Why are we still in need for novel anti-obesity medications?

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Summary

From the pioneering moment in 1987 when the insulinotropic effect of glucagon-like peptide 1 (GLP-1) was first demonstrated in humans, to today's pharmaceutical gold rush for GLP-1-based treatments of obesity, the journey of GLP-1 pharmacology has been nothing short of extraordinary. The sequential conceptual developments of long-acting GLP-1 receptor (GLP-1R) mono-agonists, GLP-1R/glucose-dependent insulinotropic polypeptide receptor (GIPR) dual-agonists, and GLP-1R/GIPR/glucagon receptor (GcgR) triple agonists, have led to profound body weight-lowering capacities, with benefits that extend past obesity and towards obesity-associated diseases. The GLP-1R/GIPR dual-agonist tirzepatide has demonstrated a remarkable 23% body weight reduction in individuals with obesity over 72 weeks, eclipsing the average result achieved by certain types of bariatric surgery. Meanwhile, the GLP-1R/GIPR/GcgR triple-agonist retatrutide achieves similar body weight loss (~25%) in just two-thirds of the time, potentially surpassing the efficacy of Roux-en-Y gastric bypass. These remarkable achievements rightfully raise the question whether and why there is still need for novel anti-obesity medications (AOMs) in the future.

Keywords: Obesity; Anti-obesity medication (AOM); GLP-1; GIP; Diabetes

Should we step off the scale?

New versions and variations of dual- and triple agonists are on the horizon, offering subtle alterations in chemical structure or target that may further enhance body weight-lowering capacity, tolerability, and convenience. However, with each new peptide formulation comes a diminishing return on therapeutic improvement relative to the conceptual approaches that already exist. Indeed, chemical novelty may gradually be replaced by the simple necessity of reliable efficacy over time.

However, as pharmacological technology continues to develop and the interfaces of targetable disease networks continue to unveil themselves — it is perhaps time to peer into the future of GLP-1-based therapeutics to assess what can and needs to be improved, and towards what capabilities are we moving now? These fields are suggested to be at the frontier of anti-obesity and anti-diabetes pharmacological development.

- AOM's and gastrointestinal side effects: Generally transient in nature but associated with a significant degree of real-world treatment discontinuation — can gastrointestinal adverse events be a thing of the past?
- AOM's and excessive lean mass loss: While lean mass loss associated with GLP-1-based therapies are generally not considered a significant health risk in most treated populations, strategies that incorporate supplemental pharmacology to prevent lean mass loss — or even promote lean mass gain — could further reduce residual risks, particularly in elderly patients.
- AOM's and weight regain after discontinuation: With pharmacological strategies proving increasingly effective for acute body weight loss, is there hope for future AOM strategies to confer protection again weight regain after treatment discontinuation?
- AOM's as antibody-drug conjugates: Rather than using hybridized unimolecular dual-agonists, GLP-1-conjugated GIPR antibodies that function as both agonists and antagonists for enhanced weight loss are on the horizon. How close is this innovation to clinical application?
- AOM's as a trojan horse: By conjugating a range of potent small molecules to GLP-1, researchers have developed new synergistic strategies that improve the therapeutic targeting of insulin sensitivity, liver dysfunction, and other conditions. What potential does this innovative combinatorial toolbox hold for the future? Can such future AOMs specifically target obesity- and/or diabetes-linked co-morbidities?

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AOM's and gastrointestinal side effects

Incretin-based AOMs are well-known to effectivity treat type 2 diabetes (T2D) and obesity, but are associated

with dose-dependent appearance of nausea, diarrhea, and vomiting which may potentially limit therapeutic adherence.[1] Generally, these gastrointestinal (GI) adverse events are transient in nature and occur primarily during the initial dose-escalation phases of treatment, and may be mitigated via gradual dose-titration.[2] Phase 3 clinical trials of incretin-based AOMs generally show that only a very small percentage of treated individuals discontinue treatment due to GI adverse effects, suggesting high-promise in treatment adherence.[3,4] However, a recent study analyzing real-world, longitudinal, medical claims databases showed that 39% of patients with obesity treated with GLP-1R agonists discontinue therapy within the first 3 months.[5] At 12 months, treatment discontinuation may even increase up to 50%, suggesting an underappreciated population unable to reach maximal clinically-demonstrated therapeutic benefit. Multiple real-world studies and clinical trials demonstrate that reduced treatment tolerability is significantly associated with treatment discontinuation and decreased likelihood for treatment reinitiation.[5–7] Therefore, a significant discrepancy between discontinuation rates reported in clinical trials and those observed in real-world settings seems apparent. This difference may stem from the regular lifestyle counseling offered in clinical trials to support adherence, which is less accessible in real-world scenarios. Furthermore, insurance-related higher out-of-pocket costs, the absence of lifestyle counseling, and onset of new GI adverse effects likely synergize to contribute to higher discontinuation rates in everyday practice.[5] However, the recent SELECT trial demonstrated that a slower, flexible, and patient-determined titration schedule allowed more patients to tolerate the GLP-1R agonist long-term while maintaining both weight loss and cardiovascular benefits.[8] This suggests that dose-titration strategies could be further refined, with patient-centered approaches potentially providing greater adherence and thus therapeutic outcomes compared to fixed dose-escalation methods.

Nonetheless, potential in reducing GI adverse effects by further refinement of drug structure and polypharmacological approach is on the rise. First, self-reported data seems to indicate short-acting GLP-1 analogs to be more closely associated with GI adverse events relative to their long-acting counterparts.[9] Further, in gold-standard pre-clinical and clinical models, agonism or co-agonism of GIPR strongly reduces the nausea and vomiting associated with chemotherapy and GLP-1R agonism, suggesting decisive potential for polypharmacological approaches in enhancing patient tolerability.[10,11] Indeed, in retrospect, anti-emetic influence potentially inherent within the GLP-1R/GIPR dual-agonist tirzepatide (15 mg) may underly its 6.25-fold maximal dosing strategy over semaglutide (2.4 mg), while retaining essentially the same adverse event profile.[3,4] In line with this, semaglutide (2.4 mg) in comparison to the lowest dosing strategy of tirzepatide (5 mg), exhibits 19% and 13% greater occurrence of nausea and diarrhea, despite both treatments strategies achieving approximately 15% body weight reduction by end of treatment.[3,4]

Direct targeting of nausea with prophylactic anti-emetic medication, typically used as an adjunct to chemotherapy, has shown potential to mitigate the key adverse events behind acute GLP-1R agonism.[12] However, the safety profile for (sub)chronic adjunct use remains uncertain.

On a cellular level, the neural subtypes that separate GLP-1R-induced satiety from GI adverse effects have remained elusive. Promisingly, a recent preclinical study has identified two GLP-1R + neuron-containing regions of the hindbrain, the nucleus of the solitary tract (NTS) and the area postrema (AP), which appear to functionally separate GLP-1-induced satiety from the aversive state.[13] It is not determined yet if or how it may be possible to target NTS GLP-1R + subneuronal populations, or their related downstream networks. Nonetheless, this new finding will likely spur momentum toward innovation.[14]

While phase 3 clinical trials have shown that GI side effects of current incretin-based AOMs can be effectively managed, maintaining patient adherence in real-world settings is still a challenge. Future AOMs will likely need to have adverse event profiles that promote compliance, even in the absence of regular lifestyle counseling. By minimizing or eliminating GI adverse effects, especially during the initial treatment phase and dose-titration, patients may be better positioned to focus on strategies to overcome the financial aspects of treatment, rather than contending with both financial and gastrointestinal issues on a daily basis.

AOM's and excessive lean mass loss

Lean mass loss resulting from significant body weight reductions during incretin-based anti-obesity therapy is often erroneously regarded as loss of muscle mass, which might result in sarcopenia, a condition associated with an increased risk of all-cause and cardiovascular disease-related mortality.[15,16] While the lean mass loss observed with incretin-based AOMs does not appear to be disproportionate relative to other weight loss interventions, it may still present a significant risk for certain subpopulations, such as older adults or those with more severe diseases.[17,18] Nevertheless, despite potential reductions in lean mass during GLP-1R agonist-induced weight loss in older patients, long-term trials like STEP HFpEF and STEP HFpEF DM have demonstrated functional improvements in muscle-based activities, such as better 6-min walk test performance.[19,20] These improvements are likely in part attributable to enhanced muscle quality, reflected in both strength and function, potentially due to increased

insulin sensitivity and reduced ectopic fat deposition.[18] Notably, even bariatric surgery, which is also associated with lean mass loss, has not shown significant correlation with reduction in hand grip strength.[21] However, loss of lean mass may result in a predisposition towards a lower resting metabolic rate, which can make it more difficult for individuals to sustain long-term weight management. The use of high protein supplementation to counteract treatment-induced lean mass loss, however, may not be as effective as required.[18,22,23] Therefore, novel pharmacological strategies to minimize both food intake and lean mass loss are currently being developed.

Bimagrumab is a monoclonal antibody antagonist of activin type II receptors that stimulates skeletal muscle growth, and has been shown to safely and efficiently decrease fat mass, increase lean mass, and improve cardiometabolic parameters within patients with pre-obesity or obesity and type 2 diabetes.[24] While a phase 2 co-therapy study with semaglutide and bimagrumab in individuals with pre-obesity or obesity is currently ongoing (NCT05616013), preclinical studies in diet-induced obese mice have shown co-therapy to achieve equal body weight-lowering efficacy to semaglutide, but with significantly greater fat mass loss, lean mass preservation, and reductions in food intake.[25] Further, in obese male cynomolgus monkeys, semaglutide-based tri-therapy with trevogrumab, a myostatin antibody inhibitor, and garetosmab, another activin A antibody inhibitor, doubled fat mass loss (50% vs. 25%) and increased lean mass by 11.7% relative to semaglutide treatment alone over 20 weeks.[26] A phase 2 clinical trial assessing the combinatorial efficacy and safety of semaglutide, trevogrumab, and garetosmab in adult patients with obesity is currently underway with an expected completion date of June 2026 (NCT06299098).

By employing these strategies, or those like them, we can potentially minimize the risks of lean mass loss in vulnerable subpopulations during incretin-based anti-obesity treatment. Moreover, these approaches may help establish a body composition that better resists weight regain once treatment is discontinued.

AOM's and weight-regain after discontinuation

The body weight-lowering effects of incretin pharmacology are profound but intrinsically dependent on continued dosing. Cessation of treatment often results in weight regain and recurrence of obesity,[27–29] which is not conceptually unlike other chronic disease-specific treatments.

In currently pre-published work, gradual dose-tapering of the GLP-1R agonist semaglutide following full-dosage cessation has been tentatively suggested to help maintain reductions in body weight for at least 20 weeks.[30] This finding is particularly relevant when considering that weight loss from low-calorie diets often triggers an increase in hunger hormones and a decrease in satiety hormones — a shift that can persist for up to a year after stopping the diet, thereby increasing risk of weight regain.[31] The apparent success of semaglutide dose-tapering raises the possibility that gradual cessation of AOMs, or diets, could facilitate a more gradual hormonal adjustment to fit a new body weight set point, thereby reducing the risk of rapid weight regain potentially inherent to abrupt discontinuation and subsequent hormonal maladaptation. Alternatively, this data may indicate that lower doses of AOMs are required to maintain body weight once the desired goal is met. This concept remains speculative and requires further extensive clinical validation, but it may be of value to monitor the potential of dose-tapering as a strategy for long-term weight maintenance. However, as anti-obesity medications are typically priced at a fixed rate in most countries, financial incentives are unlikely to encourage dose reduction. Gradual dose-tapering, however, may be appropriate for certain patient groups who continue to experience adverse effects after achieving stable weight loss. In these cases, reducing the dose could offer therapeutic benefits and improve quality of life beyond what the current dosage provides. A dose-tapering strategy should not be considered unusual for anti-obesogenic therapy, as such strategies have been routinely implemented in other chronic diseases such as asthma, diabetes, hypertension, and psychiatric disorders, following sufficient control of the condition.

Favorable changes in body composition during anti-obesity pharmacology may also offer an avenue for potential retention of body weight loss following treatment discontinuation. A clinical cohort assessing the influence of supervised exercise combined with GLP-1R agonist treatment showed greater retention of body weight loss one year after treatment cessation compared to GLP-1R agonist therapy alone.[32] However, following treatment cessation the rate of body weight and fat mass regain between treatments were similar, suggesting that the comparative superiority in body weight loss retention was not driven by exercise-induced body compositional changes, but rather by a treatment-facilitated lower body weight prior to cessation.[33] Nonetheless, as previously mentioned, combining GLP-1 therapy with myostatin or activin type II receptor inhibition could promote favorable body compositional changes, leading to a predicted increase in resting energy expenditure, and thus potentially an easier path toward weight and fat mass loss maintenance.

At the frontier of science, futuristic gene therapies promoting ectopic production of GLP-1 may provide a cutting edge for dramatic weight reduction and subsequent long-term maintenance of body weight. In another yet-to-be published work, diet-induced obese mice given a one-time intraperitoneal injection of adeno-associated virus gene therapy, GLP-1PGTx, which

induces ectopic GLP-1 expression under the insulin promoter, effectively sustains fat mass loss following semaglutide discontinuation.[34] This suggests that inducible ectopic expression of GLP-1, even if it potentially results in lower effective circulating levels compared to pharmacological doses of semaglutide, may be sufficient to maintain the new body weight set point achieved following semaglutide intervention.

Weight regain following AOM discontinuation is an inherent aspect of the pharmacological approach. The future of anti-obesity drug development may potentially focus on strategies to indirectly side-step this phenomenon, whether through modified dosing protocols, strategic co-therapy for enhancements in lean mass, or the use of gene therapy to ensure continuous treatment benefits.

AOM's as antibody-drug conjugates

Antibody-drug conjugates (ADCs) are a class of therapeutics that utilize antibody-facilitated delivery of small molecules to antigen-expressing tissues. While this concept is further explored in the context of GLP-1-based targeting in the next section, ADC strategies have been implemented to allow for unimolecular parallel agonism and antagonism of select receptors for enhanced body weight loss. AMG 133 (maridebart cafraglutide) is an example of this, featuring an antibody-based GIPR antagonist conjugated to two GLP-1RA peptides at the Fc domain.[35] Recent phase 1 clinical trial data shows that chronic administration of AMG 133 can induce profound body weight loss of 14% within just 12–13 weeks, and can as well sustain a 10% decrease over the course of 150 days following a single injection at the highest dose used (840 mg).[35]

Despite a paradoxical contrast in targeting relative to GLP-1R/GIPR dual-agonists like tirzepatide, the body weight-lowering synergy of combining GIPR antagonism with GLP-1R agonism has been demonstrated in both murine and non-human primate models.[35–38] The mechanisms underlying the efficacy of this approach is currently the subject of intense study, as researchers try to understand why both GIPR agonism and antagonism synergize with GLP-1R agonism.[39] Additionally, while AMG 133 shows significant potential for body weight reduction, it is also associated with moderate, dose-dependent increases in nausea and vomiting, similar to the side effects seen with semaglutide and tirzepatide.[35] Although the phase 1 study involved a relatively small population, additional promising results, as AMG 133 progresses through current and future clinical trials, may validate this approach.

AOM's as a trojan horse

Building on the success of clinically-trialed ADCs, researchers have developed peptide-based small molecule conjugates that specifically target tissues expressing GLP-1R, GIPR, or GcgR.[40] These peptide-conjugates capitalize on GPCR-expressing tissue targeting, thus integrating parallel GPCR signaling with the intracellular delivery of small molecule therapeutics. This approach has shown promise in producing synergistic anti-obesity and anti-diabetic effects, without off-target effects associated with loose small molecule administration.

The first of these small molecule conjugation approaches were nuclear hormone-based, with GLP-1 conjugated to estrogen (GLP-1/E2),[41] and glucagon conjugated to triiodothyronine (Gcg/T3).[42] Preclinical targeting of E2 into GLP-1R-expressing tissues via GLP-1/E2 peptide conjugation synergistically reduces body weight by means of food intake reduction, and importantly, has shown potential to restore β-cell function in chemically-induced type 1 diabetic mice.[41,43] Targeting of T3 into GcgR-expressing tissues via Gcg/T3 synergistically corrects for hyperlipidemia, steatohepatitis, atherosclerosis, and metabolic syndrome.[42] These successes have raised the possibility that combining GPCR agonism with nuclear receptor-acting small molecules could greatly enhance body weight-lowering efficacy and produce significantly better outcomes in comorbidities addressed by small molecule therapy. As well, this synergistic strategy could enable the use of lower doses while still achieving the same metabolic benefits as traditional AOM's, potentially leading to treatments with minimal side effects. As research has progressed, new iterations of GLP-1/small molecule conjugates have emerged. The latest involves conjugating the non-nuclear-acting N-methyl-D-aspartate (NMDA) receptor antagonist MK-801 with GLP-1, designed to modify the food-seeking neural adaptations implicit within starvation to enhance anti-obesogenic effects.[44]

Further, GLP-1R-conjugated delivery of antisense oligonucleotides, and GLP-1-conjugated lysosome-targeting chimeras (LYTAC), have suggested a promising therapeutic utility in the targeted silencing or degradation of specific proteins within GLP-1R+ tissues.[45,46] However, despite these extremely innovative approaches that suggest a plethora of case-specific combinations for diverse therapeutic strategies, the safety and feasibility of these approaches for implementation into human trials has not yet arrived.

Scaling up progress

The introduction of long-acting GLP-1R mono-agonists, GLP-1R/GIPR dual-agonists, and GLP-1R/GIPR/GcgR tri-agonists has significantly advanced body weight-lowering potential through mechanisms involving (1) satiety, (2) synergized satiety with anti-emesis, and (3) synergized satiety, anti-emesis, and increased energy expenditure, respectively. Despite the effectiveness of these therapies, further developmental iterations of drugs within these frameworks have begun to yield

Search strategy and selection criteria

References for this Viewpoint were identified through searches of PubMed with the search terms "Diabetes", "obesity", "GLP-1", "GIP", "anti-obesity medication", "co-agonist", "MASH" and "dementia" from 1995 until August 2024. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Viewpoint.

diminishing returns in terms of efficacy gains. These initial successes in achieving transformative body weight loss can be compared to the invention of the wheel — a fundamental breakthrough that sets the stage for future innovations.

Looking ahead, the next generation of anti-diabetic and anti-obesity pharmacotherapies, supported by emerging technologies, should aim to address the negative side effects of current treatments, such as gastrointestinal issues and lean mass loss. Moreover, these advancements may also bring unprecedented improvements, including better long-term retention of weight loss following discontinuation, implementation of unimolecular ADC strategies for prolonged efficacy, and novel pharmacological approaches that combine peptide-based targeting with nuclear hormone dual-pharmacology for synergistic effects. Ultimately, these innovative, perhaps customizable strategies, seek to ensure that maximal treatment benefits can be consistently evoked among patients, leading to a higher proportion reaching transformative therapeutic endpoints.

Contributors

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Declaration of interests

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