Is it true that new medications treat obesity?

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"Obesity is a complex metabolic disease with a clear biological basis, and we can treat it with targeted therapy aimed at the biology," says Ania Jastreboff, MD, PhD, a Yale Medicine adult and pediatric endocrinologist. Credit: Anthony DeCarlo

There is no magic pill that will cure obesity, a condition that affects over 40% of adults in the United States. But there is a new type of medicine

that is a potential game-changer. It's an anti-obesity medication, and doctors say that part of what makes it unique is how it's prescribed: It is used to treat obesity as the chronic metabolic disease that it is rather than perpetuating the misconception that obesity is a problem that can be overcome by willpower.

The medication is called semaglutide (it's available by prescription under the brand name Wegovy), and it is given once a week by self-injection under the skin. It was approved by the Food and Drug Administration (FDA) for the treatment of overweight and obesity in June 2021 (with similar medications being developed as well). Semaglutide doesn't work for everyone, but when it's successful, it can help someone shed 15% of their body weight. (If you weigh 200 pounds, for example, that would be 30 pounds.)

"This medicine helps you feel full earlier," says Ania Jastreboff, MD, Ph.D., a Yale Medicine adult and pediatric endocrinologist, and a nationally recognized obesity medicine expert. "It means you will have little desire to reach for 'seconds' or a snack later."

Anti-obesity medications have been around for decades, and there are several currently in use. But semaglutide is the first of a new generation of highly effective hormone-based obesity medications. Semaglutide mimics a hormone called glucagon-like peptide-1 (GLP-1), which is secreted in the gut and targets receptors throughout the body, including the brain. When a person is eating, GLP-1 sends the brain the "I'm full" signal, Dr. Jastreboff says.

Semaglutide also decreases "gastric emptying," the process by which stomach contents are moved into the first part of the small intestine as part of the digestive process. "But this effect wanes over time," says Dr. Jastreboff. "The main way semaglutide helps treat obesity is through its action in the brain."

The drug—and class of medications—is not new, though; this class of GLP-1 analog medications has been used for over 15 years to treat type 2 diabetes (semaglutide specifically was FDA-approved in 2017 for diabetes). Individuals with type 2 diabetes secrete less GLP-1 in response to eating compared to those who do not have the condition. Experts believe that's also true for people with obesity, Dr. Jastreboff explains. "With semaglutide, people are receiving more GLP-1, albeit in a synthetic form," she says. "They're essentially getting back more of that hormone, which helps them feel full."

For many people, the medication appears to work. The results of a clinical trial, published in the *New England Journal of Medicine*, showed that—in addition to the 12.5% mean weight reduction above the placebo group (which included lifestyle interventions only)—more than a third of the participants (many of whom weighed more than 200 pounds) lost 20% of their weight.

We sat down with Dr. Jastreboff and her colleagues. They answered commonly asked questions about anti-obesity medications.

Do anti-obesity medications actually work?

One of Dr. Jastreboff's study participants, a 49-year-old mother of three with a full-time job (who did not want her name used), has been participating in a clinical trial at Yale that involves weekly injections to test a drug similar to semaglutide, called tirzepatide, that combines GLP-1 and another hormone called glucose-dependent insulinotropic peptide (GIP). Dr. Jastreboff is the site principal investigator.

The participant had tried numerous diets and exercise plans to lose extra weight she'd carried for decades, but nothing worked. Even though she worked hard at maintaining a healthy lifestyle, she gained 25 pounds working at home during the pandemic. "But the rest of it, I've carried all

my life," she says.

Since it was a double-blind trial, in which some participants were given a placebo, at first she didn't know if she was taking the drug, but says over a period of about a year, "the weight melted off of me." Near the end of the trial, she had lost 85 pounds, so she believes she was taking the drug.

"It worked for me because my issue is mindlessly overeating. Because the drug often makes me feel incredibly full after just a few bites, it has been a real change to my eating habits," the participant says. She used to consume 3,000 calories a day "easily," and in the trial, she has been unable to take in more than 1,500. "One serving of Oreos is three cookies, and it was always a struggle to stop at three," she says. "In the trial, I found it a real struggle to eat more than three."

"These drugs [like semaglutide and tirzepatide] have the potential to help many more people," says Artur Viana, MD, a Yale Medicine gastroenterologist and clinical director of the Metabolic Health & Weight Loss Program, where he has prescribed semaglutide. He notes that the performance of the drug—15% to 20% weight loss—is impressive because it signifies a trend in which anti-obesity medications are starting to approach the 25% to 30% weight loss mark that so far has only been achieved with bariatric surgery.

Medication treatment for obesity is less invasive and works more gradually than surgery. Patients typically start with a low dose of .25 milligrams and work up to the target dose of 2.4 milligrams over a period of about 5 months. "The weight loss is gradual, but tends to slow down with time, leading to a new plateau," Dr. Viana says.

It can take more than a year for the drug to reach full effectiveness, although some patients hit their plateau earlier than that. For any anti-obesity medication, doctors want to see a benchmark of 5% total body

weight loss in the first three months, which is a good predictor of whether the medication will continue to work, Dr. Viana explains.

What are the side effects of anti-obesity medications?

Side effects for semaglutide were monitored in the trials leading up to its FDA approval. The most common side effects with semaglutide are gastrointestinal—and include nausea—and that is often managed by adjusting the dosage, says Dr. Viana. "You consider how the patient feels as the dosage increases, and you can always go back to a lower one," he says.

Dr. Jastreboff's participant in the tirzepatide clinical trial had side effects that included stomach problems, some exhaustion, and difficulty staying hydrated, but the participant thought they were minor compared to the side effects and complications of obesity.

"When I was obese, my joints were aching, I couldn't fit into my clothing—I was embarrassed to go out and be seen," she says. "We all know airplane seats are getting smaller, but that logic does nothing when you're trying to wedge yourself in between the arms and have to extend the seatbelt to its fullest."

Scientists continue to study the long-term benefits and safety of anti-obesity medications, and will do the same with drugs that are still in the clinical trial phase.

Meanwhile doctors say patients will need to take the medications for years—and probably for life—to avoid having the weight come back. "We talk about diabetes remission, and, in the same way, patients have obesity remission," Dr. Jastreboff says.

"Patients are not 'cured' once they lose the weight," Dr. Jastreboff adds.

"They need to continue treatment with anti-obesity medications in order to maintain the weight they lost, just as they would need to continue taking diabetes medication to maintain blood sugar levels."

Is everyone eligible for anti-obesity medications?

Doctors still prescribe older FDA-approved medications, which also target the brain. Those medications can help people lose 5% to 10% of their weight, an amount that can reduce the risk of cardiovascular disease in adults with obesity or overweight. The older generation of anti-obesity medications includes those that need to be taken once a day or more—one requires daily injections.

But not everyone is eligible for treatment with semaglutide. Doctors can prescribe it for adults who have obesity, with a body mass index (BMI) of greater than 30; or overweight, with a BMI greater than 27 accompanied by weight-related medical problems such as high blood pressure, type 2 diabetes, or high cholesterol. (BMI is a measure used to determine weight categories. The Centers for Disease Control and Prevention [CDC] provides BMI calculators on its website.) The medication is not recommended for those with a personal or family history of certain endocrine or thyroid tumors, specifically, medullary thyroid cancer.

Another caveat is that not everyone will respond—about 13% of individuals with obesity in the semaglutide clinical trials didn't lose any weight, Dr. Jastreboff says. That doesn't surprise her, because there are different kinds—or subtypes—of obesity, she says. "We just don't know what they are yet."

"We don't yet have biomarkers where we can subtype obesity, similar to what's done for cancer or other disease," Dr. Jastreboff says. "There are no blood tests that could let someone know they're going to respond to a

given therapy or medication, such as a GLP-1 analog like semaglutide."

Researchers need to learn more about the different subtypes of obesity before anyone can know what the best strategy is for a given patient, she adds.

Will there be 'trial and error' in finding the right anti-obesity medication for me?

Until they learn more, doctors gather information about such factors as a patient's eating behavior and other components. There also may be some necessary "trial and error" in identifying the best medication for you, Dr. Viana says.

But there can also be educated choices. For instance, if someone has a history of depression and seems to be overeating to cope, they might benefit from an older-generation medication called bupropion (brand names: Wellbutrin and Zyban, among others), which is also an antidepressant—and typically combined with a medication called naltrexone (Contrave). "By using that drug or combination of drugs, we might be hitting the mechanism that's most responsible for that patient's obesity," he says.

For those who want to reduce their weight even more—and further reduce such related symptoms as gastrointestinal reflux—another approach may be using several medications, or combining a medication with another intervention, says Dr. Viana.

All anti-obesity medications are prescribed along with a lifestyle program that addresses eating and exercise. Dr. Viana has also combined medication treatment and an endoscopic procedure, such as endoscopic sleeve gastroplasty, a minimally invasive procedure aimed at reducing

the size of the stomach. Dr. Viana says patients can lose 15% of their weight from that procedure, but then they hit a plateau. "If you reach that plateau—and your personal goal has not been achieved—you can add a medication that will help you lose more weight," he says.

What is the goal of treatment—losing weight or getting healthy?

Losing weight can improve self-perception and mood, but Dr. Jastreboff emphasizes that the goal of treating obesity is not about achieving a certain size—it's about health.

The goal of treatment with anti-obesity medications is to reset "the set point," a term that describes a weight range the body tries to maintain, and one which is elevated in the setting of obesity, she explains. "If you lose weight by restricting calories, your body thinks it's starving," Dr. Jastreboff says, adding that this spurs a person to keep eating to maintain the elevated set point. Anti-obesity medications work in the brain to help to bring that set point down, enabling individuals not only to lose weight but also to maintain the weight loss.

Depending on the patient and their other diseases, anti-obesity medications can also help with other weight-related medical problems, such as improving blood pressure or cholesterol levels, improving blood sugar levels in patient with diabetes, and delaying the onset of type 2 diabetes. The class of GLP-1 analog medications has also been found to decrease the occurrence of repeat heart attacks and strokes in those who have type 2 diabetes.

Will these drugs finally change the way people think about obesity?

The doctors hope that knowing medications can treat the pathophysiology of obesity will change common misconceptions that people should be able to control the condition on their own.

"When people think, "If I can will myself to not be hungry, to not have cravings, to control what I eat every moment of every day, I will lose the weight and keep it off," it's like saying, "If I just concentrate hard enough, my blood sugar levels will become normal,'" Dr. Jastreboff says. People need to know that there are physiological reasons why that strategy doesn't work, she adds. "Obesity is a complex metabolic disease with a clear biological basis, and we can treat it with targeted therapy aimed at the biology."

But there is more work to be done before more doctors, patients, and insurance providers perceive obesity as a disease.

Tirzepatide is not available outside of the trial, and semaglutide is an expensive drug that is not necessarily covered by insurance at this point, says Dr. Jastreboff's study participant from the tirzepatide trial. "The research says that when you stop the medication, you gain the weight back, so I'm likely to be on medication for the rest of my life," she says. "But what will insurance cover? This needs to be available to everyone who needs it, and that's one reason why it's important to start looking at this as a medical issue and not a personal problem."

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