Health Monitor®

Clinician Update

Weight Management

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MODEL OF CARE

WHY OBESITY *MUST* BE TREATED

Research suggests that treating overweight/obesity can lower the risk of major cardiovascular events (MACE). Here, experts cite robust evidence that shows targeting overweight and obesity helps save lives.

For patients with obesity, managing cardiovascular (CV) risk means treating their overweight. And the stakes for these patients have never been higher: Obesity prevalence has risen over the last 2 decades, and deaths from obesity-related cardiovascular disease (CVD) have tripled.[1] Fortunately, research, is uncovering options to help providers stem this deadly tide. Recent data suggest a direct link between treating overweight/obesity and lowering the risk of major cardiovascular events (MACE),[2] and offers powerful evidence that targeting overweight and obesity saves lives.

"The link between obesity and CV risk has always been clear, but until now, we just haven't had the evidence that treating obesity with medications would decrease CV events," says Melanie Jay, MD, MS, internist and associate professor of medicine and population health at New York University Grossman School of Medicine in New York City. Clinicians should assume that any patient who presents with overweight or obesity requires intervention for CV risk, experts say. So, as part of an evaluation, it's important to assess CV risk by doing the following:

Continued on next page ►

- ***Check statin status.*** Make sure any patient with overweight or obesity who has elevated low-density lipoprotein (LDL) cholesterol or a 7.5% risk of atherosclerotic CVD within 10 years is receiving, and adhering to, a statin or other cholesterol-lowering regimen.[3] "I tell these patients, 'You need this statin to increase your chances of reaching older age,' " says Ken Fujioka, MD, clinical professor of medicine and director of the Nutrition and Metabolic Research Center at the Scripps Clinic in San Diego, CA. But regular statin use does not mitigate the CV threat of overweight/obesity, so weight treatment still needs to be aggressive, Dr. Fujioka adds.
- ***Look at the lipids.*** Patients with normal LDL levels but low high-density lipoprotein (HDL) and high triglycerides are also at elevated CV risk. "With low HDL and high triglycerides, I have to change my thinking because this is just as deadly as high LDL, but a statin won't work," Dr. Fujioka says. "Weight loss is the best treatment we know in this case, as it will improve this dyslipidemic picture."

Comorbidities influence overweight/obesity treatment

Diabetes is all too common in patients with overweight and obesity, and dysglycemia goes hand in hand with CV risk. "Prediabetes and diabetes are a continuum," Dr. Fujioka says. "The minute your patient has prediabetes, that patient is at high risk for cardiovascular disease."

Other comorbidities that raise CV risk are also prevalent in patients with overweight or obesity.[3] These include:

- ***Metabolic dysfunction-associated fatty liver disease (MAFLD).*** CVD is the leading cause of death among patients with MAFLD, which is also common among patients with type 2 diabetes.[4] Existence of MAFLD with or without metabolic dysfunction-associated steatohepatitis warrants aggressive weight management, Dr. Jay says.
- ***Obstructive sleep apnea (OSA).*** Untreated OSA spikes the risk of CVD, heart failure and arrhythmias.[5] While data have not shown a direct link between continuous positive airway pressure (CPAP) and MACE reduction, "It's still helpful from a CV standpoint to ensure the patient's sleep apnea is diagnosed and treated," Dr. Jay says.

Dr. Jay also notes that tirzepatide, a combination glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist (GLP-1 RA), has been shown in clinical trials to also decrease OSA severity and liver fibrosis[6,7] and could be considered for patients with overweight or obesity and comorbid OSA or MAFLD.

Target both CV risk and weight loss

Medication is frequently a necessary adjunct to diet and exercise in treating overweight/obesity. Two drug classes developed for glycemic control in type 2 diabetes—GLP-1 RAs and SGLT2 inhibitors—have been shown in studies to reduce the risk of MACE in patients with type 2 diabetes in addition to helping them lose weight.[8,9] The American Association of Clinical Endocrinology (AACE) supports use of both agents for weight loss,[10] and the American Diabetes Association (ADA) recommends their use for both treating overweight and lowering CV risk.[11,12] The SELECT trial found that a GLP-1 RA was shown to reduce the risk of MACE in patients with overweight or obesity and pre-existing CVD but without type 2 diabetes.[2] (see box on p. 5).

Drs. Fujioka and Jay recommend offering a GLP-1 RA early in the treatment course. But first, the patient needs to be thoroughly educated on how a GLP-1 RA works as part of a shared decision-making process. "When starting a GLP-1 RA, you need to find out if the patient has been misinformed," Dr. Fujioka cautions. "There's so much social media on GLP-1 RAs; you hear everything from, 'This is the magic drug' to 'This is the devil's advocate.'"

> "Until now, we haven't had the evidence that treating obesity with medications would decrease cardiovascular events."
>
> —*Melanie Jay, MD, MS*

Screen before you start

Before starting any drug for overweight or obesity, first review the patient's history to see whether any current medications promote weight gain, Dr. Fujioka advises. "Unfortunately, there are times when the practitioner has no choice and has to use a medication that is associated with weight gain," he adds. "This is where the HCP needs to be empathetic and help with other options."

Experts also suggest screening the patient for the following mental health conditions:

- ***Anxiety.*** Stress can increase the risk of both CVD and obesity, Dr. Jay says.[13]
- ***Depression and mood disorders.*** Some medications used to treat them can promote weight gain.[14] Once those mental health disorders have been diagnosed by a mental health professional, monitor for weight gain and work with the patient's mental health providers to choose a more weight-neutral agent, when possible, Dr. Jay advises.
- ***Depression and suicidal ideation.*** Of note, the FDA has fielded case reports of depression and suicidal ideation among patients receiving GLP-1 RAs, but has not found a causal link.[15] Still, avoid a GLP-1 RA in patients with suicidal ideation and severe depression, and make sure the patient is stable and closely monitored by a mental health provider before starting weight management, Dr. Jay adds.
- ***Binge eating or other eating disorders.*** GLP-1 RAs have not been tested in people with eating disorders, Dr. Jay notes, so refer the patient for eating disorder therapy before attempting a GLP-1 RA.

Discuss possible side effects

Once the patient is cleared for and agrees to a GLP-1 RA, review the potential for rare side effects, such as pancreatitis, medullary thyroid cancer, gallstones and hypoglycemia. Also review the potential for nausea, vomiting and constipation due to slowed gastric emptying with these agents and stress the need to alter dietary habits to prevent these effects.

"GI effects with GLP-1 RAs are a given, especially when patients first start the medication or titrate to higher doses," Dr. Jay says. "I tell patients, 'You'll have to eat smaller meals and avoid fatty or spicy foods.' I've had patients who can't tolerate the medication because they were unable to stop eating fast food or big meals, which can make them sick on these medications." Additional considerations with GLP-1 RAs include constipation, so clinicians should urge patients to take a stool softener and report this reaction, as becoming constipated while gastric emptying is slowed can lead to potentially serious intestinal impaction or blockage.

Substantial weight loss with a GLP-1 RA may also decrease lean tissue as well as fat tissue, so Dr. Fujioka urges his patients to do resistance training to preserve muscle mass. "When somebody loses 4 pounds, usually about 1 pound will be lean tissue," Dr. Fujioka says. "Exercise can dramatically lower that ratio, and this is important, particularly for elderly patients who don't have as much

What SELECT findings mean for your practice

Originally developed as antihyperglycemics, GLP-1 RAs have been shown to reduce the risk of MACE in patients with overweight or obesity and comorbid type 2 diabetes.[8,9] Now, findings from the SELECT study suggest that GLP-1 RAs also can reduce MACE risk in patients with overweight or obesity regardless of glycemic status or comorbidities.[2]

The randomized SELECT trial enrolled 17,604 patients ages 45 and older with a body mass index of 27 kg/m2 and preexisting CV disease, but without type 2 diabetes. Participants received a GLP-1 RA (2.4 mg/week) or placebo over a mean 34-month interval. After follow-up of approximately 4 years, the composite risk of CV death, nonfatal myocardial infarction or nonfatal stroke was 20% lower in the therapy group compared with the placebo.[2] Participants were already following aggressive secondary CV prevention regimens with statins, platelet-aggregation inhibitors, ACE inhibitors, beta-blockers and/or angiotensin receptor blockers.[2]

This suggests the added CV benefit of a GLP-1 RA could be significant. "To do this study in people without diabetes and show that they did better than the placebo group is impressive," says Ken Fujioka, MD.

lean tissue as younger adults."

If a GLP-1 RA is not an option, combination phentermine/topiramate, combination naltrexone/bupropion and orlistat may be viable choices depending on patient characteristics and concurrent medications, Dr. Jay notes. Increased HDL cholesterol and reduced triglycerides concurrent with weight loss have been reported with all three agents.[10] An SGLT2 inhibitor may be another alternative, as noted earlier.

Encourage lifestyle changes with medication

Lifestyle changes are another critical step to weight loss and reducing CV risk, experts say. Counseling and behavior modification can be a long journey, but here are some starting points:

- ***Meet patients where they are.*** "Find out what patients are doing and have them come up with goals for change," says Dr. Jay, noting that this requires taking a thorough history and some probing. "Ask patients: 'What did you eat yesterday?' and 'What do you eat in a typical day?' If you find out they're having 4 sugary sodas a day, thereare some easy changes that patients can come up with themselves."
- ***Suggest simple changes,*** such as eating no later than 6 pm, if possible. "People who eat past 9 pm change hormones in their brain and gut, and this will drive their weight up," Dr. Fujioka says.
- ***Refer to an evidence-based weight-loss program,*** such as the National Diabetes Prevention Program, or commercial programs such as Weight Watchers or Jenny Craig.

—by Pete Kelly

"The minute your patient has prediabetes, that patient is at high risk for cardiovascular disease."
—Ken Fujioka, MD

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Make motivational interviewing the key to promoting lifestyle change

Motivational interviewing (MI) is a patient-centered approach that acknowledges how difficult behavioral change is and helps patients commit to new habits. Here, experts explain the four principals of MI.

Illustration by Jeannie Phan

Successful management of obesity and its related complications is complex and requires numerous behavioral changes, from reducing daily calories and making healthier choices at meals to being physically active, getting enough sleep and reducing stress.[1] In contrast to the way many diseases are treated, most of these changes—which often entail altering behaviors that have been ingrained for decades—are ultimately managed by the patient, presenting a challenge not just for them but also for their healthcare team.

Although healthcare providers are traditionally trained to interact with patients in a directive style, which can be effective in some circumstances, it's less successful when the goal is behavioral change. "We have the knowledge and we want to share it and tell them what to do," says Liz Smith, PhD, RD, LD, Assistant Professor of Nutrition who teaches the principles of effective behavioral counseling at Middle Tennessee State University in Murfreesboro. "But what we've found is that people don't respond well to that."

Indeed, research has shown that patients with obesity have a negative opinion of standard care, describing it as paternalistic and demeaning. By contrast, motivational interviewing (MI)—a patient-centered approach that acknowledges how difficult behavioral change is and aims to help patients find their motivation and commit to making changes—is seen as positive.[2] And it works: "The HCPs who implement the technique are the ones who are successful," Smith says.

The four principles of MI, as outlined in a systematic review by Concert, et al, are:[3]

1. Express empathy.

That involves listening to the patient's perspective, identifying with it and forming an alliance. In short: Be on your patient's side and show that you "get it."
Example: "I see it's difficult to plan meals when your schedule is so unpredictable."

2. Develop discrepancy.

Explore how the patient's behavior is at odds with what they are trying to achieve.
Example: "It sounds like you're concerned that managing your (blood sugar, cholesterol, weight, etc.) will be challenging if you don't get a handle on your diet."

3. Roll with resistance.

When a patient pushes back, voicing frustration and presenting obstacles to change, reframe your approach.
Example: "I understand your schedule revolves around your job, so it will remain erratic. In that case, how can you time your meals and snacks?"

4. Support self-efficacy.

Boost your patient's confidence by letting them know that you believe they have what it takes to put the change in motion.
Example: "I believe you can work through this challenge. A registered dietitian can help you come up with healthy eating strategies despite your hectic work schedule."

William Miller, who developed the theory of motivational interviewing, stresses the importance of "creating an atmosphere of acceptance and compassion" in his book, *Motivational Interviewing: Helping People Change*. The following strategies can help you engage patients and increase their odds of adopting healthy lifestyle changes.

Learn about your patient.

"In order to successfully use MI as a tool, you have to know who your patient is and understand what motivates them," says Lucille Hughes, DNP, MSN/ED, Assistant Vice President of Education and Program Design at Catholic Health in Long Island, NY. Some questions she asks: "What do you struggle with?" "What keeps you up at night?" "When you leave here today, what do you hope to have learned?" "There is so much to gain from what you hear," she says. "My patient may not struggle with sweetened beverages but instead might love cake or use honey on everything. I'm not going to know that unless I listen."

Put them in charge.

"With MI, we allow patients to have a voice. They set the agenda. This is different from what many providers are used to,"

says Smith. It's important to treat each patient as an individual, adds Hughes. "We have no preconceived notions of what the patient is willing to do. Our job is to be a coach and guide."

Determine their goals.
When Hughes provides education about lifestyle changes, she follows it up with questions: "What part of what I'm sharing is meaningful to you?" "How can I help you?" "What do you think you'd be willing to do, and how can I be a part of that?" The goal is for the patient to make the decisions about how to proceed.

> "Motivational interviewing is a collaborative way of working, as opposed to a hierarchy where we have all the knowledge."
> —*Liz Smith, PhD, RD, LD*

Flatten the hierarchy.
"MI is a collaborative way of working, as opposed to a hierarchy where we have all the knowledge," Smith says. "Patients have knowledge about themselves and their bodies and what they can accomplish." And each patient is at a different stage. "Some can't accept the diagnosis they've been given. They shut down. But if you allow them to say, 'Maybe I'm not ready to do *this* yet, but I can do *that*,' you're letting them take the lead."

Ask open-ended questions.
They yield more information than yes or no questions, Smith says. An example: If you ask, "Do you think you can give up soda?" the patient will say yes or no. But if you say instead, "Let's talk about how you might see yourself making changes in the area of sugar-sweetened beverages. What do you think you could do instead of drinking three a day?" The patient might respond, "I could drink two." "We want them to drink zero," Smith acknowledges. "But honestly, they're not going to go home and do that anyway. So start with small changes and support them with what they're willing to do."

Help them feel comfortable during the discussion.
Hughes wants appointments to feel like a conversation, like she's sitting in the patient's kitchen. Her preferred setup is to be seated at a round table with the patient. If the only option is to sit at a desk, she keeps the computer off to the side so it feels less like an office and more like she's sharing a table with the patient. She takes notes (on paper) throughout the visit and tells the patient, "I'm going to jot down some things you say so I don't forget any of this. I want to write down what's important to you."

Avoid the fear factor.
Fear can work as a motivator—but only for a limited time. "If you scare people into making changes, they most likely won't last long," Hughes says. "What we want to do is promote positive health behaviors that have an impact on the patient's life forever." So instead of saying, "If you don't do this, you're going to have a heart attack," she says, "We're going to educate you on complications associated with excess weight so you know what you're working so hard to prevent."

Create a safe zone.
Patients have their own angst and guilt about having obesity, so they don't need more of it from their healthcare provider, Hughes says. "They did not cause this, so we have to let that go," she says. "Many of them are already beating themselves up, so it's our role to provide acceptance and avoid passing judgment." She will say to her patients, "This is a safe zone. We see you as a fellow human being, and we're here to coach you and guide you. You're on the bus, and we'll give you the tools to drive the bus."

Remember this mantra.
Hughes heard this saying related to motivational interviewing many years ago and still uses it as a guide: "When you start feeling friction, ask yourself, 'Am I dancing or wrestling with my patient?' That's the key to MI," she says. "When we're working well with our patients, it feels like a dance. But when you feel like you're wrestling, that's the time to step back and put the patient back into the center." Ask the patient, "What are you willing to do, and how can I help you with that?"

Skip these words.
"*Need* and *should* are words to leave out of the conversation," says Hughes. "People don't want to be told what to do." As a study by Hood, et al, found, "Efforts at promoting behavior change by the care providers tend to be ineffective or insufficient when they are strictly educational or focus largely on 'you should' approaches."[4] Similarly, Hughes says, "We don't train our patients; we educate our patients." What she says to patients to make this distinction clear: "We've been doing this for a long time, and we're sharing what we know is helpful based on evidence."

Target minimal—and manageable—areas of improvement.
While it's important to educate patients about the behavioral changes that can improve their ability to manage their disease, it's also important to avoid bombarding them with information. "If you cover all the changes at once, you'll overwhelm them," Smith says, adding that this could cause patients to feel the tasks are insurmountable. For example, increasing physical activity may be overwhelming until patients have succeeded at establishing healthier eating habits. "Until they start to eat better and lose weight, they may not be comfortable exercising. It's not going to happen." So start with what they can achieve in the next few weeks and go from there. A review of studies in *Chronic Illness* supports this approach, finding that MI sessions are most effective when they target a minimal number of self-management behaviors.[5]

Set SMART goals.
They should be Specific, Measurable, Attainable, Relevant, and Timely. Set one during each appointment. "The patient might say, 'Long term, I want to lose 50 pounds.' But we prefer for them to set a short-term goal," Smith says. Once they achieve that, you can set another SMART goal. At times you may need to guide a patient's goal-setting so that it's truly attainable. If a patient is so motivated that they want to walk 20 minutes a day, seven days a week, Hughes might say, "Something could happen. It might rain. Why don't we say four days?" That way, if the patient walks five days, they won't internalize it as a failure. "We want to put a safety net in so patients will have continually succeeded."

Write down the patient's action plan.
At the end of each appointment, after the goals are set, write them down, keeping one copy and giving the other to the patient. "You want them to take the goal and put it on the fridge or the dashboard of the car—a reminder where they'll see it," says Smith, who adds that this helps as a reminder for clinicians, as well. "When they come to their next appointment, you can say, 'Okay, this was your goal.' It helps you be their cheerleader as opposed to not remembering who they are," she says. "They need to know we care."

Expect relapses.
"People are creatures of habit, and you are not going to change 40 years of habits in a half hour," Smith says. Likewise, most patients' behavioral changes don't follow a straight line. However, remind patients that they can learn from and grow stronger after each relapse, which provides valuable information about what does and doesn't work for them.

Reward success.
"Sometimes patients only see the things they didn't do, not the things they did do," Hughes says. They might say, for example, "I can't believe I only lost a pound. I tried so hard." However, Hughes spins that into a plus: "You lost a pound. You didn't gain it." "If you can reframe patients' thoughts, over time they will start doing it on their own," she says. "They are good at knocking themselves down. Our job is to point out the positive."

—by Andrea Barbalich

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p<0.001, one-sided *p*-value

STEP 5 Study Design: A 104-week trial of 304 adults with obesity (BMI ≥30 kg/m²) or with overweight (BMI 27 kg/m²-29.9 kg/m²) and at least one weight-related comorbid condition, such as treated or untreated dyslipidemia or hypertension, cardiovascular disease, or obstructive sleep apnea; patients with diabetes mellitus were excluded. Patients were randomized in a 1:1 ratio to either once-weekly Wegovy® 2.4 mg or placebo (with a 16-week dose escalation), both in conjunction with a reduced-calorie diet and increased physical activity. Discontinuation rate: 13% Wegovy®; 27% placebo.[2]

§Observed data include only patients who had a body weight assessment at week 104 (144 of 152 for Wegovy® arm and 128 of 152 for placebo arm) and do not include all randomized patients.
†*p*<0.0001 (unadjusted 2-sided) for superiority.
‡Supportive secondary end points were not included in the statistical testing hierarchy and, as such, not controlled for multiplicity.

SELECT Study Design: Multi-national, double-blind, placebo-controlled, event-driven superiority CVOT (N=17,604) for adults with BMI ≥27 kg/m² and established CVD (prior MI, prior stroke, or PAD), without diabetes, randomized 1:1 to receive once-weekly Wegovy® 2.4 mg or placebo. Both groups received SOC for CV risk reduction (medical management and individualized healthy lifestyle counseling, including diet and physical activity). Median duration of follow-up: 41.8 months. Discontinuation rate: 31% Wegovy®; 27% placebo. Adverse event discontinuation: 16% Wegovy®; 8% placebo.[1,3]

Primary composite end point: time from randomization to first occurrence of a 3-part composite MACE, defined as CV death, non-fatal MI, or non-fatal stroke.[3]

‖1.5% ARR at 40 months (mean duration of follow-up).

Indications and Usage

Wegovy® (semaglutide) injection 2.4 mg is indicated in combination with a reduced calorie diet and increased physical activity:

- to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight
- to reduce excess body weight and maintain weight reduction long term in adults and pediatric patients aged 12 years and older with obesity and adults with overweight in the presence of at least one weight-related comorbidity

Limitations of Use: Wegovy® contains semaglutide. Coadministration with other semaglutide-containing products or with any GLP-1 receptor agonist is not recommended

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- **Wegovy® is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Wegovy® and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Wegovy®**

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- Wegovy® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2, and in patients with a prior serious hypersensitivity reaction to semaglutide or to any of the excipients in Wegovy®. Serious hypersensitivity reactions, including anaphylaxis and angioedema have been reported with Wegovy®

Warnings and Precautions

- **Risk of Thyroid C-Cell Tumors:** Patients should be further evaluated if serum calcitonin is measured and found to be elevated or thyroid nodules are noted on physical examination or neck imaging
- **Acute Pancreatitis:** Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists, including semaglutide. Acute pancreatitis was observed in patients treated with Wegovy® in clinical trials. Observe patients carefully for signs and symptoms of acute pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, and which may or may not be accompanied by vomiting). If acute pancreatitis is suspected, discontinue Wegovy® promptly, and if acute pancreatitis is confirmed, do not restart
- **Acute Gallbladder Disease:** Treatment with Wegovy® is associated with an increased occurrence of cholelithiasis and cholecystitis. The incidence of cholelithiasis and cholecystitis was higher in Wegovy® pediatric patients aged 12 years and older than in Wegovy® adults. In clinical trials in adult patients, cholelithiasis was reported by 1.6% of Wegovy® patients and 0.7% of placebo patients. Cholecystitis was reported by 0.6% of Wegovy® patients and 0.2% of placebo patients. In a clinical trial in pediatric patients aged 12 years and older, cholelithiasis was reported by 3.8% of Wegovy® patients and 0% placebo patients. Cholecystitis was reported by 0.8% of Wegovy® pediatric patients and 0% placebo patients. Substantial or rapid weight loss can increase the risk of cholelithiasis; however, the incidence of acute gallbladder disease was greater in Wegovy® patients than in placebo patients, even after accounting for the degree of weight loss. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated
- **Hypoglycemia:** Wegovy® lowers blood glucose and can cause hypoglycemia. In a trial of adult patients with type 2 diabetes, hypoglycemia was reported in 6.2% of Wegovy® patients versus 2.5% of placebo patients. Patients with diabetes taking Wegovy® with an insulin or insulin secretagogue (e.g. sulfonylurea) may have an increased risk of hypoglycemia, including severe hypoglycemia. The use of Wegovy® in patients with type 1 diabetes or in combination with insulin has not been evaluated. Inform patients of the risk of hypoglycemia and educate them on the signs and symptoms. Monitor blood glucose in patients with diabetes
- **Acute Kidney Injury:** There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which in some cases required hemodialysis, in patients treated with semaglutide. Patients with renal impairment may be at a greater risk of acute kidney injury, but some events have been reported in patients without known underlying renal disease. A majority of the events occurred in patients who experienced nausea, vomiting, or diarrhea, leading to volume depletion. Monitor renal function when initiating or escalating doses of Wegovy® in patients reporting severe adverse gastrointestinal reactions and in patients with renal impairment reporting any adverse reactions that could lead to volume depletion
- **Hypersensitivity Reactions:** Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with Wegovy®. If hypersensitivity reactions occur, discontinue use of Wegovy®, treat promptly per standard of care, and monitor until signs and symptoms resolve. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist
- **Diabetic Retinopathy Complications in Patients with Type 2 Diabetes:** In a trial of adult patients with type 2 diabetes, diabetic retinopathy was reported by 4.0% of Wegovy® patients and 2.7% of placebo patients. Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy
- **Heart Rate Increase:** Mean increases in resting heart rate of 1 to 4 beats per minute (bpm) were observed in Wegovy® adult patients compared to placebo in clinical trials. More Wegovy® adult patients compared with placebo had maximum changes from baseline of 10 to 19 bpm (41% versus 34%) and 20 bpm or more (26% versus 16%). In a clinical trial in pediatric patients aged 12 years and older with normal baseline heart rate, more patients treated with Wegovy® compared to placebo had maximum changes in heart rate of 20 bpm or more (54% versus 39%). Monitor heart rate at regular intervals and instruct patients to report palpitations or feelings of a racing heartbeat while at rest. If patients experience a sustained increase in resting heart rate, discontinue Wegovy®
- **Suicidal Behavior and Ideation:** Suicidal behavior and ideation have been reported in clinical trials with other weight management products. Monitor patients for depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue Wegovy® in patients who experience suicidal thoughts or behaviors and avoid in patients with a history of suicidal attempts or active suicidal ideation

Adverse Reactions

- Most common adverse reactions (incidence ≥5%) are: nausea, diarrhea, vomiting, constipation, abdominal pain, headache, fatigue, dyspepsia, dizziness, abdominal distention, eructation, hypoglycemia in patients with type 2 diabetes, flatulence, gastroenteritis, gastroesophageal reflux disease, and nasopharyngitis

Drug Interactions

- The addition of Wegovy® in patients treated with insulin has not been evaluated. When initiating Wegovy®, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia
- Wegovy® causes a delay of gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications. Monitor the effects of oral medications concomitantly administered with Wegovy®

Use in Specific Populations

- **Pregnancy:** May cause fetal harm. When pregnancy is recognized, discontinue Wegovy®. Discontinue Wegovy® in patients at least 2 months before a planned pregnancy
- **Pediatric:** Adverse reactions with Wegovy® in pediatric patients aged 12 years and older were similar to those reported in adults. Pediatric patients ≥12 years of age treated with Wegovy® had greater incidences of cholelithiasis, cholecystitis, hypotension, rash, and urticaria compared to adults treated with Wegovy®. There are insufficient data in pediatric patients with type 2 diabetes treated with Wegovy® for obesity to determine if there is an increased risk of hypoglycemia with Wegovy® treatment similar to that reported in adults
- **Geriatric:** In the cardiovascular outcomes trial, patients aged 75 years and older reported more hip and pelvis fractures on Wegovy® than placebo. Patients aged 75 years and older (Wegovy® and placebo) reported more serious adverse reactions overall compared to younger adult patients

Please see the Brief Summary of Prescribing Information about Wegovy® on the following pages.

ARR, absolute risk reduction; BMI, body mass index; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; PAD, peripheral arterial disease; RRR, relative risk reduction; SOC, standard of care.

References: 1. Wegovy® [package insert]. Plainsboro, NJ: Novo Nordisk Inc. **2.** Garvey WT, Batterham RL, Bhatta M, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. *Nat Med*. 2022;28(10):2083-2091. **3.** Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389(24):2221-2232. **4.** Data on file. Novo Nordisk Inc.; Plainsboro, NJ.

US24SEMO00646 May 2024

novo nordisk®

WEGOVY® (semaglutide) injection

Rx Only

BRIEF SUMMARY: Please consult package insert for full prescribing information.

WARNING: RISK OF THYROID C-CELL TUMORS: In rodents, semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether WEGOVY® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions]*. WEGOVY® is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Contraindications]*. Counsel patients regarding the potential risk for MTC with the use of WEGOVY® and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with WEGOVY® *[see Contraindications and Warnings and Precautions]*.

INDICATIONS AND USAGE: WEGOVY® is indicated in combination with a reduced calorie diet and increased physical activity: to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and either obesity or overweight; to reduce excess body weight and maintain weight reduction long term in: Adults and pediatric patients aged 12 years and older with obesity; Adults with overweight in the presence of at least one weight-related comorbid condition. Limitations of Use: WEGOVY® contains semaglutide. Coadministration with other semaglutide-containing products or with any other GLP-1 receptor agonist is not recommended.

CONTRAINDICATIONS: WEGOVY® is contraindicated in the following conditions: A personal or family history of MTC or in patients with MEN 2 *[see Warnings and Precautions];* A prior serious hypersensitivity reaction to semaglutide or to any of the excipients in WEGOVY®. Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with WEGOVY® *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS: Risk of Thyroid C-Cell Tumors: In mice and rats, semaglutide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures. It is unknown whether WEGOVY® causes thyroid C-cell tumors, including MTC, in humans, as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined. Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans. WEGOVY® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of WEGOVY® and inform them of symptoms of thyroid tumors (e.g. a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with WEGOVY®. Such monitoring may increase the risk of unnecessary procedures, due to the low-test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin value may indicate MTC and patients with MTC usually have calcitonin values greater than 50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated. **Acute Pancreatitis:** Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists, including semaglutide. Acute pancreatitis was observed in patients treated with WEGOVY® in clinical trials *[see Adverse Reactions]*. After initiation of WEGOVY®, observe patients carefully for signs and symptoms of acute pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, and which may or may not be accompanied by vomiting). If acute pancreatitis is suspected, WEGOVY® should promptly be discontinued, and appropriate management should be initiated. If acute pancreatitis is confirmed, WEGOVY® should not be restarted. There is limited experience from clinical trials with WEGOVY® in patients with a history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on WEGOVY®. **Acute Gallbladder Disease:** Treatment with WEGOVY® is associated with an increased occurrence of cholelithiasis and cholecystitis. The incidence of cholelithiasis and cholecystitis was higher in WEGOVY®-treated pediatric patients aged 12 years and older than in WEGOVY®-treated adults. In randomized clinical trials in adult patients, cholelithiasis was reported by 1.6% of WEGOVY®-treated patients and 0.7% of placebo-treated patients. Cholecystitis was reported by 0.6% of WEGOVY®-treated adult patients and 0.2% of placebo-treated patients. In a clinical trial in pediatric patients aged 12 years and older, cholelithiasis was reported by 3.8% of WEGOVY®-treated patients and 0% placebo-treated patients. Cholecystitis was reported by 0.8% of WEGOVY®-treated pediatric patients and 0% placebo-treated patients *[see Adverse Reactions]*. Substantial or rapid weight loss can increase the risk of cholelithiasis; however, the incidence of acute gallbladder disease was greater in WEGOVY®-treated patients than in placebo-treated patients, even after accounting for the degree of weight loss. If cholelithiasis is suspected, gallbladder studies and appropriate clinical follow-up are indicated. **Hypoglycemia:** WEGOVY® lowers blood glucose and can cause hypoglycemia. In a trial of adult patients with type 2 diabetes and body mass index (BMI) greater than or equal to 27 kg/m^2, hypoglycemia (defined as a plasma glucose less than 54 mg/dL) was reported in 6.2% of WEGOVY®-treated patients versus 2.5% of placebo-treated patients. One episode of severe hypoglycemia (requiring the assistance of another person) was reported in one WEGOVY®-treated patient versus no placebo-treated patients. Patients with diabetes mellitus taking WEGOVY® in combination with insulin or an insulin secretagogue (e.g., sulfonylurea) may have an increased risk of hypoglycemia, including severe hypoglycemia. Hypoglycemia has been observed in patients treated with semaglutide at doses of 0.5 and 1 mg in combination with insulin. The use of WEGOVY® (semaglutide 2.4 mg or 1.7 mg once weekly) in patients with type 1 diabetes mellitus or in combination with insulin has not been evaluated. Inform patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. In patients with diabetes, monitor blood glucose prior to starting WEGOVY® and during WEGOVY® treatment. When initiating WEGOVY®, consider reducing the dose of concomitantly administered insulin or insulin secretagogue (such as sulfonylureas) to reduce the risk of hypoglycemia *[see Drug Interactions]*. **Acute Kidney Injury:** There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which have in some cases required hemodialysis, in patients treated with semaglutide. Patients with renal impairment may be at greater risk of acute kidney injury, but some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, or diarrhea, leading to volume depletion *[see Adverse Reactions]*. Monitor renal function when initiating or escalating doses of WEGOVY® in patients reporting severe adverse gastrointestinal reactions. Monitor renal function in patients with renal impairment reporting any adverse reactions that could lead to volume depletion. **Hypersensitivity Reactions:** Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with WEGOVY®. If hypersensitivity reactions occur, discontinue use of WEGOVY®, treat promptly per standard of care, and monitor until signs and symptoms resolve. WEGOVY® is contraindicated in patients with a prior serious hypersensitivity reaction to semaglutide or to any of the excipients in WEGOVY® *[see Adverse Reactions]*. Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to these reactions with WEGOVY®. **Diabetic Retinopathy Complications in Patients with Type 2 Diabetes:** In a trial of adult patients with type 2 diabetes and BMI greater than or equal to 27 kg/m^2, diabetic retinopathy was reported by 4.0% of WEGOVY®-treated patients and 2.7% placebo-treated patients. In a 2-year trial with semaglutide 0.5 mg and 1 mg once-weekly injection in adult patients with type 2 diabetes and high cardiovascular risk, diabetic retinopathy complications (which was a 4-component adjudicated endpoint) occurred in patients treated with semaglutide injection (3.0%) compared to placebo (1.8%). The absolute risk increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (semaglutide injection 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (semaglutide injection 0.7%, placebo 0.4%). Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. The effect of long-term glycemic control with semaglutide on diabetic retinopathy complications has not been studied. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy. **Heart Rate Increase:** Treatment with WEGOVY® was associated with increases in resting heart rate. Mean increases in resting heart rate of 1 to 4 beats per minute (bpm) were observed in WEGOVY®-treated adult patients compared to placebo in clinical trials. More adult patients treated with WEGOVY® compared with placebo had maximum changes from baseline at any visit of 10 to 19 bpm (41% versus 34%, respectively) and 20 bpm or more (26% versus 16%, respectively). In a clinical trial in pediatric patients aged 12 years and older with normal baseline heart rate, more patients treated with WEGOVY® compared to placebo had maximum changes in heart rate of 20 bpm or more (54% versus 39%) *[see Adverse Reactions]*. Monitor heart rate at regular intervals consistent with usual clinical practice. Instruct patients to inform their healthcare providers of palpitations or feelings of a racing heartbeat while at rest during WEGOVY® treatment. If patients experience a sustained increase in resting heart rate, discontinue WEGOVY®. **Suicidal Behavior and Ideation:** Suicidal behavior and ideation have been reported in clinical trials with other weight management products. Monitor patients treated with WEGOVY® for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue WEGOVY® in patients who experience suicidal thoughts or behaviors. Avoid WEGOVY® in patients with a history of suicidal attempts or active suicidal ideation.

ADVERSE REACTIONS: The following serious adverse reactions are described below or elsewhere in the prescribing information: Risk of Thyroid C-Cell Tumors *[see Warnings and Precautions];* Acute Pancreatitis *[see Warnings and Precautions];* Acute Gallbladder Disease *[see Warnings and Precautions];* Hypoglycemia *[see Warnings and Precautions];* Acute Kidney Injury *[see Warnings and Precautions];* Hypersensitivity Reactions *[see Warnings and Precautions];* Diabetic Retinopathy Complications in Patients with Type 2 Diabetes *[see Warnings and Precautions];* Heart Rate Increase *[see Warnings and Precautions];* Suicidal Behavior and Ideation *[see Warnings and Precautions]*. **Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. **Adverse Reactions in Clinical Trials in Adults with Obesity or Overweight:** *WEGOVY® 2.4 mg Subcutaneous Weekly Dosage:* WEGOVY® was evaluated for safety in 3 randomized, double-blind, placebo-controlled trials that included 2,116 adult patients with obesity or overweight treated with 2.4 mg WEGOVY® for up to 68 weeks and a 7 week off-drug follow-up period. Baseline characteristics included a mean age of 48 years, 71% female, 72% White, 14% Asian, 9% Black or African American, and 5% reported as other or unknown; and 85% were not Hispanic or Latino ethnicity, 13% were Hispanic or Latino ethnicity, and 2% reported as unknown. The baseline characteristics were 42% with hypertension, 19% with type 2 diabetes, 43% with dyslipidemia, 28% with a BMI greater than 40 kg/m^2, and 4% with cardiovascular disease. In these clinical trials, 6.8% of patients treated with 2.4 mg WEGOVY® and 3.2% of patients treated with placebo permanently discontinued treatment as a result of adverse reactions. The most common adverse reactions leading to discontinuation were nausea (1.8% versus 0.2%), vomiting (1.2% versus 0%), and diarrhea (0.7% versus 0.1%) for WEGOVY® and placebo, respectively. Adverse reactions reported in clinical trials in adults and greater than or equal to 2% of WEGOVY®-treated patients and more frequently than in placebo-treated patients are shown in **Table 3**.

Table 3. Adverse Reactions (≥2% and Greater Than Placebo) in WEGOVY®-treated Adults with Obesity or Overweight

	Placebo N=1,261 %	WEGOVY® 2.4 mg N=2,116 %
Nausea	16	44
Diarrhea	16	30
Vomiting	6	24
Constipation	11	24
Abdominal Pain[a]	10	20
Headache	10	14
Fatigue[b]	5	11
Dyspepsia	3	9
Dizziness	4	8
Abdominal Distension	5	7
Eructation	<1	7
Hypoglycemia in T2DM[c]	2	6
Flatulence	4	6
Gastroenteritis	4	6
Gastroesophageal Reflux Disease	3	5
Gastritis[d]	1	4
Gastroenteritis Viral	3	4
Hair Loss	1	3
Dysesthesia[e]	1	2

[a]Includes abdominal pain, abdominal pain upper, abdominal pain lower, gastrointestinal pain, abdominal tenderness, abdominal discomfort and epigastric discomfort
[b]Includes fatigue and asthenia
[c]Defined as blood glucose <54 mg/dL with or without symptoms of hypoglycemia or severe hypoglycemia (requiring the assistance of another person) in patients with type 2 diabetes not on concomitant insulin (Study 3, WEGOVY® N=403, Placebo N=402). See text below for further information regarding hypoglycemia in patients with and without type 2 diabetes. T2DM = type 2 diabetes mellitus
[d]Includes chronic gastritis, gastritis, gastritis erosive, and reflux gastritis
[e]Includes paresthesia, hyperesthesia, burning sensation, allodynia, dysesthesia, skin burning sensation, pain of skin, and sensitive skin

In a cardiovascular outcomes trial, 8,803 patients were exposed to WEGOVY® for a median of 37.3 months and 8,801 patients were exposed to placebo for a median of 38.6 months. Safety data collection was limited to serious adverse events (including death), adverse events leading to discontinuation, and adverse events of special interest. Sixteen percent (16%) of WEGOVY®-treated patients and 8% of placebo-treated patients, respectively, discontinued study drug due to an adverse event. Additional information from this trial is included in subsequent sections below when relevant. **Adverse Reactions in a Clinical Trial of Pediatric Patients Aged 12 Years and Older with Obesity:** WEGOVY® was evaluated in a 68-week, double-blind, randomized, parallel group, placebo-controlled, multi-center trial in 201 pediatric patients aged 12 years and older with obesity. Baseline characteristics included a mean age of 15.4 years; 38% of patients were male; 79% were White, 8% were Black or African American, 2% were Asian, and 11% were of other or unknown race; and 11% were of Hispanic or Latino ethnicity. The mean baseline body weight was 107.5 kg, and mean BMI was 37 kg/m^2. **Table 4** shows adverse reactions reported in greater than or equal to 3% of WEGOVY®-treated pediatric patients and more frequently than in the placebo group from a study in pediatric patients aged 12 years and older.

Table 4. Adverse Reactions (≥3% and Greater than Placebo) in WEGOVY®-Treated Pediatric Patients Aged 12 Years and Older with Obesity

	Placebo N=67 %	WEGOVY® 2.4 mg N=133 %
Nausea	18	42
Vomiting	10	36
Diarrhea	19	22
Headache	16	17
Abdominal Pain	6	15
Nasopharyngitis	10	12
Dizziness	3	8
Gastroenteritis	3	7
Constipation	2	6
Gastroesophageal Reflux Disease	2	4
Sinusitis	2	4
Urinary tract infection	2	4
Ligament sprain	2	4
Anxiety	2	4
Hair Loss	0	4
Cholelithiasis	0	4
Eructation	0	4
Influenza	0	3
Rash	0	3
Urticaria	0	3

Other Adverse Reactions in Adults and/or Pediatric Patients: *Acute Pancreatitis:* In WEGOVY® clinical trials in adults, acute pancreatitis was confirmed by adjudication in 4 WEGOVY®-treated patients (0.2 cases per 100 patient years) versus 1 in placebo-treated patients (less than 0.1 cases per 100 patient years). One additional case of acute pancreatitis was confirmed in a patient treated with WEGOVY® in another clinical trial. *Acute Gallbladder Disease:* In WEGOVY® clinical trials in adults, cholelithiasis was reported by 1.6% of WEGOVY®-treated patients and 0.7% of placebo-treated patients. Cholecystitis was reported by 0.6% of WEGOVY®-treated adult patients and 0.2% of placebo-treated patients. In a clinical trial in pediatric patients aged 12 years and older, cholelithiasis was reported by 3.8% of WEGOVY®-treated patients and 0% placebo-treated patients. Cholecystitis was reported by 0.8% of WEGOVY®-treated pediatric patients and 0% placebo-treated patients. *Hypoglycemia: Patients with Type 2 Diabetes:* In a trial of adult patients with type 2 diabetes and BMI greater than or equal to 27 kg/m^2, clinically significant hypoglycemia (defined as a plasma glucose less than 54 mg/dL) was reported in 6.2% of WEGOVY®-treated patients versus 2.5% of placebo-treated patients. A higher rate of clinically significant hypoglycemic episodes was reported with WEGOVY® (semaglutide 2.4 mg) versus semaglutide 1 mg (10.7 vs. 7.2 episodes per 100 patient years of exposure, respectively); the rate in the placebo-treated group was 3.2 episodes per 100 patient years of exposure. In addition, one episode of severe hypoglycemia requiring intravenous glucose was reported in a WEGOVY®-treated patient versus none in placebo-treated patients. The risk of hypoglycemia was increased when WEGOVY® was used with a sulfonylurea. *Patients without Type 2 Diabetes:* Episodes of hypoglycemia have been reported with GLP-1 receptor agonists in adult patients without type 2 diabetes mellitus. In WEGOVY® clinical trials in adult patients without type 2 diabetes mellitus, there was no systematic capturing or reporting of hypoglycemia. In a cardiovascular outcomes trial in adult patients without type 2 diabetes, 3 episodes of serious hypoglycemia were reported in WEGOVY®-treated patients versus 1 episode in placebo. Patients with a history of bariatric surgery (a risk factor for hypoglycemia) had more events of serious hypoglycemia while taking WEGOVY® (2.3%, 2/87) than placebo (0%, 0/97). *Acute Kidney Injury:* Acute kidney injury occurred in clinical trials in 7 adult patients (0.4 cases per 100 patient years) receiving WEGOVY® versus 4 patients (0.2 cases per 100 patient years of exposure) receiving placebo. Some of these adverse reactions occurred in association with gastrointestinal adverse reactions or dehydration. In addition, 2 patients treated with WEGOVY® had acute kidney injury with dehydration in other clinical trials. The risk of renal adverse reactions with WEGOVY® was increased in adult patients with a history of renal impairment (trials included 65 patients with a history of moderate or severe renal impairment at baseline), and occurred more frequently during dose titration. *Retinal Disorders in Patients with Type 2 Diabetes:* In a trial of adult patients with type 2 diabetes and BMI greater than or equal to 27 kg/m^2, retinal disorders were reported by 6.9% of patients treated with WEGOVY® (semaglutide 2.4 mg), 6.2% of patients treated with semaglutide 1 mg, and 4.2% of patients treated with placebo. The majority of events were reported as diabetic retinopathy (4.0%, 2.7%, and 2.7%, respectively) and non-proliferative retinopathy (0.7%, 0%, and 0%, respectively). *Increase in Heart Rate:* Mean increases in resting heart rate of 1 to 4 beats per minute (bpm) were observed with routine clinical monitoring in WEGOVY®-treated adult patients compared to placebo in clinical trials. In trials in which adult patients were randomized prior to dose-escalation, more patients treated with WEGOVY®, compared with placebo, had maximum changes from baseline at any visit of 10 to 19 bpm (41% versus 34%, respectively) and 20 bpm or more (26% versus 16%, respectively). In a clinical trial in pediatric patients aged 12 years and older with normal baseline heart rate, more patients treated with WEGOVY® compared to placebo had maximum changes in heart rate of 20 bpm or more (54% versus 39%). *Hypotension and Syncope:* Adverse reactions related to hypotension (hypotension, orthostatic hypotension, and decreased blood pressure) were reported in 1.3% of WEGOVY®-treated adult patients versus 0.4% of placebo-treated patients and syncope was reported in 0.8% of WEGOVY®-treated patients versus 0.2% of placebo-treated patients. Some reactions were related to gastrointestinal adverse reactions and volume loss associated with WEGOVY®. Hypotension and orthostatic hypotension were more frequently seen in patients on concomitant antihypertensive therapy. In a clinical trial in pediatric patients aged 12 years and older, hypotension was reported in 2.3% of WEGOVY®-treated patients versus 0% in placebo-treated patients. *Appendicitis:* Appendicitis (including perforated appendicitis) occurred in 10 (0.5%) WEGOVY®-treated adult patients and 2 (0.2%) patients receiving placebo. *Gastrointestinal Adverse Reactions:* In clinical trials in adults, 73% of WEGOVY®-treated patients and 47% of patients receiving placebo reported gastrointestinal adverse reactions, including severe reactions that were reported more frequently among patients receiving WEGOVY® (4.1%) than placebo (0.9%). The most frequently reported reactions were nausea (44% vs. 16%), vomiting (25% vs. 6%), and diarrhea (30% vs. 16%). Other reactions that occurred at a higher incidence among WEGOVY®-treated adult patients included dyspepsia, abdominal pain, abdominal distension, eructation, flatulence, gastroesophageal reflux disease, gastritis, hemorrhoids, and hiccups. These reactions increased during dose escalation. In the pediatric clinical trial, 62% of WEGOVY®-treated patients and 42% of placebo-treated patients reported gastrointestinal disorders. The most frequently reported reactions were nausea (42% vs. 18%), vomiting (36% vs. 10%), and diarrhea (22% vs. 19%). Other gastrointestinal-related reactions that occurred at a higher incidence than placebo among WEGOVY®-treated pediatric patients included abdominal pain, constipation, eructation, gastroesophageal reflux disease, dyspepsia, and flatulence. Permanent discontinuation of treatment as a result of a gastrointestinal adverse reaction occurred in 4.3% of WEGOVY®-treated adult patients versus 0.7% of placebo-treated patients. In a pediatric clinical trial, 2.3% of patients treated with WEGOVY® versus 1.5% of patients who received placebo discontinued treatment as a result of gastrointestinal adverse reactions. *Injection Site Reactions:* In clinical trials in adults, 1.4% of WEGOVY®-treated patients and 1.0% of patients receiving placebo experienced injection site reactions (including injection site pruritus, erythema, inflammation, induration, and irritation). *Hypersensitivity Reactions:* Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with WEGOVY®. In a pediatric clinical trial, rash was reported in 3% of WEGOVY®-treated patients and 0% of placebo-treated patients, and urticaria was reported in 3% of WEGOVY®-treated patients and 0% of placebo-treated patients. In adult clinical trials, allergic reactions occurred in 16%

(8/50) of WEGOVY®-treated patients with anti-semaglutide antibodies and in 7% (114/1659) of WEGOVY®-treated patients who did not develop anti-semaglutide antibodies. *Fractures:* In the cardiovascular outcomes trial in adults, more fractures of the hip and pelvis were reported on WEGOVY® than on placebo in female patients: 1.0% (24/2448) vs. 0.2% (5/2424), and in patients ages 75 years and older: 2.4% (17/703) vs. 0.6% (4/663), respectively. *Urolithiasis:* In a cardiovascular outcomes trial, 1.2% of WEGOVY®-treated patients and 0.8% of patients receiving placebo reported urolithiasis, including serious reactions that were reported more frequently among patients receiving WEGOVY® (0.6%) than placebo (0.4%). *Dysgeusia:* In clinical trials in adults, 1.7% of WEGOVY®-treated patients and 0.5% of placebo-treated patients reported dysgeusia. *Laboratory Abnormalities: Amylase and Lipase:* Adult and pediatric patients treated with WEGOVY® had a mean increase from baseline in amylase of 15-16% and lipase of 39%. These changes were not observed in the placebo group. The clinical significance of elevations in lipase or amylase with WEGOVY® is unknown in the absence of other signs and symptoms of pancreatitis. *Liver Enzymes:* In a pediatric clinical trial, increases in alanine aminotransferase (ALT) greater than or equal to 5 times the upper limit of normal were observed in 4 (3%) WEGOVY®-treated patients compared with 0% of placebo-treated patients. In some patients, increases in ALT and AST were associated with other confounding factors (such as gallstones). In the cardiovascular outcomes trial in adults, increases in total bilirubin greater than or equal to 3 times the upper limit of normal were observed in 0.3% (30/8585) of WEGOVY®-treated patients versus 0.2% (14/8579) of placebo-treated patients. **Postmarketing Experience:** The following adverse reactions have been reported during post-approval use of semaglutide, the active ingredient of WEGOVY®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Gastrointestinal Disorders:* acute pancreatitis and necrotizing pancreatitis, sometimes resulting in death; ileus *Hypersensitivity:* anaphylaxis, angioedema, rash, urticaria *Renal and Urinary Disorders:* acute kidney injury

DRUG INTERACTIONS: Concomitant Use with Insulin or an Insulin Secretagogue (e.g., Sulfonylurea): WEGOVY® lowers blood glucose and can cause hypoglycemia. The risk of hypoglycemia is increased when WEGOVY® is used in combination with insulin or insulin secretagogues (e.g., sulfonylureas). The addition of WEGOVY® in patients treated with insulin has not been evaluated. When initiating WEGOVY®, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia *[see Warnings and Precautions and Adverse Reactions]*. **Oral Medications:** WEGOVY® causes a delay of gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials with semaglutide 1 mg, semaglutide did not affect the absorption of orally administered medications. Nonetheless, monitor the effects of oral medications concomitantly administered with WEGOVY®.

USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Exposure Registry: There will be a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to semaglutide during pregnancy. Pregnant women exposed to WEGOVY® and healthcare providers are encouraged to contact Novo Nordisk at 1-877-390-2760 or www.wegovypregnancyregistry.com. Risk Summary: Based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy. Additionally, weight loss offers no benefit to a pregnant patient and may cause fetal harm. When a pregnancy is recognized, advise the pregnant patient of the risk to a fetus, and discontinue WEGOVY® *(see Clinical Considerations)*. Available pharmacovigilance data and data from clinical trials with WEGOVY® use in pregnant patients are insufficient to establish a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. In pregnant rats administered semaglutide during organogenesis, embryofetal mortality, structural abnormalities and alterations to growth occurred at maternal exposures below the maximum recommended human dose (MRHD) based on AUC. In rabbits and cynomolgus monkeys administered semaglutide during organogenesis, early pregnancy losses and structural abnormalities were observed at below the MRHD (rabbit) and greater than or equal to 2-fold the MRHD (monkey). These findings coincided with a marked maternal body weight loss in both animal species (see Data). The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Clinical Considerations: *Disease-associated maternal and/or embryo/fetal risk:* Appropriate weight gain based on pre-pregnancy weight is currently recommended for all pregnant patients, including those who already have overweight or obesity, because of the obligatory weight gain that occurs in maternal tissues during pregnancy. Data: *Animal Data:* In a combined fertility and embryofetal development study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day (0.04-, 0.1-, and 0.4-fold the MRHD) were administered to males for 4 weeks prior to and throughout mating and to females for 2 weeks prior to mating, and throughout organogenesis to Gestation Day 17. In parental animals, pharmacologically mediated reductions in body weight gain and food consumption were observed at all dose levels. In the offspring, reduced growth and fetuses with visceral (heart blood vessels) and skeletal (cranial bones, vertebra, ribs) abnormalities were observed at the human exposure. In an embryofetal development study in pregnant rabbits, subcutaneous doses of 0.0010, 0.0025 or 0.0075 mg/kg/day (0.01-, 0.1-, and 0.9-fold the MRHD) were administered throughout organogenesis from Gestation Day 6 to 19. Pharmacologically mediated reductions in maternal body weight gain and food consumption were observed at all dose levels. Early pregnancy losses and increased incidences of minor visceral (kidney, liver) and skeletal (sternebra) fetal abnormalities were observed at greater than or equal to 0.0025 mg/kg/day, at clinically relevant exposures. In an embryofetal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (0.4-, 2-, and 6-fold the MRHD) were administered throughout organogenesis, from Gestation Day 16 to 50. Pharmacologically mediated, marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with the occurrence of sporadic abnormalities (vertebra, sternebra, ribs) at greater than or equal to 0.075 mg/kg twice weekly (greater than or equal to 2 times human exposure). In a pre- and postnatal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (0.2-, 1-, and 3-fold the MRHD) were administered from Gestation Day 16 to 140. Pharmacologically mediated marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with an increase in early pregnancy losses and led to delivery of slightly smaller offspring at greater than or equal to 0.075 mg/kg twice weekly (greater than or equal to 1-time human exposure). **Lactation:** Risk Summary: There are no data on the presence of semaglutide or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. Semaglutide was present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for WEGOVY® and any potential adverse effects on the breastfed infant from WEGOVY® or from the underlying maternal condition. Data: In lactating rats, semaglutide was detected in milk at levels 3 to 12-fold lower than in maternal plasma. **Females and Males of Reproductive Potential:** Because of the potential for fetal harm, discontinue WEGOVY® in patients at least 2 months before they plan to become pregnant to account for the long half-life of semaglutide *[see Use in Specific Populations]*. **Pediatric Use:** The safety and effectiveness of WEGOVY® as an adjunct to a reduced calorie diet and increased physical activity for weight reduction and long-term maintenance have been established in pediatric patients aged 12 years and older with obesity. Use of WEGOVY® for this indication is supported by a 68-week, double-blind, placebo-controlled clinical trial in 201 pediatric patients aged 12 years and older with a BMI corresponding to ≥95th percentile for age and sex and from studies in adult patients with obesity. Adverse reactions with WEGOVY® treatment in pediatric patients aged 12 years and older were generally similar to those reported in adults. Pediatric patients aged 12 years and older treated with WEGOVY® had greater incidences of cholelithiasis, cholecystitis, hypotension, rash, and urticaria compared to adults treated with WEGOVY® *[see Adverse Reactions]*. There are insufficient data in pediatric patients with type 2 diabetes treated with WEGOVY® for obesity to determine if there is an increased risk of hypoglycemia with WEGOVY® treatment similar to that reported in adults. Inform patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. In pediatric patients aged 12 years and older with type 2 diabetes, monitor blood glucose prior to starting WEGOVY® and during WEGOVY® treatment. When initiating WEGOVY® in pediatric patients aged 12 years and older with type 2 diabetes, consider reducing the dose of concomitantly administered insulin secretagogue (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia *[see Warnings and Precautions]*. The safety and effectiveness of WEGOVY® have not been established in pediatric patients less than 12 years of age. **Geriatric Use:** In the WEGOVY® clinical trials for weight reduction and long-term maintenance, 233 (9%) WEGOVY®-treated patients were aged 65 to 75 years and 23 (1%) WEGOVY®-treated patients were aged 75 years and older. In a cardiovascular outcomes trial, 2656 (30%) WEGOVY®-treated patients were aged 65 to 75 years and 703 (8%) WEGOVY®-treated patients were aged 75 years and older. No overall difference in effectiveness was observed between patients aged 65 years and older and younger adult patients. In the cardiovascular outcomes trial, patients aged 75 years and older reported more fractures of the hip and pelvis on WEGOVY® than on placebo. Patients aged 75 years and older (WEGOVY®-treated and placebo-treated) reported more serious adverse reactions overall compared to younger adult patients *[see Adverse Reactions]*. **Renal Impairment:** No dose adjustment of WEGOVY® is recommended for patients with renal impairment. In a study in patients with renal impairment, including end-stage renal disease, no clinically relevant change in semaglutide pharmacokinetics was observed. **Hepatic Impairment:** No dose adjustment of WEGOVY® is recommended for patients with hepatic impairment. In a study in patients with different degrees of hepatic impairment, no clinically relevant change in semaglutide pharmacokinetics was observed.

OVERDOSAGE: Overdoses have been reported with other GLP-1 receptor agonists. Effects have included severe nausea, severe vomiting, and severe hypoglycemia. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. In the event of an overdose of WEGOVY®, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of WEGOVY® of approximately 1 week.

More detailed information is available upon request.

Manufactured by: Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark

For additional information about WEGOVY® contact: Novo Nordisk Inc., 800 Scudders Mill Road, Plainsboro, NJ 08536, 1-833-934-6891

Version: 4

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PATENT INFORMATION: http://www.novonordisk-us.com/products/product-patents.html

wegovy®
semaglutide injection **2.4 mg**

US24SEM000498 March 2024

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PATIENT ENGAGEMENT

Breaking through the **portion control** barrier

As a clinician, you're well aware that large portion sizes can thwart a patient's goals. Yet "downsizing" is not as simple as it sounds. Here's how to help patients make this key dietary change.

Eating smaller portions can significantly reduce body weight, BMI and waist circumference, according to a meta-analysis of studies on portion control. While more studies are needed to determine if weight loss can be sustained over time, research also shows that people tend to consume more calories when served larger portions,[1] and that practicing portion control can reduce calorie intake in adults by almost one-third—about 527 calories per day.[2] "People fail on diets because a diet, by definition, implies some food deprivation over a specific time," says Lisa R. Young, PhD, RDN, CDN/LDN, an adjunct professor of nutrition at New York University. As an alternative to restrictive diets, Young advocates a daily eating plan using portion control across different food groups, the goal being to promote satiety with fewer calories. "Portion control is about eating big portions of foods with smaller calories and normal portions of other healthy foods while steering away from unhealthy choices," says Young, a nutritionist in private practice and author of *Finally Full, Finally Slim*. "It isn't a diet, but a lifestyle."

While surveys suggest portion control—a key principle in the Dietary Guidelines for Americans, 2020-2025 publication from the U.S. Departments of Agriculture (USDA) and Health and Human Services (HHS)[3]—is catching on as a strategy to shed pounds, many people aren't sure how much food they should eat for optimal weight loss.[4] To this end, clinicians can play a key role in portion-control education, says Young, who suggests clinicians help patients do the following:

Understand portion size versus serving size

Servings sizes listed on the nutrition labels on food and beverage products are sometimes confused with recommendations for how much to eat or drink. These are set by the U.S. Food and Drug Administration based on survey data about the amount people typically consume of the product.[5] "A serving size is just a unit of measure that tells you how much sugar, fat and calories are found in a standard serving," Young says. In comparison, a portion is the amount of food a person puts on their plate or how much they actually eat or drink, Young explains, which can be more or less than serving sizes found on food labels. "Many portion sizes are bigger than they were decades ago, which reinforces overeating," she adds.

Note: If patients are taking obesity medications, emphasize that portion control is still important, as the two work together to aid weight loss. Portion control can also help mitigate common medication side effects like nausea. ►

Stick to "normal" portion sizes

Growing portion sizes reflect what researchers have termed "portion distortion" and are the direct result of packaged food companies' and fast-food chains' desire to sell products up to 5 times larger than when first introduced, according to Young's research.[6] A typical "regular" soda, once about 7 ounces, is now supersized to 32 or 42 ounces; a bagel, once 3 inches, is now 6 inches in diameter. Pizza, salad, French fries, burgers and other popular foods have gone through similar supersizing, according to the National Heart, Lung and Blood Institute.[7]

Young says that consuming large portions on a regular basis is blinding people to the relationship between portion size, calorie intake and weight gain. Research shows that when presented with bigger portions, people will eat or drink more because they assume the amount they are served is what they should eat.[2] "It is hard to stick to normal portions when people are bombarded by ridiculous sizes," Young warns.

Focus on nutrition

Combating portion distortion is not the only barrier to building healthy eating habits given that most adults do not consume a nutritious diet.[8] "Patients need to eat the right balance of food portions to get their essential nutrients and to feel full with fewer calories," Young advises. "It's not just about losing weight—optimizing health is also important."

There is evidence that the amount of food people should eat daily from each food group depends on a variety of factors, including age, gender, height, weight-loss goals and activity level. She suggests patients go to the USDA's MyPlate website, which has a calculator where they can enter their personal characteristics to find recommended daily calorie intakes, as well as information on how much to eat of certain foods within calorie allowances (*myplate.gov*).[9]

Changing food choices is difficult for many patients, but studies show that managing portion size may be an effective tool for progressive weight loss, in part, because people can still eat many of the foods they like.[10] "The emphasis is less on what you eat and more on how much you eat of any food," Young says. "Almost any foods are allowed, but in smaller portions."

However, implementing portion control for weight loss and health benefits should be based on making better food choices and should not feel overwhelming for patients. She offers the following strategies for preparing meals:

- **Plate mapping.** Fruits and nonstarchy vegetables should take up about half the plate, and the other half split evenly between a lean protein and fiber-rich grains such as rice, bread or starchy vegetables, Young says. Dairy, fats, sweets and treats should be side items.
- **Supersize vegetables and fruits.** Fresh and frozen nonstarchy varieties, not canned, are nutritious and full of fiber and not only aid in digestion, but also promote satiety, Young says. She recommends one cup each at meals and unlimited servings throughout the day of "freebies" like spinach, broccoli, cauliflower, melons, berries, apples and pears.
- **Swap out starches.** People generally eat too much starchy food such as pasta, bread and cereals, Young says. Refined grains have been stripped of most of their nutrients, including fiber. Instead, patients should consider swapping these out for whole grain alternatives and legumes like black beans or sweet potatoes, 4 to 6 times daily.
- **Avoid certain proteins.** Protein is a key building block for the body and helps stabilize blood sugar and keep sugar cravings at bay. Young tells clients to ditch the ultra-processed proteins like bacon, hot dogs and processed sandwich meats for 2 to 3 daily servings of fish, skinless poultry, extra-lean cuts of meat, eggs or plant-based proteins.
- **Downsize sides and treats.** Consuming alcohol and sugary and salty treats should be kept to a minimum. "If patients have a sweet tooth, chances are good that by following this program their cravings will diminish because they're eating fiber rich foods, adequate protein and healthy fats and healthy snacks instead," she says. "It's like a hidden bonus."

Use visual cues

Using measuring spoons and cups is a best way for patients to calculate how much food they're eating daily, Young says. But measuring out portions isn't a sustainable habit for most people. For many, their bowl of breakfast cereal is over two cups—twice as much as a healthy portion should be. Instead, a simple way to determine portion sizes is to visualize common objects that are approximately the same portion size when cooking or eating out.

These include:

- **Baseball** = 1 cup fruits, vegetables, cereal, pasta or cooked grains
- **Deck of cards** = 3 ounces salmon, chicken or meat
- **Four dice** = 1 ounce cheese
- **CD case** = 1 slice of bread
- **Computer mouse** = 1 sweet potato or baked potato
- **Dental floss container** = 1 ounce chocolate or a cookie
- **Golf ball** = ¼ cup nuts or seeds

Another tip is to use dinner plates that are no larger than 9 inches, Young says. "The larger the plate, the more we serve ourselves and tend to eat." She suggests using dinner plates for vegetable and fruits and eating on smaller salad or dessert plates for proteins and grains, as well as for starchy selections such as rice or pasta. Research confirms that adjusting plate size is an effective way to change food proportions and help patients feel more sated.[11]

Keep it simple

Encourage patients to make slow changes that build into sustainable habits, such as downsizing one food at a time and upsizing a healthier alternative, instead of doing an immediate overhaul of their diet, Young says. "Work with them from where they are," she advises. "Focus on the positive by emphasizing that portion control isn't about going hungry." She notes that many people she works with are surprised about how much they can eat using portion control. "They think they're eating more food, but really it's just healthier, more satisfying food than they're used to and fewer calories." ●

—by Linda Keslar

Adopting portion control when eating out

"There's no need to abandon restaurants or social events when trying to lose weight," says Lisa R. Young, PhD, RDN, CDN/LDN, adjunct professor of nutrition at New York University. Instead, patients should learn to make healthy choices. Some of her portion-control tips for dining out include:

- Snack on fruits, vegetables or nuts before leaving to curb hunger and prevent overeating.
- Limit alcohol to one drink and choose a glass of sparkling water, water with lemon or a cup of herbal tea instead.
- Start with a small, tossed salad, vegetable soup or other healthy appetizer and avoid the bread basket, butter and chips.
- Ask to share an entrée or appetizer with a dining partner or order a reduced-portion entrée.
- Take half of a regular entrée home to enjoy later.
- Skip or split a dessert.

When going to a reception, people should fill a small plate with a few selections and not go back for seconds," Young adds..

Illustration by HannaAdobe Stock

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PATIENT: SAMUEL, 49, HAD OBESITY, DYSLIPIDEMIA AND HYPERTENSION. HE WAS DIAGNOSED WITH PREDIABETES AROUND AGE 45.

"SAMUEL'S PRIMARY CHALLENGE WAS ADHERING TO A DIETARY PLAN"

PHYSICIAN:

Karl Nadolsky, DO, FACE

Diplomate, American Board of Obesity Medicine; Assistant Clinical Professor of Medicine, Michigan State University; Chair, AACE Obesity & Nutrition Disease State Network

History:
Previously diagnosed with obesity, dyslipidemia and hypertension, Samuel understood that those conditions, as well as his genetic makeup, put him at high risk of type 2 diabetes, cardiovascular disease and metabolic dysfunction associated with fatty liver disease. His most recent labs showed a fasting hyperglycemia (124 mg/dL) along with ALT 80 iU/L and AST 60 iU/L. At his initial visit, he weighed 224 lbs. and his BMI was 32. Although Samuel had met with dietitians and used commercial weight-loss programs for several years, his primary challenge was adhering to a dietary plan. After achieving a 5% weight loss on phentermine, he gradually regained weight after stopping the therapy and adopting a carb-ketogenic diet. Metformin had little benefit and produced diarrhea. He told me he struggled with portion control and satiety, and that he often felt hungry and frequently thought about food.

We discussed treatment goals for prediabetes, metabolic syndrome and high cardiometabolic risk that included nutritional quality, physical fitness and a >15% weight reduction to lower the risk of type 2 diabetes and to put these obesity-related diseases (ORD) into "remission."

Initiating treatment:
Anti-obesity pharmacotherapy was strongly indicated for Samuel, who had responded modestly to phentermine monotherapy in the past. We discussed incretin therapy with a GLP-1 receptor agonist (GLP-1 RA) or a gastric inhibitory polypeptide (GIP) due to his ORDs. We started the GLP-1 RA at 0.25 mg subcutaneously weekly and titrated up to 2.4 mg weekly over four months. Samuel experienced some nausea, but he consulted with our dietitians and ultimately tolerated the medication. At subsequent visits, he said his "food noise" ceased, and he felt satiated after eating smaller portions of healthy meals. His adherence to dietary efforts resulted in his dropping to 184 lbs., and he was also able to do more exercise and strength training.

Considerations:
It's important to emphasize that "weight," per se is not the goal, but it can act as a surrogate for the actual clinical health goals we need to prioritize. In Samuel's case, achieving more than 15% weight reduction normalized his lipids, blood pressure and blood sugars without any specific required medications for those conditions. For those with obesity, especially those with prediabetes/metabolic syndrome without type 2 diabetes, obesity medications are preferred options due to the anticipated amount of weight loss to ameliorate ORDs and having direct effects on cardiometabolic health.

NEW!
KOL ON DEMAND VIDEO
Scan here for more insight on Samuel's case.

PATIENT: SARAH, 65, WEIGHED 197 LBS. WITH A HISTORY OF GESTATIONAL DIABETES. SHE WAS DIAGNOSED WITH PREDIABETES, HYPERTENSION, DYSLIPIDEMIA AND CHRONIC KIDNEY DISEASE.

"SARAH'S METABOLIC SYNDROME AND CKD INCREASED HER CARDIORENAL RISK"

History:
At her initial visit, Sarah's AIC was 6.1%, her BMI was 34.9 and she had a urine albumin-to-creatinine ratio of 34 mg/g. She had been diagnosed with obesity and prediabetes in the past year and had been treated with statins for her dyslipidemia and angiotensin receptor blockers (ARBs) for her hypertension and chronic kidney disease (CKD). Sarah was referred to me for evaluation and management to prevent type 2 diabetes. She was previously prescribed metformin for diabetes prevention but was intolerant of the medication. Sarah also tried phentermine/topiramate in the past with a modest response (5% weight reduction) and experienced tolerance issues. She was started on a GLP-1 RA and titrated to 2.4 mg weekly with a 12% weight reduction but stopped taking the medication when Medicare no longer covered it.

Sarah was a retired schoolteacher who worked part time at the library. She had excellent nutritional habits that included a Mediterranean diet, a low intake of processed starches and sugars, and a high intake of vegetables, fruits, beans and legumes, as well as protein from fish, poultry, nuts and seeds. On the days she doesn't work, she and her husband enjoy outdoor activities such as walking or biking for 60 minutes a day. Despite this, her severe obesity and prediabetes, along with a metabolic syndrome and CKD, made her a high cardiorenal risk.

Initiating treatment:
Although Sarah responded well to the GLP-1 RA for obesity and had cardiorenal benefits, she could not continue with the medication because of insurance coverage, and so regained weight. We discussed bariatric surgery, which she was not interested in, but said she would consider it in the future if her weight and metabolic health warranted it. Our goal was to optimize her risk reduction through weight loss with medication and lifestyle modification.

While Sarah's diet was good and she engaged in aerobic activity, we talked about adding resistance training to her exercise regimen. I also prescribed an SGLT2 inhibitor, which has been shown to have significant cardiorenal benefits for those at high risk, specifically CKD with albuminuria. It also has glycemic benefits, even in prediabetes, along with some weight reduction if it addresses the compensatory physiological drive for increased energy intake. Sarah agreed to start resistance training, which is essential for everyone regardless of weight, but is especially needed for those with obesity and metabolic complications. We developed a plan to incorporate weight training into her exercise regimen by taking small steps. She started by doing basic pushing and pulling upper body exercises twice weekly, along with stair climbing, walking and biking.

Sarah was able to maintain the weight she lost on the GLP-1 RA with continued nutrition and exercise after taking the SGLT2 inhibitor, and her urine albumin-creatinine ratio improved to < 30 mg/g with stable eGFR. Her AIC dropped to < 5.7% and remained stable.

Considerations:
Sarah's case demonstrates the increased cardiorenal risk of many struggling with obesity and prediabetes. We must find ways to optimize treatment with lifestyle changes and utilize other beneficial medications, such as SGLT2 inhibitors, that may not produce as much weight reduction but that improve health outcomes. We should also consider surgical therapy, if warranted.

Illustration by Juhee Kim

Q

A

Expert insight on managing overweight/obesity

Illustration by Adam Mccauley Collection

When BMI falls short

Q: Which patients are good candidates for obesity medications?

A: Anti-obesity medications are currently FDA-approved for patients with a BMI of 27 or higher and at least one weight-related condition—such as prediabetes, type 2 diabetes, hypertension, hyperlipidemia, fatty liver disease or sleep apnea—or a BMI of 30 or higher. While HCPs should consider BMI when determining eligibility for anti-obesity medication it also has limitations. BMI does not account for body fat distribution, muscle mass or ethnic variations. For example, Asian Americans may face higher metabolic risks at lower BMI levels.

When I evaluate patients in my clinic, we offer body composition analysis by either bioimpedance or DEXA scan. If you do not have access to advanced technologies like these, aside from using a scale, I encourage providers to track weight loss or assess metabolic risk by measuring waist and hip circumference. Losing inches, especially from the waist area, is an excellent indicator of a reduction of visceral adipose tissue. A comprehensive evaluation beyond BMI is crucial for setting weight-loss goals and assessing overall health.

—Stephanie Ortiz Page, MD, *Diabetologist and Obesity Medicine Specialist Carteret Health Care, Morehead City, NC*

Individualizing weight-loss goals

Q: What do you say to patients about setting weight-loss goals?

A: I work with patients to set realistic, sustainable weight-loss goals. These goals are highly individualized, which is why it's important to have open and honest conversations with your patients. As mentioned in the previous question, I do not use BMI to set weight loss goals for patients. Research, such as the Look AHEAD trial, demonstrates that even a modest weight loss of 5–10% can significantly improve metabolic health. Often, an initial target of 10% weight loss is a good starting point.

I also emphasize the importance of improving metabolic markers and overall quality of life. This might include increased mobility, better sleep, reduced joint pain and the ability to enjoy activities. Focusing on improvement of health and wellness, not just the number on the scale, helps patients remain positive in their journey. Newer obesity medications and surgical options also can facilitate more substantial weight loss, but the focus should remain on long-term health and well-being.

—Stephanie Ortiz Page, MD

Follow-up strategy

Q: What's your strategy for follow-up when starting patients on an obesity management plan?

A: When a patient starts an obesity management program, they will initially require frequent follow-up visits to ensure accountability, support and safety. The initial appointment is usually a thorough assessment visit where medical history, weight history, nutrition, physical activity, sleep and mental health are assessed. In addition, diagnostic tests and labs are ordered as needed to evaluate the patient's obesity and related complications. A follow-up is typically scheduled within the next month to review results and to initiate a comprehensive treatment plan. This involves lifestyle changes and may also include obesity medications and referral to bariatric surgery. A follow-up is usually scheduled 2 to 4 weeks later, and then monthly for the first few months after that. Frequent visits allow the provider and the patient to focus on one to three behavior goals at a time, while also monitoring and adjusting medications as necessary.

As the patient progresses through the program, the visits may be spaced out to every 6 to 12 weeks and progress to every 3 to 6 months during the maintenance phase. It is important to remember that obesity is a chronic disease just like diabetes or hypertension and must be treated as such. The treatment that allowed the patient to reach a healthier weight will likely need to continue long-term. Weight regain is not a sign of failure on the patient's part but simply an indication of the chronic and progressive nature of the disease of obesity.

—Karli Burridge, PA-C, MMS, FOMA, *obesity medicine specialist, Glen Ellyn, IL, owner, Gaining Health (gaininghealth.com)*

The maintenence challenge

Q: How do you help patients maintain their weight loss?

A: The first key to weight maintenance is proving education. I remind my patients that it may take more effort to keep the weight off than to lose it. For example, I'll explain that if they are 200 pounds and walk a mile, they'll burn a certain number of calories. Yet if they get down to 150 pounds and walk the same mile, they'll burn fewer calories, so they may need to expend more energy to maintain the weight loss.

When they come back for a visit, I ask how they're doing, what's working, what's not and make modifications to help them adhere to their weight maintenance plan. For patients who are tied to their cellphones, we also send text reminders—studies show this helps with adherence. It takes persistence and engagement on the part of both the patient and the provider.

—Ved Gossain, MD, *Professor of Medicine Emeritus/endocrinology and metabolism, Michigan State University*

> "Weight regain is not a sign of failure on the patient's part but simply an indication of the chronic and progressive nature of the disease of obesity." *—Karli Burridge, PA-C, MMS*

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Health Monitor

Clinician Update

EXAM TOOL

Screening for overweight/obesity

The American Association of Clinical Endocrinology recognizes obesity as a chronic disease and recommends annual screening of BMI and other health parameters. When a patient presents with excess weight, use the checklist below to gauge the need for medical intervention, including lifestyle therapy and, when appropriate, obesity medication or surgery. And keep in mind: The success of treatment should be measured not solely by number of pounds lost but also by improvements in weight-related complications and overall health.

1. Does the patient have a body mass index (BMI) and weight-related complications that meet indications for prescribing obesity medication?

- ☐ **BMI ≥30** (obesity) (all BMI cutoffs may be lower in certain ethnicities)
- ☐ **BMI ≥27** (overweight) with at least one weight-related complication, such as:
  - Prediabetes or type 2 diabetes
  - Metabolic syndrome
  - Hypertension
  - Dyslipidemia
  - Cardiovascular disease
  - Nonalcoholic fatty liver disease
  - Obstructive sleep apnea
  - Asthma/reactive airway disease
  - Osteoarthritis
  - Hormonal issues (e.g., polycystic ovarian syndrome)
  - GERD
  - Urinary stress incontinence

2. If BMI <35, is waist circumference indicative of cardiometabolic disease (use gender- and ethnicity-specific cutoffs)?

- ☐ **Women: ≥35 inches**
- ☐ **Men: ≥40 inches**

3. Has the patient attempted lifestyle therapy, including nutritional and behavioral changes and increased physical activity)?

- ☐ **Yes;** measures tried: _____
- ☐ **No**

4. Is the patient aware obesity is a chronic disease caused by genetic, metabolic, behavioral and environmental factors?

- ☐ **Yes**
- ☐ **No**

5. Is the patient motivated to set weight-loss goals and work with you on a personalized treatment plan?

- ☐ **Yes**
- ☐ **No**

Note: For detailed recommendations on weight management, see Garvey WT, et al. AACE/ACE Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity. *Endocrine Practice.* 2016;22(suppl 3):1-203.