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Pharmacologic Treatment of Overweight and Obesity in Adults

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ABSTRACT

Obesity pharmacotherapy has evolved significantly over the past 60 years. Today, four anti-obesity medications (AOMs) are approved by the Federal Drug Administration (FDA) for the long-term treatment of obesity. Similar in approach to other chronic diseases, AOMs are indicated in combination with lifestyle modification for the management of overweight and obesity. Current guidelines recommend that individuals who have implemented lifestyle improvements for at least 6 months and have a body mass index (BMI) of ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with an obesity-related comorbidity are eligible for weight loss medication treatment. The AOMs reviewed in this chapter include the FDA-approved medicines for chronic weight management, FDA-approved medicines for short-term use of weight management, and off-label use of medicines that have demonstrated benefits for weight control.

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INTRODUCTION

Obesity is recognized as a major pandemic of the 21st century, contributing to increased morbidity, mortality, and the burden of healthcare costs (1). Overweight and obesity are defined by the World Health Organization (WHO) as a BMI of 25-29.9 kg/m^2 and a BMI ≥ 30 kg/m^2, respectively (2). In the United States, the prevalence of obesity had risen to 42.4% in 2017-2018 (3) and predictive models now suggest that the prevalence will grow to one in two adults by 2030 (4). Internationally, one in five adults now have obesity (5). The Global Burden of Disease study reports that overweight and obesity are the fourth leading risk for global deaths, and more than 4.7 million adults die each year as a result of overweight or obesity (6). Obesity is a major risk factor in the development of cardiovascular disease (CVD), type 2 diabetes (T2D), musculoskeletal disorders, and several cancers (2). In certain ethnic populations (i.e., East Asian or South Asian), these comorbidities can develop at lower BMIs (7).

The associations between obesity, central obesity (increased waist circumference, especially intra-abdominal/visceral fat) and the risks for cardiometabolic diseases as well as obstructive sleep apnea, asthma and nonalcoholic fatty liver disease (NAFLD) are well established (8,9). Cytokines secreted from visceral adipocytes, including interleukin-6, tumor necrosis factor alpha, resistin, and plasminogen activation inhibitor-1, have been implicated in the pathogenesis of these diseases, in part by promoting local and systemic states of inflammation and thrombosis (10-12). A reduction in body weight of 5-10% significantly lowers inflammatory and pro-thrombotic makers, as well as chronic disease incidence (13,14).

OBESITY PHARMACOTHERAPY

Principles of Obesity Pharmacotherapy

As with other chronic diseases, the initial management of overweight and obesity emphasizes sustainable nutritional, physical activity, and behavioral changes that have been shown to reduce weight and lower cardiometabolic risk. However, lifestyle interventions that include caloric restriction and/or portion control alone are insufficient in achieving long-term weight loss maintenance in most patients, with one-third to two-thirds of lost weight regained within one-year following end of treatment, and > 95% weight regained within 5 years (15).

For patients who have failed to achieve clinically significant weight loss, defined as ≥ 5% of baseline weight (16) after 6 months of lifestyle interventions (16-19), professional organizations including The Obesity Society, the Endocrine Society, and the American Association of Clinical Endocrinologists recommend AOMs for individuals with BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with comorbidities.

For health care professionals using pharmacotherapy for weight management, the following basic principles can be kept in mind:

- **Lifelong treatment:** Because obesity is a chronic disease, pharmacotherapy should be prescribed with the intent of lifelong use and as part of a comprehensive management plan that includes nutrition, physical activity, and behavioral counseling. Discontinuation of an AOM often leads to weight regain.
- **AOM's affect pathophysiological pathways that lead to obesity:** Current obesity pharmacotherapy targets the underlying neurohormonal dysregulations that cause weight gain and prevent sustained weight loss. Changes in hormones in response to diet-induced weight loss, such as reduction in the anorexigenic hormone leptin and increase in the orexigenic hormone ghrelin, create a physiologic environment conducive to the body returning to its previously established, higher body weight set point (20,21). Additional adaptation responses to diet-induced weight loss affecting energy expenditure, including reductions in basal metabolic rate, also challenge weight loss maintenance (22,23).
- **Treatments benefit both weight and comorbidities:** The goals of obesity treatment are primary, secondary, and tertiary prevention (17); that is, to prevent the development or exacerbation of obesity and its complications. For example, improvements in cardiometabolic risk factors and reduced diabetes risk have been consistently reported in the Phase 3 trials for AOM's.
- **Expect heterogeneity in weight loss response:** Phase 3 trials have consistently demonstrated that AOMs achieve significantly greater weight loss than placebo when combined with lifestyle modifications (24-30) The average efficacy in these studies ranges from 5-10% total body weight loss. However, as with any medical therapy, significant inter-individual response variability (31,32) has been reported, including the possibility of no weight loss (non-responders) to 20% or greater weight loss.

History of Anti-Obesity Medications

The development of AOMs dates as far back as the 1940s, predating the standard FDA rules and regulations that are familiar today. Drug approval in the 1940s necessitated only proof of efficacy beyond placebo; evaluation of benefit versus risk with controlled investigations was not a requirement until passage of the Kefauver-Harris amendment in 1962. Approval of the first AOM, desoxyephedrine, in 1947 led to the development of a number of amphetamine derivatives for weight loss that have all since been removed from the market due to this amendment (33). Since the FDA's adoption of stricter regulations and proof of *clinical* efficacy, only a couple of the recently approved AOMs have been removed from the U.S. market for safety concerns (Table 1).

Table 1.

Recently Recalled Anti-Obesity Medications

Name (Trade Name)	Years Approved	Reason for Removal

Name (Trade Name)	Years Approved	Reason for Removal
Sibutramine (Meridia)	1997-2010	Patients at high risk for CVD were found to have elevated risk of CVD events when given sibutramine (34)
Lorcaserin (Belviq)	2012-2020	Re-analysis of a safety clinical trial showed an increased incidence of certain cancers (35)

Only two AOMs have been removed from the market in recent history. The administration of sibutramine to individuals at high risk of CVD in the SCOUT trial was widely criticized by the medical community as it did not reflect real-life clinical practice; subgroup analysis of patients with T2D without CVD in SCOUT actually showed no increase in CVD events and a decrease in mortality with sibutramine compared to placebo (36). The voluntary recall of lorcaserin in 2020 occurred among significant confusion, as long-term data from the CAMELLIA-TIMI 61 trial did not demonstrate an imbalance in adverse events between treatment groups (37,38). In a recent communication, the FDA has clarified their findings that led to this withdrawal recommendation. When all post-randomization adverse events were considered, not just those that occurred "on treatment" (i.e., those that occurred within 30 days of drug discontinuation) as analyzed in CAMELLIA-TIMI 61 (39), even though similar numbers of patients experienced cancers (n=462 out of 6000 on lorcaserin and n=423 out of 6000 on placebo), a greater number of participants who received lorcaserin compared to placebo were reported with multiple primary cancers (n=20 vs. 8), total cancers (n=520 vs. 470), metastases (n=34 vs. 19), and cancer deaths (n=52 vs. 33). The latency period to reach significance for differences in all cancers between the treatment groups was a little over 2 years, and although the overall cancer rates were low, the FDA felt that benefits of lorcaserin could not yet be judged to outweigh this adverse risk.

FDA-Approved Medications for Weight Management

Today, seven FDA-approved AOMs remain on the market, with five approved for long-term weight loss (Table 2).

Table 2.

FDA Approved Anti-Obesity Medications

Name (Trade Names)	Year Approved	Mechanism of Action / Clinical Effect	Average placebo-subtracted weight loss (%)	Achieved ≥5% Weight Loss, Intervention vs. placebo (%)
*Approved for short-term use**				
Phentermine (Adipex, Lomaira) (40)	1959	Sympathomimetic / Suppresses appetite	4.4 at 28 wks	49 vs.16 at 28 wks
Diethylpropion (41)	197 1979	Sympathomimetic / Suppresses appetite	6.6 at 6 months	67.6 vs. 25.0
Approved for long-term use				
Orlistat (Alli, Xenical) (42)	1999	Intestinal lipase inhibitor / Reduces fat absorption by up to 30%	3.8	50.5 vs. 30.7
Phentermine-topiramate (Qsymia) (26)	2012	Combination sympathomimetic and carbonic anhydrase inhibitor / Decreases appetite and binge eating behaviors	8.6	70 vs. 21

Name (Trade Names)	Year Approved	Mechanism of Action / Clinical Effect	Average placebo-subtracted weight loss (%)	Achieved ≥5% Weight Loss, Intervention vs. placebo (%)
Bupropion-naltrexone (Contrave) (43)	2014	Combination of a dopamine and norepinephrine re-uptake inhibitor and mu-opioid receptor antagonist / Decreases appetite and cravings	4.8	48 vs. 16
Liraglutide 3.0mg (Saxenda) (28)	2014	GLP-1 receptor agonist / Decreases appetite, increases fullness, increases satiety	5.4	63.2 vs. 27.1
Gelesis100 (Plenity) (44)	2019	Superabsorbent hydrogel particles of a cellulose-citric acid matrix / Increases fullness	2.0 at 6 months	58.6 vs. 42.2

Weight loss outcomes reported are based on intention-to-treat or intention-to-treat last observation carried forward analyses from RCTs using the maximum doses of medications for 56 weeks unless otherwise stated (17). GLP-1, glucagon-like peptide-1. * Short-term use is generally accepted as 3 months

PHENTERMINE AND DIETHYLPROPION

Phentermine (trade name Adipex) was among the first FDA approved *short-term* medications for weight loss and remains available today. Phentermine is a sympathomimetic anorexigenic agent. A study from 1968 is the only longer-term controlled trial of phentermine (45). In this 36-week study, 64 patients were randomized to placebo, phentermine 30 mg daily, or intermittent phentermine 30 mg daily (4 weeks on, 4 weeks off). Both phentermine groups lost approximately 13% of their initial weight, while the placebo group lost only 5%. As discussed below, phentermine in combination with topiramate has been approved for long-term use.

Diethylpropion (trade name Tenuate), another sympathomimetic and derivative of bupropion, is also an approved *short-term* drug for treating obesity. It acts through modulation of norepinephrine action. A 6-month double-blinded placebo-controlled RCT followed by an open-label 6-month extension in 69 adults with obesity demonstrated diethylpropion 50 mg twice a day resulted in average weight loss of 9.8% at 6 months vs. 3.2% with placebo (41).

Phentermine's and diethylpropion's main side effects are related to their sympathomimetic properties, including elevation in blood pressure and pulse, insomnia, constipation, and dry mouth (46). Sympathomimetic agents are contraindicated in individuals with uncontrolled hypertension, known CVD (e.g., coronary artery disease, stroke, arrhythmias, congestive heart failure), hyperthyroidism, glaucoma, or exposure to monoamine oxidase inhibitors during or within 14 days of administration. Caution should be used in patients with pulmonary hypertension.

ORLISTAT

Orlistat (trade name Xenical) is approved for adult and adolescent obesity (ages 12 to 16) (47). It promotes weight loss by inhibiting gastrointestinal lipases, thereby decreasing the absorption of fat from the gastrointestinal tract. On average, 120 mg of orlistat taken three times per day will decrease fat absorption by 30% (48). Orlistat has been found to be more effective in inhibiting the digestion of fat in solid foods, as opposed to liquids (49). Orlistat at a lower dose of 60 mg 3 times daily, called Alli, is approved for over-the-counter use in the United States (50).

Efficacy

Several trials support orlistat's efficacy for weight loss and maintenance. Rossner et al. found that subjects receiving orlistat lost significantly more weight in the first year of treatment, and fewer regained weight during the second year of treatment, than those taking placebo (51). Subjects taking orlistat had significantly lower serum levels of vitamins D, E, and B-carotene. However, these nutritional deficiencies are easily treated with oral multivitamin supplementation.

Trials in Europe demonstrated similar results over a two-year period. Subjects in the orlistat group lost significantly more weight in the first year (10.2 vs. 6.1%) and regained half as much weight during the second year of treatment, as compared to the placebo group (52).

Effect on Metabolic Profile

In addition to promoting weight loss and maintaining lost weight, orlistat has been shown to improve insulin sensitivity and lower serum glucose levels. In a 2-year trial, Davidson et al. reported less weight regain rates and lower levels of serum glucose and insulin in patients maintained on a 120 mg three times per day dose of orlistat, as compared to those on placebo (53). In the 4-year XENDOS study conducted in Sweden, the cumulative incidence of T2D was 9.0% in the placebo plus diet and lifestyle group and 6.2% in the subjects receiving orlistat (24), corresponding to a risk reduction in development of T2D of 37.3%.

In patients with obesity and T2D with or without insulin treatment, orlistat resulted in improved glycemic control, determined via serum blood glucose levels and hemoglobin A1c (HbA1c) measurements, and reduced total cholesterol, low density lipoprotein (LDL) cholesterol, triglyceride, and apolipoprotein B levels (54,55). In subjects with obesity and T2D, hypercholesterolemia, or hypertension, orlistat treatment also led to greater weight loss and reductions in HbA1c, LDL, and total cholesterol (56).

Safety and Side-Effects

The gastrointestinal side effects of orlistat, including fatty/oily stool, fecal urgency, oily spotting, increased defecation, fecal incontinence, flatus with discharge, and oily evacuation (47), are the main reasons for discontinuation of therapy. These symptoms are usually mild to moderate and decrease in frequency the longer the medication is continued. Administration of orlistat with psyllium mucilloid reduced the incidence of GI side effects to 29% with psyllium vs. 71% without psyllium (57). Orlistat may reduce the absorption of fat-soluble vitamins A, D, E, and K, which can be mitigated with separate administration of vitamin supplementation.

PHENTERMINE/TOPIRAMATE

The controlled-release, single-tablet combination phentermine plus topiramate (trade name Qsymia) was approved by the FDA in 2012 as a long-term treatment for obesity for adults with BMI $\geq$ 30 kg/m^2 or BMI $\geq$27 kg/m^2 with at least one weight-related comorbidity. Phentermine is thought to promote weight loss by increasing norepinephrine release and decreasing its uptake in hypothalamic nuclei, leading to a decrease in food intake (58). It also acts as an adrenergic agonist that activates the sympathetic nervous system (59) to possibly increase energy expenditure. Topiramate is an FDA-approved medicine for epilepsy and migraine prophylaxis that has been shown to reduce body weight by promoting taste aversion and decreasing caloric intake (60). A carbonic-anhydrase inhibitor, topiramate was found to stimulate lipolysis in preclinical studies (61). Phentermine/topiramate is available in 4 doses: 3.75/23 mg (starting dose), 7.5/46 mg (lowest treatment dose), 11.25/69 mg or 15/92 mg (maximum treatment dose) daily.

Efficacy

Multiple Phase 1, 2, and 3 studies including more than 5000 subjects have evaluated the efficacy and safety of phentermine/topiramate combination therapy. The one-year EQUIP trial, a phase three 56-week RCT enrolled 1267 patients with obesity (mean BMI of 42.0 kg/m^2) and showed 3.5% weight loss in the starting dose group (3.75 mg/23 mg) and 9.3% placebo-subtracted weight loss in the top treatment dose (15 mg/92 mg) group (27). The 52-week CONQUER trial randomized 2487 patients with obesity and a comorbidity (e.g. hypertension, dyslipidemia, prediabetes, diabetes, or abdominal obesity) to placebo, mid-dose treatment dose (7.5mg/46 mg), or maximum treatment dose (15/92 mg) and found 6.6% and 8.6% placebo-subtracted weight loss in the mid and maximum dose arms, respectively (26). A two-year extension of the CONQUER trial was published (SEQUEL) demonstrating mean placebo-subtracted weight loss of 7.5% in the mid-dose group and 8.7% in the maximum-dose group and (62).

Effect on Metabolic Profile

Improvements in systolic and diastolic blood pressure, triglycerides, and high density lipoprotein (HDL) cholesterol were seen in subjects treated with phentermine plus topiramate compared with placebo in both EQUIP and CONQUER (26,27). Improvements in fasting glucose and insulin levels were seen in the SEQUEL study, and a 54% and 76% reduction in progression to T2D in the two treatment groups was noted in subjects without diabetes at baseline (62).

Safety and Side Effects

Phentermine-topiramate is not recommended for patients with significant cardiac history such as coronary disease and uncontrolled hypertension (63). However, in individuals without coronary disease and with well-controlled hypertension, it is considered safe to use this drug along with regular blood pressure monitoring. Phentermine/topiramate exposure carries an increased risk of cleft lip/palate in infants exposed to the combination drug during the first trimester of pregnancy. Women of child-bearing age should have a pregnancy test prior to starting the medicine and be using contraception while taking it. Clinicians who prescribe phentermine-topiramate and pharmacists who dispense it should enroll in a Risk Evaluation and Mitigation Strategy (REMS), which includes education on prescribing information, monitoring during treatment, and side effects. This medication is also contraindicated in patients with hyperthyroidism, glaucoma, and in patients who have taken monoamine oxidase (MAO) inhibitors within 14 days. Topiramate can increase the risk of acidosis and renal stones so should be used cautiously in patients who have had stones previously (64).

In order to mitigate side effects, which include paresthesias, dizziness, dry mouth, constipation, dysgeusia, insomnia, and anxiety, a step-wise dosage titration is recommended. Phentermine-topiramate is initiated at the 3.75/23 mg dose daily for 14 days, followed by 7.5/46 mg daily thereafter. If after 12 weeks, a 3 percent loss in baseline bodyweight is not achieved, the dose can be increased to 11.25/69 mg for 14 days, and then to 15/92 mg daily. If an individual does not lose 5 percent of body weight after 12 weeks on the highest dose, phentermine-topiramate should be discontinued due to lack of response. Discontinuation should be performed gradually because rapid withdrawal of topiramate may provoke seizures.

BUPROPION/NALTREXONE

The combination tablet of bupropion and naltrexone (trade name Contrave) was FDA-approved for weight loss in September 2014. Bupropion is a reuptake inhibitor of dopamine and norepinephrine that promotes activation of the central melanocortin pathways (65). Naltrexone is an opioid receptor antagonist that diminishes the mu-opioid receptor auto-inhibitory feedback loop on anorexigenic hypothalamic neurons activated by bupropion, thereby allowing for sustained weight loss (66). Bupropion/naltrexone comes in tablets containing 90 mg of bupropion HCl sustained-release and 8 mg of naltrexone HCl. The recommended starting dose is 1 tablet daily and increasing by 1 tablet each week until a total dose of 2 tabs twice daily is reached (total daily dose: bupropion 360 mg/naltrexone 32 mg).

Efficacy

Four 56-week multicenter, double-blind, placebo-controlled trials (CONTRAVE Obesity Research: COR-I, COR-II, COR-BMOD, and COR-Diabetes) were conducted to evaluate the effect of bupropion/naltrexone in conjunction with lifestyle modification compared to a placebo-controlled cohort of 4536 patients. The COR-I, COR-II, and COR-BMOD trials enrolled patients with BMI $\geq$ 30 kg/m^2 or BMI $\geq$ 27 kg/m^2 with at least one comorbidity (25,30,43). The COR-Diabetes trial enrolled patients with BMI greater than 27 kg/m^2 with T2D with or without hypertension or dyslipidemia (67). The primary endpoints were percent change from baseline body weight and the proportion of patients achieving at least a 5% reduction in body weight. In the 56-week COR-I trial, significantly greater mean weight loss (6.1%) occurred in patients assigned to naltrexone 32 mg/bupropion 360 mg dose compared with the placebo group (1.3%), and 48% of active treatment group achieved ≥5% weight loss compared to only 16% of placebo group (43). Similar weight loss efficacy was reported in COR-II (25) and COR-Diabetes (67) trials. Bupropion/naltrexone can be combined with intensive behavioral therapy (IBT) to achieve even greater weight loss (5.2% with placebo and 9.3% with bupropion/naltrexone) (30).

Effect on Metabolic Profile

In all of the COR trials, secondary cardiovascular risk endpoints were met, including statistically significant greater improvements in waist circumference (WC), visceral fat, HDL cholesterol, and triglyceride levels in the participants treated with the bupropion 360 mg/naltrexone 32 mg dose compared with placebo-treated participants (25,30,43,67). Participants with diabetes in the COR-Diabetes trial using bupropion/naltrexone also showed a significantly greater 0.6% reduction in HbA1c from baseline, compared to a 0.1% reduction in placebo (67).

Safety and Side Effects

The most common side effects of bupropion/naltrexone include nausea/vomiting, constipation, headache, dizziness, insomnia, and dry mouth. Medication interactions include MAO inhibitors (use during or within 14 days of administration), opioids and opioid agonists (including partial agonists) that are inactive in the presence of naltrexone, and abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs that can increase risk for seizure. Bupropion/naltrexone should be avoided in patients with uncontrolled hypertension, history of seizures, history of bulimia or anorexia nervosa, and in individuals taking narcotics for pain control (68).

The FDA recommends monitoring patients for worsening or emergence of suicidal thoughts or behaviors. Women of child-bearing age should have a pregnancy test prior to starting the medicine and be using contraception while taking it.

LIRAGLUTIDE 3.0

Liraglutide 3.0 mg (trade name Saxenda) was approved by the FDA in December 2014 for adult obesity and has proven efficacy in adolescents age 12 to <18 years of age (69). Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue that activates the GLP-1 receptor. In animal studies, peripheral administration of liraglutide results in uptake in specific brain regions regulating appetite, including the hypothalamus and brainstem (70). A short-term study (5 weeks) involving individuals with obesity and without diabetes demonstrated that liraglutide 3.0 mg/d suppressed acute food intake, subjective hunger, and delayed gastric emptying (71). Energy expenditure in subjects treated with liraglutide 3.0 mg/d decreased, even when corrected for weight loss (71), which may reflect metabolic adaptation to weight loss.

Efficacy

SCALE Obesity and Prediabetes (n=3731) and SCALE Diabetes (n=846) evaluated the effect of liraglutide 3.0 mg on overweight and obesity with normoglycemia, prediabetes, and diabetes respectively (28,72). Both 56-week, randomized, placebo-controlled, double-blind clinical trials demonstrated significantly greater mean weight loss than placebo (8% vs. 2.6% in SCALE Obesity and Prediabetes (28) and 6.0% vs. 2% in SCALE Diabetes (72). The efficacy of liraglutide 3.0 in maintaining weight loss was examined in the SCALE Maintenance study. Four hundred and twenty-two subjects who lost ≥ 5% of their initial body weight on a low-calorie diet were randomly assigned to liraglutide 3.0 mg daily or placebo for 56 weeks. Mean weight loss on the initial diet was 6.0%. By the end of the study, participants in the liraglutide 3.0 group lost an additional 6.2% compared to 0.2% with placebo (73).

Effect on Metabolic Profile

Secondary endpoints in the SCALE Obesity and Prediabetes included waist circumference, lipids, HbA1c, and blood pressure, all of which showed significantly greater improvement than placebo (28). Systolic blood pressure dropped by 4.2 mmHg vs. 1.5 mmHg in the liraglutide 3.0 mg vs. placebo groups. Diastolic blood pressured was reduced by 2.6 mm Hg vs. 1.9 mm Hg. The most significant change in lipid profile was in the triglycerides that were reduced by 13.0 mg/dl in the liraglutide 3.0 mg group vs. 5.5 mg/dl in the placebo group. Participants assigned to liraglutide 3.0 had a lower frequency of prediabetes and were less likely to develop T2D than those assigned to placebo (28), an outcome that persisted in a 3-year extension analysis (74). For participants with obesity and moderate/severe obstructive sleep apnea, liraglutide 3.0 mg treatment resulted in significantly greater reductions than placebo in apnea-hypopnea index, body weight, systolic blood pressure, and HbA1c levels (75).

In the SCALE Diabetes study, HbA1c levels were 0.93% lower in the liraglutide 3.0 vs. placebo treated group, and similar significant benefits on triglyceride (lower) and HDL cholesterol (higher) as in the SCALE Obesity study were

reported (72).

Although liraglutide 3.0 mg was not evaluated in a cardiovascular outcomes trial (CVOT), the lower dose liraglutide 1.8 mg (Victoza), approved for T2D, was assessed in the LEADER trial (76). The primary outcome was a composite of major adverse cardiovascular events (MACE) including CVD death, nonfatal myocardial infarction (MI), and nonfatal stroke. Adults with T2D and baseline average BMI 32.5 kg/m^2 were randomized to liraglutide 1.8 mg vs. placebo. Approximately 81% of participants had established CVD. After a median of 3.8 years, individuals on liraglutide 1.8 mg demonstrated a 13% risk reduction in 3-point MACE compared to placebo. Analysis of additional outcomes showed a 22% reduction in CVD death and a 15% reduction in all-cause deaths. This risk reduction was driven primarily by a reduction in death from CV causes (p=0.01 for superiority) and all-cause mortality was reduced by 15%. Statistical significance was not achieved with individual endpoints of nonfatal MI or nonfatal stroke. Liraglutide 1.8 mg is now FDA-approved for secondary CV prevention in adults with T2D (77).

Safety and Side Effects

Gastrointestinal symptoms, such as nausea, vomiting and abdominal pain, were the most common reason subjects withdrew from the SCALE trials. In a secondary analysis of these trials, treatment with liraglutide 3.0 resulted in dose-independent, reversible increases in amylase/lipase activity (7% for amylase and 31% for lipase) (78). Thirteen subjects (0.4%) in the liraglutide 3.0 group compared to one (0.1%) with placebo developed pancreatitis, but nearly half of these had evidence for gallstones as well (78). Even though liraglutide treatment showed improvements in blood pressure and lipids, it was found to increase heart rate by an average of 2 beats/min in SCALE Diabetes (72). Animal studies with liraglutide showing an association with medullary thyroid cancer have led to FDA label warnings. Even though the relevance of this observation to humans has not been determined, a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2 (MEN 2) is considered a contraindication for treatment with this medication (79).

Women of child-bearing age should have a pregnancy test prior to starting the medicine and be using contraception while taking it.

GELESIS 100

Gelesis100 (Plenity) is the newest FDA-approved option for obesity treatment and is the first AOM indicated for adults with overweight (BMI 25-40 kg/m^2) with or without comorbidities. Gelesis100 is a hydrogel matrix composed of modified cellulose cross-linked with citric acid. Its mechanism of action is to absorb water to occupy about one-fourth of the average stomach volume, promoting fullness. Because it achieves its primary intended purpose through a mechanical mode of action, it is considered a device rather than a drug and has no systemic effects. One dose is three oral capsules (2.25 g/dose) that is ingested with 500 ml of water 20-30 min prior to lunch and dinner.

Efficacy

The efficacy of Gelesis100 was evaluated in the Gelesis Loss of Weight (GLOW) randomized double-blind placebo-control trial (80). Adults with overweight or obesity with or without comorbidities were randomized to Gelesis100 (n=223) or placebo (n=213) for 6 months, and completers who had lost ≥ 3% of baseline weight after 24 weeks were offered to continue in the 24-week open-label single cross-over extension trial GLOW-EX(80). At 6 months, weight loss was 6.4% vs. 4.4% (p=0.0007) in the Gelesis100 vs. placebo groups, respectively, and 58.6% vs. 42.2% of individuals lost ≥ 5% of baseline weight (p=0.0008). Gelesis100 was not significantly more effective in individuals with prediabetes or drug-naïve T2D with respect to mean percent change in body weight, which had been a notable observation in the pilot study First Loss of Weight (FLOW) (80). However, weight loss of ≥ 10% in this subgroup was achieved by 44% vs. 14% of those on Gelesis100 vs. placebo, respectively. In GLOW-EX (n=39), participants in the Gelesis100 group had achieved at mean of 7.1% weight loss at end of the GLOW trial, and continuation of Gelesis100 resulted in a mean weight loss of 7.6% at 48 weeks, demonstrating weight loss maintenance.

Effect on Metabolic Profile

Overall, there were no significant differences between Gelesis100 or placebo in cardiovascular risk factors of LDL-C, HDL-C, triglycerides, systolic BP, diastolic BP, or HOMA-IR. In a subgroup of individuals with elevated LDL-C, blood pressure, or HOMA-IR, there was a greater reduction in LDL-C, resolution of hypertension, and reduction in HOMA-IR in those treated with Gelesis100.

Safety and Side Effects

Side effects due to Gelesis100 are commonly gastrointestinal, including abdominal distension, infrequent bowel movements, or dyspepsia. There were no significant differences between groups with regards to serum vitamin levels. Gelesis100 is contraindicated in pregnancy or individuals with allergies to cellulose, citric acid, sodium stearyl fumarate, gelatin, or titanium oxide (44). It should be avoided in patients with esophageal anatomic anomalies, suspected strictures, or post-operative complications that affect gastrointestinal transit and motility. The manufacturer recommends caution in patients with active gastrointestinal reflux diseases. The impact of Gelesis100 on the absorption of other medications was investigated only with metformin. Concurrent administration of Gelesis100 with metformin in the fasting state reduced the median area-under-the-curve (AUC) for metformin but had no effect on metformin AUC when administered during a meal. It is recommended that Gelesis100 be considered “food” when counseling patients on administration of other medications that require ingestion “on an empty stomach” vs. “with food.”

NON-FDA APPROVED (OFF-LABEL) MEDICATIONS THAT CAUSE WEIGHT LOSS

Several medications prescribed for conditions other than obesity have been found to be effective weight loss drugs in patients with obesity. If used for weight loss, the prescribed use of these medications would be off-label.

Bupropion

Bupropion (trade name Wellbutrin or Zyban) is used for depression and smoking cessation and can cause weight loss as a side effect. While the mean weight loss seen with bupropion is small, it is a preferred alternative to most antidepressants, which commonly cause weight gain.

A 48-week randomized placebo-controlled trial randomized individuals with obesity to placebo, 300 mg, or 400 mg of bupropion sustained release (SR). Percentage losses of initial body weight for subjects completing 24 weeks were 5.0%, 7.2%, and 10.1% for placebo, bupropion SR 300, and 400 mg/d, respectively (81). In subjects with obesity and depressive symptoms, bupropion SR was more effective than placebo in achieving weight-loss when combined with a 500 kcal deficit diet (4.6% vs.1.8% loss of baseline body weight, $P<0.001$) (82). Bupropion is contraindicated in patients with seizures, current or prior diagnosis of bulimia or anorexia nervosa, and concurrent use with MAOs (83). Caution should be used in patients with hypertension, mania/hypomania, psychosis, and angle-closure glaucoma.

Metformin

Metformin (trade name Glucophage) is an antihyperglycemic agent that acts by suppressing gluconeogenesis and increasing peripheral insulin sensitivity (84). Potential weight loss mechanisms include:

1. Activation of AMP-activated protein kinase (AMPK) to mimic an “energy deficient” state (85,86)
2. Increasing anorexigenic hormones GLP-1 (87), growth/differentiation factor-15 (GDF-15) (88), neuropeptide Y (NPY), and agouti-related protein (AgRP) (89)
3. Increasing leptin sensitivity (90)

In the landmark Diabetes Prevention Program (DPP), 3234 participants without T2D but with fasting and post-prandial hyperglycemia were randomized to intensive lifestyle intervention (ILI), metformin, or placebo (14). ILI consisted of a 7% weight loss goal, 150 minutes per week of physical activity, and a low-fat diet. The mean age was 51 years and mean BMI was 34.0 kg/m^2. The metformin group was not offered ILI and was assigned to metformin 850 mg twice a day. After an average follow-up of 2.8 years, patients in the metformin group achieved greater weight loss than placebo but less than the ILI group. The average weight loss was 0.1 kg, 2.1 kg, and 5.6 kg in the placebo, metformin, and ILI

groups, respectively (*P*<0.001, cross-group comparison) (14). The extended observational trial DPP Observation Study showed that the group on metformin maintained 3% weight reduction compared to placebo for 6-15 years after DPP ended (91). Short-term studies and meta-analyses in individuals with obesity and without prediabetes/diabetes consistently demonstrate ~2% weight loss beyond placebo, with a greater response in those with more insulin resistance (92). Metformin is therefore considered a first line drug in treating patients with type 2 diabetes and obesity. The most common side effects of metformin are nausea, flatulence, diarrhea, and bloating (93). The most serious side effect is lactic acidosis, but this is rare (<1/100,000) (94). Monitoring for vitamin B12 deficiency is recommend as long-term use of metformin has been associated with low vitamin B12 levels and neuropathy (95).

Pramlintide

Pramlintide acetate (trade name Symlin) is an injectable agent that is FDA-approved for the treatment of type 1 and type 2 diabetes. Pramlintide mimics the action of the pancreatic hormone amylin, which along with insulin regulates postprandial glucose control. Its effect on weight loss is thought to be mediated through central (brain) receptors (96) that improve appetite control (97). In a pooled, post-hoc analysis of overweight and obese insulin-treated patients with T2D, pramlintide-treated patients (receiving 120 μg twice daily) had a body weight reduction of -1.8 kg (P<0.0001) compared with placebo-treated patients (98). In this study, pramlintide-treated patients experienced a 3-fold increase in successfully achieving a total body weight loss of ≥ 5%, when compared to those who received placebo. Subsequently, randomized trials combining pramlintide or placebo with a lifestyle intervention were undertaken in obese participants without diabetes. Treatment with pramlintide (up to 240 μg three time daily) for 16 weeks resulted in a placebo-corrected reduction in body weight of 3.7% (P<0.001) and 31% of pramlintide-treated subjects achieved ≥5% weight loss vs. 2% with placebo (P<0.001) (99). In another study with one year follow-up, placebo-corrected weight loss in those taking 120 ug three time daily and 360 ug twice daily averaged 5.6% and 6.8% (100). Nausea is the most common adverse event with pramlintide treatment in these studies.

Semaglutide

Semaglutide (trade name Ozempic) is a GLP-1 receptor agonist administered via weekly subcutaneous injection used in the treatment of T2D. A 52-week multicenter phase 2 RCT conducted in adults with obesity and without T2D demonstrated weight loss superiority of daily semaglutide in doses ranging from 0.2-0.4 mg/d as compared to liraglutide 3.0 mg/d or placebo (101). Unpublished data from phase 3 trials subsequently demonstrated weight loss efficacy of once-weekly semaglutide 2.4 mg compared to placebo over 68 weeks (102). STEP2 was conducted in adults with obesity and T2D and found an average placebo-subtracted weight loss of 6.2%, with 68.8% achieving ≥5% weight loss compared to 28.5% with placebo. STEP3 enrolled adults with obesity or overweight with comorbidities and investigated semaglutide 2.4 mg as an adjunct to IBT; average placebo-subtracted weight loss was 12.6%, and 89.8% achieved ≥5% weight loss compared to 50.0% in the placebo plus IBT group.

Outcomes results of semaglutide 2.4 mg on cardiovascular events and mortality remain pending at this time. However, CVOT results for the lower dose semaglutide 1.0 approved for T2D have been published. In the CVOT SUSTAIN-6, adults with T2D were randomized to semaglutide 1.0 mg weekly vs. placebo to evaluate the primary outcome of 3-point MACE (CV death, nonfatal MI, nonfatal stroke). At baseline, average BMI was 32.8 kg/m^2 and 83.0% had established CVD (103). After a median follow-up time of 2.1 years, the semaglutide group demonstrated a 26% reduction in risk of the primary outcome compared to placebo, which was driven by nonfatal MI and nonfatal stroke. There was no significant difference in the number of deaths from CV causes between semaglutide and placebo.

Semaglutide may cause gastrointestinal side effects (e.g., nausea, vomiting, constipation), and renal impairment may occur in individuals reporting severe adverse gastrointestinal reactions (104). Like liraglutide, semaglutide is contraindicated in the setting of a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2. In rodents, semaglutide was found to cause thyroid C-cell tumors, but no human cases have been linked to semaglutide use. Reports of pancreatitis were rare in the SUSTAIN trials. Semaglutide at doses indicated for T2D resulted in a mean increase in heart rate of 2-3 beats/min in clinical trials.

Sodium-Glucose Transporter-2 Inhibitors

Sodium-glucose transport-2 (SLGT2) inhibitors are a class of medications used for the treatment of T2D. Inhibition of SGLT2 in the kidney lowers the renal threshold for glucose reabsorption, resulting in glucosuria and improved plasma glucose levels. As of 2020, there are four SLGT2 inhibitors approved in the U.S.: canagliflozin (Invokana), dapagliflozin (Farxiga), ertugliflozin (Steglatro), and empagliflozin (Jardiance). Pooled analyses of four phase 3 trials in adults with T2D showed about 2-3% placebo-subtracted weight loss with canagliflozin 100-300 mg/d at 26 weeks (105). Dapagliflozin on a background of metformin was found to result in a placebo-subtracted weight loss of 2.42kg at 102 weeks in adults with T2D and obesity (106). In the landmark EMPA-REG CVOT, average placebo-subtracted weight loss of about 2 kg was maintained out to 220 weeks with empagliflozin 25 mg (107). The fourth SGLT2 inhibitor, ertugliflozin, also resulted in about 2kg weight loss over placebo in adults with T2D treated for 26 weeks (108). A meta-analysis of EMPA-REG, CANVAS (109,110), and DECLARE-TIMI 58 (111) found that SGLT2 inhibitors were associated with a 24% reduction in hospitalization for heart failure and CVD death in individuals with T2D and established CVD (112). This same meta-analysis concluded that SGLT2 inhibitors were also associated with nearly a 50% reduction in the composite outcome of end-stage renal disease, renal worsening, or renal failure in individuals with T2D and CVD or CVD risk factors. The reno-protective effect may be independent of baseline A1c given attenuated estimate glomerular filtration rate (eGFR) declines observed in CREDENCE and DAPA-HF trials with little change in A1c (113,114), suggesting a role of SGLT2 inhibitors in individuals with nephropathy without T2D. Dapagliflozin was recently approved by the FDA for the treatment of heart failure in individuals with or without T2D based on the results of the DAPA-HF trial (114). DAPA-CKD and EMPA-KIDNEY are ongoing trials evaluating the effect of SGLT2 inhibitors in the broader CKD population (115,116).

Due to the mechanism of action, all SGLT2 inhibitors may cause urinary tract infections, genital mycotic infections, and dehydration. They are contraindicated in severe renal impairment (eGFR < 30 ml/min/1.73m^2), end-stage renal disease, and dialysis (117-120).

Topiramate

Topiramate (trade name Topamax) is an antiepileptic agent that has been found to reduce body weight in patients with a variety of disorders including epilepsy, bipolar disorder, and binge eating disorder (121). Randomized controlled trials have shown that topiramate is both tolerable and effective in promoting weight loss (60). In addition to use for epilepsy, topiramate has received FDA approval for the prevention of migraine headaches. Topiramate can cause paresthesias and cognitive side effects, such as word-finding difficulty and memory loss. Caution should be taken if used in patients predisposed to renal stones, acute angle glaucoma, or metabolic acidosis (122).

Zonisamide

Zonisamide (trade name Zonegran) is another antiepileptic medication that has also been found to reduce body weight in patients. Short (16 weeks) and longer (one year) randomized-controlled studies in patients with obesity have shown that 400 mg of zonisamide daily is effective in promoting modest weight loss (~5 kg placebo-subtracted weight) (123,124). The most commonly reported side effects compared to placebo were gastrointestinal (nausea/vomiting), nervous system (headaches), and cognitive (anxiety, impaired memory, language problems) (124). Zonisamide should not be given to patients hypersensitive to sulfonamides (125).

MEDICATION-INDUCED OBESITY

The role of medications as a factor that can induce weight gain is often overlooked. Several commonly prescribed medications as well as over-the-counter medications are associated with significant weight gain. This includes medications used to treat T2D, hypertension, depression, schizophrenia, and insomnia (126-128). When evaluating a patient with obesity for the first time, the clinician should perform a thorough review of all current prescription and over-the-counter medications to investigate for potential weight-gaining medications. Whenever possible, the clinician should consider alternatives to medications known to cause weight gain (129), or should consider measures that would ameliorate the weight-gaining effect of the prescribed drug.

FUTURE DIRECTIONS FOR WEIGHT-LOSS MEDICATIONS

Medical providers, policy makers, and pharmaceutical industries have increasingly recognized the need for safe and effective pharmacotherapy for patients with overweight or obesity. A number of AOMs are currently in various stages of development. Some, like setmelanotide, a melanocortin receptor-4 agonist, are marketed for rare genetic disorders that cause obesity. Others are designed as "tri-target" agents with agonist or antagonist properties depending on the target hormone receptor (130). Providers may also find familiar medications being repurposed for the treatment of obesity at specific dose ranges, such as semaglutide.

IMPLICATIONS FOR PRACTICE

The plethora of on- and off-label AOMs creates the unique challenge for physicians to decide which medication may be most appropriate for the individual patient. Akin to management of other chronic diseases, selection of an AOM is often based on specific disease characteristics, contraindications, and AOM side effect profiles.

The following principles could serve as a guide the physician in choice of AOM:

- **Contraindications and side effect profiles:** A patient with HTN and lower extremity edema may be better treated with a diuretic rather than amlodipine, which may have the side effect of leg swelling. Analogously, in a patient with obesity and HTN or anxiety, sympathomimetics like phentermine and bupropion/naltrexone should be avoided or used with caution due to potential side effects of these AOMs.
- **Dual indications**: A patient with HTN and T2D complicated by microalbuminuria would be recommended for an angiotensin converting enzyme inhibitor (ACEi) or aldosterone receptor blocker (ARB) instead of a calcium channel blocker because of the dual benefits of ACEi's or ARBs. In obesity and T2D, liraglutide is logical choice for AOM because of it is approved for obesity at the 3.0 mg dose and for T2D at the 1.8 mg dose.
- **Comprehensive care team:** Since comorbidities are common in the obesity population, the choice of AOM is often made in conjunction with different specialists, such as the patient's psychiatrist. A patient on a selective serotonin reuptake inhibitor (SSRI) for depression may be experiencing weight gain due to the antidepressant, and a discussion on cross-titration to a more weight-neutral medication like bupropion may be beneficial.
- **Combinations of AOMs:** Combining medications with complementary mechanisms of action is a rational management strategy to target the pathophysiology of obesity and metabolic adaptation. For example, a patient who has lost weight with metformin and reached a weight loss plateau may experience increased hunger due to higher levels of ghrelin, a mechanism that has been reported after diet-induced weight loss; an appetite suppressant such as phentermine or phentermine/topiramate may be helpful to mitigate this compensatory mechanism. While some of these combinations have been investigated (131,132), most AOM permutations have not been tested in RCTs, and the "how" and "when" of AOM combinatorial approaches remains in the realm of clinical judgement and future research.

CONCLUSION

The obesity pandemic continues to grow at an alarming rate. Because lifestyle modifications have been limited in their success in weight loss maintenance, pharmacotherapy plays an important role in achieving clinically significant weight loss and preventing the development or exacerbation of comorbid conditions. As society and the scientific community furthers our understanding of obesity, obesity management will evolve to match the standard of care of other chronic conditions, recognizing polypharmacotherapy as a vital component of comprehensive care.

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