# The Next Generation of Pharmacological Treatments for Chronic Disease

**The success of GLP-1 receptor agonists as obesity therapeutics has initiated a seismic shift in the treatment paradigm and conceptual understanding of non-communicable chronic diseases. Originally developed for type 2 diabetes, this drug class has demonstrated that pharmacological interventions can meaningfully address chronic conditions long considered incurable or manageable only through behavioural modification or surgical intervention.**

Recently approved incretin-mimetic-based therapies, such as semaglutide and tirzepatide, may achieve weight reductions that rival bariatric surgery, reframing obesity as a pharmacologically modifiable disease.[1] These agents have also shown that behavioural interventions, once the cornerstone of obesity management, can be more effective when supported by pharmacologic treatment, improving adherence and long-term outcomes.[2]

Beyond weight loss, GLP-1 receptor agonists have demonstrated the systemic impact of glucose metabolism modulation, which influences an array of interconnected conditions not traditionally linked to obesity in clinical or therapeutic development contexts. This has elevated interest in the broader class of upstream metabolic modulators, drugs that mimic nutrient-stimulated hormones, which regulate glucose homeostasis and energy balance.[3]

Nutrient-stimulated hormones are hormones released in response to specific nutrients. Examples of nutrient-stimulated hormones include insulin, glucagon, GLP-1, ghrelin and gastric inhibitory peptide (GIP). These hormones play a crucial role in regulating metabolism, appetite and other physiological processes through receptor binding in the liver, pancreas and brain, including the hypothalamus and hindbrain. For example, in the pancreas, GLP-1 receptor activation stimulates insulin release, facilitating glucose uptake and lowering blood sugar. In the brain, GLP-1 receptor activation suppresses appetite and enhances satiety. These multi-organ actions help explain the broad clinical benefits observed with nutrient-stimulated hormone-based (NUSH-based) therapies, which span from treatment of chronic brain disorders such as addiction to diseases of the heart, liver and kidney.[3]

The demonstrated efficacy of GLP-1 receptor agonists has profoundly altered the clinical management of obesity, a condition historically viewed by providers and payers as best addressed through lifestyle modification, except in extreme cases. Their impact on interrelated chronic conditions has triggered a high-stakes innovation race, redefining how chronic diseases are understood and treated across therapeutic domains. In fact, semaglutide, a GLP-1 agonist, recently received accelerated approval for the treatment of adults with MASH with moderate to advanced liver fibrosis.[4]

## Future Obesity Therapies Will Be More Potent, Tolerable and Targeted

Despite recent advances in NUSH-based therapeutic development, the tide of innovation remains in its infancy. At present, obesity affects approximately 40.3% of the US adult population.[5] However, only 2% of adult patients in the US took a GLP-1 drug in 2024, underscoring the vast undertreatment of obesity in the US.[6] This lag reflects restricted access to treatment, including limited treatment coverage by payers. It also reflects a wide range of untapped opportunities for therapeutic development.

In the coming years, clinical developers will fill the opportunity gaps for NUSH-based therapies by increasing the potency and durability of treatments, addressing therapeutic barriers to access and adherence, developing therapies for a wider breadth of interrelated chronic conditions, and personalising treatments to patient needs.

## Increasing Potency and Durability

Building on the success of GLP-1 receptor agonists, the next wave of innovation is advancing toward dual and triple agonist therapies, agents that co-activate multiple NUSH pathways to achieve more potent and durable treatment. These multi-receptor agonists offer enhanced efficacy by targeting complementary hormonal axes involved in appetite regulation, energy expenditure and glucose homeostasis.[7]

The leading example is Tirzepatide, a dual GLP-1/GIP receptor agonist, which has demonstrated average weight reductions exceeding 20% in clinical trials, surpassing GLP-1 monotherapy and approaching bariatric outcomes.[8] Tirzepatide's dual mechanism enhances insulin secretion, delays gastric emptying and amplifies satiety signals, while GIP co-activation may improve insulin sensitivity of adipose tissue and reduce postprandial lipid excursions.[9] Beyond weight loss, Tirzepatide has been approved for the treatment of patients with obstructive sleep apnea and obesity.[10] Clinical studies have also demonstrated that Tirzepatide improved outcomes in patients with metabolic dysfunction-associated fatty liver disease (steatohepatitis) and reduced clinical events in heart failure patients with preserved ejection fraction.[11,12]

Looking ahead, triple agonists such as retatrutide, which targets GLP-1, GIP and glucagon receptors, are under active investigation for their ability to simultaneously suppress appetite, increase energy expenditure and improve glycemic control. Early phase trials suggest these agents may induce weight loss exceeding 24%, with additional benefits in metabolic dysfunction-associated steatohepatitis and cardiovascular risk reduction.[13]

A multi-hormonal approach reflects a deeper understanding of obesity as a multi-systemic disease that can be treated through a reversal of entrenched metabolic dysfunction. As new agents progress through late-stage development and regulatory review,

they are poised to redefine the standard of care for a constellation of chronic diseases linked to dysregulated metabolism.

**Improving Access and Adherence**

The next generation of metabolic therapies must also overcome barriers to access and adherence. While current GLP-1 therapies are administered via weekly subcutaneous injections, ongoing research is exploring oral formulations and longer-acting injectables to reduce dosing frequency and improve convenience.[7]

Addressing side effects is another area of active research. The potency of many GLP-1 therapies is limited by dose-dependent gastrointestinal side effects, particularly nausea. Alternative formulations and combination therapies that reduce side effects and dosing burden are likely to improve long-term adherence and expand patient eligibility.

**Broader Indications and Precision Therapeutics**

NUSH-based therapies are increasingly viewed as systemic agents with relevance across cardiometabolic, hepatic, neurological and behavioural domains. To capitalise on the multi-indication potential of therapies for chronic diseases, developers are designing trials with cross-speciality endpoints, adaptive protocols and regulatory strategies that support broader therapeutic positioning.[14]

As therapeutic options grow, precise patient selection becomes crucial. Historically, obesity has been defined by body mass index (BMI) alone, encouraging a one-size-fits-all approach. In 2025, the Lancet Diabetes & Endocrinology Commission proposed a new definition and diagnostic criteria for clinical obesity, emphasising that BMI alone is an incomplete measure of its clinical impact and should not be used for individual health assessment. They suggested distinguishing clinical obesity, a systemic disease caused by excess adiposity, from preclinical obesity, which involves excess adiposity without organ dysfunction but with elevated future risk. Future classifications will likely categorise obesity into subtypes, enabling more targeted therapies and management.[15]

NUSH–based treatments are also being adapted for specific patient subpopulations. For example, older adults or those with sarcopenic obesity may be at higher risk of muscle loss during treatment. The BELIEVE Phase 2b study, a global clinical trial in adults who are overweight or obese, evaluated combination therapy with bimagrumab, a monoclonal antibody that promotes muscle preservation, and semaglutide. Results demonstrated enhanced fat loss while preserving lean mass, highlighting the potential of combination therapies to improve metabolic outcomes without compromising functional health.[16]

**Insights From Today's Clinical Developers**

Already, the adoption of multi-indication approaches to therapeutic pipelines is widespread. In a 2025 ICON survey of 155 biopharma sponsors actively developing therapies for obesity or related comorbidities, 83% reported pursuing multi-indication strategies for at least one therapy in their pipelines.[17] The survey findings reflect a shared view of obesity therapeutics as systemic agents with relevance across cardiometabolic, hepatic, neurological and behavioural domains and suggest that the race towards pharmacologic treatment of chronic diseases has only just begun.[14]

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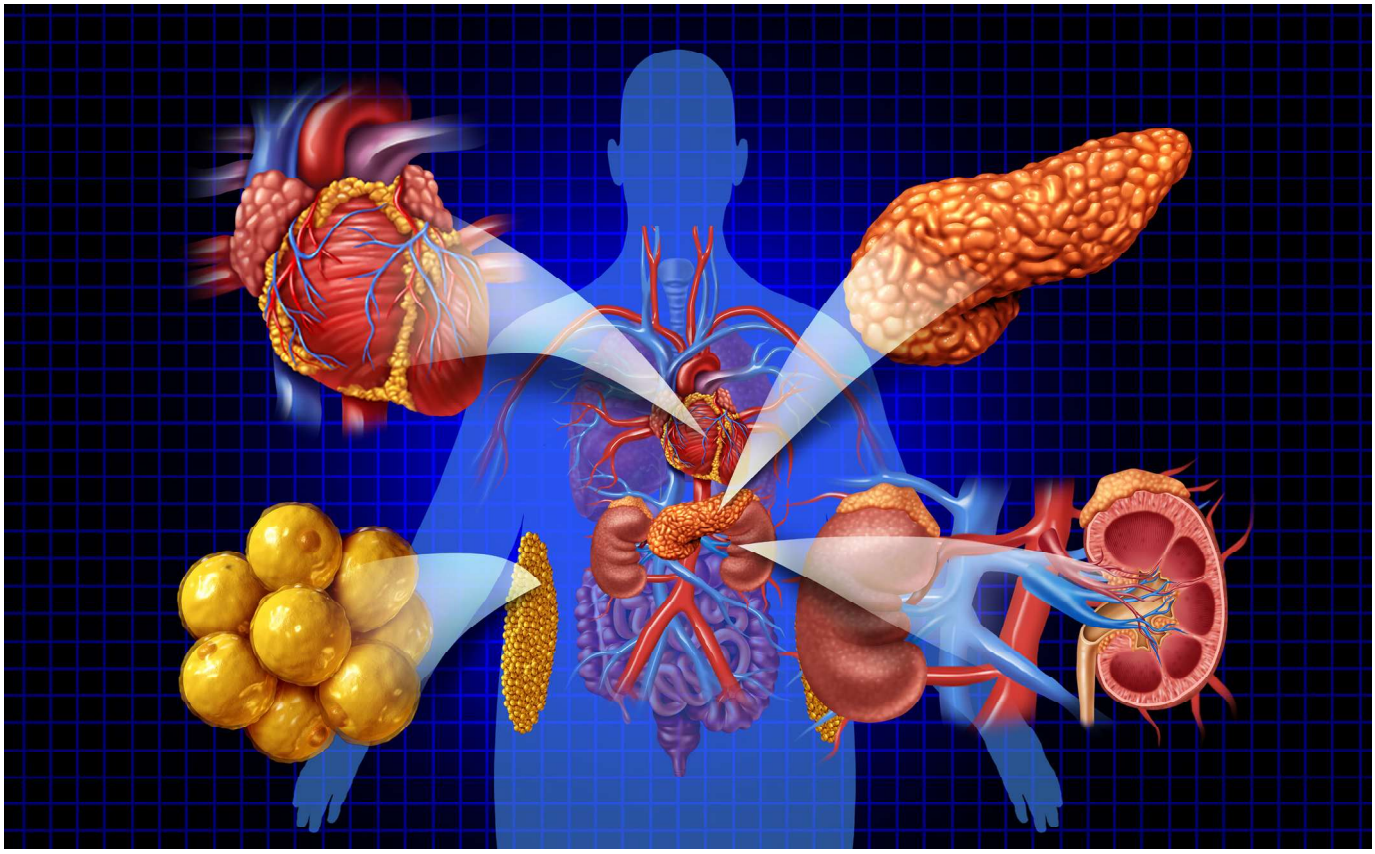

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