nature medicine

Review article

https://doi.org/10.1038/s41591-025-04124-5

The expanding landscape of GLP-1 medicines

Received: 22 August 2025

Accepted: 14 November 2025

Published online: 2 January 2026

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Glucagon-like peptide-1 medicines are being prescribed to growing numbers of patients worldwide, for type 2 diabetes, obesity and associated comorbidities, including cardiovascular disease, peripheral artery disease and obstructive sleep apnea, and are revolutionizing public health strategies for these conditions. These medicines improve health through reduction of blood glucose and body weight, by attenuation of inflammation and via direct activation of receptors in target tissues. New, more effective molecules with optimized pharmacokinetics produce greater weight loss and some may be more effective for various metabolic disorders, through incorporation of one or more additional peptide epitopes. Parallel efforts are exploring new indications, including neurodegenerative and substance use disorders, metabolic liver disease, arthritis, type 1 diabetes and inflammatory bowel disease. Here we highlight data informing the safety, efficacy, and potential utility of new and emerging glucagon-like peptide-1 medicines. We outline new mechanistic concepts, future therapeutic opportunities, potential for differentiation from currently available medicines and areas of uncertainty requiring additional investigation.

The insulin-stimulating and glucose-regulating actions of glucagon-like peptide-1 (GLP-1) were first reported in 1987 (refs. 1–3). The first approved GLP-1 medicine was the GLP-1 receptor agonist (GLP-1RA) exenatide, approved in 2005 as a twice-daily subcutaneous injection for the treatment of type 2 diabetes (T2D). Since then, the landscape of GLP-1 medicines has undergone rapid and extensive development.

Longer-acting GLP-1 medicines followed, including once-weekly exenatide, once-daily acylated liraglutide and once-weekly immunoglobulin-based dulaglutide[4] (Fig. 1). Concepts of GLP-1 action expanded to include reduction of food intake enabling weight loss, reduction of blood pressure and atherosclerosis, as well as improved cardiac function and cardioprotection in heart failure and ischemic cardiac injury, respectively (Fig. 2). The broadening indications (approved and emerging) for GLP-1 medicines now include treatment of obesity, obstructive sleep apnea, metabolic liver disease, kidney disease, peripheral artery disease and osteoarthritis, and reducing the risk of myocardial infarction, stroke and chronic kidney disease. In people with osteoarthritis, heart failure with preserved ejection fraction (HFpEF) and obstructive sleep apnea, these benefits primarily reflect the extent of weight loss; however, post hoc analysis of clinical trial data also reveals weight loss-independent benefits, notably in heart disease, metabolic liver disease and peripheral artery disease[5,6]. Collectively, this wide range of benefits beyond glucose and weight control has increased enthusiasm for the use of GLP-1 medicines to treat a wide range of chronic disorders to improve healthspan. However, issues with tolerability and challenges with access currently limit realization of the full potential of the GLP-1 medicine class.

Buttressed by extensive preclinical studies and observations from clinical trials, there is great interest in understanding whether GLP-1 medicines might be useful in treating substance use disorders (SUDs), miscellaneous neuropsychiatric disorders and neurodegenerative disorders. In parallel, ongoing research is focused on diseases characterized by dysregulated inflammation, including psoriatic arthritis, inflammatory skin disorders and inflammatory bowel disease[4]. In this Review, we discuss recent data supporting the expansion of GLP-1 medicines beyond T2D and obesity, outlining opportunities for new molecules, delivery modalities and indications, and highlighting emerging questions and challenges surrounding the benefits and long-term safety of new GLP-1 medicines.

Current landscape of GLP-1 drugs for T2D and obesity

The two most widely used GLP-1 medicines are semaglutide (approved in 2017 for T2D and 2021 for obesity) and tirzepatide (approved for T2D

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https://doi.org/10.1038/s41591-025-04124-5

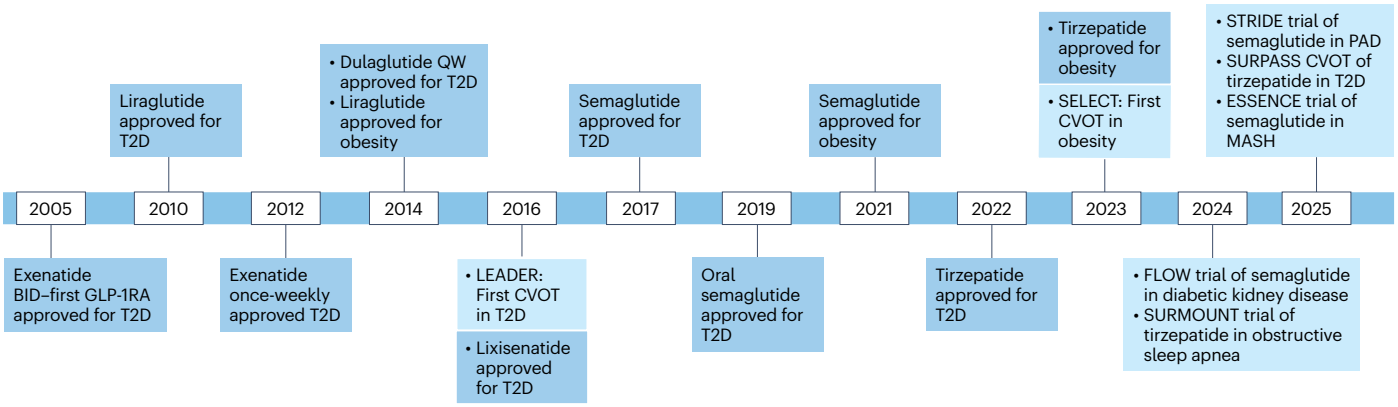

Fig. 1 | Timeline of major trials and approvals for GLP-1 medicines. Key approval dates for individual medicines and indications are indicated with dark-blue shading, whereas key outcome trials are indicated in light blue. BID, twice daily; CVOT, cardiovascular outcomes trial; MASH, metabolic dysfunction-associated steatohepatitis; PAD, peripheral artery disease.

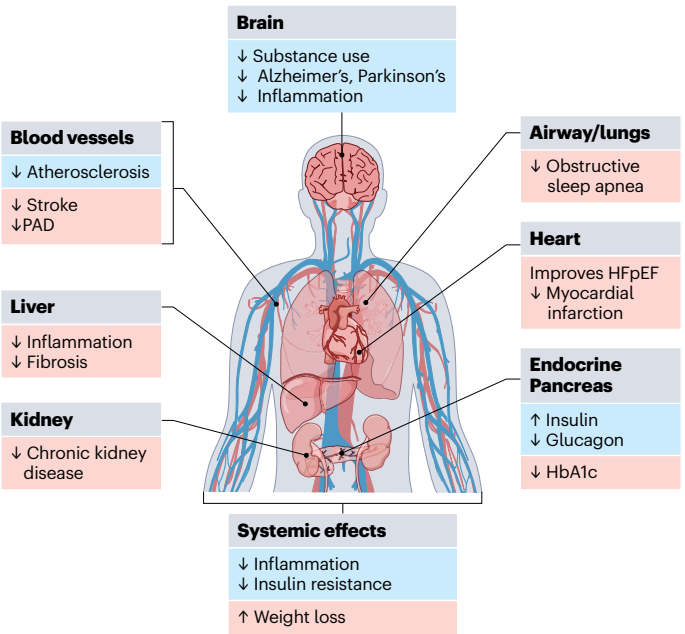

Fig. 2 | Mechanisms of action of GLP-1 medicines. The benefits of GLP-1 medicines have been demonstrated in multiple outcome trials for people with cardiovascular disease[26,106], peripheral artery disease[30], liver disease[27], kidney disease[28], HFpEF[23,24] and obstructive sleep apnea[34] with multiple new GLP-1 medicines under investigation for a wide range of indications[4].

and obesity in 2022 and 2023, respectively)[4] (Fig. 1), the latter being a dual agonist of GLP-1R and glucose-dependent insulinotropic polypeptide (GIP) receptor (GIPR). Semaglutide is currently used at doses ranging from 0.5–2 mg once weekly (QW) for T2D and up to 2.4 mg QW by injection for weight loss, whereas the doses of tirzepatide (5, 10 or 15 mg QW) are similar for T2D or obesity. Higher doses of semaglutide (up to 7.2 mg QW) have been studied in 1,407 people with obesity with or without T2D in the phase 3 STEP-UP trials[7,8]. Trial participants with obesity receiving 7.2 mg semaglutide QW achieved 20.7% weight loss after 72 weeks, compared to 17.5% with 2.4 mg semaglutide and 2.4% with placebo, with the 7.2-mg dose now pending approval by regulatory authorities. In a phase 2 trial, incremental benefits were obtained with 16 mg semaglutide QW in patients with T2D, encompassing a 0.5% greater reduction in A1c and 4.5 kg additional weight loss compared to treatment with a 2-mg QW dose; however, gastrointestinal adverse events and treatment discontinuations were numerically greater with higher doses of semaglutide[9]. These higher doses of semaglutide produce additional metabolic benefits, as extensively validated in clinical trials, yet the major glycemic or weight loss advantages do not go beyond those already achieved with tirzepatide[10,11].

A slightly modified sodium *N*-(8-[2-hydroxybenzoyl] amino) caprylate formulation for oral semaglutide was studied at doses up to 50 mg once daily in people with overweight or obesity, producing up to 15.1% weight loss over 68 weeks at the 50 mg dose[12]. The 25-mg once-daily dose of oral semaglutide studied in the OASIS 4 trial over 52 weeks (NCT05564117) produced 13.6% weight loss compared with 2.2% in the placebo group[13] and is awaiting regulatory approval. Corrected for circulating drug levels, there is little difference in a broad range of pharmacodynamic outcomes when semaglutide is delivered by the oral versus the injectable route[14].

The incremental benefit of higher-dose oral or injectable semaglutide does not result in a pharmacodynamic profile of greater weight loss relative to what can be achieved with tirzepatide. Nevertheless, the substantial outcome data highlighting benefits of semaglutide in people at risk for cardiorenal disorders and metabolic liver disease makes semaglutide an appealing choice for achievement of evidence-based outcomes beyond control of glucose or body weight[4].

Head-to-head trials have directly compared the two. The SURPASS-2 trial compared the efficacy and safety of semaglutide versus tirzepatide in 1,879 patients with T2D randomized to either 1 mg QW of semaglutide, or 5, 10 or 15 mg QW of tirzepatide, over 40 weeks[10]. All three doses of tirzepatide produced greater reductions of hemoglobin A1C (HbA1c) and body weight relative to 1 mg QW of semaglutide, with −2.01, −2.24 and −2.30% decreases in HbA1c from baseline at 5 mg, 10 mg and 15 mg of tirzepatide, respectively, and a −1.86% reduction with semaglutide. Reductions in body weight were −7.6 kg, −9.3 kg and −11.2 kg for 5 mg, 10 mg and 15 mg tirzepatide QW, respectively, versus −5.7 kg with 1 mg QW of semaglutide. Rates of adverse events, predominantly gastrointestinal complaints, were similar across treatment arms[10].

The SURMOUNT-5 trial compared the maximum tolerated doses of tirzepatide (10 or 15 mg QW) versus semaglutide (1.7 or 2.4 mg QW) in 751 people with overweight or obesity, without T2D, over 72 weeks[11]. Greater weight loss was achieved with tirzepatide (−20.2%) versus semaglutide (−13.7%), along with a greater reduction in weight circumference. Weight loss was ~6% greater in women versus men in both treatment groups. The flexible dosing protocol deployed in SURMOUNT-5 may more closely approximate prescribing behavior and hence achievable outcomes in the real world. Collectively, these trials highlight the superiority of tirzepatide at currently approved doses for glycemic control of T2D and for achievement of weight loss.

The SURPASS-PEDS trial demonstrated unprecedented reduction of HbA1c (2.32%) and weight loss (up to 13.8%) with up to 10 mg QW of

https://doi.org/10.1038/s41591-025-04124-5

BOX 1

GLP-1 medicines in children and adolescents

GLP-1 medicines appear safe and effective in younger and older populations, yet the evidence base is limited. Liraglutide up to 1.8 mg daily was studied in 135 children and adolescents (ages 10–17 years) with T2D and overweight or obesity, on a background of oral metformin therapy[107]. HbA1c decreased by 0.64% with liraglutide and increased by 0.42% with placebo, with ~86% versus 66.7% of participants completing the 26-week study period without rescue medication. At week 52, body weight reduction was −1.91 kg with liraglutide versus 0.87 kg for placebo-treated participants[107].

Exenatide 2 mg QW was studied over 26 weeks in 83 children and adolescents (ages 10–17 years) with T2D and mean baseline body mass index (BMI) ~ 36 kg/m^2. HbA1c change from baseline was −0.36% with exenatide versus +0.49% with placebo, and body weight change was −0.59 kg versus +0.63 kg[108]. Dulaglutide 0.75 mg versus 1.5 mg QW was also studied over 26 weeks in 154 children and adolescents (ages 10–18 years), with mean baseline BMI 34.1 kg/m^2 (ref 109). The change in HbA1c was −0.6% for dulaglutide at 0.75 mg and −0.9% for the 1.5-mg QW dose, and +0.6% for placebo-treated individuals. No differences in body weight were detected over 26–52 weeks of observation[109].

Liraglutide and semaglutide have also been investigated for weight loss in adolescents with overweight or obesity without T2D. Liraglutide was studied in 251 participants aged 12–18 years with obesity who had suboptimal responses to previous lifestyle management interventions[110]. Following a 12-week run-in period and 56 weeks of treatment, change in body weight was −2.7 kg in the liraglutide group versus +2.1 in the placebo group (corresponding to ~5.01% relative placebo-subtracted difference)[110]. No significant between-group differences were reported for blood pressure, plasma lipid profiles, high sensitivity C-reactive protein, parameters of beta cell function or quality-of-life questionnaire scores. Changes in bone age and parameters of growth or pubertal development were not different between groups[110].

The STEP Teens trial studied semaglutide at 2.4 mg QW versus placebo over 68 weeks in 201 adolescents (ages 12–18 years) with obesity or overweight, and at least one weight-related comorbidity[111]. The completion rate was >95%; 73% of the semaglutide-treated patients lost at least 5% of their body weight, 62% lost >10% and 53% lost >15% (versus 23%, 8% and 5% in the placebo-treated arm, respectively). The mean relative change in body weight was −14.7% for semaglutide versus +2.7% for placebo[111]. Mental health questionnaire scores were not different between groups; however, fewer psychiatric adverse events were reported for semaglutide (7%) versus placebo (15%) treatment groups[111].

tirzepatide in children and adolescents (ages 10–18 years) with T2D studied over 52 weeks (30 weeks plus a 22-week open-label extension)[15]. Nevertheless, additional data on the efficacy and long-term safety of GLP-1 medicines in children (Box 1) and older people remain limited.

The weight loss attributable to the current generation of GLP-1 medicines primarily reflects reductions in appetite and not preservation or augmentation of energy expenditure, which generally declines with weight loss in patients treated with semaglutide or tirzepatide[16]. Gastrointestinal adverse events such as nausea, diarrhea, constipation and vomiting are seen with all GLP-1 medicines and, to date, rates are similar with semaglutide versus tirzepatide[10,11,17]. Gallbladder-related adverse events are reported in ~1% of treated patients; sustained gastrointestinal adverse events may predispose individuals to dehydration and the risk of acute kidney injury—now added as a warning in the prescribing information for all GLP-1 medicines—and warrants close monitoring, particularly in patients who already have impaired renal function.

Overall, tirzepatide is currently the most effective GLP-1 medicine for achieving glucose control and weight loss, whereas semaglutide has shown efficacy in a larger number of outcome trials in people with cardiovascular disease (CVD), and in individuals with obesity-associated disorders (as reviewed below). The relatively greater efficacy of tirzepatide versus semaglutide—achieved without higher rates of gastrointestinal adverse events[10,11]—has been attributed to the anti-aversive actions of GIP, described in preclinical and some clinical studies[18,19].

Benefits of GLP-1 medicines beyond T2D and obesity

Clinical reports have spurred interest in studying GLP-1 medicines in people with newly diagnosed or established type 1 diabetes (T1D) (Box 2). Equally intriguing is the possibility that GLP-1 medicines might be useful to reduce rates of heart disease in people without T2D or obesity, either in people with established CVD at risk for recurrent events, or in individuals with ongoing risk factors despite initiation of optimal medical therapy. No trials are yet underway with GLP-1 medicines that examine these two opportunities. There is, however, accumulating clinical evidence on the cardiometabolic outcomes of GLP-1 medicines, their ability to prevent or bring about remission of T2D, and their ability to treat neurodegenerative disorders and SUDs.

Cardiometabolic outcomes

Multiple cardiovascular safety trials have reported reductions in major adverse cardiovascular events with long-acting GLP-1 medicines in T2D, in the setting of established atherosclerotic CVD and in individuals with risk factors for CVD[20]. Tirzepatide was shown to be non-inferior to the GLP-1RA dulaglutide in 13,165 patients with T2D (mean duration 14.7 years) and established CVD in the SURPASS-CVOT trial[21]. The design of SURPASS-CVOT sets a new standard for outcome studies in T2D, as it included an active comparator, dulaglutide, already shown to be robustly cardioprotective in this patient population (in the REWIND trial[22]). Approximately 80% of SURPASS-CVOT participants completed the trial on the study drug, and baseline use of sodium–glucose cotransporter 2 (SGLT-2) inhibitors was ~30% (higher than in previous GLP-1 cardiovascular outcome trials). Tirzepatide therapy was associated with greater reductions in HbA1c, body weight and the rate of decline in estimated glomerular filtration rate, and a 16% reduction in all-cause mortality. A prespecified secondary analysis demonstrated a clear cardioprotective benefit of tirzepatide versus a matched placebo population represented in the REWIND trial[21].

The cardiovascular benefits of semaglutide and tirzepatide extend to patients with HFpEF, with evidence for symptomatic improvement, reduced rates of cardiovascular death and decreased need for hospital visits and intensification of therapy[23,24]. The ongoing SURMOUNT-MMO trial (NCT05556512) is studying the cardiovascular safety of tirzepatide (at doses up to 15 mg QW) in adults over 40 years with established CVD and overweight/obesity, but without T2D, or in older individuals without CVD but with a history of multiple cardiovascular risk factors[25]. The primary outcome is any component event of a composite endpoint, with an estimated study completion date of October 2027. The outcome trials of tirzepatide are of particular interest as limited safety data are available for medicines acting in part through the GIPR.

The SELECT trial, the only GLP-1 cardiovascular outcome study to date in people without T2D, studied the safety of 2.4 mg QW

https://doi.org/10.1038/s41591-025-04124-5

BOX 2

Emerging utility in T1D

Liraglutide was studied at doses up to 1.8 mg daily in people with T1D over 52 weeks; however, the small magnitude of the reduction in HbA1c, coupled with the increased rates of hypoglycemia and hyperglycemia with ketosis, limited enthusiasm[112]. A smaller study examined the efficacy of semaglutide at doses up to 1 mg QW for 26 weeks (n = 36 on semaglutide and 36 on placebo) in people with T1D and obesity who were using an automated insulin delivery system[113]. Semaglutide reduced HbA1c by 0.3% and increased the proportion of individuals achieving glucose time-in-range targets, together with achievement of at least 5% weight loss without incidents of ketoacidosis. An even smaller trial (24 individuals randomized to placebo or semaglutide) studied semaglutide up to 1 mg QW as adjunctive therapy together with automated insulin delivery in adults with T1D for 15 weeks[114]. Semaglutide therapy increased time in range over the last 4 weeks of the treatment period (the primary endpoint), without increasing the time spent below 3.9 mM glucose; although episodes of recurrent euglycemic ketosis were reported in two individuals treated with semaglutide.

Several trials are underway to study the safety and efficacy (glucose control, time in range, weight loss) of GLP-1 medicines in patients with T1D. ADJUST-T1D (NCT05537233) is a 26-week trial of 1 mg QW semaglutide in 115 individuals with T1D and obesity who are using hybrid closed-loop therapy. Tirzepatide is being studied versus placebo in ~905 adults with T1D and either overweight or obesity over 49 weeks in the SURPASS-T1D-1 trial (NCT06914895), with a primary outcome of change from baseline in HbA1c over 40 weeks. The SURPASS-T1D-2 trial (NCT06962280) is assessing tirzepatide in adults with T1D and overweight or obesity over 20 months, with an identical primary outcome of change in HbA1c from baseline at week 40. Progress in accurate, noninvasive ketone monitoring may help reduce the risk of euglycemic ketoacidosis that is associated with the reduction of insulin dosing enabled by adjunctive use of insulin-sparing agents, including GLP-1 medicines. Several case series and small clinical trials highlight the potential of GLP-1 medicines to sustain C-peptide therapy and insulin independence in newly diagnosed patients with T1D[115], suggesting that GLP-1 medicines might be useful in preserving beta cell function, either alone or in combination with disease-modifying therapies such as teplizumab (anti-CD3). Nevertheless, no evidence supports a durable benefit in patients with T1D following cessation of GLP-1 therapy.

semaglutide in 17,604 people with overweight or obesity and a prior history of atherosclerotic CVD. Weight loss of only 9.39% was observed over 104 weeks, somewhat less than observed in most semaglutide weight loss trials, yet there was a 20% reduction in major adverse cardiovascular events, a 19% reduction in all-cause mortality and a 22% reduction in the heart failure composite endpoint[26]. Reductions in rates of major adverse cardiovascular events were seen rapidly (within several months of drug initiation), well before maximum weight loss was achieved. Post hoc analyses reported that the reduced rates of cardiovascular events in SELECT were observed irrespective of the starting body weight and independent of the extent of weight loss achieved[5].

Benefits of semaglutide have also been identified in people with a variety of other cardiometabolic and linked conditions, including metabolic liver disease[27], diabetic kidney disease[28], knee osteoarthritis[29] and peripheral artery disease[30]. The renal benefits of semaglutide in the FLOW trial (involving patients with T2D and kidney disease) were independent of concomitant use of SGLT-2 inhibitors and mineralocorticoid receptor antagonists[28,31,32], agents with known renoprotective activity[33]. Tirzepatide improved outcomes (assessed through changes in the apnea–hypopnea index) in patients with obstructive sleep apnea treated with or without continuous positive airway pressure[34]. While weight loss achieved with GLP-1 medicines likely confers substantial benefit in patients with HFpEF, obstructive sleep apnea and knee osteoarthritis, post hoc analyses reveal weight loss-independent benefits for semaglutide in metabolic liver disease, CVD and peripheral artery disease[35–37], potentially through pathways linked to reduction of inflammation[35]. Whether the dose–response relationships for achieving therapeutic benefit for these conditions are different than those observed for control of glucose and body weight is not known, and would benefit from additional clarification.

Prevention and remission of T2D

Might these agents prevent T2D, perhaps through preservation of beta cell mass and secondarily through weight loss and increased insulin sensitivity? The STEP-10 trial studied 2.4 mg QW semaglutide (n = 138) versus placebo (n = 69) plus nine sessions of lifestyle counseling in individuals with obesity and prediabetes for 52 weeks, followed by 28 weeks without active therapy—enabling assessment of the durability of the response after cessation of the drug[38]. Reduction in body weight was −13.9% in the semaglutide group versus −2.7% in the placebo-treated group at 52 weeks, and −7.9% versus −1.3% at week 80 (after 28 weeks off drug). Predictably, more individuals reverted to normoglycemia on semaglutide (81%) versus placebo (14%). However, by week 80, normoglycemia was maintained in 44% of semaglutide-treated patients versus 18% of placebo-treated patients[38]. No analysis of reversion to normoglycemia by extent of weight loss, insulin sensitivity or improvement of beta cell function was provided.

More compelling data were presented in the SURMOUNT-1 trial studying tirzepatide (5–15 mg QW) versus placebo over an initial 72-week period in 2,539 patients with obesity, including 1,032 with prediabetes. Trial participants received lifestyle advice including recommendations to achieve a 500-kcal deficit per day, and at least 150 min of physical activity per week. The mean body weight change at 176 weeks was −12.3%, −18.7% and −19.7% with 5 mg, 10 mg and 15 mg of tirzepatide QW, respectively. During the active treatment period, a new diagnosis of T2D was reported in 1.3% versus 13.3% of patients randomized to tirzepatide versus placebo[39]. More than 99% of tirzepatide-treated patients remained diabetes free over the extended active treatment period of 176 weeks. After 17 weeks off treatment, rates of T2D were 2.4% versus 13.7% for tirzepatide versus placebo, respectively. Post hoc mediation analysis suggested that up to 50% of the delay to onset of T2D with tirzepatide could be attributed to weight reduction[39]. The benefits of tirzepatide for diabetes prevention or remission may reflect greater weight loss and improved insulin sensitivity through weight loss-independent mechanisms via the GIPR[40]. Nevertheless, the limited duration of follow-up off drug restricts broader conclusions about the long-term benefits of tirzepatide for sustained diabetes prevention.

Neurodegenerative disorders

Substantial preclinical experimentation, real-world analyses and limited clinical trial data suggest GLP-1 medicines attenuate decline in cognitive (and motor) function associated with neurodegenerative disorders such as Parkinson's and Alzheimer's disease. Analysis of US Medicare claims data from 2016 to 2020 for people with T2D revealed significantly lower rates of new diagnoses of Parkinson's disease (hazard ratio (HR) 0.77) among 30,091 users of GLP-1 medicines versus 58,983 users of DPP-4 inhibitors (another class of drug used to control blood glucose)—with the findings largely consistent across age, sex and type of GLP-1 medicine[41].

Five clinical trials assessed the efficacy of exenatide or its derivatives in the treatment of Parkinson's disease in addition to dopaminergic medication[42–46]. Three of the trials, using exenatide twice daily (45

patients, 12 months plus a 2-month washout period), exenatide once weekly (62 patients followed for 48 weeks plus a 12-week washout) and lixisenatide (106 patients, 12 months plus a 2-month washout), reported positive results even after cessation of study medication—usually reported as less deterioration in the motor subscale of the Movement Disorders Society Unified Parkinson's Disease Rating Scale[42,43].

In contrast, two larger and longer trials did not show benefit. The first studied two doses, 2.5 mg and 5 mg QW of NLY01—a brain-penetrant, pegylated, long-acting exenatide derivative—over 36 weeks in 255 participants with mild symptoms, receiving no other medicines for Parkinson's disease. The study failed to show differences in motor or non-motor symptoms[44]. A second trial studied the efficacy of 2 mg QW exenatide over 96 weeks in 194 patients, who were on stable dopaminergic medication. Compliance was assessed through monitoring of plasma and cerebrospinal fluid (CSF) levels of exenatide (which were ~1% of the circulating plasma levels). No difference in the rates of the primary outcome, or a range of secondary outcomes—including dopamine transporter–single-photon-emission computed tomography imaging—was detected between groups, even in secondary analyses examining outcomes in younger participants (<60 years of age)[46]. The inconsistent results across five trials may reflect differences in patient populations, variability in brain penetration and insufficient target engagement in the central nervous system (CNS), reflected in part by modest weight loss.

Reduced rates of cognitive dysfunction have been reported with GLP-1 medicines in real-world analyses and in clinical trials studying patients without proven Alzheimer's disease. Serial assessments of cognitive function in 8,828 participants with T2D in the REWIND cardiovascular outcome trial—using the Montreal Cognitive Assessment and Digit Symbol Substitution Test—revealed significantly lower rates of deterioration in cognitive function in dulaglutide-treated patients (HR 0.86) over a median follow-up period of 5.4 years[47]. Mechanistically, therapy with either 2 mg exenatide once weekly in the EXSCEL trial[48], or with 2.4 mg QW semaglutide in the STEP-1 and STEP-2 weight loss trials[49], revealed reductions in circulating biomarkers of inflammation that also serve as indirect proxies for neuroinflammation in people with Alzheimer's disease. A registry study in Denmark assessed rates of hospitalization with a diagnosis of mild or major cognitive impairment in all Danish citizens with T2D aged > 65 years, between 2005 and 2018, who were treated with either DPP-4 inhibitors or GLP-1 medicines (n = 36,115) for at least 3 years[50]. Use of GLP-1 medicines, predominantly exenatide and liraglutide, was associated with reduced rates of major cognitive impairment.

Analysis of a US Department of Veterans Affairs database of individuals with T2D (~95% men) initiating GLP-1 medicines from 1 October 2017 to 2 June 2021 and followed for a median of 3.6 years, revealed significantly reduced rates of Alzheimer's disease (HR 0.88) and dementia (HR 0.92) in 215,970 people initiating GLP-1 medicines compared to use of other glucose-lowering agents[51]. The impact of GLP-1 medicines is being studied in trials of people with or at risk of Alzheimer's disease. The ELAD study was a 12-month randomized trial evaluating the efficacy of liraglutide (up to 1.8 mg daily) in 204 people with mild Alzheimer's disease. Results reported to date revealed no differences in the primary outcome of change in cerebral glucose metabolic rate in different brain regions. However, rates of cognitive decline (assessed by the ADAS-Cog-Exec, a composite cognitive outcome that includes measures of executive function) were reduced by 18%, and loss of temporal lobe and cortical volume was reduced by ~50% in liraglutide-treated patients[52].

Oral semaglutide up to 14 mg daily was studied in two large trials, Evoke and Evoke+, in adults (~1,840 per trial) aged 55–85 years, with enrollment of up to 30% of patients with T2D. Entry criteria include mild cognitive impairment or dementia secondary to Alzheimer's disease, with abnormalities of CNS amyloid confirmed by positron emission tomography or CSF analysis[53]. Evoke+ enrolled patients with evidence of small-vessel pathology in baseline imaging, in addition to criteria for Alzheimer's disease. The primary outcome assessed in week 104 is the change in the Clinical Dementia Rating Sum of Boxes score. A sub-study will explore changes in disease activity in the CSF in 210 patients from baseline to week 78, including CSF biomarkers reflective of disease activity, and assessment of neuroinflammation, neurodegeneration, oxidative stress, blood–brain barrier function, as well as vascular and synaptic integrity[53]. Top line results for the EVOKE trials revealed no reduction in rates of cognitive decline in patients treated with semaglutide, despite evidence for improvement in Alzheimer's disease-related biomarkers[54].

Overall, while independent lines of basic science and clinical evidence support the investigation of GLP-1 medicines in neurodegenerative disorders, the evidence for utility in Parkinson's disease is mixed. Whether GLP-1 medicines might prevent the development of Alzheimer's prior to the detection of amyloid plaque deposition is uncertain.

SUDs

Bariatric surgery is frequently accompanied by elevated levels of circulating GLP-1, yet exhibits a greater risk of some SUDs[55], particularly alcohol use disorder (AUD). By contrast, real-world data, preclinical experimentation and observations from small clinical trials support investigation of GLP-1 medicines in people with a wide range of SUDs. Among 227,866 individuals in Sweden with AUD and T2D or obesity, use of semaglutide (n = 4,321) and liraglutide (n = 2,509) was associated with significantly reduced rates of hospitalization for AUD (HRs 0.64 and 0.72) and for any SUD (HRs 0.68 and 0.78) compared to hospitalization rates during periods when patients were not taking these drugs[56]. Consistent with these findings, in people with obesity and/or T2D in the US-based TriNetX database, rates of incident AUD (HR 0.44) and recurrent AUD (HR 0.50) were significantly lower with semaglutide compared to other weight-reducing agents after propensity-matched analyses[57]. Similarly, retrospective analysis of real-world data in the TriNetX platform including 85,223 individuals with obesity revealed significantly reduced rates of incident cannabis use disorder (CUD; HR 0.56) and recurrent CUD (HR 0.62) in patients taking semaglutide versus non-GLP-1 obesity medications, and similar findings were noted in the same database scrutinizing 596,045 people with T2D, with HRs of 0.4 and 0.66 for new and recurrent diagnosis of CUD, respectively[58].

Use of GLP-1 medicines in the US Department of Veterans Affairs healthcare database was associated with significantly reduced rates of SUDs, including AUD (HR 0.89), CUD (HR 0.88), stimulant use disorders (HR 0.84) and opioid use disorders (HR 0.87), compared to users of other glucose-lowering agents[51]. Another analysis of electronic health records from the US Department of Veterans Affairs revealed greater reduction in alcohol use (assessed using the AUDIT-C alcohol screening tool) in patients exposed to GLP-1 medicines, compared to non-users or propensity-matched controls taking DPP-4 inhibitors. The greatest reductions in alcohol use were seen in individuals with a prior diagnosis of AUD and individuals with higher AUDIT-C scores consistent with hazardous drinking behavior[59].

A randomized clinical trial assigned 48 nontreatment-seeking participants with AUD to 9 weeks of treatment with either semaglutide or placebo. Semaglutide did not impact the overall average drinks per day or number of drinking days, but it reduced the number of drinks consumed per drinking day and decreased the amount of alcohol ingested during a posttreatment self-administration task in the laboratory[60]. Interestingly, semaglutide use was also associated with a reduction in the number of cigarettes consumed per day. On the other hand, a randomized, placebo-controlled study (N = 255) in people with moderate nicotine dependence did not show a reduction in cigarette use (abstinence rates) with 1.5 mg QW dulaglutide for 12 weeks versus placebo (both in addition to 2 mg varenicline per day and behavioral counseling)[61]. However, body weight was reduced, and self-reported alcohol intake was decreased by 29%, representing around −1.3 fewer drinks per week, in the individuals randomized to dulaglutide[62].

Collectively, the predominantly retrospective, real-world clinical data highlight the therapeutic potential of GLP-1 medicines in people with SUDs. These observations are consistent with substantial preclinical data demonstrating that GLP-1 medicines modify the activity of reward pathways and dopamine availability[63]. Much larger randomized trials are needed, using a range of GLP-1RA doses, with monitoring of participants on drug and after discontinuation, to understand the safety, practicality and therapeutic utility of these medicines in people with a range of SUDs.

Heterogeneity in responses to GLP-1 medicines

Substantial interindividual differences in the magnitude of HbA1c reductions and weight loss obtained with GLP-1 medicines are observed in clinical trials and in the real world, which remain poorly understood. Genome-wide association studies and analysis of *GLP1R* variants from 4,571 individuals revealed that the rs6923761G→A (Gly168Ser) *GLP1R* variant is associated with reduced glycemic responses to GLP-1 drugs, and rare, low-frequency variants in the *ARRB1* gene (encoding β-arrestin) are associated with greater glycemic responses to these medicines after 6 months of therapy[64]. Notably, none of these variants were associated with baseline BMI or differential weight loss responses. Modestly greater (30%) reductions in HbA1c were detected in 4% of the population harboring specific *ARBB1* variants relative to the 9% of the population without these variants, findings with marginal clinical utility. The importance of β-arrestin for optimization of GLP-1R signaling is notable in that tirzepatide and several investigational GLP-1 medicines are biased toward the cAMP pathway versus β-arrestin recruitment, which may elicit more sustained GLP-1R signaling and greater pharmacodynamic efficacy[4,65].

A study involving data from 10,960 individuals (6,750 using GLP-1 medicines, 4,210 undergoing bariatric surgery, almost half with T2D) from nine multi-ancestry biobank studies spanning six countries sought to analyze the utility of genetic variation in predicting weight loss responses to GLP-1 medicines[66]. Mean weight loss was −3.93% in the GLP-1 cohort, and higher baseline body weight and female sex were associated with greater weight loss. However, no significant associations were detected between polygenic risk scores and the extent of weight loss over at least 6–12 months, nor was there an association with missense variants in the *GLP1R*. Another study interrogated the utility of calories to satiation (CTS) and associated genetic variability—assessed via a gene risk score (CTS_{GRS})—in predicting the weight loss response to liraglutide[67]. In a 16-week trial, individuals with a low CTS or low CTS_{GRS} score lost more weight relative to individuals with higher scores. Whether the proposed predictive utility of these instruments will be independently validated in much larger cohorts, treated for longer periods of time and with more powerful GLP-1 medicines (such as semaglutide and tirzepatide) requires further evaluation.

Considerable variability in the weight loss response to GLP-1 medicines is observed in clinical trials, and to a greater extent in the real world, fostering the concept of nonresponders, poor responders, or super-responders. Across the STEP trials assessing weight loss with semaglutide up to 2.4 mg QW, ~10–17% of patients lost <5% of their body weight, while ~32–40% experienced >20% weight loss[68]. In the SELECT cardiovascular outcome trial, almost one-third of semaglutide-treated patients failed to lose >5% body weight and several hundred individuals gained weight over the first 104 weeks[69]. The HbA1c and weight loss response to GLP-1 medicines was assessed in a registry spanning four European countries, including adults with T2D[70]. Only 14% of study participants achieved clinically meaningful reductions in both HbA1c and body weight, defined as 0.5% reduction in HbA1c and ≥5% reduction in body weight. Overall, 35.7% achieved a reduction only in HbA1c, 7.4% achieved a reduction only in body weight, while 42.9% of participants failed to exhibit a clinically meaningful reduction in either HbA1c or body weight. Neither age nor duration of diabetes predicted reductions in HbA1c or body weight, although females exhibited greater weight loss responses than males. Higher baseline BMI and lower estimated glomerular filtration rate were associated with greater weight loss responses, whereas a higher baseline HbA1c predicted a lower weight loss response[70]. Among patients treated for weight loss with semaglutide or liraglutide over a mean follow-up period of 520 days in a real-world clinic setting, 17.8% had a nonresponse (<5% weight loss), 48.4% had a moderate response (5–15% weight loss) and 33.8% reported >15% weight loss, with a greater proportion of females reporting >15% weight loss[71].

Overall, the available data do not support the current utility of using biomarkers, clinical phenotypes or genetics to predict the initial glucose-lowering or weight loss response to GLP-1 medicines[66]. Neither is it possible to use genetic analyses to prospectively identify individuals more susceptible to rapid weight regain following cessation of therapy. Currently, we cannot explain the variability in response. It is possible that some individuals may have differences in relative expression of the GLP-1R in key target tissues, such as the brain or pancreatic islets, which contribute to gradations of responsivity. Indeed, more than tenfold interindividual variation in relative expression of *GLP1R* mRNA transcripts was identified in the four chambers of the human heart[72]; however, the potential clinical significance of these findings has not been explored.

Evolving safety of established and investigational GLP-1 medicines

Most randomized controlled trials of GLP-1 medicines are too small in size and too short in duration to detect imbalances in rare side effects that occur in less than 1:1,000 individuals, including rare ocular events such as non-arteritic anterior ischemic optic neuropathy[73], a disorder with an incidence rate of several cases per 100,000 individuals. Similarly, interpretation of an imbalance in incidence of neovascular age-related macular edema in users of GLP-1 medicines for T2D—detected using real-world registry data – is confounded by lack of propensity-matched controls simultaneously started on non-GLP-1 medicines[74]. The randomized FOCUS trial (NCT03811561) may begin to fill this gap, investigating the effects of semaglutide (1 mg for up to 260 weeks) versus placebo on diabetic retinopathy. Nevertheless, the estimated enrollment of ~1,500 participants will preclude conclusions about the risk of rare ocular events such as non-arteritic anterior ischemic optic neuropathy or age-related macular edema.

Information informing the safety of using GLP-1 medicines immediately before or during pregnancy is currently limited. Retrospective analyses using the TriNetX database suggest reduced rates of adverse pregnancy-associated obstetric outcomes in women exposed to a GLP-1 medicine within the 2 years before a pregnancy, compared to propensity-matched nonexposed controls[75]. Current recommendations mandate stopping GLP-1 medicines several months before conception. However, GLP-1 medicines are not teratogenic and have not been associated with an imbalance in maternal outcomes or major birth defects, including fetal cardiac or kidney malformations, following inadvertent exposure in the first trimester in women with T2D ($n = 1,826$)[76] or women with T2D or obesity ($n = 168$)[77].

Reports of retained gastric contents and risks for aspiration pneumonia have led to multiple guidelines and recommendations surrounding perioperative assessment and individualized recommendations surrounding continuation or cessation of GLP-1 medicines in people undergoing elective endoscopy or surgical procedures[78]. The risks versus benefits of stopping GLP-1 medicines in all patients before surgery is challenged by reports demonstrating no imbalance of adverse perioperative outcomes in thousands of users of GLP-1 medicines admitted to hospital who required immediate emergency surgery[79].

Real-world data support the safety of using GLP-1 medicines in people with a wide range of neuropsychiatric disorders, including patients with a history of suicidal ideation. However, these individuals are not well represented in clinical trials of people with T2D and obesity.

Table 1 | Examples of clinical trials for muscle-sparing agents

Drug and dose	Trial duration	Clinical trial identifier	Results
Bimagrumab (30 mg per kg body weight intravenously at weeks 4, 16, 28 and 40) ± semaglutide (2.4 mg weekly)	48 weeks	BELIEVE trial (NCT05616013)	Combination therapy led to 22.1% weight loss versus 10.8% (bimagrumab alone) and 15.7% (semaglutide alone). Combination showed preferential fat loss and less lean mass loss (2.9% versus 7.4% with semaglutide alone). Side effects with bimagrumab included muscle spasms, diarrhea, acne and elevated low-density lipoprotein.
Semaglutide ± trevogrumab ± garetosmab semaglu tide 2.4 mg alone or in combination with trevogrumab 200 mg (lower dose), trevogrumab 400 mg (higher dose) or higher-dose trevogrumab plus garetosmab 10 mg per kg body weight (triplet).	26 weeks	COURAGE trial (NCT06299098)	Weight loss: ~10% with semaglutide alone or with trevogrumab; ~13.2% with semaglutide + trevogrumab + garetosmab. Lean mass loss: 34.5% (semaglutide alone), ~17% (with trevogrumab) and 6.6% (with both antibodies). Greater fat mass loss with combinations. Adverse events include muscle spasms.
Tirzepatide (weekly) ± apitegromab (10 mg per kg body weight intravenously every 4 weeks)	24 weeks	EMBRAZE trial (NCT06445075)	No additional weight loss with combination. However, ~50% less lean mass loss observed with apitegromab + tirzepatide.

Reduction in appetite and reduced interest in food secondary to use of GLP-1 medicines may be associated with more generalized anhedonia, and depression. Analysis of the psychiatric safety of semaglutide in the STEP-1, STEP-2, STEP-3 (n = 2,116) and STEP-5 (n = 152) weight loss trials—using symptoms captured in the Patient Health Questionnaire and the Columbia-Suicide Severity Rating Scale—did not reveal differences in reported depression or suicidal ideation, and rates of a range of psychiatric conditions were not different in semaglutide-treated versus placebo-treated groups[80]. Rates of new or recurrent suicidal ideation and suicide have been assessed in multiple real-world cohorts. These include patients with T2D enrolled in nationwide registries in Sweden and Denmark (n = 298,553)[81]; patients with overweight or obesity (n = 240,618) and T2D (n = 1,589,855) in the TriNetX network[82]; propensity-matched cohorts of Spanish adults with obesity initiating GLP-1 medicines for the treatment of T2D (n = 3,040)[83]; the UK Clinical Practice Research Datalink linked to the Hospital Episodes Statistics Admitted Patient Care and Office for National Statistics Death Registration databases[84]; and the US Veterans Affairs healthcare system[51]. Collectively, these analyses do not demonstrate an increased risk of suicidal ideation with use of GLP-1 medicines, with the majority of analyses revealing a similar or lower risk for incident or recurrent suicidal ideation among users of semaglutide[82] and other GLP-1 medicines compared to standard of care for people with T2D and/or obesity[51,81,83,84].

New drugs may combine agonists of GLP-1 and amylin (which exerts similar pharmacological actions to GLP-1, such as reduction of appetite, gastric emptying and glucagon secretion, through different neural pathways)[4]. Given the abundance of amylin and calcitonin receptors in the brain that potentially influence a wide range of behaviors, scrutiny of the psychiatric safety of amylin-based medicines will be particularly important. As the field of GLP-1 medicines expands to encompass molecules targeting additional receptors in new disease indications, it is incumbent on researchers to remain vigilant for new adverse events not previously detected in studies of first-generation GLP-1 therapies[17].

Achieving healthy weight loss

GLP-1 medicines such as semaglutide and tirzepatide commonly produce 15–20% weight loss in people with obesity, and newer medicines, exemplified by retatrutide (a triple agonist targeting GLP-1R, GIPR and glucagon receptor (GCGR)), will enable even greater weight loss, from 25–35% in some individuals[85]. Extensive and rapid weight loss, whether achieved through diet and exercise, bariatric surgery, medications or arising secondary to catabolic disorders such as cancer, is frequently accompanied by 20–40% reductions in lean mass, including muscle[86]. Although older people with sarcopenic obesity are often excluded from clinical trials, older or frail individuals may be at risk for muscle weakness following rapid weight loss with GLP-1 medicines. A sub-study of a phase 2 trial analyzed changes in body composition (using dual-energy X-ray absorptiometry) and revealed reductions in lean mass of up to 12.5% and reductions in fat mass of 26.1%, in patients with T2D treated with retatrutide (8 mg QW) over 36 weeks[87]. A structured exercise program several times per week, when combined with GLP-1 medicines for weight loss, preserves lean mass and maintains body weight while improving insulin sensitivity—consistent with achievement of healthier weight loss[88]. Whether preservation of lean mass will attenuate weight regain after cessation of GLP-1 therapy (by augmenting metabolic rate) requires further study. Greater rates of nutritional deficiencies, including vitamin deficiencies, were reported in users of GLP-1 medicines, although the relative increase was modest when compared to metformin-treated controls[89].

Muscle mass declines with age, often exacerbated by a poor diet, sedentary lifestyle and the pro-inflammatory state of accompanying obesity. Investigational medications to preserve functional muscle strength target or mimic the actions of a wide range of proteins important for control of muscle mass and regeneration, including myostatin, activin, their receptors, apelin, insulin-like growth factor 1, growth hormone and selective androgen receptor modulators[4]. Many such medications are being evaluated in combination with semaglutide or tirzepatide, with the goal of sparing loss of muscle mass and ultimately achieving healthier weight loss.

Beyond relative sparing of lean mass, interrogation of the efficacy of these medicines should answer a range of clinically relevant questions. How long must the treatment continue for and how enduring are the effects? What are the clinically relevant endpoints, beyond improvements in quality-of-life questionnaires, 6-min walk time, grip strength and stair climbing? What are the merits versus limitations of the various investigational agents, and will some be better suited for specific populations? How do the potential benefits of these medicines compare with or augment intensive lifestyle management—including adequate protein supplementation and resistance and/or aerobic exercise—and are the results additive to concomitant lifestyle management? How does one prospectively determine the ideal patient for muscle-sparing anabolic therapy when initiating treatment with GLP-1 medicines? Results from the ongoing trials (Table 1) and long-term follow-up will provide important directions for this emerging field that seeks to optimize the health of individuals using GLP-1 medicines.

New GLP-1 medicines and the challenge of differentiation

Dozens of investigational GLP-1 medicines are being evaluated in phase 2 trials, with several poised to enter phase 3 in the near future[4]. Medicines in phase 3 trials include orforglipron (an oral small-molecule GLP-1RA), survodutide (a GCGR–GLP-1R co-agonist), retatrutide (a GIPR–GCGR–GLP-1R triple agonist), maridebart cafraglutide (Maritide; a GIPR antagonist–GLP-1R agonist) and cagrilintide–semaglutide (Cagri-Sema; a co-formulated amylin and GLP-1R agonist)[4,90–98] (Table 2). Glucagon and

Table 2 | Late-stage investigational GLP-1 medicines

Drug and dose	Trial duration	Trial identifier	Dose and results
Cagri-Sema 2.4 mg subcutaneously each for cagrilintide and semaglutide	68 weeks	REDEFINE-1 (NCT05567796) REDEFINE-2 (NCT05394519)	In REDEFINE-2 (overweight/ obesity with T2D)[97], 10.4% placebo-subtracted weight loss from BMI 36.1; 73.5% reached HbA1c < 6.5% from 8% baseline. Weight loss > 15% in 51.6%, >20% in 29.2%. In REDEFINE-1 (without T2D)[98], 17.3% placebo-subtracted weight loss from BMI 38. Body composition (DXA): −35.7% fat and −14.4% lean mass loss versus −5.7% and −4.2% with placebo. Max dose achieved in 57.4% of Cagri-Sema participants. Safety consistent with GLP-1 class.
Amycretin Up to 60 mg subcutaneously	Up to 36 weeks	NCT06064006	Studied in 125 participants (101 active, 24 placebo)[103]. Doses 0.3–60 mg QW. Up to 23.2% placebo-subtracted weight loss from BMI 30. High discontinuation in both groups. Sample size is too small for full tolerability assessment. Phase 3 trials to begin 2026.
Maridebart cafraglutide (Maritide) Up to 420 mg once every four weeks	52 weeks	NCT05669599	Antibody activating GLP-1R while blocking GIPR. 17.3% placebo-subtracted weight loss in non-T2D, 16.6% in T2D (BMI ~ 38). HbA1c reductions: −1.2% to −1.6% versus 0.1% with placebo. Gastrointestinal adverse events higher without dose escalation[104].
Orforglipron Up to 36 mg once daily	40 weeks	ACHIEVE-1 (NCT05971940)	Oral small-molecule GLP-1RA. Studied in early T2D (baseline HbA1c 8%): −1.07% HbA1c and 5.9% weight reduction versus placebo. Adverse events consistent with GLP-1 class; no off-target toxicity[105].
Survodutide Up to 4.8 mg QW	46 weeks	NCT04667377	A GCGR–GLP-1 receptor co-agonist. Up to 12.1% placebo-subtracted weight loss in people with overweight or obesity[96]. Adverse events were predominantly gastrointestinal.

DXA, dual-energy X-ray absorptiometry.

amylin agonism may promote additional weight loss through separate anorexic pathways; whether glucagon agonism also attenuates the reduction in metabolic rate seen with weight loss is under investigation[4]. Intriguingly, genetic or pharmacological loss of GIPR signaling in the CNS appears to enhance a subset of anorectic GLP-1R signaling pathways, which may explain the efficacy of Maritide[99–101].

Each of these new entities will require extensive evaluation in large safety and outcome trials that will take years to complete, to define the risk:benefit ratio and the unique value proposition of each agent. Such data may allow for differentiation of newer agents from current ones in various patient subgroups. Moreover, the efficacy of established GLP-1 medicines has been extended well beyond T2D and obesity in phase 3 trials. Therefore, it seems likely that one or more new GLP-1 medicines will demonstrate superior efficacy in some disorders, while others may fail to match results achieved to date with semaglutide and tirzepatide.

Opportunities for differentiation include greater weight loss, enhanced tolerability, more convenient and less frequent dosing regimens, fewer adverse events, greater reduction of obesity-associated complications and reduced cost. In addition to the investigational drugs described above, GLP-1 medicines are being evaluated in multiple new indications, frequently in individuals with concomitant overweight or obesity, including T1D (NCT06914895), psoriatic arthritis (NCT06588296), hidradenitis suppurativa (NCT06301256), Crohn's disease (NCT06937099), ulcerative colitis (NCT06937086), benign intracranial hypertension (NCT06027567), migraine[102] and polycystic ovary syndrome (NCT05819853).

Small-molecule agonists under investigation might also be combined to produce single tablets targeting multiple receptors (GLP-1R, AMLNR, GIPR) and could be combined with SGLT-2 inhibitors, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers thyroid hormone receptor beta agonists or selective mineralocorticoid receptor antagonists to produce highly effective medicines for reduction of cardiorenal and related metabolic disorders.

Conclusion

The surge in interest in GLP-1 medicines, exemplified by dozens of new molecules and ongoing studies of multiple new disease indications, holds great promise for providing new therapeutic solutions that fulfill unmet medical needs and improve human health. Greater global access to effective yet more affordable GLP-1 medicines will be required to improve population health and lower overall healthcare costs.

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Acknowledgements

D.J.D. is supported in part by a Banting and Best Diabetes Centre Novo Nordisk Chair in Incretin Biology, and a Sinai Health Novo Nordisk Foundation Fund in Regulatory Peptides. Research in the Drucker lab is supported by CIHR grants 154321 and 192044 and a Diabetes Canada-Canadian Cancer Society grant (OG-3- 24-5819-DD).

Competing interests

D.J.D. has received financial remuneration from Alnylam, Amgen, AstraZeneca, Crinetics, Eli Lilly, Insulet, Kallyope, Metsera, Pfizer and Sanofi for consulting and from Novo Nordisk for speaking, and Mt. Sinai Hospital receives investigator-initiated grant support from Amgen, Eli Lilly, Novo Nordisk and Zealand Pharma for preclinical studies in the Drucker lab.

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Peer review information *Nature Medicine* thanks John Wilding and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Karen O'Leary, in collaboration with the *Nature Medicine* team.