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Side Effects of GLP-1 Drugs: What Doctors Should Know

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Just a few years after some TikTok videos spiked the demand, one in eight US adults has tried Ozempic (semaglutide) or another drug in its class. Glucagon-like peptide 1 (GLP-1) receptor agonist medications have revolutionized obesity medicine.

But they're not without problems. In the early days of the social media craze, news reports often featured patients whose gastrointestinal side effects sent them to the emergency room (ER).

"It happened a lot then. Patients didn't want to complain because they were losing weight, and they wound up in the ER with extreme constipation or a small bowel obstruction," said Caroline Apovian, MD, co-director of the Center for Weight Management and Wellness at Brigham and Women's Hospital and professor of medicine at Harvard Medical School, Boston.

Caroline Apovian, MD

"But that's not really happening now," she added.

Research backs up her assertion: A recent clinical review of studies found that many patients still experience side effects, but only at a mild to moderate level, while the dosage increases — and the unpleasantness tapers with time. Roughly 7% of patients discontinue the medications due to these symptoms.

- Case: Exertional Dyspnea, Fatigue, & Peripheral Edema

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Here's what the latest research shows about GLP-1s' side effects.

Most Common: Gastrointestinal Issues

Depending on the symptom and the specific drug, anywhere from one third to one half of patients will experience some kind of stomach trouble.

- In that clinical review, which looked at studies of three GLP-1 medications — semaglutide (Ozempic, Wegovy, Rybelsus), liraglutide (Saxenda, Victoza), and tirzepatide (Mounjaro, Zepbound) — semaglutide users fared comparatively worse.
- Nausea was reported most frequently — 44.2% of semaglutide users dealt with it, compared with 40.2% for liraglutide and 31% for tirzepatide. Diarrhea, constipation, and vomiting also struck one quarter to one third of semaglutide patients, and slightly fewer for the other two medications.

Apovian finds that careful dosage helps her patients avoid the worst effects.

"We don't know who's going to do well and who's not," she said. "We start slowly, and usually things go OK."

If a patient does react poorly, she'll hold off on increasing the dosage until they acclimate and advise using over-the-counter meds like MiraLAX to address the symptoms.

Few documented severe adverse gastro events appeared in the data, affecting less than 1% of liraglutide and tirzepatide patients and 2.6% of semaglutide users. The majority of these events were gallbladder-related.

Questions About Causation: Depression and Suicidality

About a year ago, a study used 18 years' worth of data from the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) to examine how often patients reported suicidal ideation and/or depression while using GLP-1 medications. Compared with metformin and insulin, researchers found disproportionate reporting by patients using semaglutide and liraglutide. Other GLP-1 medications didn't show this effect. The researchers pointed out: These statistics don't show causation — there's no clear reason why those two medications were linked to more reports.

Further research has been more reassuring:

- Another study also used FAERS but looked only at data from 2018 to 2022, when usage of these drugs was ramping up, and found no link between suicidal or self-injurious behaviors and GLP-1.
- A recent cohort study, which looked at data from nearly 300,000 people, found that GLP-1 users aren't at increased risk for death by suicide.
- Both the FDA and the European Medicines Agency have issued statements that the evidence doesn't support a causal association.

There are several factors at play here. People with obesity and diabetes are more likely to have depression to begin with. And more importantly, even if there is a link, causality remains unclear. For instance, patients who lose weight via bariatric surgery are at increased risk for depression, substance abuse, and self-harm. These symptoms may be related to the weight loss itself, not the medications.

"Some people use food as something other than nutrition. They use food to soothe other psychological issues," Apovian said. "When that's taken away, the psychological issues are still there."

In her practice, she's seen the risk for mental health issues rise with more substantial weight loss — 50-100 lb.

This lack of clarity regarding causation means it's important to perform a detailed patient history before prescribing, so you can monitor more closely with preexisting psychiatric disorders.

Possible Link: Ocular Symptoms

Here, too, the research isn't definitive but leans toward no clear association. Several studies have looked for a link between GLP-1 and vision-related issues:

- One examined FAERS data and network pharmacology and found semaglutide and lixisenatide were significantly associated with adverse events like blurred vision, visual impairment, and diabetic retinopathy.
- This summer, a cohort study of almost 17,000 people with diabetes or overweight/obesity suggested a link between semaglutide and nonarteritic anterior ischemic optic neuropathy

(NAION), a common cause of blindness due to optic nerve damage. The study found "a substantially increased risk of NAION among individuals prescribed semaglutide relative to those prescribed other medications to treat type 2 diabetes and obesity or overweight."

- But this month, another cohort study with 135,000 participants looked at NAION in people with type 2 diabetes, obesity, or both. It compared results with common non-GLP-1 medications and found just the opposite: No increased risk for NAION.

One drawback with all these studies is that they're based on large databases rather than randomized controlled trials (RCTs). When researchers focused on RCTs in a 2023 meta-analysis, they found a significant association with only one form of GLP-1, albiglutide — which was withdrawn from the market in 2017. The other six FDA-approved drugs didn't show a statistically significant link.

Possible Trouble: Pulmonary Aspiration Under Sedation

Earlier this month, the FDA updated labeling for semaglutide, liraglutide, and tirzepatide to include a warning about the risk for aspiration during surgery. While there are no published studies, several case reports have appeared.

GLP-1 medications delay gastric emptying, so even though a patient may have fasted before surgery as usual, some food or liquid may remain. In response to this possibility, a group of professional medical societies issued guidelines for using these medications during the perioperative period. They include:

- Consideration of dosage, symptoms, and other medical conditions: The risk is higher during the escalation phase, and in general, higher doses mean higher risk.
- Potential discontinuation of GLP-1 usage when assessment shows an elevated risk.
- Assessment on the day of the procedure for possible delayed gastric emptying.
- Preoperative dietary modifications, which might include switching to a liquid diet.

Rare: Serious Effects

And then there are the outliers, the frightening issues that make headlines. On their own, none of these are common enough to affect consideration of GLP-1 use:

- Studies in rats suggested an increased risk for thyroid cancer, but subsequent research has found no evidence.

- Colonic ischemia in association with tirzepatide.
- Acute pancreatitis leading to death leading to death in association with semaglutide.
- Speaking of pancreatitis, that clinical review of studies did find that both liraglutide and semaglutide led to an elevated risk for pancreatitis, bowel obstruction, and gastroparesis. But the numbers were so small as to be insignificant — for instance, just 0.2% of patients experienced pancreatitis.

Benefits Outweigh Risks

When you lay out these side effects against the countless known benefits of weight loss and blood sugar management — the lower risk for high blood pressure, heart disease, stroke, metabolic syndrome, fatty liver disease, several cancers, and more — the advantages of GLP-1 drugs seem clear. Ultimately, of course, it's the patient's decision whether to begin and continue taking any medication for a chronic disease.

Apovian recommends having in-depth conversations before you write that first prescription — she compares the situation to using an antihypertensive drug. If your patient understands potential side effects, they're more likely to maintain long-term compliance.

"We educate our patients how to use these drugs, indefinitely, if you want to maintain a lower, healthier body weight," she said. "I don't see patients who stop using them, but they're out there. These are people desperate to lose weight, who aren't given the education to understand we're treating a disease. It's not a matter of willpower."

And once a patient starts taking a GLP-1, monitor them closely, with in-person visits rather than telehealth, while increasing the dosage. If they experience side effects, stay at that level until they ease. And if the patient has a good weight-loss response at a lower dose, stay there. Just because you *can* go higher, it doesn't mean you should.