Karen Langhauser
Chief Content Director

PHARMA'S WEIGHT LOSS CHALLENGE

Can the industry rewrite the script for obesity care?

From William the Conqueror's alcohol-only regime in the Middle Ages to Lord Byron's 19th century vinegar diet to Lucky Strikes' 'smoking for weight loss' campaigns in the 1920s, history is heavy with questionable methods of weight management.

Ancient Greek physician Hippocrates, considered the 'father of medicine,' recognized excess weight as a health risk nearly 2,500 years ago, recommending lifestyle modifications such as diet and exercise. And according to Dr. Ethan Lazarus, past president of the Obesity Medicine Association, not much has changed in terms of modern-day treatment plans.

"The majority of doctors that I know still think that obesity is a function of willpower. I regularly have patients with BMIs as high as 50 or 60 who have been told that the treatment for their obesity should be eating more vegetables," says Lazarus, who began his career in family medicine before taking over a specialized obesity management practice close to 20 years ago.

Despite the American Medical Association officially recognizing obesity as a disease in 2013, medical and societal stigma has persisted — and so has obesity. Today, more than two-thirds of U.S. adults are either overweight or obese — a growing problem that adds over $170 billion to the country's health care costs each year.[1]

It's an epidemic that has long lacked safe and effective pharmacologic solutions — until now.

A fast-growing class of drugs known as incretin mimetics, originally developed to treat type 2 diabetes, may rewrite the script for obesity care.

"These drugs are not silver bullets," warns Dr. Marcus Schabacker, president and CEO of ECRI, a global independent authority on health care technology and safety. "Obesity is a multifactorial issue and you need to take a multifactorial approach, but in that context, the drugs are very effective and could truly be a turning point."

Faced with a sizable potential patient population and a global market now projected to hit $100 billion in sales by 2030, pharma has the opportunity to raise the missing pillar in comprehensive obesity care.[2]

But there's a hefty caveat. Treatment options come with a high price tag and right now, pickings are slim.

> "The majority of doctors that I know still think that obesity is a function of willpower."
>
> — Dr. Ethan Lazarus

So slim that Novo Nordisk currently owns the entire incretin obesity market with the only two FDA approved drugs. In the absence of options, off-label demand for incretin-based diabetes treatments, specifically Novo's Ozempic and Eli Lilly's Mounjaro, has triggered ongoing shortages.

The hunger for Novo Nordisk's pricey new anti-obesity drug, Wegovy, is so great that the drugmaker's CEO recently said it could take "some years" for the company to meet the demand.[3] Even as the drugmaker scrambles to fill orders, lack of competition has padded its pockets; Novo Nordisk is now valued more than the entire Danish economy.

Continued momentum in obesity care will be predicated on access to new drugs. In order to truly transform obesity into a treatable disease for all patients, pharma must overcome current supply and pricing issues and get more drugs through development and within reach of those who need them most.

The incretin effect

While they don't date back to antiquity, incretin mimetics are not as new as their recent TikTok popularity implies.

The term 'incretin' is credited to Belgian physiologist Jean La Barre, who in 1932 proposed that diabetes could be treated with naturally occurring human hormones. The two main incretin hormones released by the small intestines, glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1), were officially identified back in the 1970s and 1980s, respectively.[4]

In what is now known as the 'incretin effect,' scientists discovered that in healthy individuals, glucose responsive receptors in the gastrointestinal tract trigger the release of GIP and GLP-1 hormones in response to food — but in people with type 2 diabetes, this effect is blunted.

From those new advances in diabetes understanding came the idea that long-acting stable receptor agonists of the GLP-1 hormone could be used to stimulate insulin secretion. As their name implies, incretin mimetics work to mimic the glucose-lowering actions of incretins.

In 2005, the FDA approved the first incretin mimetic, developed by Amylin Pharmaceuticals and Eli Lilly, as an add-on therapy for patients with type 2 diabetes. By binding to GLP receptors in the pancreas, the drug, branded Byetta, triggered the effects of the GLP-1 hormone.

Byetta's weight loss properties, which were consistently demonstrated in clinical trials, were used to position the drug against other type 2 diabetes drugs, many of which were commonly associated with weight gain. But Byetta's ability to stimulate weight loss set the stage for the exploration of incretin mimetics in obesity care.

Nourishing an obesity market

As more incretin mimetics advanced through pipelines for type 2 diabetes, their weight loss properties began to shift from a nice perk to a lucrative opportunity.

"The drugs were proving very effective in managing non-insulin dependent diabetes. Then secondarily, as pharmaceutical companies often do, they looked for additional indications for the drugs, to quite simply, make more money," points out Schabacker.

Profits (and judgment) aside, there is a verifiable health link between obesity and type 2 diabetes, which are often referred to as 'twin epidemics.' It's estimated that 90% of type 2 diabetes patients are overweight or obese, and people battling obesity face the highest risk of developing diabetes.[5] The risk of many of the common complications faced by patients with diabetes, such as kidney disease and cardiovascular issues, can be lessened by losing weight.

Long-time diabetes giant Novo Nordisk wasted no time getting out of the anti-obesity gate. By 2006, the Danish drugmaker was testing its GLP-1 agonist, liraglutide, in both type 2 diabetes and obesity.

In 2009, the drug ran into some safety delays on its road to approval in type 2 diabetes and Novo temporarily halted the phase 3 obesity studies while working with regulators to resolve concerns over pancreatitis and a rare type of thyroid cancer.[6] The following year, Novo secured approval for

FDA approved GLP-1 receptor agonists

2005 Byetta (exenatide)
Amylin/Eli Lilly (now AstraZeneca)
type 2 diabetes

2010 Victoza (liraglutide)
Novo Nordisk
type 2 diabetes

2012 Bydureon (exenatide)
Amylin/Alkermes (now AstraZeneca)
type 2 diabetes (discontinued, reformulated 2017)

**first once-weekly treatment for type 2 diabetes*

2014 Tanzeum (albiglutide)
GSK
type 2 diabetes (discontinued)

2014 Trulicity (dulaglutide)
Eli Lilly
type 2 diabetes

2014 Saxenda (liraglutide)
Novo Nordisk
chronic weight management

**first GLP-1 approved for obesity/overweight*

2016 Adlyxin (lixisenatide)
Sanofi
type 2 diabetes (discontinued)

2017 Ozempic (semaglutide)
Novo Nordisk
type 2 diabetes

2019 Rybelsus (semaglutide)
Novo Nordisk
type 2 diabetes

**first oral GLP-1*

2021 Wegovy (semaglutide)
Novo Nordisk
chronic weight management

2022 Mounjaro (tirzepatide)
Eli Lilly
type 2 diabetes

**Mounjaro is a dual GIP/GLP-1 receptor agonist*

liraglutide, branded Victoza, for type 2 diabetes and was able to confidently resume its trials in obesity.

Other drugmakers, including Amylin, GSK and Eli Lilly began grabbing up approvals of GLP-1 analogues in type 2 diabetes, and with each approval, trust — and data — in the drug class was mounting.

In 2014, the FDA approved a higher dose version of Novo's liraglutide, branded Saxenda, marking the first GLP-1 receptor agonist to get the green light as an obesity treatment — and the start of a pharmacologic shift in obesity care.

"For the first time, there was something with manageable side effects that seemed to be relatively safe even in the long term because diabetic patients had been using it for years," notes Schabacker.

Celebrities weigh in

While Novo Nordisk's Saxenda had the distinction of being the first anti-obesity incretin, it was the drugmaker's next-gen GLP-1s that catapulted the drug class into weight loss stardom.

The FDA approved semaglutide, branded Ozempic, for diabetes in 2017 and a higher dose version to treat obesity, branded Wegovy, in 2021. The drugs' effectiveness when it came to weight loss — in some cases up to a 20% reduction in body weight — along with some unsolicited celebrity endorsements on social media and even at the Oscars, sent prescriptions soaring.

The therapies have stolen the show financially too. When Novo Nordisk rolled out its recent second-quarter results, diabetes and obesity care sales had increased by 36%, driven predominately by the demand for GLP-1 therapies.[7] Following the drugmaker's early September launch of Wegovy in the UK, Novo usurped luxury brand company Moët Hennessy Louis Vuitton to become Europe's most valuable firm.[8]

Novo's anti-obesity drug is also racking up accolades in the clinic. The results from two international trials reinforced Wegovy's potential to enhance cardiovascular care. In the larger SELECT trial, the drug reduced the risk of major adverse cardiovascular events by 20% in adults with overweight or obesity.

Martin Holst Lange, the drugmaker's executive vice president of Development, heralded the SELECT results as a major pharmacologic breakthrough, saying that Wegovy now "has the potential to change how obesity is regarded and treated." Many doctors, including Ethan Lazarus, agree — but there is a catch.

"The treatment with pharmacotherapy is now becoming more compelling both because of the safety profile and potential benefits, but also the magnitude of the weight loss," says Lazarus. "But right now, we have a significant problem in that we only have one highly effective drug approved for obesity, and Novo Nordisk can't come anywhere close to meeting the demand for that drug."

Wegovy first hit the FDA drug shortage list in March 2022 and currently remains there. It is joined by sister drug Ozempic — a supply issue that many attribute to off-label use of the drug for weight loss. One recent analysis found that 56% of patients newly prescribed Ozempic or Eli Lilly's type 2 diabetes drug, Mounjaro, did not have diabetes.[9]

For Novo Nordisk, manufacturing snags have further worsened the shortages. On two separate occasions, the FDA cited quality control issues at the CDMO plant that fills Wegovy syringes, later revealed by Reuters to be a Catalent facility. Novo has responded by ramping up production to 24/7, investing up to $4 billion a year to expand capacity and signing a second CDMO.[10]

The incretin frenzy isn't limited to Novo Nordisk drugs either. Between the drug's impressive ability to reduce glucose levels in those with type 2 diabetes and off-label demand presumably inspired by weight loss, Eli Lilly has run into shortages with Mounjaro as well.

In May 2022, tirzepatide, branded Mounjaro, earned the distinction of becoming the first and only FDA-approved medicine that activates two different incretin receptors, GLP-1 and GIP, which the drugmaker says contributes to superior blood sugar control. The dual agonist also produced incredible results in a late-stage obesity trial, with patients losing as much as 22.5% of their weight.

With the treatment's anti-obesity approval fast-tracked and in the hands of regulators, Eli Lilly has been ramping up supply efforts.

"We continue to invest and add manufacturing and supply capacity around the world," says an Eli Lilly spokesperson. "With the addition of our manufacturing facility in North Carolina, coupled with additional actions and expansions at other sites, we are on track to achieve the goal we shared in November 2022 to double our incretin capacity by the end of this year."

Despite extraordinary promise, for now, supplies of incretin drugs are limited — which means so is their impact on the obesity epidemic.

1 in 3

Nearly 1 in 3 U.S. adults are overweight. More than 2 in 5 U.S. adults have obesity.

— National Health and Nutrition Examination Survey

A hefty price tag

Shortages aren't the only issue that manufacturers must lean into if the industry wants to upend the obesity epidemic.

According to ECRI, the biggest barrier to weight loss drug adoption is pharma's familiar nemesis: price. Currently, Wegovy injections list for $1349 per month. The price tag means that most Americans can only access the next-gen medication through health insurance — and right now, coverage is a work in progress.

While most private insurance companies will cover the new incretin medications for patients with diabetes, those seeking out treatment for obesity are still battling historical biases in the form of plan exclusions.

On the public side, only nine states have placed GLP-1 weight-loss drugs like Wegovy on their Medicaid preferred drug lists.[11] Medicare, however — under the Medicare Modernization Act, which passed in 2003 in the shadow of the Fen-Phen fallout — is prohibited from covering medications used for weight loss.

"Insurers' unwillingness to cover weight-loss medication puts it out of reach, especially for people with low incomes who experience obesity disproportionately," says Schabacker. "It's really important to stress the point that the non-payment further drives the inequity in our health care system."

Lawmakers recently reintroduced the Treat and Reduce Obesity Act (TROA), an 11-year-old bipartisan piece of legislation which, among other improvements, would expand Medicare Part D coverage to include FDA-approved anti-obesity medications. The bill has been endorsed by a host of medical groups including the Obesity Medicine Association and, not surprising, pharma companies such as Boehringer Ingelheim, Novo Nordisk and Eli Lilly.

With many private insurers modeling their benefits after Medicare coverage, the passage of a bill like TROA would have effects beyond just the senior population covered by federal insurance. But legislation still faces an uphill battle because the large potential patient population requiring long-term treatment translates to enormous government payouts. One NEJM perspective piece from health policy researchers at Vanderbilt University Medical Center calculated that if all Medicare beneficiaries with obesity were to be prescribed Wegovy, the cost would exceed the entire Medicare Part D budget.[12]

The onus of course, can't be placed entirely on payers. "Price is not determined by production cost. Price is determined by what the market bears," reminds Schabacker. Yet with demand skyrocketing and supplies dwindling, patients are unlikely to see price reductions until more drugs are commercialized and competition ramps up.

As is typically the case with any new category of drugs, the pharma industry's focus has been on payer coverage. The versatility of incretin mimetics and their potential to prove effective in additional conditions that are often linked to excess weight has helped upped the odds for pharma. Having learned lessons from the drugs that hit the market first, manufacturers are building their case in the clinic.

Obesity advanced pipeline snapshot

Regulatory review

- Eli Lilly, tirzepatide
  dual GIP/GLP-1 receptor agonist

Phase 3

- Eli Lilly, orforglipron
  oral GLP-1 receptor agonist
- Eli Lilly, retatrutide
  GIP/GLP-1/glucagon receptor agonist
- Novo Nordisk, cagrilintide
  +semaglutide (CagriSema)
  amylin analogue plus GLP-1
  receptor agonist
- Novo Nordisk, semaglutide
  oral GLP-1 receptor agonist
- Novo Nordisk, semaglutide (7.2 mg)
  high dose GLP-1 receptor agonist
- Boehringer Ingelheim/Zealand
  Pharma, survodutide
  GLP-1/glucagon receptor agonist

Phase 2

- Amgen, maridebart cafraglutide
  GIP/GLP-1 receptor agonist
- Structure Therapeutics, GSBR-1290
  oral GLP-1 receptor agonist
- Pfizer, danuglipron
  oral GLP-1 receptor agonist

One example is Boehringer Ingelheim's experimental once-weekly injectable, survodutide, born out of a longstanding partnership with Zealand Pharma and now advancing into phase 3 clinical studies in obesity. While the drugmaker says it's too early to comment on pricing, Ioannis Sapountzis, global head of Therapeutic Areas at Boehringer Ingelheim advocates a more comprehensive view of treatment value.

"It is important to consider the long-term costs associated with obesity especially since it is a leading risk factor for several cardiovascular, renal and metabolic conditions," says Sapountzis. "We are convinced that conversations with payers will evolve given the changing perception of obesity."

In addition to obesity and type 2 diabetes, survodutide is also being tested in liver diseases such as non-alcoholic steatohepatitis (NASH). NASH, one of the major causes of liver fibrosis and cirrhosis, is especially prevalent in people with metabolic disorders such as obesity.

Eli Lilly is also studying Mounjaro as a potential treatment for NASH, as well as in sleep apnea and HFpEF, the most common form of heart failure.

Grabbing the obesity approval hasn't stopped the research for Novo Nordisk, with the drugmaker's 17,600-person SELECT trial proving a major win for semaglutide and GLP-1 agonists in general in terms of cardiovascular indications.

As drugmakers push to expand their incretin drug labels, their findings lend more evidence to the case for obesity as a serious medical condition in need of pharmacologic treatment.

"Studies like the SELECT trial are going to change this discussion," says Lazarus. "Let's say a patient comes to see a family doctor and has sky high blood pressure — ignoring it in this day and age would be malpractice. Similarly, I think we are getting to a point where we are going to have to address weight."

Full pipelines

Whether attributed to the temptation of a looming $100 billion market or the genuine hunger to fill an unmet need for millions of patients, drugmakers have taken a seat at the obesity care table.

Citeline's Pharmaprojects database found that globally, there are 51 active drugs in development with incretin mimetics as the mechanism of action. Within these compounds, 22 are being explored in obesity.

While the first drugs on the market were limited to single GLP-1 agonists, new drugs are pushing boundaries in incretin pathways as drugmakers pursue drugs with dual modes of action.

Boehringer Ingelheim-Zealand Pharma's phase 3 drug, survodutide — which has demonstrated up to 19% weight loss in trials — is a dual agonist that activates both GLP-1 receptors and receptors for glucagon, a hormone that plays a role in energy balance through receptors in adipose tissue (body fat) and the brain.

"Survodutide has the potential to become the first anti-obesity medication to induce significant weight loss by reducing appetite while increasing energy expenditure through direct action on the liver to help people with overweight or obesity reduce their body weight," says Boehringer's Sapountzis.

Eli Lilly has a triagonist in phase 3 trials for obesity and diabetes. The asset, known as retatrutide, activates receptors for GLP-1, glucagon and GIP.

"The incretin-based treatments that are currently approved to treat obesity only activate the body's receptors for GLP-1. We believe combining glucagon receptor agonism with GIP and GLP-1 receptor agonism may contribute to higher levels of reduction than that seen in trials for single- or dual-receptor agonists," says an Eli Lilly spokesperson.

Another trending area in the clinical space has pharma squaring off against a long-established challenge — converting injectable drugs to shelf stable, oral medications. Currently, the only GLP-1 medication offered in oral form is Novo Nordisk's Rybelsus, a once-daily pill version of semaglutide, approved for type 2 diabetes.

In 2020, Novo acquired Emisphere Technologies and its proprietary drug delivery technology known as Eligen sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC). The technology, used in the Rybelsus formulation, is an acylated amino acid designed to improve the oral bioavailability of parenteral drugs. SNAC enables the transport of therapeutic molecules, including large peptides and proteins, across biological membranes, such as those of the gastrointestinal tract — a notorious stumbling point for oral biologics.[13]

Both Novo and Lilly are advancing once-daily oral GLP-1 receptor agonists in phase 3 trials for obesity and Pfizer has a twice-daily oral obesity drug in mid-stage trials.

The oral formulations have shown comparable efficacy to their subcutaneous counterparts and the needle-free administration is a major selling point with patients. But the drugs still come with some hurdles. Novo Nordisk's oral semaglutides, for example, must be taken on an empty stomach with only a sip of water, and patients must wait 30 minutes before intake of food or other medications.

However, for drugmakers, oral formulations have established manufacturing, storage and distribution advantages that will not only result in lower costs but could ultimately facilitate a more global availability of much-needed anti-obesity drugs.

The big reveal

"The standard of care for the treatment of obesity in primary care has essentially been to do nothing," says Dr. Lazarus. "Ignoring the problem is really missing the mark in terms of offering patients evidence-based treatments."

But after hundreds of years of stagnating treatment, a critical moment for obesity care hangs in the balance — and incretin mimetics could tip the scales in a very big way.

"People living with obesity deserve action, not just hope. The stakes are too high to let another 10 years go by without more change," wrote Eli Lilly in a recent blog post.[14]

With the final piece of the multifaceted approach needed to combat obesity in its hands, all eyes are on the pharma industry. What the industry does next in terms of facilitating access to this innovative new class of anti-obesity treatments has the potential to not only better the health of millions, but forever transform the way the world views obesity.

References

1 | *Adult obesity facts. Centers for Disease Control. Accessed Aug. 25, 2023.*
2 | *Woods, Bob. Big pharma's blockbuster obesity drug battle is just getting started, and it's headed for $100 billion. CNBC. (Sept 9, 2023).*
3 | *Tirrell, Meg. Ozempic and Wegovy maker 'just scratching the surface' in meeting demand for weight loss drugs, CEO says. CNN. (Sept. 5, 2023).*
4 | *Chia, Chee and Egan, Josephine. Incretins in obesity and diabetes. Ann N Y Acad Sci. (Aug. 7, 2019).*
5 | *Nianogo, R. and Arah, O. Forecasting Obesity and Type 2 Diabetes Incidence and Burden: The ViLA-Obesity Simulation Model. Front. Public Health. (April 2022).*
6 | *Ringstrom, Anna. Novo Nordisk to restart liraglutide obesity studies. Reuters. (June 22, 2010).*
7 | *Annual Report 2022. Novo Nordisk. (2022).*
8 | *Kollewe, Julia. Wegovy maker Novo Nordisk becomes Europe's most valuable firm. The Guardian. (Sept. 5, 2023).*
9 | *Ozempic, Wegovy, and Mounjaro: On- and off-label prescribing trends. Truveta Research. (Jun 6, 2023).*
10 | *Fick, Maggie. Novo hires Thermo Fisher as second manufacturer for Wegovy weight-loss drug - source. Reuters. (Aug. 23, 2023).*
11 | *Wilson, Rylee. 9 states negotiating Medicaid prices for Wegovy. Becker's Payer Issues. (July 26th, 2023).*
12 | *Baig, K., et. al. Medicare Part D Coverage of Antiobesity Medications — Challenges and Uncertainty Ahead. N Engl J Med. (March 16, 2023).*
13 | *Novo Nordisk to acquire Emisphere Technologies and obtain ownership of the Eligen® SNAC oral delivery technology. Novo Nordic press release. (Nov. 6, 2020).*
14 | *Taking on a Disease That Can't Be Ignored. Eli Lilly, Stories. (June 22, 2023).*