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Various Allopathic Drugs Used in the Treatment of Obesity

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ABSTRACT :

Obesity is an epidemic and a health threat. Obesity is an epidemic and a public health threat. Medical weight management remains one of the options for the treatment of excess weight and recent advances have resolved how we treat, and more importantly how we will be treating obesity soon. Metreleptin and Setmelanotide are currently indicated for rare obesity syndromes, and 5 other medications (orlistat, phentermine/topiramate, naltrexone/bupropion, liraglutide, semaglutide) are approved for non-syndromic obesity. Tirzepatide is about to be approved, and other drugs, with exciting novel mechanisms of action primarily based on incretins, are currently being investigated in different phases of clinical trials. Most of these compounds act centrally, to reduce appetite and increase satiety, and secondarily, in the gastrointestinal tract to slow gastric emptying. All anti-obesity medications improve metabolic parameters, with variable potency and effects depending on the specific drug. The choice of the anti-obesity medication needs to take into consideration the patient's clinical and biochemical profile, and drug contraindications, as well as expected degree of weight loss and improvements in cardiorenal and metabolic risk. It also remains to be seen whether precision medicine may offer personalized solutions to individuals with obesity, and whether it may represent the future of medical weight management along with the development of novel, very potent, anti-obesity medications currently in the pipeline. [1]

Keywords: Various Allopathic Drugs, Obesity

INTRODUCTION :

Obesity can be defined as a disease in which excess body at has accumulated to an extent that health is adversely affected. Obesity is characterized by weight exceeding 120% of median weight for height. Obesity is now recognized as a chronic or noncommunicable disease. It is caused in most cases simply by an imbalance of energy intake and energy expenditure. [2]Obesity is a major public health threat. It is a pathological condition in with excess body fat. It is being characterized by high cholesterol, fatty acid levels, Insulin desensitization, high blood pressure, and excessive adipose mass accumulation. Currently more than 1 billion adults are overweight and at least 300 millions of them are clinically obese. It is defined by body mass index and further evaluated by both percentage body fat and total body fat. Obesity is a risk to many secondary conditions like cardiovascular disorder, insulin pathological resistance, retinopathy, neuropathy and cancer. Monogenic obesity syndromes are rare and constitute <5% of all obesity cases. Most commonly, obesity is multifactorial, with several factors contributing to the excess weight, including dietary pattern, physical activity, sleep patterns, medications, in addition to genetic, epigenetic, and environmental determinants. Therefore, the treatment of obesity is very challenging, and one size does not fit all. Obesity treatment guidelines agree that the appropriate approach for weight management should be multidisciplinary, including lifestyle modifications, behavioral therapy, pharmacotherapy. Antiobesity medications (AOM) are indicated in individuals with a BMI $\geq$30 kg/m^2 or if $\geq$27 kg/m^2 in the presence of one or more co-morbidities. However, the history of AOM was marked by the failure of several ones after their widespread use in the market, secondary to serious adverse effects, namely cardio-vascular events, suicidality, risk for abuse and dependence and recently cancer. Therefore, the Food Drug Administration (FDA) and European Medicines Agency (EMA) revised their regulatory approval criteria of AOM, highlighting in particular the importance of cardiovascular and central nervous system safety. The aim of our project is to review the pharmacological management of obesity in adults, suggest an algorithm for the treatment approach of excess weight, and describe potential drugs that are currently under investigation. [3]

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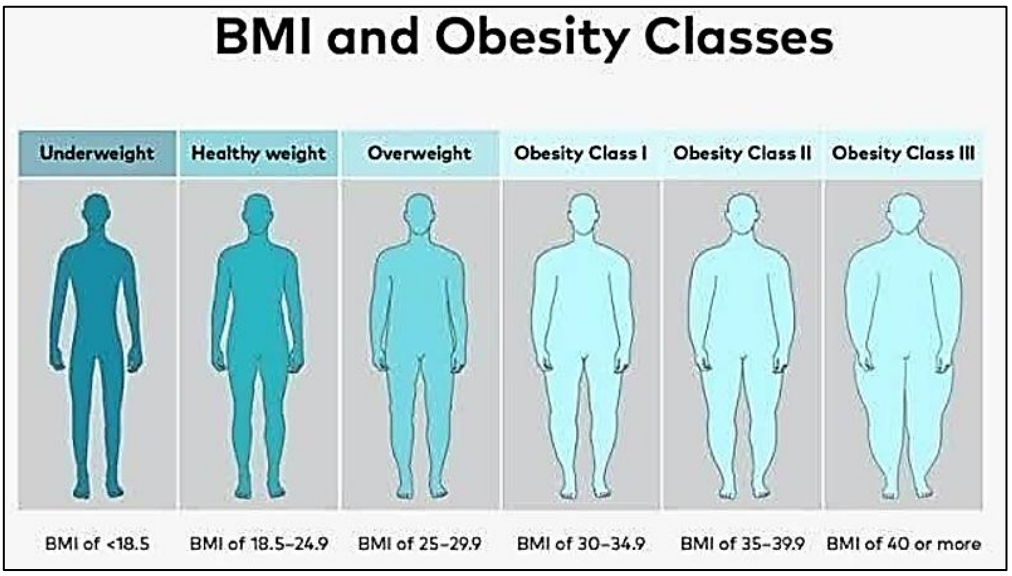
Classification of obesity based on BMI :

BMI	SPECIFICATIONS
< 18.5	Underweight
18.5-24.9	Normal weight
25.0-29.9	Overweight
30.0-34.9	Class 1 obesity (Obese)
35.0-39.9	Class 2 obesity (Severe obesity)
> 40.0	Class 3 obesity (Morbid obesity)
> 40-50	Super obese



Causes of obesity :

1. Lifestyle Factors

➤ Diet

• Eating more calories than the body needs leads to weight gain.

• High consumption of:

-Fast foods, fried foods, and processed snacks.

-Sugary drinks (soda, juices, energy drinks).

• Foods rich in saturated fats and refined carbohydrates.

• Skipping meals or irregular eating patterns can also contribute to overeating later.

➤ Physical Inactivity

• Modern lifestyles involve sitting for long hours (desk jobs, TV, computers, phones).

• Lack of exercise means fewer calories burned, slowing metabolism.

➤ Sleep

• Poor or insufficient sleep disrupts hormones that regulate appetite (ghrelin increases hunger; leptin decreases when sleep-deprived).

• This leads to more cravings, especially for sugary and fatty foods. [5]

2. Depression and anxiety

Depression may be both a cause and a consequence of obesity. Additionally, in a clinical sample of obese adolescents, a higher life-time prevalence of anxiety disorders was reported compared to non-obese controls. A role for heredity is implied by studies in twins and in genetic epidemiology is well documented. [6]

3. Hormones

Ghrelin as human natural hormones are involved in fundamental regulatory process of eating and energy balance. Its properties include increasing appetite.

TNF-α causes deterrence of lipoprotein lipase and stimulates lipolysis in adipocytes and leads to increase of unsaturated fatty acids in the blood which causes increased insulin resistance and diabetes.

Interleukin -6: Interleukin -6 (IL-6) is produced in many cells and some tissues such as adipose tissue and its production is increased in obesity.

Resistin is a cysteine-rich peptide hormone which has 108 amino acids. The level of this hormone is high in diabetic and obese people.

Obesity and the Metabolic Syndrome are distinguished by an increase in circulating leptin concentrations, in parallel to a drop in the levels of adiponectin. [7]

4. Medications

Some prescription medicines cause weight gain as a side effect, such as:

• **Corticosteroids** (used for asthma, arthritis).

• **Antidepressants & antipsychotics** (affect appetite and metabolism).

• **Antiepileptics** (seizure medicines). [8]

5. Other Contributing Factors

• **Age:** As people age, metabolism slows and muscle mass decreases, making weight gain easier.

• **Pregnancy:** Some women retain excess weight gained during pregnancy.

• **Gut microbiota:** Imbalance in gut bacteria may affect how the body stores fat and uses energy. [9]

Complications :

1.Renal disease

Obesity is one of the strongest risk factors for new-onset chronic kidney disease, and also for kidney stones and for kidney cancer.

The mechanisms behind the increased risk of kidney cancers observed in obese individuals include insulin resistance, chronic hyperinsulinemia, and increased production of insulin like growth factor.

2.Cardiovascular disease

A. Hypertension - Due to increased blood volume and resistance.

B. Atherosclerosis-Due to lipid imbalance and hardening of arteries and thus narrowing arteries.

C. Coronary artery disease -Due to plaque buildup in coronary artery.

D. Heart failure -Due to increased cardiac workload.

3.Diabetes

-Risk of type 2 diabetes due to increased body weight.

-Risk of type 2 diabetes is 3-7times higher in obese person than normal adult.

-Raises the risk of insulin resistance.

4.Cancer

Obesity may increase the risk of cancer of-

•Uterus, cervix, ovary

•Breast, gall bladder

•Pancreas, kidney

5.Gall bladder disease

30% individual with morbid (class 3 obesity) refered to surgical intervention have gallstones. [10]

Mechanism of Action :

Obesity contributes to complex cycle of metabolic & cardiovascular dysfunction. Now, antiobesity drugs intervene to break this cycle. In obesity, there is excess of visceral adipose tissue & abnormal secretion of adipokines & inflammatory mediators. Tumor necrosis factoralpha (TNF-α) & interleukin-6 (IL-6) are secreted at elevated level & adiponectin (a protective hormone which improves insulin sensitivity) is reduced. This leads to development of insulin resistance & it is central mechanism linking obesity to metabolic disease. Insulin resistance promotes production of reactive oxygen species (ROS) which increase oxidative stress. It also stimulates the liver to produce C-reactive protein (CRP), a key inflammatory marker; leads to endothelial dysfunction characterized by increased levels of adhesion molecules such as ICAM-1, which accelerates vascular injury and atherosclerosis.

Obesity drugs act at different points in this pathway to disrupt the harmful cascade. Agents such as GLP-1 receptor agonists, SGLT2 inhibitors, and lifestyle interventions reduce adipose tissue mass, thereby lowering the secretion of proinflammatory cytokines and increasing adiponectin levels. Drugs like thiazolidinediones can directly enhance adiponectin, improving insulin sensitivity, while metformin and GLP-1 receptor agonists also help reduce oxidative stress and systemic inflammation. Statins and other anti-inflammatory agents decrease CRP levels, thereby improving vascular health, and in turn ameliorating endothelial dysfunction.

Through these mechanisms, pharmacologic interventions address both the upstream drivers, such as excessive fat accumulation and inflammation, and the downstream consequences, such as insulin resistance, oxidative stress, and cardiovascular dysfunction, breaking the vicious cycle linking obesity to chronic metabolic and vascular disease. [11]

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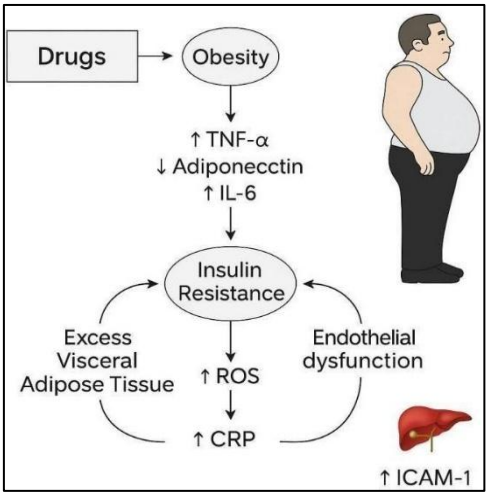
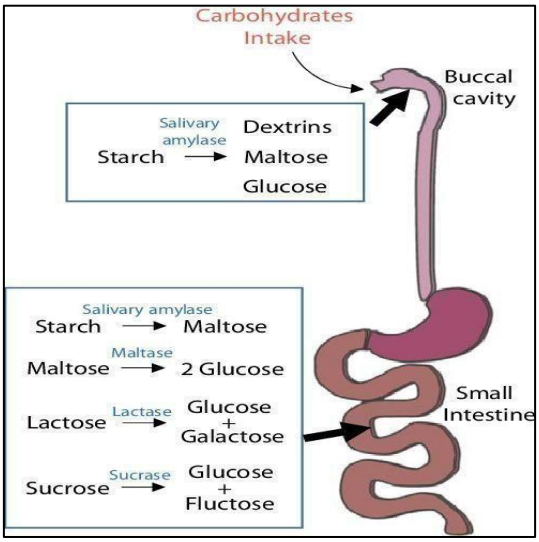


Carbohydrate digestion and absorption :

In humans, between 40% and 80% of total caloric intake is accounted for by carbohydrates in their various forms, making them the most important energy source. According to their chemical structure carbohydrates can be classified into absorbable (undigested), digestible, fermentable and non-fermentable forms. Absorbable carbohydrates (Monosaccharides, comprising a single unit such as glucose, galactose, fructose, xylose and ribose) by definition do not need to be digested in order to be transported into the body. However, once a carbohydrate comprises two or more units, it has to be enzymatically digested for it to be absorbed. In the human diet, the main digestible carbohydrates comprise disaccharides such as sucrose (sugar) and lactose, and larger polysaccharides such as starch which constitute a main source of calories in most Western diets. In contrast, fermentable carbohydrates cannot be digested as enzymes cannot readily break the inter saccharide bonds. However, once in the colon these carbohydrates are readily metabolized by colonic bacteria through the process of fermentation. Similarly, if digestible carbohydrates such as sucrose and lactose are maldigested or malabsorbed, they will also be fermented in the large intestine.

The digestion of carbohydrates begins in the mouth by the action of salivary α-amylase, which hydrolyzes the α-1,4 bonds in starch, the products of this process are maltose, maltriose, and small dextrins. The starch digestion process continues in the small intestine by the action of pancreatic α-amylase. The digestion process is completed by enzymes in the brush border of the small intestine (maltase, sucrase, and lactase, also known as disaccharidases or αglucosidases) which yields the absorbable monosaccharides glucose, fructose, and galactose. A small proportion of monosaccharides can be absorbed passively; however, a carrier protein is required to absorb the amount ingested in a normal diet. [12]



Acarbose

Introduction

Acarbose is an oral α-glucosidase inhibitor used primarily for type 2 diabetes. It delays intestinal carbohydrate digestion, blunting post-prandial glycemia without directly stimulating insulin secretion. Because post-prandial insulin excursions and caloric uptake are attenuated, acarbose has also been explored for weight management and cardiometabolic risk reduction. [13]

Mechanisms relevant to obesity/weight reduction:

1. **Reduced carbohydrate absorption and caloric uptake:**

By competitively and reversibly inhibiting pancreatic α-amylase and brush-border αglucosidases (sucrase, maltase, isomaltase), acarbose slows conversion of complex carbs to absorbable monosaccharides, thereby decreasing post-prandial glucose and insulin spikes and modestly reducing effective caloric intake.

2. **Incretin (GLP-1/GLP-2) signaling:**

Delayed carbohydrate digestion delivers substrates distally, promoting L-cell hormone release; human studies have shown increased post-prandial GLP-2 (and reports of GLP-1 augmentation), which may contribute to satiety and slower gastric emptying.

3. **Lower insulin exposure:**

By reducing post-prandial glycemia, acarbose lessens compensatory hyperinsulinemia; unlike sulfonylureas, it does not augment insulin secretion and can attenuate the insulinotropic/weight-increasing effects of sulfonylureas when combined. [14]

Pharmacological actions (metabolic/cardiometabolic):

Glycemic control: Lowers post-prandial glucose and HbA1c as mono- or add-on therapy.

Weight: Meta-analyses and comparative trials generally show small, favorable weight changes (≈0.5–1.2 kg vs control or DPP-4 inhibitors), with heterogeneity across studies/populations.

Pre-diabetes: In impaired glucose tolerance, acarbose reduced progression to diabetes (STOPNIDDM). Weight effects in these trials were modest.

Vascular surrogates: In IGT, slowed carotid intima-media thickness progression has been reported (mechanistic relevance to post-prandial spikes). [15]

Pharmacokinetics:

Absorption: <2% of the dose is systemically absorbed as active drug; ~35% of total radioactivity (metabolites) is absorbed. Peak active-drug levels ≈1 h; metabolite radioactivity peaks 14–24 h.

Metabolism: Occurs almost entirely within the gut by intestinal bacteria and digestive enzymes; ≥13 metabolites identified (major 4-methylpyrogallol conjugates).

Excretion: ~51% of dose recovered in feces; the small absorbed fraction is renally excreted. Active-drug t½ ≈2 h; negligible accumulation with TID dosing.

Special populations: Severe renal impairment (CrCl <25 mL/min/1.73 m²) yields ~5–6× higher exposure—use not recommended. Elderly show ~1.5× higher exposure (not statistically significant). [16]

Drug interactions (clinically relevant):

Sulfonylureas/insulin: Increased risk of hypoglycemia when combined; treat hypoglycemia with *oral glucose (dextrose)*—sucrose correction is delayed because its hydrolysis is inhibited.

Digoxin: Decreases digoxin exposure (AUC ~-16%, Cmax ~-26% on average); monitor and adjust digoxin dose as needed. Case reports/PK studies corroborate reduced absorption.

Digestive enzymes / intestinal adsorbents: Concomitant amylase/pancreatin products or charcoal can reduce acarbose's effect; stagger or avoid.

Hyperglycemia-inducing drugs: Thiazides, corticosteroids, thyroid products, estrogens/oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, some calcium-channel blockers, isoniazid may worsen glycemic control; monitor if added/withdrawn.

Adverse effects and complications:

Common (dose-related, GI): Flatulence, diarrhea, abdominal pain—reflect increased colonic fermentation of undigested carbohydrates; often abate with time/dose titration.

Hepatic: Asymptomatic transaminase elevations (dose-related); rare cases of clinically apparent liver injury and fulminant hepatitis reported—monitor AST/ALT every 3 months during the first year, then periodically. Risk higher with >50 mg TID and body weight <60 kg.

Hypoglycemia: Uncommon with acarbose alone; risk increases when combined with insulin secretagogues/insulin (see above).

Rare GI complications: Ileus/subileus and pneumatosis cystoides intestinalis have been reported post-marketing.

Contraindications & cautions:

Contraindications: Diabetic ketoacidosis; cirrhosis; inflammatory bowel disease; colonic ulceration; partial intestinal obstruction or predisposition; chronic intestinal disorders with marked malabsorption; conditions likely to deteriorate with increased intestinal gas; hypersensitivity. Not recommended in significant renal dysfunction (e.g., serum creatinine >2.0 mg/dL).

Pregnancy/lactation: Insufficient human data; insulin preferred in pregnancy for tight control. Trace excretion in rat milk; avoid during nursing per label. [17]

Uses of Acarbose:

1. **Primary Indication Type 2 Diabetes Mellitus (T2DM):** Acarbose is approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. It can be used as monotherapy in patients inadequately controlled with lifestyle measures or in combination with other antidiabetic drugs (e.g., sulfonylureas, metformin, insulin).

2. **Prevention of Diabetes:**

Impaired Glucose Tolerance (IGT) / Prediabetes: Clinical trials (e.g., STOP-NIDDM) have shown acarbose reduces the risk of progression from IGT to overt diabetes. It also demonstrated a reduction in cardiovascular events in this highrisk group. *Clinical positioning:* Considered in patients with prediabetes who have post-prandial glucose excursions.

3. **Weight Management and Obesity:**

Adjunct in obesity and metabolic syndrome: By delaying carbohydrate absorption and blunting insulin surges, acarbose may promote modest weight loss or help prevent weight gain. Several trials and meta-analyses show small reductions in body weight (≈0.5–1.5 kg), especially when combined with lifestyle modification.

Limitation: Not an anti-obesity drug per se; benefits are modest.

4. **Cardiometabolic benefits cardiovascular risk modification:** Beyond glycemic control, acarbose has been linked to reduced risk of myocardial infarction and hypertension in prediabetic and diabetic patients. It may also improve endothelial function and lower triglyceride excursions post-meal.

5. **Other Investigational / Off-label Uses:**

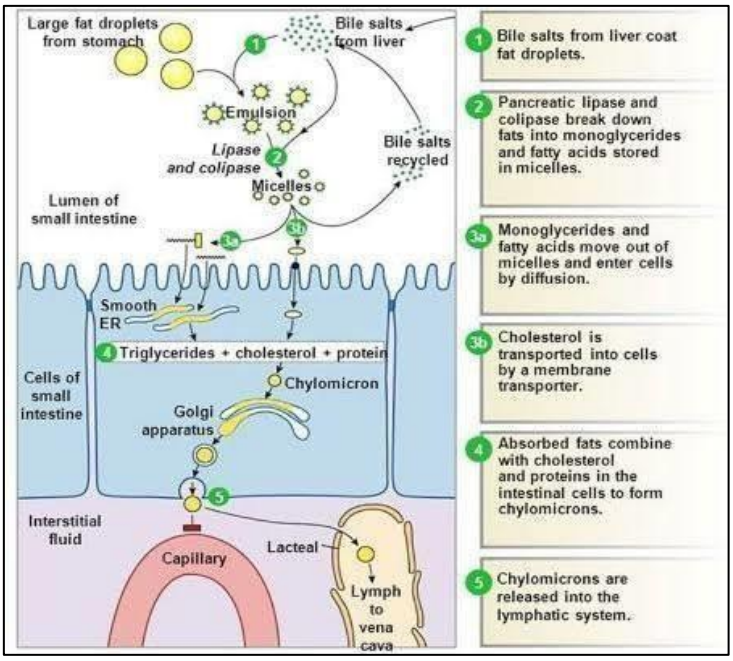
Polycystic Ovary Syndrome (PCOS): Some studies suggest acarbose may improve insulin resistance and ovulatory function in

women with PCOS, though it is not standard therapy. **Non-alcoholic fatty liver disease (NAFLD):** By reducing post-prandial glycemia and hyperinsulinemia, acarbose has been investigated for possible benefits in NAFLD. [18]

Fat digestion and absorption :

Dietary fats are absorbed in the intestine, and they function as an energy supply, thermal regulators, membrane constituents, energy storage and some play an important role in body function as essential fatty acids and fat-soluble vitamins. The human intestine is able to completely absorb approximately 95% of ingested fat. Given the efficient absorption of dietary fat, it is not surprising that long term intake of a high fat diet is readily converted to adipose tissue particularly in those with low levels of physical activity. [19]

The main fat constituents (90%) of a typical Western diet are triacylglycerols or triglycerides (TG). TG consists of a single molecule of glycerol, attached by ester bonds to three fatty acids. TG cannot be absorbed; therefore, intestinal enzymes must hydrolyze the ester bonds on the glycerol backbone in order for the molecule to be absorbed. The products of this hydrolysis are mainly free fatty acids (FFA) and 2-monoglycerides (2-MG) which can be absorbed by the duodenum. In vivo TG hydrolysis is catalyzed by several digestive lipases. There are several human lipases which include the pre-duodenal (lingual and human gastric lipase (HGL)) and the extra-duodenal (pancreatic, hepatic, lipoprotein and endothelial) lipases. Lingual lipase is secreted by a serous gland at the back of the tongue and initiates fat digestion. HGL is secreted by the chief cells of the fundic mucosa of the stomach, this enzyme is active at a broad pH range (3 to 6) and is stable even at the low pH present in the stomach.The acinar cells of the pancreas synthesize and secrete several lipolytic enzymes such ascolipase-dependent lipase, classical pancreatic lipase or triacylglycerol acyl hydrolase (HPL), pancreatic lipase relatedprotein 1 and 2 (HPLRP1, HPLRP2), carboxyl ester hydrolase (also known as bile salt stimulated lipase, carboxyl ester lipase, cholesterol esterase, cholesterol ester lipase, human milk lipase, monoglyceride lipase and pancreatic non-specific lipase) and phospholipase A. [20]



Orlistat

Introduction:

Orlistat is a drug used in the management of obesity. Its mechanism of action is directly related to fat metabolism in the gastrointestinal tract rather than systemic absorption. Normally, dietary fats (mainly triglycerides) must be broken down by the enzyme pancreatic lipase into free fatty acids and monoglycerides before they can be absorbed in the small intestine. Orlistat works by reversibly inhibiting gastric and pancreatic lipases in the lumen of the stomach and small intestine. As a result, about 30% of dietary triglycerides are not hydrolyzed and therefore cannot be absorbed. These unabsorbed fats are then excreted in the feces, reducing caloric intake and promoting weight loss. [21]

Mechanism of action:

Class: Peripherally acting gastro-intestinal lipase inhibitor.

Covalently binds the active serine site of gastric and pancreatic lipases in the gut lumen → prevents hydrolysis of dietary triglycerides → undigested fat isn't absorbed and is excreted in stool. Effect appears in 24–48 h of dosing; returns to baseline 48–72 h after stopping. Fatsoluble vitamin absorption (A, D, E, K, β-carotene) can be reduced.

Pharmacokinetics (ADME):

Absorption: Minimal systemic exposure. Intact is usually <10 ng/mL in plasma, with sporadic detectability; no accumulation.

Distribution: >99% protein bound (mainly to lipoproteins and albumin); negligible partition into erythrocytes. Volume of distribution not meaningfully characterized because absorption is minimal.

Metabolism: Two GI/biliary metabolites: M1 (open β-lactone) and M3 (after side-chain cleavage). They are 1,000× and 2,500× less active than orlistat and considered pharmacologically inconsequential at therapeutic exposures.

Elimination: ~97% of a dose recovered in feces (≈83% unchanged); <2% in urine; complete excretion in 3–5 days. [22]

Drug Interactions:

- **Cyclosporine:** ↓ levels; separate by ≥3 h and monitor levels (OTC label advises to avoid).
- **Levothyroxine:** Reports of hypothyroidism; separate by ≥4 h and monitor TSH.
- **Warfarin/anticoagulants:** Possible ↓ vitamin K absorption → ↑ INR; monitor INR closely.
- **Amiodarone:** ↓ exposure; watch for reduced effect.
- **Antiepileptics:** Seizures reported; monitor control.
- **Antiretrovirals (e.g., atazanavir, lopinavir/ritonavir, TDF/FTC/EFV):** Loss of virologic controlreported; monitor HIV RNA and stop orlistat if viral load increases.
- **Fat-soluble vitamin/analog supplements (e.g., β-carotene, vitamin E acetate):**

Absorption reduced; take multivitamin at a different time.

Adverse Effects:

Very common / GI (dose & fat-intake related): Oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, fecal incontinence, abdominal pain. More likely if meals are high in fat (>30% calories).

Nutritional: ↓ absorption of fat-soluble vitamins; advise multivitamin.

Serious but uncommon/rare: Severe liver injury (hepatocellular necrosis or acute hepatic failure; stop if symptoms like jaundice, pruritus, dark urine, RUQ pain). Oxalate nephrolithiasis/oxalate nephropathy → renal failure (risk higher with CKD, hyperoxaluria, dehydration). Monitor renal function in at-risk patients. Cholelithiasis risk increases with substantial weight loss.

Contraindications:

- **Pregnancy.**
- **Chronic malabsorption syndrome.**

• **Cholestasis.**

• **Hypersensitivity to orlistat or any component.**

• **OTC (Alli®)** "Do not use" also includes: organ transplant (due to interactions with antirejection meds) and if taking cyclosporine. [23]

Uses of Orlistat:

• Obesity management: For weight loss and weight maintenance with a reduced-calorie diet.

• Also reduces risk of weight regain after prior loss.• Indicated for BMI ≥ 30 kg/m², or ≥ 27 kg/m² with risk factors (e.g., hypertension, diabetes, dyslipidemia). [24]

Semaglutide

Introduction:

Semaglutide is a long-acting glucagon-like peptide-1 receptor agonist (GLP-1 RA) developed initially for type 2 diabetes and later approved at higher dose (2.4 mg weekly, brand Wegovy®) for chronic weight management in adults with overweight/obesity (with lifestyle intervention). It mimics endogenous GLP-1 activity with structural modifications that prolong albumin binding and slow DPP-4 degradation, enabling once-weekly dosing. [25]

Mechanism of action:

Semaglutide reduces body weight through several complementary mechanisms:

1. **Central appetite suppression / increased satiety:** Semaglutide activates GLP-1 receptors in hypothalamic and brainstem nuclei (appetite/hedonic centers), lowering hunger and food intake.

2. **Slowed gastric emptying / reduced post-prandial reward:** Delayed gastric emptying increases fullness and reduces meal size and caloric intake, especially early in treatment.

3. **Peripheral metabolic effects:** Improved insulin sensitivity, reduced glucagon secretion, and favorable effects on lipids and cardiometabolic markers contribute to reductions in fat mass and improvements in risk factors.

(These mechanisms explain why semaglutide produces clinically meaningful and sustained weight loss when combined with diet and exercise.) [26]

Pharmacological actions:

STEP programme / pivotal trials: In the STEP-1 trial (adults with overweight/obesity without diabetes), once-weekly subcutaneous semaglutide 2.4 mg produced a mean weight change at 68 weeks of **−14.9%** vs **−2.4%** with placebo (estimated treatment difference −12.4 percentage points). Large proportions achieved ≥5%, ≥10%, and ≥15% weight loss. These results have been reproduced across STEP trials and in adolescents; two-year extension data show maintenance of large weight losses with continued therapy.

Magnitude vs other agents: Semaglutide's magnitude of weight loss (≈15% at 68–104 weeks with continued therapy) is substantially greater than older agents (and much greater than the modest impact seen with acarbose). [27]

Pharmacokinetics:

Formulations & dose: Available as once-weekly subcutaneous injection (Wegovy® for obesity; Ozempic® for diabetes at lower doses) and as an oral tablet formulation (Rybelsus®) for diabetes at lower doses. The obesity indication uses the subcutaneous 2.4 mg weekly regimen after stepwise titration.

Absorption & half-life: For subcutaneous semaglutide the elimination half-life is approximately **145–165 hours (~6–7 days)**,

which supports once-weekly dosing; tmax is generally in the 12–24 h range. Oral semaglutide has very low absolute bioavailability (~0.8%) when dosed under recommended fasting/administration conditions.

Dose adjustments: No routine dose reductions are required for mild–moderate renal or hepatic impairment according to product information, but clinical monitoring is advised. [28]

Drug interactions:

Mechanistic driver: Semaglutide **delays gastric emptying**, which can alter the absorption (Tmax and potentially Cmax) of concomitant oral drugs—particularly those with narrow therapeutic windows or whose effect depends on rapid absorption (e.g., oral contraceptives, some antibiotics, warfarin). Monitor clinical effect or consider timing adjustments for critical oral medications.

Hypoglycemia risk with other glucose-lowering agents: When combined with insulin or insulin secretagogues (sulfonylureas), semaglutide can increase the risk of hypoglycemia; dose reduction of the concomitant agent may be required.

Minimal CYP enzyme interactions: In vitro/clinical data show low potential for semaglutide to be a significant CYP inducer/inhibitor, so classic CYP-mediated interactions are limited; main concern remains absorption changes via slowed gastric emptying.

Adverse effects and complications:

Common adverse effects-

• **Gastrointestinal:** Nausea, vomiting, diarrhea, constipation, and abdominal pain are the most frequent and the major reason for dose titration and discontinuation. These are usually dose-related and lessen with time.

Serious / notable risks-

• **Gallbladder events:** Increased risk of cholelithiasis/cholecystitis has been observed and appears related to the degree of weight loss. Monitor for biliary symptoms.

• **Pancreatitis:** Cases of acute pancreatitis have been reported; causal relationship is not definitively established but clinicians should stop therapy and evaluate if pancreatitis is suspected.

• **Diabetic retinopathy worsening:** Some trials reported progression of diabetic retinopathy in patients with preexisting disease, possibly related to rapid glucose lowering — monitor ophthalmic status in patients with diabetes.

• **Thyroid C-cell tumor boxed warning (rodent data):** Semaglutide carries a contraindication/boxed warning for patients with a personal or family history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia syndrome type 2 (MEN2) because C-cell tumors occurred in rodents; human relevance is unknown. Avoid use in these populations.

• **Acute kidney injury:** Mostly related to severe GI adverse effects with dehydration; monitor renal function in at-risk patients.

Contraindications:

1. **Personal or Family History of Medullary Thyroid Carcinoma (MTC):** Semaglutide carries a boxed warning due to findings of thyroid C-cell tumors in rodent studies. Although the relevance to humans is uncertain, patients with a personal or family history of MTC are at increased theoretical risk and must not receive the drug. Screening for thyroid nodules or history of thyroid malignancy is recommended before initiation.

2. **Multiple Endocrine Neoplasia Syndrome Type 2 (MEN2) :** MEN2 is strongly associated with medullary thyroid carcinoma and pheochromocytoma. Because semaglutide may stimulate C-cells, its use in individuals with MEN2 is contraindicated. These patients are at inherently higher risk of thyroid neoplasia, making semaglutide an unsafe option.

3. **Pregnancy:** Weight loss during pregnancy offers no clinical benefit and may harm fetal development. Animal studies with semaglutide have shown embryofetal toxicity and structural abnormalities at clinically relevant exposures. For this reason, semaglutide should be discontinued at least 2 months before a planned pregnancy due to its long half life.

4. Hypersensitivity to Semaglutide or Excipients: Patients with a history of serious hypersensitivity reactions such as anaphylaxis or angioedema to semaglutide or its formulation components should not receive the drug. Hypersensitivity reactions, although rare, can be life-threatening. Careful assessment of prior reactions is essential before prescribing. [29]

Uses of Semaglutide:

1. Approved indications

2. Type 2 Diabetes Mellitus (T2DM):

• Subcutaneous semaglutide (Ozempic®, once-weekly) and oral semaglutide (Rybelsus®, once-daily) are approved to improve glycemic control in adults with T2DM, as monotherapy (when metformin is unsuitable) or in combination with other agents.

• Benefits: strong HbA1c reduction (~1–1.5%), weight reduction, and low risk of hypoglycemia (unless combined with sulfonylurea/insulin).

3. Chronic Weight Management (Obesity):

• At higher doses (2.4 mg weekly, Wegovy®), semaglutide is approved for adults with obesity (BMI ≥30) or overweight (BMI ≥27 with at least one weight-related comorbidity) as an adjunct to diet and exercise.

• STEP clinical trials demonstrate clinically meaningful weight loss (~12–16% of baseline body weight).

4. Cardiovascular risk reduction

• In adults with T2DM and established cardiovascular disease, semaglutide reduces the risk of major adverse cardiovascular events (MACE: CV death, nonfatal myocardial infarction, nonfatal stroke).

• This benefit is included as an indication for some formulations (e.g., Ozempic®).

5. Investigational / off-label uses

• Adolescents with obesity: Recent STEP TEENS trial showed significant weight reduction; semaglutide has FDA approval for obesity management in adolescents ≥12 years.

• Non-alcoholic fatty liver disease (NAFLD) / NASH: Emerging evidence suggests semaglutide improves liver enzymes, reduces steatosis, and may promote NASH resolution.

• Polycystic Ovary Syndrome (PCOS): Early studies suggest benefits on weight and insulin resistance, though not yet standard therapy.

• Cardiorenal protection: Ongoing trials are investigating kidney outcomes (slowing CKD progression) and further CV prevention in high-risk populations. [30]

Liraglutide

Introduction:

Liraglutide is a synthetic glucagon-like peptide-1 (GLP-1) receptor agonist used in the management of type 2 diabetes mellitus and obesity. It is a long-acting analog of the natural incretin hormone GLP-1, which regulates blood glucose levels by enhancing glucosedependent insulin secretion, delaying gastric emptying, and reducing appetite. It is administered as a once-daily subcutaneous injection and has a structural modification (addition of a fatty acid chain) that prolongs its half-life by enabling binding to albumin and resisting degradation by dipeptidyl peptidase-4 (DPP-4). [31]

Brand names: Victoza® (for type 2 diabetes), Saxenda® (for obesity management).

Mechanism of Action of Liraglutide:

Liraglutide is a GLP-1 receptor agonist (incretin mimetic). It works by binding to and activating GLP-1 receptors in the pancreas, brain, gastrointestinal tract, and cardiovascular system, thereby mimicking the natural incretin hormone GLP-1 (glucagon-like peptide-1).

Stepwise Mechanism-

1. At the Pancreas:

β-cells (insulin-secreting): Stimulates glucose-dependent insulin secretion → lowers blood glucose without causing hypoglycemia.

α-cells (glucagon-secreting): Inhibits glucagon secretion, especially in the postprandial state

→ reduces hepatic glucose production.

β-cell protection: Promotes survival, proliferation, and reduces apoptosis of β-cells.

2. At the Gastrointestinal Tract:

Delays gastric emptying → slows nutrient absorption and reduces postprandial glucose spikes.

3. At the Brain (Hypothalamus):

Increases satiety and reduces appetite → leads to decreased food intake and supports weight loss.

Acts on appetite-regulating centers in the arcuate nucleus of the hypothalamus.

4. At the Cardiovascular System:

Improves endothelial function and reduces oxidative stress. Lowers systolic blood pressure and may reduce risk of major adverse cardiovascular events (MACE). [32]

Pharmacological Actions:

Liraglutide is a GLP-1 receptor agonist that mimics the effects of the natural incretin hormone glucagon-like peptide-1 (GLP-1). Its pharmacological actions are mainly on the endocrine, gastrointestinal, cardiovascular, and central nervous systems.

1. Endocrine (Pancreatic actions): Stimulates insulin secretion → increases glucose dependent insulin release from pancreatic β-cells. Suppresses glucagon secretion

→ reduces hepatic glucose output, especially in the postprandial state. Preserves β-cell function → promotes proliferation and reduces apoptosis of pancreatic β-cells (long-term benefit).

2. Metabolic Actions: Lowers fasting and postprandial blood glucose → improves glycemic control. Promotes weight loss by reducing appetite and food intake. Improves insulin sensitivity indirectly through weight reduction and improved metabolic profile.

3. Gastrointestinal Action: Delays gastric emptying → slows glucose absorption, blunting postprandial glucose rise. Increases satiety via central appetite regulation in the hypothalamus.

4. Cardiovascular Actions: Reduces major adverse cardiovascular events (MACE) in patients with type 2 diabetes and high CV risk. Modest reduction in systolic blood pressure. Improves lipid profile slightly (↓ triglycerides, ↓ LDL, ↑ HDL). Possible cardioprotective effect via direct action on GLP-1 receptors in the heart and vessels.

5. Other Actions: Neuroprotective effects (under investigation): GLP-1 receptors in the brain may improve cognition and protect against neurodegeneration. Hepatic effects: Reduces hepatic fat accumulation, beneficial in non-alcoholic fatty liver disease (NAFLD). [33]

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Pharmacokinetics:

Absorption: Administered subcutaneously (SC). Slowly absorbed, with maximum plasma concentration (Tmax) reached in 8–12 hours after injection. Absolute bioavailability: ~55%. Absorption is not significantly affected by injection site (abdomen, thigh, or upper arm).

Distribution: Highly bound to plasma albumin (>98%), due to the fatty acid side chain. This strong binding prolongs circulation time and protects against rapid degradation. Volume of distribution (Vd): ~13 L (small, indicating limited tissue distribution).

Metabolism: Not metabolized by a single organ (like liver or kidney) or specific enzyme. Undergoes endogenous proteolytic degradation into small peptides and amino acids. Resistant to DPP-4 enzyme degradation because of its structural modification.

Elimination: Metabolites are eliminated mainly via urine and feces. Half-life (t½): ~13 hours

→ allows once-daily dosing. No accumulation with daily administration. [34]

Drug Interactions:

Liraglutide has relatively few direct pharmacokinetic interactions, since it is metabolized by general proteolysis (not CYP enzymes). However, its pharmacodynamic effects (like delayed gastric emptying and glucose lowering) can influence other drugs.

1. **Antidiabetic Agents:** Sulfonylureas (e.g., glimepiride, glibenclamide) → Increased risk of hypoglycemia when combined. Insulin → Risk of hypoglycemia may increase; dose adjustment often required. Metformin, SGLT2 inhibitors, DPP-4 inhibitors → Generally safe, additive glycemic effect.

2. **Oral Drugs Affected by Delayed Gastric Emptying:** Liraglutide slows gastric emptying, which may reduce or delay absorption of orally administered drugs. Examples: oral contraceptives, antibiotics, thyroid hormones, warfarin, digoxin. Usually clinically mild, but spacing administration time may be recommended for narrow therapeutic index drugs.

3. **Anticoagulants / Antiplatelets:** Warfarin → Delayed absorption may affect INR monitoring; caution advised. No major pharmacokinetic interaction, but monitor INR closely.

4. **Other Agents:** Drugs requiring rapid GI absorption (e.g., pain medications, antibiotics) may have slower onset of action. Beta-blockers → May mask hypoglycemia symptoms (as with all antidiabetic drugs).

Adverse effect and complications:

1. **Gastrointestinal (most common):** Nausea (very common, dose-dependent), Vomiting, Diarrhea, Constipation, Dyspepsia, Abdominal pain, Bloating, Decreased appetite (can be beneficial in obesity treatment, but sometimes excessive).

2. **Metabolic Effects:** Hypoglycemia → more likely when combined with insulin or sulfonylureas; rare when used alone. Weight loss (usually beneficial, but can be excessive)

3. **Local Reactions:** Injection site reactions → redness, rash, itching, or discomfort

4. **Neurological Effect:** Headache, Dizziness, Fatigue

5. **Serious Adverse Effects (rare but important):**

- Pancreatitis (acute/chronic) → abdominal pain, nausea, vomiting.
- Gallbladder disease → cholelithiasis, cholecystitis.
- Renal impairment → dehydration from vomiting/diarrhea may worsen kidney function.
- Thyroid C-cell tumors (seen in rodents; human risk uncertain but caution in patients with history of medullary thyroid carcinoma or MEN2).

• Hypersensitivity reactions (urticaria, angioedema, anaphylaxis – rare).

6. Cardiovascular Effects: Mild increase in heart rate. Usually beneficial on cardiovascular outcomes, but monitor in patients with tachyarrhythmias.

Contraindications:

1. Absolute Contraindications:

Hypersensitivity to liraglutide or any of its components. Personal or family history of medullary thyroid carcinoma (MTC). Multiple Endocrine Neoplasia syndrome type 2 (MEN2).

2. Relative / Precautions:

• Severe gastrointestinal disorders (e.g., gastroparesis, severe GI disease) → worsens delayed gastric emptying.

• History of pancreatitis → may increase risk of recurrence.

• Severe renal impairment or end-stage renal disease → dehydration from vomiting/diarrhea can worsen kidney function.

• Severe hepatic impairment → caution advised (limited data).

• Pregnancy and breastfeeding → not recommended (animal studies show fetal risk).

• Children/adolescents (<18 years for Victoza®, <12 years for Saxenda® unless specifically approved) → safety not fully established [35]

• **Uses of Liraglutide:**

1. Type 2 Diabetes Mellitus: Improves glycemic control as monotherapy or in combination with: Metformin, Sulfonylureas, Insulin (with dose adjustment to avoid hypoglycemia), Particularly useful in patients who need weight reduction along with glucose control.

2. Obesity / Weight Management:

Approved as Saxenda® for chronic weight management in: Adults with BMI ≥30 kg/m² (obese)

Adults with BMI ≥27 kg/m² (overweight) plus at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes, dyslipidemia).

Helps by reducing appetite, increasing satiety, and lowering food intake.

3. Cardiovascular Protection: Reduces risk of major adverse cardiovascular events (MACE) such as heart attack, stroke, or cardiovascular death in adults with type 2 diabetes and established cardiovascular disease.

4. Other Emerging/Investigational Uses:

Non-alcoholic fatty liver disease (NAFLD) / NASH → improves liver fat and inflammation.

Polycystic ovarian syndrome (PCOS) → studied for weight reduction and metabolic benefits.

Neuroprotection → ongoing research in Alzheimer's and Parkinson's disease. [36]

Tirzepatide

Introduction:

Tirzepatide is a novel medication approved by the US Food and Drug Administration (FDA) for treating type 2 diabetes mellitus (T2DM). This medication also demonstrates efficacy in weight loss, leading to its off-label use for obesity treatment. Tirzepatide is a dual agonist for the glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors. The drug leads to significantly improved glycemic control and weight reduction in patients with T2DM, maximizing benefits similar to GLP-1 medications such as semaglutide. [37]

Mechanism Of Action:

Tirzepatide is a synthetic polypeptide dual agonist for GLP-1 and GIP. Tirzepatide, "twincretin," exhibits distinct characteristics from GLP-1 receptor agonists [38].The medication comprises 39 amino acids and is an analog of the gastric inhibitory polypeptide. Functionally, tirzepatide stimulates insulin release from the pancreas and reduces hyperglycemia. In addition, tirzepatide also increases the levels of adiponectin.

The dual agonism ability decreases hyperglycemia significantly more than GLP-1 agonist agents and reduces the patient's appetite [39]. Among patients without diabetes, administering tirzepatide 5 to 15 mg once weekly for managing obesity led to remarkable reductions in body weight, ranging from 16.5% to 22.4% over 72 weeks. Post hoc analyses of fasting biomarkers indicated that tirzepatide exhibited more significant improvements in markers of insulin sensitivity and β-cell function.

Pharmacokinetics:

Absorption: Tirzepatide has a bioavailability of approximately 80%. The time it takes to reach peak serum levels can range from 8 to 72 hours.

Distribution: The mean steady-state volume of distribution (Vd) of tirzepatide is approximately 10.3 L. Tirzepatide is highly bound to plasma albumin (99%).

Metabolism: When injected, the peptide structure undergoes proteolytic cleavage. In addition, the C20 fatty diacid composition undergoes β-oxidation and amide hydrolysis. Being a modified polypeptide, tirzepatide undergoes metabolism into individual amino acids in various tissues, including the liver. [40]

Elimination: Tirzepatide has a half-life of 5 days, facilitating weekly dosing, and is cleared in urine and feces as metabolites. [41]

Drug Interactions:

1. Patients using other GLP-1 agents, such as semaglutide or liraglutide, should not be prescribed tirzepatide. Patients on insulin therapy can be initiated on tirzepatide therapy and cautiously have the insulin dose decreased to minimize the risk of hypoglycemia.

2. The efficacy of oral hormonal contraceptives is decreased, so patients should be advised to use non-oral contraceptive methods or add a barrier contraceptive for 4 weeks after initiation and each dose escalation with tirzepatide.

3. Tirzepatide delays gastric emptying, impacting the absorption of concurrently administered oral medications. This is particularly significant in those with preexisting delayed gastric emptying, as it can exacerbate these symptoms. Caution is advised when using oral medications dependent on threshold concentrations or with a narrow therapeutic index (TI) and tirzepatide. [42]

Adverse Effects:

1. Gastrointestinal: Decreased appetite is often reported. Nausea and diarrhea may occur in up to 10% of patients, in addition to some infrequent reports of vomiting and acid reflux. Constipation has also been reported in some users.

2. Cardiovascular: Sinus tachycardia is reported but may be blunted by concurrent medication use.

3. Renal: Infrequent cases of acute kidney injury have been reported, likely secondary to dehydration from gastrointestinal losses. These may occur in healthy and preexisting chronic renal disease patients. Monitoring for signs of dehydration is likely to prevent renal injury.

4. Dermatologic: Hypersensitivity reactions have been infrequently reported at the injection site. The prevalence is similar to those reported by patients using GLP-1 agonists. Such events should be discussed with a clinician and may warrant medication discontinuation.

5. Pancreatitis: GLP-1 medications are a known risk factor for acute pancreatitis. The risk level for tirzepatide is similar to GLP-1 agonist medications. Patients should be advised to immediately seek care at the local emergency department if they develop severe abdominal pain on tirzepatide therapy. Asymptomatic elevation of lipase and amylase may be seen in some patients.

6. Hepatobiliary: Reports of cholelithiasis and cholecystitis have occurred in patients on tirzepatide therapy. These adverse effects may be due to the rapid weight loss induced by tirzepatide.

7. Ocular: Patients with preexisting diabetic retinopathy should be advised that symptoms may temporarily worsen if glycemic control quickly improves. Any vision changes should be discussed with a clinician.

8. Endocrine: A small risk of hypoglycemia (dose-dependent) exists. This risk is more significant for insulin therapy patients and those utilizing sulfonylureas. Patients should be advised on the potential symptoms of hypoglycemia. [43]

Contraindication:

Tirzepatide is contraindicated in patients with medullary thyroid cancer. Tirzepatide is also contraindicated in multiple endocrine neoplasia syndrome type-2 (MEN-2). For further information, refer to the boxed warning below. Furthermore, the use is contraindicated in patients with known severe hypersensitivity to tirzepatide or any excipients, as it has been associated with severe hypersensitivity reactions, including anaphylaxis and angioedema. In patients who have experienced angioedema or anaphylaxis due to GLP-1 receptor agonists, it is important to use tirzepatide cautiously.

Box Warning

Thyroid C-cell tumors: Data obtained from animal studies have demonstrated the potential for developing medullary thyroid carcinoma. It is unknown whether this would also occur in humans. Given the theoretical risk, tirzepatide should be avoided in those with a personal or family history of medullary thyroid carcinoma. Patients with a history of MEN-2 should also avoid tirzepatide. Patients with other thyroid cancer-related risk factors should be advised of the theoretical risks. Routine serum calcitonin or thyroid ultrasound monitoring is inconclusive for early detection of medullary thyroid cancer. [44]

Warnings and Precautions

Relative contraindications also exist, such as gallbladder disease or diabetic retinopathy. Tirzepatide is only approved for those with T2DM and should not be used for those with T1DM. Furthermore, tirzepatide does not have approval for other forms of diabetes, like latent autoimmune diabetes in adults.

Uses:

1. Type 2 Diabetes Treatment

• **Blood Sugar Control**: Tirzepatide helps improve glycemic control by enhancing insulin secretion (especially after meals), reducing glucagon (a hormone that raises blood sugar) secretion, and slowing gastric emptying. These actions help stabilize blood sugar levels.

• **HbA1c Reduction**: Clinical studies show that tirzepatide can significantly lower HbA1c levels, which is a marker of long-term blood sugar control.

2. Weight Loss

• **Appetite Regulation**: Tirzepatide helps reduce appetite by mimicking GLP-1 and GIP, both of which promote satiety. This makes it effective for weight loss, particularly in people with obesity or overweight conditions.

• **Body Weight Reduction**: Tirzepatide has shown promising results in clinical trials for reducing body weight in patients, making it a potential option for those with obesity or weight-related metabolic issues.

3. Cardiovascular Benefits (Ongoing Research)

• **Heart Health**: Though still being studied, tirzepatide may offer cardiovascular benefits, such as reducing the risk of heart attacks and strokes in people with type 2 diabetes. This is similar to other GLP-1 receptor agonists that have shown heart protective effects.

4. Improving Insulin Sensitivity

• **Better Insulin Response**: Tirzepatide can improve insulin sensitivity, which may make it beneficial for those with insulin resistance, a common feature in type 2 diabetes.

Appetite Suppressant :

Appetite suppressants are substances that reduce your feeling of hunger or make you feel full more quickly after eating. They are often used as part of a comprehensive weight-loss plan, particularly for individuals with obesity, and are most effective when combined with a reduced-calorie diet and regular exercise.

Appetite suppressants work by influencing the body's complex system of hunger and satiety signals. This system is regulated by a combination of hormones, neurotransmitters, and central nervous system pathways. Most appetite suppressants, particularly prescription medications, target these pathways to either reduce the feeling of hunger or increase the feeling of fullness.

1. Neurotransmitter Modulation (Affecting Brain Chemicals): The brain's hypothalamus is the "appetite control center." It receives and processes signals from the body and then communicates with the rest of the brain to regulate hunger. Many appetite suppressants work by altering the levels of specific neurotransmitters in the hypothalamus:

Norepinephrine: This neurotransmitter is part of the "fight or flight" response. By increasing norepinephrine levels, some drugs can reduce appetite and increase energy expenditure.

Serotonin: Known for regulating mood, serotonin also plays a key role in appetite. Higher serotonin levels can lead to a feeling of satiety (fullness) and can reduce food cravings.

Dopamine: This neurotransmitter is part of the brain's reward system. Some appetite suppressants, like naltrexone-bupropion, work by affecting dopamine pathways to reduce the reward and craving for food.

2. Hormonal Regulation: The gut and fat cells produce hormones that signal the brain about hunger and fullness. Some of the newest and most effective weight-loss medications work by mimicking or influencing these hormones.

3. GLP-1 (Glucagon-like peptide-1): This gut hormone is released after you eat. It signals the brain that you're full, slows down the rate at which food leaves your stomach (gastric emptying), and increases insulin production. By mimicking GLP-1, medications can significantly reduce appetite and lead to substantial weight loss.

4. (Glucose-dependent insulinotropic polypeptide): Another gut hormone, GIP works alongside GLP-1 to regulate blood sugar and energy balance. Newer medications are combining the effects of both GLP-1 and GIP for even more powerful results.

5. Increasing Bulk and Promoting Fullness: Some over the counter or natural supplements work in a more physical way rather than by affecting brain chemistry.

6. High-Fiber Supplements: When consumed with water, certain types of fiber, like glucomannan, absorb liquid and swell in the stomach. This creates a physical sensation of fullness, which can lead you to eat less. [45] [46]

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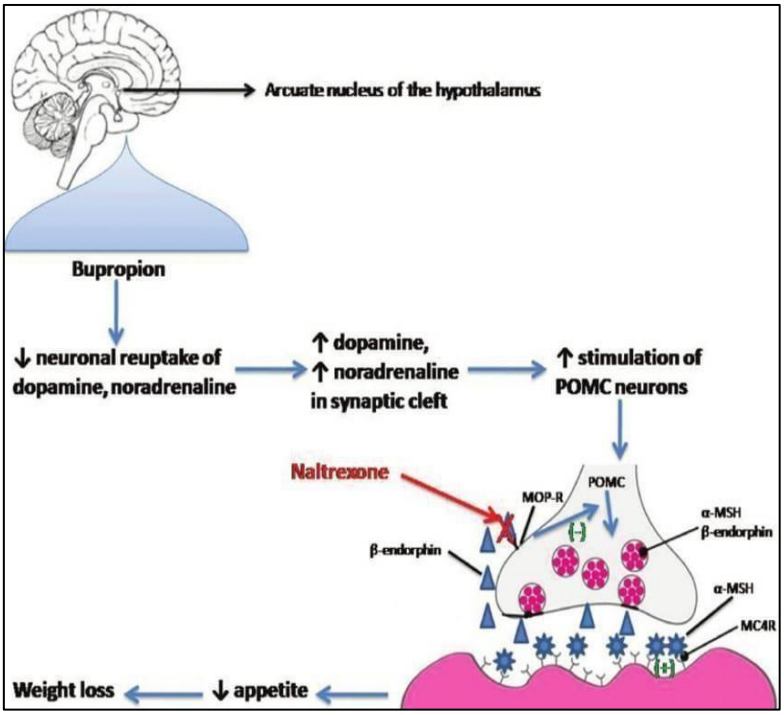

Naltrexone+ Bupropion:

Introduction:

Naltrexone HCl (opioid receptor antagonist) + bupropion HCl (aminoketone antidepressant: norepinephrine–dopamine reuptake inhibitor + nicotinic antagonist properties) — indicated as an adjunct to diet + exercise for chronic weight management in adults with BMI ≥30, or ≥27 with comorbidity. The combination targets reward/craving (mesolimbic) and hypothalamic appetite circuits. [47]

Mechanisms of action:

• Bupropion:

Pharmacology: aminoketone antidepressant; relatively weak inhibitor of neuronal norepinephrine (NET) and dopamine (DAT) reuptake — increases synaptic NE and DA. It also exhibits nicotinic receptor antagonism (relevant to smoking cessation). These central actions can reduce appetite and increase energy expenditure / reward-related behavior changes.

• Naltrexone:

Pharmacology: competitive antagonist at μ-opioid receptors (highest affinity), with weaker κ and δ antagonism. Naltrexone blocks endogenous opioid signaling that contributes to reward/craving (including food reward), and in combination with bupropion it is thought to modulate mesolimbic pathways involved in hedonic eating. Its main active metabolite is 6βnaltrexol.

• Combination (rationale for weight loss):

Preclinical and human data suggest bupropion stimulates pro-opiomelanocortin (POMC) neurons in the hypothalamus (decreasing appetite) while naltrexone blocks an autoinhibitory opioid feedback on those neurons — together producing additive/synergistic reduction in appetite/cravings and effects on reward circuits. The exact mechanism is not fully mapped in humans, but clinical trials showed greater weight loss with the combo vs placebo or either alone. [48]

Pharmacokinetics — ADME:

• Naltrexone:

Absorption: Rapid oral absorption; Tmax typically ~1 hour for naltrexone and its metabolite; oral bioavailability subject to first-pass metabolism (variable). CONTRAVE tablets are extended-release formulation so absorption profile differs from immediate-release naltrexone. Avoid high-fat meals (significantly increases exposure of both components).

Distribution: Large apparent volume of distribution after IV administration ≈ ~1,350 L; plasma protein binding ~~20–21%. This reflects wide tissue distribution.

Metabolism: Hepatic metabolism (major pathway = reduction by cytosolic aldoketoreductases to 6-β-naltrexol, plus conjugation). 6-β-naltrexol is pharmacologically active (weak antagonist) and attains higher plasma levels after oral dosing because of first pass generation.

Elimination / Excretion: Primarily renal excretion of metabolites. Urinary excretion accounts for a large fraction of dose (naltrexone unchanged <2% of oral dose), renal clearances reported in the range ~30–127 mL/min (naltrexone) and ~230–369 mL/min (6βnaltrexol), suggesting glomerular filtration plus active tubular secretion for the metabolite.

• Bupropion:

Absorption: Rapid GI absorption; Tmax depends on formulation: IR ≈ 1–2 h, SR ≈ 3 h, XL ≈ 5 h. CONTRAVE ER tablet is a trilayer extended-release matrix designed to release 8 mg naltrexone / 90 mg bupropion per tablet. High-fat meals ↑ systemic exposure — avoid taking with high-fat meal.

Distribution: Highly distributed; volume of distribution (Vss) large — literature reports ~19 L/kg (m any studies report ~19 L/kg or a range, e.g., 20–47 L/kg), and plasma protein binding ~80–88%. Bupropion and metabolites cross the blood–brain barrier.

Metabolism: Extensive hepatic metabolism; primary pathway CYP2B6 → hydroxybupropion (major active metabolite). Other metabolites: threohydrobupropion, erythrohydrobupropion (via reductive pathways). Hydroxybupropion is pharmacologically active and attains much higher steady-state exposure than parent drug.

Elimination / Excretion: Mostly renal as metabolites; unchanged bupropion excreted in urine is very small (~0.5% of dose). Apparent oral clearance (Cl/F) reported in single-dose studies ~135–209 L/hr (varies by study/formulation); steady-state apparent Cl/F ~160 L/hr in one dataset. [49]

Drug–drug interactions:

Opioids — pharmacodynamic/clinical (naltrexone)

Strong interaction (contraindicated): naltrexone blocks opioid receptors → precipitated opioid withdrawal in opioid-dependent patients and decreased effect of analgesic opioids. Patients on chronic opioids or opioid substitution therapy (e.g., methadone, buprenorphine) must not take CONTRAVE. If intermittent opioids are necessary, CONTRAVE should be stopped and an appropriate opioid-free interval/washout considered; caution on reintroducing opioids after naltrexone because of increased sensitivity/overdose risk.

1. MAOIs

Contraindicated within 14 days before/after MAOI therapy — risks of hypertensive crises and interactions.

2. CYP2B6 inhibitors / inducers (affect bupropion)

Bupropion is primarily metabolized by CYP2B6 to hydroxybupropion. Strong CYP2B6 inhibitors (e.g., ticlopidine, clopidogrel, prasugrel) can increase bupropion exposure and alter metabolite balance; label recommends dose limits (max 2 tablets/day) when given with CYP2B6 inhibitors. CYP2B6 inducers (ritonavir, efavirenz, carbamazepine, rifampicin) may decrease bupropion exposure — may reduce efficacy.

3. CYP2D6 inhibition by bupropion (victim & perpetrator)

Bupropion (and its metabolites) inhibit CYP2D6 — can increase concentrations of CYP2D6 substrates (e.g., metoprolol, certain antidepressants, some antipsychotics, tramadol, tamoxifen etc.). The CONTRAVE label documents a study where it increased metoprolol AUC ~4-fold and Cmax ~2-fold — consider dose adjustment/monitoring for CYP2D6 substrates.

4. Drugs that lower seizure threshold

Concomitant use of drugs that reduce seizure threshold (antipsychotics, other antidepressants, systemic stimulants, theophylline, high-dose systemic steroids, tramadol, quinolones, etc.) increases seizure risk with bupropion — avoid or monitor closely.

Adverse Effect:

1.Naltrexone (opioid antagonist)

• **Main action**: Naltrexone blocks the effects of opioids and can reduce cravings for food or addictive behaviors (like alcohol or drug use).

• **Common side effects**: o**Nausea** o**Headache** o**Dizziness** o**Fatigue** o**Sleep disturbances** o**Anxiety, Liver toxicity** (rare but significant, especially in higher doses)

2.Bupropion (dopamine-norepinephrine reuptake inhibitor)

• **Main action**: Bupropion is an antidepressant that affects the brain's neurotransmitters, particularly dopamine and norepinephrine. It is also used to help with smoking cessation and depression.

• **Common side effects**: o**Insomnia** o**Dry mouth** o**Headache** o**Dizziness** o**Increased sweating** o**Anxiety or agitation** o**Seizures** (a serious risk, particularly at higher doses)

3.Adverse Effects of Combining Naltrexone and Bupropion:

• **Seizures**:

Bupropion increases the risk of seizures, and while the combination is generally considered safe at prescribed doses, there is still concern about the **potential for seizures** due to bupropion's known side effect. Seizure risk may be heightened if there's an overdose or if other factors (like eating disorders or alcohol use) come into play.

• **Mental Health Effects**:

Anxiety, **irritability**, **nervousness**, or even **depression** can occur, particularly with bupropion, which has stimulant-like effects. Naltrexone can sometimes worsen depression or mood changes in certain individuals as well.

• **Liver Function**:

Liver toxicity is a risk with **naltrexone**. Although the risk is generally low at recommended doses, combining naltrexone with bupropion, which also has some metabolic effects, may increase the potential for liver issues, especially in individuals with pre-existing liver conditions.

• **Increased Blood Pressure**:

Bupropion can cause **increased blood pressure** in some people, and this effect might be more pronounced when combined with other medications.

• **Gastrointestinal Issues**:

Nausea and **vomiting** are common side effects with **naltrexone**, and they may be exacerbated by **bupropion**, which can also lead to digestive upset.

• **Sleep Disturbances**:

Both medications can cause **insomnia**, so when used together, they may intensify sleep problems, including difficulty falling asleep or staying asleep.

• **Cardiovascular Effects**:

The combination could potentially cause an **elevated heart rate** or other cardiovascular effects, especially in people with underlying heart conditions.

Contraindications:

CONTRAVE is contraindicated in patients with:

• Uncontrolled hypertension.

• Seizure disorder, or history of seizures; anorexia nervosa or bulimia nervosa (increased seizure risk).

• Concurrent use of other bupropion-containing products (risk of overdose/seizure).

• Chronic opioid use, acute opioid withdrawal, or patients dependent on opioids — because naltrexone will precipitate withdrawal and can make opioid analgesia ineffective. CONTRAVE is contraindicated with opioid analgesics. [50]

Obesity and Weight Management

Approved use: For adults with **obesity** (BMI ≥30), or **Overweight** (BMI ≥27) with weight related conditions like type 2 diabetes, hypertension, or dyslipidemia.

Mechanism of Action in Weight Loss

The combination acts **synergistically** on the **central nervous system** to help control **appetite** and **cravings**:

• Stimulates **POMC neurons** in the hypothalamus → releases **α-MSH**, which promotes **satiety** and reduces appetite.

• **Blocks opioid receptors**, preventing **autoinhibition** of POMC neurons → **enhances and prolongs** bupropion's effect. [51]

Phentermine + Topiramate

Introduction:

Phentermine: A sympathomimetic amine structurally similar to amphetamines. It primarily acts as an appetite suppressant by increasing norepinephrine release in the hypothalamus.

Topiramate: Originally developed as an antiepileptic drug, it also has weight reducing effects via multiple mechanisms including appetite suppression, increased satiety, and altered taste.

Combination rationale: Phentermine acts to suppress appetite; topiramate maintains long-term appetite control and reduces cravings. Together, they produce synergistic weight loss while allowing lower doses of each drug, reducing side effects. [52]

Mechanisms of Action:

Phentermine

• Acts as a CNS stimulant.

• Increases release of norepinephrine (NE), dopamine, and serotonin in the hypothalamus.

• Hypothalamic satiety center stimulation → appetite suppression.

• Increases sympathetic activity → reduced food intake, mild increase in basal metabolic rate.

Topiramate

• Multiple mechanisms:

1. Enhances GABA-A activity → increased inhibitory neurotransmission → decreased appetite signals.
2. Blocks AMPA/kainate glutamate receptors → reduces excitatory signals in appetite regulation.
3. Inhibits carbonic anhydrase → mild metabolic acidosis → reduced appetite.
4. Alters taste perception (makes carbonated drinks taste unpleasant, reduces preference for sweets).

• Net effect: Reduced food intake, increased satiety, and possible energy expenditure increase

Pharmacokinetics (ADME):

Phentermine

• **Absorption:**

o Rapidly absorbed orally. o Peak plasma concentration: 3–4.4 hours after ingestion.

• **Distribution:**

o Volume of distribution (Vd): ~5 L/kg.

o Low protein binding (~17%).

• **Metabolism:**

o Minimal hepatic metabolism. o ~70– 80% excreted unchanged in urine.

• **Excretion:** o Renal elimination (pH-dependent) o Acidic urine increases clearance o Half-life: ~20 hours.

Topiramate

• **Absorption:**

o Oral bioavailability ~80%. o Peak plasma concentration: 2 hours, longer for extended release.

• **Distribution:**

o Volume of distribution: 0.6–0.8 L/kg. o Protein binding: ~15–41%.

• **Metabolism:**

o ~70% excreted unchanged in urine. o Minor hepatic metabolism

• **Excretion**:

o Renal (unchanged drug + metabolites). o Clearance reduced in renal impairment.

oHalf-life: ~21 hours [53]

 Drug Interactions:

• **Phentermine:**

oMAOIs: hypertensive crisis. o Other stimulants: ↑ risk of tachycardia, hypertension.

oSSRIs/SNRIs: risk of serotonin syndrome (rare).

• **Topiramate:** o Oral contraceptives: ↓ effectiveness (at higher doses). o CNS depressants (alcohol, benzodiazepines): additive CNS depression. o Carbonic anhydrase inhibitors (acetazolamide): ↑ risk of kidney stones, metabolic acidosis.

oAntiepileptics (valproate): risk of hyperammonemia, encephalopathy

 Adverse Effects;

Phentermine-related

• Insomnia, restlessness, anxiety.

• Increased heart rate, palpitations, hypertension .

• Dry mouth, constipation.

• Risk of dependence (amphetamine-like structure).

• **Topiramate-related**

• Cognitive dysfunction (“word-finding difficulty,” memory issues).

• Paresthesias (tingling).

• Taste alteration, anorexia.

• Metabolic acidosis, kidney stones (due to carbonic anhydrase inhibition).

• Ocular effects: acute myopia, secondary angle-closure glaucoma.

• Teratogenicity → risk of oral clefts in infants.

• **Combination**

• Dizziness, fatigue.

• Depression, mood changes, suicidal ideation.

• Hypokalemia, metabolic abnormalities.

 Contraindications:

• **Absolute:**

oPregnancy (teratogenic: oral clefts). o Glaucoma. o Hyperthyroidism. o Concurrent use with MAO inhibitors (risk of hypertensive crisis). o Known hypersensitivity to either component.

• **Relative/Precautions:**

oCardiovascular disease (HTN, arrhythmia, CAD).o Psychiatric illness (depression, suicidal ideation, psychosis). o Renal impairment (dose adjust).

oHistory of kidney stones. o Metabolic acidosis [54]

Uses:

• **Primary Indication**: o Chronic weight management in adults with:

▪ BMI ≥30 kg/m² (obese) OR

▪ BMI ≥27 kg/m² (overweight) with at least one comorbidity (HTN, T2DM, dyslipidemia).

• **Other Potential Uses (off-label):**

oAppetite suppression in refractory obesity.

oPossibly adjunct in binge eating disorder (under study). o Not first-line for epilepsy or psychiatric uses (topiramate alone used in epilepsy/migraine) [55]

Conclusion:

Obesity is a complex and multifactorial chronic disease that significantly contributes to global morbidity and mortality through its association with metabolic disorders such as type 2 diabetes, dyslipidemia, hypertension, and cardiovascular diseases. Effective pharmacological management of obesity therefore remains a crucial component of comprehensive weight management strategies. The currently available anti-obesity drugs—such as Orlistat, Liraglutide, Phentermine/Topiramate, Naltrexone/Bupropion, and newer GLP-1 receptor agonists—target distinct physiological pathways that regulate appetite, energy expenditure, and fat metabolism.

Orlistat acts peripherally by inhibiting gastrointestinal lipases and reducing fat absorption, while Liraglutide and other GLP-1 receptor agonists act centrally to enhance satiety, delay gastric emptying, and improve glycemic control. Combination agents like Naltrexone/Bupropion influence hypothalamic reward and appetite pathways, thereby complementing behavioral interventions. Although these drugs have shown clinically meaningful benefits in weight reduction and metabolic improvement, long-term safety, adherence, and cost remain important considerations.

Overall, pharmacotherapy should be used as an adjunct to lifestyle modification, including dietary changes, increased physical activity, and behavioral counseling. Future research should aim to optimize individualized therapy based on genetic, metabolic, and behavioral profiles, while minimizing adverse effects. The advent of next-generation agents—such as dual and triple incretin receptor agonists—holds promise for safer, more effective, and sustained obesity management. A holistic approach integrating pharmacological and nonpharmacological measures remains essential for achieving long-term success in combating the global obesity epidemic.

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