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Medical Management of Obesity: Current Trends and Future Perspectives

REVIEW

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ABSTRACT

Obesity and overweight have become increasingly significant conditions, affecting more than 70% of the adult population in the United States. These conditions are caused by a combination of factors, including genetic, behavioral, environmental, and medical influences. Obesity is a major risk factor for cardiovascular and metabolic diseases. A comprehensive treatment plan for individuals with obesity must recognize the chronic nature of the condition and offer strategies for weight reduction and long-term cardiometabolic benefits. Over the past several decades, multiple therapeutic options have been implemented to address weight loss, appetite regulation, and caloric expenditure, with the goal of reducing the burden of obesity and improving cardiovascular outcomes. Pharmacological treatment of obesity has focused primarily on the central regulation of appetite and food intake behavior. The introduction of incretin agonists for obesity treatment has ushered in a new era of cardiometabolic health, with a multitargeted mechanism that achieves weight loss, glycemic control, decreased cardiovascular mortality, and other metabolic benefits. This review explores the current pharmacological options and the future of obesity treatment.

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INTRODUCTION

The global obesity epidemic has become a significant public health concern, with 1.9 billion adults estimated to be overweight and roughly 650 million of those with obesity.[1] Obesity is associated with a wide range of metabolic consequences, including an increased risk of chronic diseases such as type 2 diabetes mellitus (T2DM), cardiovascular disease, and certain types of cancers.[2] Anti-obesity medications offer a comprehensive strategy by focusing on the complex interplay of genetic, metabolic, behavioral, socioeconomic, and environmental factors that contribute to the development of obesity.[3] In this review, we delve into the broad classes of medications and their potential role in addressing the global obesity epidemic.

INCRETIN-BASED THERAPIES

Incretin hormones are peptides produced in the gastrointestinal track and are secreted in response to nutrient intake. Glucagon-like peptide 1 (GLP-1) is produced mainly by intestinal mucosal cells from the distal small intestine. GLP-1 receptors are widely distributed in the pancreatic islet, brain, gastrointestinal tract, and muscle cells,[4] and it acts on these organs to regulate satiety, glucose absorption, and metabolism. In the pancreas, it promotes insulin secretion in a glucose-dependent manner and also inhibits glucagon secretion.[4] GLP-1 slows gastric emptying, which in turns limits post prandial glucose excursions. The brain also expresses GLP-1 receptors, especially in the hypothalamus in areas that are involved in food intake regulation. GLP-1 has been shown to also increase glucose uptake in muscle tissue.[4]

The glucose-dependent insulinotropic polypeptide (GIP) is secreted by cells from the proximal small intestine. GIP increases glucose-dependent insulin secretion from the pancreas and promotes beta cell survival.[5] Similar to GLP-1, GIP also has receptors in the central nervous system in the areas that regulate food intake.[5] Due to these effects, incretin-based therapies have revolutionized the management of patients with T2DM and obesity.

In 2014, the United States (US) Food and Drug Administration (FDA) approved the GLP-1 receptor agonist liraglutide for the management of obesity. Patients without diabetes were able to achieve a mean weight loss of 8% at 56 weeks with liraglutide 3 mg compared to 2% with placebo in the SCALE (Effect of Liraglutide on Body Weight in Non-diabetic Obese Subjects or Overweight Subjects With Co-morbidities: SCALE™ - Obesity and Pre-diabetes) trial.[5,6] A meta-analysis that included 18 randomized controlled trials showed that liraglutide was associated with a 4.7% weight loss in patients with and without diabetes.[7]

DRUG NAME	INDICATIONS	PRIMARY MECHANISM	MEAN WEIGHT LOSS	SIDE EFFECTS	CONTRAINDICATIONS	SPECIAL CONSIDERATIONS	PRICING OPTIONS*
Liraglutide (*Saxenda*)	Indicated in patients with BMI ≥ 30 kg/m^2, or in patients with a BMI ≥ 27 kg/m^2 and at least one weight-related comorbidity in conjunction with diet and physical activity	GLP-1 receptor agonist	8%	Nausea (39%), diarrhea (21%), vomiting (16%), constipation (19%), headache (14%), dyspepsia (10%)	Personal or family history of medullary thyroid carcinoma, or MEN2A syndrome	Acute pancreatitis (OR 0.65-1.34), gallbladder disease (OR 1.23-1.52) diabetic retinopathy (OR 0.11-1.03)	**$$$$** Discount/coupon available online No generic alternatives
Semaglutide (*Wegovy*)			14.9%	Nausea (44%), diarrhea (30%), vomiting (24%), constipation (24%), abdominal pain (20%), headache (14%), fatigue (10%)			**$$$$** Discount/coupon available online No generic alternatives
Tirzepatide (*Zepbound*)		GLP-1 and GIP receptor agonist	20.9%	Nausea (25-29%), diarrhea (19-23%), constipation (11-17%), vomiting (8-13%), abdominal pain (10%), dyspepsia (10%)			**$$$$** Discount/coupon available online No generic alternatives

Table 1 Incretin-based therapies. All listed medications are contraindicated in pregnancy and are best avoided in women who are pregnant, trying to become pregnant, or are breastfeeding. MEN2A: multiple endocrine neoplasia syndrome type 2; OR: odds ratio

*Insurance coverage of individual medications will depend upon individual plan.

Semaglutide was approved in 2021 for the management of obesity. The Semaglutide Treatment Effect in People with Obesity Program (STEP) trial showed the efficacy of this medication in obese patients without diabetes. Compared to placebo, patients in the treatment group (semaglutide 2.4 mg) were able to achieve a 14.9% reduction in body weight compared to 2.4% with placebo at 68 weeks.[8]

Tirzepatide, which was approved in 2023 for the management of obesity, is a dual hormone medication that acts as an agonist of both the GLP-1 and GIP receptors. In the SURMOUNT-1 (A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight) trial, patients were randomized to receive either 15 mg, 10 mg, 5 mg or placebo combined with lifestyle counseling, physical activity, and diet with a caloric deficit of 500 kcal per day. At 72 weeks, the mean weight loss was 20.9% in the 15 mg group, 19.5% in the 10 mg group, 15% in the 5 mg group, and 3.1% for the placebo group.[9] Although no direct comparisons have been made, tirzepatide 10 mg and 15 mg seems to be more effective than the maximum dose of semaglutide.[9] As with other incretin-based therapies, the most common reported side effects are nausea, diarrhea, constipation, and vomiting occurring mainly with dose escalation (Table 1).[10]

Rates of discontinuation are dose-dependent, with 4.3% of patients stopping tirzepatide with 5 mg, 7.1% with 10 mg, and 6.2% with 15 mg.[9]

INCRETIN EFFECT BEYOND WEIGHT BENEFITS

DIABETES MANAGEMENT

GLP-1 and GIP receptor agonists have proven efficacy in the treatment of diabetes. A large meta-analysis found that semaglutide and liraglutide lowered glycated hemoglobin (HbA1c) by 1.45 and 1.48%, respectively, at the highest dose.[11] The SURPASS-1 (Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes) phase I trial showed a mean 2.05% decrease in HbA1c in patients who received tirzepatide at a maximal dose of 15 mg once weekly.[12] A meta-analysis comparing the glycemic control between tirzepatide and semaglutide showed a mean percentage decrease in HbA1c of 1.96% in the tirzepatide group compared with a 1.56% decrease in the semaglutide group.[13]

Current guidelines recognize the impact of GLP-1 and GIP agonists in obesity and diabetes and do not recommend one over the other; however, tirzepatide might offer an added benefit due to the potential weight loss and better diabetes control compared with semaglutide and liraglutide.

CARDIOVASCULAR BENEFITS

The expression of GLP-1 receptors in the vascular endothelium and cardiac tissue has rendered clinical interest in cardiovascular outcomes. Recent publications showed cardiovascular benefit of GLP-1 and GIP receptor agonists in patients with and without diabetes.

In the SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) trial, patients assigned to the semaglutide group had a lower composite incidence of death due to cardiovascular events, nonfatal myocardial infarction, and nonfatal stroke compared to the placebo group.[14] The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial enrolled patients with diabetes and high cardiovascular risk to receive liraglutide versus placebo. At 3.8 years, the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke was significantly lower in the liraglutide group compared with placebo.[15]

The SUMMIT (A Study of Tirzepatide (LY3298176) in Participants With Heart Failure) trial analyzed the impact of tirzepatide in patients with heart failure and reduced ejection fraction and a BMI of 30 kg/m^2 or more. At the end of 52 weeks, there was a 38% lower incidence of heart failure hospitalizations, need for treatment intensification, and lower mortality due to cardiovascular causes. Notably, 50% of the patients had a diagnosis of T2DM prior to randomization.[16]

METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

Dual agonists have been shown to be effective in preventing progression of metabolic dysfunction-associated steatohepatitis (MASH). In the SYNERGY-MASH trial, 152 patients with biopsy-proven MASH and moderate-to-severe fibrosis received tirzepatide at 5, 10 and 15 mg or placebo. The rate of steatohepatitis resolution with no worsening fibrosis ranged between 44% and 62%.[17]

CONTRACEPTION CONSIDERATIONS

Because of the gastric emptying delay with dual agonists, there is potential interference in absorption, decreased bioavailability, and failure of therapeutic effect of combined oral contraception (COC).

A systematic review including six studies analyzed the pharmacokinetics of COC in patients receiving GLP-1 or dual agonists (semaglutide, liraglutide, dulaglutide, and tirzepatide). Tirzepatide was found to have a clinically significant decrease in progestins and ethynyl estradiol area under the curve.[18]

In another systematic review, five studies tested the effect of GLP-1 receptor agonists on pharmacokinetics of COC and found a delayed time to maximal plasma concentration and decreased plasma maximal concentration of both ethynyl estradiol and progestins. However, the bioequivalence was found to be unchanged, hence the authors concluded that the impact was non-clinically significant.[19]

These mixed results are yet to be clarified; however, clinicians should discuss the potential decreased contraceptive efficacy of COC and educate patients regarding alternative options, if feasible. Currently, drug manufacturers advise to switch to a nonhormonal contraceptive method or adding a barrier contraceptive method for 4 weeks after initiation of tirzepatide and for 4 weeks after any dose escalation.[20]

Currently, GLP-1 and GIP receptor agonists are contraindicated during pregnancy due to potential teratogenesis and pregnancy loss based on animal studies. Studies in humans, however, have not demonstrated a significantly higher incidence of fetal malformations, pregnancy loss, or pregnancy termination in women exposed to GLP-1 and GIP receptor agonists before or after conception.[21,22]

Although there is no evidence regarding the effects of incretins in pregnancy and teratogenesis, many experts recommend that pregnant women switch to medications that have been proven to be safe during pregnancy, especially for prevention of hyperglycemia in women with diabetes. The current management of obesity during pregnancy endorsed by the American College of Obstetrics and Gynecology includes lifestyle modifications and nutritional assessment.[23]

MANAGEMENT OF SIDE EFFECTS

The side-effects profile of GLP-1 and GIP receptor agonists should be discussed prior to initiating treatment. Due to an increased risk of dyspepsia, nausea, and vomiting, compliance to treatment can be hindered. As many as 50% of patients will report clinically significant nausea. The development of nausea and vomiting is dose-dependent and can be aggravated by other medications such as metformin. Liraglutide appears to have the highest incidence of gastrointestinal side effects. Generally, nausea and vomiting are tolerable, disappear over time, and can be managed with smaller meal portions.[24]

Acute pancreatitis is a dreaded and potentially life-threatening adverse effect, and its incidence has been studied in several retrospective studies. A meta-analysis including 113 studies found that the risk of developing acute pancreatitis was not statistically significant when compared to other treatments.[25] In a large retrospective study, cases of acute pancreatitis linked to hypoglycemic agents were found to have a strong correlation with the use of GLP-1 receptor agonists and dipeptidyl-peptidase IV inhibitors.[26] For patients with a prior history of pancreatitis due to other etiologies (cholelithiasis, alcohol, trauma, hypertriglyceridemia, etc), GLP-1 and GIP receptor agonists may be prescribed on a case-by-case basis once the etiology of pancreatitis has been treated. Patients should be educated about stopping the medication and seeking medical care if symptoms of pancreatitis arise.

A large meta-analysis assessed the risk for biliary diseases after starting GLP-1 receptor agonists and found that patients have a 1.27- and 1.36-times higher risk of developing cholelithiasis and cholecystitis, respectively. Higher doses and prolonged duration of treatment increase the risk of developing biliary tract diseases.[27]

Diabetic retinopathy has been a controversial topic surrounding GLP-1 receptor agonists. The SUSTAIN-6 (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) trial showed a higher incidence of vitreal hemorrhage and blindness in patients receiving semaglutide. Diabetic retinopathy was thought to be a drug-specific adverse event with semaglutide since trials with other GLP-1 receptor agonists formulations did not see similar impact. However, a retrospective analysis found no difference in the incidence and progression of diabetic retinopathy in patients taking either GLP-1 receptor agonists or SGLT2 inhibitors for diabetes.[28] Patients with diabetes should follow up with an ophthalmologist at least once yearly for screening of diabetic retinopathy.

GLP-1 receptor agonists have been shown to cause increased resting heart rate, potentially due to its stimulating action on the sinoatrial node. Yet, less than 5% of patients using a GLP-1 receptor agonist will see a higher resting heart rate, and less than 2% of patients will need additional measures for managing tachycardia and palpitations. Although generally tolerable, few patients have reported the need to stop GLP-1 receptor agonists due to tachycardia refractory to beta blockers.

NON–INCRETIN-BASED THERAPIES

While incretin-based therapies have thrust obesity focused pharmacotherapy into the spotlight, other non–incretin-based therapies are available for the treatment of obesity (Table 2). Such therapies include anything from the amphetamine phentermine, which has been approved as a short-term antiobesity medication since 1959, to the more recently approved hydrogel capsules. However, while there

DRUG NAME	INDICATIONS	PRIMARY MECHANISM	MEAN WEIGHT LOSS	SIDE EFFECTS	CONTRAINDICATIONS	SPECIAL CONSIDERATIONS	PRICING OPTIONS
Orlistat[3] (*Xenical*/*Alli*) Approved 1999 and 2007 OTC	Indicated in patients with BMI ≥ 30 kg/m^2, or in patients with a BMI ≥ 27 kg/m^2 and at least one weight-related comorbidity in conjunction with diet and physical activity. Also indicated to reduce the risk for weight regain after prior weight loss	Gastrointestinal lipase inhibitor, prevents absorption of ~30% of ingested fat	10.2%	Oily fecal spotting (27%), flatus with discharge (24%), fecal urgency (22%), steatorrhea (20%), oily discharge (12%), increased defecation (11%)	Chronic malabsorption, cholestasis	May cause malabsorption of other medications	**$$$** Pharmacy coupon available **$** Lower cost over-the-counter option available (Alli) however is half the dose of Xenical with less efficacy
Phentermine (*Adipex-P*)/ Sympathomimetic amines[3] Approved 1959	Short-term adjunct for weight reduction in patients age ≥ 16 with initial body mass index ≥ 30 kg/m^2, or ≥ 27 kg/m^2 in the presence of other risk factors	Catecholamine release in the hypothalamus	6.1%	Xerostomia (12%), insomnia (11%), headache (10%)	History of CAD, w/in 14 days of MAOIs, glaucoma, agitated states, substance use disorder	Avoid in CAD, hyperthyroidism, hypertension, seizure	**$** Pharmacy coupon available
Phenteremine Topiramate ER[3] (*Qsymia*) Approved 2012	Indicated in patients with BMI ≥ 30 kg/m^2, or in patients with a BMI ≥ 27 kg/m^2 and at least one weight-related comorbidity in conjunction with diet and physical activity	Phentermine: see above Topiramate: GABA augmentation	10.9%	Paresthesia (20%), xerostomia (19%), constipation (16%), headache (11%	Same contraindications as phentermine alone in addition to history of CVD (CAD, stroke, arrhythmias, CHF, uncontrolled hypertension)	Avoid in glaucoma and hyperthyroidism Monitor for increased HR, suicidal behavior/ideation, mood/sleep disturbance, cognitive impairment, metabolic acidosis, elevated creatinine, and low blood sugars in in patients on anti-diabetes medication	**$$** Pharmacy coupon available 12-week supply available direct to consumer for reduced price Can be prescribed as two separate medications for a more cost-effective option
Naltrexone Buproprion ER[3] (*Contrave*) Approved 2014	Chronic obesity management in patients ≥ 18 with a BMI ≥ 30 kg/m^2 OR BMI ≥ 27 kg/m^2 with at least one weight-related comorbidity	Bupropion: aminoketone antidepressant; POMC neuron stimulation Naltrexone: opioid antagonist	6.1%	Nausea (33%), constipation (19%), headache (18%), vomiting (11%), dizziness (10%)	Uncontrolled hypertension, seizure disorders, drug/ alcohol withdrawal	Monitor for suicidal ideation	**$$$** No generic alternatives available direct to consumer for reduced price Can be prescribed as two separate medications for a more cost effective option
Gelesis100 [32] (*Plenity*, *Gelesis*) Approved 2019	Overweight and obese adults with a BMI of 25-40 kg/m^2, when used in conjunction with diet and exercise	Cellulose-citric acid which expands to occupy 25% of stomach volume	6.4%	Diarrhea (12.6%), abdominal distention (11.7%), infrequent bowel movements (9.4%) and flatulence (8.5%)	Esophageal anatomic anomalies, and complications from prior gastrointestinal (GI) surgery that could affect GI transit and motility	Use with caution in patients with active gastrointestinal conditions such as gastro-esophageal reflux disease, ulcers, or heartburn May cause malabsorption of concomitantly taken medications	**$$** Pharmacy coupon available No generic options available

Table 2 Non-incretin-based therapies. All above obesity medications are contraindicated in pregnancy and are best avoided in women who are pregnant, trying to become pregnant, or are breastfeeding. POMC: pro-opiomelanocortin; MAOIs: monoamine oxidase inhibitors; CVD: cardiovascular disease; CAD: coronary artery disease; CHF: congestive heart failure; BMI: body mass index; HR: heart rate; MAOI: monoamino oxidase inhibitors; GABA: gamma aminobutyric acid

*Insurance coverage of individual medications will depend upon individual plan.

DRUG CLASS	INTERVENTION	MEAN WEIGHT LOSS*	SIDE EFFECTS*	TRIAL
GLP-1 / GIP / GCGR agonist	Retatrutide, 1 to 12 mg once weekly for 26 weeks.	17.5%	Nausea (27%), decreased appetite (18%), diarrhea (13%), vomiting (10%), constipation (9%)	NCT04881760
Melanocortin-4 receptor agonist	Setmelanotide 1 to 3 mg once daily for 16 weeks.	15% BMI reduction	Nausea (61%), vomiting (33%), skin hyperpigmentation (33%), diarrhea (22%), abdominal pain (17%)	NCT04725240
Non-peptide oral GLP-1 receptor agonist	Orforglipron 12 to 45 mg daily for 26 weeks.	12.6%	Nausea (42%), vomiting (29%), constipation (19%), diarrhea (16%), GERD (13%)	NCT05051579
Long-acting amylin receptor agonist	Cagrilintide 0.3 to 4.5 mg weekly for 26 weeks.	10.8%	Nausea (47%), constipation (21%) fatigue (20%), injection-site erythema (17%), vomiting (8%)	NCT03856047
Activin receptor type 2b monoclonal antibody	Bimagrumab 10 mg/kg every 4 weeks for 48 weeks.	6.5%	Diarrhea (41%), muscle spasms (41%), nausea (11%), lipase elevation (11%), hypertension (8%)	NCT03005288

Table 3 Drugs under investigation for the management of obesity. GCGR: glucagon receptor; GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide 1; BMI: body mass index

*With highest intervention drug dose

DRUG NAME	PHARMACOLOGIC CLASS
Dulaglutide Liraglutide Semaglutide	GLP-1 receptor agonist
Tirzepatide	GLP-1 receptor agonist GLP-1 receptor agonist
Phentermine	Catecholaminergic
Phentermine/Topiramate	Catecholaminergic/GABAergic
Bupropion/Naltrexone	POMC stimulation/Opioid antagonist
Orlistat	Gastrointestinal lipase inhibitor
Setmelanotide	Melanocortin-4 receptor agonist
Retatrutide	GLP-1 / GIP / GCGR agonist
Orforglipron	Non-peptide oral GLP-1 receptor agonist
Cagrilintide	Long-acting amylin receptor agonist
Bimagrumab	Activin receptor type 2b monoclonal antibody

Table 4 Summary of drugs for management of obesity, with mechanism of action. GLP-1: glucagon-like peptide 1; POMC: pro-opiomelanocortin; GIP: glucose-dependent insulinotropic polypeptide; GCGR: glucagon receptor

are a variety of options available, other considerations such as side effect profiles, contraindications, and individual cost must be carefully considered and discussed with patients prior to prescribing. Sympathomimetic oral amines such as phentermine, diethylpropion, benzphetamine, and phendimetrazine are among some of the oldest non-GLP-1 weight-loss medications. These medications act by increasing norepinephrine release and blocking norepinephrine uptake, leading to appetite suppression.[29] Of these, phentermine is one of the most well-known. Individually, sympathomimetic oral amines are only approved for short-term use (12 weeks or less), with weight gain after discontinuation being common regardless of lifestyle changes.[30] Additionally, while approved for the short-term by the FDA, it must be acknowledged that such medications are not addressing the chronic nature of obesity. Alternatively, combination therapy of phentermine hydrochloride (HCL) combined with topiramate extended release (ER) has been approved for safe long-term use in select patients. The combination of phentermine and topiramate has demonstrated an average weight loss of 10% body weight. However, given that it is classified as a schedule IV stimulant, both phentermine and its combination form have a considerable side effect profile that includes headaches, irregular heart rate, overstimulation, tremor, and insomnia.[31] Furthermore, its use is limited by patient population as current guidelines advise against prescribing to patients with a history of cardiovascular disease, agitated states, and even hyperthyroidism.[31] Additionally, while studies have reported no evidence of abuse or psychological dependence when used for obesity, phentermine's categorization as an amphetamine is pertinent; therefore, it is not usually recommended in patients with a history of drug abuse.[31]

Notably, while pregnancy is a contraindication to all anti-obesity medications, it should be noted that sympathomimetic amines and their combination forms are categorized as pregnancy category X.[31] As such, patients should use reliable contraception and undergo pregnancy testing before initiation and monthly following initiation of

treatment.[8] Finally, patients should have frequent progress check-ins with their provider to track progress. Despite being approved for long-term use, if no significant weight loss (< 5%) has been achieved after 12 to 16 weeks at maximum tolerated dose, therapy should be discontinued and alternative treatment options considered.[31]

Orlistat, which is a pancreatic lipase inhibitor that acts by preventing triglycerides from being hydrolyzed in the gut, is not appreciably absorbed systemically and is therefore considered a safer option for many patients.[30] While side effects are usually limited to the gastrointestinal system (ie, oily discharge from the rectum, flatus, increased defecation, etc),[31] weight loss is often also limited, ranging from 2.8% to 4.8%.[29] Furthermore, it can also alter the absorption of medications taken concomitantly, such as cyclosporine or levothyroxine, and can result in decreased levels of vitamin D, K and E.[31]

Another potential pharmacotherapy option is the combination medication naltrexone HCL and bupropion HCL ER. The combination of an opioid antagonist and aminoketone antidepressant acts to simultaneously stimulate the hypothalamic proopiomelanocortin neurons while also blocking opioid mediated proopiomelanocortin autoinhibition, therefore reducing reactivity to food cues and improving eating control via the mesolimbic pathway.[29] After completing a dosage ramping process over 4 weeks, patients can lose an average of 5% to 6% body weight. Naltrexone can also be particularly useful in those with comorbid depression or the need for smoking/alcohol use reduction.[30] Side effects are somewhat more mild than phentermine but also include nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea.[31] However, the medication also necessitates additional considerations, such as avoidance in chronic opioid users or in patients who have taken monoamine oxidase inhibitors within the last 14 days.[31] Furthermore, given bupropion's classification as an antidepressant, similar caution to selective serotonin and serotonin norepinephrine reuptake inhibitors must be taken, especially in the context of potential/undiagnosed bipolar disorder. Finally, while officially removed as a contraindication in 2020, prescribing information still recommends discontinuation once the patient is pregnant.[31]

Of the non–incretin-based weight loss options, hydrogel-based therapies may be the most unique. While ingested orally, the hydrogel capsule contains thousands of super absorbent hydrogels that hydrate up to 100 times their original weight once the capsule gets disintegrated disintegrates in the stomach.[31,32] These particles occupy a quarter of the average stomach volume to promote fullness while providing no nutritional value or calories.[31] Given its unique mechanism of action, this product was approved in 2019 as a class II medical device by the FDA.[31] Unfortunately, product data is limited due to its relatively recent approval and new availability concerns given bankruptcy filing by the current manufacturer in 2023.[8]

Other medications have been used off-label for their weight-loss capabilities. The most notable include metformin and SGLT2 inhibitors. Metformin, though approved for use as an adjunct to diet and exercise to improve glycemia in patients with T2DM, can also aid in weight loss by improving insulin sensitivity and reducing hunger. Metformin can also be particularly useful in managing weight gain associated with concurrent medications such as antipsychotics or even insulin use.[31] Alternatively, SGLT2 inhibitors, which are not approved for weight loss alone but have indications that include T2DM, congestive heart failure, and chronic kidney disease, have been referred to as "ketosis in a pill." As such, it promotes moderate weight loss by causing a relative deficiency of insulin and glucose, therefore inducing preferential metabolism of fats/triglycerides.[31] However, while both medications have shown as much as 1 kg to 3 kg weight loss when used in the appropriate patient population, the overwhelming consensus among expert guidelines continues to recommend against using such medications solely for producing weight loss and should therefore only be used in the correct clinical context.[30]

FUTURE PERSPECTIVES

In recent years, other pathways were discovered and have been implicated in the pathogenesis of obesity, providing novel therapeutic targets to treat obesity (Table 3). One of the best characterized alternative pathways is the hypothalamic leptin-melanocortin signaling pathway that plays a key role in regulating appetite, feeding behavior, and energy expenditure (Figure 1). Pro-opiomelanocortin (POMC) and agouti-related peptide (AgRP) play crucial and opposing roles in the hypothalamic leptin-melanocortin signaling pathway. POMC neurons, located in the arcuate nucleus of the hypothalamus, produce α-melanocyte-stimulating hormone (α-MSH),[33] leading to decreased food intake and increased energy expenditure via the melanocortin-4 receptor (MC4R).[33,34] AgRP acts as an inverse agonist of MC4R, inhibiting the anorexigenic effects of α-MSH, and promoting increased food intake and reduced energy expenditure (Table 4).[35]

MELANOCORTIN-4 RECEPTOR AGONISTS

Setmelanotide, an MC4R agonist, is an FDA-approved drug for the chronic treatment of hypothalamic obesity due to POMC, PCSK9, and LEPR deficiencies. It has been shown to

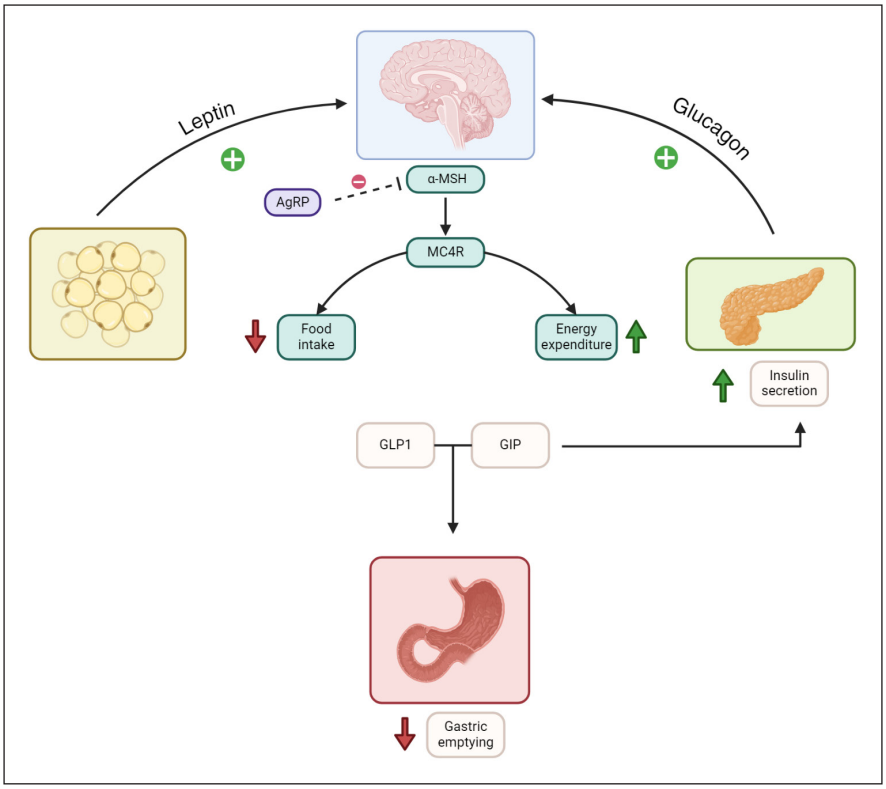

Figure 1 Appetite and energy expenditure regulation in obesity. Leptin, released by the arcuate nucleus neurons in the hypothalamus, induces α-MSH release, which stimulates MC4R, resulting in decreased appetite, increased nonshivering thermogenesis, and energy expenditure. Glucagon activates the leptin-melanocortin pathway. AgRP opposes the leptin-melanocortin pathway. GLP-1 and GIP cause decreased gastric emptying and stimulate insulin secretion. Created in BioRender by Calderon A; (2024) BioRender.com/a11c077.
α-MSH: alpha melanocortin stimulating hormone; AgRP: agouti-related peptide; GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide 1

achieve clinically significant weight loss in patients with hypothalamic obesity as a result of hypothalamic damage in a phase II clinical trial (NCT04725240). Eighteen patients with MRI evidence of hypothalamic damage and obesity (average BMI 38 kg/m^2) received escalating doses of setmelanotide for 16 weeks. The primary end point was reduction in at least 5% BMI from baseline at the end of 16 weeks. At the end of the study, 89% of the patients achieved the primary end point, with an average 15% reduction in BMI. As a secondary outcome, patients were also noted to have reduced appetite based on appetite scale. The most common adverse effects were nausea, vomiting, diarrhea, and skin hyperpigmentation.[36]

Currently, clinical trials are being conducted to assess the safety and efficacy of setmelanotide in patients with non-monogenic or hypothalamic causes of obesity (NCT02041195, NCT01867437, NCT02431442).[37-39]

TRIPLE RECEPTOR AGONISTS

Preclinical and human studies have shown that glucagon receptor (GcGR) activation promotes weight loss by increasing energy expenditure and non-shivering thermogenesis, exerting its action in the brown adipose tissue via the intracellular cyclic AMP (cAMP) pathway.[40] Agonism of the GIP receptor prevents weight gain and has shown to cause significant weight loss in combination with GLP-1 agonists. Its receptor located in the arcuate nucleus causes a reduction in appetite when stimulated and enhances the leptin-mediated appetite suppression (Figure 1).

Combined targeting of GcGR, GIP, and GLP-1 receptor has been studied with an investigational triagonist called retatrutide in a phase II placebo-controlled clinical trial (NCT04881760). In this trial, 338 adult patients with obesity (mean BMI 37.3 kg/m^2) received retatrutide or placebo for 24 weeks. The primary outcome was to assess percentage change in weight at the end of the treatment. Patients achieved a mean weight loss of 17.5% from baseline at the highest dose of 12 mg and 7.2% at the lowest dose of 1 mg compared to placebo, where the weight loss was 1.2%. Other outcomes registered included reversal of prediabetes, decreased blood pressure, decreased low-density lipoprotein, and a decrease in the number of antihypertensive medications.[41]

NONPEPTIDE GLP-1 RECEPTOR AGONISTS

The GLP-1 receptor is a G-protein coupled receptor that, once stimulated, induces a cAMP intracellular cascade,

responsible for the metabolic effects. However, a parallel pathway—the β-arrestin recruitment—is activated. These multifunctional proteins bind to the phosphorylated receptor and cause internalization and desensitization of the receptor, downregulating its action. A GLP-1 receptor agonist has been designed to act on the receptor with greater effect on the cAMP pathway and less β-arrestin recruitment to extend the sensitivity and survival of the receptor in the cell membrane.[42]

One such drug is orforglipron, which has been studied in a phase II placebo-controlled clinical trial (NCT05051579). Orforglipron was administered to 235 patients with obesity (mean BMI 37.9 kg/m^2) for 36 weeks. The primary outcome was weight-loss percentage at the end of 26 weeks of treatment. At that time, patients taking orforglipron experienced weight loss ranging from 8.6% to 12.6%, with greater reductions observed at higher doses compared with the placebo group.[43]

AMYLIN RECEPTOR AGONISTS

Amylin is a peptide secreted by pancreatic beta cells alongside insulin in response to food intake. Its receptors, located in the brainstem and hypothalamus, promote fullness sensation, slow gastric emptying, and reduced glucagon secretion, leading to lower postprandial glucose levels and increased energy expenditure.[44]

Pranlintide, a short-acting amylin receptor agonist, is used as an adjunct treatment for type 1 and T2DM to reduce postprandial glucose spikes, resulting in better glycemic control and weight loss.[45]

Cagrilintide, a long-acting amylin receptor agonist, was compared with liraglutide in a phase II trial (NCT03856047) with 703 patients. Participants received escalating doses of cagrilintide (0.3 to 4.5 mg weekly) or liraglutide (0.6 to 3 mg daily) for 26 weeks, with the primary outcome being weight change. The average baseline BMI was 37.8 kg/m^2. The cagrilintide group lost a mean 6.0% to 10.8% of weight, while liraglutide and placebo groups lost 9.0% and 3.0%, respectively.[46]

ACTIVIN TYPE 2 RECEPTOR MONOCLONAL ANTIBODY

The activin type 2 receptor is involved in the metabolism of brown adipose tissue and myocytes. Preclinical studies indicated that blocking this receptor improved insulin sensitivity and reduced incidence of metabolic dysfunction-associated steatotic liver disease.[47] This was confirmed in humans who received a single dose of the monoclonal antibody against activin 2 receptor bimagrumab.[48]

In a phase II placebo-controlled trial (NCT03005288) with 75 patients, participants received bimagrumab or a placebo every 4 weeks for 48 weeks. At baseline, the average fat mass was 34.7 kg, and BMI was 32.9 kg/m^2. By the end of the study, the bimagrumab group saw a 20.1% reduction in body fat mass, a 3.6% increase in lean mass, a 9.0 cm reduction in waist circumference, and a 6.5% decrease in body weight.[49]

CONCLUSION

Older non–incretin-based pharmacological options have been FDA approved for treatment of obesity for over 60 years. These drugs primarily work by suppressing appetite, leading to clinically significant weight loss; however, their effect is generally less pronounced compared to newer agents.

Currently, several drugs are being prescribed by primary care doctors, endocrinologists, cardiologists, and gastroenterologists to mitigate the metabolic effects of obesity and provide cardiovascular protection. For more than a decade, the GLP-1 receptor agonists have shown impressive response with both weight reduction outcomes and improved cardiovascular health indices.

The comprehensive understanding of obesity in recent years has led to the development of new drugs with pharmacodynamics focused on energy expenditure and appetite regulation. While awaiting FDA approval of these treatments, clinicians should remain vigilant of the clinical trial results of these future prospects.

KEY POINTS

- Obesity is a growing problem affecting several millions of people and has cardiometabolic effects. Current treatments are effective in weight reduction and have pleiotropic effects that improve cardiovascular health.
- Glucagon-like peptide-1 receptor agonists are currently the most effective pharmacologic strategy for the treatment of obesity.
- Patients on non–incretin-based therapies should be carefully selected and monitored frequently for side effects given the pharmacologic profile of appetite inhibition.
- Medication cost, side effects, and pregnancy considerations should be contemplated prior to initiating pharmacological treatment for obesity.

COMPETING INTERESTS

Dr. Kansara is a site principal investigator for clinical trials sponsored by Medtronic, Eli Lilly, Calcilytix, Endogenex, Arrowhead Pharmaceuticals, and Amolyt Pharma. The other authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

Andres Calderon Valladares, Maria Aguilera Astudillo, and Alexsandra Rojas Drinnon are equal contributors to the manuscript.

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