RESEARCH PAPER

Obesity as a Chronic Disease: Emerging Pharmacological Therapies and Future Therapeutic Perspectives

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Abstract
Obesity has emerged as a major global chronic disease and is now widely recognized as a complex, relapsing metabolic disorder rather than merely the result of excessive caloric intake or insufficient physical activity. Its prevalence has increased markedly worldwide over recent decades, contributing to a substantial burden of obesity-related complications, including type 2 diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, metabolic dysfunction-associated steatotic liver disease, obstructive sleep apnea, osteoarthritis, several malignancies, and reduced quality of life. The recognition of obesity as a chronic disease has shifted the therapeutic paradigm from short-term weight reduction toward sustained, long-term disease management.
Lifestyle modification, including dietary intervention, increased physical activity, and behavioural strategies, remains the foundation of obesity management. However, many individuals are unable to achieve or maintain clinically meaningful weight loss with lifestyle interventions alone, highlighting the need for effective pharmacological therapies. The therapeutic landscape has been substantially transformed by incretin-based treatments, particularly glucagon-like peptide-1 (GLP-1) receptor agonists such as semaglutide and the glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor co-agonist tirzepatide. These therapies have demonstrated considerable efficacy in reducing body weight and improving several metabolic risk factors.
Recent drug development has expanded beyond single-receptor agonist toward multi-hormonal therapies, oral small-molecule GLP-1 receptor agonists, amylin-based agents, and combination regimens. Retatrutide, a triple GIP/GLP-1/glucagon receptor agonist, has produced substantial weight reduction in phase 2 clinical studies and represents a promising investigational approach. Orforglipron, an oral non-peptide GLP-1 receptor agonist, may offer an important alternative to injectable therapies and has the potential to improve treatment convenience and accessibility. Other emerging strategies include combinations such as semaglutide with cagrilintide and next-generation multi-receptor agonists designed to target complementary metabolic pathways.
Despite these advances, several challenges continue to influence the long-term management of obesity. Gastrointestinal adverse effects, treatment discontinuation, weight regain following pharmacological withdrawal, uncertainties regarding long-term safety, high treatment costs, limited accessibility, and healthcare-system capacity remain important considerations. Future therapeutic development is therefore focused not only on achieving greater weight reduction but also on improving treatment tolerability, durability, accessibility, and long-term cardio metabolic outcomes. This narrative review examines the evolution of obesity management, established pharmacological therapies, and emerging treatment strategies, with particular emphasis on their mechanisms of action, clinical efficacy, limitations, and potential role in the long-term management of obesity as a chronic disease.

Keywords: obesity; chronic disease; GLP-1 receptor agonists; semaglutide; tirzepatide; retatrutide; orforglipron; amylin; pharmacotherapy; weight management.

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Introduction

Obesity is a major global public health crisis and one of the fastest-growing chronic conditions today. Defined by an excessive or abnormal accumulation of fat tissue that compromises overall health, it is far more than a uniform state. Rather, obesity is a complex, multifaceted metabolic disease shaped by a combination of genetic traits, neuroendocrine pathways, environmental conditions, daily habits, socioeconomic status, and early developmental factors..[1]

The health consequences of obesity extend well beyond increased body weight, with substantial effects on multiple organ systems. Obesity is strongly associated with an increased risk of type 2 diabetes mellitus, hypertension, dyslipidaemia, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease,

obstructive sleep apnea, osteoarthritis, and several types of cancer.[1,2] In particular, excess visceral adipose tissue plays a critical role in the development of obesity-related metabolic complications. Adipose tissue is an active endocrine and immunological organ that secretes a range of adipokines and inflammatory mediators. Excess visceral fat promotes chronic low-grade inflammation, insulin resistance, dysregulated adipokine production, and progressive metabolic dysfunction, thereby contributing to the development and progression of obesity-associated diseases. The recognition of obesity as a chronic disease represents a major conceptual change in clinical practice. Historically, treatment frequently focused on short-term caloric restriction and behavioral modification, with the expectation that patients could independently maintain weight loss after reaching a target weight. However, biological adaptations occurring during weight loss—including increased appetite, altered satiety signalling and changes in energy expenditure—can promote weight regain.[3] Consequently, obesity should be managed similarly to other chronic diseases in which long-term treatment may be required.

Pharmacological therapy has consequently assumed an increasingly important role in the comprehensive management of obesity, particularly among individuals who do not achieve adequate or sustained weight loss with lifestyle interventions alone. Earlier anti-obesity medications generally provided modest reductions in body weight and were often constrained by adverse effects, tolerability issues, or safety concerns. The emergence of incretin-based therapies has substantially transformed the pharmacological management of obesity. Agents such as semaglutide and tirzepatide have demonstrated greater and more sustained weight loss than many traditional anti-obesity medications, while also providing clinically meaningful improvements in glycemic control and other cardio metabolic risk factors..[4-7]

The World Health Organization (WHO) 2025 guideline marks a significant development in the management of obesity by conditionally recommending GLP-1–based therapies for the long-term treatment of obesity in adults. The guideline emphasizes that pharmacological treatment should be incorporated into a comprehensive approach that includes a healthy diet, regular physical activity, and appropriate professional behavioral support.[8] This shift further reinforces the recognition of obesity as a chronic disease requiring sustained, multidimensional management, with pharmacotherapy serving as an important therapeutic component rather than being regarded solely as an intervention for cosmetic weight reduction.

2. Obesity as a Chronic and Relapsing Disease

The chronic nature of obesity is supported by physiological mechanisms that defend body weight. Following weight loss, compensatory biological responses may increase hunger and reduce energy expenditure, thereby favoring restoration of the previous body weight.[3,9] These mechanisms include changes in leptin, ghrelin, peptide YY, glucagon-like peptide-1 (GLP-1), cholecystokinin and other appetite-regulating signals.

The central nervous system integrates peripheral signals related to energy availability, gastrointestinal function and adipose tissue stores. The hypothalamus and other brain regions regulate appetite, satiety and energy expenditure. In obesity, this regulatory system may become dysregulated, while environmental exposure to energy-dense foods and sedentary behavior can further promote weight gain.

Weight loss can also produce persistent neuroendocrine adaptations. Increased hunger and reduced satiety may continue even after substantial weight reduction, explaining why maintenance of weight loss is difficult for many individuals.[3] Therefore, recurrence of obesity after discontinuation of effective treatment should not necessarily be interpreted as treatment failure or poor patient adherence. Instead, it reflects the biological chronicity of the disease.

This understanding supports the use of long-term pharmacotherapy in appropriate patients. Similar to antihypertensive or lipid-lowering treatment, anti-obesity medication may need to be continued to maintain its therapeutic effects.

3. Role of Lifestyle Intervention

Lifestyle-based interventions remain the primary foundation of obesity treatment and encompass healthy dietary practices, regular physical activity, behavioral modification, adequate sleep, and limitation of sedentary activities.[8] Nevertheless, lifestyle measures alone may provide limited and difficult-to-maintain weight loss, particularly in individuals with severe or persistent obesity. Pharmacological therapy is therefore appropriate for patients who fail to achieve or sustain clinically meaningful weight reduction despite adequate lifestyle interventions, especially when obesity is associated with related metabolic or clinical complications. Accordingly, contemporary obesity care increasingly emphasizes a comprehensive, multimodal strategy in which pharmacotherapy is used alongside lifestyle modification rather than as a substitute for it..

4. Evolution of Pharmacological Treatment of Obesity

Historically, pharmacological management of obesity has included sympathomimetic agents, lipase inhibitors, and centrally acting appetite suppressants, with commonly used examples such as orlistat, phentermine, phentermine/topiramate, naltrexone/bupropion, and liraglutide. Although these medications continue to have clinical utility in selected patients, their overall effectiveness and tolerability have generally been exceeded by newer incretin-based therapies.

The introduction of glucagon-like peptide-1 (GLP-1) receptor agonists marked a major advancement in obesity pharmacotherapy. GLP-1 is an endogenous incretin hormone that enhances glucose-dependent insulin secretion, inhibits glucagon release, delays gastric emptying, and promotes satiety. Consequently, pharmacological stimulation of GLP-1 receptors influences multiple physiological mechanisms involved in appetite regulation, energy intake, and glucose homeostasis.

Semaglutide, a long-acting GLP-1 receptor agonist, has demonstrated clinically meaningful weight loss in adults with overweight or obesity when administered once weekly at a dose of 2.4 mg in combination with lifestyle

modification.[4] Subsequent clinical evidence has further established that its therapeutic benefits extend beyond weight reduction.

The SELECT trial provided important evidence of these broader benefits in adults with established cardiovascular disease and overweight or obesity who did not have diabetes. Semaglutide was associated with a lower incidence of major adverse cardiovascular events than placebo, with the primary endpoint occurring in 6.5% of participants receiving semaglutide compared with 8.0% receiving placebo, corresponding to a hazard ratio of 0.80.[6] These findings have strengthened the concept that effective obesity pharmacotherapy may improve clinically relevant cardiovascular outcomes in addition to reducing body weight.

5. Semaglutide and Next-Generation GLP-1 Therapies

Semaglutide has emerged as a major pharmacological option for the management of obesity. Its therapeutic effects are mediated predominantly through activation of GLP-1 receptors in the central nervous system and peripheral tissues, leading to suppression of appetite, enhanced satiety, and decreased overall energy intake. Clinical trials have demonstrated significant weight loss with once-weekly semaglutide at a dose of 2.4 mg.[4,5] Evidence demonstrating cardiovascular benefits has further strengthened its clinical importance in obesity management.[6]

The development of higher-dose semaglutide formulations aims to achieve greater weight reduction and enhance therapeutic efficacy. In parallel, oral formulations of semaglutide are being developed and evaluated as potential alternatives to injectable therapy. Oral administration may improve treatment convenience and acceptability while potentially increasing access to incretin-based pharmacological treatment.

However, GLP-1 receptor agonists are commonly associated with gastrointestinal adverse effects, including nausea, vomiting, diarrhoea and constipation. Treatment discontinuation may occur in some patients, particularly during dose escalation. Careful dose titration and patient counselling are therefore important.

6. Tirzepatide: Dual GIP/GLP-1 Receptor Agonism

Tirzepatide is considered a significant advancement in the pharmacological treatment of obesity because it acts as a dual agonist at glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors. By targeting both incretin pathways, it promotes substantial weight loss while also producing favorable effects on glucose metabolism.

The SURMOUNT-1 trial demonstrated marked weight reduction over 72 weeks among adults with obesity or overweight accompanied by at least one weight-related complication.[7] Subsequent long-term evidence has further confirmed the sustained efficacy of tirzepatide. In a three-year analysis of individuals with obesity and prediabetes, mean weight loss was approximately 12.3%, 18.7%, and 19.7% with tirzepatide doses of 5, 10, and 15 mg, respectively, compared with 1.3% with placebo.[10] Notably, tirzepatide was also associated with a substantially lower risk of progression to type 2 diabetes, with diabetes developing in 1.3% of participants receiving tirzepatide compared with 13.3% in the placebo group.[10]

These findings are clinically important given the frequent coexistence of obesity and prediabetes. Thus, pharmacological treatment may provide benefits beyond weight reduction by potentially slowing or preventing the progression of obesity-related metabolic complications.

Despite its efficacy, tirzepatide has limitations similar to other GLP-1–based therapies. These include gastrointestinal adverse effects, the requirement for gradual dose escalation, high treatment costs, and the possibility that long-term or continued therapy may be required to sustain weight loss.

7. Retatrutide: Triple Hormonal Receptor Agonism

One of the most promising emerging pharmacological approaches is multi-receptor agonism. Retatrutide is a once-weekly investigational triple agonist targeting the GIP, GLP-1 and glucagon receptors.

The rationale for combining these pathways is based on their complementary metabolic actions. GLP-1 and GIP signalling can suppress appetite and improve glucose metabolism, whereas glucagon receptor activation may increase energy expenditure and promote lipid metabolism.

In a phase 2 trial published in the New England Journal of Medicine, retatrutide produced dose-dependent weight reduction. At 48 weeks, mean weight loss reached approximately 24.2% in the 12-mg group compared with 2.1% with placebo.[11] Gastrointestinal adverse effects were the most frequent treatment-related events and were generally mild to moderate.

Retatrutide is particularly important because it demonstrates the potential of moving beyond single-hormone receptor activation toward coordinated multi-hormonal modulation of energy balance. Nevertheless, it remains investigational and should not be considered an established clinical treatment outside approved indications or clinical trials. As of August 2026, retatrutide has not received FDA approval for obesity; phase 3 development remains ongoing.[12]

8. Orforglipron: An Oral Small-Molecule GLP-1 Receptor Agonist

A key limitation of currently available incretin-based therapies is that many are administered through the subcutaneous route. Orforglipron represents a newer approach and is being developed as an orally administered, non-peptide, small-molecule GLP-1 receptor agonist.

The introduction of oral GLP-1 receptor agonists could offer important advantages in obesity management. Small-molecule agents may potentially simplify manufacturing and storage while providing greater convenience of administration and improved treatment acceptability for patients.

A multinational phase 3 randomized clinical trial evaluated once-daily orforglipron at doses of 6, 12, and 36 mg in adults with obesity receiving treatment alongside a healthy diet and regular physical activity over a 72-week period.[13] The development of oral GLP-1 receptor agonists therefore represents a promising new direction in pharmacological obesity management.

An important question for future clinical practice is whether oral agents can achieve weight-loss efficacy and

long-term cardio metabolic benefits comparable to injectable incretin therapies while maintaining favorable tolerability, safety, and treatment adherence.

9. Amylin-Based Therapies and CagriSema

Amylin is a pancreatic hormone that contributes to postprandial satiety and helps regulate gastric emptying. Consequently, modulation of the amylin pathway has emerged as another promising pharmacological approach to obesity management.

Cagrilintide is a long-acting amylin analogue currently being investigated both as a standalone therapy and in combination with semaglutide. This combination, known as CagriSema, is designed to simultaneously target complementary pathways involved in appetite regulation and energy balance. The rationale for combining GLP-1 and amylin signalling is that their complementary mechanisms may provide greater suppression of appetite and enhanced weight reduction compared with targeting either pathway alone.

Phase 3 clinical studies have reported substantial reductions in body weight with CagriSema, although the magnitude of benefit has varied depending on study design and participant characteristics. However, CagriSema remains an investigational treatment, and additional evidence is required to establish its long-term cardiovascular, metabolic, and safety outcomes.[14]

Beyond amylin-based therapies, several next-generation anti-obesity agents, including dual- and multi-receptor agonists and orally administered metabolic therapies, are under development. These approaches aim to achieve greater and more sustained weight reduction while improving tolerability, convenience, and overall treatment accessibility.

10. Emerging Therapeutic Strategies Beyond GLP-1

The future of obesity pharmacotherapy is unlikely to depend exclusively on GLP-1 receptor activation. Several biological pathways are being investigated.

10.1 Multi-receptor agonists

Multi-receptor agonists simultaneously target pathways involved in appetite regulation, glucose metabolism, lipid metabolism and energy expenditure. Examples include GIP/GLP-1 dual agonists and GIP/GLP-1/glucagon triple agonists.

This approach seeks to reproduce the physiological effects of multiple endogenous metabolic hormones within a single therapeutic molecule.

10.2 Amylin receptor agonists

Amylin analogues may reduce appetite and slow gastric emptying. Combining amylin signalling with GLP-1 activation may provide complementary effects on satiety and energy intake.

10.3 Oral incretin therapies

Oral small-molecule GLP-1 receptor agonists may overcome some limitations associated with injectable biologics. Their development may substantially expand the number of patients willing to initiate long-term pharmacotherapy.

10.4 Combination pharmacotherapy

Future obesity treatment may increasingly resemble combination treatment used in hypertension, diabetes and dyslipidaemia. Combining agents with complementary mechanisms could permit greater efficacy while reducing dose-dependent adverse effects.

10.5 Therapies targeting energy expenditure

Agents targeting glucagon signalling, mitochondrial metabolism, adipose tissue thermogenesis and other mechanisms of energy expenditure are being investigated. The goal is to move beyond appetite suppression toward simultaneous reduction of energy intake and enhancement of energy expenditure.

11. Clinical Benefits Beyond Weight Loss

An important advancement in obesity pharmacotherapy is the understanding that treatment effectiveness should not be assessed exclusively on the basis of the percentage reduction in body weight. Weight loss can produce multiple metabolic and functional benefits, including improved insulin sensitivity, reduced blood pressure, better lipid profiles, decreased hepatic fat accumulation, improvement in obstructive sleep apnoea, and enhanced physical functioning. In certain patient populations, pharmacological treatment may also provide meaningful cardiovascular benefits.

The SELECT trial provided significant evidence that semaglutide can lower the incidence of major cardiovascular events among individuals with overweight or obesity and established cardiovascular disease who do not have diabetes.[6] Likewise, long-term treatment with tirzepatide has demonstrated substantial and sustained weight reduction while significantly decreasing the risk of progression to type 2 diabetes in people with obesity and prediabetes.[10]

Collectively, these findings highlight a broader therapeutic goal in obesity management: addressing the metabolic consequences and reducing obesity-related complications, rather than focusing solely on BMI or the magnitude of weight loss.

12. Adverse Effects and Safety Considerations

Despite their therapeutic efficacy, emerging anti-obesity medications are not free from adverse effects. Gastrointestinal symptoms—including nausea, vomiting, diarrhoea and constipation—are among the most frequently reported adverse events with GLP-1-based therapies and related multi-receptor agonists.[5,7,11]

Adverse effects are often most prominent during dose escalation and may be reduced through gradual titration. Clinicians should evaluate patient-specific contraindications, concomitant medications, nutritional status and comorbidities before initiating treatment.

Long-term surveillance remains essential because many emerging therapies have substantially shorter safety histories than established cardiovascular or metabolic medications. In addition, the effects of long-term treatment on body composition, lean mass, bone health, nutritional status and other organ systems require continued investigation.

13. Weight Regain and the Need for Long-Term Therapy

Treatment discontinuation is a critical consideration in the pharmacological management of obesity. Because body weight is regulated by strong biological homeostatic mechanisms, cessation of effective anti-obesity medication may lead to increased appetite and subsequent regain of lost weight.

This pattern reinforces the view that obesity pharmacotherapy should generally be considered as a long-term management strategy rather than a temporary treatment course. Similar to other chronic metabolic conditions, such as hypertension and dyslipidaemia, discontinuing an effective therapy may allow the underlying disease process and associated phenotype to re-emerge.

Accordingly, the World Health Organization emphasizes the importance of incorporating long-term pharmacological treatment into comprehensive chronic-care programmes rather than treating GLP-1–based therapy as an isolated intervention.[8] Future studies should focus on defining the appropriate duration of therapy, optimal maintenance dosing, approaches to treatment de-escalation, and the potential role of combination therapies in sustaining long-term weight reduction and preventing weight regain.

14. Challenges of Cost, Access and Health Equity

The rapid emergence of highly effective pharmacological therapies for obesity has created a significant challenge: the treatments capable of producing the greatest clinical benefits may remain inaccessible to individuals and communities experiencing the highest burden of obesity. Factors such as medication cost, insurance coverage, drug availability, manufacturing capacity, and healthcare infrastructure can substantially influence access to treatment.

These challenges are particularly relevant in low- and middle-income countries, where the prevalence of obesity is rising while healthcare systems often operate with limited financial and infrastructural resources. The World Health Organization has emphasized affordability, healthcare-system readiness, the availability of long-term evidence, and health equity as important considerations in its conditional recommendation concerning GLP-1–based therapies.[8]

In countries such as India, the use of pharmacological therapies for obesity therefore needs to be evaluated within the broader context of treatment affordability, regional differences in obesity phenotypes, diabetes risk, accessibility of healthcare services, and the ability of patients to maintain long-term treatment. A sustainable approach will require not only effective medications but also strategies that improve equitable access and support continued adherence.

15. Future Directions

The future management of obesity is likely to shift toward increasingly personalized pharmacological approaches. Instead of adopting a uniform treatment strategy, therapeutic choices may be tailored according to individual factors such as metabolic phenotype, severity and distribution of adiposity, diabetes status, cardiovascular risk, coexisting liver disease, appetite-related characteristics, genetic determinants, and response to previous therapy.

Multi-hormonal receptor agonists are among the most promising developments in obesity pharmacotherapy. Retatrutide has demonstrated the potential of simultaneous activation of three metabolic hormone pathways, producing substantial weight loss that approaches the magnitude reported with certain metabolic interventions.[11] Similarly, oral GLP-1 receptor agonists, including orforglipron, may offer greater convenience and could potentially improve accessibility to pharmacological treatment.[13]

Future therapeutic strategies may also incorporate combinations targeting GLP-1, GIP, glucagon, and amylin pathways to achieve greater and more sustained metabolic benefits. However, future research should extend beyond weight reduction alone and place greater emphasis on preservation of lean body mass, cardiovascular outcomes, quality of life, long-term safety, and treatment affordability.

Overall, the development of obesity therapies should increasingly adopt a chronic disease management model focused on sustained disease control, prevention of obesity-related complications, and improvement of overall health and quality of life, rather than relying solely on the magnitude of weight loss.

16. Conclusion

Obesity is now firmly recognized as a chronic, relapsing and multifactorial disease requiring long-term management. The emergence of highly effective incretin-based therapies has fundamentally changed the pharmacological treatment landscape. Semaglutide has demonstrated substantial weight reduction and cardiovascular benefit, while tirzepatide has produced even greater weight reduction and demonstrated an important effect on progression from prediabetes to type 2 diabetes.

The next generation of therapies is moving toward multi-receptor agonism, oral GLP-1 receptor activation and combination approaches involving amylin and other metabolic pathways. Retatrutide and orforglipron are particularly notable examples of this rapidly evolving field, although their regulatory status and evidence base differ from currently approved therapies.

Despite these advances, pharmacotherapy should not be considered a replacement for healthy dietary patterns, physical activity and behavioural support. The major challenge for the coming decade will be translating impressive clinical-trial efficacy into affordable, equitable and sustainable long-term obesity care.

Ultimately, the therapeutic goal should extend beyond achieving a lower number on the weighing scale. Successful obesity management should reduce metabolic and cardiovascular risk, improve physical function and quality of life, prevent disease progression and maintain health benefits over the long term.

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