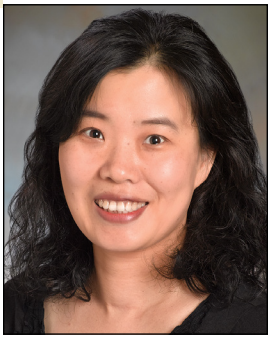
Yan


Wray

Safety Considerations When Prescribing GLP-1 RAs

Meijuan Yan, MD
Diabetes and Endocrinology Specialist
Penn Medicine Lancaster General Health

Virginia Wray, DO
Bariatric Physician Specialist
Penn Medicine Lancaster General Health

Stories about celebrities using glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for weight loss have put them in the spotlight but have not emphasized the need for in-depth conversation about anti-obesity and antidiabetic medication in high-risk individuals.

The U.S. Food and Drug Administration (FDA) approved semaglutide in 2017 as Ozempic® to treat type 2 diabetes and then as Wegovy® in 2021 to treat obesity. This GLP-1 receptor agonist works in the gut, brain, and pancreas to exert its metabolic effects. Tirzepatide, which is a dual GLP-1 receptor agonist/glucose-dependent insulinotropic polypeptide (GIP), was FDA approved as Mounjaro® for diabetes in 2022 and Zepbound® for obesity in 2023. Both medications have gained popularity.

A survey from May 2024 suggested that as many as one in eight U.S. adults have tried a GLP-1 receptor agonist or GLP-1 RA/GIP, and more than 15 million people are currently using these medications.[1]

This class of medications is effective in reducing body weight, as well as lowering blood sugar levels and benefitting the cardiovascular system.[2] However, clinicians need to discuss related risks with patients when prescribing.

Discussed in this article are safety concerns related to these medications. For simplicity, these medications are jointly referred to here as GLP-1 receptor agonists.

DRUG SIDE EFFECTS

The most common side effects of GLP-1 receptor agonist use are gastrointestinal symptoms, such as nausea, vomiting, heart burn, diarrhea, constipation, and stomach pain associated with bloating from gas. Starting with the lowest dose and titrating slowly can mitigate these risks.

Fatigue, dizziness, depression, hypoglycemia, and gall bladder disease have also been reported, and the risk of developing pancreatitis is increased. In addition, prescribing GLP-1 receptor agonists warrants telling patients that medullary thyroid tumor risk is increased based on results of rodent studies.

NUTRITIONAL CONCERNS

GLP-1 receptor agonists reduce appetite, which helps with weight loss. The following should be emphasized.

- *Adequate hydration.* Encourage pure water intake (at least 64 ounces per day). Patients often reduce both food and water intake when using these medications, and thus dehydration may result. Acute kidney injury from dehydration has been reported. Good water intake also helps prevent constipation. Monitoring kidney function is also recommended.
- *Adequate protein intake.* The goal is to lose body fat but preserve muscle. In general, when an individual loses one pound of body weight, about 25% is due to muscle loss. To help retain muscle mass, adequate protein intake is essential, thus 1.0-1.2 g/kg protein per day using adjusted body weight, which is ideal body weight plus 25% of remaining weight; for chronic kidney disease with glomerular filtration rate less than 30, a protein intake of 0.8g/kg per day is recommended, best divided into multiple servings throughout the day.
- *Regular exercise.* It is appropriate to recommend resistance exercise be performed at least 20 minutes twice weekly and cardiovascular exercise be performed at least 150 minutes per week.
- *Balanced diet including a variety of foods.* Eating less should not mean eating fewer kinds of food. Human beings are omnivores who need variety. A rule-of-thumb is that half of intake should be vegetables and fruit, which will also provide needed fiber.
- *Screening for mineral and vitamin deficiencies.* Patients with inadequate nutritional intake run the risk of anemia and vitamin D or B_{12} deficiencies, based on clinical scenarios.

DOSING OF OTHER MEDICATIONS

GLP-1 receptor agonists can help patients lose 10% to 20% of body weight, and this may decrease patients' other prescription drug dosage requirements. It is not uncommon to find that blood pressure and diabetes parameters improve with weight loss, which can increase the risk for postural hypotension and hypoglycemia. Therefore, antihypertension and diabetic regimens may need to be reduced.

Psychiatry medications, such as Adderall®, may cause over-stimulation if the dose is not reduced after weight loss, and thyroid hormone requirements may need to be re-assessed due to possible change in absorption. Therefore, patients need continued holistic clinical evaluations when using GLP-1 receptor agonists.

SPECIAL CONSIDERATIONS FOR GERIATRIC PATIENTS

Geriatric patients can be more prone to developing drug side effects and at greater risk for developing more severe effects, including dehydration and malnutrition with GLP-1 receptor agonists.[3] This warrants individual assessment to balance medication benefits and risks.

COMPOUND DRUG SAFETY

GLP-1 receptor agonists are expensive medications. Some insurances do not cover anti-obesity medications at all. Pharmaceutical companies have begun to offer their FDA-approved GLP-1 receptor agonist products directly to consumers at considerable savings, about half the cost of obtaining them at the local pharmacy. This service is available to consumers on certified pharmaceutical websites.

While GLP-1 receptor agonists are only available by prescription, pharmaceutical companies will facilitate online prescriber availability. The cost is around $500 per month, which is comparable to prices on GoodRx®. Therefore, many consumers choose online non-FDA-approved compounded versions for about half the price of the consumer-direct FDA-approved medicines.

The FDA recently eliminated the shortage allowance for compounded GLP-1 receptor agonists, but compounding pharmacies now make their own brands of GLP-1 receptor agonists by adjusting dosage or adding cyanocobalamin (vitamin B_{12}). However, there must be a valid prescription from a licensed medical provider and a pharmacy with a pharmacist who are both FDA registered and credentialed to compound. Patients must be advised to steer clear of using products that come from an unidentified licensed prescriber who may not have access to their medical records, and also not to buy if they cannot identify the FDA-registered compounding pharmacy where the product is produced.

It is very important to reconcile the medication list each time patients encounter the medical establishment and ask about additional medications and supplements that may have been obtained elsewhere.

Counterfeit semaglutide has been reported in the United States. The FDA issued this statement:

> [We] recognize the substantial consumer interest in using compounded semaglutide products for weight loss. However, compounded drugs pose a higher risk to patients than FDA-approved drugs because compounded drugs do not undergo FDA premarket review for safety, effectiveness, or quality. Therefore, compounded drugs should only be used to meet a patient's needs if the patient's medical needs cannot be met by an available FDA-approved drug.[4]

Jasmine Gonzalvo, PharmD, a clinical professor in the College of Pharmacy and director of the Center for Health, Equity and Innovation at Purdue University, noted:

> [R]isks can likely be minimized if patients get their prescriptions filled at state-licensed compounding pharmacies that are able to obtain the base form of semaglutide from FDA-registered facilities, ensure sterility during the compounding process, and avoid the addition of other ingredients with unknown potential for interactions.[5]

UNWANTED CHANGES IN APPEARANCE

Weight loss can result in sagging facial skin ("Ozempic face") and body skin, along with a more aged look after significant weight loss. While this may not always be prevented, focusing not on rapid weight loss but rather on adequate nutritional goals, especially proteins, plant-based antioxidants, and good hydration, is important.

Generally, one pound per week is a reasonable rate of weight loss. Sometimes, weight loss can be more rapid at first but decelerates over time. Clinicians should ensure patients have reasonable expectations about physical appearance.

DISSATISFACTION WITH RESULTS

Every patient who is treated with GLP-1 receptor agonists responds uniquely, yet they need to understand that 10% to 20% weight loss from these medications may occur over the course of treatment. A 300-pound person who settles out at 240-270 pounds may be happier with the results if they have been counselled regarding these expectations ahead of time. Some do respond more, while others respond less.

It is worth reminding patients that health benefits may begin with merely 5% to 10% weight loss. Focusing on health goals rather than scale goals may help patients understand expectations.

RISK OF OPTIC NERVE STROKE AND BLINDNESS

According to a new study by Mass General Brigham researchers, patients taking semaglutide face a greater risk of optic nerve stroke, which can cause blindness.[6] Further evidence review is warranted. There are also some post-marketing concerns about retinopathy, especially with diabetes, so patients should continue to get their annual eye exams.[7]

WEIGHT REGAIN WITH ABRUPT CESSATION

Obesity is a chronic relapsing disease, so regaining weight is common regardless of the means by which excess weight is lost. GLP-1 receptor agonists are meant for long-term use. Data confirms significant weight regain after these medications are stopped. STEP extension trials are currently underway, and the published STEP 1 trial extension concluded:

> [O]ne year after withdrawal of once weekly subcutaneous semaglutide 2.4 mg and lifestyle intervention, participants regained two-thirds of the prior weight loss, with similar changes in cardiometabolic variables. Findings confirm the chronicity of obesity and suggest ongoing treatment is required to maintain improvement in weight and health.[8]

It is very important to explain to patients prior to starting a GLP-1 receptor agonist that this is a long-term investment, possibly lifelong, so that they understand the need for ongoing surveillance, and the long-term financial investment as well.

CONCLUSION

In summary, GLP-1 receptor agonists are very effective in treating diabetes and obesity, but use of these medications comes with potential risks. Upfront discussions and ongoing communication will help patients remain clear about the opportunities this class of medications may offer.

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Meijuan Yan, MD
Penn Medicine Lancaster General Health
51 Peters Rd., Ste. 204
Lititz, PA 17543
717-544-3059
Meijuan.Yan@pennmedicine.upenn.edu

Virginia Wray, DO
Healthy Weight Management
Penn Medicine Lancaster General Health
2150 Harrisburg Pike, Ste. 300, Lancaster, PA 17601
717-544-2935
Virginia.Wray@pennmedicine.upenn.edu