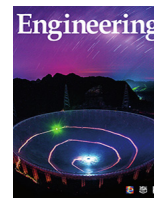




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## News &amp; Highlights

## Effective Anti-Obesity Drugs Make Losing Weight a Big Deal

Sarah C.P. Williams<sup>a</sup><sup>a</sup> Senior Technology Writer

In early September 2023, when its market cap jumped to 428 billion USD, a valuation topping the estimated 2022 gross domestic product of its Scandinavian home country, the drugmaker Novo Nordisk (Bagsværd, Denmark) briefly eclipsed the French luxury brand conglomerate LVMH (Paris, France) as Europe's most valuable company [1]. The reason for the company's soaring worth? Its already best-selling weight loss drug Wegovy was being released to patients in the United Kingdom.

Wegovy, an injectable form of the drug semaglutide, is one of a new class of weight-loss drugs that mimic the natural effects of glucagon-like peptide-1 (GLP-1) and similar gut-secreted hormones involved in regulating the body's energy homeostasis. Wegovy injections, also sold by Novo Nordisk to treat type 2 diabetes under the brand name Ozempic (Fig. 1), were approved for obesity by the US Food and Drug Administration (FDA) in June 2021 after several large, randomized phase 3 trials—reported in March 2021 in the prestigious medical journals the *New England Journal of Medicine* (NEJM) and the *Lancet*—showed they led to average losses of body weight of about 15% and 10% in individuals with obesity and without and with type 2 diabetes, respectively, over the course of 68 weeks [2,3].

Two years after its approval, semaglutide use has soared, in part because the market for weight loss is so large. The worldwide prevalence of obesity and metabolic diseases has continued to rise, with an estimated five million deaths a year attributed, at least in part, to obesity [4]. At the same time, celebrity influencers touting their success in losing weight with Ozempic and Wegovy across social media platforms has led to widespread demand for the drugs, even among people not classified as having obesity, as well as drug shortages for those who rely on the medications to control their type 2 diabetes [5].

But other compounds are already raising the bar initially set by semaglutide for weight loss. Most prominent among these is the Indianapolis, IN, USA-headquartered Eli Lilly's Mounjaro (tirzepatide), which augments the effects of two gut hormones, GLP-1 (like Wegovy) and gastric inhibitory polypeptide (GIP). Like semaglutide, Mounjaro also holds a previous approval for use in patients with type 2 diabetes. The anticipation for Mounjaro's FDA approval in obesity, received in early November 2023, had already caused Lilly's stock price to skyrocket, making it—by valuation—the largest pharmaceutical company in the world [6].

For Lilly investors, the good news began with the publication of a July 2022 issue of NEJM, in which clinical researchers reported the results of a phase 3 trial of Mounjaro showing a more than 20% average loss of body weight after 72 weeks in individuals with obesity but without type 2 diabetes [7]. Then, in April 2023, Lilly announced the results of a second phase 3 trial of Mounjaro that yielded similarly significant average weight losses of about 16% in individuals with obesity and type 2 diabetes after 72 weeks [8]. Most recently, in an August 2023 issue of NEJM, researchers reported the results of a phase 2 trial of the company's investigational drug retatrutide, which augments the activity of three separate gut hormones, including GLP-1, GIP, and glucagon (GCG), yielding an average weight loss of 24.2% in patients with obesity after 48 weeks of treatment [9].

Oral pill formulations—greatly preferred by patients over injections—of the drugs are also poised to further balloon the market. Both Rybelsus, Novo Nordisk's pill version of semaglutide, as reported in a recently completed phase 3 trial published in an August 2023 issue of the *Lancet* (approval for obesity expected by the end of 2023) and Lilly's oral GLP-1 drug orforglipron, as reported in a mid-stage (phase 2) study published in a September 2023 issue of NEJM, produced average body weight losses of around 15% after 68 and 36 weeks, respectively [10–13].

“These drugs are completely changing the paradigm on how we treat obesity,” said Robert Kushner, professor of medicine (endocrinology) and medical education at Northwestern University Feinberg School of Medicine in Chicago, IL, USA, and senior author on the seminal phase 3 trial NEJM report for semaglutide in obesity published in March 2021. “Until now, there were no drugs with anywhere close to this level of effectiveness.”

Semaglutide, tirzepatide, and retatrutide all work by augmenting the effects of hormones produced in the gut (intestines and pancreas) in response to meals. Activating these pathways, even in the absence of food, reduces appetite, slows the passage of food through the digestive tract, and stimulates insulin production [14]. It is because of their impact on insulin that drugs mimicking GLP-1 were first developed to treat type 2 diabetes, in which the body does not make enough insulin. The FDA approved exenatide, the first GLP-1 mimicking drug (mimetic), or agonist, in 2005, followed by approvals of others for diabetes, including Victoza (liraglutide) in 2010, Trulicity (dulaglutide) in 2014, and Ozempic in 2017 [15].

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**Fig. 1.** Ozempic (semaglutide) was approved by the US Food and Drug Administration (FDA) in 2017 for treating patients with type 2 diabetes but its 2021 FDA approval for the treatment of obesity and unprecedented success as a weight loss drug, rebranded as Wegovy, has led to substantially increased demand and shortages. Credit: Chemist4U (public domain).

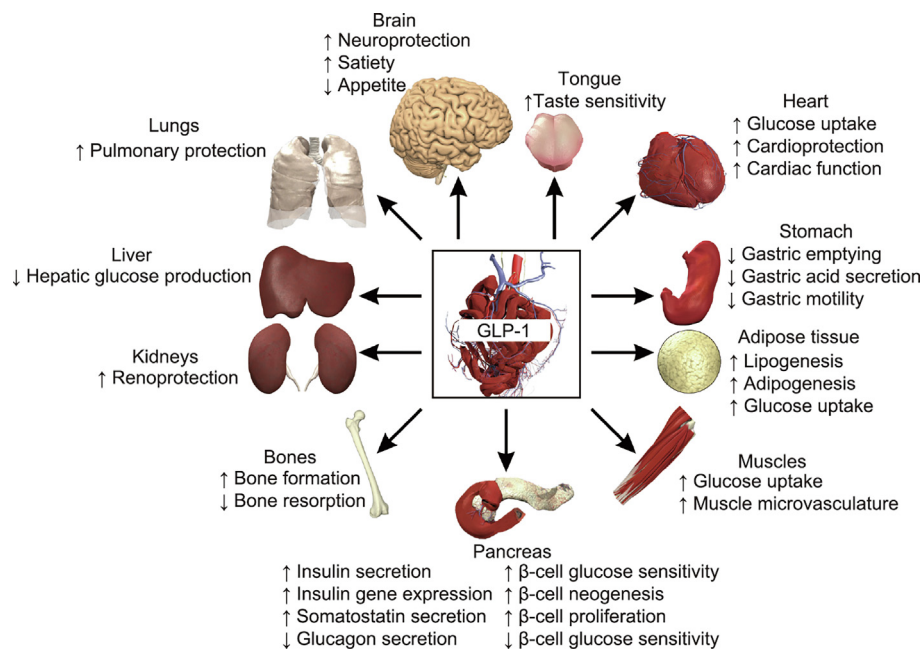
“People talk about these drugs as if they are completely new, which is not the case,” said Daniel Drucker, a professor of medicine at the University of Toronto in Canada who led many of the early laboratory and clinical studies on GLP-1 in the 1980s and 1990s. “We have already treated tens of millions of people with this class of drugs.”

Worldwide, more than a third of all adults are classified as overweight or having obesity [16]. Having a high body mass index (BMI) raises people’s risk of cardiovascular diseases, musculoskeletal disorders, and some cancers. But older drugs aimed at obesity had only small effects on body weight. Then, clinicians using GLP-1 agonists to treat diabetes noticed the large weight losses their patients experienced at the same time control of their blood sugar levels improved.

Drugs have now been developed that act on nearly every combination of GLP-1, GIP, and GCG [14]. Each hormone has a unique set of actions on the digestive tract and brain—as well as on other tissues, including the liver, kidneys, heart, and blood vessels (Fig. 2). Because of those wide-ranging cellular targets, the gut hormone mimetics are also showing success in treating diseases besides diabetes and obesity. “The widespread use of these drugs is now prompting additional observations about their actions in the body, and those observations are leading to clinical trials,” said Drucker. “If you had told me fifteen years ago that GLP-1 was going to be useful for not only diabetes but obesity, heart failure, Alzheimer’s, peripheral artery disease, and so on, I would have said ‘I do not think so,’ but that is where we are at now.”

Highlighting these additional potential benefits, Novo Nordisk announced the results of another landmark phase 3 study in August 2023; with almost 18 000 patients randomized, treatment with semaglutide decreased by 20%, versus a placebo, the occurrence of major cardiovascular events over a five-year period in adults who were overweight or had obesity, with pre-existing cardiovascular disease but without diabetes [17]. Adding to the excitement, in September 2023, a small trial, again reported in NEJM, showed semaglutide treatment early after their initial diagnosis of type 1 diabetes enabling patients to discontinue insulin injections—the essential component of type 1 diabetes treatment for decades [18]. Doctors have also anecdotally reported that gut hormone mimetics may also help treat addictive and compulsive behaviors outside of eating, including drinking and smoking, presumably acting through the drugs’ impact on reward circuits in the brain [19].

“The effects we see in all these areas are pretty robust, but the mechanisms are still elusive,” said Drucker, who is now studying how GLP-1 agonists can impact the liver and heart, despite liver and heart cells not having high levels of the GLP-1 receptor. He said his research has shown that the effects on the heart and liver can be completely separated from the drugs’ ability to promote weight loss, although there are also benefits of weight loss on both organs.



**Fig. 2.** Basic research on the gut hormone GLP-1 has shown diverse effects across many organ systems, which may help explain the potential of GLP-1 mimetics to have wide-ranging impacts on health that—beyond diabetes and obesity—might also provide benefits to patients with cardiovascular and liver disease, and perhaps even Alzheimer’s. Credit: Lthoms11/Wikimedia (CC BY-SA 4.0).

Amid these potential new medical applications for gut hormone agonists, as well as the swelling demand for them that has led to unsupervised use of the drugs from non-approved sources, physicians remain focused on ensuring that the drugs are being used in safe and evidence-based ways [5]. Even for the evidence-based treatment of obesity, the drugs may not be right for all patients, and much remains to be discovered about their optimal use. “It is not just a race to see how much weight you can lose how quickly—we need to be careful of getting caught up in that,” said Kushner. “We need to be shifting our discussion to how we can best harness the health improvements that these drugs bring.”

To date, the gut hormone mimetics have only been studied for weight loss in people classified as overweight or having obesity. That means researchers do not know what the effects of the drugs are for people with a healthy BMI. In studies of individuals with obesity, side effects include headaches, nausea, and diarrhea, and more rare and severe complications like intestinal blockages and pancreatitis [5]. “These drugs need to be prescribed with regular follow-up and counseling,” said Michael Weintraub, a clinical assistant professor of medicine, endocrinology, New York University Langone Health (New York City, NY, USA). “I am concerned about people who are not approved for the drugs taking them, because we do not know at what point the risks might outweigh any small benefits.”

The long-term effects of the drugs are also unclear. Even though GLP-1 agonists have been used to treat millions of people with diabetes for nearly two decades, the patient population with obesity is different and much larger. Dosages may also be higher for weight loss. Ozempic, for instance, was initially approved at a 0.5 or 1.0 mg dose for diabetes but patients taking Wegovy for weight loss can ramp up to taking as much as 2.4 mg. And since stopping the drug can lead to a quick regaining of weight [20], some patients could end up taking the drugs for years.

In addition, as with any weight loss, the loss associated with semaglutide and other weight-loss drugs includes losing not just fat but also muscle. Some experts have voiced concerns that this muscle loss could be dangerous, particularly in older adults at risk for falls and frailty, calling for more research into exactly how muscle and fat loss are balanced out in different patient groups and whether some drugs are better than others at helping people lose weight while preserving muscle mass [21].

Even with the potential side effects and questions that remain unanswered, the promise of melting away pounds in the millions of people whose weight puts them at risk for chronic diseases has captured the rapt attention of doctors and patients—and the market. “We know that weight loss leads to improvements in quality of life and better overall health outcomes,” said Weintraub. “And ultimately that is why these drugs are so exciting. Profound weight loss can decrease the risk of heart attacks, strokes, cancer among many other devastating complications of obesity.”

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