HEALTH

Are You Sure You Want an Ozempic Pill?

Pharmaceutical companies are racing to create obesity drugs you can swallow. They might not be as great as they sound.

By Yasmin Tayag

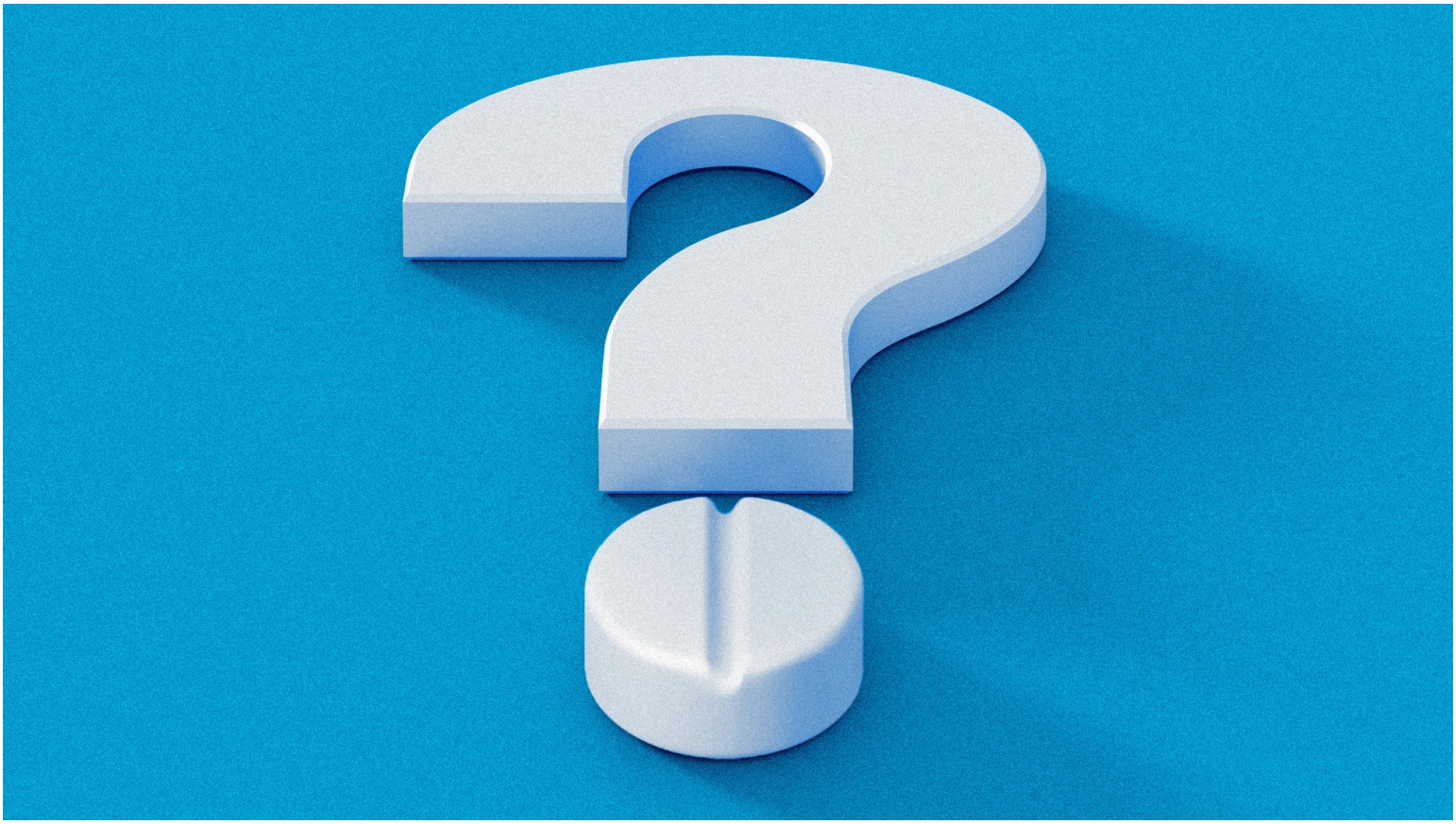

Illustration by Matteo Giuseppe Pani. Source: Getty

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Within the first five seconds of a recent Ozempic commercial, a sky-blue injector pen tumbles toward the viewer, encircled by a big red *O*. Obesity drugs have become so closely associated with injections that the two are virtually synonymous. Like Ozempic, whose name is now a catchall term for obesity drugs, Wegovy and Zepbound come packaged in Sharpie-like injection pens that patients self-administer once a week. Patients "don't come in asking for Wegovy," Laura Davisson, a professor of medical weight management at West Virginia University, told me. "They come in asking for one of 'those injectables.'"

Needles are the present, but supposedly not the future. Nobody really likes injections, and taking a pill would be far easier. In the frenzy over obesity drugs, a class known as GLP-1 agonists, drugmakers have raced to create them in pill form, and Wall Street investors are hungry at the prospect. Earlier this year, Pfizer's CEO, Albert Bourla, estimated that obesity pills could be worth $30 billion, or a third of the total obesity-drug market. Because people have a "preference" for pills, he said at a conference, they will be what ultimately "unlocks the market" for obesity medications. By one count, at least 32 oral GLP-1 drugs, from many different companies, are in the works.

But a future dominated by obesity pills is hardly certain. So far, the only oral GLP-1 that exists is a pill for diabetes called Rybelsus. Like Ozempic and Wegovy, its active ingredient is a compound called semaglutide, but the shots come in far more powerful doses, making it possible to lose even more weight. Developing oral obesity drugs that are as tolerable and effective as their injectable counterparts has so far been a challenge. Earlier this month, Pfizer stopped testing one of its pill candidates, citing concerns about side effects and patient adherence. Even when pills do come to market, doctors told me, there's no guarantee that people will flock to them.

That drugmakers view the injectable nature of GLP-1s as one of their biggest flaws is no surprise. Getting a shot is a broadly despised experience, something people generally tolerate rather than choose. Children get stickers for enduring immunizations; adults who get vaccinated do so only because they must (and they are often rewarded with stickers too). The CDC estimates that one in four adults, and two out of three children, have strong fears about needles. "Some people hate needles, plain and simple," Ted Kyle, an obesity-policy expert, told me.

But not all needles are made equal. Wegovy and Zepbound are injected subcutaneously, or just under the skin. Relative to COVID or flu shots, which are jabbed into muscle, they don't cause much discomfort. "I've been really surprised at how receptive my patients have been to using injectable medications," Davisson said. Other doctors I spoke with agreed. "More patients than you would expect really don't mind injectables," because they're easy and relatively painless to administer, Katherine Saunders, a clinical-medicine professor at Weill Cornell Medicine, told me.

The unobtrusive dosing schedule of the injectables adds to their appeal. Wegovy and Zepbound are administered once weekly, unlike many of the pills in

development, which are meant to be taken once or more daily. That can be a hassle, especially if they have to be taken at the same time every day, or if they come with restrictions on eating or drinking. “For some people, it’s easier to take an injection and forget about it for a week” than to remember to take a pill every day, Eduardo Grunvald, an obesity-medicine physician at UC San Diego Health, told me. Assuming pills are preferable to shots is a “knee-jerk reaction,” he added.

Despite the unexpected upsides of the shots, they’re far from perfect. Making injectable pens is generally more expensive than pills and requires a lot of hardware, including the pen casing, cap, and needle cover. On top of that, the injectable obesity drugs must be refrigerated before they are first used, adding to storage and production costs. Pills are generally shelf-stable and don’t require much packaging beyond a child-proof bottle. Saunders predicts they would be less expensive and less prone to shortages that have plagued Wegovy.

Still, creating an obesity pill isn’t as simple as packaging the same drugs in capsule form. Drugmakers have already run into a number of issues. Absorption is a big one: Because pills pass through the stomach before entering the bloodstream, they must be able to withstand a large degree of degradation. One way to get these drugs to lead to greater weight loss is to

increase the dose. While the highest dose of Wegovy is 2.4 milligrams, Rybelsus maxes out at 14 milligrams.

Hiking up the dose seems to work, though doing so could have consequences beyond weight loss. All GLP-1 drugs come with a range of unpleasant side effects involving the gastrointestinal system, and patients report nausea at similar rates in Rybelsus and Ozempic, according to the FDA. But this may differ in practice, as other doctors have noted. Saunders said that her patients on oral semaglutide report more nausea than those using injectables. Regardless, newer oral medications may have even more distinct differences, as drugmakers race to create more potent pills. In Pfizer's discontinued trial of danuglipron, nausea rates reached up to 73 percent.

Drugmakers also skirt the issue of degradation by pursuing sturdier drugs. The problem with semaglutide is that it's a peptide—essentially a small protein—precisely the kind of molecule that the stomach excels at digesting. Some new drugs in the pipeline are so-called non-peptide small molecules, which are sturdier but still have the same biological effect. Orforglipron, a pill that Eli Lilly is testing, falls into this category, as does danuglipron, the drug responsible for Pfizer's recent setbacks. Small-molecule drugs have the added benefit of being cheaper to produce at scale than peptides, Kyle, the obesity-

policy expert, added.

Another pesky problem with oral drugs is that they tend to come with strict dosing requirements. People on Rybelsus, for example, are instructed to take it 30 minutes before eating or drinking anything and can drink only four ounces of plain water along with it, because otherwise absorption could be compromised. "It can be a nuisance," Grunvald said. Similarly bothersome instructions likely played a part in the drop-out rates reaching more than 50 percent in Pfizer's recently discontinued trial: Danuglipron had to be taken twice daily. "A lot of people found it not worth the trouble," Kyle said, noting that Pfizer is still pursuing a once-daily version of the same drug. A recent review of GLP-1 drugs showed that, compared with the injectable form, oral semaglutide is associated with lower rates of side-effect reporting but *higher* discontinuation rates, potentially reflecting its bothersome dosage requirements.

Despite these hurdles, it seems inevitable that obesity-drug pills will eventually become available. Novo Nordisk is expected to file for FDA approval for its high-dose semaglutide obesity pill this year; Pfizer is forging ahead with a once-daily version of danuglipron, with more data expected "in the first half of 2024," a spokesperson told me. A report from BMO Equity

Research published in September predicted that oral formulations could be approved "by the late 2020s." The biggest upside to pills may not be that they are pills but that they will, eventually, be cheaper than injectables—and cost is among the biggest impediments to more people taking obesity drugs.

Whether they'll replace injectables outright is far from certain. "It will come down to patient preference," Grunvald said. Most likely, pills and injections will coexist to meet different needs, and perhaps even be used together to treat individual patients. In the so-called phased approach, obesity treatment could start with more expensive and powerful injectable drugs, then transition to less potent but cheaper orals for the long term. Eli Lilly, for one, sees its oral candidate, orforglipron, as a potential weight-loss-maintenance drug.

There is so much competition in the obesity-drug space that future medications may take more unexpected forms. Amgen is studying a once-monthly injection; Novo Nordisk is developing a hydrogel form of semaglutide that would need to be taken only three times a year. If the future of obesity drugs will come down to what patients prefer, then the more options, the better.

Yasmin Tayag is a staff writer at *The Atlantic*.

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