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Editorial article

From Liraglutide to Tirzepatide: New Frontiers in Anti-Obesity Pharmacotherapy

Running Title: From Liraglutide to Tirzepatide

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Abstract

Obesity is a global health challenge, with over one billion people affected worldwide. While lifestyle changes remain essential, pharmacological interventions have become increasingly crucial in managing this complex condition. This editorial explores the evolution of anti-obesity medications, from liraglutide to the more recent breakthroughs like semaglutide and tirzepatide. These drugs, especially the newer GLP-1 and dual GIP/GLP-1 receptor agonists, have shown remarkable efficacy—comparable to bariatric surgery in some cases. The discussion highlights not only their clinical benefits but also their mechanisms, limitations, and future potential. As science advances, the integration of these therapies into mainstream care could significantly transform obesity treatment and improve long-term health outcomes.

Keywords: Liraglutide; Tirzepatide; Obesity; GLP-1 Agonists; GIP Agonists; Incretin

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Introduction

Obesity, a chronic and multifactorial disease, has reached epidemic proportions worldwide. As of 2025, the World Health Organization estimates that more than 1.1 billion people globally are living with obesity (1). Despite extensive efforts in lifestyle modification and behavioral therapies, the long-term success rate in maintaining weight loss remains low. Pharmacotherapy has thus become a critical adjunct in the comprehensive management of obesity. Over the past two decades, the therapeutic landscape has dramatically evolved, most notably with the development of GLP-1 receptor agonists. The progression from liraglutide to semaglutide and now tirzepatide marks a significant advancement in the medical treatment of obesity.

Liraglutide: A Turning Point in Obesity Treatment

Liraglutide, a GLP-1 receptor agonist, marked a major advance in obesity pharmacotherapy. Initially approved for type 2 diabetes under the brand name Victoza, liraglutide later received approval for chronic weight management at a higher dose (3.0 mg) as Saxenda. GLP-1 is an incretin hormone that stimulates insulin secretion, delays gastric emptying, and reduces appetite via central mechanisms in the hypothalamus.

Clinical trials demonstrated that liraglutide leads to a significant reduction in body weight (~8% on average), along with improvements in glycemic control and cardiometabolic markers. This efficacy, combined with a relatively favorable safety profile, positioned liraglutide as a foundational agent in obesity treatment (2).

Semaglutide and the Rise of Weekly GLP-1 Agonists:

Semaglutide, another GLP-1 receptor agonist, addressed several limitations of liraglutide. With a longer half-life allowing once-weekly administration, semaglutide quickly gained traction.

The STEP (Semaglutide Treatment Effect in People with Obesity) trials showed unprecedented weight loss results—up to 15–17% of body weight. These findings shifted the paradigm of obesity treatment from modest benefits to near-surgical efficacy, generating enormous interest from both clinicians and patients. Moreover, semaglutide demonstrated significant improvements in blood pressure, lipid profile, and glycemic control, even in non-diabetic individuals. These pleiotropic effects underscore the value of GLP-1 agonists in addressing the broader cardiometabolic risks associated with obesity (3).

Tirzepatide: Dual Agonism and Superior Outcomes

Tirzepatide, a dual GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 receptor agonist, represents a new class of agents in obesity pharmacotherapy. Approved by the FDA in 2022 for type 2 diabetes (Mounjaro), it was later approved for chronic weight management.

Tirzepatide combines the effects of GLP-1 and GIP, offering enhanced weight loss and metabolic improvements. The trials demonstrated weight loss of up to 22.5%, setting a new benchmark for non-surgical interventions.

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Patients also showed improved insulin sensitivity, reduced waist circumference, and favorable shifts in lipid profiles. These outcomes suggest that tirzepatide may not only rival bariatric surgery in terms of efficacy but also offer a non-invasive, pharmacologic alternative (4).

Mechanistic Insights and Clinical Implications

GLP-1 and GIP receptors are widely expressed in pancreatic β-cells, the gastrointestinal tract, and the central nervous system. Activation of these receptors leads to appetite suppression, delayed gastric emptying, and improved insulin secretion.

The dual receptor targeting of tirzepatide enhances these effects and may reduce compensatory mechanisms that often blunt long-term weight loss. Moreover, evidence suggests that incretin-based therapies can positively modulate gut microbiota and reduce systemic inflammation, contributing to overall metabolic health. These mechanisms support the use of tirzepatide not just for weight loss, but as a metabolic disease-modifying agent (5, 6).

Safety and Tolerability

Although these agents are generally well tolerated, gastrointestinal symptoms such as nausea, vomiting, and diarrhea remain the most common adverse events. These effects are dose-dependent and tend to diminish over time. Rare but serious risks include pancreatitis and gallbladder disease. The long-term safety profile of tirzepatide is still under evaluation, though interim analyses are promising. There is ongoing discussion about the risk-benefit ratio in non-diabetic individuals and the ethical considerations of prescribing potent metabolic drugs for cosmetic or societal pressures rather than health-related reasons (2-4).

Cost, Accessibility, and Health Policy

Despite their efficacy, GLP-1 receptor agonists and related therapies are expensive and not universally covered by insurance plans. This raises issues of accessibility and equity, particularly in low-resource settings.

Policymakers and healthcare systems must balance innovation with affordability. Several countries are evaluating cost-effectiveness models and considering these therapies as essential medicines, given their dual role in weight and metabolic disease management (7).

Future Directions: Triple Agonists and Beyond

The success of tirzepatide has spurred the development of triple agonists targeting GLP-1, GIP, and glucagon receptors. Early-phase trials of agents like retatrutide show even greater weight loss potential (up to 24%) (8). These agents may redefine obesity treatment, possibly replacing bariatric surgery for selected patients.

Personalized medicine approaches, incorporating genetic and metabolic profiling, may help identify responders and guide treatment choices. Future research should also explore long-term cardiovascular outcomes and the sustainability of weight loss beyond pharmacologic support (9, 10).

Conclusion

The transition from liraglutide to tirzepatide illustrates a remarkable evolution in obesity pharmacotherapy. These agents offer not only

significant weight loss but also improvements in metabolic health and quality of life. As research continues to expand the arsenal of anti-obesity drugs, it is crucial to ensure equitable access and long-term sustainability. The future of obesity treatment lies in a multidisciplinary approach that combines pharmacological, behavioral, and policy-driven interventions.

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