

10 Jan 2022 | Analysis

The Other Pandemic

COVID-19 Highlighted Risks And Costs Of Obesity. Pharma Is Getting Interested

by **Melanie Senior**

When Novo Nordisk's anti-obesity medicine Wegovy launched in June 2021, patients and physicians could not get enough. As COVID-19 underscored the risks of obesity, along came the most effective drug yet – on a par with surgery, in terms of weight loss achieved. Pharma's interest in this disease has reawakened, and Wegovy may be just the first of a new generation of more powerful anti-obesity medicines.

When [Novo Nordisk AS](#) launched anti-obesity drug Wegovy (semaglutide) in the US in June 2021, physicians and patients could not get enough. Supplies quickly ran out, even though the drug is not covered by government insurers Medicare or Medicaid. "This drug is at least twice as effective as anything we've seen before," said Louis Aronne, professor of metabolic research at Weill Cornell Medicine's Comprehensive Weight Control Center. "We are inundated with patients."

Trials of Wegovy, a glucagon-like peptide (GLP)-1 agonist, showed a 15% average weight loss, in combination with diet and exercise, versus lifestyle change alone. Only bariatric surgery can achieve this kind of weight loss; no single anti-obesity medicine has come close.

Obesity specialists hope the drug marks the start of a new era of more effective medicines, better access to treatment and a renewed understanding of the condition – as a disease, not a lifestyle choice.

Wegovy, a weekly injection, works on GLP-1 receptors in the brain, stomach and adipose tissue, triggering insulin release and a feeling of fullness. It is a higher-dose formulation Novo's diabetes drug Ozempic. The Danish company is not alone in expanding into obesity. Fronting a growing pipeline of new, potentially even more effective obesity drugs is another blockbuster-in-

the-making, *Eli Lilly and Company*'s tirzepatide. Tirzepatide hits both GLP-1 and glucose-dependent insulintropic polypeptide (GIP), which also boosts insulin secretion. It is under FDA review for Type 2 diabetes and being tested in over 5,000 patients as part of a multi-trial Phase III obesity program.

Pharma's interest is overdue. Obesity is the less-talked-about pandemic. It has spread rapidly over the last few decades to more than 10% of the world's population, including over 100 million Americans. The American Medical Association recognised obesity as a disease in 2013, but due to limited reimbursement, "only 1% of those that meet the criteria for anti-obesity medicines are getting access," said Fatima Cody Stanford, obesity specialist at Massachusetts General Hospital and Harvard Medical School. Stigma and misunderstanding have left this condition woefully under-acknowledged, and under-treated.

The coronavirus pandemic provided a wake-up call at just the right time for Wegovy. Numerous studies document how obesity raises the risk of severe illness from COVID-19, as well as a host of other better-known conditions such as heart disease, diabetes and some cancers. Doug Langa, Novo Nordisk's EVP North America said the company had achieved 60% coverage across the US commercial market, via agreements with three big pharmacy benefit managers. Those employer and health plans that do reimburse the drug cover an estimated 16-20 million Americans. That is not bad after just six months. "The pandemic has finally convinced everyone that obesity is a disease, associated with health risks," said Aronne.

Analysts expect Wegovy to be big, but, like Novo Nordisk, they are not sure exactly how big (\$5bn? \$9bn?). Some commercial insurers and employers are still hiding behind the Centers for Medicare and Medicaid Services' (CMS) outdated rule to avoid paying for the \$1400-per-month medicine. Those that are covering it – including big names like Aetna,

Lifestyle Or Disease?

Obesity is still widely seen as a side-effect of over-eating and an unhealthy lifestyle. The story is actually much more complicated. Obesity is, at core, a disease of the brain, influenced by genetics, environment, development and behavior.

The hypothalamus regulates our weight through signals to and from the stomach, pancreas and gut. These signals tell us how much to eat, and how much to store. But not everyone's brain is wired the same way. Some favor signalling pathways that lead to a higher set weight. A neurotransmitter called brain derived neurotrophic factor (BDNF) appears to play a key role. Studies have found that those with high levels of BDNF are more likely to be lean than those with low BDNF. The latter group – which includes many more Hispanic and African Americans – are more susceptible to obesity.

Anthem, and Express Scripts – are not making it easy. High cost shares and prior authorizations are commonplace. Like other anti-obesity medicines, Wegovy must be taken in conjunction with diet and exercise – as a condition for reimbursement, and for optimal effect. It must also be taken long-term. “As soon as you stop taking it, your body will return to whatever weight it was before,” explained Cody Stanford, who has consulted for Novo and other companies, but was not involved in Wegovy trials. The life-time cost of the treatment, therefore, will be in the hundreds of thousands of dollars.

That may be a worthwhile investment. Obesity costs the US \$147bn in medical care and over \$6bn in absenteeism each year, according to the Center for Diseases Control. (For context: that is more than double the total savings expected over 10 years from the new drug pricing plans working their way through Congress.) Even a 5% weight loss cuts the risk of diabetes in half; a 15% loss brings “virtually all the health benefits” you’d expect from returning to a healthy weight, including lowering the risk of heart disease, said Aronne.

It is a claim worth quantifying, particularly given how few heavyweight studies exist to date showing the potential savings from using obesity medicines. The US-based Institute for Clinical and Economic Review, which shares its views on many new drugs’ cost-effectiveness, has not yet said whether it will tackle Wegovy (though it acknowledges that the drug has many of

The condition also runs in families. Indeed, weight is “more heritable than height,” said Fatima Cody Stanford. Children with one obese parent have a 50-80% higher chance of having obesity than those with normal weight parents. They are exposed during fetal development to the increased inflammation, insulin resistance and cholesterol associated with the condition.

The upshot: individuals with obesity may be eating and exercising well, but still suffer with a condition that compels their bodies to pile on the pounds and maintain a high set weight. Racial and socio-economic disparities associated with obesity, plus stigma and bias within many corners of society, make the issue as challenging to navigate as it is urgent.

COVID-19 And Obesity

Multiple studies have shown that people with obesity are much more likely to suffer from serious disease and death due to COVID-19. This is in part because those with obesity are at higher risk of other chronic conditions that make them vulnerable, such as diabetes, cardiovascular disease, kidney dysfunction and some cancers. Scientists have also uncovered additional, independent risk factors. Obesity leads to low-level inflammation, impairs the immune system, and adipose tissue itself may even provide a

the criteria to be a topic of consideration, notably health and budgetary impact, and patient access). Calculating the net health benefits of this kind of medicine is hard: it requires extensive data around co-morbidities, long-term weight trends and adherence. And, especially in the fragmented US health system, those that pay for the drug are not always those who directly benefit from complications avoided and money saved down the road.

What is clear is that, at a price equivalent to almost half the median US take-home income, most people will not be paying for Wegovy out of pocket. Novo Nordisk is working hard to convince US employers, including by funding research showing the value of adding medicines to weight management programs.

In England and Wales' single-payer system, cost-watchdog NICE plans to compare Wegovy's cost-effectiveness to that of Novo's Saxenda (liraglutide, another GLP-1 used in diabetes) and orlistat (Roche's Xenical, also sold OTC as Alli) in an analysis due in March 2022. UK incidence of obesity has grown 25% since 2014.

Alongside patchy reimbursement and poor understanding of obesity, Novo Nordisk is also up against a dearth of trained specialists in the US. Doctors are not taught about obesity at medical school. There are fewer than 4,000 board-certified obesity doctors, and only about 50 that are fellowship trained, notes Cody Stanford. That means few know how to use anti-obesity medicines which, until now, often needed to be combined to achieve meaningful weight loss. Yet mixing medications is tricky and can be dangerous. Some doctors are "terrified" of using any anti-obesity drug, let alone combining them, given the patchy safety history of the class.

Wegovy has a long history of safe usage in diabetes; few of the specialists In Vivo spoke to were worried about long-term safety. Novo Nordisk says that over two thirds of prescriptions so far have gone to patients new to anti-obesity meds. But up to 60% of those are being given away through a six-month assistance program. It is unclear how many will be covered once that ends.

virus reservoir. (It has lots of Angiotensin Converting Enzyme (ACE)-2 receptors that work as cellular entry points for the virus.)

None of that is good news in the context of a viral disease that causes additional, highly dangerous inflammation and clotting. That is why the average age of hospitalized patients of normal weight is over 10 years higher than those with obesity.

Obesity Drugs' Patchy History

Obesity medicines have had a bumpy ride. Most famously, fenfluramine-phentermine (Fen-Phen) was found during the 1990s to cause heart valve issues, even though its

So, notwithstanding Wegovy's early success, Novo is having to work hard to open this untapped market. "We will continue to negotiate with insurers and employers to expand coverage and remove barriers to treatment," said Langa. Still, he added, "There's a long way to go."

Waiting In The Wings

Eli Lilly is first in line to benefit from the Novo's groundwork preparing the obesity market. Both companies are trying to diversify beyond the commoditizing insulin market; their GLP-1 diabetes drugs compete fiercely for share in diabetes. Tirzepatide was submitted to the FDA in October 2021 with a priority review voucher for diabetes, but Lilly is hoping it makes its mark in obesity, too.

One of tirzepatide's five registration studies showed a greater reduction in body weight versus the lower, 1mg dose of semaglutide used in diabetes. (Wegovy's maintenance dose is 2.4mg.) Tirzepatide's dual mechanism of action may give it an edge. Combining the GLP-1 and GIP peptides appears to be additive, even though some of GIP's standalone effects appear counter-productive (it may increase fat storage, for example.)

Novo Nordisk will make the most of Wegovy's head start to build confidence and a safety record. (A 17,500-strong cardiovascular outcomes trial is underway, due to complete in 2023.) It will also begin Phase III trials in 2022 of its own combination: Wegovy plus cagrilintide, an analog of amylin. Amylin is another satiety-inducing hormone, whose effects could be additive to those of GLP-1.

Renewed Industry Interest

The growing obesity drug pipeline includes a handful of other mid- and late-stage candidates built around a GLP-1 backbone, typically in trials for several cardio-metabolic conditions, and candidates with other mechanisms of action too. (See Exhibit 1.) The disorder is pulling in big pharma heavyweights and fuelling start-ups like Versanis, launched in August 2021 with a discarded asset from Novartis.

weight loss effects were dramatic. Phentermine, a compound similar to amphetamine which is now generic, remains the most widely prescribed anti-obesity medicine in the US, according to Louis Aronne. Since 2012, it has been available in the US in combination with topiramate (an epilepsy drug), as Qsymia. European authorities rejected the drug in 2012 and 2013, due to concerns over cardiovascular side-effects.

Sanofi's cannabinoid receptor antagonist rimonabant (Acomplia/Zimulti) was withdrawn in 2008 due to serious psychiatric side-effects, after two years on the European market. It never made it to the US. In February 2020, Eisai's serotonin receptor agonist Belviq (lorcaserin) and Belviq XR were whipped off the US market due to increased risk of cancer. Europe never approved the drugs.

In a turn of the tables, tiny [Versanis Bio](#) is testing, in the biggest chronic disease of all, a compound that failed in a rare muscle wasting condition under big pharma's watch. Bimagrumab is an activin type II receptor blocker that stimulates muscle growth. Versanis raised \$70m for a Phase II obesity study. (Versanis' board includes Joe Jimenez and Mark Fishman, respectively former CEO and head of research at Novartis.)

Exhibit 1:

[Click here to explore this interactive content online](#) ✎

Will CMS Cover Obesity? Not soon

The obesity drug pipeline looks more exciting than it has for decades. But its dozen or so clinical stage programs still pale in number compared to the many hundreds in line to treat cancer, even though cancer affects just one sixth as many people.

That gap is unlikely to close anytime soon. Even if COVID-19-catalyzed awareness of obesity, plus a flurry of more effective drugs does compel wider US coverage, any change at CMS would require a new law. That is unlikely, given the existing legislative pile-up in Congress. The Treat to Reduce Obesity Act has tried and failed to get over the line several times since 2013. "Each year, we get a bit closer," said Cody Stanford, citing as the main barrier misunderstanding rather than cost concerns.

Several of those developing GLP-1-based obesity medicines are working in related indications that would be reimbursed, like heart failure, diabetic kidney disease, NASH and fibrosis. If successful, these treatments will eventually get to patients with obesity, even though the logic appears backwards. Right now, "we must wait until a patient [with obesity] develops diabetes before we can medicate with a GLP-1 – at a lower dose," said one exasperated specialist.

Prescribing Algorithms

Meanwhile, technology is helping some US patients access the right obesity medicines through non-specialist providers. In 2020, software developer IntelliHealth launched Evolve, a digital platform designed to help nurse practitioners and health managers to safely and effectively diagnose and treat obesity, using lifestyle support, educational resources, online appointments and access to dietitians and health coaches, as well as medicine. "We wanted to democratize the kind of [obesity management] we have developed here" at Weill's Comprehensive Weight Control Center, said Aronne, co-founder and CMO at Intellihealth. "We need to get beyond the 1-2% being treated currently."

Evolve deploys an algorithm to determine which treatment(s) work for a given patient, considering their underlying condition, medications and their insurance coverage. Not everyone may get Wegovy. But the system at least flags up when patients need anti-obesity medication. It

can recommend drugs – including combinations of cheaper generics – that may work, even if less effective or convenient than Wegovy. Evolve is now used at Brigham & Women’s Hospital in Boston, following a successful PCORI-funded trial, and at a half dozen other major hospital systems, including New York Presbyterian-Weill Cornell Medical Center, Massachusetts General Hospital, Geisinger Health System and Vanderbilt University.

The US is Wegovy’s most valuable market today, but the opportunity is global.

Wegovy is now approved in the UK, Canada and has been recommended for approval by the European Medicines Agency. More than 20% of Chinese adults will have obesity within a decade, according to a February 2021 paper in the International Journal of Obesity. Novo has a small Wegovy trial underway in China; Lilly is running a Phase III trial of tirzepatide in Chinese patients with obesity who do not have diabetes.

As Wegovy rolls out across the US and Europe, employers and health systems will be watching closely. If it moves the needle on health outcomes, costs and employee productivity, obesity treatment may shift into the mainstream – a mere 60 years after FDA approved the first obesity drug. The health impact would be huge. It may even mitigate the impact of the next infectious disease outbreak.