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Updates in Weight Management Pharmacotherapy: Essential Knowledge For The Urgent Care Clinician

Urgent Message: As more glucagon-like peptide-1 and gastric inhibitory polypeptide agonists are prescribed, it is important for clinicians to have a familiarity with adverse reactions and complications that may present in urgent care.

Sergio Ramoa, MD, MS; Darya Zakirov, MS, APRN, FNP-C; Pascale Carbonara, MD; Deann Isherwood, MSN, FNP; Tu-Mai Tran, MD, MSc

Citation: Ramoa S, Zakirov D, Carbonara P, Isherwood D, Tran TM. Updates in Weight Management Pharmacotherapy: Essential Knowledge For The Urgent Care Clinician. *J Urgent Care Med.* 2024; 18(6): 17-21

Keywords: obesity, weight management, GLP-1 agonist

Introduction

Obesity is a chronic disease with rising prevalence both in the United States (US) and worldwide. The prevalence of US obesity was more than 40% in 2017[1] and is expected to rise to nearly 49% by 2030 with almost 1 in 4 Americans with severe obesity.[2] Severe obesity, also called class 3 obesity, is a body mass index (BMI) equal to or greater than 40 kg/m^2. Patients with obesity have 46% higher inpatient costs, 80% higher prescription spending, and have a higher frequency of physician visits.[3]

Lifestyle interventions for the treatment of obesity (ie, dietary modification and regular exercise) have been shown to reduce the risk of cancer in almost every organ system, decrease or resolve insulin resistance, decrease mass effect on joints and muscles, reduce cardiovascular risk, and improve sleep apnea. However, lifestyle modifications alone—while more effective than no intervention—only result in modest weight loss, which is often difficult to sustain and speaks to the chronic disease nature of obesity.[4] Over the last decade,

Author affiliations: Sergio Ramoa, MD, Atrius Health. Darya Zakirov MS, APRN, FNP-C, Atrius Health. **Pascale Carbonara, MD,** Atrius Health. **Deann Isherwood MSN, FNP,** Atrius Health. **Tu-Mai Tran, MD, MSc,** Atrius Health. The authors have no relevant financial relationships with any ineligible companies.

pharmacologic interventions have become increasingly utilized to treat obesity.[5] With the growing popularity of such interventions, side effects and adverse reactions have also been reported with increasing frequency.[6,7]

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There are currently 3 medication formulations outside of the glucagon-like peptide-1 (GLP-1) class of agents that are approved by the Food and Drug Administration (FDA) to treat obesity. Examples of such medications include combinations of phentermine and topiramate, naltrexone and bupropion, and orlistat.[8] Phentermine was FDA approved for "short term" use (ie, <12 weeks duration) but now is more frequently prescribed for longer durations of therapy in combination with topiramate. Phentermine is a controlled substance, which can complicate prescribing and monitoring. However, in combination, phentermine-topiramate has shown similar efficacy to the GLP-1 agonists in weight reduction. Phentermine-topiramate combination, however, did seem to have higher rates of side effects and less sustained weight loss when compared to the GLP-1 agonists in a 2022 systematic review.[9] Orlistat, the only FDA-approved over-the-counter weight loss medication, inhibits lipases for fat excretion and is commonly associated with significant gastrointestinal (GI) upset. This is a barrier to long-term therapy with orlistat as <2% of patients can tolerate remaining on therapy for >2 years.[10] More recent reviews and meta-analyses of all these medications have demonstrated that the GLP-1 agents are superior to these agents, with tirzepatide showing the greatest weight reduction overall.[8]

For refractory cases, surgical options exist. Surgery, while effective for many, is limited by surgical candidacy. Bariatric surgery is an overall safe procedure associated with a risk of death of about 0.08%[11] and a risk of major complications of about 4%.[12] This is comparable to cholecystectomy, hysterectomy, and hip replacement. There are a number of bariatric procedures available to assist in weight loss with varying risks, benefits, and durability of weight loss. Roux-en-Y Gastric Bypass, for example, yielded an average of 21% weight loss from the baseline weight of participants.[13] Therefore, surgical options remain viable and attractive for many patients. However, due to barriers around patient engagement needed for a surgical intervention, financial considerations, availability of surgeons, and need for nutrition and mental health screening involved in bariatric surgery, clinicians have been turning increasingly to GLP-1 agents with over 9 million prescriptions in the United States in 2023.[14] With such high demand, many GLP-1 agents have been on the FDA shortage list, and many compounding pharmacies have begun producing formulations of these medications in an attempt to fill this supply-demand gap.[15] Given their rising popularity for the extremely common and risky situation of excessive fat mass, the remainder of this review will focus on the most commonly encountered formulations of GLP-1 and related agents.

GLP-1 Agonists and Glucose-Dependent Insulinotropic Polypeptide Medications

Although developed for the treatment of type 2 diabetes (T2DM), in recent years, there has been a surge in demand and prescribing of the GLP-1 agonist class of medications for weight loss. Currently, the demand for GLP-1 agonists has been greatest for the following agents:

1. Liraglutide (Saxenda) daily subcutaneuous injection
2. Semaglutide (Wegovy, Ozempic) weekly subcutaneous injection; orally formulated as daily Rybelsus
3. Tirzepatide (Mounjaro, Zepbound) weekly subcutaneous injection; also active at gastric inhibitory polypeptide receptors

Additional medications in this class include exentatide and dulaglutide. Albiglutide was discontinued in 2017.

Liraglutide and semaglutide have been FDA approved for weight loss and T2DM for a number of years and exclusively exert activity as GLP-1 agonists. Tirzepatide, a dual-acting GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, initially approved only for T2DM, was also FDA approved for weight loss in November 2023.[16]

Table 1. Frequency Of Side Effects, Percentage[21,22,23,28,29]

	Tirzepatide	Semaglutide	Liraglutide
Nausea	13-24	44	40
Diarrhea	12-23	32	21
Constipation	6-8	23	20
Vomiting	6-14	25	11
Headache	4-11	15	13
Dizziness	N/A	N/A	7

Mechanism of Action

Drugs active at GLP-1 and GIP receptors are known as insulinotropic peptides and work to improve post prandial metabolism and glucose equilibrium by stimulating insulin from the beta cells in the pancreas. These hormones also assist in increasing satiety by slowing gastric emptying and decrease drive for overeating.[17]

Side Effects

As would be expected based on the mechanism of action, the GLP-1 agents tend to have predominantly GI side effects including nausea, vomiting, diarrhea, constipation, and bloating, however, generally less than 10% of patients are unable to tolerate these medications due to GI side effects.[18] There have been conflicting reports regarding any increased risk of pancreatitis and gallstone disease related to the GLP-1 agents.[19] Despite their effects on insulin secretion, episodes of hypoglycemia attributable to the GLP-1 agonists are rare, even in cases of overdose.[20]

Liraglutide

Side effects in liraglutide included mild to moderate gastrointestinal disorders such as nausea and vomiting. However, more significant GI disorders have also been attributed to the medication. In one randomized controlled study, out of roughly 2,400 participants over a 56-week study period, 2.5% of liraglutide patients developed gallbladder (cholelithiasis or cholecystitis) events versus 1.0% in the placebo group. Ten patients in the liraglutide group developed pancreatitis (90% of which were mild) versus one patient in the placebo group.[21]

Semaglutide

Similarly, the most common side effects reported by patients receiving semaglutide are nausea, vomiting and diarrhea. In one placebo controlled trial, patients receiving semaglutide experienced cholelithiasis in 2.6% of the treatment group versus 1.2% in placebo group, and pancreatitis occurred in 0.2% versus 0% in the placebo group.[22]

Tirzepatide

As with the other GLP-1 agents, tirzepatide, the only GLP-1/GIP agonist also caused GI side effects most commonly including nausea, diarrhea, and constipation. In a 72-week double blind, randomized, placebo-controlled trial of more than 2,500 patients, there was no difference in hypoglycemia, cholecystitis, or pancreatitis in the tirzepatide group compared to the placebo group.[23]

Urgent Care Cases

Pain After Eating in a Patient Taking Semaglutide

A 34-year-old female with a medical history of non-alcoholic steatohepatitis, asymptomatic biliary sludge during a previous pregnancy, and class II obesity presented to the emergency department (ED) with right upper and lower quadrant abdominal pain. She was taking omeprazole for occasional dyspepsia and semaglutide for weight loss. She had been taking semaglutide for 2 months and had already lost 25 pounds. Laboratory evaluation revealed elevated hepatic enzymes, and a right upper quadrant ultrasound demonstrated cholelithiasis with a positive sonographic Murphy's sign. She subsequently underwent laparoscopic cholecystectomy with resolution of her symptoms. Her worsening gallstone disease was attributed to her use of the GLP-1 agent in addition to rapid weight loss, which can precipitate worsening formation of cholesterol stones.[24]

Severe Epigastric Pain in a Patient Taking Semaglutide

A 32-year-old female with past medical history of gastroesophageal reflux disease (GERD) presented with severe epigastric pain that radiated to the back. When not eating, pain was a 3 out of 10. With any form or type of food, the pain became more severe. She endorsed nausea and diarrhea as well. She was taking

esomeprazole 20mg daily. The patient had been also recently started on semaglutide. Her dose of esomeprazole was increased and sulfrafate was added for concern for gastritis. The patient endorsed improvement of overall pain but was still experiencing discomfort shortly after eating. Therefore, a gastric emptying study was ordered, which demonstrated moderate gastroparesis. While certain studies have shown no apparent impairment of gastric emptying associated with GLP-1 agonists,[25] there have been numerous case reports of delayed gastric emptying noted in the anesthesiology literature among fasted patients who have experienced aspiration in the setting of induction of general anesthesia.[26,27]

"Given the latency period for cancers to develop, it is likely that uncertainty will remain regarding associations between the GLP-1 agents and cancers for some years."

Patients may present to urgent care (UC) while receiving GLP-1 (and/or GIP) agonist therapy related to GI side effects. It is important to for UC clinicians to be aware of the frequency of these side effects to guide further work-up. Most patients, however, may be treated symptomatically. In patients who are not severely dehydrated and tolerating fluids, they may be encouraged to follow-up with their prescriber. Table 1 demonstrates the frequency with which various adverse reactions may occur with each agent.

Concerns Over Risks of Suicidal Ideation

Monitoring of drug safety with the FDA Adverse Event Reporting System (FAERS) from 2005-2023 seems to suggest that there is a slightly increased risk of suicidal ideation among patients taking semaglutide.[30] However, in a more recent, real-world cohort study of over 200,000 patients receiving semaglutide, it was shown that the risk of suicidal ideation was actually reduced among patients taking semaglutide compared to con trols with T2DM not receiving semaglutide.[31]

GLP-1 Agents and Risk of Renal Disease

Acute kidney injury (AKI) relates to a sudden change in renal function, typically measured by glomerular filtration rate. This can occur with states of volume depletion. Initially, there were concerns of the safety of GLP-1 agents for kidney disease.[32] However, more recent studies have shown that GLP-1 agents are largely protective against chronic kidney disease when used to treat T2DM compared to other anti-diabetic agents.[33] It is speculated that AKI risk was largely associated with volume losses associated with nausea, vomiting, and diarrhea. Therefore, it is likely that renal hazards may be avoided if these GI side effects are treated symptomatically, if they occur.

GLP-1 Agents and Cancer Risk

Animal experiments and some observational human studies have shown an increased risk of certain cancers associated with GLP-1 agonists, particularly of thyroid and pancreas.[34,35] However, results of these studies have been mixed and have failed to show consistent increases in the incidence of these cancers.[36] Given the latency period for cancers to develop, it is likely that uncertainty will remain regarding associations between the GLP-1 agents and cancers for some years. Currently, semaglutide is deemed to be contraindicated in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia, type 2.[37]

Summary

Obesity is a highly prevalent and chronic disease in the developed world. Increasingly, patients and clinicians are turning to medications to mitigate long-term obesity and its consequences. The adverse events of older weight loss medications, such as phentermine, are more well established given the time the drugs have been on the market.

As newer medications, especially GLP-1 and GIP agonists, are prescribed, it is important for UC clinicians to have familiarity with common and less common adverse reactions and complications. Many patients taking these medications will experience GI side effects such as nausea, vomiting, diarrhea, and constipation. In some cases, pancreatitis and gallstone disease may be associated with, or exacerbated, by their use. Especially with newer agents used for obesity and weight management, it is important to monitor the medical literature updates as controversies continue to exist regarding their safety profiles and associations with disease with longer latency periods (eg, cancer) remain largely unknown.

Takeaway Points

- Prevalence of obesity in the US is rising, projected to reach nearly 49% in the near future. These rising rates of obesity are associated with increasing rates of diabetes and other metabolic diseases, which drive increased healthcare costs and risks of chronic morbidity.
- GLP-1 and GIP agonist therapy is increasing in popularity and may help to mitigate the obesity epidemic and consequent morbidity and mortality, however, these therapies are associated with many GI side effects. Patients may present to UC with GI symptoms, and obtaining an accurate medication history can guide further work-up and symptom management.
- Any uncertain side effects can be reported to the FDA, which actively monitors for adverse drug reactions. ■

Manuscript submitted June 25, 2023; accepted January 31, 2024.

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