Pharmacological Agents in the Management of Obesity.

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Abstract
Obesity is a chronic, relapsing metabolic disorder characterized by excessive adiposity and dysregulated energy homeostasis. The global increase in obesity prevalence has resulted in a parallel rise in cardiometabolic diseases, creating a substantial public health burden. While lifestyle modification remains the cornerstone of therapy, pharmacological interventions are increasingly recognized as essential adjuncts for long-term weight management. This comprehensive review critically examines approved and emerging pharmacological agents used in the management of obesity, detailing mechanisms of action, clinical efficacy, safety profiles, and future therapeutic prospects.

Keywords
Obesity; Anti-obesity drugs; Pharmacotherapy; GLP-1 receptor agonists; Weight management

Introduction
Obesity has emerged as one of the most challenging public health problems of the twenty-first century. Changes in dietary patterns, reduced physical activity, and increased sedentary behavior have collectively contributed to a sustained positive energy balance in large segments of the population.
The clinical significance of obesity extends beyond excess body weight. It is strongly associated with type 2 diabetes mellitus, cardiovascular disease, musculoskeletal disorders, respiratory complications, and certain malignancies, thereby reducing life expectancy and quality of life.
Although lifestyle interventions remain fundamental to obesity management, their effectiveness is often limited by poor long-term adherence and biological compensatory mechanisms. Pharmacological agents aim to address these limitations by modulating appetite, nutrient absorption, and energy regulation.

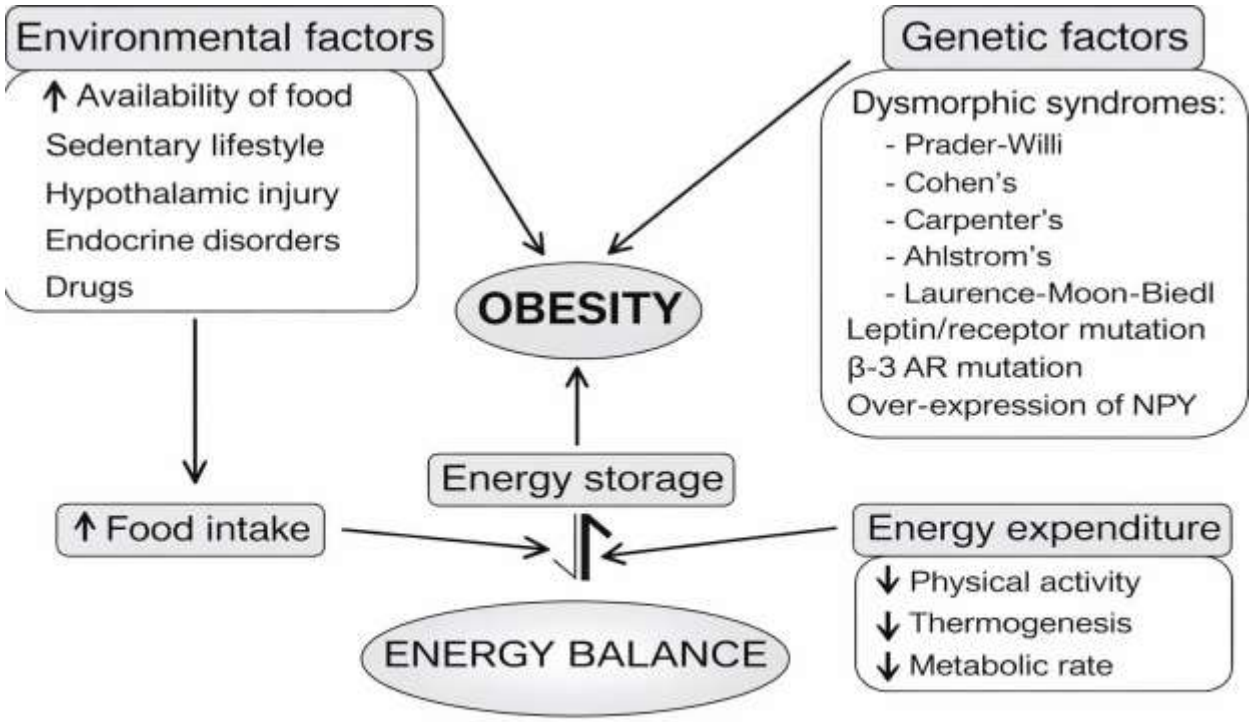

Figure 1: Determinants of energy imbalance leading to obesity

Epidemiology of Obesity:

Obesity is a chronic, relapsing metabolic disorder characterized by excessive accumulation of body fat that negatively affects health. Its prevalence has increased dramatically worldwide, making it a major public health concern. The development of obesity cannot be attributed to a single cause; rather, it arises from a complex interaction between genetic susceptibility, biological mechanisms, lifestyle behaviors, and environmental influences. Understanding the multifactorial etiology of obesity is essential for effective prevention and management strategies.

Genetic Contributions

Genetic factors play a significant role in determining individual susceptibility to obesity. Family and twin studies suggest a strong heritable component, with multiple genes influencing appetite regulation, energy balance, and fat storage. Rare cases of monogenic obesity result from mutations affecting leptin signaling or melanocortin pathways. More commonly, obesity is polygenic, where numerous genetic variants interact with environmental factors to promote weight gain.

Neuroendocrine and Hormonal Mechanisms

The central nervous system, particularly the hypothalamus, plays a crucial role in regulating hunger and satiety. Disruptions in neuroendocrine signaling can lead to increased food intake and reduced energy expenditure. Hormones such as leptin, ghrelin, insulin, and cortisol are key regulators of appetite and metabolism. Leptin resistance, insulin resistance, and elevated cortisol levels contribute to abnormal fat accumulation. Endocrine disorders such as hypothyroidism and Cushing's syndrome are also associated with secondary obesity.

Dietary Factors

Excessive caloric intake is a fundamental contributor to obesity. Modern dietary patterns are often characterized by high consumption of energy-dense foods rich in fats, sugars, and refined carbohydrates. Increased portion sizes, frequent snacking, and consumption of sugar-sweetened beverages further promote positive energy balance. Poor dietary quality, rather than calorie intake alone, also influences metabolic health and fat deposition.

Physical Inactivity

Reduced physical activity is a major behavioral determinant of obesity. Technological advancements and urban lifestyles have led to sedentary behaviors, including prolonged screen time and reduced occupational

physical demands. Inadequate physical activity lowers total energy expenditure, facilitating weight gain when caloric intake remains high.

Environmental and Socioeconomic Influences

Environmental factors strongly shape lifestyle behaviors related to obesity. Easy access to fast food, limited availability of healthy food options, and urban environments that discourage physical activity contribute to obesity risk. Socioeconomic status influences dietary choices, health literacy, and opportunities for physical activity, with higher obesity rates often observed in disadvantaged populations.

Psychological and Behavioral Factors

Psychological conditions such as stress, depression, and anxiety are closely linked to obesity. Emotional eating, binge-eating behaviors, and poor coping mechanisms can lead to excessive caloric intake. Additionally, chronic sleep deprivation alters appetite-regulating hormones, increasing hunger and preference for high-calorie foods.

Medication-Induced Obesity

Several commonly used medications are associated with weight gain. These include corticosteroids, antipsychotics, antidepressants, antiepileptic drugs, and some antidiabetic agents. Such medications may promote obesity by increasing appetite, altering metabolism, or reducing physical activity.

Early-Life and Developmental Factors

Factors acting early in life significantly influence obesity risk later in adulthood. Maternal obesity, gestational diabetes, abnormal birth weight, and rapid weight gain during infancy are associated with long-term metabolic changes. Early feeding practices and childhood lifestyle habits further contribute to obesity development.

Role of Gut Microbiota

Emerging evidence suggests that alterations in gut microbiota composition may affect energy harvest, fat storage, and inflammation. Differences in microbial diversity have been observed between obese and lean individuals, indicating a potential contributory role of intestinal flora in obesity pathogenesis.

Pathophysiology of Obesity

Body weight regulation is controlled by complex interactions between central neural circuits and peripheral hormonal signals. The hypothalamus integrates afferent signals related to hunger, satiety, and energy stores.

Hormones such as leptin, ghrelin, insulin, peptide YY, and glucagon-like peptide-1 play critical roles in maintaining energy homeostasis. Resistance to these signals contributes to persistent weight gain.

Chronic low-grade inflammation associated with obesity further disrupts metabolic regulation and promotes insulin resistance.

Indications for Pharmacotherapy

Pharmacological therapy is recommended for individuals with a body mass index of 30 kg/m² or greater, or 27 kg/m² or greater in the presence of obesity-related comorbidities such as diabetes or hypertension.

Appropriate patient selection requires careful assessment of medical history, previous weight loss attempts, potential contraindications, and patient readiness for long-term treatment.

Classification of Anti-Obesity Drugs

Anti-obesity medications are classified based on their mechanisms of action, including centrally acting appetite suppressants, peripherally acting absorption inhibitors, and hormone-based therapies.

Class	Examples	Primary Mechanism
Centrally acting agents	Phentermine, Bupropion-Naltrexone	Appetite suppression
Peripherally acting agents	Orlistat	Inhibition of fat absorption
Hormone-based therapies	Liraglutide, Semaglutide	Enhanced satiety

Table 1: Classification of anti-obesity drugs

Centrally Acting Agents

Centrally acting drugs modulate neurotransmitter pathways involved in appetite regulation and reward behavior.

While effective in reducing food intake, these agents require cautious use due to potential cardiovascular and

neuropsychiatric adverse effects.

Drug	Mechanism	Common Adverse Effects
Phentermine	Sympathomimetic appetite suppression	Insomnia, tachycardia
Bupropion-Naltrexone	Dopamine-opioid modulation	Nausea, headache

Table 2: Centrally acting anti-obesity drugs

Peripherally Acting Agents

Peripherally acting drugs reduce dietary fat absorption by inhibiting gastrointestinal enzymes.

Drug	Mechanism	Limitations
Orlistat	Pancreatic lipase inhibition	Gastrointestinal intolerance

Table 3: Peripherally acting anti-obesity drugs

GLP-1 Receptor Agonists

GLP-1 receptor agonists enhance satiety, delay gastric emptying, and reduce appetite through incretin pathways.

Clinical trials have demonstrated significant and sustained weight loss with these agents, along with improvements in glycemic control.

Safety and Adverse Effects

The safety profiles of anti-obesity drugs vary according to pharmacological class and mechanism of action.

Long-term monitoring is essential to identify adverse effects early and ensure sustained therapeutic benefit.

Future Directions

Emerging therapies focus on multi-targeted approaches that simultaneously influence appetite regulation and energy expenditure.

Advances in precision medicine may enable individualized pharmacological strategies based on genetic and metabolic characteristics.

Current Anti-Obesity Medications:

Obesity pharmacotherapy has evolved substantially over recent decades, reflecting a deeper understanding of the biological mechanisms that regulate appetite, satiety, and energy balance. A range of medications are now available to support weight management, with several approved by the U.S. Food and Drug Administration (FDA) for chronic obesity treatment. In addition, clinicians sometimes use other drugs off-label to address obesity when approved options are contraindicated or unavailable.

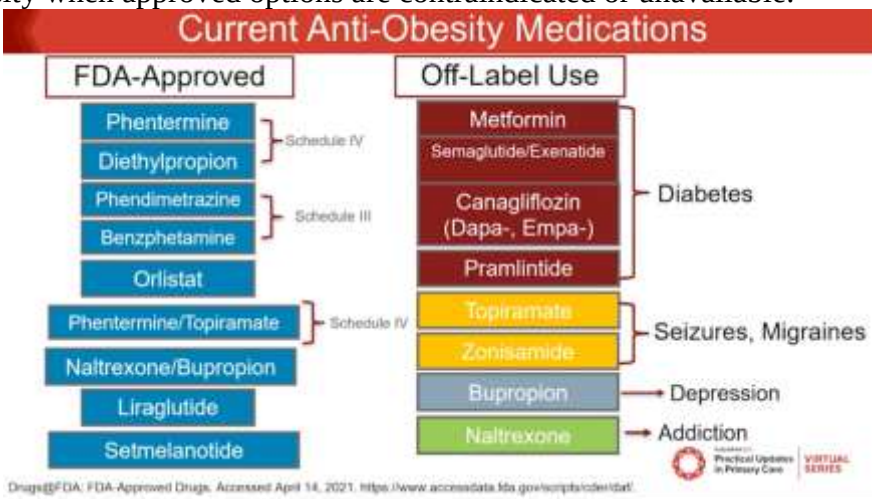

Figure 2: Current Anti-Obesity Medications

FDA-Approved Anti-Obesity Medications

The FDA has sanctioned several medications specifically for long-term management of obesity, typically in conjunction with dietary modification and increased physical activity. Indications generally include adults

with a body mass index (BMI) ≥30 kg/m² or individuals with BMI ≥27 kg/m² and weight-related comorbidities such as type 2 diabetes, hypertension, or dyslipidemia.

1. Semaglutide (Wegovy)

Semaglutide, marketed as Wegovy, is a weekly glucagon-like peptide-1 receptor agonist (GLP-1 RA) that modulates appetite and glycemic control by acting on central and peripheral pathways regulating energy intake. It induces significant weight loss—often in the range of double-digit percentages of baseline body weight—and has demonstrated cardiovascular benefits in some populations.

- Formulations & Indications: An injectable form has long been approved for weight management; an oral tablet form was recently approved by the FDA, expanding administration options.
- Additional Approval: Semaglutide also received April 2025 accelerated approval for treating metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis, underscoring its broader metabolic effects.

2. Tirzepatide (Zepbound)

Tirzepatide is a dual agonist targeting both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors. It has been shown to promote substantial weight loss and improve glycemic parameters, reflecting its enhanced metabolic signaling compared with GLP-1 RA alone. (TechTarget)

3. Liraglutide (Saxenda)

Liraglutide is another GLP-1 RA approved for chronic weight management at a higher daily dose than when used for type 2 diabetes. It exerts its effect by enhancing satiety and reducing caloric intake. (NCBI)

4. Phentermine/Topiramate Extended-Release (Qsymia)

This combination couples a sympathomimetic appetite suppressant (phentermine) with an anticonvulsant (topiramate) to reduce hunger and binge eating behaviors. Its approval marked an important advance in combination pharmacotherapy for obesity. (NCBI)

5. Bupropion/Naltrexone (Contrave)

The bupropion–naltrexone combination targets central reward pathways and appetite regulation. Bupropion's dopaminergic and noradrenergic activity together with naltrexone’s opioid antagonism modulates hunger and cravings.

6. Orlistat

Representing a non-central nervous system approach, orlistat inhibits gastrointestinal lipases, reducing dietary fat absorption. While weight loss is modest compared with incretin-based agents, its peripheral mechanism offers an alternative for select patients.

Off-Label Use in Obesity Management

Off-label prescribing refers to the use of medications outside their approved indications when supported by clinical judgment and evidence. In obesity care, this strategy is sometimes utilized when approved therapies are inadequate, contraindicated, or inaccessible.

1. Phentermine (Monotherapy)

Although FDA-approved for short-term use (typically up to 12 weeks), phentermine is frequently prescribed off-label for longer durations, given historical evidence of weight loss efficacy and a well-characterized safety profile in clinical practice.

2. Diethylpropion

Like phentermine, diethylpropion is formally approved for short-term weight reduction but may be used off-label beyond this period with careful patient monitoring.

3. Other Agents

Certain antidepressants, antiepileptics (e.g., topiramate outside its combination formulation), and atypical stimulants may be considered off-label for weight reduction in specific clinical scenarios, especially when comorbid psychiatric conditions coexist. These uses require individualized risk–benefit assessment given potential side effects.

Emerging Therapies and Future Directions

In addition to current FDA-approved drugs, several investigational agents with novel mechanisms—such as multi-receptor agonists and oral non-peptide weight-loss compounds—are in late-stage development, promising further expansion of pharmacologic options for obesity. Agents like dual and triple incretin receptor agonists aim to enhance metabolic regulation and weight reduction beyond existing treatments.

Conclusion

Pharmacological agents play an important role in comprehensive obesity management when used alongside lifestyle interventions.

Continued research into novel targets and long-term safety will further strengthen the role of pharmacotherapy in addressing the global obesity epidemic.

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