The evolution of obesity pharmacotherapy from sympathomimetics to incretin-based therapies

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Abstract

Obesity is a chronic metabolic disorder that has reached epidemic proportions globally and in South Africa, contributing to the increasing burden of cardiometabolic diseases. Although lifestyle modifications remain a fundamental approach, long-term weight loss is often limited, necessitating the use of pharmacotherapy. Historically, centrally acting sympathomimetics, such as phentermine, have been predominant in South African treatments, albeit with restrictions concerning their safety and duration. This review examines the evolution of obesity pharmacotherapy from traditional agents, including phentermine and orlistat, to contemporary incretin-based therapies. Particular emphasis is placed on glucagon-like peptide-1 receptor agonists and dual incretin agonists, such as semaglutide and tirzepatide, which have demonstrated unprecedented efficacy in clinical trials involving patients with obesity. Emerging multi-hormonal and non-injectable agents are also discussed. This article underscores the transition from short-term appetite suppression to sustained pharmacological management of obesity and its comorbidities.

Keywords: incretin-based therapies, obesity, pharmacotherapy, weight management

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Introduction

Obesity has reached epidemic proportions worldwide. There has been a startling rise in obesity rates, with prevalence having tripled since 1975 and now affecting over 13% of the global adult population.[1] This rapid increase, together with the rising burden of obesity-related comorbidities, has intensified the need for more effective therapeutic strategies.[1] Obesity is commonly defined as an accumulation of abnormal or excessive adipose tissue associated with an increase in Body Mass Index (BMI).[2] The BMI is a calculation that utilises a person's weight in kilograms divided by their height in meters. The World Health Organization (WHO) proposes that obesity and morbid obesity are proportional to a BMI of ≥ 30 kg/m^2 and ≥ 40 kg/m^2, respectively.[3] Although this calculation is ubiquitously used, it is not without pitfalls. The BMI calculation does not account for body composition, as it does not consider other tissues such as muscle, and can thus under- or overestimate adiposity.[4] Despite contention of the usefulness of the index, it is currently the surrogate to determine risks associated with DM and other metabolic illnesses. It can be argued that abdominal adiposity would be a more effective indicator as it is linked with insulin resistance and other metabolic disorders.[5] Some experts propose that obesity should be viewed as a disease, but no consensus has been reached on this matter.[4]

The rising prevalence of obesity reflects the complex interplay of environmental, behavioural, and socioeconomic factors. As a result of urbanisation and evolving socioeconomic dynamics, processed foods have become more popular, and these contain high levels of refined sugars, flavouring agents, and emulsifiers.[6] These additives have demonstrated addictive properties,[6-7] inferring repetitive use. Multiple studies have indicated a strong association between these factors and obesity. Numerous observational and experimental studies have demonstrated a strong association between these dietary patterns and excess weight gain.[6] Clinicians have been managing obesity and its sequelae for years. However, despite these efforts, it is now the fifth leading cause of mortality globally.[3] Care and prevention have mainly revolved around lifestyle modifications, but these are less effective in isolation.[8] Additionally, severely obese patients have mentioned having difficulty implementing changes owing to their environment and schedules.[9]

Pathophysiology of obesity

The aetiology of obesity is multifactorial, involving genetic and environmental factors that ultimately lead to sustained dysregulation of energy homeostasis.[10] While single-gene defects or syndromic forms contribute to rare cases of paediatric obesity, cases arise from a complex interplay between inherited susceptibility and environmental influences.[10] Central regulation of appetite is disrupted within the arcuate nucleus of the hypothalamus, where an imbalance between orexigenic agouti-related peptide and neuropeptide Y neurons and anorexigenic pro-opiomelanocortin and cocaine and amphetamine-regulated transcript neurons impairs satiety signalling.[11] Normally, these hypothalamic satiety signalling pathways are reinforced by gut-derived incretin hormones such as glucagon-like peptide 1 (GLP-1) and the glucose-dependent insulinotropic polypeptide (GIP).[12-13] In obesity, responsiveness to these signals is attenuated, contributing to persistent appetite drive.[12] Concurrently, sustained positive energy balance promotes adipocyte hypertrophy

and hyperplasia, leading to the expansion of adipose tissue.[14] This expansion disrupts adipokine secretion, leading to high leptin levels and the development of central leptin resistance.[14] Additionally, the release of pro-inflammatory cytokines[15] and activation of the endocannabinoid system[16] drive chronic low-grade inflammation and insulin resistance. Together, these neurohormonal and metabolic shifts render obesity a chronic disease in which the body's internal systems actively maintain an elevated baseline weight. Pharmacological approaches to obesity often overlap with those used in type 2 diabetes mellitus.[17]

Pharmacological therapies

Lifestyle measures, including dietary modification, physical activity, and behavioural interventions, achieve modest initial weight loss and improve metabolic health.[18] However, long-term maintenance is often hindered by adaptive thermogenesis, increased appetite, and the practical difficulty of sustaining habits in daily life.[19] Consequently, pharmacotherapy plays a vital role as an adjunct to lifestyle modifications in the treatment of obesity, especially for patients who do not achieve sufficient weight loss through lifestyle interventions alone.[20] A variety of centrally acting, peripherally acting, and incretin-based agents are currently available or in development, each with distinct mechanisms of action and efficacy profiles, as shown in Table I.

Centrally acting sympathomimetic appetite suppressants

Centrally acting drugs, such as phentermine (Duromine®), have long been used as adjuncts in the management of obesity. These agents work by increasing the concentrations of norepinephrine, dopamine, and serotonin within the hypothalamic nuclei, consequently enhancing satiety and suppressing appetite. Phentermine was approved by the United States Food and Drug Administration in 1959 for short-term weight management, with treatment duration limited to 12 weeks, though it remains used off-label long-term. In South Africa, Duromine® is registered for short-term obesity management in doses of 15 or 30 mg daily.[20] Phentermine monotherapy is associated with modest short-term weight loss, with controlled trials reporting reductions of approximately 3–5% of baseline body weight. A quantitative analysis of clinical trials of phentermine monotherapy revealed a mean weight loss of 3.6 kg over a mean of 13 weeks.[21] Common side-effects of phentermine include tachycardia, restlessness, insomnia, dry mouth and constipation.[30] Despite weight loss typically leading to reduced blood pressure, phentermine can increase blood pressure and is thus not recommended for people with uncontrolled hypertension.[30] To enhance efficacy, phentermine is commonly combined with topiramate, which modulates γ-aminobutyric acid (GABA) receptors, synergistically increasing satiety.[22] The landmark CONQUER trial demonstrated that this dual approach achieves a superior 10.2% mean weight loss over 56 weeks, nearly doubling the efficacy of monotherapy, while allowing for lower, better-tolerated dosing for long-term obesity management.[22]

Centrally acting combination therapies

Combination therapies that target multiple central pathways involved in appetite regulation include the naltrexone-bupropion combination, marketed as Contrave. Approved in South Africa in 2020, this fixed-dose combination contains 16 mg of naltrexone and 180 mg of bupropion per tablet, administered twice daily.[20] Naltrexone is an opioid receptor antagonist that inhibits β-endorphin-mediated autoinhibitory feedback of pro-opiomelanocortin neurons, thereby sustaining satiety signals. Conversely, bupropion functions as a dopamine and norepinephrine reuptake inhibitor that stimulates these neurons and further enhances satiety. In the COR-I trial, treatment over 56 weeks resulted in a mean weight loss of 6.1% compared to 1.3% in the placebo group, with 48% of participants achieving at least

Table I: Pharmacological agents used for the management of obesity

Drug/ Combination	Drug class	Primary mechanism of action	Typical dosing	Reference(s)
Phentermine (Duromine®)	Centrally acting sympathomimetic	Increases hypothalamic norepinephrine, dopamine, and serotonin to suppress appetite	15–30 mg once daily	21
Phentermine + Topiramate	Centrally acting combination	Sympathomimetic appetite suppression plus GABA modulation	Titrated combination dosing	22
Naltrexone + Bupropion (Contrave®)	Centrally acting combination	POMC activation and inhibition of β-endorphin feedback	16 mg/180 mg twice daily	23
Orlistat (Xenical®)	Peripheral lipase inhibitor	Inhibits gastric and pancreatic lipases, reducing fat absorption	120 mg three times daily	24
Liraglutide (Saxenda®)	GLP-1 receptor agonist	Enhances satiety; delays gastric emptying; improves glycaemic control	3.0 mg once daily (SC)	25
Semaglutide (Wegovy®)	GLP-1 receptor agonist	Central appetite suppression and peripheral metabolic effects	2.4 mg once weekly (SC)	26
Tirzepatide (Mounjaro®)	Dual GLP-1/GIP receptor agonist	Multi-hormonal appetite and metabolic regulation	Weekly SC dosing (titrated)	27
Emerging agents (e.g. retatrutide, orforglipron, cagrilintide)	Multi-agonists/novel incretins	Target multiple metabolic and appetite pathways	Under investigation	28,29

Abbreviations: GABA: gamma-aminobutyric acid; GI: gastrointestinal; GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide-1; SC: subcutaneous

5.0% weight loss.[23] Common adverse effects include nausea, constipation, and headache. Owing to the bupropion component, this combination is contraindicated in patients with seizure disorders or uncontrolled hypertension, and it should not be co-administered with opioids.[20]

Peripheral gastrointestinal lipase inhibitors

Peripheral gastrointestinal lipase inhibitors decrease fat absorption in the gastrointestinal tract, with orlistat (Xenical®) representing the main clinically used agent. Registered in South Africa since 1997, orlistat is a potent inhibitor of gastric and pancreatic lipases and functions by binding covalently to the active serine residues of these enzymes in the gastric and intestinal lumen.[20] Unlike central-acting drugs, orlistat acts peripherally to inhibit the hydrolysis and absorption of dietary triglycerides, leading to a subsequent faecal excretion of approximately 30% of ingested fat.[31] Clinical evidence from a recent systematic review of 22 randomised controlled trials indicates that orlistat, taken at a dose of 120 mg three times daily, results in a mean weight loss of approximately 2.4 kg greater than placebo.[32] Beyond its role in weight reduction, the landmark XENDOS trial has demonstrated that orlistat, when administered as an adjunct to lifestyle intervention, significantly reduces the cumulative incidence of type 2 diabetes by 37.3% in patients with impaired glucose tolerance.[24] However, the clinical utility of orlistat is often limited by gastrointestinal side-effects due to fat malabsorption. Such side-effects include steatorrhoea, oily spotting, faecal urgency, diarrhoea, abdominal pain, and fatty/oily stools.[33] Additionally, orlistat can impair the absorption of fat-soluble vitamins A, D, E, and K, occasionally leading to reduced plasma concentrations; thus, supplementation with a multivitamin is recommended during therapy to prevent deficiencies.[33]

Incretin-based therapies and metabolic appetite regulation

Incretin-based therapies have expanded the pharmacological options available for obesity management by mimicking endogenous hormones involved in the regulation of satiety and glucose homeostasis.[34] Liraglutide and semaglutide are the most commonly used agents within this class, and they are glucagon-like peptide-1 receptor agonists (GLP-1 RAs) that target the hypothalamic pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript neurons, thereby enhancing satiety and reducing hunger.[35] Peripherally, these agents slow gastric emptying and modulate glucose metabolism by stimulating glucose-dependent insulin secretion and suppressing glucagon release.[35] The SCALE trial demonstrated that liraglutide administered at a dose of 3 mg daily over 56 weeks results in a mean weight loss of approximately 8%.[36] Moreover, the more potent, once-weekly 2.4 mg semaglutide led to a mean weight loss of 14.9% in the STEP 1 trial.[26] Direct comparative data from the STEP 8 trial further demonstrated the superior efficacy of semaglutide, with a mean weight loss of 15.8% compared with 6.4% for liraglutide.[37] Despite their efficacy, GLP-1 RAs are commonly associated with dose-dependent gastrointestinal side-effects, such as nausea and vomiting, which typically require gradual dose escalation to improve tolerability.[35]

Emerging therapies and combination regimens

Obesity pharmacotherapy is rapidly developing, with a shift towards the use of multi-hormonal co-agonists that target multiple pathways to achieve weight loss comparable to that achieved with bariatric surgery. Tirzepatide, a dual GLP-1 and GIP receptor agonist, demonstrated a mean weight loss of up to 22.5% at the highest dose in the SURMOUNT-1 trial,[27] leading to its recent approval for obesity management in South Africa.[20] Beyond dual agonism, triple agonists such as retatrutide which targets the GLP-1, GIP, and glucagon receptors, have shown unprecedented efficacy. In a Phase 2 trial, participants achieved a mean weight loss of 24.2% at 48 weeks,[38] and subsequent Phase 3 TRIUMPH-4 data reported to achieve weight loss of 28.7% over 68 weeks.[39]

There is also a renewed interest in treating obesity by modulating the endocannabinoid system through the use of peripherally restricted cannabinoid-1 (CB1) receptor blockers such as monlunabant and nimacimab.[40-41] Unlike the first-generation CB-1 receptor antagonist rimonabant,[42] which was withdrawn due to psychiatric risks, these newer agents are designed to target metabolic tissues while avoiding the central nervous system, thus minimising neuropsychiatric side-effects.[43] Additionally, the development of oral incretins such as orforglipron[28] and amylin-based combinations such as cagrilintide[29] indicates that there is an emerging focus on highly potent, scalable, and non-injectable options for long-term obesity management.

Conclusion and future directions

Obesity is a chronic metabolic disorder that requires a comprehensive therapeutic approach. In South Africa, pharmacological management has relied on the short-term use of centrally acting sympathomimetics, such as phentermine, which offers modest efficacy but is limited by safety concerns. The advent of more effective incretin-based therapies marks a significant advance in obesity pharmacotherapy, providing durable weight reduction and metabolic improvements. These agents have redefined therapeutic expectations by enabling sustained control of appetite and energy balance rather than temporary weight loss. As the therapeutic landscape evolves to include dual and triple hormonal agonists, clinical practice must align with emerging evidence and guidelines. The integration of pharmacotherapy with lifestyle interventions remains crucial for effective obesity management and reducing obesity-related morbidity.

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