The end of obesity?

Obesity is one of the most daunting health challenges America faces. Nationally, 41.6% of Americans qualify as obese; in the 1950s only 10% were obese. Rates are also soaring among children and adolescents, with nearly 20% of U.S. children ages 2 to 19 having obesity— triple the rate in the mid-70s.

It's not merely a cosmetic problem: overweight increases the risk of virtually every physical and psychiatric ailment.

Enter a new class of drugs that are revolutionizing our approach to overweight: GLP-1 agonists. The latest are the semaglutides, the ingredient in Ozempic, Wegovy, and Rybelsus. Originally intended for non-insulin dependent diabetes, their propensity to yield double-digit percentages of body mass reduction has propelled them to ubiquity.

So successful have they been that they've created a boom in the country that's the home base of Novo Nordisk, the pharmaceutical firm that makes them. Denmark has doubled its economic forecast for the year; share price of Novo Nordisk has tripled since June of 2021.

The newest weight loss drug, dual-action Mounjaro, which combines semaglutide with a gastric intestinal peptide (GIP) analogue, just saw its quarterly sales grow year

over year from $16 million to nearly $1 billion.

The medications don't just provide cosmetic benefits. In addition to helping to normalize blood sugar, they've been shown to lower the risk of heart disease. It's been proposed that semaglutides—or their even more potent successors—will join the ranks of statins as mainstays of cardiovascular prevention. Their market share is projected to top $82.8 billion per year by 2032.

Most of the current drugs are injectable, requiring self-administered weekly shots, but it's expected the options will soon expand to more oral alternatives, and soon, *triple*-action drugs that promise even more spectacular weight loss. There's even talk on an "exercise pill", pioneered in mice, that conferred the weight loss benefits of exercise *without* the appetite suppression of current GLP-1 drugs.

A barrier is the price of the current medications—up to $15,000 per year—which many insurances cover only for diabetes but not for weight loss per se; patients' rights groups argue that we can't restrict access to the privileged rich; even the Congressional Black Caucus has advocated coverage as an equity issue. Following the money trail reveals that some of these initiatives are underwritten by BigPharma.

A Kaiser Foundation Fund survey found that:

"Nearly half of adults (45%) say they would generally be interested in taking a safe and effective prescription weight loss drug, including nearly six in ten (59%) of those who are currently trying to lose weight and half (51%) of those who are trying to lose less than 10 pounds . . . 80% of adults thought insurers should cover the new weight loss drugs for those diagnosed as overweight or obese. Just over half wanted it covered for anyone who wanted to take it. Half would still support insurance coverage even if doing so could increase everyone's monthly premiums."

Will the inevitable ubiquity of these drugs bring about the end of obesity as we know it?

First, let's consider their limitations and side effects.

It's well known that, once new drugs are introduced and administered to millions of people, problems emerge that were unforeseen in the limited clinical trials that led to their approval. For example, a new analysis of over 16 million patients found the incidence of pancreatitis, gastroparesis, and intestinal obstruction to be higher than expected in patients who took semaglutides. The authors caution:

"Given the wide use of these drugs, these adverse events, although rare, must be considered by patients who are contemplating using the drugs for weight loss because the risk-benefit calculus for this group might differ from that of those who use them for diabetes . . . Randomized trials examining efficacy of GLP-1 agonists for weight loss were not designed to capture these events due to small sample sizes and short follow-up."

In fact, a black box warning has just been added to the package insert for these drugs:

"The US Food and Drug Administration has provided safety-related labeling changes for semaglutide (Ozempic) products, warning users of the potential for increased risk of ileus, a blockage that keeps food or liquid from passing through the colon."

The problem is of such a magnitude that anesthesiologists are now reporting that some patients on these drugs are being told to get off them prior to surgery because

of the risk of aspiration of undigested stomach contents—something that's usually obviated by routinely asking patients to avoid eating and drinking a few hours before operations.

Then there's "the Ozempic blues": While the exact mechanisms that underlie semaglutide drugs' ability to induce weight loss are unclear, it's clear they work on the brain, increasing satiety. But they also likely affect neurotransmitters. Their blockage of gratification, largely mediated by the brain chemical dopamine—associated with motivation and reward—may impact more than just appetite pathways. Instead, they may blunt individuals' delight in other pleasurable pursuits.

We'll take up that topic in an upcoming podcast with Dr. Joan Ifland, author of *Processed Food Addiction*. She contends that *"Dealing with food cravings by artificially flipping the switch in the brain's reward centers is NOT a good way to get healthy long term because once the person is off the drug, they will be back at square one when it comes having the behavioral skills needed to cope with compulsive eating."*

And quit they will. A new report finds 2 out of 3 people on GLP-1 drugs like Ozempic stop within a year. Notwithstanding the prohibitive cost of these drugs, the low-grade nausea and constipation that these meds cause leads a high percentage of users to discontinue. Moreover, many are frustrated when they reach a weight plateau as the body adjusts its metabolism to reduced caloric intake. Once they stop, much or all of the lost weight comes roaring back.

And therein lies *my* primary concern. Losing considerable weight rapidly invariably entails loss of lean muscle along with adipose tissue. Besides, protein is the most satiating food, and users of weight loss meds tend to underconsume it, accelerating *sarcopenia*, the progressive age-related loss of muscle mass that leads to frailty. Users of these meds are well-advised to up their dietary protein and engage in resistance exercise—but that will only partially offset the invariable muscle loss.

Even if attainable, what would a world without obesity look like? What becomes of the Fat Acceptance movement? Would the few overweight medication "refuseniks" end up even more stigmatized?

What about those weight loss companies? The multi-billion dollar diet industry is already pivoting to the reality of weight loss drugs, offering affiliate programs with drug prescribers to complement the diet food and behavioral support they traditionally purvey. Now that obesity is redefined as a disease, with a medical fix, Weight Watchers is apologizing for having told clients that shedding pounds was simply a matter of will power.

And how about the food industry? It's predicated on tempting people to gobble huge quantities of savory caloric foods and beverages. Snacking is encouraged with a plethora of tasty offerings. In a recent article in the *Wall Street Journal* ("America's Food Giants Confront the Ozempic Era"), Nicholas Fereday, executive director of food and consumer trends for agricultural lender Rabobank, is quoted as saying the drugs pose a new threat to the packaged-food industry's growth:

"'If two-thirds of Americans are the target audience, it's a huge thing,' Fereday said, referring to the portion of the U.S. population that is considered overweight."

The company that markets Atkins-branded food products is trying to catch the wave by offering foods targeting people on weight loss drugs, or trying not to regain weight

after going off them.

The end of obesity? While these drugs will make a dent, it’s not clear whether side effects or cost constraints will limit their universal embrace. While I’ll continue to help people taking these drugs, and carefully monitor their new iterations, I won’t be prescribing them. One thing is for sure—people won’t lack for ways of getting them, and the unintended consequences of their use may be profound.