3 Obesity Pharmacotherapy: From Conventional Agents to Emerging Therapies

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Abstract

An ideal anti-obesity medication should achieve substantial and sustained weight reduction while maintaining an acceptable safety profile and minimizing adverse effects. However, the regulation of energy balance is governed by highly complex and redundant physiological networks that interact extensively with multiple biological systems. Consequently, the history of anti-obesity drug development has been marked by numerous setbacks, including failures during clinical development and the withdrawal of approved agents due to unforeseen safety concerns. Several therapeutic approaches targeting metabolic tissues such as adipose tissue, liver, and skeletal muscle have demonstrated promising results in preclinical studies. The particular attention has been directed toward gastrointestinal peptide hormones involved in hunger and satiety signaling, including ghrelin, cholecystokinin (CCK), peptide YY (PYY), and glucagon-like peptide-1 (GLP-1). Similarly, improved knowledge of leptin-mediated pathways and hypothalamic mechanisms regulating energy balance has expanded opportunities for the development of innovative anti-obesity therapies. Among these emerging therapeutic options, GLP-1 receptor agonists have demonstrated remarkable clinical success. Originally developed for the treatment of type 2 diabetes mellitus, these agents have consistently shown clinically meaningful reductions in body weight, thereby establishing a new benchmark for obesity pharmacotherapy. Their success has stimulated the development of additional incretin-based therapies and has reinforced the concept that targeting multiple pathways involved in appetite regulation and energy expenditure may offer superior therapeutic outcomes. Given the multifactorial nature of obesity, there is growing recognition that future treatment strategies may require a paradigm shift beyond single-target interventions. Similar to the management of chronic diseases such as diabetes and hypertension, combination therapies employing lower doses of multiple agents that act through complementary mechanisms may provide enhanced efficacy while minimizing adverse effects.

Keywords: Obesity, Weight Management, Appetite Regulation, Body Weight Reduction.

Introduction

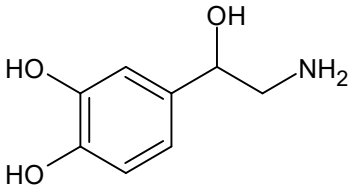
Excessive body fat buildup that negatively impacts health is the hallmark of obesity, a complicated, chronic, multifactorial metabolic condition. Adults with a body mass index (BMI) of ≥30 kg/m² are typically classified as obese, although other anthropometric measurements, such as waist circumference and body fat distribution, are becoming more widely accepted for evaluating the health concerns associated with obesity. A mix of genetic, physiological, environmental, behavioral, and socioeconomic variables contribute to the condition's long-term imbalance between energy intake and expenditure. Obesity has become one of the biggest global public health issues in recent decades, impacting both industrialized and developing countries. Its incidence has sharply increased across all age groups, burdening healthcare systems and raising rates of morbidity and mortality. According to historical epidemiological estimates, several hundred million of adults globally were obese, and an even greater percentage were overweight, underscoring the epidemic's quick global spread. The rising incidence of childhood and teenage obesity is especially concerning. The risk of developing chronic non-communicable diseases, such as type 2 diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, non-alcoholic fatty liver disease, and some types of cancer, is greatly increased by excess body weight gained during early life and is strongly linked to persistence into adulthood. As a result, obesity is today acknowledged as a serious metabolic disease as well as a pressing public health issue that calls for all-encompassing preventative and treatment approaches at the individual and population levels. A major rise in illness, early mortality, a lower quality of life, and a substantial socioeconomic burden are all linked to obesity. Diabetes type 2 mellitus, a typical metabolic syndrome, high blood pressure, dyslipidemia, coronary artery disease, myocardial infarction, stroke, sleep apnea with obstruction, osteoarthritis, non-alcoholic fatty liver disease, and a number of obesity-related cancers are among the many chronic non-communicable diseases for which it is a significant risk factor.

Historical Background

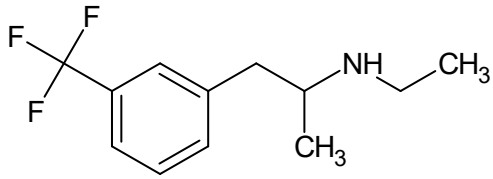
Amphetamine derivatives such as desoxyephedrine, phentermine, and diethylpropion, as well as centrally acting sympathomimetic drugs, were the mainstay of the first pharmacological attempts to managing obesity. By inducing the central nervous system's release of catecholamines, which suppresses appetite and reduces food intake, these medications aid in weight loss. These drugs were widely used in clinical settings in the 1950s and 1960s because they were successful in causing temporary weight loss. However, by the early 1970s, their therapeutic use had significantly decreased due to worries about their cardiovascular side effects, potential for misuse and dependence, and limited long-term efficacy. Serotonergic appetite suppressants, especially fenfluramine and its stereoisomer dexfenfluramine, essentially supplanted phentermine and diethylpropion in the 1970s and 1980s,

ISBN: 978-93-49468-84-9

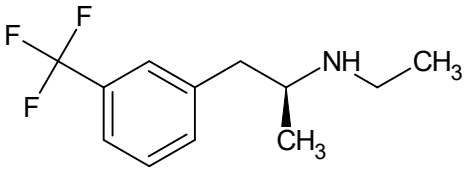
despite the fact that these medications are still authorized in a number of countries for the short-term treatment of obesity. By increasing central serotonergic neurotransmission, these drugs mostly promoted satiety and decreased calorie intake. Early research found a link among fenfluramine derivatives and a higher risk of primary pulmonary hypertension despite their therapeutic effectiveness. At first, this danger was thought to be minimal in comparison to the therapeutic advantages attained in certain individuals. Early in the 1990s, research showed that the combination of phentermine and fenfluramine, known as "Fen-Phen," was more effective at helping people lose weight than either medication used alone. Nevertheless, post-marketing surveillance later showed a strong correlation between this combination treatment and major cardiovascular problems, specifically valvular fibrosis and cardiac valve disease. The voluntary removal of fenfluramine and dexfenfluramine from the international market in 1997 as a result of these safety concerns marked a significant turning point in the development of anti-obesity medications. Orlistat works by reversibly blocking gastric and pancreatic lipases, which prevents the hydrolysis and subsequent intestinal absorption of about 30% of dietary fat, in contrast to centrally acting anti-obesity drugs that mainly suppress appetite or increase energy expenditure.



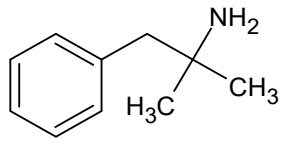
Noradrenaline



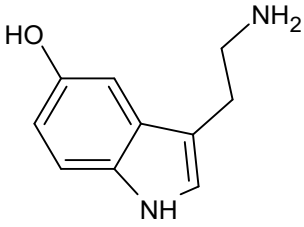
Fenfluramine



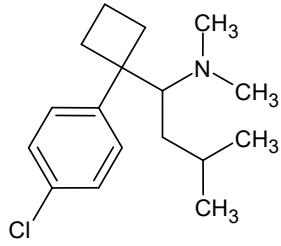
Dexfenfluramine



Phentermine

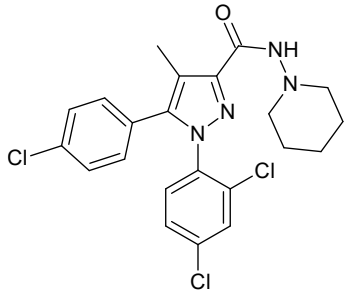


Serotonin

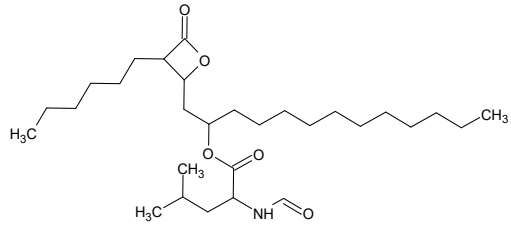


Sibutramine

ISBN: 978-93-49468-84-9



Rimonabant



Orlistat

Table 1: Evolution of Pharmacological Therapies for Obesity: Mechanisms, Clinical Benefits, and Safety Concerns

S. No.	Drug/Class	Period of Clinical Use/Approval	Mechanism of Action	Clinical Benefits	Major Limitations / Adverse Effects	Current Status
1.	**Desoxyephedrine (Methamphetamine)**	1950s–1960s	Centrally acting sympathomimetic; stimulates release of catecholamines (dopamine and noradrenaline) leading to appetite suppression	Effective short-term weight loss	High abuse potential, dependence, cardiovascular toxicity, limited long-term efficacy	No longer recommended for obesity treatment
2.	**Phentermine**	1959–Present (short-term use)	Sympathomimetic amine; increases central noradrenaline release to suppress appetite	Effective short-term reduction in food intake and body weight	Insomnia, tachycardia, hypertension, abuse potential; unsuitable for long-term monotherapy	Approved for short-term obesity treatment; also used in combination with topiramate
3.	**Diethylpropion**	1960s–Present (short-term use)	Sympathomimetic appetite suppressant	Moderate short-term weight loss	Cardiovascular adverse effects, dependence potential	Approved in several countries for short-term use
4.	**Fenfluramine**	1973–1997	Enhances serotonergic neurotransmission by increasing serotonin release	Improved satiety and significant weight loss	Pulmonary hypertension, cardiac valvular disease	Withdrawn worldwide (1997)
5.	**Dexfenfluramine**	1996–1997	Selective serotonin-releasing anorectic agent	Effective appetite suppression	Cardiac valvulopathy and pulmonary hypertension	Withdrawn worldwide (1997)
6.	**Fen-Phen (Phentermine + Fenfluramine)**	Early 1990s–1997	Combined catecholaminergic and serotonergic appetite suppression	Greater efficacy than monotherapy	Severe cardiac valvular fibrosis and cardiovascular toxicity	Withdrawn following safety concerns

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7.	**Sibutramine**	1997–2010	Inhibits reuptake of noradrenaline and serotonin; increases satiety and energy expenditure	Moderate long-term weight loss; improved cardiometabolic parameters	Increased cardiovascular events in susceptible patients	Withdrawn from most international markets (2010)
8.	**Rimonabant**	2006–2008 (Europe)	Selective cannabinoid CB_1 receptor antagonist/inverse agonist	Weight reduction, improved glycaemic control, metabolic syndrome parameters	Anxiety, depression, suicidal ideation	Withdrawn by EMA (2008); CB_1 antagonist development largely discontinued
9.	**Orlistat**	FDA approval: 1998; currently available	Peripheral inhibitor of gastric and pancreatic lipases; reduces dietary fat absorption by ~30%	Modest sustained weight loss; lowers LDL cholesterol, blood pressure, glucose; reduces diabetes risk	Gastrointestinal adverse effects (steatorrhea, flatulence, diarrhea); reduced absorption of fat-soluble vitamins	Remains approved worldwide for long-term obesity management

Current Status

The endocannabinoid system is still thought to be a potential therapeutic target for weight management, despite the major setback in obesity pharmacotherapy caused by the withdrawal of rimonabant and the termination of several cannabinoid type 1 (CB_2) receptor antagonist development programs. The creation of more secure and efficient cannabinoid-based anti-obesity medicines may be made possible by new insights gained from developments in the understanding of CB_2 receptor pharmacology. The fact that rimonabant and other first-generation CB_2 receptor blockers acted as inverse agonists rather than neutral antagonists is a crucial factor to take into account. Due to concerns raised by the withdrawal of several previous medicines, anti-obesity pharmacotherapies have traditionally undergone comprehensive examination of their long-term efficacy and safety prior to regulatory clearance. Before being approved for long-term weight control, naltrexone/bupropion extended-release first faced regulatory delays due to the need for more cardiovascular safety evidence. Similar concerns about tumor formation seen in preclinical studies led to the original rejection of lorcaserin, a selective 5-HT2C receptor agonist, although it was later approved following more evaluation. However, it was voluntarily removed from the market in 2020 after post-marketing clinical evidence indicated a potential rise in cancer risk. Concerns about teratogenicity, including the possibility of orofacial clefts linked to topiramate exposure during pregnancy, led to a thorough regulatory examination of the phentermine/topiramate extended-release combination. The combination was approved by regulators after suitable risk-reduction measures were put in place, and it is still a significant pharmaceutical option for managing chronic weight in carefully chosen individuals.

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Table 2: Emerging Therapeutic Strategies Targeting the Endocannabinoid System for Obesity Management

S. No.	Therapeutic Strategy	Target/Mechanism	Potential Advantages	Current Status / Challenges
1.	**First-generation CB_1 receptor inverse agonists (e.g., Rimonabant)**	Block ligand-induced and constitutive CB_1 receptor activity	Significant weight loss; improved glucose metabolism and metabolic syndrome	Withdrawn due to severe psychiatric adverse effects (anxiety, depression, suicidal ideation)
2.	**Neutral CB_1 receptor antagonists**	Block receptor activation without suppressing constitutive signaling	Preserve weight-loss efficacy with reduced CNS-related adverse effects	Promising preclinical evidence; clinical evaluation ongoing
3.	**Partial CB_1 receptor agonists**	Partial modulation of CB_1 receptor signaling	Potential metabolic benefits with improved safety profile	Early-stage drug development
4.	**Allosteric CB_1 receptor modulators**	Fine-tune receptor activity through allosteric binding sites	Improved receptor selectivity and fewer adverse effects	Preclinical investigation
5.	**Peripheral CB_1 receptor antagonists**	Selectively inhibit CB_1 receptors in adipose tissue, liver, skeletal muscle, and gastrointestinal tract without crossing the blood–brain barrier	Weight reduction, improved insulin sensitivity, reduced hepatic steatosis, minimal psychiatric toxicity	Highly promising preclinical strategy; limited clinical translation
6.	**Endocannabinoid metabolism modulators**	Regulate synthesis or degradation of endogenous cannabinoids	Physiological regulation of appetite and energy homeostasis	Experimental stage

Among these drugs, liraglutide was the first GLP-1 receptor agonist authorized expressly for long-term weight control at a dosage higher than that of diabetes. Long-term clinical trials showed improvements in cardiometabolic risk variables together with decreases in body weight. The introduction of semaglutide, a long-acting GLP-1 receptor agonist, has significantly enhanced the treatment of obesity in recent years. Large randomized clinical trials have shown typical weight reductions of about 15% of baseline body weight. Additionally, the advent of dual

ISBN: 978-93-49468-84-9

incretin receptor agonists, such tirzepatide, which concurrently activates GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, has led to exceptional weight loss in certain individuals that is comparable to that attained with bariatric surgery. These developments have completely changed the treatment landscape for obesity and made incretin-based treatments the mainstay of modern pharmacological care.

Table 3: Evolution of Contemporary Anti-Obesity Pharmacotherapy

S. No.	Drug/ Drug Class	Primary Target/Mechanism	Major Clinical Benefits	Safety/ Regulatory Considerations	Current Status
1.	**Naltrexone/Bupropion ER (Contrave®)**	Opioid receptor antagonism + dopamine/noradrenaline reuptake inhibition	Appetite suppression and sustained weight reduction	Initial regulatory delay due to cardiovascular safety concerns	Approved for chronic weight management
2.	**Lorcaserin (Belviq®)**	Selective **5-HT_2C receptor agonist**	Weight loss and improved glycemic control	Withdrawn (2020) following possible increased cancer risk	Withdrawn
3.	**Phentermine/Topiramate ER (Qsymia®)**	Sympathomimetic appetite suppression + modulation of GABAergic/glutamatergic pathways	Significant long-term weight loss	Teratogenicity concerns managed through Risk Evaluation and Mitigation Strategies (REMS)	Approved for chronic obesity management
4.	**Liraglutide**	GLP-1 receptor agonist	Sustained weight loss, improved glycemic control, cardiometabolic benefits	Generally well tolerated; gastrointestinal adverse effects	Approved
5.	**Semaglutide**	Long-acting GLP-1 receptor agonist	Approximately 15% mean body weight reduction; improved metabolic health	Excellent efficacy with acceptable safety	Current first-line pharmacotherapy
6.	**Tirzepatide**	Dual GIP/GLP-1 receptor agonist	Weight loss approaching bariatric surgery; improved glycemic control	Gastrointestinal adverse effects; ongoing long-term outcome evaluation	One of the most effective approved therapies

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The Future

Standard medication monotherapies for obesity have shown promise in causing clinically significant weight loss; however, physiological counter-regulatory systems that encourage weight gain often restrict their long-term efficacy. The complex nature and diversity of the biological systems controlling appetite control and energy homeostasis are reflected in these adaptive responses, which include increased hunger, decreased energy expenditure, and changes in neuroendocrine signaling. As a result, it is frequently difficult to achieve long-term weight loss with a single pharmaceutical medication, especially in people who are chronically obese. Combination pharmacotherapy, which concurrently targets several molecular and physiological pathways involved in body weight management, has become the preferred therapeutic approach as a result of the recognition of these limitations. Combination medicines seek to improve obesity-related metabolic problems while achieving higher and longer-lasting weight loss than monotherapy by modifying complimentary mechanisms of action.This strategy is justified by the multifaceted nature of obesity, which is characterized by interrelated cerebral and peripheral circuits that together control energy expenditure, satiety, food intake, and nutrient metabolism. The idea of combination therapy is not new; it dates back to the phentermine–fenfluramine (Fen-Phen) regimen's earlier clinical use, which showed improved weight-loss success as compared to either agent provided alone, even if it was eventually discontinued due to safety concerns.

Table 4: Comparison of Monotherapy and Combination Pharmacotherapy in Obesity Management

S. No.	Parameter	Conventional Monotherapy	Combination Pharmacotherapy
1.	**Therapeutic principle**	Targets a single molecular pathway involved in appetite or metabolism	Simultaneously targets multiple complementary pathways regulating energy homeostasis
2.	**Mechanism of action**	Single receptor or neurotransmitter modulation	Multiple receptors, hormones, or signaling pathways
3.	**Weight-loss efficacy**	Moderate; often diminishes over time	Greater and more sustained weight reduction
4.	**Physiological adaptation**	Pronounced counter-regulatory responses (increased appetite, reduced energy expenditure)	Reduced compensatory responses due to multi-target modulation
5.	**Dose requirement**	Higher dose of a single drug	Lower doses of individual agents
6.	**Therapeutic interaction**	Limited	Additive or synergistic effects

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7.	**Safety profile**	Higher incidence of dose-dependent adverse effects	Improved tolerability through dose reduction and complementary mechanisms
8.	**Representative examples**	Orlistat, Phentermine, Liraglutide (monotherapy)	Phentermine–Topiramate, Naltrexone–Bupropion, Dual/Triple Incretin Agonists
9.	**Current clinical significance**	Useful for selected patients	Preferred strategy for long-term obesity management

The creation of multifunctional single-molecule peptide therapies, which are intended to concurrently activate several metabolic receptors involved in the control of appetite, energy expenditure, and glucose homeostasis, is a significant development in modern obesity pharmacotherapy. These engineered peptides combine several pharmacological actions into a single molecular entity, in contrast to traditional combination therapies that call for the co-administration of two or more distinct medications. This offers the possibility of increased efficacy, easier dosing, and better patient adherence. Dual glucagon receptor (GCGR) and glucagon-like peptide-1 receptor (GLP-1R) co-agonists were among the first and most significant instances of this strategy. The pancreatic hormone glucagon, which is mainly known for its function in glucose metabolism, also has thermogenic, lipolytic, and appetite-suppressive qualities that help people burn more energy and lose weight.On the other hand, glycemic control may be hampered by excessive glucagon receptor activation, which may raise hepatic glucose production. On the other hand, GLP-1 receptor activation improves glycemic management, reduces hunger, slows stomach emptying, and increases glucose-dependent insulin secretion. As a result, the combination of GLP-1 receptor activation with glucagon receptor agonism offers a logical treatment approach in which both pathways work together to promote weight reduction while the glucose-lowering effects of GLP-1 offset any possible hyperglycemic effects of glucagon.

Table 5: Paradigm Shift in Anti-Obesity Drug Discovery

S. No.	Traditional Strategy	Modern Strategy
1.	Single molecular target	Multiple complementary targets
2.	Centrally acting appetite suppressants	Gut–brain axis modulation
3.	Synthetic neurotransmitter modulators	Endogenous peptide hormones
4.	Monotherapy	Combination therapy
5.	Single receptor agonists	Dual and triple receptor agonists
6.	Symptomatic weight loss	Restoration of metabolic homeostasis
7.	Uniform treatment approach	Precision medicine and personalized therapy
8.	Limited long-term efficacy	Sustained weight loss with metabolic improvement
9.	Higher adverse-effect burden	Improved efficacy with better safety profile

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Conclusion

Recent developments in molecular biology, neuroendocrinology, and metabolic medicine have culminated in a new era of therapeutic innovation, despite the history of anti-obesity pharmacotherapy being replete with setbacks. The development of multi-target pharmacological methods and the effective clinical translation of incretin-based medicines have shown that significant and long-lasting weight loss is possible with acceptable safety profiles. However, creating good anti-obesity drugs is still a difficult scientific task, and more research is needed to maximize long-term efficacy, safety, and patient-specific treatment results. Regulations pertaining to anti-obesity drugs have also changed significantly. Emerging treatments should show evidence of long-term improvements in obesity-related comorbidities, such as type 2 diabetes mellitus, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease (MASLD), obstructive sleep apnea, and overall quality of life, in addition to clinically significant and sustained weight loss. Given the chronic nature of treating obesity and the lessons learnt from past pharmaceutical failures, it is equally crucial to demonstrate long-term cardiovascular, mental, and general safety through rigorous clinical trials and post-marketing surveillance.

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ISBN: 978-93-49468-84-9