Utilizing incretin mimetics for the treatment of obesity and overweight

By Jaclyn M. Piasta, RN, RNFA, MSN, WHNP-BC, NCMP

Mitigating the obesity epidemic in the United States is increasingly important as it is a major risk factor for health conditions including metabolic and cardiovascular issues, cancer, and psychological and musculoskeletal disorders. This article focuses on incretin mimetics, glucagon-like peptide 1 receptor agonists that mimic gut hormones known to have an integral role in satiety and digestion. The evidence on their efficacy and safety as well as guidelines for prescribing and managing potential side effects in the treatment of obesity and overweight are provided.

KEY WORDS: incretin mimetics, obesity, overweight, antiobesity medications

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The United States is grappling with an escalating obesity epidemic. Recent data from the Centers for Disease Control and Prevention reveal that 41.9% of US adults have obesity.[1] Obesity is characterized by the World Health Organization as abnormal or excessive fat accumulation that presents a risk to health.[2] It is a multifaceted health condition influenced by a variety of genetic, environmental, and behavioral factors.[2] It is now recognized as a chronic disease that amplifies an individual's susceptibility to a host of illnesses and significantly heightens the risk of premature mortality. The primary concern with obesity is that it serves as a major risk factor for numerous other health conditions, ranging from metabolic and cardiovascular issues to cancer to psychological and musculoskeletal disorders.[3,4] Comorbidities specific to women's health include conditions such as polycystic ovary syndrome (PCOS), menstrual cycle abnormalities, infertility, pregnancy complications, and gynecologic cancers.[5]

The perception of obesity remains steeped in prejudice and bias, with a significant portion of US healthcare providers continuing to regard obesity as a result of individual shortcomings rather than acknowledging it as a complex, multifactorial disease.[6] Yet, a shortage of endocrinologists and obesity medicine specialists makes the role of other health practitioners in the treatment of obesity vital.[7] The women's health nurse practitioner (WHNP)

stands at a unique juncture to assist women in managing their weight challenges. Multiple pharmacologic and nonpharmacologic interventions are available in the current healthcare sphere. Among these interventions are antiobesity medications. Studies indicate that only 2.5% of ideal medical candidates are currently receiving treatment with antiobesity medications.[4] This article focuses on incretin mimetics, a class of medication that mimics gut hormones known to play an integral role in satiety and digestion. A review of the evidence on efficacy and safety of incretin mimetics and guidelines for prescribing and managing potential side effects are provided.

Incretin mimetics overview

In the past 10 years, the pharmaceutical industry has introduced a handful of medications to the market to treat obesity. However, none has taken the world by storm like the incretin mimetics, glucagon-like peptide 1 (GLP-1) receptor agonists (RAs). The term incretin was introduced in 1932 to describe compounds produced by intestinal mucosa in response to nutrient ingestion with the capacity to reduce blood glucose.[8] The human incretin hormone, GLP-1, was identified in the 1980s. GLP-1 is an intestinal peptide hormone that is generated in the endocrine L cells of the intestinal lining through specialized modification of proglucagon. This hormone primarily functions to encourage the release of insulin, serving as an incretin hormone, and to inhibit secretion of glucagon, which helps regulate blood glucose levels after meals. Additionally, GLP-1 slows down the movement and secretion within the digestive system, functioning as an enterogastrone (a hormone secreted by the duodenal mucosa) and playing a role in the "ileal brake" system, the primary inhibitory feedback mechanism to control transit of a meal through the gastrointestinal tract. It also acts as a physiologic regulator of appetite and food intake.[9] It was not until 1992 that endocrinologist and researcher Dr. John Eng isolated a compound in the venom of the Gila monster, a lizard found in the US and Mexico, with similar properties to human GLP-1. This led to the development of exenatide, the first GLP-1 receptor agonist, approved by the US Food and Drug Administration in 2005.[10] Since then, several next-generation incretin medications have been introduced.

Incretin mimetics are a class of drugs initially approved to treat type 2 diabetes and more recently obesity and overweight. Functionally, they mimic and enhance the actions of natural incretin hormones in the body, leading to an increase in insulin secretion in response to meals and a decrease in glucagon release, both of which can help control blood glucose levels.[9] Currently, only two of the many FDA-approved incretin medications are approved for weight management.[11,12] These include the GLP-1 RAs liraglutide, FDA approved in 2014, and semaglutide, FDA approved for weight loss in 2021. GLP-1 RAs promote weight loss through several mechanisms including appetite reduction by acting on the hypothalamus and enhancing satiety and the feeling of fullness, delayed gastric emptying, and decreased caloric intake.[13]

The SCALE [Satiety and Clinical Adiposity – Liraglutide Evidence in individuals with and without diabetes] trial was a series of randomized, double-blind, placebo-controlled clinical trials evaluating liraglutide for weight management in individuals with obesity or overweight individuals with at least one weight-related comorbidity. Key findings showed a total of 63.2% of patients in the liraglutide group as compared to 27.1% in the placebo group achieved 5% or more of baseline weight loss, and 33.1% and 10.6%, respectively, lost more than 10% of their body weight (with a 21-lb mean weight loss) over a 56-week period. The secondary end point of waist circumference also was measured, and the findings showed reduction of 3.2 inches with liraglutide versus 1.6 inches with placebo.[14]

The STEP [Semaglutide Treatment Effect in People with obesity] trials were conducted to evaluate the efficacy and safety of semaglutide for weight management in individuals with obesity or overweight individuals with certain comorbidities. Currently, there are 15 different STEP trials that have been published or are under way. The original STEP trial, STEP 1, focused on participants with obesity without type 2 diabetes. The results showed that semaglutide treatment led to substantial weight loss over the course of 68 weeks, revealing an average 14.9% reduction in bodyweight from baseline with semaglutide 2.4 mg plus a lifestyle intervention, compared with just a 2.4% reduction in the placebo plus lifestyle intervention group. In total, 86.4% of the semaglutide group lost at least 5% of their bodyweight, and adverse effects were in line with those expected for the medication class. The results of the subsequent STEP trials have demonstrated similarly significant results.[15,16]

In addition to weight reduction, incretin mimetics demonstrate substantial cardiometabolic advantages, largely attributed to the profound weight loss induced by these medications. Research indicates that a mere 5% weight loss in individuals with obesity can reduce the risk of diabetes and cardiovascular diseases while enhancing metabolic functions in the liver, adipose tissue, and muscles.[15] The weight loss achieved through incretin medications often exceeds this benchmark, yielding significant

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benefits for the cardiovascular system including improvements in hypertension, hypercholesterolemia, insulin resistance, and fatty liver disease.[17] The most recent findings released from the SELECT study in August 2023 found a 20% reduction in risk of major cardiac events in individuals utilizing semaglutide therapy for weight loss.[18] These findings are profound, and given that heart disease is the number one cause of death among women, have substantial implications for women's healthcare.

By effectively lowering circulating glucose levels, stimulating insulin response, and inhibiting glucagon secretion, incretin mimetics play a pivotal role in curtailing the onset of atherosclerosis and related cardiovascular conditions, mitigate inflammation, and bolster endothelial function.[19] Furthermore, incretin medications have shown positive impacts on numerous women's health-related disorders, many of which are associated with cardiometabolic dysfunction. Conditions such as PCOS, gestational diabetes and hypertension, certain female-specific cancers, and fertility issues are often linked to obesity. Improved glucose regulation and insulin sensitivity often results in improved fertility, symptom amelioration of PCOS, and better long-term cardiometabolic health. Additionally, prepregnancy weight reductions for individuals with obesity has been shown to lower risk for pregnancy complications such as gestational diabetes, hypertensive disorders, preeclampsia, and large-for-gestational-age newborns. Considering that these conditions can lead to increased cardiometabolic health risks later in life, the implementation of a preventive approach involving incretin medications could be highly beneficial.[20–24]

Incretin mimetic use in the treatment of obesity

Clinically, obesity is assessed using body mass index (BMI), with a BMI of 30.0 or higher indicating obesity and a BMI over 25.0 indicating overweight.[2] Liraglutide and semaglutide are approved for use in adults with obesity or overweight with at least one weight-related condition (eg, high blood pressure, type 2 diabetes, high cholesterol) in the absence of contraindications.

Incretin medications are generally contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 due to a potential risk of thyroid C-cell tumors, although thyroid C-cell tumors have only been seen in rodent studies. They also should be avoided in patients with severe renal impairment or end-stage renal disease. Furthermore, individuals with a history of pancreatitis or gallbladder disease should exercise caution or avoid these drugs, as they may exacerbate these conditions.

More recently, there has been concern surrounding the potential of sarcopenia with rapid weight loss facilitated by GLP-1 medications. Clinicians need to be aware of the potential for sarcopenia (generalized loss of skeletal muscle) with incretin mimetic use and should provide proper counseling to mitigate this potential side effect including maintaining a balanced diet rich in protein, ensuring adequate hydration, engaging in regular physical activity, and ensuring consistent follow-up.[25]

Additionally, the potential side effect of gastroparesis has been under review. Incretin mimetics slow gastric emptying as part of their mechanism of action and should be avoided in individuals with known gastroparesis.

If symptoms of gastroparesis develop after medication initiation, discontinuation would be advised along with an appropriate workup for potential underlying causes of the occurrence outside of the incretin mimetic because the condition is more likely exacerbated rather than caused by the medication itself.[26]

Incretin medications are not recommended in pregnancy or for individuals attempting to conceive and should be discontinued 2 months prior to pregnancy. To date, there are no safety data on the use of incretin mimetics during lactation; therefore, their use in this population is not recommended. Although liraglutide and semaglutide have not been shown to impact the effectiveness of oral contraceptives, a newer medication, tirzepatide, was shown to impact the metabolite concentration of oral contraceptives by as much as 66%. Therefore, clinicians should instruct patients taking oral contraceptives also to use a barrier method for 4 weeks after first dose administration and for 4 weeks following dose escalation on tirzepatide. Counseling on non-oral methods of contraception also would be appropriate.[27] The common side effects of incretin medications include gastrointestinal disturbances like nausea, vomiting, diarrhea, reflux, and occasional constipation. Additionally, these medications may lead to reduced appetite, injection site reactions, and a potential risk of hypoglycemia, especially when combined with other diabetes drugs. Although rare, pancreatitis has been associated with GLP-1 medications, warranting immediate medical attention if symptoms like severe abdominal pain arise. Headaches and feelings of fatigue are other possible side effects, but these are typically mild and improve over time.[28,29]

While incretin drug manufacturers have published standardized dose escalation recommendations, the decision to alter a patient's dose should be individualized. Unlike clinical trials that follow strict regimens to assess dose efficacy, clinical practice affords clinicians the flexibility to escalate doses more slowly and tailor them to an individual's circumstances. Clinicians should consider the person's current BMI and body fat percentage, pre-existing comorbidities, past surgical history, and medication tolerance in their dosing decisions. Persons with gastroesophageal reflux and those with a history of bariatric surgeries are more likely to experience significant gastrointestinal side effects and clinicians should exercise caution when opting for a dose escalation.[28,29]

Increased dose titration is not recommended unless the patient is tolerating the medication without significant side effects. Conversely, if a person is losing more than 0.5 to 1 lb per week, a dose escalation should be avoided or delayed. Rapid weight loss beyond 1 lb weekly increases the risk for sarcopenia, dehydration, and malnutrition.[22] Strategies for assisting patients with medication side effects include gradual dose escalation, dietary modifications, addressing hydration needs, temporary pauses in medication administration and/or dose reduction, and when necessary, short-term use of over-the-counter or prescription pharmaceuticals for specific side effects needs (*Table*).

Table. Clinical practice pearls for prescribing incretin mimetics for weight loss[25,27,28]

Best practices	Recommendations
Use "people-first" language	Patients with obesity vs are obese
Expectations setting	Weight should be lost at a rate of 0.5–1 lb per week to avoid sarcopenia. Ensuring optimal protein intake will prevent muscle loss. A goal 0.8–1.0 g protein per pound of bodyweight can be used as a guide.
Dose escalation	Gradual, individualized, and flexible. It should be based on patient tolerance of medication and degree of response to a particular dose.
Education/explanation of side effects and reassurance	The most common side effects include nausea, vomiting, diarrhea, and constipation. They are dose dependent, usually mild to moderate in severity, transient, and mostly occur during initiation and up-titration.
Troubleshooting strategies for side-effect mitigation	Differential diagnosis of possible coexisting GI disorders Offer advice on hydration and dietary modifications. Consider OTC or Rx GI remedies for short-term use. Consider lowering dose if symptoms are persistent or changing medication.
Potential treatment options for lessening of side effects	Diet strategies: eat slowly, reduce meal size, avoid spicy or fatty foods, avoid eating when not hungry, limit alcohol consumption Reflex/vomiting/nausea: Treat GERD if present. Hydration, antiemetics, lower dose Constipation: increase fiber intake, ensure adequate hydration and consider stool softeners, lower dose Diarrhea: hydration, antidiarrheal, lower dose

GERD, gastroesophageal disease; GI, gastrointestinal; OTC, over the counter; Rx, prescription.

Challenges to prescribing incretin medications

Significant challenges do exist when it comes to prescribing incretin medications for obesity, primarily due to issues of insurance coverage and drug shortages. One of the key challenges is a lack of comprehensive insurance coverage for obesity treatment. Despite obesity recognition as a chronic disease by leading medical organizations, most insurance providers do not cover antiobesity medications. This leaves patients facing high out-of-pocket costs that act as a substantial barrier to treatment.

Furthermore, nationwide incretin supply shortages remain problematic. Manufacturing issues, increased demand, and disruptions in the supply chain have all contributed to widespread drug shortages. These challenges highlight the need for policy changes to improve access to these effective treatments for obesity. Better insurance coverage and measures to prevent drug shortages are critical steps in ensuring patients can access the care they need.[30]

More options on the horizon

The future appears bright with several more antiobesity medication options on the horizon. Phase 3 results for the PIONEER PLUS and OASIS 1 clinical trials investigating semaglutide in an oral formulation have been released in mid-2023 and exhibit noteworthy reductions in weight through its use. The study in the *Lancet* highlights these findings, and there is anticipation for FDA approval in the coming period.[31] Furthermore, the SURMOUNT-1 trial, a phase 3 study examining tirzepatide for obesity and overweight, unveiled its results in June 2022. The prospects of FDA approval for tirzepatide in the treatment of obesity and overweight are highly anticipated.[32] Additionally, ongoing progress is being made in the development of a novel antiobesity medication, retatrutide, which combines semaglutide, gastric inhibitory polypeptide, and glucagon.[33] This compound is currently in phase 3 clinical trials focusing on its potential as a treatment for obesity.

Implications for practice

It is important to remember that obesity is a chronic, progressive, and relapsing disease. Individuals with obesity require a long-term multimodal and holistic treatment plan considering psychological, physical, and nutritional needs. Obesity is commonly associated with mental health conditions such as disordered eating and depression. Mental health needs should be addressed concomitantly with medication initiation. Patients also should be counseled on the importance of maintaining regular exercise as it not only improves insulin sensitivity but also minimizes loss of muscle mass, which in turn improves long-term success. Adequate nutrition is equally vital, requiring an individualized diet plan that complements the medication and ensures macronutrient needs are met. Medication discontinuance is an excellent goal to strive for, but it is important to consider the chronicity and complexity of obesity and individualize duration of treatment and medication dosing based on individual patient needs and circumstance.

As WHNPs, we are uniquely situated to aid our patients with obesity and overweight and the associated health conditions. As it currently stands, over 40% of the patients we encounter daily could benefit from intervention. We still face many challenges in the treatment of obesity with medical insurance barriers and medication supply shortages, but the future indeed looks bright. The landscape continues to expand, and there is much innovation occurring in this space. Access to these medications is essential in mitigating the obesity epidemic in our nation. ■

Jaclyn M. Piasta is a nurse practitioner who is the owner and founder of Monarch Health, LLC, in Marietta, Georgia. The author has no actual or potential conflicts of interest in relation to the contents of this article.

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