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Drugs Used in the Treatment of Obesity – A Systematic Review

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Abstract

Obesity, a disease of complex etiology whose global prevalence continues to rise, has reached the status of a worldwide pandemic. It leads to a significant increase in the risk of numerous disorders. The scale of the problem, combined with the limitations of non-pharmacological methods, has increased the importance of pharmacotherapy in the treatment of obesity. The aim of this study was to analyze currently available anti-obesity medications and highlight emerging directions in pharmacotherapy of obesity. Based on a literature review, five major drug groups were evaluated: orlistat, the combined preparation of naltrexone and bupropion, phentermine, GLP-1 analogues, and dual GLP-1/GIP agonist. The results showed that traditional drugs such as orlistat and phentermine demonstrate only modest weight-loss potential and a higher risk of adverse events, which limits their overall role in obesity treatment. The combined naltrexone–bupropion preparation offers greater efficacy than the previously described agents and provides a favorable effect on central appetite regulation, making it an attractive therapeutic option for selected patients. The most groundbreaking and currently widespread drug group remains GLP-1 analogues mainly liraglutide and semaglutide, which enable weight reduction of approximately 16% of baseline body weight and offer beneficial metabolic effects. Even greater potential for weight loss is demonstrated by the dual GLP-1/GIP receptor agonist tirzepatide. Further development of anti-obesity pharmacotherapy includes agents such as retatrutide, a triple agonist of GLP-1, GIP, and glucagon receptors, whose efficacy exceeds that of currently

available medications. Research conducted in this field suggests that the future of obesity treatment will likely rely on multireceptor therapy, tailored to the patient's profile. In the face of the rising global prevalence of obesity, the development of new medications remains a key element in improving public health.

Keywords: Obesity, Anti-obesity pharmacotherapy, GLP-1 receptor agonists, Weight loss, Incretin-based therapy, Multireceptors agonists

Introduction:

Obesity, defined by the World Health Organization (WHO) as excessive or abnormal fat accumulation that adversely affects health, is one of the greatest public health challenges that must be addressed today. Obesity is diagnosed based on the Body Mass Index (BMI), calculated as the ratio of body weight in kilograms to the square of height in meters, with values of 30 kg/m^2 or higher indicating obesity. Currently, several limitations of this index are recognized, potentially contributing to both under- and over-diagnosis of obesity. BMI does not provide information about body composition or fat distribution, and therefore it is recommended that BMI assessment be supplemented with direct measurements of fat mass or anthropometric indicators, such as waist circumference, waist-to-hip ratio, or waist-to-height ratio, standardized for age, sex, and ethnicity [1].

According to available data, in 2021 there were approximately 1 billion men and 1.1 billion women worldwide living with overweight or obesity. This represented an increase of 155.1% in men and 104.9% in women compared with 1990. If these trends persist, more than half of the adult population will be overweight or obese by 2050 [2]. Based on a survey conducted between 2017 and 2018, it was estimated that in Europe, 54.1% of men and 42.5% of women had excessive body weight, defined as a BMI of over $25 \text{ kg}/\text{m}^2$ (overweight and obesity). The highest prevalence of obesity was observed in Greece and Romania, and the lowest in Italy and France [3]. The obesity problem is also significant in Poland. According to a 2020 study, 42.2% of Polish adults were overweight and 16.4% were obese [4]. These data indicate that obesity has indeed reached the status of a global pandemic.

Obesity is not merely an accumulation of excess adipose tissue but is associated with a wide range of complications. It has been demonstrated that individuals with obesity have an increased risk of developing numerous diseases, including type 2 diabetes, cardiovascular diseases such as hypertension, heart failure, myocardial infarction, stroke, atrial fibrillation, as well as fatty liver disease, osteoarthritis, and obstructive sleep apnea [5]. Excessive body weight is also a

significant factor influencing carcinogenesis. Cancers whose risk increases with obesity include colorectal, gastric, liver, gallbladder, thyroid, cervical, bladder, esophageal, endometrial, ovarian, and renal cancers, as well as brain tumors and Hodgkin lymphoma [6]. In addition to somatic diseases, obesity may also affect the prevalence of depression. According to a meta-analysis published in 2017, individuals with obesity were 32% more likely to develop depression compared with individuals with a BMI of 18.5–24.9 kg/m² (normal weight) [7].

The treatment of obesity is complex and often challenging. Lifestyle modification—including appropriate dietary intervention, physical activity, and behavioral therapy—remains the foundation of management; however, non-pharmacological interventions frequently fail to achieve desired outcomes. Currently, several medications with different mechanisms of action are available to support weight reduction [8]. The aim of the present article is to describe available pharmacological options, compare their efficacy, and discuss additional potential indications.

Methodology:

For this review, publications available in the PubMed, Scopus, and Web of Science databases from 1997 to 2025 were analyzed. The analysis included primarily clinical trials, observational studies, meta-analyses, and systematic reviews concerning currently available anti-obesity medications as well as drugs in subsequent phases of clinical development.

Characteristics of Medications Used in the Treatment of Obesity

1. Orlistat

1.1 Mechanism of Action:

Orlistat acts locally in the gastrointestinal tract by irreversibly inhibiting the active site of gastric and pancreatic lipases, thereby preventing the effective hydrolysis of dietary triglycerides. As a result, fat absorption is reduced by approximately 30%, creating an additional caloric deficit without affecting other digestive enzymes or gastrointestinal motility [9].

1.2 Efficacy:

In a U.S. study conducted across 17 primary care centers, patients receiving 60 mg of orlistat achieved a mean weight reduction of 7.08 kg over one year, while those receiving 120 mg lost an average of 7.94 kg. In contrast, the placebo group experienced a mean weight reduction of 4.14 kg during the same period [10]. Additional benefits were observed in lipid metabolism, including reductions in total cholesterol and low-density lipoprotein (LDL) levels [11].

1.3 Adverse Effects:

The most common adverse effects involve the gastrointestinal tract and include steatorrhea, fecal incontinence, abdominal pain, and anal fissures. Elevated liver enzyme levels and isolated cases of liver failure have also been reported [11].

1.4 Summary:

Orlistat is currently not widely used, primarily due to the availability of newer medications with significantly greater efficacy in weight reduction [12].

2. Combined Preparation: Naltrexone + Bupropion

2.1 Mechanism of Action:

The anti-obesity effect of combined bupropion and naltrexone results from modulation of central regulatory pathways, although the mechanism is not fully understood. Bupropion, a norepinephrine and dopamine reuptake inhibitor used as an antidepressant, stimulates proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus, inducing the release of α -MSH (alpha-melanocyte-stimulating hormone). This activates melanocortin-4 receptors (MC4R), leading to appetite suppression while simultaneously initiating a feedback loop mediated by β -endorphin. Naltrexone, a μ -opioid receptor antagonist, blocks this inhibitory feedback loop, allowing for stronger and more sustained activation of POMC neurons. The synergistic effect of both agents results in greater appetite reduction than either drug used alone [13]. The combination also influences the brain's reward circuitry, reducing the reinforcing value of food [14].

2.2 Efficacy:

Studies have demonstrated an 8% reduction in baseline body weight over one year using a combination of 32 mg naltrexone and 360 mg bupropion. In the placebo group, weight reduction was 1.5%. When combined with non-pharmacological interventions, patients treated with naltrexone–bupropion achieved an 11% reduction in baseline weight compared with 7% in the placebo group [14].

2.3 Adverse Effects:

The most common adverse effects include gastrointestinal complaints such as nausea, vomiting, and constipation. Patients may also experience headaches, dizziness, insomnia, tremors, hot flashes, and tinnitus [15]. The adverse effect profiles of both bupropion and naltrexone are well known, which underscores the importance of appropriate patient selection to minimize undesirable events [14].

2.4 Summary:

The combination of naltrexone and bupropion is an effective and relatively safe option for obesity treatment, offering superior outcomes compared with orlistat [8,14].

3. Phentermine

3.1 Mechanism of Action:

Phentermine is a sympathomimetic agent that increases norepinephrine release in the central nervous system. In the hypothalamus, this stimulates adrenergic receptors, leading to potent appetite suppression. At therapeutic doses, its effects on dopamine and serotonin are minimal, which distinguishes it from agents acting primarily through serotonergic pathways. The result is decreased appetite and enhanced satiety [16].

3.2 Efficacy:

In a post-marketing observational study in South Korea, average weight loss after 12 weeks of therapy ranged from 3.8 to 4.0 kg (approximately 5.2% of baseline weight). A reduction of $\geq 5\%$ was achieved in 45.6% of patients [17]. Contemporary literature reviews indicate that phentermine is associated with clinically meaningful weight loss in adults and is generally well tolerated [18].

3.3 Adverse Effects:

The most frequently reported adverse effects include symptoms involving the nervous and cardiovascular systems, such as tachycardia, elevated blood pressure, insomnia, emotional irritability, and dizziness. Additionally, dry mouth and constipation may occur [19].

3.4 Summary:

Despite its long history of use, current data on the long-term safety and effectiveness of phentermine remain limited. Most available data are observational, with a need for large randomized controlled trials. Due to the risk of adverse events, many authors recommend limiting phentermine therapy to 12 weeks, combined with dietary restrictions and increased physical activity [20].

4. Glucagon-Like Peptide-1 (GLP-1) Analogues – Liraglutide, Semaglutide

4.1 Mechanism of Action:

GLP-1 analogues are among the most extensively studied and clinically important medications for obesity treatment. They act by stimulating GLP-1 receptors located in the gastrointestinal tract, pancreas, and central nervous system. This leads to increased insulin secretion, reduced

glucagon secretion, delayed gastric emptying—resulting in earlier satiety—and decreased food intake. They also reduce activation of hypothalamic hunger centers [21]. The primary representatives are liraglutide (maximum dose 3.0 mg) and semaglutide (maximum dose 2.4 mg subcutaneously or 14 mg orally).

4.2 Efficacy:

Large randomized clinical trials have confirmed the efficacy of GLP-1 analogues. A global study of liraglutide 3.0 mg in patients with a BMI of $38.3 \pm 6.4 \text{ kg/m}^2$ demonstrated a mean weight reduction of $8.4 \pm 7.3 \text{ kg}$ after 56 weeks, compared with $2.8 \pm 6.5 \text{ kg}$ in the placebo group [22]. In a semaglutide 2.4 mg trial, participants achieved a mean weight reduction of 16% after 56 weeks, compared with 5.7% in the placebo group [23]. A review of 23 randomized trials comparing liraglutide and semaglutide found the latter to be more effective both in weight reduction and HbA1c improvement [24].

4.3 Adverse Effects:

The most common adverse effects of GLP-1 analogues involve the gastrointestinal tract, including nausea, vomiting, diarrhea, and early satiety. These were also the most frequent causes of treatment discontinuation in liraglutide trials, although symptoms typically improved within 4–8 weeks. An increased incidence of gallstones and cholecystitis was observed in liraglutide-treated patients. Notably, patients who continued therapy after gallstone treatment achieved greater weight reduction than those without gallbladder-related conditions. Less common adverse effects included tachycardia and injection-site reactions [22]. Overall, GLP-1 analogues are considered safe, with most adverse effects classified as mild to moderate.

4.4 Summary:

GLP-1 analogues are among the most essential medications in modern obesity pharmacotherapy. Through their multifaceted mechanisms, they provide robust weight reduction and metabolic improvement, including beneficial effects on glycemic control and blood pressure. Semaglutide 2.4 mg, administered as subcutaneous injection, is the most effective agent in this class [21–24]. The therapeutic relevance of GLP-1 analogues is expected to grow as new studies demonstrate their benefits in fatty liver disease, nephroprotection, atherosclerosis progression, cardiovascular risk reduction, and potential neuropsychiatric benefits such as reduced depressive symptoms and lower risk of Alzheimer’s disease, Parkinson’s disease, and dementia [25].

5. Tirzepatide

5.1 Mechanism of Action:

Tirzepatide is a dual agonist of the GLP-1 and GIP receptors. By activating these incretin pathways, it enhances insulin secretion, suppresses glucagon release, slows gastric emptying, decreases appetite, and increases satiety, ultimately reducing daily caloric intake [26].

5.2 Efficacy:

Numerous randomized controlled trials and meta-analyses involving individuals with overweight or obesity (both with and without type 2 diabetes) have demonstrated significant weight reduction with tirzepatide. A June 2025 meta-analysis by Sharath Kommu, Param P. Sharma, and Rachel M. Gabor reported a mean difference in weight loss of 13.95 kg compared with placebo [27]. Another meta-analysis by Bryan Tan and Xin-Hui Pan found clinically significant proportions of patients achieving >5 kg, >10 kg, and >15 kg weight loss [28]. Tirzepatide also improves metabolic markers—including reductions in body weight, waist circumference, BMI, and improved glycemic control in individuals with diabetes [29]. Trials conducted prior to market authorization demonstrated greater weight reduction and glycemic improvement with dual GLP-1/GIP agonism compared with GLP-1 agonism alone [30].

5.3 Adverse Effects:

The most common adverse effects include gastrointestinal symptoms such as nausea, vomiting, diarrhea, constipation, dyspepsia, and decreased appetite, as well as dizziness and injection-site reactions [27].

5.4 Summary:

Although the overall incidence of serious adverse events does not appear significantly higher compared with placebo, treatment discontinuations increase with higher doses [31]. Nonetheless, tirzepatide demonstrates substantial efficacy and promising outcomes in obesity treatment [30]. Long-term safety data are still limited, necessitating further research on chronic use, particularly given the long duration of obesity management [32]. Additional indications are being explored, and a study published in the *New England Journal of Medicine* reported reduced cardiovascular mortality and improved clinical status in patients with heart failure with preserved ejection fraction [33].

Future Directions in Research:

As discussed in the introduction, the widespread prevalence of obesity has reached pandemic proportions, fueling ongoing global research into innovative pharmacological weight-loss therapies. One particularly promising agent currently in advanced stages of development is retatrutide. It is a triple receptor agonist targeting GLP-1, GIP, and glucagon receptors, thereby modulating three key hormonal pathways involved in appetite regulation. Initial animal studies were confirmed in phase I and II clinical trials, demonstrating substantial weight loss exceeding that achieved by currently available obesity medications, as well as reductions in HbA1c and improvements in parameters related to fatty liver disease and diabetic kidney disease [34]. A meta-analysis of three clinical trials reported a mean weight reduction of 14.33% along with improvements in other metabolic markers [35]. Ongoing phase III trials aim to assess long-term outcomes, safety, and potential adverse effects [34].

Conclusions:

Obesity, as one of the most significant challenges in modern medicine, requires a multidirectional therapeutic approach in which pharmacotherapy is playing an increasingly important role. Current evidence demonstrates that anti-obesity medications differ in mechanisms of action and efficacy, and their selection should be individualized based on patient characteristics, potential adverse effects, and financial considerations. Traditional therapies such as orlistat or phentermine, while effective in selected populations, offer limited tolerability and moderate weight-loss outcomes. In contrast, therapies targeting central and hormonal regulation—such as GLP-1 analogues and the dual GIP/GLP-1 agonist tirzepatide—have transformed obesity treatment by enabling weight loss exceeding 15% in many patients and significantly improving metabolic parameters.

Given the complex pathophysiology of obesity and the variability of treatment responses among patients, there is a continuous need for more potent medications offering broader health benefits. Retatrutide, a triple agonist of GLP-1, GIP, and glucagon receptors, exemplifies the future direction of obesity pharmacotherapy through synergistic modulation of multiple metabolic pathways. Early clinical results suggest that such agents may provide weight reduction surpassing currently available treatments while conferring additional metabolic and cardiovascular benefits.

As the prevalence of obesity and its associated complications continues to rise, further research into novel pharmacological and non-pharmacological therapies is essential. Current clinical

evidence shows that pharmacotherapy can be an effective tool for achieving durable weight loss; however, optimal results require comprehensive patient care that integrates lifestyle modification—including appropriate diet and physical activity. Advances in incretin-based therapies and their derivatives hold promise for improving treatment efficacy and better tailoring therapy to the individual needs of patients, which is especially important given the chronic and multifactorial nature of obesity.

Disclosure:

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Conflict of Interest

All authors declare no conflict of interest.

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