Miracle Drugs?

by Margherita Fronte

Groundbreaking new drugs, semaglutide and tirzepatide, originally made to treat diabetes, are revolutionizing weight-loss treatment. They are a goldmine for the pharmaceutical companies that make them, but is all that glitters gold?

Some of the most significant and innovative recent achievements in pharmacological research include new drugs such as semaglutide and tirzepatide. They treat two of the conditions that pose the greatest threat to our health: diabetes and obesity. Plus, pending confirmation from ongoing studies, they could help treat a plethora of other illnesses and disorders, ranging from cardiovascular diseases to neurodegenerative diseases, depression, infertility, as well as addictions, certain sleep disorders, and chronic kidney diseases.

Known collectively by the hard-to-remember name of "GLP-1 hormone analogues," their individual active ingredients have become perhaps even too famous. Semaglutide, tirzepatide, and similar drugs have become so prevalent on social media and the internet that we risk forgetting that their side effects are only partially known, and they should only be taken with a doctor's prescription.

HOW THEY WORK

"GLP-1 analogues work on the same targets as GLP-1 (*glucagon-like peptide-1)*, a hormone produced after a meal by the intestine – and, to a lesser extent, the brain. It has a number of effects, including stimulating the pancreas to secrete insulin, lowering the concentration of sugars in the blood. It also affects the stomach by slowing digestion and the brain by inducing a sense of satiety," as Silvana Gaetani, a professor of pharmacology at the Sapienza University of Rome, explains. Unlike GLP-1, which is only active for a few minutes, these drugs stay in circulation for a long time, so long "that they only need to be taken once a week. Efforts are underway to further extend the time between injections," according to Gaetani.

The drug benefits for diabetes and obesity have been well documented by studies conducted by pharmaceutical companies. "These drugs help control blood sugar, and, for obese people, they help achieve weight reduction of 15–20%. Tirzepatide is new to the market and seems even more effective. Not only does it mimic the action of GLP-1, but it also works on the receptors of another hormone produced by the intestine after a meal: GIP (glucose-dependent insulinotropic polypeptide), which further stimulates the release of insulin as well as glucagon, the other hormone that regulates the metabolism of sugars," Gaetani says. Still, others are coming down the pipeline. According to Norberto Perico, Head of the Laboratory of Advanced Stages of Drug Development in Humans of the Istituto Mario Negri di Milano, "Retatrutide is especially promising, as it can activate three receptors, those of GLP-1, GIP, and glucagon. Its safety profile is comparable to those of semaglutide and tirzepatide, and half of the patients have achieved at least 25% weight loss, and a quarter of them at least 30%. This is a level of efficacy greater than that of other weight-loss drugs, and the same that can be achieved with bariatric surgery."

SO WHAT'S THE COST?

Even though these medications seem like a dream come true, they do have multiple possible pitfalls. Prime among them is the fact that they do not always work. In semaglutide studies, 14% of patients did not lose significant weight. Perico explains, "There is individual variability, and right now we can't predict whether or not the drugs will be effective."

Then, if they do work, they must be taken for one's entire life. “If the treatment is stopped, the weight will be gained back,” Gaetani notes. Because it is a very costly medicine, this includes a considerable expense, which is currently borne by the patients when the use is for weight loss. Italy's national health service only reimburses GLP-1 analogues when they are for diabetes control. Prescriptions to fight obesity are at the patients' expense. They can expect a monthly layout ranging between €220 and €350 a month. “That very high price is not justified by these drugs' complexity,” Perico notes. “In response to criticism in the United States, Novo Nordisk (the Danish maker of semaglutide) pointed out the considerable investment it took to develop them – over 10 billion dollars.”

THE UNKNOWNS ABOUT ADVERSE EFFECTS

Some factors about their side effects are yet to become clear. “The most common short-term effects are nausea, vomiting, and diarrhea, of mild to moderate intensity, which resolve as the treatment continues,” according to Gaetani. Some of the less common side effects, which are reported on the package inserts, include more serious ones, such as heart rhythm alterations, gallstones, and, in rare cases, pancreatitis (affecting about 1 in 100 people) and intestinal blockages (for semaglutide).

The long-term side effects are still completely unknown. “These products have been on the market for too little time. We will have to wait for several years to see how they behave in the real world, outside of clinical trials,” says Gaetani.

“We can, however, make assumptions based, for example, on the effect that they have on the brain. Appetite regulation is tied to pleasure and reward circuits. There is a possibility that altering these mechanisms in continuation could promote the onset of mood or psychiatric disorders. This is one among many hypotheses that must be verified or disproven over time.”

The biggest fear keeping the drug makers up at night is the possibility of developing a tolerance to the drugs, which would make them ineffective. “It is a possibility that must be considered. Over time, the receptors that the drugs work on could adapt and change. This has, however, not yet happened, even for semaglutide which was the first to go on the market,” Gaetani says. In any event, “starting treatment ought to be accompanied by a lifestyle change, which should be continued if the weight-loss treatment has to be interrupted or has become ineffective, to limit weight regain,” Perico adds.

GOOD FOR THE BRAIN TOO?

The action that GLP-1 analogues exert on pleasure circuits is the foundation of one of the other applications being studied for these drugs: addiction treatment. Gaetani explains, “Because they act on parts of the brain connected to the reward system, such as the nucleus accumbens and the ventral tegmental area, these drugs reduce the gratification connected to eating food, as well as consuming alcohol, nicotine, and other often abused substances. Preliminary studies, conducted on animals as well as human volunteers, suggest that GLP-1 analogues might decrease the desire to take these substances, and potentially decrease addiction.” These mechanisms could make these drugs also useful against anxiety and depression. Some studies conducted on obese and diabetic patients have indeed shown such benefits, though those could be connected to weight loss or the realization that the treatment is working.

Another application that experts consider the most interesting, also involving the central nervous system, is treating neurodegenerative diseases. The mechanism of action is different here. “GLP-1 receptors modulate inflammation, oxidative stress, and neuron degeneration. Their activation through the drugs could reduce the accumulation of toxic proteins that damage the nerve tissue,” according to Gaetani. “Liraglutide and semaglutide have already been tested to treat Alzheimer's, and some data suggest they improve cognitive function. There are studies for Parkinson’s that suggest a neuroprotective effect, but more research is needed.”

FOR THE HEART AND KIDNEYS, TOO

The inflammation-reducing effect of GLP-1 analogues could also help treat cardiovascular and kidney diseases. As for cardiovascular diseases, a study published in 2023 in the *New England Journal of Medicine*, conducted on 17,000 overweight or obese patients with atherosclerosis, found that semaglutide achieved a 20% reduction in the risk of having fatal and non-fatal strokes and heart attacks. For chronic kidney diseases, also in the *New England Journal of Medicine*, the results were published this year of the Flow study, conducted on 3,533 patients with type 2 diabetes and chronic kidney diseases. Compared to a placebo, semaglutide reduced the risk of serious complications (requiring dialysis or kidney transplants) by 24% and also reduced serious cardiovascular events by 18% as well as deaths from all causes by 20%.

In both cases, the benefits could also be linked to weight loss. Nonetheless, Gaetani notes that “the results do suggest a possible use of these drugs to prevent cardiovascular and kidney diseases too, which could eventually apply to patients who are not diabetic or obese.”

UNEXPECTED PREGNANCIES

There is even more as GLP-1 analogues appear to act in an impressively broad spectrum. Weight loss helps those who suffer from sleep apnea, reduces arthritis pains, and improves polycystic ovary syndrome. In the United States, some women being treated have reported unwanted pregnancies, prompting studies on its potential use for infertility. Here too, the observed effect could be tied to weight loss (infertility is linked to obesity), but that could be another reason. For example, tests on tirzepatide showed that the drug reduces the absorption of oral contraceptives in the intestine by as much as 66% (for other GLP-1 analogues, the effect seems lesser). Additionally, a study conducted as far back as 2015 on mice at the University of Vigo, Spain, found that administering the GLP-1 hormone promoted the production of luteinizing hormone, which stimulates ovulation.

BOX1

Shots Are All the Rage

In the United States, getting shots to lose weight has become a huge trend among the celebrities of the star system. Elon Musk, Oprah Winfrey, the singer Boy George, and the actresses Kathy Bates and Tori Spelling (Donna of *Beverly Hills 90210*), plus countless influencers, have said they are using them to lose weight, spurring others to do the same. Not only does this run the risk of people taking these drugs without medical supervision, but this wave of popularity has also led to a shortage of medication for patients who need it. In spring 2023, Novo Nordisk stopped its advertising campaign because it could no longer meet demand (in the U.S., unlike in Italy, advertising prescription drugs is allowed). Twelve percent of Americans have said that they have taken GLP-1 analogues to treat diabetes or to lose weight. In the wake of this success, some U.S. media sources have suggested that the obesity rates in the country are going down and that they won't go back up.

Some predictions are more curious, such as by the investment firm Jefferies that U.S. airlines could save over 100 million liters of fuel per year if passengers lost an average of 4.5 kilograms each.

Experts stress that long-term trends cannot be predicted, especially since they are very costly drugs for the patient and need to be taken for one's whole life.

BOX2

The Rise of Biosimilars

The GLP-1 analogue market is currently worth $47 billion and is expected to increase tenfold by 2032. The high cost is an obstacle, especially for low and middle-income countries, where obesity

rates are growing and which account for 77% of the burden of obesity worldwide. With this market in mind, pharmaceutical companies in India and China have started to study biosimilar drugs, which are very similar to those on the market and with similar or even better effects, that could be launched at a lower cost once the patents expire. Biosimilars of liragutide, whose patent has already expired, are being sold in India and China and have been approved in the UK as well. New biosimilars will arrive in 2026 when the semaglutide patent is set to expire too.

Captions

P2

SIZE REDUCTION

These new weight-loss drugs make it possible to lose considerable weight, but the side effects are not yet completely known.

P3

The new drugs are sold only with a doctor's prescription.

“Do-it-yourself" treatment can be extremely risky.”

BILLBOARDS

Advertisement for weight-loss drugs in New York.

Ad campaigns like this are prohibited in Europe.

EXTRA WEIGHT

The possible market in Italy is also considerable, with 10% of its population obese.

P4

COMING OUT

The influential Oprah Winfrey admitted that she lost weight with semaglutide.

P5

WHERE THE DRUGS HAVE EFFECT

It is not yet fully understood how the GLP-1 analogues work. The figure shows the main mechanisms involved in their action.

The GLP-1 analogues activate parts of the brain associated with appetite and reward. But it is not clear that how deep in the brain these drugs penetrate.

Parkinson's disease

Alzheimer's disease

The drugs bind to GLP-1 receptors on immune cells, reducing inflammation in multiple organs.

Anti-inflammatory action

Cardiovascular diseases

Chronic kidney diseases

Reduction of appetite, addictions, and depression

Regulating blood glucose levels

Weight loss

Slowed digestion

Diabetes

The drugs bind to GLP-1 receptors in the pancreas, stimulating the release of insulin.

This helps regulate the concentration of blood glucose.

KEY MOLECULES

The interaction between the GLP-1 hormone (red) and its receptor (blue).

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China seems to be preparing to fight the obesity epidemic with self-produced drugs.

Studies are underway to evaluate GLP-1 analogues' efficacy for many other diseases.

NEUROPROTECTIVE EFFECTS

Parkinson's is among the diseases for which beneficial effects have been observed, although more studies are needed to confirm efficacy.