The Era of Compounded GLP-1 Drugs Is Over. What Now?

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Now that the US Food and Drug Administration has removed both tirzepatide and semaglutide from its Drug Shortages List, the widespread compounding of these drugs is ending. Tirzepatide's deadline has already passed, while physicians and pharmacies have until April 22 for semaglutide. An estimated 2 million Americans have been using these more affordable copycats every month.

Even with direct-to-consumer discounts, monthly doses of brand-name versions cost hundreds more than compounded ones, putting them beyond the reach of many people. This means a significant number of compounded glucagon-like peptide 1 (GLP-1) users will be forced to go cold turkey — but studies consistently show weight regain when patients stop taking them abruptly. So how can you help your patients?

Forced Off GLP-1s

While published research into best practices for discontinuing the use of GLP-1s is scant, accessibility and price issues have already forced physicians and patients to devise workarounds. Not everyone was willing to rely on the compounded versions, after all. And some who succeeded on a brand name were reluctant to spend that much money every month for the rest of their lives.

As a result, anecdotal information already exists about tactics like stretching out the time between injections, tapering the dosage, and adding strength training to patients' exercise routines.

Jennifer Manne-Goehler, MD

"Anecdotally, some doctors and patients are being forced into this," said Jennifer Manne-Goehler, MD, a researcher at Harvard Medical School, Boston, and the lead author of a paper in *JAMA Internal Medicine* that looked at what we know about off-ramping these drugs.

"I get messages from people saying, 'Do you think microdosing is okay?' or, 'I had a patient who ran out, or they couldn't get more tirzepatide, so they started taking it every other week,'" she said.

So far, success seems to be dependent on the individual patient's level of motivation and their ability to commit to lifestyle changes. Regular communication with the patient goes a long way toward determining what might work.

"Subjectively, patients know when things are working for them or not," said Jeremy Korman, MD, medical director of the Cedars Sinai Marina Weight Management Center in Marina del Rey, California. "That's a way, without any concrete algorithm, that I work with my patients who've reached a target weight. We start using those subjective measures of hunger and cravings and tapering in that way, whether it's tapering on time interval or tapering on dose."

Slow Tapering May Work

Last year, researchers presented findings on a slow tapering method at the European Congress on Obesity. When participants reached their goal weight, their dosage was gradually reduced over an average of 9 weeks while they continued with coaching on diet and exercise. Data was available for 85 participants — 6 months after tapering to zero, and their weight remained stable.

"Because they've engaged in some of the lifestyle changes, when they eventually taper off, they keep the weight off without semaglutide," lead researcher Henrik Gudbergsen, MD, told *Medscape Medical News* at the time. "I think there's a strong linkage between the initial phase of using this medication with lifestyle changes and actually being capable of keeping the kilos off once they've stopped."

Given the small number of participants, more research is necessary. But those initial results are promising, Korman said.

"The European study, tapering over 9 weeks, is very interesting," Korman said. "The original studies just stopped the medication, and all the weight came back. We still have to be a little skeptical, even if we taper properly, that it's going to be as durable as we hope. It could be, but it's very early on."

Of course, the end of mass-produced compounded GLP-1s is less than 9 weeks away. But in Reddit discussions among compounded tirzepatide users, many said they have stockpiled a supply, enough to last for months. A slow taper could work for them. For those without a ready supply, a short-term prescription for a brand-name GLP-1 might do the trick.

Turn to Older Generation Weight-Loss Drugs

Another option that shows potential is simply migrating from a GLP-1 to an older generation, generic version of an anti-obesity medication. A study in the December issue of *Obesity* followed patients on this protocol. Out of an initial group of 105 participants, 40 used a GLP-1 medication for 12 months to reach a body mass index of less than 30, then transitioned to generic phentermine, phentermine/topiramate, topiramate, metformin, bupropion, and/or naltrexone. They maintained their initial weight loss for up to 2 years when the study ended.

Gitanjali Srivastava, MD

Gitanjali Srivastava, MD, medical director at Vanderbilt Obesity Medicine in Nashville, Tennessee, co-authored the study. She compared this approach to cancer treatment: If a patient comes in with an aggressive tumor, the oncologist might use expensive therapies to decrease the size of the tumor burden. Once that's achieved, the oncologist can move the patient to less intense, less costly therapies.

"In the same way, when we think about obesity as a disease process, patients with severe obesity have a very high disease burden," she said. "With GLP-1 medications, you're shrinking the size of that disease burden, then exposing them to the older generation armoire."

She's been using this approach in her practice for several years.

"Even though the GLP-1 drug classes have created hype, I don't think we should forget some of these older-generation medications that are less expensive, that patients still do really well on and respond very favorably to, if there are no contraindications," she said. "For instance, metformin is free at Publix. Topiramate is just a few dollars. A combination of phentermine and topiramate, which is sold under the brand name Qsymia, you can get for less than $20 a month."

Discoveries Still to Come

With so many patients being forced off compounded GLP-1s at once, we're likely to learn a lot about what helps — and what does not — to maintain a substantial weight loss. One thing will almost certainly be a crucial factor: Guiding patients toward a healthier lifestyle in general.

“Regardless of what treatment we give a patient, even with surgery, our weight loss outcomes and the durability of them depend on lifestyle modification,” Korman said. “That has to be the foundational concept. If we’re just going to rely on the meds, and we’re not going to commit to that, nothing is going to work.”

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