasma glucose, mean hemoglobin A1c) tended to favor liraglutide to orlistat at 20 weeks. Improvement in select quality of life parameters also significantly favored liraglutide 3.0 mg to orlistat, including mean physical function, mean self-esteem, and mean work score. After 20 weeks of treatment, similar reductions in waist circumference and blood pressure occurred with liraglutide 3.0 mg and orlistat therapy.[41]

6.2.1 *Comparative Safety*

At 20 weeks, numerically more patients in the liraglutide arm experienced any AE and discontinued treatment due to an AE compared to orlistat and placebo. SAEs were infrequent at 20 weeks.[41] After 1 year, 7.5% of liraglutide 3.0 mg-treated patients versus 2.1% of orlistat-treated patients reported a SAE. SAEs leading to trial withdrawal among liraglutide arms (any dose) at 1 year included cholelithiasis with acute pancreatitis (n=1), atrial fibrillation (1), cancer of the breast or lung (n=2), uterine leiomyoma (n=1), and anaphylaxis to a non-study medication (n=1).[42]

Both liraglutide and orlistat were associated with increased gastrointestinal side effects compared to placebo. Whereas users of liraglutide tended to experience increased vomiting and nausea, users of orlistat experienced increased diarrhea.[41,42] According to Astrup et al, common AEs with liraglutide were usually mild to moderate in intensity and tended to improve after dose-titration completion.[41] Refer to **Table 8** for a summary of AEs from the primary 20-week Astrup et al 2009 trial.

Table 8. Serious Adverse Events and Select Adverse Events from the Astrup 2009 Clinical Trial[a, 41]

	LIR 3.0 mg daily	ORL 120 mg TID	Placebo
	Number of participants (%)		
Participants with AEs	88 (94.6%)	81 (85.3%)	81 (82.7%)
Any SAE	1 (1.0%)	0	1 (1.0%)
AEs leading to treatment discontinuation	5 (5.4%)	3 (3.2%)	3 (3.1%)
AEs ≥ 10% in one or more arms and with ≥5% difference between active treatment arms			
Constipation	13 (14.0%)	6 (6.3%)	12 (12.2%)
Diarrhea	12 (12.9%)	24 (25.3%)	7 (7.1%)
Vomiting	11 (11.8%)	2 (2.1%)	2 (2.0%)
Nausea	44 (47.3%)	4 (4.2%)	5 (5.1%)
General disorders and administration-site conditions	24 (25.8%)	4 (4.2%)	11 (11.2%)
Fatigue	10 (10.8%)	1 (1.1%)	2 (2.0%)
Injury, poisoning, and procedural complications	6 (6.5%)	13 (13.7%)	8 (8.2%)
Metabolism and nutrition disorders	11 (11.2%)	6 (6.3%)	11 (11.2%)
Nervous system disorders	19 (20.4%)	13 (13.7%)	21 (21.4%)

Table 8. Serious Adverse Events and Select Adverse Events from the Astrup 2009 Clinical Trial[a, 41]

	LIR 3.0 mg daily	ORL 120 mg TID	Placebo
	Number of participants (%)		

[a] *Events from randomization, including those worsening from screening*

Abbreviations: AE, adverse events; LIR, liraglutide; ORL, orlistat; SAE, serious adverse events; URTI, upper respiratory tract infection

Fatigue, injection-site reactions, and nervous system reactions also tended to occur more frequently during treatment with liraglutide.[41] At 1 year, psychiatric disorders were reported among 12.9% of patients treated with liraglutide vs 5.1% and 5.3% with placebo and orlistat, respectively. An association between a particular psychiatric AE and liraglutide treatment was not established. The most reported psychiatric events in the liraglutide arms at 1 year were insomnia, stress, depression, and anxiety; all events were not serious. At 2 years, 12 symptomatic hypoglycemic events were reported among liraglutide-treated patients, whereas only 1 hypoglycemic event occurred with placebo, but exposure to placebo was likely shorter (only 1 year). Compared to orlistat at year 2, treatment with liraglutide was associated with a significantly greater reduction in systolic blood pressure and a significantly greater increase in heart rate (+3.2 beats per minute with liraglutide vs –0.4 beats per minute with orlistat).[42]

6.3 Phentermine versus Phentermine-topiramate ER

The **EQUATE trial** (Aronne et al 2013) was a phase 3, randomized, double-blinded, multi-site, short-term (6 month) trial conducted in the US. This trial compared the efficacy of combination phentermine-topiramate (PHEN/TOP) ER to the individual active ingredients (PHEN or TOP monotherapy) or placebo to establish the benefits and risks of combination therapy for weight loss. Each study drug was initiated at a low dose (ie, PHEN 3.75 mg/day and PHEN/TOP ER 3.75/23 mg/day) and titrated to the target doses of PHEN 7.5 mg daily (n=109), PHEN 15 mg daily (n=108), PHEN/TOP 7.5/46 mg daily (n=107) or PHEN/TOP 15/92 mg daily (n=108) over 4 weeks. All participants also received low-intensity co-interventions from the *LEARN Manual***,** which included increased physical activity and caloric intake monitoring with the goal of a caloric deficit of 500 kcal/day. Follow-up was for 24 weeks after reaching the target dose (28 weeks including titration).[43] A limitation of this comparison is the maximum dose of daily phentermine (37.5 mg)[28] was not compared to the maximum daily dose of phentermine-topiramate ER (15/92 mg).[36]

Included patients were adults (18-70 years) with obesity (BMI ≥ 30 and ≤ 45 kg/m^2). People recently (within the prior 3 months) undergoing weight changes ≥ 5 kg, taking medications for weight loss (or taking PHEN or TOP for any reason), or using a very low calorie diet or a weight loss program were excluded.[43] Additionally, patients with major or uncontrolled cardiovascular conditions, type 2 diabetes diagnosis, severe or uncontrolled mental health conditions including eating disorders, drug/alcohol abuse history, prior bariatric surgery, and known genetic/endocrine-induced obesity were excluded.[91]

Enrolled participants were primarily female (79.2%) and White (79.2%) with a mean age ± standard deviation of approximately 46 ± 12 years. Participants mean baseline weight was about 101 kg with a mean BMI of 36.3 kg/m^2. Study arms were relatively well-balanced with respect to age, sex, race baseline weight, waist circumference, blood pressure, and use of selective-serotonin reuptake

inhibitors. Numerically fewer participants in the PHEN/TOP ER 7.5/46 mg arm had a history of hypertension or dyslipidemia compared to the phentermine 7.5 mg and 15 mg arms. The phentermine 15 mg arm had the numerically highest percent of patients with dyslipidemia or hypertension at baseline compared to other study arms.[43]

At week 28, numerically greater weight loss occurred in each study arm (including PHEN and TOP monotherapies) compared to placebo. Both doses of PHEN/TOP resulted in significantly greater weight loss (for mean percent change in body weight, and proportion losing ≥5% or ≥10% of weight) from baseline to 28 weeks compared to PHEN 7.5 mg and 15 mg daily. A reduction in systolic blood pressure (SBP) from baseline was observed in all study arms, with a significant difference in SBP change for the PHEN/TOP ER 7.5/46 mg arm versus PHEN 7.5 mg arm but not for other comparisons between other dosages of those products. Changes in glycemic parameters (hemoglobin A1c [A1c], fasting glucose) from baseline were modest; the small difference in change in A1c significantly favored PHEN/TOP ER to PHEN monotherapy of the same PHEN dosage. Significantly greater reductions in waist circumference occurred in both PHEN/TOP ER arms compared to each PHEN monotherapy arm.[43]

Refer to **Table 9** for details of the primary weight loss outcomes from the EQUATOR trial.

Table 9. Primary and Select Secondary Weight Loss Outcomes from the PHEN vs PHEN/TOP ER RCT

	Placebo	PHEN 15 mg daily	PHEN/TOP ER 7.5/46 mg daily	PHEN/TOP ER 15/92 mg daily
EQUATE phase 3 RCT (Arrone et al 2013, NCT00563368)[43]				
LS mean BW % change from baseline to **week 28‡**[a]	–2.3	–7.4	–10.7*	–11.6*
% patients achieving weight loss ≥5% at **week 28‡**[b]	15.5%	46.2%	62.1%**	66%**
% patients achieving weight loss ≥10% at **week 28**[b]	6.8%	20.8%	38.8%**	40.8%**

**P<0.05 vs placebo and PHEN 15 mg daily (in the ITT with LOCF population); **P<0.0001 vs placebo and P<0.05 vs PHEN 15 mg daily (in the ITT with LOCF population); ‡ denotes the primary outcome(s)*

[a] *Numeric values calculated for the modified-ITT population, which included all randomized patients receiving ≥1 study drug dose and with specific weight measurements (baseline, and ≥1 weight measured within 7 days of the last drug dose).*

[b] *Reported values are from the ITT population (all randomized who received at least 1 study drug dose and who had a baseline and ≥1 post-drug dose weight measurement) using the LOCF method for any missing values.*

Abbreviations: BW, body weight; CI, confidence interval; ER, extended-release; LOCF, last observation carried forward; ITT, intention-to-treat; LS, least squares; PHEN, phentermine; RCT, randomized controlled trial; TOP, topiramate

6.3.1 Comparative Safety

During the 28-week EQUATE trial, most AEs were mild to moderate in severity. SAEs that occurred in the PHEN monotherapy and PHEN/TOP ER arms, were as follows: PHEN 7.5 mg (2 patients: pelvic mass, hypotension, cholestatic jaundice, malignant neoplasm); PHEN 15 mg (1 patient: chest pain); PHEN/TOP

7.5/46 mg (1 patient: appendicitis); and PHEN/TOP 15/92 mg (2 patients: blurred vision, humerus fracture). None of the SAEs were considered related to the study drug by investigators. Compared to placebo, numerically more patients receiving any dose of PHEN/TOP ER discontinued the treatment due to an AE; however, no comparison between those groups and the PHEN monotherapy arms were reported.[43]

Regarding treatment-emergent AEs occurring among ≥10% patients in ≥1 study arm, paresthesia, dry mouth, constipation, and nasopharyngitis occurred numerically more frequently among the higher-dose PHEN/TOP (15/92 mg) arm compared to the other study arms. Numerically increased rates of paresthesia and dysgeusia occurred in the PHEN/TOP ER arms compared to the PHEN-only arms. More frequent insomnia (numerically) was observed among the PHEN 15 mg, and both PHEN/TOP ER arms compared to placebo. Disturbed attention was a less frequent AE overall, but occurred numerically more frequently among PHEN/TOP ER arms (3.7% each) compared to PHEN arms (0.9% each).[43]

Refer to **Table 10** for a summary of select AEs from the EQUATE trial.

Table 10. Serious Adverse Events and Select Adverse Events from the EQUATE Clinical Trial[a,43]

	PHEN		PHEN/TOP ER		Placebo
	7.5 mg	15 mg	7.5/46 mg	15/92 mg	
	Number of participants (%)				
Deaths	0	0	0	0	0
Any SAE	2 (1.8%)	1 (0.9%)	1 (0.9%)	2 (1.9%)	0
AEs leading to treatment discontinuation	NR	NR	15.1%	21.3%	7.3%
TEAEs[a] ≥ 10% in one or more arms and with ≥5% difference between active treatment arms					
Paresthesia	3 (2.8%)	5 (4.6%)	17 (16%)	25 (23.1%)	4 (3.7%)
Dry mouth	8 (7.3%)	13 (12%)	14 (13.2%)	20 (18.5%)	0
Constipation	4 (3.7%)	9 (8.3%)	7 (6.6%)	17 (15.7%)	9 (8.3%)
Dysgeusia	1 (0.9%)	1 (0.9%)	9 (8.5%)	16 (14.8%)	0
Nasopharyngitis	6 (5.5%)	10 (9.3%)	3 (2.8%)	14 (13%)	11 (10.1%)
Insomnia	7 (6.4%)	12 (11.1%)	13 (12.3%)	11 (10.2%)	6 (5.5%)

[a] Events among patients who received ≥1 study drug dose.

[b] TEAEs included any events occurring during study drug treatment and up to 28 days after the last dose

Abbreviations: AE, adverse events; ER, extended-release; NR, not reported; PHEN, phentermine; SAE, serious adverse events; TEAE, treatment-emergent adverse events; TOP, topiramate

Compared to baseline, small numeric increases in the mean heart rate were observed in both PHEN only arms (about 1 beat-per-minute increase) whereas decreases in the mean heart rate were observed in the other arms (1.6 beat-per-minute decrease in PHEN/TOP ER arms). Cognitive function domains were assessed using a validated scale, showing clinically relevant (ie, effect size ≥ 0.50) impaired attention throughout the 28-week trial among participants receiving PHEN/TOP ER versus placebo. Small changes in overall cognitive impairment (total index score) among patients in the PHEN/TOP ER arms versus

placebo were observed earlier in the trial, but the overall difference (except impaired attention) tended to improve by the end of the trial.[43]

6.4 Phentermine versus Diethylpropion

A small (n=99), 12-week randomized, active-controlled trial among 5 medical practices in the United Kingdom (**Vallé-Jones et al 1983**) compared oral phentermine 30 mg daily (n=50) to oral diethylpropion 75 mg daily (n=49) among adults with excess body weight. The formulation of each study drug was sustained release. No details about randomization procedures (other than random allocation was used) or blinding were reported by authors of this report.[39] Trial patients were instructed to consume no more than 1500 calories daily[39]; because the degree of caloric deficit was not normalized among patients, there could have been differences in the degree of caloric deficit among patients.

Included patients were adults (18-69 years) with a baseline bodyweight exceeding their desired weight by ≥ 20%,[††] and whose increased weight was not attributed to an endocrine or metabolic condition. Pregnant patients and patients with recent use (within prior 1 month) of any anorectic agent were excluded.[39]

Few details about the baseline characteristics of enrolled patients were reported. Participant characteristics were considered well-balanced between study arms per the study investigators. Most patients in both arms were female (phentermine: 64%; diethylpropion: 69%) with a mean age of approximately 50 years. The mean baseline weight in pounds was about 182 (33% overweight) and 177 (33.5% overweight) in the phentermine and diethylpropion arms, respectively.[39] Notably, BMI measures were not used, perhaps related to the clinical standards during that time (1983).

Significantly greater mean weight loss occurred with phentermine compared to diethylpropion at 12 weeks: –18.20 versus –13.84 pounds (P<0.01), respectively. A significant effect favoring phentermine persisted when analyzed as total weight loss as percent of initial overweight. Significant differences in mean weight loss emerged at 8 weeks between treatment arms, followed by the largest difference in weight loss occurring between week 8 and 12 (~5 pounds vs ~3 pounds for phentermine vs diethylpropion). The investigators suggested the greater difference from 8 to 12 weeks with phentermine could be due to more patients developing tolerance to the effects of diethylpropion.[39] A limitation of the statistical analysis is investigators did not report adjusting for multiple comparisons.

6.4.1 Comparative Safety

Overall, 20 (40%) of phentermine-treated and 24 (48.9%) of diethylpropion-treated patients reported any AE during the 12-week trial. Most AEs were considered to be of minor severity; no severe AEs were reported.[39]

Generally, similar AEs were reported by each treatment arm. The most frequently reported AEs (occurring among ≥5% in at least 1 arm) were dizziness/giddiness, drowsiness, dry mouth, and constipation. Dry mouth (14.3%. vs 8%) and dizziness (10.2% vs 6%) were reported numerically more

[††]This trial might have pre-dated use of BMI for assessing weight status. It is unclear to the authors of this report whether patients who would be classified as 'normal' weight by BMI were included in this trial using their definition of having an excess weight ≥20% higher than the patient's desired weight.

frequently by diethylpropion-treated vs phentermine-treated patients, respectively. Whereas, numerically more patients in the phentermine arm reported drowsiness (12% vs 8.2%) and constipation (8% vs 4%) versus the diethylpropion arm. Events reported only by patients in the phentermine arm were insomnia (2%) and slight tremor (2%); whereas, headache (2%) and nausea (2%) were reported only by patients in the diethylpropion arm.[39]

7.0 SAFETY

Pharmacologic treatments for obesity have a long and fraught history, starting in approximately the 1920s with thyroid extracts.[92] Over the years, many products have been removed from the market due to safety concerns. Recently removed products from the US market include lorcaserin (2020) due to increased cancer risk, and sibutramine (2010) due to an increased risk for serious cardiovascular events.[93] Fenfluramine, a popular weight loss medication in the 1980s and 1990s, was removed from the market due to increased risk for valvulopathy and pulmonary hypertension.[92] These drugs were amphetamine analogs (fenfluramine, sibutramine) which boosted serotonin and/or norepinephrine,[94] and a serotonin 2C receptor agonist (lorcaserin).[92] Available weight management medications in the US do not appear to carry these same risks[16,22] – at least to the magnitude of these prior therapies – but the history of safety issues with weight management medications underscores the importance of long-term safety follow-up.

Cardiovascular concerns: Overweight and obesity are risk factors for fatal and nonfatal cardiovascular disease.[72] Consequently, the cardiovascular safety of weight management medications is an important consideration.

- *Short-term sympathomimetic amine agents:* These products potentiate the effects of norepinephrine, and may increase blood pressure.[23-32] Ischemic events in patients receiving some of these products have been reported.[23,26,29-32] Use in patients with significant cardiovascular disease is contraindicated.[23-32] Another concern is the potential for valvulopathies and pulmonary hypertension. Rare cases of these disorders have been reported with some of these products.[24,27-32] However, the AGA described that these risks seem to be primarily driven by studies of patients also receiving fenfluramine, which binds strongly to serotonin receptors in cardiac tissue, potentially causing cardiotoxicity.[22]
- *Long-term agents:*
    - Increases in heart rate may occur in patients receiving liraglutide, semaglutide, phentermine/topiramate ER, or naltrexone/bupropion ER.[34-37] Blood pressure elevations, including among people without hypertension, have occurred with naltrexone/bupropion ER.[37] Unlike other long-term agents, naltrexone/bupropion ER is contraindicated in patients with uncontrolled hypertension.[37]
    - Significant weight loss (≥10%) is associated with a reduced risk for cardiovascular events in patients with overweight or obesity.[95] Nevertheless, it remains important to establish that weight maintenance pharmacotherapies do not increase the risk for cardiovascular events. As of 2012, the FDA requires new weight management medications to demonstrate superiority or non-inferiority for the hazard of major adverse cardiovascular (MACE) outcomes in clinical trials.[96,97] Despite this, there is a lack of robust long-term cardiovascular primary outcome trial data for phentermine/topiramate ER and naltrexone/bupropion ER.[22,36,37] Mandated

cardiovascular safety trials for naltrexone/bupropion were terminated prematurely and the interim analysis of completing patients was inconclusive for MACE risk.[96] SRs of observational and RCT data[98] and meta-analyses of RCTs[99] for naltrexone/bupropion ER or the individuals components have not demonstrated significant MACE risk; however, in the majority of individual studies, the MACE rate was low.[98] A cardiovascular outcome trial for phentermine/topiramate ER in patients with established cardiovascular disease (AQCLAIM) has been planned since 2013; it is unclear if it will be completed.[96] Cardiovascular outcome trials for liraglutide and semaglutide are limited to patients with T2DM. Semaglutide 0.5-1 mg weekly and liraglutide 1.8 mg daily – doses lower than those for weight loss–reduced the risk of MACE compared to placebo in patients with T2DM.[76,77] The effect of semaglutide 2.4 mg weekly on MACE among adults with a BMI ≥ 27 kg/m^2 with cardiovascular disease is under study in the SELECT trial.[100] Although there is a lack of long-term cardiovascular outcome data for orlistat, orlistat does not exert sympathomimetic effects and orlistat improved cardiometabolic parameters in clinical trials.[16] In their 2016 guideline, the AACE/ACE considered orlistat as a preferred treatment of overweight or obesity in patients with atherosclerotic cardiovascular disease or arrythmias; and recommended other agents (liraglutide, naltrexone/bupropion ER and phentermine/topiramate ER) to be used cautiously in people with those conditions.[16]

Select safety information, primarily from product prescribing information, including the most common adverse events in clinical trials (Section 7.1) and warnings and precautions (Section 7.2) is summarized in the following subsections.

7.1 Adverse Events

Products of the same medication class (ie, GLP-1 RAs semaglutide and liraglutide, and sympathomimetic amines, respectively) carry a similar safety profile. Each weight management product carries risks associated with use. In a meta-analysis of clinical trials, naltrexone/bupropion ER was associated with the highest rate of treatment discontinuations in clinical trials due to adverse events versus comparator (129 more per 1000), for example placebo, relative to diethylpropion (12 more per 1000), orlistat (26 more per 1000), semaglutide (34 more per 1000), phentermine (76 more per 1000), liraglutide (91 more per 1000), or phentermine-topiramate (91 more per 1000).[22] However, such comparisons are limited as they are from primarily indirect comparisons of different trials, with discontinuation rates assessed at different time points possibly biasing higher rates to agents studied in longer-term studies. The most frequent reasons for treatment discontinuations in clinical trials for agents approved for long-term use according to prescribing information are as follows:

- *Semaglutide* (rate in adult trials vs placebo): nausea (1.8% vs 0.2%), vomiting (1.2% vs 0%), diarrhea (1.2% vs 0%)[34]
- *Liraglutide* (rate in adult trials vs placebo): nausea (2.9% vs 0.2%), vomiting (1.75 vs 0.1%), diarrhea (1.4% vs 0%)[35]
- *Phentermine/topiramate ER*: not reported[36]
- *Naltrexone/bupropion* (rate in adult trials): nausea (6.3%), headache (1.7%), vomiting (1.1%)[37]
- *Orlistat* (adult trials): gastrointestinal[33]

The sympathomimetic amines (diethylpropion, phentermine, phendimetrazine, benzphetamine) have a similar safety profile.[23-27,29-32] Adverse event incidence rate and comparison to placebo was not included by prescribing information, limiting characterization of adverse events. Adverse events associated with the drug class were described as "…headache, insomnia, nervousness, dry mouth, constipation, euphoria, palpitations, hypertension, and irritability"[101] (Page 321) by review authors Harrell et al. Changes in sexual function were also reported by prescribing information for each short-term treatment product[23-27,29-32]; and allergic reactions (eg, urticaria) were reported for diethylpropion, phentermine, or benzphetamine.[23,25,26,28-32] Unlike the other short-term products,[23-27,29-32] hematopoietic reactions (eg, bone marrow suppression) were reported among adverse events for diethylpropion products, but the incidence or prevalence of these reactions is unknown.[24,27]

Common adverse events during clinical trials for weight management pharmacotherapies are summarized in **Table 11.**

Table 11. Weight Management Agents Common Adverse Events from the Package Insert

Active Ingredient	Common[a] Adverse Events from Clinical Trials
Agents Approved for Short-term Treatment	
Diethylpropion[24,27]	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[28-32]	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[23,26]	Selected 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

Table 11. Weight Management Agents Common Adverse Events from the Package Insert

Active Ingredient	Common[a] Adverse Events from Clinical Trials
Benzphetamine[25]	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[33]	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
Liraglutide[35]	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 T2DM. 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 T2DM, but no hypoglycemic events were severe.
Semaglutide[34]	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 (T2DM 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[37]	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

Table 11. Weight Management Agents Common Adverse Events from the Package Insert

Active Ingredient	Common[a] Adverse Events from Clinical Trials
Phentermine/ topiramate ER[36]	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; T2DM, type 2 diabetes mellitus; x, times;

7.2 Warnings and Precautions

7.2.1 Long-term Weight Management Agents

Contraindications, warnings, and precautions for use of the long-term weight management agents differ between products except for semaglutide and liraglutide, which have similar safety concerns associated with the GLP-1 RA drug class.

See **Table 12** for labeled major safety concerns for each product.

Table 12. Long-term Agents Contraindications, Warnings and Precautions

Select Labeled Contraindications, Warnings or Precautions	
GLP-1 RAs Drug-class: *Liraglutide[35] (Saxenda) and Semaglutide (Wegovy)[34]*	
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. Employ cautionary measures (ie, renal function monitoring) in patients with renal impairment. ***Hypoglycemia potential*** with concomitant use of insulin or insulin secretagogues (eg, sulfonylurea); inform patients of risks and consider dose modifications. The package insert of liraglutide also highlights that hypoglycemia can occur in patients without T2DM, as a few pediatric cases occurred 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[35] (Saxenda)	**Contraindications:** • Pregnancy: there is a risk of fetal harm, and weight loss is not recommended during pregnancy
Additional Warning for Semaglutide[34] (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.
Phentermine/topiramate ER[36] (Qsymia)	
Contraindications	
• Pregnancy • Glaucoma • Hyperthyroidism	• Hypersensitivity to Qsymia or components, including sympathetic amine drug class • Within 14 days of starting/stopping MAOI
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.[36] In patients with childbearing potential, a negative pregnancy test is recommended before therapy initiation and monthly during therapy. A Risk Evaluation and Mitigation Strategy (REMS) program is in place for this agent that limits distribution to certified pharmacies only. ***Increased heart rate*** is possible due to 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 avoiding 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 the medication does not adversely affect their operating ability.	

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

Table 12. Long-term Agents Contraindications, Warnings and Precautions

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 pediatric patients 12-17 years of age with obesity.
Metabolic acidosis with hyperchloremic non-anion gap is associated with use of this medication. Some conditions (eg, renal disease, surgery, respiratory disorders, concurrent use with other carbonic anhydrase inhibitors) increase risk for metabolic acidosis. Measure electrolytes such as serum bicarbonate prior to and during treatment.
Decrease in renal function, usually within 4-8 weeks of starting this medication, may occur. Renal function may improve during treatment, but usually remains worse than baseline 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 patient without a history of seizures. Gradually taper the medication for discontinuation in patients receiving the highest dose.
Increased risk of kidney stones, hypokalemia, oligohidrosis and hyperthermia, and serious skin reactions (eg, Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis) due to the topiramate component. Risk for decreased sweating and overheating may be higher in pediatric patients. Potassium should be monitored before and during treatment. Monitor patients for these adverse reactions; stop Qsymia for signs of a rash unless drug-induced rash can be clearly ruled out.
Allergic reactions to FD&C Yellow No. 5 contained in this medication are possible in susceptible persons.

Orlistat[33] (Xenical)

Contraindications

- Pregnancy
- Chronic malabsorption syndrome
- Cholestasis
- Hypersensitivity to orlistat or other product components

Warnings or Precautions

***DDI potential with may 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[37] (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 Contrave treatment (due to the bupropion component). Suicidal ideation was rarely reported (0.2%) in Contrave clinical trials among adults. Monitor at-risk patients for changes in thoughts or behaviors during Contrave treatment; and prescribe the lowest number of tablets needed per prescription to reduce overdose risk.
Neuropsychiatric adverse events and suicide risk during smoking cessation*:* Serious neuropsychiatric events (eg, depression, mania, psychosis, agitation, aggression, suicide attempts) have occurred among patients with or without pre-existing mental health conditions when using bupropion for smoking cessation (a non-approved use for Contrave). Depression and suicidal events with an unknown causal relationship to naltrexone treatment have been reported. Stop Contrave and seek medical care immediately if these symptoms develop.

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

Table 12. Long-term Agents Contraindications, Warnings and Precautions

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 it 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 not take Contrave since naltrexone use may precipitate opioid withdrawal. It is recommended to be opioid free for 7-10 days after short-acting opioids, or longer (eg, 2 weeks) after long-acting opioids (eg, buprenorphine, methadone) before starting Contrave.
Increases in blood pressure and heart rate may occur during Contrave treatment including among 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 Contrave clinical trials, so effects in this population are unknown.
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;

7.2.2 Short-term Weight Management Agents

Although product labeling slightly differs among the sympathomimetic amine anorectics, all products carry similar contraindications, warnings/precautions, or risks associated with use (eg, abuse potential). Sympathomimetic amines are contraindicated in patients at risk for increased sensitivity to sympathomimetic effects (ie, severe or uncontrolled cardiovascular disease, hyperthyroidism, glaucoma, agitated condition), and among patients with a history of drug abuse. Concurrent use or use within 14 days of monoamine oxidase inhibitors is also contraindicated due to the risk of a hypertensive crisis. Key warnings for use of these agents include the following: (1) avoiding co-use with other drugs for weight loss and potential increased risk for (2) pulmonary hypertension and (3) regurgitant cardiac valvopathies.[23-32] Longer-term use of these agents may have limited utility since tolerance to their effects commonly develops[23-32]; furthermore, use of anorectic agents for longer than 3 months was associated with a significantly increased (23-fold) risk for developing pulmonary hypertension in one case-control study.[26,27] Phendimetrazine,[26] and diethylpropion[24,27] (but specifically not benzphetamine[25]) were reportedly among anorectic agents included in that case-control study. The AGA guideline reported that cardiotoxicity risks seem to be especially driven by fenfluramine, which binds strongly to serotonin receptors in cardiac tissue potentially causing cardiotoxicity, but not phentermine, based on a prospective study.[22]

Based on comparison of multiple sections of the prescribing information for each agent, the following warnings or risks may differ among the sympathomimetic amines (this list is not comprehensive):

- *Abuse potential:* Both phendimetrazine and benzphetamine products are Schedule 3 controlled substances,[23,25,26] whereas phentermine and diethylpropion products are Schedule 4 controlled substances.[24,27-32] Nevertheless, labeling for each product notes the risk for abuse or dependence, which can manifest as psychosis in severe cases of chronic increased use.[23-32]
- *Recommended duration between anorectic agent regimens:* Labeling for phendimetrazine, benzphetamine, and diethylpropion products warn against using any of these products within 1 year of an anorectic agent,[24-27] whereas phentermine labeling does not specifically recommend against such use.[28-32] Since the rationale for this warning is unknown, it is unclear if there would be similar concerns for phentermine regardless of product labeling.
- *Increased seizures among patients with seizure disorders:* Diethylpropion products uniquely carry a precaution for increased seizures in at-risk patients, which may necessitate dose-reducing or stopping treatment.[24,27] Diethylpropion is structurally related to bupropion,[102] which is known to lower the seizure threshold.[37]

Refer to **Table 13** for details about contraindications, and select warnings, or precautions from product labeling for phentermine, diethylpropion, benzphetamine, and phendimetrazine.

Table 13. Short-Term Agents Contraindications, Select Labeled Warnings or Precautions[a]

Sympathomimetic Amines Drug-class: *Diethylpropion,*[24,27] *Phentermine* (Adipex-P, Lomaira),[28-32] *Phendimetrazine,*[23,26] and *Benzphetamine*[25]	
Contraindications • Cardiovascular disease (eg, CAD, stroke, arrythmia, 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 (prescription or OTC) or serotonergic agents (eg, SSRIs*).** Products are indicated for short-term (ie, a few weeks) use as monotherapy (Phentermine). Efficacy and safety as combined use is not established. ***Primary pulmonary hypertension*** (PPH)**:** Rare cases of PPH associated with phentermine monotherapy (and more cases when used in combination with discontinued drugs fenfluramine or dexfenfluramine) or diethylpropion monotherapy 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. An "Increased risk of pulmonary hypertension with repeated courses of therapy cannot be excluded." (Phendimetrazine, Page 4 and 5; benzphetamine, Page 4; diethylpropion, Page 4) ***Valvular heart disease:*** Serious disease of cardiac mitral, aortic and/or tricuspid valves have occurred in patients without a history of valvular disease taking anorectic agents (eg, discontinued drugs fenfluramine and dexfenfluramine or rare cases with phentermine or diethylpropion alone). A causal role of phentermine or diethylpropion in development of these disorders has not been ruled out. Longer length of use, co-use of anorectic agents, and use of higher than recommended doses might increase risk. Use is not recommended in patients with known vascular heart disease or heart murmur (phendimetrazine, benzphetamine, diethylpropion). Continue treatment after 4 weeks only if there is a satisfactory response (eg, at least 4 pounds weight loss) by 4 weeks (phendimetrazine, benzphetamine, diethylpropion). ***Discontinue treatment if tolerance develops***: A tolerance to effects may develop; do not increase the dose to attempt to overcome this effect if it occurs. ***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.	
Additional for ***Diethylpropion***[24,27]	**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.*** ***Withdrawal syndrome:*** There is a risk of withdrawal syndromes upon cessation after prolonged use. ***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. ***Use with alcohol*** can lead to adverse effects. ***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. ***Prescribe the lowest dose and amount needed at one time*** to prevent overdosage.
Additional for ***Phentermine***[28-32]	**Contraindications** • Pregnancy (may cause fetal harm) or nursing **Warnings or Precautions** ***Impaired ability to engage in hazardous tasks:*** May impair ability to safely operate machinery or drive; advise patients to exercise caution. ***Abuse and dependence risk****:* Phentermine has a similar structure to and properties of 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.* ***Use with alcohol*** can lead to adverse effects. ***Hypoglycemic DM medication dose reductions:*** Reductions in insulin or oral hypoglycemic medications may be needed when used with this medication.

[a] *Labeled contraindications, warnings or precautions specifically listed in those sections in prescribing information for each active ingredient are listed together first, and followed by sections for information specific to one or more (but not all) other active ingredients. Although prescribing information for each product is not identical, it appears that most concerns are similar across the products; some products organize information differently (eg, information classified as a warning/precaution for one product is in a separate section for another product).*

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;

Table 13. Short-Term Agents Contraindications, Select Labeled Warnings or Precautions[a]

Additional for ***Phendimetrazine***[23,26]	**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)** ***Extreme fatigue and depression with abrupt discontinuation:*** There is a risk for these conditions when abruptly stopping high dosages. ***Use not recommended if another anorectic agent has been used in the past year.*** ***Co-use may decrease the hypotensive effect of guanethidine*** (an adrenergic neuron blocking antihypertensive)[103] ***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) ***Prescribe the lowest dose and amount needed at one time*** to prevent overdosage. (Phendimetrazine ER capsule only)
Additional for ***Benzphetamine***[25]	**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 amount of Insulin needed may be altered when used with benzphetamine along with restricted caloric intake. ***Prescribe the lowest dose and amount needed at one time*** to prevent overdosage.

[a] *Labeled contraindications, warnings or precautions specifically listed in those sections in prescribing information for each active ingredient are listed together first, and followed by sections for information specific to one or more (but not all) other active ingredients. Although prescribing information for each product is not identical, it appears that most concerns are similar across the products; some products organize information differently (eg, information classified as a warning/precaution for one product is in a separate section for another product).*

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;

8.0 PHARMACOKINETICS

Minimal pharmacokinetic (PK) data was reported for the older agents approved for short-term use, and no PK information was reported for benzphetamine.[25] The remaining agents (diethylpropion, phendimetrazine, phentermine) are principally renally eliminated.[24,26-32] Naltrexone/bupropion ER and phentermine/topiramate ER (and/or their metabolites) are principally renally excreted.[36,37] Orlistat is primarily excreted in feces and is minimally absorbed.[33] Both semaglutide and liraglutide may undergo some renal or fecal elimination and exhibit very high protein-binding.[34,35]

Among the agents approved for long-term use, semaglutide has the longest elimination half-life[34] and orlistat has the shortest elimination half-life.[33]

Rare development of anti-drug antibodies (ADA), including some with cross-sensitivity to endogenous GLP-1, were reported in clinical trials for semaglutide and liraglutide.[34,35] For both agents, ADA positivity was associated with greater adverse events, including hypersensitivity reactions for semaglutide[34] and injection site reactions and hypoglycemia for liraglutide.[35]

Select PK details from prescribing information is summarized in **Appendix F.**

9.0 SPECIAL POPULATIONS

9.1 Pediatric

Weight-loss pharmacotherapies with pediatric indications or with sufficient evidence for the risks versus benefits are recommended for consideration as adjunctive therapy for adolescents 12 years or older by the AAP. In certain situations, adjunctive weight-loss pharmacotherapy may be offered to children 8-11 years old according to the AAP.[18] However, none of the weight management therapies addressed by this report are FDA-approved for children younger than 12 years old[23-38] with the exception of setmelanotide.[38] Imcivree (setmelanotide) is approved for chronic weight management in children ages ≥ 6 years old with specific rare genetic causes of obesity.[38]

Orlistat, liraglutide, semaglutide, and phentermine/topiramate ER are FDA-indicated or evidence supports their adjunctive use for chronic weight management in pediatric patients with obesity 12 years or older.[33-36] Product labeling for the short-term management agents recommends against their use for patients less than 17 years old.[23-32] Use of naltrexone/bupropion ER is not established for people under 18 years old.[37]

9.2 Pregnancy

Obesity during pregnancy is associated with increased maternal and fetal morbidity and mortality. Weight loss before pregnancy should be encouraged for women with overweight or obesity. The American College of Obstetricians and Gynecologists (ACOG) does not recommend using weight management medications during pregnancy or during the immediate pre-pregnancy period due to safety concerns. Weight loss during pregnancy has been associated with an increased risk of giving birth to a small-for-gestational age infant in some women with obesity. ACOG encourages controlled weight

gain (ie, weight gain within a recommended amount) during pregnancy, managed with non-pharmacologic methods (eg, exercise, diet, behavioral changes).[104]

According to prescribing information, use during pregnancy is specifically contraindicated for all short-term weight management agents[23,25,26,28-32] except for diethylpropion.[24,27] There is a lack of animal data for phentermine and phendimetrazine,[23,26,28-32] and there is evidence of fetal harm with compounds similar to benzphetamine in animals.[25] The long-term agents liraglutide, orlistat, and phentermine/topiramate ER are also contraindicated during pregnancy.[33,35,36] Neither semaglutide nor naltrexone/bupropion ER are specifically contraindicated during pregnancy; however, their use during pregnancy is not recommended due to weight loss not being beneficial during pregnancy.[34,37] There is a lack of human data, but semaglutide may theoretically cause fetal harm.[34]

9.3 Breastfeeding

Recommendations from PIs for short-term agents:

- Diethylpropion and amphetamines (extended to benzphetamine) are secreted in human milk.[24,25,27] It is unknown if phendimetrazine and phentermine are secreted in human milk, but it is possible they are also secreted due to similarities to amphetamines.[26,29-32] According to phentermine/topiramate ER prescribing information, phentermine is secreted in human milk.[36]
- Benzphetamine prescribing information recommends against use while breastfeeding,[25] and similarly, prescribing information for diethylpropion recommends using the agent with caution if breastfeeding.[24,27]
- Phentermine and phendimetrazine prescribing information suggest weighing the benefits to the mother versus potential risks to the infant (which includes potentially serious reactions) before use while breastfeeding.[26,28-32]

Recommendations from PIs for long-term agents:

- There is a lack of human data about secretion of orlistat, semaglutide, or liraglutide in human milk[33-35]; liraglutide and semaglutide are secreted in rat milk, suggesting secretion might also occur in humans.[34,35] Topiramate, naltrexone, and phentermine are secreted in human milk.[36,37] It is unknown whether bupropion is secreted in human milk.[37]
- Prescribing information for orlistat advises caution when using orlistat in nursing patients.[33] Similarly, prescribing information for liraglutide, semaglutide, naltrexone/bupropion ER recommend weighing the potential benefits to the mother versus risks to the infant before use during breastfeeding.[34,35,37] Rare reports of seizures in infants exposed to bupropion have occurred, though it is unknown whether these events were due to bupropion.[37]
- Prescribing information for phentermine/topiramate ER recommends against breastfeeding while using that product due to the risk of adverse effects in the infant. Topiramate exposure during nursing has been associated with diarrhea and somnolence in infants. While adverse events in breastfed infants exposed to phentermine have not been reported (lack of data), its use may theoretically cause serious adverse events (eg, irritability, insomnia, hypertension, weight loss).[36]

9.4 Hepatic or Renal Impairment

Renal impairment (RI): Renal dose adjustment and avoidance for patients with end-stage renal disease is recommended by prescribing information for the following products: phentermine (Adipex-P and generic capsules/tablets),[28,30,31] naltrexone/bupropion ER,[37] and phentermine/topiramate ER.[36] Accumulation of phendimetrazine and diethylpropion is predicted with worsening renal impairment; dosage adjustments may be necessary, but there is a lack of guidance from prescribing information.[23,24,26,27] Intravascular volume depletion may occur with GLP-1 RAs secondary to adverse effects (eg, vomiting), which can cause acute kidney injury; the risk for renal adverse events with volume depletion is increased among patients with moderate-severe renal impairment.[34,35] Liraglutide should be used cautiously in patients with mild to severe renal impairment due to lack of data.[35] The risk for oxalate nephrolithiasis/oxalate nephropathy with orlistat use is increased in patients with renal impairment.[33]

Hepatic impairment (HI): Hepatic dose adjustment and avoidance for patients with severe HI is recommended by prescribing information for the following products: naltrexone/bupropion ER, and phentermine/topiramate ER.[36,37] Liraglutide should be used cautiously in patients with mild to severe hepatic impairment due to lack of data.[35] Hepatic toxicity has been reported with naltrexone treatment, particularly in patients with other risk factors for toxicity.[37]

Risk for cholelithiasis is increased in patients with obesity and in patients undergoing weight loss through any means, particularly rapid weight loss.[16] GLP-1 RAs and orlistat were associated with numerically higher rates of cholelithiasis (or cholecystitis) than placebo in clinical trials.[33-35] Rare cases of serious liver injury (not necessarily related to cholelithiasis) have occurred with orlistat.[33]

Refer to **Appendix A** for recommended dose adjustments, and **Appendix C** for recommended selection of management of weight management pharmacotherapies per the AACE/ACE in patients with RI or HI.

10.0 DRUG INTERACTIONS

Each weight management medication carries the risk for potential drug-drug interactions (DDIs). Refer to **Table 14** for a summary of potential DDIs for each weight management agent according to prescribing information.

Table 14. Information about Potential Drug-Drug Interactions and Metabolism from Package Insert

Active Ingredient	Interacting Medication and Effect and/or Recommended Action from PI	Metabolism/ CYP450 Effect
Agents Approved for Short-term Treatment		
Diethylpropion[24,27]	**MAOIs**: concomitant use is contraindicated; separate administration by at least 14 days **Anorectic agents** (eg, other sympathetic amines for weight loss): concomitant use is contraindicated due to risk for cardiac problems **Antidiabetic drugs**: need for these drugs may change **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. Interaction(s) with CYPs not reported.
Phentermine hydrochloride[28-32]	**MAOIs**: concomitant use is contraindicated; separate administration by at least 14 days **Alcohol**: co-use increases the risk for ADRs	No information provided by PI
Phendimetrazine tartrate[23,26]	**Hypoglycemic meds**: needs for these meds may be altered during co-use **Adrenergic neuron blocking drugs**: co-use may decrease the anti-hypertensive effect of these drugs	Metabolized to ≥ 2 metabolites with unknown activity. Interaction(s) with CYPs not reported.
Benzphetamine[25]	**MAOIs**: concomitant use is contraindicated; separate administration by at least 14 days **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 **Insulin**: insulin needs may be altered during co-use	No information provided by PI
Agents Approved for Long-Term Treatment (>12 weeks)		
Orlistat[33]	**Amiodarone:** slightly reduced systemic exposure to amiodarone **Cyclosporine:** separate administration advised	Metabolized within GI wall to inactive metabolites[105]

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

Table 14. Information about Potential Drug-Drug Interactions and Metabolism from Package Insert

Active Ingredient	Interacting Medication and Effect and/or Recommended Action from PI	Metabolism/ CYP450 Effect
	Levothyroxine: monitor for thyroid function change **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	
Liraglutide[35]	**Orally administered medications:** delays gastric emptying; monitor for effect on other drugs **Hypoglycemic drugs:** hypoglycemic risk increased	Catabolism like large proteins. Interactions with CYPs not expected.
Semaglutide[34]		Proteolytic cleavage
Naltrexone/bupropion ER[37]	**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 digoxin levels; monitor digoxin 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[36]	**MAOIs:** concomitant use is contraindicated; separate administration by at least 14 days **Oral contraceptive:** co-use may lead to irregular bleeding **CNS depressants:** co-use may potentiate CNS AE; may consider PHEN-TOP ER dose reduction for significant cognitive dysfunction	Neither PHEN nor TOP ER undergo extensive metabolism. PHEN is a minor substrate of CYP3A4.

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

Table 14. Information about Potential Drug-Drug Interactions and Metabolism from Package Insert

Active Ingredient	Interacting Medication and Effect and/or Recommended Action from PI	Metabolism/ CYP450 Effect
	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	

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

REFERENCES

1. Rubino DM, Greenway FL, Khalid U, et al. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. *JAMA*. 2022;327(2):138-150. doi:https://dx.doi.org/10.1001/jama.2021.23619

2. Khera R, Pandey A, Chandar AK, et al. Effects of Weight Loss Medications on Cardiometabolic Risk Profiles: A Systematic Review and Network Meta-Analysis. *Gastroenterology*. 2018;154(5):1309-1319.e1307. doi:10.1053/j.gastro.2017.12.024

3. Deng Y, Park A, Zhu L, Xie W, Pan CQ. Effect of semaglutide and liraglutide in individuals with obesity or overweight without diabetes: a systematic review. *Ther Adv Chronic Dis*. 2022;13(101532140):20406223221108064.

4. Canoy D, Bundred P. Obesity in children. *BMJ Clin Evid*. 2011;2011

5. Centers for Disease Control and Prevention. Defining Adult Overweight & Obesity. CDC.gov. 2022. Last Updated June 3, 2022. Accessed February 7, 2023. Available at https://www.cdc.gov/obesity/basics/adult-defining.html

6. Li M, Gong W, Wang S, Li Z. Trends in body mass index, overweight and obesity among adults in the USA, the NHANES from 2003 to 2018: a repeat cross-sectional survey. *BMJ Open*. 2022;12(12):e065425. doi:10.1136/bmjopen-2022-065425

7. Skinner AC, Skelton JA. Prevalence and trends in obesity and severe obesity among children in the United States, 1999-2012. *JAMA Pediatr*. 2014;168(6):561-566. doi:10.1001/jamapediatrics.2014.21

8. Tsoi MF, Li HL, Feng Q, Cheung CL, Cheung TT, Cheung BMY. Prevalence of Childhood Obesity in the United States in 1999-2018: A 20-Year Analysis. *Obes Facts*. 2022;15(4):560-569. doi:10.1159/000524261

9. Fitch AK, Bays HE. Obesity definition, diagnosis, bias, standard operating procedures (SOPs), and telehealth: An Obesity Medicine Association (OMA) Clinical Practice Statement (CPS) 2022. *Obesity Pillars*. 2022;1:100004. doi:https://doi.org/10.1016/j.obpill.2021.100004

10. Kumar RB, Srivastava G, Reid TJ, Aronne LJ. Understanding the pathophysiologic pathways that underlie obesity and options for treatment. *Expert Rev Endocrinol Metab*. 2021;16(6):321-338. doi:10.1080/17446651.2021.1991310

11. Centers for Disease Control and Prevention. Consequences of Obesity. CDC.gov. 2022. Last Updated July 15, 2022. Accessed February 7, 2023. Available at https://www.cdc.gov/obesity/basics/consequences.html

12. Warren M, Beck S, Lieberman D. *The State of Obesity: Better Policies for a Healthier America 2021. Special Feature: COVID-19, Social Determinants of Health, and Obesity*. Health TfAs; 2021: 92 pages. Last Updated September 2021. Accessed February 7, 2023. Available at https://www.tfah.org/wp-content/uploads/2021/09/2021ObesityReport_Fnl.pdf

13. Hammond RA, Levine R. The economic impact of obesity in the United States. *Diabetes Metab Syndr Obes*. 2010;3:285-295. doi:10.2147/dmsott.S7384

14. Herbozo S, Brown KL, Burke NL, LaRose JG. A Call to Reconceptualize Obesity Treatment in Service of Health Equity: Review of Evidence and Future Directions. *Curr Obes Rep*. 2023, 10.1007/s13679-023-00493-5:1-12. doi:10.1007/s13679-023-00493-5

15. Warren M, Beck S, West M. *The State of Obesity: Better Policies for a Healthier America 2022. Special Feature: Food and Nutrition Insecurity among Youth and Families*. Health TfAs; 2022: 92 pages. Last Updated September 2022. Accessed February 7, 2023. Available at https://www.tfah.org/wp-content/uploads/2022/09/2022ObesityReport_FINAL3923.pdf

16. Garvey WT, Mechanick JI, Brett EM, et al. Americian Association of Clinical Endocrinologists and America College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity *Endocr Pract*. 2016;22 Suppl 3:1-203. doi:10.4158/ep161365.Gl

17. The Management of Adult Overweight and Obesity Work Group. *VA/DoD Clinical Practice Guideline for the Management of Adult Overweight and Obesity*. Department of Veterans Affairs (VA)/Department of Defense (DodD); 2020: 147 pages. Accessed March 8, 2023. Available at https://www.healthquality.va.gov/guidelines/CD/obesity/VADoDObesityCPGFinal5087242020.pdf

18. Hampl SE, Hassink SG, Skinner AC, et al. Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents With Obesity. *Pediatrics*. 2023, 10.1542/peds.2022-060640doi:10.1542/peds.2022-060640 Accessed 1/27/2023. Available at https://doi.org/10.1542/peds.2022-060640

19. Mayer SB, Graybill S, Raffa SD, et al. Synopsis of the 2020 U.S. VA/DoD Clinical Practice Guideline for the Management of Adult Overweight and Obesity. *Mil Med*. 2021;186(9-10):884-896. doi:10.1093/milmed/usab114

20. Styne DM, Arslanian SA, Connor EL, et al. Pediatric Obesity—Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2017;102(3):709-757. doi:10.1210/jc.2016-2573 Accessed 3/10/2023. Available at https://doi.org/10.1210/jc.2016-2573

21. Marc-André Cornier MD. A Review of Current Guidelines for the Treatment of Obesity. *Supplements and Featured Publications*. 2022;28Accessed 27-February-2023. Available at https://www.ajmc.com/view/review-of-current-guidelines-for-the-treatment-of-obesity

22. Grunvald E, Shah R, Hernaez R, et al. AGA Clinical Practice Guideline on Pharmacological Interventions for Adults With Obesity. *Gastroenterology*. 2022;163(5):1198-1225. doi:10.1053/j.gastro.2022.08.045 Accessed 2023/01/18. Available at https://doi.org/10.1053/j.gastro.2022.08.045

23. Phendimetrazine Tartrate Tablets, USP 35 mg, CIII. Package Insert. A-S Medication Solutions; 2023. Accessed April 26, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f1d265e1-522e-4a62-afda-29477fb94b8d

24. Diethylpropion Hydrochloride Extended Release Tablets, 75 mg CIV. Package Insert. A-S Medication Solutions; 2023. Accessed February 15, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=04f1a804-00f1-48f5-acfa-0ed1a8544784

25. Benzphetamine Hydrochloride Tablets, CIII. Package Insert. Solutions A-SM; 2023. Accessed February 15, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2845f479-f4f3-4ae6-856d-4c0df9eeccf9

26. Phendimetrazine Tartrate Extended-Release Capsules CIII. Package Insert. Virtus Pharmaceuticals L; 2022. Accessed February 15, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=669fafd4-ac03-4bbc-ba86-28d1efbaf8c6

27. Diethylpropion HCl USP CIV 25 mg tablets. Package Insert. PD-Rx Pharmaceuticals I; 2022. Accessed February 15, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ad0c3dc9-ae13-4853-bc8c-a66e2a69cc10

28. Adipex-P (phetermine hydrochloride) tablets, for oral use CIV. Adipex-P (phentermine hydrochloride) capsules, for oral use CIV. Package insert. PD-Rx Pharmaceuticals I; 2022. Accessed February 15, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cf6e2aa5-e8e1-4478-93b9-47632a924482

29. PHENTERMINE HYDROCHLORIDE orally disintegrating tablets, for oral use CIV. Package Insert. Cadila Healthcare Limited; 2022. Accessed February 15, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=0a1088ea-2c96-4565-aa43-28d6a98d6996

30. Phentermine Hydrochloride Tablets and Capsules, USP 37.5 mg (phentermine hydrochloride, USP) CIV for oral use. Package Insert. KVK-Tech I; 2021. Accessed February 15, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3b44d104-a7d0-4366-9d42-63f784f3cb22

31. PHENTERMINE Hydrochloride Capsules USP CIV. Package Insert. TAGI Pharma I; 2019. Accessed February 15, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2acb0c69-0089-4817-86ad-6df592c0356e

32. LOMAIRA (phentermine hydrochloride USP) tablets, CIV. Package Insert. Kvk-Tech I; 2018. Accessed February 15, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cde9fb09-e5af-434d-8874-e4f9f974d893

33. Orlistat Capsules for oral use. Package Insert. H2-Pharma LLC; 2023. Accessed February 15, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f81dfaeb-46d5-47ce-9ef6-19259f5ac61c

34. Wegovy (semaglutide) subcutaneous injection. Package Insert. Novo Nordisk A/S; 2022. Accessed February 15, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ee06186f-2aa3-4990-a760-757579d8f77b

35. Saxenda (liraglutide) 3 mg injection. Package Insert. Novo Nordisk A/S; 2022. Accessed February 15, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3946d389-0926-4f77-a708-0acb8153b143

36. QSYMIA (phentermine and topiramate extended-release capsules), for oral use, CIV. Package Insert. Catalent Pharma Solutions LLC; 2022. Accessed February 15, 2022. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=40dd5602-53da-45ac-bb4b-15789aba40f9

37. CONTRAVE (naltrexone hydrochloride and bupropion hydrochloride) extended-release tablets. Package Insert. Nalpropion Pharmaceuticals LLC; 2021. Accessed February 15, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=485ff360-32c8-11df-928b-0002a5d5c51b

38. IMCIVREE (setmelanotide) injection, for subcutaneous use. . Package Insert. Rhythm Pharmaceuticals I; 2022. Accessed February 15, 2023. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=70c3ccf7-4df0-4c75-ba07-fede9970c8d9

39. Vallé-Jones JC, Brodie NH, O'Hara H, O'Hara J, McGhie RL. A comparative study of phentermine and diethylpropion in the treatment of obese patients in general practice. *Pharmatherapeutica*. 1983;3(5):300-304.

40. O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. *Lancet*. 2018;392(10148):637-649. doi:10.1016/s0140-6736(18)31773-2

41. Astrup A, Rössner S, Van Gaal L, et al. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet*. 2009;374(9701):1606-1616. doi:10.1016/s0140-6736(09)61375-1

42. Astrup A, Carraro R, Finer N, et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int J Obes (Lond)*. 2012;36(6):843-854. doi:10.1038/ijo.2011.158

43. Aronne LJ, Wadden TA, Peterson C, Winslow D, Odeh S, Gadde KM. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. *Obesity (Silver Spring)*. 2013;21(11):2163-2171. doi:10.1002/oby.20584

44. Bessesen DH, Van Gaal LF. Progress and challenges in anti-obesity pharmacotherapy. *Lancet Diabetes Endocrinol*. 2018;6(3):237-248. doi:10.1016/s2213-8587(17)30236-x

45. OZEMPIC (semaglutide) injecttion, for subcutaneous use. Package Insert. A/S NN; 2022. Accessed March 17, 2023. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209637s012lbl.pdf

46. VICTOZA (liraglutide) injection, for subcutaneous use. Package Insert. Novo Nordisk A/S; 2022. Accessed March 17, 2023. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022341s037s038lbl.pdf

47. MOUNJARO (tirzepatide) injection, for subcuteanous use. Package Insert. Lilly USA L; 2022. Accessed March 17, 2023. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215866s000lbl.pdf

48. Administration. USFD. New Drug Application (NDA): 012427. AccessData.FDA.gov/Scipts/CDER/DAF; Available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=012427

49. U.S. Food & Drug Administration. New Drug Application (NDA): 011722. Tenuate Diethylpropion hydrochloride AccessData.FDA.gov/Scipts/CDER/DAF; Accessed March 17, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=011722

50. U.S. Food & Drug Administration. Abbreviated New Drug Application (ANDA): 083790. Melfiat Phendimetrazine tartrate AccessData.FDA.gov/Scipts/CDER/DAF; Accessed March 17, 2023. Available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=083790

51. Medicaid Policy for Pharmacy Program § R14, 60 ch. 5 § 11 (2021). Accessed April 7, 2023. Available at https://adminrules.utah.gov/public/rule/R414-60/Current%20Rules?searchText=R414-60-5

52. Utah Medicaid. Utah Medicaid Preferred Drug List - Effective April 1, 2023. Medicaid.Utah.Gov; 2023. Last Updated April 1, 2023. Accessed April 7, 2023. Available at https://medicaid.utah.gov/pharmacy/preferred-drug-list/

53. Haleon. Alli. Accessed March 22, 2023. Available at https://www.myalli.com/

54. EVEKEO (amphetamine sulfate tablets, USP). Package Insert. Arbor Pharmaceuticals L; 2019. Accessed April 24, 2023. Available at https://www.evekeo.com/pdfs/evekeo-pi.pdf?v=1680099069680

55. Plenity. U.S. Food & Drug Admiistration Approval Letter. Gelesis I; 2019. Accessed March 17, 2023. Available at https://www.accessdata.fda.gov/cdrh_docs/pdf18/DEN180060.pdf

56. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med*. 2022;387(3):205-216. doi:10.1056/NEJMoa2206038

57. Lilly receives U.S. FDA Fast Track designation for tirzepatide for the treatment of adults with obesity, or overweight with weight-related comorbidities. News Release. October 6, 2022, 2022. Accessed March 17, 2023. Available at https://investor.lilly.com/news-releases/news-release-details/lilly-receives-us-fda-fast-track-designation-tirzepatide

58. McMaster University Health Information Research Unit. Search filters for Medline in Ovid syntax and the PubMed translation. hiru.mcmaster.ca; 2016. Last Updated February 9, 2016. Accessed

November 7, 2022. Available at https://hiru.mcmaster.ca/hiru/hiru_hedges_medline_strategies.aspx

59. Lefebvre C, Manheimer E, Glanville J. Searching for studies. In: Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0*. The Cochrane Collaboration; 2011:chap 6. Accessed November 7, 2022. Available at https://handbook-5-1.cochrane.org/

60. Shi Q, Wang Y, Hao Q, et al. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. *Lancet (London, England)*. 2022;399(10321):259-269. doi:https://dx.doi.org/10.1016/S0140-6736(21)01640-8

61. Zhao G, Zhang Q, Wu F, Yin S, Xie Y, Liu H. Comparison of weight loss and adverse events of obesity drugs in children and adolescents: a systematic review and meta-analysis. *Expert Rev Clin Pharmacol*. 2022;15(9):1119-1125. doi:https://dx.doi.org/10.1080/17512433.2022.2117152

62. Xie Z, Yang S, Deng W, Li J, Chen J. Efficacy and Safety of Liraglutide and Semaglutide on Weight Loss in People with Obesity or Overweight: A Systematic Review. *Clin Epidemiol*. 2022;14(101531700):1463-1476. doi:https://dx.doi.org/10.2147/CLEP.S391819

63. Rosen H. Is Obesity A Disease or A Behavior Abnormality? Did the AMA Get It Right? *Mo Med*. 2014;111(2):104-108.

64. Jastreboff AM, Kotz CM, Kahan S, Kelly AS, Heymsfield SB. Obesity as a Disease: The Obesity Society 2018 Position Statement. *Obesity (Silver Spring)*. 2019;27(1):7-9. doi:10.1002/oby.22378

65. National Health and Nutrition Examination Survey 2017–March 2020 Prepandemic Data Files Development of Files and Prevalence Estimates for Selected Health Outcomes § National Center for Health S, Hyattsville, MD (2021). Available at https://stacks.cdc.gov/view/cdc/106273

66. Delaet D, Schauer D. Obesity in adults. *Clin Evid*. 2011;2011(no pagination)

67. Department of Health and Human Services and Centers for DIsease Control and Prevention. *Body Mass Index: Considerations for Practitioners*. 4 pages. Accessed February 6, 2023. . Available at https://www.cdc.gov/obesity/downloads/bmiforpactitioners.pdf

68. Gallagher D. *A Guide to Methods for Assessing Chilhood Obesity*. Research NCoCO; 2020: 75 pages. Last Updated June 2020. Accessed February 6, 2023. Available at https://www.nccor.org/tools-assessingobesity-guide/wp-content/uploads/2020/08/NCCOR_MR_Guide_v7-web-small.pdf

69. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *The Lancet*. 2004;363(9403):157-163. doi:https://doi.org/10.1016/S0140-6736(03)15268-3 https://www.sciencedirect.com/science/article/pii/S0140673603152683

70. Tahrani AA, Morton J. Benefits of weight loss of 10% or more in patients with overweight or obesity: A review. *Obesity (Silver Spring)*. 2022;30(4):802-840. doi:10.1002/oby.23371

71. US Department of Veterans Affairs and Department of Defense. *VA/DoD Clinical Practice Guideline for the Management of Adult Overweight and Obesity (Version 3.0)*. 2020. Available at https://www.healthquality.va.gov/guidelines/cd/obesity/

72. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol*. 2014;63(25 Pt B):2985-3023. doi:10.1016/j.jacc.2013.11.004

73. Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(2):342-362. doi:10.1210/jc.2014-3415

74. Maselli D, Atieh J, Clark MM, et al. Effects of liraglutide on gastrointestinal functions and weight in obesity: A randomized clinical and pharmacogenomic trial. *Obesity (Silver Spring)*. 2022;30(8):1608-1620. doi:10.1002/oby.23481

75. Saxenda (liraglute) 3 mg injection. Package Insert. Novo Nordisk A/S; June 2022.

76. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141 Accessed 2023/03/16. Available at https://doi.org/10.1056/NEJMoa1607141

77. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827 Accessed 2023/03/16. Available at https://doi.org/10.1056/NEJMoa1603827

78. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596-e646.

79. Dombrowski SU, Knittle K, Avenell A, Araújo-Soares V, Sniehotta FF. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. *BMJ : British Medical Journal*. 2014;348:g2646. doi:10.1136/bmj.g2646 http://www.bmj.com/content/348/bmj.g2646.abstract

80. ElSayed NA, Aleppo G, Aroda VR, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023. *Diabetes Care*. 2022;46(Supplement_1):S140-S157. doi:10.2337/dc23-S009 Accessed 2/22/2023. Available at https://doi.org/10.2337/dc23-S009

81. Association AD. Standards of Care in Diabetes—2023 Abridged for Primary Care Providers. *Clinical Diabetes*. 2022;41(1):4-31. doi:10.2337/cd23-as01 Accessed 1/24/2023. Available at https://doi.org/10.2337/cd23-as01

82. ElSayed NA, Aleppo G, Aroda VR, et al. 3. Prevention or Delay of Type 2 Diabetes and Associated Comorbidities: Standards of Care in Diabetes-2023. *Diabetes Care*. 2023;46(Suppl 1):S41-s48. doi:10.2337/dc23-S003

83. ElSayed NA, Aleppo G, Aroda VR, et al. 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes—2023. *Diabetes Care*. 2022;46(Supplement_1):S128-S139. doi:10.2337/dc23-S008 Accessed 1/24/2023. Available at https://doi.org/10.2337/dc23-S008

84. Vosoughi K, Salman Roghani R, Camilleri M. Effects of GLP-1 agonists on proportion of weight loss in obesity with or without diabetes: Systematic review and meta-analysis. *Obesity Medicine*. 2022;35doi:10.1016/j.obmed.2022.100456

85. Sultan S, Falck–Ytter Y, Inadomi JM. The AGA Institute Process for Developing Clinical Practice Guidelines Part One: Grading the Evidence. *Clin Gastroenterol Hepatol*. 2013;11(4):329-332. doi:https://doi.org/10.1016/j.cgh.2013.02.001

86. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328(7454):1490. doi:10.1136/bmj.328.7454.1490

87. Swiglo BA, Murad MH, Schünemann HJ, et al. A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab*. 2008;93(3):666-673. doi:10.1210/jc.2007-1907

88. Ryan PM, Seltzer S, Hayward NE, Rodriguez DA, Sless RT, Hawkes CP. Safety and Efficacy of Glucagon-Like Peptide-1 Receptor Agonists in Children and Adolescents with Obesity: A Meta-Analysis. *The Journal of pediatrics*. 2021;236(jlz, 0375410):137-147.e113. doi:https://dx.doi.org/10.1016/j.jpeds.2021.05.009

89. O'Neil PM, Birkenfeld AL, McGowan B. *Supplement to: O'Neil PM, Birkenfield AL, McGowan B, ett al. Efficacy and safety of semaglutide compared with liraglutide aand placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. Lancet 2018; published onlilne Aug 16. http://dx/doi.org/10.1016/S0140-6736(18)31773-2.* 2018: 125 pages. Accessed February 20, 2023. Available at https://ars-els-cdn-com.ezproxy.lib.utah.edu/content/image/1-s2.0-S0140673618317732-mmc1.pdf

90. Nordisk N. *Effect and safety of subcutaneous semaglutide 2.4 mg once weekly compared to lliraglutide 3.0 mg once daily on weight management in subjects with overweight or obesity.* . NN95536-45576 (STEP 8) 2021. Last Updated July 8, 2021. Accessed February 20, 2023. Available at https://cdn-jamanetwork-com.ezproxy.lib.utah.edu/ama/content_public/journal/jama/938843/joi210142supp1_prod_1641310203.78297.pdf

91. Aronne LJ, Wadden T, Peterson C, Winslow D, Odeh S, Gadde KM. *Supplement to Aronne LJ, Wadden TA, Peterson C, Winslow D, Odeh S, Gadde KM. Evaluation of phentermine and topiramate versus phentermine/topiramate extended-release in obese adults. Obesity (Silver Spring). 2013;21(11):2163-2171. doi:10.1002/oby.20584.* . 2013: 10 pages. Accessed March 7, 2023. Available at https://onlinelibrary-wiley-com.ezproxy.lib.utah.edu/doi/full/10.1002/oby.20584

92. Manu P, Lăcătuşu CM, Rogozea LM, Cernea S. Pharmacological Management of Obesity: A Century of Expert Opinions in Cecil Textbook of Medicine. *Am J Ther*. 2022;29(4):e410-e424. doi:10.1097/mjt.0000000000001524

93. Siebenhofer A, Winterholer S, Jeitler K, et al. Long-term effects of weight-reducing drugs in people with hypertension. *Cochrane Database Syst Rev*. 2021;1(1):Cd007654. doi:10.1002/14651858.CD007654.pub5

94. Ioannides-Demos LL, Proietto J, McNeil JJ. Pharmacotherapy for obesity. *Drugs*. 2005;65(10):1391-1418. doi:10.2165/00003495-200565100-00006 http://www.epistemonikos.org/documents/e3262cd927a3106642e36ab9330d7ebaf64eeff8

95. Ryan DH, Deanfield JE, Jacob S. Prioritizing obesity treatment: expanding the role of cardiologists to improve cardiovascular health and outcomes. *Cardiovascular Endocrinology & Metabolism*. 2023;12(1)

96. Wilding JPH, Jacob S. Cardiovascular outcome trials in obesity: A review. *Obes Rev*. 2021;22(1):e13112. doi:10.1111/obr.13112

97. Hiatt WR, Goldfine AB, Kaul S. Cardiovascular Risk Assessment in the Development of New Drugs for Obesity. *JAMA*. 2012;308(11):1099-1100. doi:10.1001/jama.2012.9931 Accessed 3/17/2023. Available at https://doi.org/10.1001/jama.2012.9931

98. Dahlberg S, Chang ET, Weiss SR, Dopart P, Gould E, Ritchey ME. Use of Contrave, Naltrexone with Bupropion, Bupropion, or Naltrexone and Major Adverse Cardiovascular Events: A Systematic Literature Review. *Diabetes, metabolic syndrome and obesity : targets and therapy*. 2022;15(101515585):3049-3067. doi:https://dx.doi.org/10.2147/DMSO.S381652

99. Sposito AC, Bonilha I, Luchiari B, et al. Cardiovascular safety of naltrexone and bupropion therapy: Systematic review and meta-analyses. *Obes Rev*. 2021;22(6):e13224.

100. Novo Nordisk A/S. Semaglutide Effects on Heart Disease and Stroke in Patients With Overweight or Obesity (SELECT). NCT03574597. ClinicalTrials.Gov; 2018. Last Updated March 1, 2023. Accessed March 17, 2023. Available at https://www.clinicaltrials.gov/ct2/show/NCT03574597

101. Harrell TK, Ross LA, King DS. Overview of pharmacologic treatment of obesity: past experiences, present options, and future directions. *J Pharm Technol*. 2005;21(6):319-324.

102. Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med*. 2005;142(7):532-546. doi:10.7326/0003-4819-142-7-200504050-00012

103. Mitchell JR, Cavanaugh JH, Arias L, Oates JA. Guanethidine and related agents. 3. Antagonism by drugs which inhibit the norepinephrine pump in man. *J Clin Invest*. 1970;49(8):1596-1604.

104. Obesity in Pregnancy: ACOG Practice Bulletin, Number 230. *Obstet Gynecol*. 2021;137(6):e128-e144. doi:10.1097/aog.0000000000004395

105. Orlistat. Lexi-Drugs; 2023. Last Updated March 11, 2023. Accessed March 23, 2023. Available at http://online.lexi.com

106. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *J Clin Epidemiol*. 2021;134:178-189. doi:10.1016/j.jclinepi.2021.03.001

107. Haddock CK, Poston WS, Dill PL, Foreyt JP, Ericsson M. Pharmacotherapy for obesity: a quantitative analysis of four decades of published randomized clinical trials. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*. 2002;26(2):262-273. doi:10.1038/sj.ijo.0801889

APPENDIX A – WEIGHT MANAGEMENT AGENTS INDICATIONS AND DOSAGE

Table A1. Weight Management Agents, Approved Indications and Usual Dosage

Active Ingredient Products	Labeled Indication	Route	Usual Maintenance Dose	Titration at initiation
Agents Approved for Short-Term Treatment				
Diethylpropion[24,27]				
• Generic Tablet: 25 mg • Generic ER Tablet (24 hour): 75 mg	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, and who have not responded to diet and/or exercise alone. *Use as monotherapy only*	Oral	• IR: 25 mg TID, before meals and in midevening to overcome night hunger, if desired • ER: 75 mg daily, in midmorning • *Pediatrics*: not recommended for use in 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
Phentermine hydrochloride[28-32]				
Adipex-P • Oral capsules and tablets: 37.5 mg **Generics** • Oral capsule: 15 mg, 30 mg, 37.5 mg • Oral tablet: 37.5 mg • ODT[a]: 15 mg, 30 mg, 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) *Use as monotherapy only*	Oral	• 8 mg **TID** before meals; or 15 mg to 37.5 mg **daily,** before or 2 hours after breakfast • Use the lowest effective dose for adequate response. • Pediatrics: not recommended in patients 16 years of age or younger (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: Maximum dose of 15 mg daily for severe RI; avoid use for ESRD (Adipex-P and generic tablets/capsules). There is a lack of data, but increased exposure expected with RI; use caution (Lomaira and ODT). All: No dose adjustments for HI.	None
Phendimetrazine tartrate[23,26]				
Generics • Oral capsule (ER): 105 mg • Oral tablet: 35 mg	Indicated for short-term (a few weeks) treatment (as an adjunct to caloric restriction) in the management of exogenous obesity (IR tablet), or for patients with an initial BMI ≥30 kg/m^2 or ≥27 kg/m^2 (ER capsule) in the presence of other risk factors (eg, controlled hypertension, diabetes, hyperlipidemia)[b], and who have not responded to diet and/or exercise alone *Use as monotherapy only*	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 use in 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
Benzphetamine[25]				
Generics • Oral 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 *Use as monotherapy only*	Oral	• 25 mg to 50 mg **daily to TID,** avoiding late afternoon ingestion • *Pediatrics:* not recommended for use in pediatric patients <17 years of age since safety/efficacy is not established in this population • *RI/HI:* No dose-adjustment mentioned	Optional titration from daily to TID depending on patient response

[a] *It is unclear if ODT phentermine is currently available as there are conflicting reports from multiple sources*

Abbreviations: BID; twice daily; BMI, body mass index: ER, extended release; ESRD, end-stage renal disease; GI, gastrointestinal; GLP-1a, glucagon like peptide-1 receptor agonist; HI, hepatic impairment; IR, immediate release; max, maximum; ODT, orally disintegrating tablets; RI, renal impairment; SubQ, subcutaneous; T2DM, type 2 diabetes mellitus; TID, three times daily

Table A1. Weight Management Agents, Approved Indications and Usual Dosage

Active Ingredient Products	Labeled Indication	Route	Usual Maintenance Dose	Titration at initiation
Agents Approved for Long-Term Treatment				
Orlistat[33] **Xenical** • Capsule: 120 mg **Generic** • Capsule: 120 mg	• Indicated for obesity management (ie, weight loss and weight maintenance) as adjunct to a reduced-calorie diet to reduce the risk for weight regain after prior weight loss. • Indicated for patients with BMI ≥30 kg/m^2 or ≥27 kg/m^2 in the presence of other risk factors (eg, hypertension, diabetes, dyslipidemia)	Oral	• 120 mg **TID** with meals containing fat • *Pediatrics*: Safety and effectiveness in pediatric patients < 12 years of age have not been established • *RI/HI:* No dose-adjustment mentioned	None
Liraglutide[35] **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-related comorbid condition (eg. hypertension, T2DM, or dyslipidemia) • **Pediatric patients ≥ 12 years** of age with body weight above 60 kg and initial BMI corresponding to ≥ 30 kg/m2 for adults by international cut-offs *Limitations of use:* (1) Not for co-administration with other GLP-1a, including other liraglutide products (2) Use in children with T2DM not established (3) Use with other weight loss products not established	SubQ	• Adult: 3 mg daily • Pediatric: 2.4 mg to 3 mg daily • 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 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.	Titrate over 5 weeks from 0.6 to 3 mg daily dose to minimize GI side effects
Semaglutide[34] **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. hypertension, T2DM, or dyslipidemia) • **Pediatric patients ≥ 12 years** of age with initial BMI at the 95th percentile or greater for age and sex *Limitations of use:* (1) Not for co-administration with other GLP-1a, including other semaglutide products (2) Not studied in patients with pancreatitis (3) Use with other weight loss products not established	SubQ	• Adult: 2.4 mg **once weekly** • Pediatric: 1.7 mg to 2.4 mg **once weekly** • 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 16 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.

[a] *It is unclear if ODT phentermine is currently available as there are conflicting reports from multiple sources*

Abbreviations: BID; twice daily; BMI, body mass index: ER, extended release; ESRD, end-stage renal disease; GI, gastrointestinal; GLP-1a, glucagon like peptide-1 receptor agonist; HI, hepatic impairment; IR, immediate release; max, maximum; ODT, orally disintegrating tablets; RI, renal impairment; SubQ, subcutaneous; T2DM, type 2 diabetes mellitus; TID, three times daily

Table A1. Weight Management Agents, Approved Indications and Usual Dosage

Active Ingredient Products	Labeled Indication	Route	Usual Maintenance Dose	Titration at initiation
Naltrexone/ bupropion ER[37]				
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 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. hypertension, T2DM, or dyslipidemia) *Limitations of use:* (1) Effect on cardiovascular outcomes not established (2) Use with other weight loss products not established	Oral	• 16 mg/180 mg **BID**, avoiding administration with high fat meals • 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 (<18 years) 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)	Titrate to target dose (4 tablets) with weekly adjustments over 4 weeks beginning with 1 tablet daily.
Phentermine/ topiramate ER[36]				
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. hypertension, T2DM, or dyslipidemia) • **Pediatric patients ≥ 12 years** of age with initial BMI at the 95th percentile or greater for age and sex *Limitations of use:* (1) Effect on cardiovascular outcomes not established (2) Use with other weight loss products not established Negative pregnancy test and blood chemistry check (bicarbonate, creatinine, potassium; and glucose in patients with T2DM treated with medication) recommended before use	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 discontinue the medication. Tapering is recommended for discontinuation to prevent seizures. • *RI/HI:* Reduce dose for moderate to severe RI or moderate HI (max 7.5 mg/46 mg daily). Avoid use for ESRD on dialysis or severe HI.	Start at 3.75 mg/23 mg daily and escalate after 14 days to 7.5 mg/46 mg daily Evaluate response after 12 weeks. Escalate dose up to 15 mg/92 mg over 14-week titration if adult patient has not lost at least 3% of baseline body weight or pediatric patient has not lost at least 3% of baseline BMI

[a] *It is unclear if ODT phentermine is currently available as there are conflicting reports from multiple sources*

Abbreviations: BID; twice daily; BMI, body mass index: ER, extended release; ESRD, end-stage renal disease; GI, gastrointestinal; GLP-1a, glucagon like peptide-1 receptor agonist; HI, hepatic impairment; IR, immediate release; max, maximum; ODT, orally disintegrating tablets; RI, renal impairment; SubQ, subcutaneous; T2DM, type 2 diabetes mellitus; TID, three times daily

APPENDIX B – LITERATURE SEARCHES

Search for Systematic Reviews

Ovid-Medline

Search date: January 30, 2023

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily, 1946 to January 27, 2023**

Search Strategy:

#	Searches	Results
1	exp Obesity/ or exp Weight Loss/ or Overweight/	290056
2	*Obesity Management/	203
3	*Adiposity/	7732
4	(obes* or "body mass inde*" or BMI or adipos* or weight or overweight or bodyweight).ti,ab,kw,kf.	1443080
5	1 or 2 or 3 or 4	1483996
6	exp Anti-Obesity Agents/ or (('anti-obes*' or antiobes* or 'weight loss') adj1 (agent* or drug* or medicat* or pharm*)).ti,ab,kw,kf. or 'appetite suppressant*'.ti,ab,kw,kf.	22115
7	Phentermine/	848
8	(phentermin* or adipex or lomaira or suprenza or duromine or t-diet or obermine or fastin).ti,ab,kw,kf.	901
9	(phendimetrazine or bontril or melfiat).ti,ab,kw,kf.	80
10	exp Diethylpropion/	318
11	(diethylpropion or tenuate or amfepramone).ti,ab,kw,kf.	306
12	exp Benzphetamine/	326
13	(benzphetamine or benzfetamine or didrex or regimex).ti,ab,kw,kf.	790
14	exp Orlistat/	1357
15	(orlistat or alli or xenical or ro-18-0647 or ro180647 or ro-180647 or tetrahydrolipstatin).ti,ab,kw,kf.	2193
16	exp Liraglutide/	2386
17	(liraglutide or nn-2211 or nn2211 or nnc-90-1170 or nnc90-1170 or nnc901170 or saxenda or victoza).ti,ab,kw,kf.	3644
18	(semaglutide or ozempic or rybelsus or wegovy or NN9535 or NN-9535).ti,ab,kw,kf.	982
19	((phentermine and topiramate) or phenterminetopiramate or qsymia or qnexa or qsiva or VI-0521 or VI0521).ti,ab,kw,kf.	299
20	((amfebutamone and naltrexone) or (bupropion and naltrexone) or contrave or mysimba or bupropionnaltrexone or "11556075").ti,ab,kw,kf.	333
21	6 or 7 or 8 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	27752

#	Searches	Results
22	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw.	500591
23	(MEDLINE or Embase or PubMed or systematic review).tw. or meta analysis.pt.	468800
24	22 or 23	582602
25	5 and 21 and 24	808
26	limit 25 to yr="2021 -Current"	150

Epistemonikos Search for All Agents

Search date: January 20, 2023; 192 results using “systematic review” filter and limited to 2021-2023 publication year

(title:((obes* OR "body mass inde*" OR BMI OR adipos* OR weight OR overweight OR bodyweight)) OR abstract:((obes* OR "body mass inde*" OR BMI OR adipos* OR weight OR overweight OR bodyweight))) AND (title:((((("anti-obes*" OR antiobes* OR "weight loss") AND (agent* OR drug* OR medicat* OR pharm*)) OR "appetite suppressant*" OR (phentermin* OR phendimetrazine OR diethylpropion OR benzphetamine))) OR abstract:((((("anti-obes*" OR antiobes* OR "weight loss") AND (agent* OR drug* OR medicat* OR pharm*)) OR "appetite suppressant*" OR (phentermin* OR phendimetrazine OR diethylpropion OR benzphetamine))))

Epistemonikos Additional Search for Short-term Agents Only

Search date: February 7, 2023; 35 results using “systematic review” filter and without a publication date limit

(title:((obes* OR "body mass inde*" OR BMI OR adipos* OR weight OR overweight OR bodyweight)) OR abstract:((obes* OR "body mass inde*" OR BMI OR adipos* OR weight OR overweight OR bodyweight))) AND (title:((phentermin* OR phendimetrazine OR diethylpropion OR benzphetamine)) OR abstract:((phentermin* OR phendimetrazine OR diethylpropion OR benzphetamine)))

Search for Randomized Controlled Trials

Ovid-Medline

Search date: February 9, 2023

Database(s): **Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to February 08, 2023**

Search Strategy:

#	Searches	Results
1	exp Obesity/ or exp Weight Loss/ or Overweight/	290547
2	*Obesity Management/	203
3	*Adiposity/	7745

#	Searches	Results
4	(obes* or "body mass inde*" or BMI or adipos* or weight or overweight or bodyweight).ti,ab,kw,kf.	1443028
5	1 or 2 or 3 or 4	1484001
6	exp Anti-Obesity Agents/ or (('anti-obes*' or antiobes* or 'weight loss') adj1 (agent* or drug* or medicat* or pharm*)).ti,ab,kw,kf. or 'appetite suppressant*'.ti,ab,kw,kf.	22132
7	Phentermine/	848
8	(phentermin* or adipex or lomaira or suprenza or duromine or t-diet or obermine or fastin).ti,ab,kw,kf.	902
9	(phendimetrazine or bontril or melfiat).ti,ab,kw,kf.	80
10	exp Diethylpropion/	318
11	(diethylpropion or tenuate or amfepramone).ti,ab,kw,kf.	306
12	exp Benzphetamine/ or (benzphetamine or benzfetamine or didrex or regimex).ti,ab,kw,kf.	954
13	exp Orlistat/	1359
14	(orlistat or alli or xenical or tetrahydrolipstatin).ti,ab,kw,kf.	2197
15	exp Liraglutide/	2393
16	(liraglutide or saxenda).ti,ab,kw,kf.	3623
17	(semaglutide or wegovy).ti,ab,kw,kf.	991
18	((phentermine and topiramate) or phenterminetopiramate or qsymia or qnexa or qsiva).ti,ab,kw,kf.	301
19	((amfebutamone and naltrexone) or (bupropion and naltrexone) or contrave or mysimba or bupropionnaltrexone).ti,ab,kw,kf.	336
20	((randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1425972
21	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 18 or 19	5078
22	15 or 16 or 17	4487
23	5 and 20 and 21	786
24	5 and 20 and 22	927
25	limit 23 to yr="2021 -Current"	49
26	limit 24 to yr="2022 -Current"	130
27	25 or 26	174

Embase

Search date: February 10, 2023

#	Searches	Results
1	**'obesity'**/exp OR **'body weight change'**/exp OR **'obese patient'**/exp OR **'body weight management'**/mj OR **'body mass'**/mj	**914,317**
2	**obes***:ti,ab,kw OR **'body mass inde*'**:ti,ab,kw OR **bmi**:ti,ab,kw OR **adipos***:ti,ab,kw OR **weight**:ti,ab,kw OR **overweight**:ti,ab,kw OR **bodyweight**:ti,ab,kw	**2,056,576**

#	Searches	Results
3	**#1** OR **#2**	**2,285,724**
4	**'phentermine'**/exp OR **phentermin***:ti,ab,kw OR **adipex**:ti,ab,kw OR **lomaira**:ti,ab,kw OR **suprenza**:ti,ab,kw OR **duromine**:ti,ab,kw OR **'t diet'**:ti,ab,kw OR **obermine**:ti,ab,kw OR **fastin**:ti,ab,kw	**3,587**
5	**'amfepramone'**/exp OR **diethylpropion**:ti,ab,kw OR **tenuate**:ti,ab,kw OR **amfepramone**:ti,ab,kw	**1,768**
6	**'phendimetrazine'**/exp OR **phendimetrazine**:ti,ab,kw OR **bontril**:ti,ab,kw OR **melfiat**:ti,ab,kw	**504**
7	**'benzphetamine'**/exp OR **benzphetamine**:ti,ab,kw OR **benzfetamine**:ti,ab,kw OR **didrex**:ti,ab,kw OR **regimex**:ti,ab,kw	**1,544**
8	**'tetrahydrolipstatin'**/exp OR **orlistat**:ti,ab,kw OR **alli**:ti,ab,kw OR **xenical**:ti,ab,kw OR **tetrahydrolipstatin**:ti,ab,kw	**7,658**
9	**'phentermine plus topiramate'**/exp OR (**phentermine**:ti,ab,kw AND **topiramate**:ti,ab,kw) OR **phenterminetopiramate**:ti,ab,kw OR **qsymia**:ti,ab,kw OR **qnexa**:ti,ab,kw OR **qsiva**:ti,ab,kw	**1,065**
10	**'amfebutamone plus naltrexone'**/exp OR (**amfebutamone**:ti,ab,kw AND **naltrexone**:ti,ab,kw) OR (**bupropion**:ti,ab,kw AND **naltrexone**:ti,ab,kw) OR **contrave**:ti,ab,kw OR **mysimba**:ti,ab,kw OR **bupropionnaltrexone**:ti,ab,kw	**1,012**
11	**'liraglutide'**/exp OR **liraglutide**:ti,ab,kw OR **saxenda**:ti,ab,kw	**12,095**
12	**'semaglutide'**/exp OR **semaglutide**:ti,ab,kw OR **wegovy**:ti,ab,kw	**3,146**
13	(**'crossover procedure'**:de OR **'double-blind procedure'**:de OR **'randomized controlled trial'**:de OR **'single-blind procedure'**:de OR **random***:de,ab,ti OR **factorial***:de,ab,ti OR **crossover***:de,ab,ti OR ((**cross** NEXT/1 **over***):de,ab,ti) OR **placebo***:de,ab,ti OR ((**doubl*** NEAR/1 **blind***):de,ab,ti) OR ((**singl*** NEAR/1 **blind***):de,ab,ti) OR **assign***:de,ab,ti OR **allocat***:de,ab,ti OR **volunteer***:de,ab,ti) AND [english]/lim	**2,890,103**
14	**#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9** OR **#10** OR **#11** OR **#12**	**13,025**
15	**#11** OR **#12**	**13,539**
16	**#3** AND **#13** AND **#14**	**2,523**
17	**#3** AND **#13** AND **#14** AND [2021-2023]/py	**166**
18	**#3** AND **#13** AND **#15**	**3,438**
19	**#3** AND **#13** AND **#15** AND [2022-2023]/py	**384**
20	**#19** OR **#23**	513
21	(**#19** OR **#23**) NOT (**'conference abstract'**/it OR **'conference review'**/it)	399

APPENDIX C – AACE/ACE GUIDELINE PREFERRED THERAPIES ACCORDING TO CO-MORBIDITIES

Table C1. AACE/ACE Preferred Weight Management Pharmacotherapies According to Co-morbidities

2016 AACE/ACE Guideline for Medical Care of Patients with Obesity[16a]
The AACE/ACE recommended particular medications (orlistat, liraglutide, naltrexone/bupropion ER, or phentermine/topiramate ER) by disease state. Each medication was preferred for 1+ unique comorbidity.
Kidney Disease • **Avoid** weight-loss medication with end-stage renal failure, except for orlistat and liraglutide 3 mg with a high level of caution (Grade B; BEL 2). • **Avoid** naltrexone ER/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 because 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). • Consider cholelithiasis in patients undergoing weight-loss therapy, regardless of the treatment modality; in high-risk patients, liraglutide 3 mg should be used with caution; effective preventive measures 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

Table C1. AACE/ACE Preferred Weight Management Pharmacotherapies According to Co-morbidities

2016 AACE/ACE Guideline for Medical Care of Patients with Obesity[16a]
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). • 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.

Table C1. AACE/ACE Preferred Weight Management Pharmacotherapies According to Co-morbidities

2016 AACE/ACE Guideline for Medical Care of Patients with Obesity[16a]
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).
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)

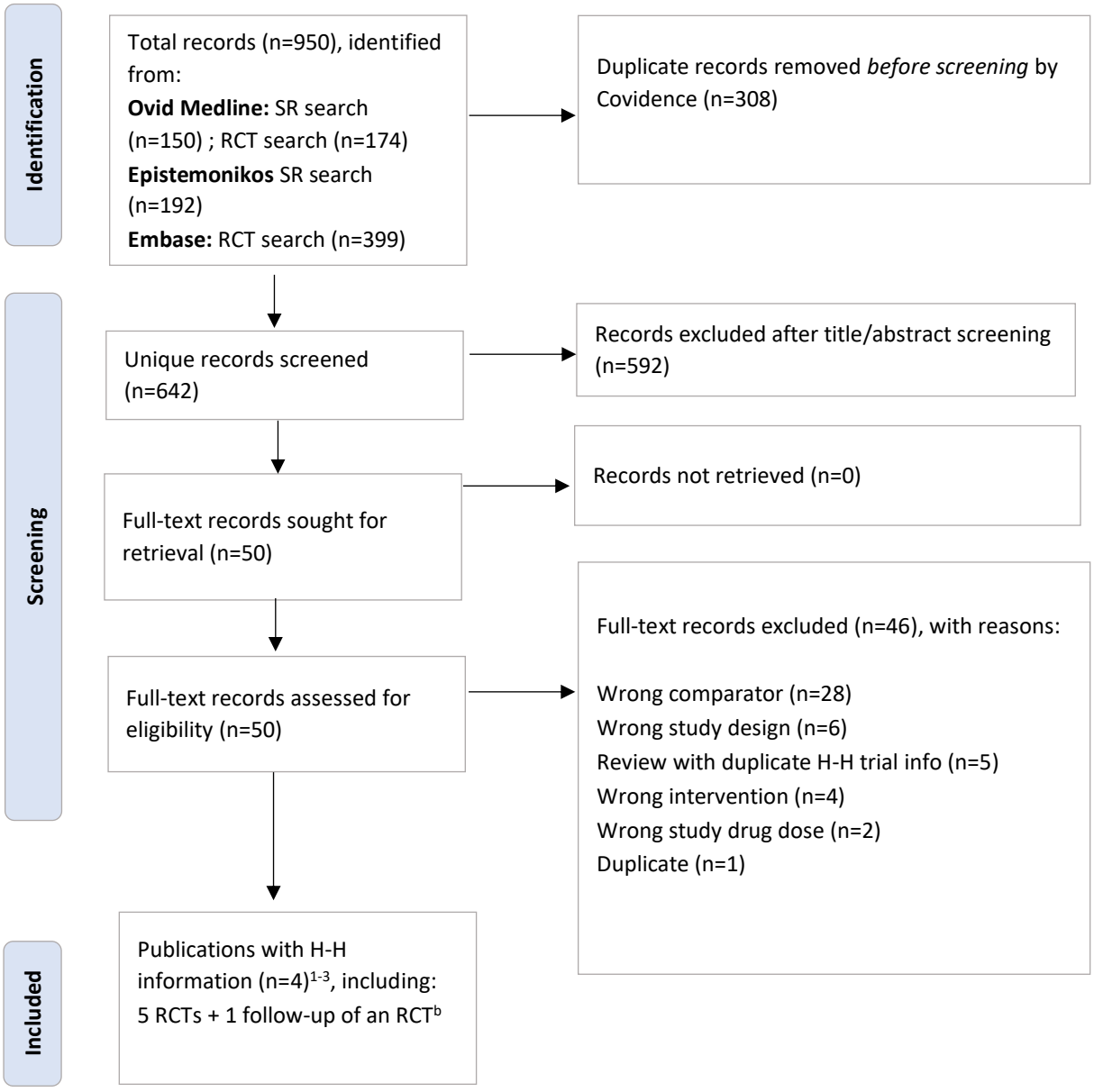
[a] *Note that this guideline was published prior to the approval of semaglutide. Although the guideline included lorcaserin, this agent has been discontinued so recommendations regarding its use are not included here.*

Abbreviations: AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; 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; WRC, weight-related complications

APPENDIX D – SCREENING OF STUDIES

Figure D1 outlines the literature screening process including the number of records identified from searches of each database, and the number of included and excluded records.

Figure D1. PRISMA Flow Chart[a] for Literature Screening



Abbreviations: H-H, head-to-head; info, information; RCT, randomized controlled trials; SR, systematic review

[a] Modified from Page et al. 2021[106]

[b] One RCT was identified from the RCT search (Rubino 2022[1]) and the remaining trials were identified from SRs (Haddock 2002,[107] Khera 2018,[2] and Deng 2022[3]). Details of the 6 trials but not the SRs were extracted.

APPENDIX E – EXCLUDED REFERENCES FROM LITERATURE SEARCH

Wrong Intervention(s)

1. Conley MM, McFarlane CM, Johnson DW, Kelly JT, Campbell KL, MacLaughlin HL. Interventions for weight loss in people with chronic kidney disease who are overweight or obese. *The Cochrane database of systematic reviews*. 2021;3:CD013119. doi:10.1002/14651858.CD013119.pub2
2. Mallhi TH, Ijaz I, Khan YH, et al. Relationship between the use of drugs and changes in body weight among patients: A systematic review and meta-analysis. *Tropical Journal of Pharmaceutical Research*. 2022;21(4):899-908. doi:10.4314/tjpr.v21i4.30 https://www.embase.com/search/results?subaction=viewrecord&id=L2018124080&from=export
3. Tall Bull S, Nuffer W, Trujillo JM. Tirzepatide: A novel, first-in-class, dual GIP/GLP-1 receptor agonist. *J Diabetes Complications*. 2022;36(12):108332. doi:https://dx.doi.org/10.1016/j.jdiacomp.2022.108332
4. Zaazouee MS, Hamdallah A, Helmy SK, et al. Semaglutide for the treatment of type 2 Diabetes Mellitus: A systematic review and network meta-analysis of safety and efficacy outcomes. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*. 2022;16(6)doi:10.1016/j.dsx.2022.102511

Wrong comparator

5. Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med*. 2005;142(7):532-546. doi:10.7326/0003-4819-142-7-200504050-00012
6. Khera R, Murad MH, Chandar AK, et al. Association of Pharmacological Treatments for Obesity With Weight Loss and Adverse Events: A Systematic Review and Meta-analysis. *JAMA*. 2016;315(22):2424-2434. doi:10.1001/jama.2016.7602
7. Garcia Ramirez AV, Filho DR, Zotarelli Filho IJ. Meta-analyses and approach of the real impact of anorexigenic drugs in the obesity in humans: the last five years of the randomized studies. *Curr Diabetes Rev*. 2020;16(7):750-758. doi:10.2174/1573399815666191113125247
8. Abdel-Maboud M, Menshawy A, Hasabo EA, et al. The comparative effectiveness of 55 interventions in obese patients with polycystic ovary syndrome: A network meta-analysis of 101 randomized trials. *PLoS One*. 2021;16(7 July 2021)doi:10.1371/journal.pone.0254412
9. Conley MM, McFarlane CM, Johnson DW, Kelly JT, Campbell KL, MacLaughlin HL. Interventions for weight loss in people with chronic kidney disease who are overweight or obese. *The Cochrane database of systematic reviews*. 2021;3:CD013119. doi:10.1002/14651858.CD013119.pub2
10. Gates A, Elliott SA, Shulhan-Kilroy J, Ball GDC, Hartling L. Effectiveness and safety of interventions to manage childhood overweight and obesity: An Overview of Cochrane systematic reviews. *Paediatrics and Child Health (Canada)*. 2021;26(5):310-316. doi:10.1093/pch/pxaa085
11. Kulak-Bejda A, Bejda G, Waszkiewicz N. Safety and efficacy of naltrexone for weight loss in adult patients - a systematic review. *Archives of medical science : AMS*. 2021;17(4):940-953. doi:https://dx.doi.org/10.5114/aoms.2020.96908
12. Moon S, Lee J, Chung HS, et al. Efficacy and Safety of the New Appetite Suppressant, Liraglutide: A Meta-Analysis of Randomized Controlled Trials. *Endocrinology and metabolism (Seoul, Korea)*. 2021;36(3):647-660. doi:https://dx.doi.org/10.3803/EnM.2020.934
13. Ryan PM, Seltzer S, Hayward NE, Rodriguez DA, Sless RT, Hawkes CP. Safety and Efficacy of Glucagon-Like Peptide-1 Receptor Agonists in Children and Adolescents with Obesity: A Meta-Analysis. *The Journal of pediatrics*. 2021;236(jlz, 0375410):137-147.e113. doi:https://dx.doi.org/10.1016/j.jpeds.2021.05.009

14. Salari N, Jafari S, Darvishi N, et al. The best drug supplement for obesity treatment: a systematic review and network meta-analysis. *Diabetol Metab Syndr*. 2021;13(1):110. doi:https://dx.doi.org/10.1186/s13098-021-00733-5
15. Vosoughi K, Atieh J, Khanna L, et al. Association of Glucagon-like Peptide 1 Analogs and Agonists Administered for Obesity with Weight Loss and Adverse Events: A Systematic Review and Network Meta-analysis. *EClinicalMedicine*. 2021;42(101733727):101213. doi:https://dx.doi.org/10.1016/j.eclinm.2021.101213
16. Anam M, Maharjan S, Amjad Z, et al. Efficacy of Semaglutide in Treating Obesity: A Systematic Review of Randomized Controlled Trials (RCTs). *Cureus*. 2022;14(12):e32610. doi:https://dx.doi.org/10.7759/cureus.32610
17. Dahlberg S, Chang ET, Weiss SR, Dopart P, Gould E, Ritchey ME. Use of Contrave, Naltrexone with Bupropion, Bupropion, or Naltrexone and Major Adverse Cardiovascular Events: A Systematic Literature Review. *Diabetes, metabolic syndrome and obesity : targets and therapy*. 2022;15(101515585):3049-3067. doi:https://dx.doi.org/10.2147/DMSO.S381652
18. Guo X, Zhou Z, Lyu X, et al. The Antiobesity Effect and Safety of GLP-1 Receptor Agonist in Overweight/Obese Patients Without Diabetes: A Systematic Review and Meta-Analysis. *Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme*. 2022;54(7):458-471. doi:https://dx.doi.org/10.1055/a-1844-1176
19. He K, Guo Q, Zhang H, Xi W, Li J, Jing Z. Once-weekly semaglutide for obesity or overweight: A systematic review and meta-analysis. *Diabetes Obes Metab*. 2022;24(4):722-726. doi:https://dx.doi.org/10.1111/dom.14612
20. Iqbal J, Wu H-X, Hu N, et al. Effect of glucagon-like peptide-1 receptor agonists on body weight in adults with obesity without diabetes mellitus-a systematic review and meta-analysis of randomized control trials. *Obesity reviews : an official journal of the International Association for the Study of Obesity*. 2022;23(6):e13435. doi:https://dx.doi.org/10.1111/obr.13435
21. Lee K, Abraham S, Cleaver R. A systematic review of licensed weight-loss medications in treating antipsychotic-induced weight gain and obesity in schizophrenia and psychosis. *Gen Hosp Psychiatry*. 2022;78(fnk, 7905527):58-67. doi:https://dx.doi.org/10.1016/j.genhosppsych.2022.07.006
22. Lin Q, Xue Y, Zou H, Ruan Z, Ung COL, Hu H. Efficacy and safety of liraglutide for obesity and people who are overweight: a systematic review and meta-analysis of randomized controlled trials. *Expert Rev Clin Pharmacol*. 2022;15(12):1461-1469. doi:https://dx.doi.org/10.1080/17512433.2022.2130760
23. Liu F, Yang Q, Zhang H, et al. The effects of glucagon-like peptide-1 receptor agonists on adipose tissues in patients with type 2 diabetes: A meta-analysis of randomised controlled trials. *PLoS One*. 2022;17(7 July)doi:10.1371/journal.pone.0270899
24. Patoulias D, Papadopoulos C, Kassimis G, Fragakis N, Doumas M. Meta-Analysis Assessing the Cardiovascular Safety of Semaglutide for the Treatment of Overweight or Obesity. *The American journal of cardiology*. 2022;175(3dq, 0207277):182-184. doi:https://dx.doi.org/10.1016/j.amjcard.2022.04.030
25. Smith I, Hardy E, Mitchell S, Batson S. Semaglutide 2.4 Mg for the Management of Overweight and Obesity: Systematic Literature Review and Meta-Analysis. *Diabetes, metabolic syndrome and obesity : targets and therapy*. 2022;15(101515585):3961-3987. doi:https://dx.doi.org/10.2147/DMSO.S392952
26. Tan HC, Dampil OA, Marquez MM. Efficacy and Safety of Semaglutide for Weight Loss in Obesity Without Diabetes: A Systematic Review and Meta-Analysis. *Journal of the ASEAN Federation of Endocrine Societies*. 2022;37(2):65-72. doi:https://dx.doi.org/10.15605/jafes.037.02.14
27. Tariq MA, Amin H, Shurjeel Q, Gang A, Mohiuddin A. Gastrointestinal adverse events of semaglutide in patients with overweight or obesity. *Eur J Intern Med*. 2022;106((Tariq M.A., m.alitariqpk@gmail.com; Mohiuddin A.) Dow University Hospital, Dow International Medical College, Karachi, Pakistan(Amin H.; Shurjeel Q.) Ruth KM Pfau Civil Hospital, Dow University of Health Sciences, Karachi, Pakistan(Gang A.) Jinnah Postgr):138-139. doi:10.1016/j.ejim.2022.08.015

28. Wu S, Lu W, Chen Z, Dai Y, Chen K, Zhang S. Association of glucagon-like peptide-1 receptor agonists with cardiac arrhythmias in patients with type 2 diabetes or obesity: a systematic review and meta-analysis of randomized controlled trials. *Diabetol Metab Syndr*. 2022;14(1):195. doi:https://dx.doi.org/10.1186/s13098-022-00970-2
29. Yu D, Zou M, Pan Q, et al. Effects of liraglutide or lifestyle interventions combined with other antidiabetic drugs on abdominal fat distribution in people with obesity and type 2 diabetes mellitus evaluated by the energy spectrum ct: A prospective randomized controlled study. *Front Endocrinol (Lausanne)*. 2022;13(101555782):951570. doi:https://dx.doi.org/10.3389/fendo.2022.951570
30. Zhao G, Zhang Q, Wu F, Yin S, Xie Y, Liu H. Comparison of weight loss and adverse events of obesity drugs in children and adolescents: a systematic review and meta-analysis. *Expert Rev Clin Pharmacol*. 2022;15(9):1119-1125. doi:https://dx.doi.org/10.1080/17512433.2022.2117152
31. He F, Chen W, Xu W, et al. Safety and efficacy of liraglutide on reducing visceral and ectopic fat in adults with or without type 2 diabetes mellitus: A systematic review and meta-analysis. *Diabetes Obes Metab*. 2023;25(3):664-674. doi:https://dx.doi.org/10.1111/dom.14908
32. Jobanputra R, Sargeant JA, Almaqhawi A, et al. The effects of weight-lowering pharmacotherapies on physical activity, function and fitness: A systematic review and meta-analysis of randomized controlled trials. *Obesity reviews : an official journal of the International Association for the Study of Obesity*. 2023, 10.1111/obr.13553:e13553. doi:10.1111/obr.13553

Wrong study design

33. Harrell TK, Ross LA, King DS. Overview of pharmacologic treatment of obesity: past experiences, present options, and future directions. *J Pharm Technol*. 2005;21(6):319-324.
34. Idrees Z, Cancarevic I, Huang L. FDA-Approved Pharmacotherapy for Weight Loss Over the Last Decade. *Cureus*. 2022;14(9):e29262. doi:https://dx.doi.org/10.7759/cureus.29262
35. Ioannides-Demos LL, Proietto J, McNeil JJ. Pharmacotherapy for obesity. *Drugs*. 2005;65(10):1391-1418. doi:10.2165/00003495-200565100-00006
36. Lazzaroni E, Ben Nasr M, Loretelli C, et al. Anti-diabetic drugs and weight loss in patients with type 2 diabetes. *Pharmacol Res*. 2021;171(phc, 8907422):105782. doi:https://dx.doi.org/10.1016/j.phrs.2021.105782
37. Mehta A, Marso SP, Neeland IJ. Liraglutide for weight management: a critical review of the evidence. *Obesity science & practice*. 2017;3(1):3-14. doi:10.1002/osp4.84
38. Wharton S, Kamran E, Muqeem M, Khan A, Christensen RAG. The effectiveness and safety of pharmaceuticals to manage excess weight post-bariatric surgery: a systematic literature review. *Journal of drug assessment*. 2019;8(1):184-191. doi:10.1080/21556660.2019.1678478

Wrong dose

39. De Block CEM, Dirinck E, Verhaegen A, Van Gaal LF. Efficacy and safety of high-dose glucagon-like peptide-1, glucagon-like peptide-1/glucose-dependent insulinotropic peptide, and glucagon-like peptide-1/glucagon receptor agonists in type 2 diabetes. *Diabetes Obes Metab*. 2022;24(5):788-805. doi:https://dx.doi.org/10.1111/dom.14640
40. Tsapas A, Karagiannis T, Kakotrichi P, et al. Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: A systematic review and network meta-analysis. *Diabetes Obes Metab*. 2021;23(9):2116-2124. doi:https://dx.doi.org/10.1111/dom.14451

Duplicate

41. Shi Q, Wang Y, Hao Q, et al. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. *Lancet (London, England)*. 2021;399(10321)doi:10.1016/S0140-6736(21)01640-8

Review with duplicate head-to-head trial information

42. Alkhezi OS, Alahmed AA, Alfayez OM, Alzuman OA, Almutairi AR, Almohammed OA. Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: A network meta-analysis of randomized clinical trials. *Obesity reviews : an official journal of the International Association for the Study of Obesity*. 2022, https://dx.doi.org/10.1111/obr.13543(100897395):e13543. doi:https://dx.doi.org/10.1111/obr.13543
43. Delaet D, Schauer D. Obesity in adults. *Clin Evid*. 2011;2011(no pagination)http://www.epistemonikos.org/documents/9fbc2774140fd8e7cda76b57a75ad020699f7e78
44. Shi Q, Wang Y, Hao Q, et al. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. *Lancet (London, England)*. 2022;399(10321):259-269. doi:https://dx.doi.org/10.1016/S0140-6736(21)01640-8
45. Twells LK, Harris Walsh K, Blackmore A, et al. Nonsurgical weight loss interventions: A systematic review of systematic reviews and meta-analyses. *Obesity reviews : an official journal of the International Association for the Study of Obesity*. 2021;22(11):e13320. doi:10.1111/obr.13320 http://www.epistemonikos.org/documents/619627dbc7d74a6c2bdcbebba36ebc58f8789b7a
46. Xie Z, Yang S, Deng W, Li J, Chen J. Efficacy and Safety of Liraglutide and Semaglutide on Weight Loss in People with Obesity or Overweight: A Systematic Review. *Clin Epidemiol*. 2022;14(101531700):1463-1476. doi:https://dx.doi.org/10.2147/CLEP.S391819

APPENDIX F – PHARMACOKINETICS SUMMARY

Table F1. Select Pharmacokinetic Information for Weight Maintenance Medications from PIs

Active Ingredient(s)	Approximate Terminal Elimination Half-life	Major Route(s) of Elimination	Additional Notes
Agents Approved for Short-term Treatment			
Diethylpropion[24,27]	~4-6 h (oral)	Renally excreted	• Increased risk of toxicity with poor renal function
Phentermine hydrochloride[28-32]	NR	Renally excreted	• Similar rate and extent of absorption for the ODT vs tablets or capsules (during fasting)[29]
Benzphetamine[25]	No human PK data		
Phendimetrazine tartrate[26]	3.7 h (oral IR and ER)	Renally excreted	• Faster absorption with IR vs ER formulation
Agents Approved for Long-Term Treatment (>12 weeks)			
Orlistat[33]	1-2 h (oral)	Primary: fecal excretion	• Minimally absorbed; accumulation not expected • Highly protein-bound
Liraglutide[35]	13 h (SubQ)	Minimal fecal or renal elimination	• Similar exposure in pediatrics vs adults • Highly protein-bound • *Immunogenicity:* ADA developed among 2.8% of tested adults and 12% of tested pediatrics. In children, 0.9% had ADA cross-reactive with native GLP-1. Any effect on effectiveness unknown. In adults, ADAs were associated with injection site reactions and hypoglycemia.
Semaglutide[34]	~1 week (subQ)	Excreted in urine and feces	• Highly protein-bound • *Immunogenicity:* ADA with cross-reactivity to GLP-1 developed in 2% of patients in clinical trials; any effect on effectiveness unknown. Hypersensitivity reactions were more common in adults with ADA.
Naltrexone/ bupropion ER[37]	NAL: 5 h BUP: 21 h (Both after a single oral dose)	NAL: primarily renal (53-79%) BUP: primarily renal (87%)	• Significantly increased exposure with high-fat meals; administration with such meals is not recommended

Table F1. Select Pharmacokinetic Information for Weight Maintenance Medications from PIs

Active Ingredient(s)	Approximate Terminal Elimination Half-life	Major Route(s) of Elimination	Additional Notes
Phentermine/ topiramate ER[36]	PHEN: 20 h (oral) TOP: 65 h (oral)	PHEN: primarily renal (70-80%) TOP: primarily renal (70%) (Both based on use alone)	• Similar exposure in pediatrics vs adults

[a] *Unknown if terminal elimination half-life*

Abbreviations: ADA, anti-drug antibodies; BUP, bupropion; ER, extended release; GLP-1, glucagon-like peptide-1; h, hour(s); IR, immediate release; NAL, naltrexone; NR, not reported in the PI; ODT, orally disintegrating tablet; PHEN, phentermine; PI, package insert; PK, pharmacokinetic; SubQ, subcutaneous; TOP, topiramate;