

Medical News & Perspectives

As Ozempic's Popularity Soars, Here's What to Know About Semaglutide and Weight Loss

Melissa Suran, PhD, MSJ

Although *semaglutide* may not ring a bell, the drug has been popping up in news headlines and social media feeds since last year. That's because the branded version called Ozempic has surged in popularity—and notoriety—for its off-label use as a weight-loss medication.

Here's what to know about this in-demand drug.

What Is Semaglutide?

Semaglutide is a peptide sold by Novo Nordisk under the brand names Ozempic, Rybelsus, and Wegovy for long-term treatment of type 2 diabetes or obesity.

The drug belongs to the family of incretin glucagon-like peptide-1 (GLP-1) receptor agonists that have been used in type 2 diabetes treatment for almost 20 years. GLP-1 receptor agonists mimic the GLP-1 hormone, which increases insulin production when blood glucose levels are elevated. The GLP-1 hormone also slows gastric emptying—in turn prolonging the feeling of fullness after eating—and works as an appetite suppressant by targeting parts of the brain responsible for hunger and cravings.

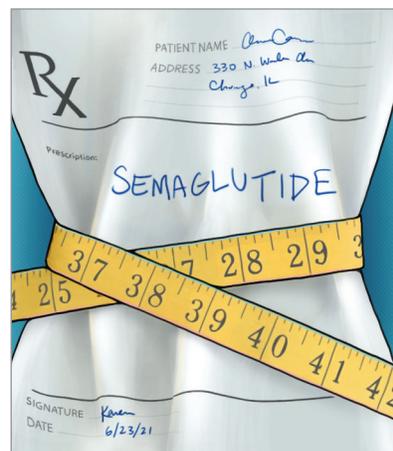
What's the Difference Between Brands?

The differences among these branded products are in the dosage, administration, and indication, explained Susan Yanovski, MD, the senior scientific advisor for clinical obesity research and codirector of the Office of Obesity Research at the National Institute of Diabetes and Digestive and Kidney Diseases.

The US Food and Drug Administration (FDA) approved Ozempic in 2017 to treat type 2 diabetes. Similar to other GLP-1 receptor agonists, it's often added to improve glycemic control when patients have already tried metformin without much success. It's available in doses of 0.5 mg to 2 mg

and self-administered weekly with injectable pens.

In 2019, the FDA approved Rybelsus, a daily oral medication, to help control blood glucose in adults with type 2 diabetes. It's available in 7-mg or 14-mg tablets.



Then, in 2021, Wegovy received FDA approval for chronic weight management for adults with obesity or those who are overweight with at least 1 weight-related condition, such as type 2 diabetes, high cholesterol, or hypertension. Last year, it was approved for adolescents aged 12 years or older.

Like Ozempic, Wegovy requires a weekly pen injection but at a higher dose of 2.4 mg. At that dose, semaglutide combined with a reduced-calorie diet and increased physical activity produced an average weight loss of about 15% at 68 weeks among clinical trial participants without type 2 diabetes, and those results were sustained at year 2 in a related trial.

There's considerable overlap among all 3 products, Yanovski said in an interview with *JAMA*. For example, they're all started at a low dose and then titrated up to limit adverse effects. Because the injectable forms of semaglutide contain the same medication, 1 mg of Ozempic is

equivalent to 1 mg of Wegovy for managing weight.

Who Can Use Semaglutide Specifically for Weight Loss?

According to its indication, people without type 2 diabetes can be candidates for Wegovy if their body mass index is 30 or higher or if it's 27 or higher and they also have a weight-related condition.

But even though Wegovy was specifically approved for this, Ozempic is better known as a weight-loss drug. "Ozempic appears to be getting more attention than Wegovy due to the name being put out more in the mainstream media and especially social media as a go-to medication for weight loss," Peminda Cabandugama, MD, an endocrinologist and obesity medicine practitioner at the Cleveland Clinic, wrote in an email.

Prescribing Ozempic for weight loss is considered an off-label use. That said, "there's nothing unethical about using the brand name Ozempic for someone with obesity," Yanovski remarked. She pointed out, however, that it's unavailable at the 2.4-mg dose shown to have the largest efficacy for weight loss.

People with uncontrolled type 2 diabetes may be ideal candidates for either injectable semaglutide product, noted Cabandugama, who is also the director of Digital Obesity at the Cleveland Clinic and a diplomate of the American Board of Obesity Medicine. Semaglutide helps bring down blood glucose levels without causing hypoglycemia, as long as it's not used alongside insulin or oral antidiabetic medications such as sulfonylureas. Moreover, people with type 2 diabetes who are at high risk of heart disease may decrease their risk by using semaglutide. It's unclear whether the same holds true for people without type 2 diabetes who use the drug strictly for weight loss, Yanovski said, but a cardiovascular outcomes trial is underway for this population.

What Are the Risks?

The most common adverse events are gastrointestinal issues, including nausea, vomiting, diarrhea, and constipation. Semaglutide may also heighten the risk of pancreatitis, kidney failure, and medullary thyroid carcinoma, especially among patients with a family history of this cancer. And Yanovski cautioned that gallbladder disease can develop when patients lose a lot of weight quickly with [semaglutide](#) or other means.

Media reports have [linked](#) the drug to facial aging. But it's not the medication as much as its potent weight-loss effects that can cause what's now known colloquially as "Ozempic face," according to Fatima Stanford, MD, MPH, an obesity medicine physician-scientist at Massachusetts General Hospital.

"This term is a misnomer as it presumes that facial aging is specific to semaglutide," Stanford wrote in an email. Instead, skin sagging is due to the loss of fat in the face, which is associated with any method of weight loss, she explained.

It may occur when weight-loss strategies become too aggressive. "When persons regain lost weight from stopping behavioral strategies or anti-obesity medication, they will likely regain fat in their face and elsewhere," said Stanford, who is also an associate professor of medicine and pediatrics at Harvard Medical School.

Patients prescribed semaglutide can mitigate excess facial fat loss by monitoring their diets carefully, advised W. Scott Butsch, MD, MSc, the director of obesity medicine at the Cleveland Clinic's Bariatric and Metabolic Institute.

"Many patients and providers alike think that the purpose of these obesity drugs is to limit the amount of food intake, so it makes sense to increase the dose as high as possible to maximize the weight loss," he wrote in an email. "This misconception around how these drugs work can lead to an inappropriate amount of weight loss."

An unintentionally restricted diet may not only lead to fat loss but also nutrient deficiencies.

Patients "should be aware of how much protein they are consuming, because with weight loss comes the loss of muscle as well in some individuals," Butsch explained, adding that the appearance of facial aging may also stem from muscle loss in the face.

He underscored that only a small percentage of people who lose weight experience facial aging, and that this reversible

effect should not overshadow the potential benefits of weight loss.

"All drugs have side effects, and semaglutide is no exception," Yanovski said. She noted that the benefits of controlling blood glucose levels, as well as lowering blood pressure and reducing the risk of fatty liver disease, may offset semaglutide's risks for people with obesity-related complications.

Patients who experience severe adverse events or don't achieve adequate weight loss should [discontinue](#) the drug, she said: "For them, the risks outweigh the benefits."

What About Compounded Versions?

Compounded versions of semaglutide, which are often advertised online as cheap alternatives, are gaining traction, according to [news reports](#).

Yanovski said it can be difficult to gauge where the compounds were mixed or how they were manufactured. Often, when people obtain compounded semaglutide, especially online, "they get the drug in a multidose vial, and a vial of saline—in some cases without ever seeing a clinician who's evaluating them—and just given instructions on how to mix this up and inject it," Yanovski explained.

She also warned of opportunities for bacterial and fungal contamination when mixing the drug with saline and using a vial with needles rather than injectable pens. And there's a risk of misdosing.

"It's not semaglutide itself that might cause serious problems but the compounded versions or inappropriate administration," she said, adding that sometimes, the drug is even [mixed with vitamins](#) without evidence of safety and effectiveness.

"That's all a recipe for bad outcomes," Yanovski cautioned.

How Long Does Semaglutide Keep the Weight Off?

A [clinical trial](#) published in *JAMA* and a [follow-up study](#) of a related trial found that semaglutide is only effective for weight loss for as long as it's used. In the follow-up study, published last year, participants who had been randomized to receive 2.4 mg of semaglutide regained up to two-thirds of their weight within a year of stopping the drug when the trial ended.

That's why semaglutide is approved for *long-term* weight management. Because obesity is a chronic disease, "semaglutide, like any other anti-obesity medication, should be prescribed with the expectation

that it will be used long term, possibly life-long," endocrinologist Daniela Hurtado, MD, PhD, wrote in an email.

Obesity stems from genetic and environmental factors that result in the dysregulation of calories that are consumed and burned, explained Hurtado, an assistant professor at the Mayo Clinic Alix School of Medicine in Florida and a researcher at the Mayo Clinic Precision Medicine for Obesity Program. "Anti-obesity medications, like semaglutide, help regulate this system. If these medications are stopped, the system goes back to where it was, resulting in weight regain."

It's also important to note that semaglutide should not be prescribed in isolation but as an adjunct to dietary changes and exercise.

"In my experience, this is seen more with patients who have been put on the medication without being given proper comprehensive therapy that also involves provider-directed lifestyle instructions involving diet and exercise," said Cabandugama, who is a spokesperson for The Obesity Society.

What About Other Weight-Loss Medications?

Beyond semaglutide, 4 [other drugs and drug combinations](#) are approved for chronic weight management in the US: liraglutide (Saxenda), orlistat (Alli and Xenical), naltrexone plus bupropion (Contrave), and phentermine plus topiramate (Qsymia).

Introduced in 1959, phentermine is the [oldest](#) FDA-approved prescription drug for obesity and, according to a 2019 government report, the [most prescribed](#) weight-loss medication in the US.

Used alone, phentermine's indication is only for [short-term use](#)—typically less than 12 weeks, although Yanovski said it's often prescribed off-label for longer periods. It remains popular because of its price, which can be [less than \\$30 per month](#). In stark contrast, the [list price](#) of a single Ozempic pen that [lasts about a month](#) is almost \$900, and a package of Wegovy for a [comparable period costs](#) upwards of \$1300. Insurance companies [often](#) don't cover weight-loss medications, and phentermine is one of the least expensive options.

"This is particularly important in populations [that are] at greater risk for diabetes or obesity yet have trouble affording the most effective drugs," Yanovski said. However, phentermine isn't as effective as semaglutide, even when combined with topiramate in Qsymia.

What's Next in the Pipeline?

Some think Eli Lilly's tirzepatide, [approved](#) as Mounjaro in 2022 for patients with type 2 diabetes, could be the [next popular weight-loss medication](#). The drug had substantial [weight-loss effects](#) in a trial involving people with obesity who did not have type 2 diabetes. In fact, the average weight loss of around 20% approached what's observed after some forms of bariatric surgery.

Tirzepatide is a GLP-1 receptor agonist, like semaglutide, combined with a glucose-dependent insulinotropic polypeptide, or GIP, analogue. Similar to semaglutide, tirzepatide mimics natural hormones that sup-

press hunger. "These 2 classes of medications give approximately 3 times the weight loss that you would see with medications like phentermine," Cabandugama said.

There are no head-to-head studies comparing semaglutide and tirzepatide, but "tirzepatide seems to result in greater diabetes control improvement and greater weight loss," Hurtado said.

The FDA is now [evaluating](#) tirzepatide for obesity treatment. However, none of these drugs work for everyone. And they're no panacea for the obesity crisis.

"We need more research and policy changes to help people not develop obe-

sity in the first place," Yanovski said. "Anti-obesity medications aren't a magic bullet." ■

Published Online: April 26, 2023.
doi:[10.1001/jama.2023.2438](https://doi.org/10.1001/jama.2023.2438)

Conflict of Interest Disclosures: Dr Butsch reported previously serving as a consultant for Novo Nordisk on education initiatives but has no current relationship with the company. Dr Cabandugama reported being a founding advisory board member of the Midwest Obesity Society, as well as a member of the Obesity Medicine Association Outreach Committee. Dr Stanford reported serving as an obesity consultant to Currax, Eli Lilly, Gelesis, Novo Nordisk, Pfizer, and Rhythm. No other disclosures were reported.

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