



Side Effects of GLP-1s: Weighing the Risks and Rewards

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Obesity trends in the U.S.



In 2023, approximately 47% of U.S. men and 55% of women stated they wanted to lose weight.¹



The Centers for Disease Control and Prevention estimates that over 41% of Americans are obese.²



As of 2022, the five states most affected by obesity are West Virginia, Oklahoma, Louisiana, Mississippi and Tennessee.³

Recently, if you have a conversation with anyone regarding weight loss, chances are you'll hear, "I've been thinking about going on Ozempic," or "It's all Ozempic!" While more Americans are openly taking GLP-1 receptor agonists such as Ozempic, Trulicity and Victoza, commonly referred to as GLP-1s, most don't realize that weight loss is a side effect of using these drugs, not the primary intent. When the first GLP-1, Byetta, was in the early stages of drug development, the intention was to manage Type 2 diabetes.

GLP-1s are effective in managing Type 2 diabetes and have become first-line treatment options in select patient populations. However, this is often overshadowed by the drugs' use in weight loss. With more than half of the U.S. population trying to lose weight and endorsements from A-list celebrities, it's no surprise that GLP-1s, which can reduce weight by up to 20%, have become a hot topic. As the use of GLP-1s continues to grow, many are questioning how safe these drugs are long-term.



How GLP-1s work

GLP-1 receptor agonists stimulate the naturally occurring GLP-1 hormone produced in the small intestine. Stimulation of this hormone helps our body increase insulin secretion, decrease glucose production, slow stomach emptying and increase satiety, the feeling of fullness. This is why GLP-1s are so effective in treating diabetes. These drugs have shown significant reductions in A1c levels, a measure of blood sugar control, and have the potential to delay or bypass the need for insulin injections in people with Type 2 diabetes.

GLP-1s induce weight loss in many ways. GLP-1s slow the release of stomach contents into the intestines and affect certain areas of the brain that control hunger and satiety. Similarly to GLP-1 receptor agonists, there are also GLP-1/GIP receptor agonists. Currently, there is only one drug on the market in this class, tirzepatide. While oftentimes grouped in with other GLP-1s, tirzepatide has an added mechanism of action, GIP stimulation, that gives this drug added efficacy in both diabetes and weight loss.

GLP-1 products on the market

Outlined in **TABLE 1**, there are four GLP-1 receptor agonists and one GLP-1/GIP receptor agonist currently on the market. Three of these drugs have two brand names, one with the FDA-approved indication for the treatment of diabetes and one for weight loss.



TABLE 1

GLP-1 & GLP-1/GIP agents currently on the market

Drug Name	Class	Brand Name for Diabetes	Brand Name for Weight Loss
Semaglutide	GLP-1 receptor agonist	Ozempic, Rybelsus	Wegovy
Dulaglutide	GLP-1 receptor agonist	Trulicity	
Liraglutide	GLP-1 receptor agonist	Victoza	Saxenda
Exenatide	GLP-1 receptor agonist	Byetta, Bydureon BCise	
Tirzepatide	GLP-1/GIP receptor agonist (dual action)	Mounjaro	Zepbound



Short-term side effects

GLP-1 side effects are closely related to how they work, with the most common complaints relating to the gastrointestinal (GI) tract. Up to 50% of patients experience nausea and vomiting when starting a GLP-1. This can be attributed to the stomach not emptying as frequently and may be mitigated by eating smaller meals. Other common complaints relating to the GI tract are diarrhea and constipation. These side effects may subside as treatment is continued or when the dosage is decreased.

An additional side effect seen in new users of GLP-1s is a skin reaction at the injection site. All GLP-1s, except Rybelsus, are injected with a short and thin needle into the fatty tissue under the skin, above the muscle. This can result in a small, red raised area around the injection site. This will usually dissipate within a few hours to a day after the injection and is harmless. Some patients report itchiness where the drug was injected, which can be treated with over-the-counter anti-itch cream. These skin reactions tend to wane as the body becomes accustomed to the injections.

The viral social media term “Ozempic face” is also commonly associated with the use of GLP-1s. However, this is not specific to Ozempic or GLP-1 drugs at all. This can happen to anyone rapidly losing weight. “Ozempic face” is characterized by changes in the lips, cheeks and chin, but is notoriously known for wrinkles, sunken eyes and sagging skin around the jaw and neck. The fast pace of weight loss with GLP-1s tends to make these facial features more obvious than if weight was lost at a slower rate.

Long-term side effects

As for the long-term side effects, there have yet to be any confirmed since the drugs are so new to the market. Most clinical trials for these drugs are less than four years in duration, not a sufficient duration for establishing long-term risks. While there have been case reports citing more serious adverse events, there is not enough evidence to know if this is a causal relationship. These case reports have contained adverse events such as pancreatitis, gallstones and acute kidney injury but GLP-1s cannot be confirmed as the cause.

More recently, an analysis published by the Journal of American Medical Association (JAMA) investigated adverse events in patients taking semaglutide that can be reasonably presumed to be the result of using GLP-1s. Using the World Health Organization’s (WHO) database of adverse events, it was found that a significant disproportionate number of patients with pre-existing anxiety and depressive disorders had a greater risk of developing semaglutide-associated suicidal ideation. This disproportional analysis cannot confirm that semaglutide causes ideation, however, it has launched an investigation by the FDA to clarify the results. As GLP-1s persist on the market, and more people have access to them, we will likely see more preliminary analyses like this one. While these preliminary analyses are extremely useful to further robust studies, they should not be taken as definitive causation at face value.

Final notes

Although weight loss was originally found to be a side effect of GLP-1 receptor agonists when used in diabetes management, manufacturers have now leveraged this coincidence to market these drugs for weight loss as well. Many of the side effects associated with GLP-1 drugs are not serious, although it has not been determined if more dangerous adverse events are associated with long-term use. If you have any concerns about using GLP-1 drugs, please talk with your doctor for more information. If you are experiencing severe vomiting and diarrhea, severe pain or tenderness in your abdomen, inability to produce a bowel movement or yellowing of the skin with GLP-1 use, please seek immediate medical attention.

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REFERENCES

1. https://www.uptodate-com.ezproxy.library.wisc.edu/contents/obesity-in-adults-drug-therapy?search=glp%201%20agonist&source=search_result&selectedTitle=5%7E127&usage_type=default&display_rank=4
2. <https://www.health.harvard.edu/staying-healthy/glp-1-diabetes-and-weight-loss-drug-side-effects-ozempic-face-and-more>
3. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2822453?utm_campaign=articlePDF&utm_medium=articlePDFlink&utm_source=articlePDF&utm_content=jamanetworkopen.2024.23335