2023 BREAKTHROUGH OF THE YEAR

OBESITY MEETS ITS MATCH

Blockbuster weight loss drugs show promise for a wider range of health benefits

By **Jennifer Couzin-Frankel**

Obesity plays out as a private struggle and a public health crisis. In the United States, about 70% of adults are affected by excess weight, and in Europe that number is more than half. The stigma against fat can be crushing; its risks, life-threatening. Defined as a body mass index of at least 30, obesity is thought to power type 2 diabetes, heart disease, arthritis, fatty liver disease, and certain cancers.

Yet drug treatments for obesity have a sorry past, one often intertwined with social pressure to lose weight and the widespread belief that excess weight reflects weak willpower. From "rainbow diet pills" packed with amphetamines and diuretics that were marketed to women beginning in the 1940s, to the 1990s rise and fall of fen-phen, which triggered catastrophic heart and lung conditions, history is beset by failures to find safe, successful weight loss drugs.

But now, a new class of therapies is breaking the mold, and there's a groundswell of hope that they may dent rates of obesity and interlinked chronic diseases. The drugs mimic a gut hormone called glucagon-like peptide-1 (GLP-1), and they are reshaping medicine, popular culture, and even global stock markets in ways both electrifying and discomfiting. Originally developed for diabetes, these GLP-1 receptor agonists induce significant weight loss, with mostly manageable side effects. This year, clinical trials found that they also cut symptoms of heart failure and the risk of heart attacks and strokes, the most compelling evidence yet that the drugs have major benefits beyond weight loss itself. For these reasons, *Science* has named GLP-1 drugs the Breakthrough of the Year.

In honoring these therapies, we also acknowledge the uncertainties, even anxieties, this sea change brings. We recognize, too, that obesity comes with medical and social complexities, and that many deemed overweight by others are healthy, and have little desire or pressing need to lose weight.

The GLP-1 story has taken decades to play out, and at first fighting fat had nothing to do with it. In the early 1980s, researchers discovered GLP-1 while investigating diabetes and blood sugar regulation. Years of painstaking and sometimes discouraging work followed, but gradually the discoveries piled up, illuminating a hormone with expansive influence on the body and brain. Scientists learned that GLP-1 lowered blood sugar in people, and drug companies began to explore it as a diabetes treatment. In the 1990s, it emerged that injecting GLP-1 into the brains of rats made them eat less. A study of 20 healthy young men found that after a hearty breakfast, those getting intravenous GLP-1 infusions indulged less at a lunch buffet than those on a placebo.

The first GLP-1 drug was exenatide (Byetta), approved in 2005 for type 2 diabetes. Instead of the human hormone, its backbone was, improbably, a similar peptide in the venom of a giant lizard, the Gila monster. Almost 5 years later Novo Nordisk released liraglutide (Victoza), modeled on human GLP-1. It, too, was a diabetes drug, but in late 2014, the U.S. Food and Drug Administration blessed it for obesity.

The drugs didn't really catch fire until 2 years ago, when Novo Nordisk's next iteration, semaglutide, was greenlit for weight management in the U.S. (It's marketed as Ozempic for diabetes and Wegovy for obesity.) Unlike its forerunners, semaglutide required an injection just weekly rather than once or twice a day. And in a pivotal trial, people taking it lost an unprecedented 15% of their body weight over about 16 months. Many on the drug also describe a dampening of "food noise," the relentless and distressing desire to keep eating.

Since then, the frenzy has only intensified. According to electronic health records, 1.7% of people in the U.S. have been prescribed either Wegovy or Ozempic this year. (GLP-1 drugs are also approved in Europe for weight loss but availability varies.) Novo Nordisk's market value now exceeds the gross domestic product of Denmark, its home country. "When I look around this room I can't help but wonder: Is Ozempic right for me?" quipped comedian Jimmy Kimmel at the Academy Awards in March, poking fun at speculation over which movie stars took the drug.

But amid the jokes and soaring sales lurked a vital question. Could GLP-1 drugs actually safeguard health in people with obesity? This year brought an answer: yes.

In August, a trial of 529 people with obesity and heart failure found that after 1 year, people on semaglutide had almost double the heart improvement, as measured by a standard heart failure questionnaire, and could walk an extra 20 meters in 6 minutes compared with those in the placebo group. That same month, Novo Nordisk announced that in a much larger trial of 17,000 people with excess weight and cardiovascular disease, people on semaglutide had a 20% lower risk of fatal or nonfatal heart attacks and strokes than those on placebo; the study was published in November in *The New England Journal of Medicine*. The trials were the first to show in large numbers that GLP-1 drugs produced meaningful health benefits beyond weight loss itself. Meanwhile, a trial examining whether semaglutide delays kidney disease progression in diabetes patients showed such positive outcomes it was stopped early.

The reach of GLP-1 drugs is now widening in ways its inventors couldn't have imagined. Trials are underway for drug addiction, after people with obesity and diabetes described less longing for wine and cigarettes while on the treatment. Researchers theorize the drugs bind to receptors in the brain that mediate desire for other pleasures in addition to food. Clinical trials are also testing GLP-1 drugs to treat Alzheimer's and Parkinson's diseases, based in part on evidence they target brain inflammation.

But medical breakthroughs are rarely straightforward, and the ebullience surrounding GLP-1 agonists is tinged with uncertainty and even some foreboding. Like virtually all drugs, these blockbusters come with side effects and unknowns. Complications including nausea and other gastrointestinal problems lead some to abandon treatment. In September, U.S. regulators updated Ozempic's label to indicate a potential risk of intestinal obstruction, and in October, a Canadian team reported an increased chance of that complication as well as pancreatitis.

Doctors also worry about people who aren't overweight or obese turning to the treatment to slim down. A 2022 study reporting that semaglutide fueled 16% body weight loss in teenagers with obesity was met with hope but also hand wringing, as it underscored a vexing question: Are GLP-1 agonists "forever" drugs that people have to take indefinitely to preserve weight loss?

Right now it appears they may be, though the jury is still out. Researchers reported that 1 year after people stopped therapy, two-thirds of their lost body weight returned. For researchers who increasingly consider obesity a chronic condition, the need for ongoing treatment isn't surprising. But the drugs' cost can be prohibitive, with a sticker price of more than $1000 a month, and the prospect of lifelong use troubles many.

Against this backdrop, the next chapter is already unfolding: therapies that mimic multiple hormones and appear to be even more slimming. One, Eli Lilly & Co.'s tirzepatide, was approved in the U.S. in November for weight loss after being greenlit last year for diabetes; a large clinical trial reported that those taking it lost up to 21% of their body weight.

As the GLP-1 story continues, one thing is clear: These new therapies are reshaping not only how obesity is treated, but how it's understood—as a chronic illness with roots in biology, not a simple failure of willpower. And that may have as much impact as any drug. ■

VIDEO AND PODCAST
GLP-1 insights from the bench to the clinic at: https://www.science.org/boty2023

ILLUSTRATION: (OPPOSITE PAGE) STEPHAN SCHMITZ/FOLIOART

Obesity meets its match

Jennifer Couzin-Frankel

Science **382** (6676), . DOI: 10.1126/science.adn4691