Clinical trials

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A revolution in obesity treatment

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Mounting evidence, including the recent (and unprecedented) phase 2 data on retatrutide, supports a role for incretin hormone agonists in treating obesity. But with great power comes great responsibility.

The worldwide obesity epidemic is continuing unabated and is projected to worsen over the next decades. While preventive interventions will be the most impactful at altering the course of the obesity epidemic in society, treatment of the disease will be life-altering for the individuals affected. Several incretin (gut-secreted hormone) pathways are now being explored therapeutically for obesity, diabetes and other obesity-related metabolic conditions (for example, non-alcoholic steatohepatitis and heart failure). Retatrutide, the first triple-incretin agonist, has just completed its phase 2 development program. The two studies that composed the phase 2 program included adults who are overweight or have obesity[1], with or without type 2 diabetes[2]. These studies were reported in recent issues of the *New England Journal of Medicine* and *The Lancet*, respectively. The level of weight loss achieved in these studies has generated justifiable excitement. Along with recent encouraging results from other incretin agonists, these drugs are poised to dramatically change how obesity is treated.

Incretins are hormones secreted by the gut in response to food intake. Their secretion is increased following metabolic surgeries that involve gut rearrangements (such as Roux-en-Y gastric bypass and biliopancreatic diversion), and they are thought to be responsible for the weight loss and other metabolic benefits observed after such surgeries. The glucagon-like peptide 1 (GLP-1) pathway — the first incretin pathway to be harnessed therapeutically — exerts beneficial effects on weight, glycemia and cardiovascular events by decreasing appetite, increasing satiety, stimulating glucose-dependent insulin production, reducing inflammation and exhibiting anti-atherosclerotic effects. Other incretin hormones also act centrally to reduce appetite; therefore, in combination with GLP-1 agonism, they potentiate the central anorexigenic effect and have complementary peripheral metabolic effects. For example, gastric inhibitory polypeptide (GIP) agonism increases lipolysis, and glucagon (GCG) agonism improves substrate utilization and increases energy expenditure[3]. As a result, single-, dual- and now triple-incretin agonists have been evaluated as a therapeutic strategy for obesity and related conditions.

The recent phase 2 studies of retatrutide evaluated four maintenance doses of up to 12 mg weekly. In people without diabetes, the highest dose of retatrutide led to a 24.2% reduction in body weight (from a mean baseline of 108.0 kg) following 48 weeks of treatment[1]. In people with type 2 diabetes, retatrutide in weekly doses of 12 mg led to a 2.16%-point reduction in HbA1c (from a mean baseline of 8.3%) and a 16.9% reduction in body weight (from a mean baseline of 99.8 kg) following 36 weeks of treatment[2]. In both studies, the weight-loss trajectory suggested the likelihood of ongoing weight loss with continued therapy. The magnitude of weight loss reported in these studies is unprecedented and approached the weight loss noted after metabolic surgery (for example, weight loss after Roux-en-Y gastric bypass surgery is 20–30%).

Head-to-head studies that compare obesity pharmacotherapies have not been conducted. As an indirect comparison, the most potent GLP-1 receptor mono-agonist, semaglutide (2.4 mg weekly), led to a 16.9% reduction in body weight after 68 weeks of treatment in patients without diabetes[4], and 10.6% in patients with type 2 diabetes[5], along with an HbA1c reduction of 1.6% points (Fig. 1). Tirzepatide, the only dual-incretin agonist (GLP-1–GIP) to have completed late-phase clinical development, led to a body-weight loss of 22.5% after 72 weeks of treatment with the 15 mg dose in patients without diabetes[6], and 15.7% in patients with diabetes[7] — along with an HbA1c reduction of 2.1% points. The best results to date with a GLP-1–GCG dual agonist were reported in a phase 2 trial of survodutide[8], in which treatment with a dose of 4.8 mg weekly for 48 weeks resulted in 18.7% body-weight loss. Of note, another bi-receptor agonist combination is also in development, harnessing the incretin (GLP-1) analog semaglutide (2.4 mg weekly) in a fixed-dose ratio combination with an amylin agonist, cagrilintide (2.4 mg weekly), which also suppresses satiety, delays gastric emptying and suppresses GCG secretion.

Incretin agonists seem to be well tolerated, with the most frequent adverse events being gastrointestinal — including nausea, vomiting, diarrhea or constipation. In all studies that evaluate the weight-loss effects of incretin agonists, the proportion of people who stopped treatment was lower in the active medication arms than in placebo arms, reflecting a positive risk/benefit ratio of these agents despite their known side effects. Retatrutide appeared to be no different, with mild-to-moderate gastrointestinal adverse events reported in 13–50% of participants.

The future availability of multiple effective treatments that harness different mechanistic pathways represents not only an opportunity to effectively treat obesity, but also the potential to individualize treatment based on each person's comorbidities, treatment response and preferences. A rich therapeutic line-up also fuels competition, which ultimately benefits patients in multiple ways. First, competition stimulates discovery and ongoing efforts to improve on existing products. Second, concerns regarding drug availability should decrease as the number of therapeutic options increases. Third, competition should positively impact pricing, therefore increasing access to these treatments to more people in need, minimizing disparities that are particularly prevalent in this field.

However, with the great power conferred by effective second-generation obesity pharmacotherapies comes great responsibility — to fully understand their effects and learn how to maximize their long-term benefits while preventing or minimizing untoward effects. The longest studies reported to date have less than 2 years of follow-up. Longer-term studies are needed to understand the full spectrum of benefits, including long-term maintenance of weight loss, impact on obesity-associated metabolic co-morbidities (for example, hypertension, hypercholesterolemia and diabetes) and metabolic complications (for example, cardiovascular disease and non-alcoholic fatty liver disease), and ultimately to determine whether use of these drugs improves quality of life and longevity. It is equally important that we understand and learn to manage the full range of potential drug-related

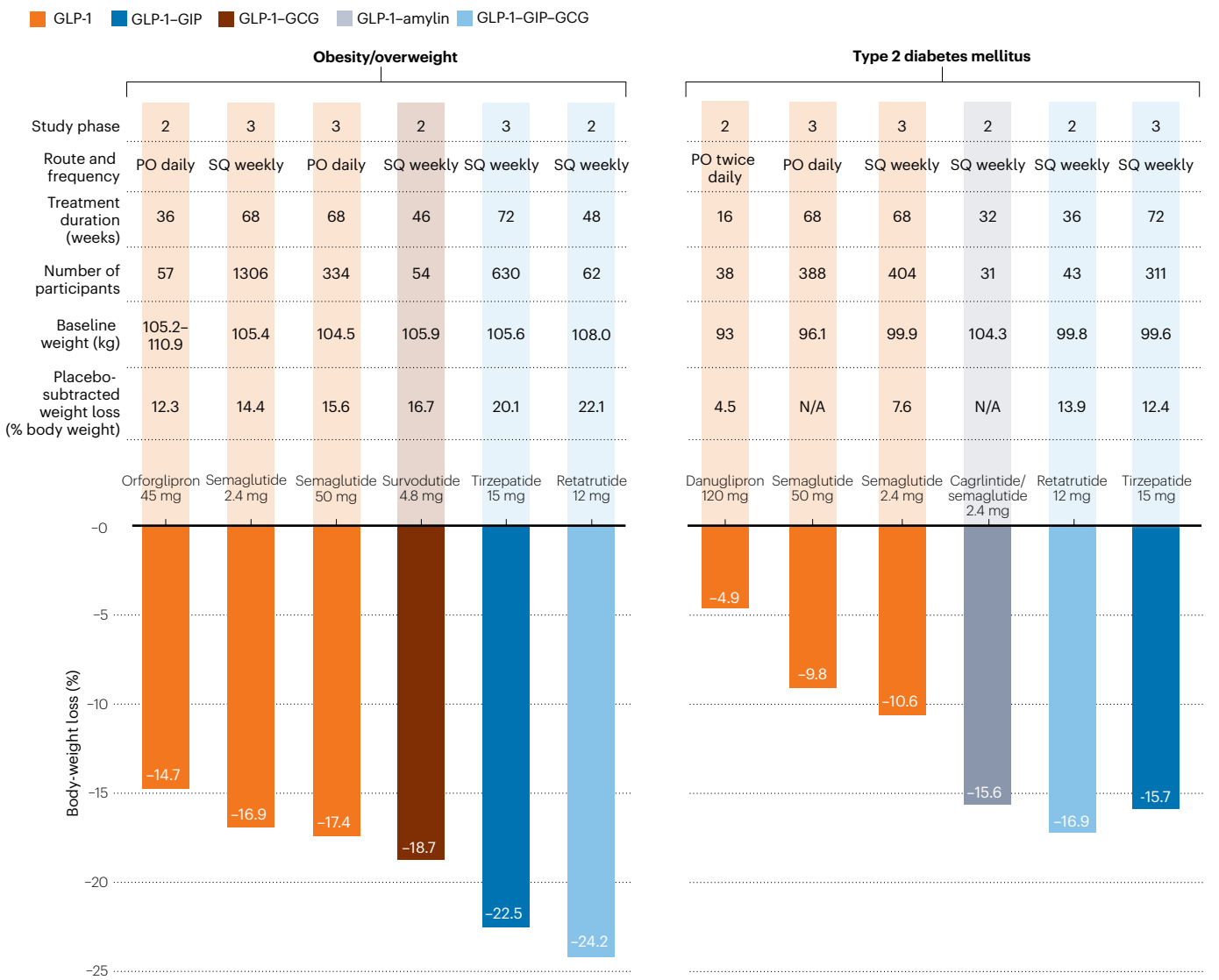

Fig. 1 | Weight loss with second-generation obesity pharmacotherapies. Percent body-weight loss in participants who are overweight or have obesity without diabetes (left)[1,4,6,8–10] or with type 2 diabetes (right)[2,5,7,11–13], from phase 2 or 3 clinical trials. For each study, the result of the highest tested dose at the longest study timepoint is shown. Percentage body-weight loss and placebo-subtracted percentage body-weight loss were calculated using the published data if not specifically provided. The number of participants listed reflects the number reported as analyzed. PO, oral; SQ, subcutaneous.

or weight-loss-related side effects. A reduction in dietary intake, coupled with consumption of food with low nutritional value or empty calories, might put patients at risk of micronutrient deficiencies. A large magnitude of weight loss could increase the risk of sarcopenia, frailty and fractures. Some useful lessons could be transferred from experience with metabolic-surgery-induced weight loss, but unique challenges and opportunities also exist. Unlike with bariatric surgery, the rate of weight loss with pharmacological agents could be individualized, but we do not know the optimal rate of weight loss or the potential harms of rapid voluntary weight loss. Moreover, non-adherence to pharmacotherapy (due to patient or payor factors) can lead to rapid regain of body weight and weight variability.

Overall, the promise of highly effective weight loss pharmacotherapy is truly revolutionary in the setting of the current global obesity epidemic. However, a great responsibility lies in understanding its short- and long-term outcomes to guide the delivery of such treatments in clinical practice and establish their cost effectiveness. Ultimately, we need to intensify obesity prevention efforts as the only effective approach to curtail the obesity epidemic. Whether pharmacology has a role in obesity prevention is an intriguing question for society to ponder.

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Competing interests

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