PERSPECTIVE

New Molecules and Indications for GLP-1 Medicines

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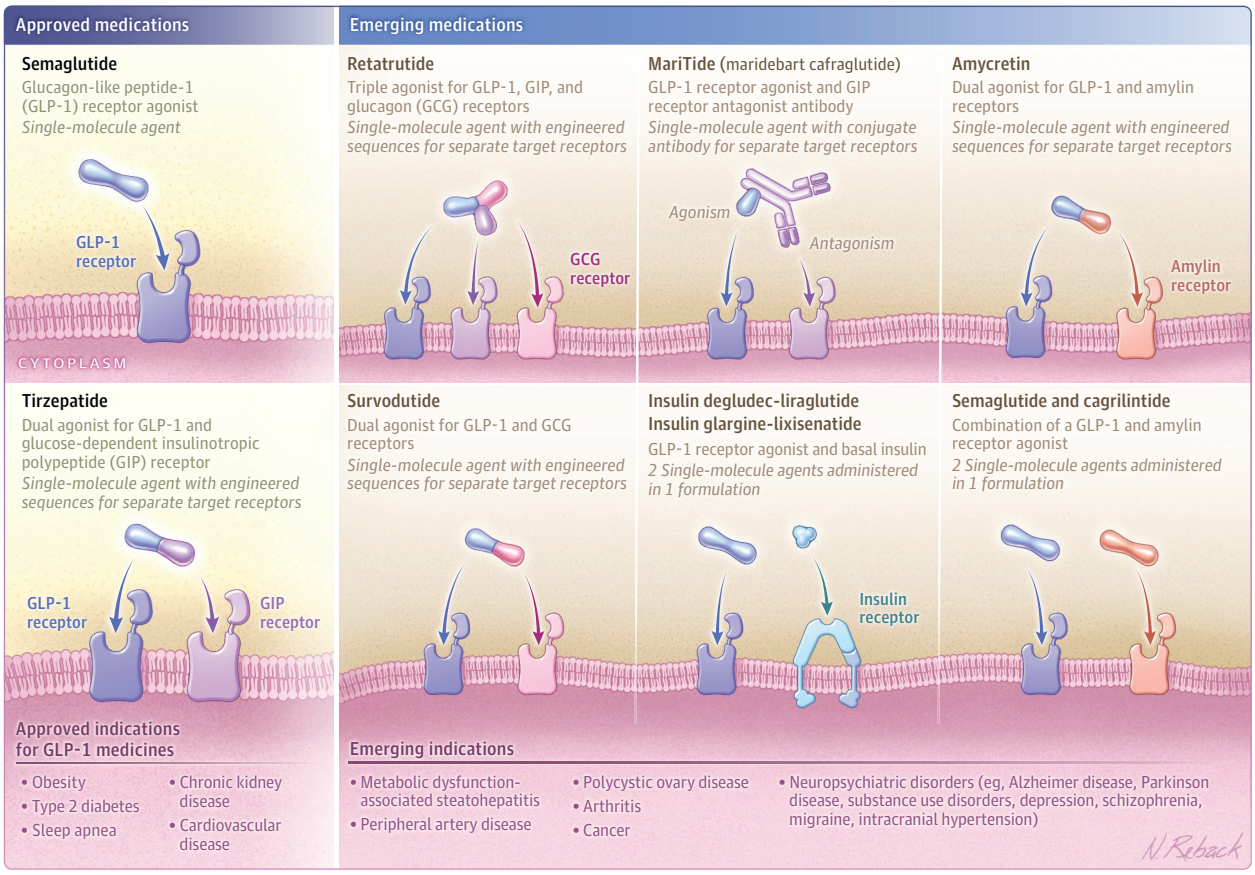
Glucagon-like peptide-1 (GLP-1) medicines, defined herein as any medicine that exerts its actions in part through the GLP-1 receptor, were initially approved for type 2 diabetes (T2D), reflecting their stimulation of insulin and inhibition of glucagon secretion and gastric emptying. Their actions to reduce appetite subsequently enabled weight loss in people with obesity or overweight and associated comorbidities. Large clinical trials revealed reduced rates of cardiovascular and kidney disease in people with T2D or obesity.[1] Moreover, the dual GLP-1 receptor and glucose-dependent insulinotropic polypeptide (GIP) receptor coagonist tirzepatide was approved for treating T2D, obesity, and moderate to severe obstructive sleep apnea.[2]

Innovation in GLP-1 medicines is unfolding along 2 simultaneous fronts: (1) development of novel molecules (including multiagonists targeting GLP-1, GIP, and glucagon receptors; combinations with amylin analogues and insulin; oral formulations; and adjunctive combination therapies to preserve muscle mass) and (2) investigation of new indications, including neuropsychiatric and substance use disorders and inflammatory diseases (**Figure**). This Perspective provides an overview of recent progress and future directions.

Figure. New Molecules and Emerging Indications for GLP-1 Medicines



Color coding is used to indicate correspondence between molecular structure and receptor targets. For single molecules, the use of multiple colors reflects the presence of sequences engineered to activate more than 1 receptor (eg, GLP-1RA, GIPR-GLP-1RA, GIPR-GCGR-GLP-1RA, GCGR-GLP-1RA, and amylin-GLP-1RA). When 2 distinct molecules are depicted, each in a single color (eg, amylin receptor agonist + GLP-1RA, insulin + GLP-1RA), this represents a fixed-ratio combination therapy composed of 2 separate agents, each targeting its specific receptor, administered in a single formulation. The GIPR antagonist + GLP-1RA molecule illustrates a structurally distinct approach, wherein a GIPR-specific antagonistic antibody is conjugated to a GLP-1RA, enabling dual functional targeting within a single molecular entity.

GCGR indicates glucagon receptor; GIPR, glucose-dependent insulinotropic polypeptide receptor; and GLP-1RA, GLP-1 receptor agonist.

Emerging GLP-1 Medicines

With semaglutide and tirzepatide widely adopted in clinical practice, new therapies must demonstrate added value. Tirzepatide achieves greater weight loss and glycemic control relative to semaglutide.[3,4] However, semaglutide is the most validated GLP-1 medicine in outcome trials, with benefits demonstrated in osteoarthritis, peripheral artery disease, atherosclerotic heart disease, heart failure with preserved ejection fraction, diabetic kidney disease, and metabolic liver disease.[5] Intriguingly, many of these outcomes appear independent of weight loss or improved glucose metabolism.[6]

GLP-1 medicines are emerging that target multiple receptors beyond GLP-1 and GIP, the targets for tirzepatide. Retatrutide, a triple agonist targeting GLP-1, GIP, and glucagon receptors, demonstrated up to 24.2% placebo-subtracted weight reduction after 48 weeks (on-treatment estimand) in a phase 2 study of individuals with obesity without diabetes. Retatrutide also improved blood pressure, lipid profiles, and glycemia.[7] In a separate trial, retatrutide improved metabolic dysfunction–associated steatohepatitis. Resolution of steatohepatitis without worsening of fibrosis was also reported in 62.9% vs 34.3% of patients treated with semaglutide vs placebo.[8] Notably, glucagon directly reduces lipid synthesis and enhances fat oxidation in hepatocytes, providing a theoretical basis for how retatrutide might produce superior hepatic benefits.

Unique mechanistic and therapeutic questions are posed by maridebart cafraglutide (MariTide), a long-acting peptide-antibody conjugate that combines GLP-1 receptor agonism with GIP receptor antagonism. In phase 2 trials over 52 weeks, MariTide led to placebo-subtracted weight reductions of up to 12.3% in individuals with obesity and T2D and 16.2% in those without T2D, based on the treatment-policy estimand.[9] MariTide's once-monthly dosing schedule may improve long-term adherence if tolerability is manageable and competitive efficacy is observed in ongoing phase 3 trials. Whether GIP receptor antagonism provides distinct metabolic benefits when combined with GLP-1 receptor agonism remains to be determined.[10]

GLP-1 receptor agonism is also being combined with analogues of amylin, a pancreatic hormone that promotes satiety and delays gastric emptying. Amycretin, a unimolecular GLP-1 and amylin receptor agonist, demonstrated a mean weight reduction of up to 24.3% from baseline (on-treatment estimand, not placebo-subtracted) in a phase 2 study,[11] results comparable with or exceeding that observed with tirzepatide and approaching the upper bound reported with retatrutide. However, the small sample size (N = 125), short trial duration, and high dropout rate limit conclusions about the ultimate potential of amycretin pending larger and longer trials.[11]

CagriSema is a fixed-dose, once-weekly combination of semaglutide and the long-acting amylin analogue cagrilintide, studied in patients with obesity with and without T2D. Absolute weight reductions of up to 20.4% and 13.7% from baseline (on-treatment estimand) were observed in people without and with T2D, respectively,[12,13] together with hemoglobin A_{1c} (HbA_{1c}) reductions of up to 2% from a mean baseline of 8%. With CagriSema, body composition analyses in a subset of the trial population revealed 35.7% and 14.4% reductions in fat and lean mass, respectively, with 67% of weight loss representing fat mass and 33% lean mass.[12] Whether separate or unimolecular combinations of amylin and GLP-1 receptor agonists will exhibit meaningful differentiation on tolerability vs efficacy will require additional studies. A range of new agonists of the calcitonin peptide family, dual amylin and calcitonin receptor agonists, are being studied, which may offer greater metabolic benefits than amylin receptor agonism alone.

Oral formulations of GLP-1 medicines represent attractive alternatives to injectables, particularly for patients averse to subcutaneous treatments. Oral semaglutide at doses of up to 14 mg daily is approved for T2D and doses as high as 50 mg daily have been evaluated for weight loss, with 25 mg daily filed for approval for the treatment of obesity.[14] Orforglipron, a nonpeptide small-molecule biased GLP-1 receptor agonist, is being evaluated in phase 3 trials for T2D and obesity. In the ACHIEVE-1 study, once-daily orforglipron reduced HbA_{1c} by up to 1.48% vs 0.41% with placebo and lowered body weight by up to 7.6% vs 1.7% with placebo (on-treatment estimand).[15] Small-molecule GLP-1 medicines should be less expensive to manufacture, require no cold storage, and most can be taken without regard to timing of meal ingestion, which may improve adherence while expanding global access.

Fixed-dose combinations of GLP-1 receptor agonists and basal insulin, such as insulin degludec/liraglutide and insulin glargine/lixisenatide, offer a streamlined therapeutic approach to control glucose and body weight. IcoSema, a once-weekly coformulation of semaglutide and insulin icodec, has shown superior HbA_{1c} reductions compared with both basal-bolus insulin and insulin icodec alone,[16,17] with the added benefits of greater weight loss (approximately 6.7 kg greater than basal-bolus regimens, placebo-subtracted, on-treatment), lower insulin requirements (up to 270 fewer units per week), and a substantially reduced risk of clinically significant hypoglycemia (up to 88% reduction). This simplified dosing schedule reduces injection burden and may improve adherence. Although the available efficacy and safety data are reasonable, long-term cardiovascular, kidney, and liver outcomes specific to IcoSema would further establish its safety and potential benefits.

Emerging Indications

Although some benefits of GLP-1 medicines, such as improvements in obstructive sleep apnea and osteoarthritis, are largely driven by weight loss, other important effects appear independent of weight or glucose control. Large clinical trials such as SELECT (cardiovascular disease), ESSENCE (metabolic liver disease), and STRIDE (peripheral artery disease) have revealed weight-independent benefits, which may reflect reduced inflammation and direct effects of GLP-1 medicines on the heart, liver, and blood vessels. Five clinical trials have evaluated the use of GLP-1 medicines, all exenatide-related peptides, in people with Parkinson disease. Although 3 of the trials reported attenuation of disease activity and improved motor scores, 2 trials did not, including the largest and longest trial studying once-weekly exenatide.[5]

Intriguingly, taking GLP-1 medicines is associated with a lower risk of all-cause dementia, including Alzheimer disease, in individuals with T2D.[18] The EVOKE and EVOKE+ trials are evaluating whether oral semaglutide (14 mg/d) can slow cognitive decline in individuals with early, symptomatic, biomarker-confirmed Alzheimer disease. The primary end point is the change in the Clinical Dementia Rating Sum of Boxes score at week 104, with results expected in 2025. Beyond dementia, more than 12 trials are evaluating whether GLP-1 medicines reduce the burden of substance use disorders. In

a large, nationwide observational study in Sweden including more than 227 000 individuals with alcohol use disorder, semaglutide and liraglutide were each associated with a significantly lower risk of alcohol use disorder–related hospitalization, with hazard ratios of 0.64 and 0.72, respectively, compared with periods of nonuse among the same individuals. These effects were stronger than those observed with approved medications for alcohol use disorder.[19] A 9-week, placebo-controlled study of 48 adults with alcohol use disorder demonstrated that once-weekly semaglutide reduced alcohol self-administration in the laboratory (β, −0.48 [95% CI, −0.85 to −0.11]; *P* = .01), craving (β, −0.39 [95% CI, −0.73 to −0.06]; *P* = .01), and drinks per drinking day (β, −0.41 [95% CI, −0.73 to −0.09]; *P* = .04), despite a short treatment duration in a non–treatment seeking population. Semaglutide also led to greater reductions in cigarette smoking.[20]

Muscle Loss and Muscle Composition

All interventions to achieve weight loss result in loss of some muscle mass. In individuals treated with GLP-1 medicines, reductions in muscle volume generally align with expectations based on age, disease burden, and degree of weight loss. Moreover, improvements in insulin sensitivity and reductions in muscle fat infiltration point toward enhanced muscle quality, potentially mitigating the risk of impaired strength or function.[21] In a post hoc magnetic resonance imaging–based substudy of the SURPASS-3 trial, tirzepatide was associated with changes in muscle composition consistent with expected physiologic responses to weight loss. Although modest reductions in muscle volume were observed, these were largely proportional to total weight loss. More importantly, significant improvements in muscle quality were noted, including marked reductions in muscle fat infiltration across all doses.[22]

Muscle loss may be particularly relevant for older adults with preexisting sarcopenia or frailty, where preservation of muscle function is critical. Several pharmacologic treatments are being studied to determine whether they will maintain or improve muscle mass in people treated with GLP-1 medicines. In news releases reporting results of the phase 2 EMBRAZE trial, the combination of tirzepatide with apitegromab, a myostatin inhibitor, resulted in significantly greater lean mass preservation compared with tirzepatide alone (54.9% vs 30% lean mass retention; *P* = .001) while maintaining comparable fat mass reduction. The phase 2b BELIEVE trial evaluated bimagrumab, an activin type II receptor antibody, both as monotherapy and in combination with semaglutide in adults with obesity without T2D. Bimagrumab alone produced an approximately 22% fat mass reduction and a 3.6% increase in lean mass over 48 weeks. The combination of semaglutide with trevogrumab (an antimyostatin antibody) with or without garetosmab (anti–activin A) was evaluated in the phase 2 COURAGE trial. A news release reporting the interim analysis revealed that the addition of trevogrumab preserved 50% to 51% of lean mass and the triplet regimen preserved up to 80% while also enhancing fat mass loss compared with semaglutide alone. The combination of semaglutide with bimagrumab (NCT05616013) resulted in predominant fat mass loss (92.8%) and only 7.2% lean mass loss, a profile that compares favorably with the 85% fat and 15% lean mass loss observed with tirzepatide and apitegromab. Although these trials primarily aim to optimize the quality of weight loss, favoring fat reduction over muscle loss, data on muscle function or quality remain limited. Importantly, these agents have generally been well-tolerated, with gastrointestinal symptoms and injection site reactions being the most frequently reported adverse events.

Conclusions and Future Directions

Expanding indications and new molecules targeting additional receptors raise important questions surrounding the efficacy and safety of emerging GLP-1 medicines (Figure). Importantly, the safety profiles defined to date with semaglutide and tirzepatide in people with obesity and T2D cannot be extrapolated to indications where individuals may be older and more frail, including patients with neurodegenerative disorders. Emerging observations suggesting the importance of weight loss–independent benefits raise key questions surrounding the optimal dose-response relationships for GLP-1 medicines to improve outcomes beyond dosing regimens established for T2D and obesity.

GLP-1 medicines are also being studied in people with a wide range of neuropsychiatric disorders, migraine, intracranial hypertension, inflammatory bowel disease, psoriasis, rheumatoid and psoriatic arthritis, and inflammatory skin diseases, such as hidradenitis suppurativa. Several trials are even underway to explore their therapeutic potential in people with type 1 diabetes for improving time in range and glucose control and longer term for reducing the risk of cardiovascular and kidney complications.[5]

Moreover, GLP-1 medicines may increase rates of conception through achievement of weight loss in individuals with polycystic ovary syndrome.[23] Additionally, the increasing incidence of obesity-associated cancer has fostered interest in whether taking GLP-1 medicines long-term may favorably alter the pro-oncogenic metabolic environment and reduce rates of metabolically sensitive cancers through weight loss, reduced inflammation, and decreasing overall cell mass in at-risk organs.[24] Achieving these benefits at a population level will require greater access to more affordable GLP-1 medicines together with major improvements in persistence and adherence, as a substantial percentage of patients (46.5% with and 64.8% without T2D) stop taking GLP-1 medicines within 12 months of drug initiation.[25] Collectively, ongoing studies of novel molecules and new disorders herald great promise for expanding the use of GLP-1 medicines to improve human health.

ARTICLE INFORMATION

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Note: Source references are available through embedded hyperlinks in the article text online.

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