https://www.nationalgeographic.com/premium/article/drugs-weight-loss-injection-pill?rid=FF526C1F1B0738788B420FE1D0034350&cmpid=org=ngp::mc=crm-email::src=ngp::cmp=editorial::add=Health_20231224

New obesity drugs are coming. Here's how they could change everything.

A steady stream of weight loss drugs, which mimic naturally occurring hormones, are in the pipeline. This competition may finally lead to lower prices and greater supplies of these highly effective drugs, and maybe replace some injectables with pills.

Ozempic (above) was not the first of the hormone-mimicking drugs to hit the market, but it was the first to become a household name as celebrities shared their weight loss success from its off-label use on social media.
Photograph by Jaap Arriens, NurPhoto/Getty Images

By Tara Haelle (Published December 22, 2023)

The recent approval of another obesity drug, Zepbound, expands the options for medications to manage weight, but it comes with the same cost and access challenges that plague other weight loss drugs in its class.

The drugs in this class are agonists, or mimics, of natural gut hormones that affect the body's metabolism and hunger signals in the brain. But the currently approved drugs, synthetic versions of these hormones, are large molecules that are expensive and time-consuming to manufacture, which has meant high prices for consumers and growing drug shortages. Further, most of these drugs are injections, rather than oral pills, and usually require refrigeration for storage. With more than four in 10 Americans—and nearly 2 billion people worldwide—affected by obesity, the promise of these new drugs to treat the world's fastest growing chronic disease has been clashing with the reality of their cost and access problems.

In addition to the complex manufacturing, the small number of obesity drugs on the market has meant less competition, driving up prices for consumers. That's a problem as many private health insurance plans still do not cover obesity medications. Although researchers are developing oral versions of these medications—including versions that are cheaper and faster to make and distribute—those aren't yet ready for review by the U.S. Food and Drug Administration, and the existing oral medications aren't as effective as the injections.

"The big issue is the fact that right now, not only are the drugs expensive, but it's also difficult to get injections to places where people may need them," Ali Zentner, a weight management physician and medical director of Revolution Medical Clinic in Vancouver, Canada, says. "And in the United States, for example, equity depends on your income and your insurance—it doesn't really matter where you are." However, a half dozen or so candidates in this same drug class have been making their way through clinical trials, and as several of them are on track to head to

the FDA in the next few years, experts hope they will finally begin expanding access so the world can begin making progress on addressing the obesity epidemic.

One drug in development that has been turning heads is orforglipron, a drug like the already approved agonist drugs but which is a smaller molecule, making it easier and cheaper to produce. It's also an oral pill, not an injection, which is not as sensitive to storage temperature as injectable medications are. Though only just entering phase 3 studies, the effectiveness seen from orforglipron in a phase 2 trial suggests that a more accessible option is not out of reach.

Existing medications are "in a form that we can use easily, but we can't make an injectable all that easily," says Sean Wharton, an adjunct professor at McMaster University and medical director of the Wharton Medical Clinic who is leading the research on orforglipron. "To have something that you have to take every week for the billions of people across the planet that are living with obesity means that you need a product that can get there, that can be mass produced, and then given out in an appropriate fashion."

A confusing collection of weight loss drugs

The rapid pace of approvals for this new drug class has led to a dizzying list of names that can be difficult to track. A major reason for the confusion is that the FDA approves the same chemical drug for different conditions, and companies give different brand names to the drug based on the condition it treats. Many people have heard of Ozempic, the brand name for semaglutide, which is approved for type 2 diabetes. That same compound, semaglutide, is also approved to treat obesity and goes by the brand name Wegovy.

Another major drug in this class is tirzepatide, which is approved for type 2 diabetes as Mounjaro, and for obesity as Zepbound. Zepbound's approval last month came after clinical trials showed people with obesity lost up to 21 percent of their body weight with the highest dose. With the pace of these approvals matched only by demand for them, what hasn't kept up is access to these medications, primarily due to drug shortages and their cost. Shortages of Mounjaro, which costs $1,023 per month without insurance, are already expected to last through August, 2024. Its competitor, Ozempic, costs $936 and is also limited. Those supply issues are expected to carry over to Zepbound (same compound as Mounjaro) and Wegovy (same compound as Ozempic)—and are similarly expensive. Zepbound's price is $1,060; Wegovy's, $1,349.

A new class of drugs

Ozempic was not the first of this new class of drugs to hit the market, but it was the first to become a household name as celebrities shared their weight loss success from its off-label use on social media. It was also the most effective drug of its kind when it was approved as Wegovy for obesity in 2021. But all of these drugs, called GLP-1 agonists, are injectable medications that mimic the effects of glucagon-like peptide-1 (GLP-1), a gut hormone that stimulates the release of insulin. And over the near-decade since the first GLP-1 agonist was approved for obesity in 2014, scientists have learned enough to begin expanding their research to include other gut hormones.

"This is new science, and this is coming from someone who has been in this field for over 40 years," says Robert Kushner, an endocrinologist at Northwestern University's Feinberg School of Medicine in Chicago, who consults for some of the companies developing these drugs. "As we start to harness the power of these intestinal and pancreatic hormones individually and as combinations, we are really learning along the way."

While these new drugs definitely have side effects—some of which can be serious—they are biologically completely distinct from the less-than-stellar legacy of past weight loss drugs. "We're now, for the first time, understanding that, in part, the gateway to regulating appetite and treating the dysregulation of appetite is through these gut hormones," Kushner adds. Zepbound is the first obesity drug to exploit more than one gut hormone: it mimics both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), another hormone involved in metabolism that plays a role in obesity. But GLP-1 and GIP are just two of the dozens of gut hormones that affect digestion and other metabolic processes.

As scientists learn more about the functions of other gut hormones, they are testing drugs that mimic those as well. Many of the newer drugs coming down the pipeline mimic two or three gut hormones, such as GLP-1, GIP, and glucagon. It often happens in medicine that one or two agents of a certain drug class are development and then the class opens up more, Zentner says. "We are on the precipice," now that researchers understand the biology of these various hormones, she says. "We've cracked the code of GLP, GIP, glucagon," and other gut hormones, so now scientists are testing what happens when they combine multiple synthetic versions in one drug.

How the new drugs work

These drugs work in multiple ways that affect metabolism and energy consumption and expenditure. By stimulating the release of insulin after eating, they help reduce glucose circulating in the blood and reduce insulin resistance. They also slow down digestion and the emptying of the stomach so that people feel full longer. They stimulate the burning of fat cells and reduce fat in the liver. Finally, importantly, they also send satiety signals to the brain, telling it not only that it doesn't *need* additional calories but also that it doesn't *want* additional calories. "I think of obesity as a multi-factorial disorder where genetics, environment, development and behavior play a role in a person's likelihood of having the disease, but the most important organ regulating the weight is the brain," says Fatima Cody Stanford, an associate professor of medicine and obesity medicine specialist for adults and children at Harvard Medical School. That's because the brain is very efficient at hunting for and storing food, essential functions in times of scarcity. "When we talk about appetite regulation or energy regulation, we evolved to endure famine," Zentner says. But many people today live among an abundance of food, and the brain's evolution hasn't kept up.

The beauty of these new medicines is that they block the inappropriate starvation response that causes obesity, Zentner says. For patients with obesity—even when they eat—their brain still thinks they're starving. With these new drugs, however, "not only do people not feel hungry, but they just don't have the craving or food thoughts they used to because their brains are not

starving." The problem is that they aren't easy or cheap to manufacture. But clinical trial findings from Wharton's drug, orforglipron, and other research findings—unveiled at the annual meetings of the American Diabetes Association (ADA) last summer and at the Obesity Society meeting last fall—suggest that researchers are finding ways to overcome those obstacles. "What we saw at ADA was a further introduction of the injectable molecules… where you're getting weight loss of more than 25 percent. That's huge," Wharton says. But these injectable drugs risk continued supply problems. "If we develop a pill that's easily stored that you can take every day, that may be the most available drug that's cheap."

Better, cheaper drugs in the pipeline

The upcoming crop of drugs in the pipeline attempt to improve on existing ones in three ways; many act on multiple gut hormones for a synergistic therapeutic effect; a couple are pills, which have wider temperature ranges for storage, making them accessible in places with less reliable refrigeration. Finally, some of the oral drugs in development, like Wharton's, are made of smaller molecules that are easier and faster to manufacture, making them cheaper and less likely to fall victim to the shortages occurring with semaglutide and tirzepatide. The main gut hormones being mimicked and combined in different medications are GLP-1, GIP, glucagon, and amylin—another hormone released by the pancreas which regulates blood glucose levels, slows down digestion, and reduces food consumption.

Novo Nordisk, the company that makes Ozempic/Wegovy, is working on a drug combination of semaglutide and cagrilintide, which mimics amylin. In a phase 2 trial of the drug—dubbed CagriSema—participants with type 2 diabetes experienced reduced blood sugar and a 16 percent loss in body weight. Two other drugs, from other pharmaceutical companies, mimic GLP-1 and glucagon, a hormone with receptors in the liver. One of these is survodutide, whose phase 2 trial resulted in participants losing 15 to 20 percent of their body weight, depending on dose. That trial is ongoing, so participants could still lose more. The other GLP-1 and glucagon combo drug is pemvidutide, being tested for both obesity and fatty liver disease. In the most recent results from late November, participants lost 10 to 20 percent of their body weight, and nearly a third of those taking the highest dose lost 20 percent or more.

Side effects

Like semaglutide and tirzepatide, however, all these drugs come with gastrointestinal side effects: nausea, vomiting, and diarrhea. One in four people taking pemvidutide, for example, dropped out because these side effects were too intense. The drug furthest along of those that attempt to mimic three gut hormones is retatrutide from Eli Lilly, the same company that makes Mounjaro/Zepbound. Retatrutide mimics glucagon, GLP-1, and GIP in combination. Participants taking the highest dose lost about 24 percent of their body weight, the most of any weight loss drug so far and rivaling the effects of some bariatric surgery types. For example, after one year, average weight loss is 25 percent of body weight for sleeve gastrectomy and an average 14 percent of body weight for adjustable gastric banding. Retatrutide also reduced liver fat, so it may be a contender for treating fatty liver disease too.

One of the oral pills showing the most effectiveness for obesity is an oral version of semaglutide from Novo Nordisk that's a higher dose than their current Rybelsus. It showed a 15 percent loss in body weight at the ADA meeting in June, but the company hasn't submitted it to the FDA for approval, yet.

Focus on oral drugs

Meanwhile, participants taking orforglipron, the drug Wharton's team is developing, in a phase 2 trial lost 15 percent of their body weight—about middle of the pack compared to other drugs. But, again, it is a small molecule that can be made and transported cheaply and easily. "That was why that presentation was such a jaw-dropping moment," Wharton says. "This was pretty good weight loss, but it's bigger than that. It's a chemical structure that can be made in a lab like that," he says, snapping his fingers. "This is groundbreaking research, because if this is for real, this is going to eclipse all of the injectables just because of price." A phase 3 trial for orforglipron began in May 2023.

These drugs are the furthest along, but more are on the way. Some will never make it to the FDA, often due to side effects, but experts hope the ones that do make the cut will drive down prices while providing more options to those who can't use—or can't access—the existing drugs. "For me, it's about finding the right tool for the right person," Cody Stanford says. "We, the world, want obesity to be easy, but it's complex. The more we learn about the disease, we learn it's not a one-size-fits-all thought process. Asthma is not the same in every person. Diabetes is not the same in every person. Cancer is not the same in every person. But these medications," she says, are the newest tools doctors can employ in addressing "obesity as a disease."

https://www.nationalgeographic.com/science/article/ozempic-tiktoks-favorite-weight-loss-drug-is-unproven

Ozempic is a serious drug with serious risks. Here's what to know.

What are the risks?

Like every medication, there can be downsides. The most common side effects are gastrointestinal issues, such as nausea, constipation, and diarrhea, Chao says—and more rarely, pancreatitis, gallbladder disease, and diabetic retinopathy. Angela Godwin, nurse practitioner and clinical assistant professor at the NYU Rory Meyers College of Nursing, explains that recent reports of extreme vomiting and gastroparesis (delayed emptying of the stomach) are to be expected. Gastroparesis "just means the food's in your stomach longer, which then makes you feel fuller longer," she explains. Nausea is one of the biggest side effects of medications like Ozempic and Wegovy, and that can always lead to vomiting, Godwin says. In June, the American Society of Anesthesiologists recommended patients stop taking these medications before surgery to avoid aspiration and vomiting.

"Normally, in my experience, it's tolerable," she says. "But then there are times when I ask [patients], 'Well, what happened?' And they [say] they ate too much and ate too quickly. And then yes, the body will vomit it up, because it just can't tolerate that much food anymore."

These drugs have been extensively studied, but their relatively recent approval means researchers still don't know what the effects of taking them long term might be.

Continuing research is helping us understand more about what happens when people stop taking these medications—which many may be forced to do amid current shortages. Research does suggest that stopping use of this medication could cause patients to regain weight, especially if they didn't make any lifestyle changes. "In almost all weight-loss studies, it really depends on your foundation," says Stanford endocrinologist Sun Kim. "Your efforts at lifestyle will determine how much weight you lose. If you have your foundations like food, exercise, and sleep, you're gonna do well." If not, you might regain as much as 20 percent of the weight lost per year. These medications can also be incredibly expensive, especially without insurance. Kim says an injection pen can run more than $1,000.