How Would You Manage This Patient With Obesity? Grand Rounds Discussion From Beth Israel Deaconess Medical Center

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In 2022, 1 in 8 people in the world were living with obesity, and lifestyle interventions that include diet, exercise, and behavioral modification have been the foundation for management of obesity. Recently, pharmacologic therapies have been developed for management of obesity, the newest of these being glucagon-like peptide 1 receptor agonists. With the development of new pharmacologic options, the American Gastroenterological Association developed a guideline in 2022 to provide evidence-based recommendations for the pharmacologic management of obesity in adults and recommended, for adults with obesity or overweight with weight-related complications who have had an inadequate response to lifestyle interventions, adding pharmacologic agents to lifestyle interventions over continuing lifestyle interventions alone. In this article, 2 experts review the available evidence to answer the following questions: How effective are lifestyle interventions for the treatment of obesity? How effective are pharmacologic interventions for the treatment of obesity? Given these options, how do you engage in a shared decision-making discussion to develop a mutually agreed-on treatment plan?

Ann Intern Med. 2024;177:1415-1424. doi:10.7326/ANNALS-24-01740
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 8 October 2024.

Ms. B is a 49-year-old woman with a history of hyperlipidemia, depression, and obesity. Her body mass index (BMI) was 21.2 kg/m^2 in 1994 and has slowly increased over the decades. At her most recent visit, her blood pressure was 115/82 mm Hg, weight was 171 pounds, and BMI was 31.2 kg/m^2. Her creatinine level was 0.9 mg/dL (79.56 µmol/L), total cholesterol level was 247 mg/dL (6.4 mmol/L), high-density lipoprotein level was 54 mg/dL (1.4 mmol/L), measured low-density lipoprotein level was 162 mg/dL (4.2 mmol/L), and hemoglobin A_{1c} (HbA_{1c}) was 5.7%.

Her only current medication is citalopram. She lives with her daughter and works as an early childhood educator. She reports no alcohol or tobacco use. She has a family history of diabetes, hyperlipidemia, and hypertension as well as end-stage renal disease in her father for whom she was a living related kidney donor.

She is interested in considering an antiobesity medication (AOM) as she has been unsuccessful with all prior weight loss attempts.

Ms B's Story (Video at Annals.org)

See the patient video (available at Annals.org) to view the patient telling her story.

ABOUT BEYOND THE GUIDELINES

Beyond the Guidelines is a multimedia feature based on selected clinical conferences at Beth Israel Deaconess Medical Center (BIDMC). Each educational feature focuses on the care of a patient who "falls between the cracks" in available evidence and for whom the optimal clinical management is unclear. Such situations include those in which a guideline finds evidence insufficient to make a recommendation, a patient does not fit criteria mapped out in recommendations, or different organizations provide conflicting recommendations. Clinical experts provide opinions and comment on how they would approach the patient's care. Videos of the patient and conference, the slide presentation, and a CME/MOC activity accompany each article. For more information, visit Annals.org/GrandRounds.

This article is based on the General Medicine Grand Rounds conference presented at the ACP Internal Medicine Meeting on 19 April 2024.

Beth Israel Lahey Health
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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

As a child, I was not overweight. I was really thin. My weight trajectory has fluctuated once I started having children. I have tried a lot of times to lose weight during the time since my weight started going up and down. I have tried different diets, I tried different strategies of trying to eat healthier, and unfortunately it didn't work. I have never tried any weight loss medications. I am definitely interested in trying a weight loss medication now, only because I am getting older and I know my metabolism is slowing down. I definitely do have some concerns. My main concern is just being consistent, maintaining what I need to maintain like a healthy balanced diet, exercising, and keeping the communication open with my physician.

When I've tried to lose weight on my own—I would probably say I've lost 2 or 3 pounds, and then gain the weight right back. My parents are Southern adults so they are constantly frying things, which I try to stay away from. Also, a lot of their food is salty, like a lot of pork and stuff, so I try to eat lots of salads and to do some lean meats and stuff. They're not having it but I tried.

To be honest with you, exercise, I only do that at work. I go up and down the stairs. I live in an apartment complex, so I am always up and down the stairs, as I don't have an elevator. I am always walking everywhere that I need to get to, but most of the time, just my commute is my exercise.

My teenage daughter makes it hard for me to lose weight, too, because she always wants to order pizza, or she wants to order fast food stuff, and I try to redirect her to eating healthy because I am like, you know, in the long run you are going to need this for your body when you get older.

I would say the depression that I went through in the past did affect my weight because when I am sad and down I am looking for that comfort food and, sometimes want to binge on snacks or even eat ice cream or something, so that does affect my weight. Now I just try to be a little more positive and not look at negative things, but just be grateful for the things I do have in my life.

Oh my goodness, for weight loss, my goals are to definitely lose some weight. I would love to lose at least about 25 pounds.

The question I would like to ask the experts—I want to know the diversity of the participants and how it affects them?

CONTEXT, EVIDENCE, AND GUIDELINES

The World Health Organization defines obesity as "excess or abnormal fat accumulation that presents a risk to health" (1), whereas the Centers for Disease Control and Prevention (CDC) defines it as "weight that is considered higher than what is considered healthy for a given height." Body mass index is a person's weight in kilograms divided by the square of height in meters. Although an imperfect measure, a BMI of 25 to 29.9 kg/m^2 is considered in the overweight range and 30 kg/m^2 or greater is considered obesity (2).

In 2022, 1 in 8 people in the world were living with obesity (1). New population data in the United States from the same year showed that 22 states now have an adult obesity prevalence at or above 35%. The data also demonstrated differences by race and ethnicity, with higher prevalence in American Indian, Alaska Native, Black, and Hispanic adults. Adults with obesity were at increased risk for many serious health conditions, including heart disease, stroke, type 2 diabetes, and some cancers (2).

Lifestyle interventions, including diet, exercise, and behavioral modification, are the foundation for the management of obesity and can provide small but significant weight loss (3). Recently, several pharmacologic therapies have been developed for the management of obesity. The newest of these agents are glucagon-like peptide 1 (GLP-1) receptor agonists (RA) such as liraglutide and semaglutide.

Glucagon-like peptide 1 is an endogenous incretin hormone produced within the intestinal mucosa in response to the intake of nutrients. The GLP-1RAs have various metabolic effects, including glucose-dependent stimulation of insulin secretion, delayed gastric emptying, and inhibition of food intake (4). The range of organs affected and modes of action may explain the extent of benefits found beyond management of obesity, including treatment of metabolic dysfunction–associated steatotic liver disease (MASLD; formerly called nonalcoholic fatty liver disease) and improvement in cardiovascular outcomes (5).

With the development of new options for pharmacologic therapy, the American Gastroenterological Association (AGA) developed a guideline, in 2022, to provide evidence-based recommendations for the pharmacologic management of obesity in adults (6). An evidence review conducted by the AGA identified 27 randomized controlled trials in adults with obesity or overweight with weight-related complications. The mean age was approximately 40 to 60 years and mean BMI was 32 to 36 kg/m^2. All trials compared pharmacologic treatment added to lifestyle interventions versus placebo or usual care and lifestyle interventions. As a minimum, lifestyle interventions included hypocaloric diets (500–600 kcal/d deficit) along with 150 minutes of physical activity per week (6).

Reported weight loss was substantially higher in the pharmacotherapy group and the mean difference ranged between 3.0% and 10.8% total body weight loss depending on the pharmacologic agent. Treatment discontinuation ranged from 34 in 1000 to 219 in 1000 more in the treatment group. The adverse event rate ranged from 7 or fewer to 27 or more, depending on the pharmacotherapy used.

Based on this review, 4 drugs (semaglutide, 2.4 mg; liraglutide, 3.0 mg; phentermine-topiramate ER; and naltrexone-buproprion ER) were deemed by the AGA to have a moderate or large magnitude of weight loss and small or nonsubstantial harms and hence a balance favoring utilization (Table 1) (6). Of note, this review was conducted and the guideline published before tirzepatide was approved by the U.S. Food and Drug Administration (FDA) for treatment of obesity and before the SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) study showed decreased cardiovascular events with semaglutide in patients with preexisting cardiovascular disease but without diabetes (5).

In summary, for adults with obesity or overweight with weight-related complications who have had an inadequate response to lifestyle interventions, the AGA recommends adding pharmacologic agents to lifestyle interventions over continuing lifestyle interventions alone. This is a strong recommendation based on moderate-certainty evidence (6).

Clinical Questions

To structure a debate between our 2 discussants, we mutually agreed on the following key questions to consider when applying this guideline to clinical practice and to Ms. B in particular:

Question 1: How effective are lifestyle interventions for the treatment of obesity?

Question 2: How effective are pharmacologic interventions for the treatment of obesity?

Question 3: Given these options, how do you engage in a shared decision-making discussion to develop a mutually agreed-on treatment plan?

Discussion

Viewpoint: Anne N. Thorndike, MD, MPH

Question 1: How effective are lifestyle interventions for the treatment of obesity?

Lifestyle modification is the foundation for obesity management. Moderate- to high-intensity multicomponent behavioral interventions can produce 5% to 10% body weight loss (3). Behavioral interventions focus on changing diet and physical activity through education, addressing barriers, peer support, motivational interviewing, self-monitoring, and goal setting (3). Digital tools can assist with self-monitoring (for example, food intake, steps), and supplemental meal replacements (for example, shakes) can help achieve a calorie deficit for weight loss.

Weight loss from lifestyle interventions improves numerous health outcomes. In the Diabetes Prevention Program (DPP) trial of adults with prediabetes, every kilogram of weight lost in the lifestyle group was associated

Table 1. Evidence Profile for Supporting the Use of Pharmacologic Interventions for the Treatment of Obesity

Outcomes	No. of Participants (Studies), Follow-up	Certainty of the Evidence (GRADE)	Relative Effect, RR (95% CI)	Anticipated Absolute Effects (Risk Difference With Treatment)
Semaglutide 2.4 mg				
%TBWL	4352 (8 RCTs)	⨁⨁⨁⨁ High	–	MD 10.76% more (8.73 more to 12.8 more)
Treatment discontinuation due to adverse events	4353 (8 RCTs)	⨁⨁⨁⨁ High*	2.10 (1.54 to 2.86)	34 more per 1000 (from 17 more to 57 more)
Liraglutide 3.0 mg				
%TBWL	5968 (8 RCTs)	⨁⨁⨁⨁ High	–	MD 4.81% lower (5.39 lower to 4.23 lower)
Treatment discontinuation due to adverse events	6362 (10 RCTs)	⨁⨁⨁⨁ High*	2.31 (1.85 to 2.88)	91 more per 1000 (69 more to 120 more)
Phentermine-topiramate ER				
%TBWL	3141 (3 RCTs)	⨁⨁⨁⨁ High†	–	MD 8.45% higher (7.89 higher to 9.01 higher)
Treatment discontinuation due to adverse events	3141 (3 RCTs)	⨁⨁⨁⨁ High*†	2.08 (1.71 to 2.52)	91 more per 1000 (from 60 more to 129 more)
Naltrexone-bupropion ER				
%TBWL	12659 (5 RCTs)	⨁⨁⨁◯ Moderate‡	–	MD 3.01% lower (3.54 lower to 2.47 lower)
Treatment discontinuation due to adverse events	12839 (5 RCTs)	⨁⨁⨁⨁ High§	2.39 (1.69 to 3.37)	129 more per 1000 (64 more to 219 more)

MD = mean difference; MID = minimal important difference; RCT = randomized controlled trial; SAE = serious adverse event; TBWL = total body weight loss.

* Serious imprecision in the SAE outcome because the absolute risk crosses threshold of 1%, which was the predetermined MID threshold. Thus, the overall certainty of evidence for this pharmacotherapy was moderate.

† Low event rate leading to serious imprecision in both %TBWL ≥15% and SAE.

‡ MID or clinically important threshold below which there is no clear benefit of the intervention in discussion with the guideline panel and technical review team was determined to be 3 kg (or approximately 3%). We noted serious imprecision as the lower confidence limit crosses the MID for benefit.

§ Low event rate leading to serious imprecision in SAE outcome.

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with 16% reduction in diabetes (7). In the Look Ahead trial of adults with type 2 diabetes, participants receiving the intensive lifestyle intervention who lost 5% to 10% body weight had improvements in systolic and diastolic blood pressure; HbA_{1c}; and low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels, and those who lost 2% to 5% body weight had improvements in systolic blood pressure, HbA_{1c}, and triglyceride level (8). Additional health benefits included improvements in obstructive sleep apnea (9), knee osteoarthritis (10, 11), MASLD (12), quality of life, and depression (13).

The U.S. Preventive Services Task Force (USPSTF) recommendations for lifestyle behavioral counseling emphasize the importance of frequency and intensity of contacts (minimum of 12 contacts over 12 months [14]). However, maintenance of weight loss requires even longer-term monitoring and counseling. The strongest predictors of weight loss maintenance include self-monitoring, increased physical activity, and adherence to eating behaviors, such as portion control and reduced energy intake (15, 16).

The time and intensity of counseling needed for successful weight loss is challenging to deliver within routine clinical practice. Barriers to clinicians providing lifestyle behavioral counseling include lack of training and knowledge, lack of time, and competing demands (17, 18). In the end, providing the necessary counseling often requires referral to outside resources, such as dietitians, community-based lifestyle programs, or commercial weight loss programs.

Question 2: How effective are pharmacologic interventions for the treatment of obesity?

Randomized clinical trials have demonstrated that long-acting GLP-1RAs produce weight loss up to 15% of body weight (6). Recently FDA-approved tirzepatide has dual-hormone agonistic activity at the GLP-1 receptor and the glucose-dependent insulinotropic polypeptide receptor (GIP/GLP-1RA) and produces weight loss up to 20% at the highest dose (10 mg subcutaneously) (19, 20). All GLP-1 and GIP/GLP-1RA weight loss trials have included counseling about diet, caloric intake, and physical activity. It is unknown if the weight loss in clinical trials can be achieved without lifestyle counseling, as often occurs in real-world practice. Trials have demonstrated that stopping GLP-1 or GIP/GLP-1RAs leads to weight regain over a year (21, 22).

Important considerations when initiating treatment with GLP-1 and GIP/GLP-1RAs include adverse effects, cost, and adherence. Gastrointestinal adverse effects, including nausea, vomiting, diarrhea, and constipation, are the most common (3, 21). In clinical trials, the rate of stopping medications due to adverse effects was 6% to 7% of participants taking the highest doses (20). In observational data, real-world adherence to GLP-1RAs prescribed for diabetes was 65% at 1 year and 30% at 2 years; adherence was highest among those with lowest insurance copays (23, 24). One estimate of the cost of GLP-1RA therapy compared with lifestyle intervention was between $237 000 and $483 000 per quality-adjusted life-year gained (25).

Question 3: Given these options, how do you engage in a shared decision-making discussion to develop a mutually agreed-on treatment plan?

Weight stigma is pervasive in society and medical care. Discussing obesity requires a patient-centered approach that avoids blame or shame, using nonstigmatizing language and focusing on overall health and well-being (26). Clinicians should approach conversations with awareness of how racial, ethnic, and socioeconomic disparities and psychological factors (for example, depression [27]) impact obesity and treatment access.

Shared decision making using the 5 As framework (Assess, Advise, Agree, Assist, and Arrange) provides a roadmap for obesity counseling (Table 2). Although many health systems systematically screen for depression and social determinants of health, regular assessment of diet and physical activity is rare (18, 28). Integrating brief, validated diet (for example, rapid Prime Diet Quality Score [29]) and activity (for example, Physical Activity Vital Sign [30]) screeners into routine care would enable efficient assessment of lifestyle at clinical visits.

Before advising about weight loss, I would ask more about Ms. B's health goals. How did she choose 25 pounds (that is, 15% body weight)? I would discuss that health benefits, such as preventing diabetes and improving blood pressure, can be achieved with lower weight loss (for example, 5% to 10% body weight, or 9 to 17 pounds for her). I would advise her about the benefits, side effects, and costs of medications and discuss current knowledge gaps in the field, including whether lifelong medication is needed to maintain weight loss.

Ms. B has unsuccessfully tried to lose weight, which is frustrating. When counseling about lifestyle, I use a collaborative approach to set achievable goals consistent with the patient's preferences, social circumstances, and readiness to change. Rather than focusing on individual foods, I discuss an overall healthy dietary pattern that allows for an ongoing dialogue about diet over time. For example, rather than telling Ms. B never to eat fried food, I would suggest she mostly prepare food by baking, grilling, or broiling, but on special occasions, she can eat fried food and enjoy it. The American Heart Association's 2021 Dietary Guidance outlines simple evidence-based recommendations to guide counseling about a dietary pattern to promote cardiovascular health, including eating plenty of fruits and vegetables, choosing mostly whole grains, choosing healthy protein sources, using liquid plant oils, and minimizing foods with added sugars and salt (31). Clinicians can advise and support patients in various dietary patterns that align with this guidance (32).

Table 2. The 5 As Framework for Obesity Counseling With Key Points for Focusing on Lifestyle and Pharmacotherapy

5 As	Components	Key Points	
		Lifestyle	**Pharmacotherapy**
Assess risk factors and readiness to change	Ask for permission to discuss weight Assess obesity-related comorbid conditions Assess social and psychological factors Review medications Review anthropometric measurements and blood tests (e.g., weight, height, waist circumference, blood pressure, lipids, and Hb_{A1c}) Ask about prior weight loss attempts Ask about patient's goals	Screen for social determinants of health (e.g., food insecurity, unstable housing) Screen for depression, anxiety; maladaptive eating behaviors (e.g., binge eating) Ask about current diet and physical activity patterns Ask about neighborhood and home environment (e.g., access to supermarket, neighborhood walkability, kitchen appliances, cooking tools)	Ask about experience with and knowledge of antiobesity medications Ask about interest in and willingness to take antiobesity medications
Advise on health risks and benefits	Discuss obesity as a chronic disease Review health risks of obesity Review health benefits of weight loss	Discuss that 5% to 10% weight loss is achievable with intensive lifestyle intervention Discuss other health benefits associated with 2% to 10% weight loss with lifestyle changes Emphasize health benefits of healthy diet and physical activity, even if weight loss not achieved	Discuss that GLP-1 and GIP/GLP-1 RAs can produce 15% to 20% weight loss Discuss that other antiobesity medications can achieve 4% to 9% weight loss Discuss that GLP-1-RAs reduce mortality for adults with preexisting CVD Discuss potential adverse effects of antiobesity medications and need for long-term use
Agree on specific and achievable goals	Collaborate to develop 1 to 3 specific, measurable, and attainable goals for weight loss and lifestyle changes (e.g., eating 5 servings of fruits and vegetables daily; walking 20 minutes 3 times a week; tracking daily dietary intake) Personalize approaches based on patient's preferences and barriers	Agree on dietary goals as part of a healthy dietary pattern adapted to patient's personal and cultural preferences Discuss physical activity goals realistic for patient's current fitness, schedule, mobility, and neighborhood Present flexible options for physical activity, such as "weekend warrior" pattern Agree on weight loss goal that is achievable with lifestyle modification	Agree on whether and when to start weight loss medication
Assist in selecting treatment using shared decision-making approach	Help patient address barriers to care (e.g., depression, social determinants of health) Offer intensive behavioral lifestyle counseling or referral to a program (e.g., www.cdc.gov/diabetes/prevention/find-a-program.html) Offer antiobesity medications, if appropriate Offer referral to bariatric surgeon, if appropriate	Assist in finding a community-based or commercial behavioral program, if desired Provide alternative options for patients unable to or not interested in attending a program (e.g., referral to dietitian or health coach, self-monitoring technology, frequent follow-up for counseling)	Assist with selecting antiobesity medication that is appropriate for the patient's weight loss goal, is affordable, and has acceptable side effects
Arrange follow-up	Follow up with patient within 2 to 3 months to assess progress with achieving goals and to adjust treatment plan as necessary Referral to multicomponent weight loss program, obesity medicine clinic, or bariatric surgery, as needed Refer to specialty care for work-up and treatment of obesity-related comorbid conditions	Provide regular follow-up to support lifestyle changes, address barriers as they arise, and emphasize consistency (e.g., "some is better than none") Provide new referrals as appropriate for diet and exercise counseling or programs	Provide regular follow-up to assess progress with weight loss, need for changing medication or dose, and side effects. Regularly assess that patient has adequate nutritional intake (i.e., following healthy dietary pattern)

Although increasing physical activity without changing diet has minimal impact on weight, I emphasize that physical activity benefits health at any weight (33). There is a dose effect on cardiovascular outcomes, even when recommended activity guidelines are not achieved (34, 35). Recent studies have shown that a "weekend warrior" exercise pattern (that is, achieving most activity over 1 to 2 days per week) has the same cardiovascular benefits as exercising several days a week (36).

I would ask Ms. B to quantify her activity (for example, number of flights of stairs) and explore how to build on this. Walking is an excellent activity that is low cost and flexible; however, other activities can be considered (for example, stationary bike, exercise videos), particularly if there are constraints related to mobility or neighborhood safety. For people with work or other responsibilities preventing them from weekday exercise, I suggest setting a goal for physical activity on weekend days, emphasizing that "some is better than none."

Participating in a multicomponent behavioral program could help Ms. B achieve moderate weight loss and address her concerns about consistency. Program choices depend on local availability, cost, and patient interest in a group or individual program; availability and insurance coverage vary by state, health care system, and community. She could consider a community-based DPP or a commercial-based program. The National DPP, available for adults with prediabetes, includes 26 modules about diet, physical activity, and behavior change delivered by a lifestyle coach over 12 months (37). The program is covered by many insurance plans, and patients and clinicians can find local programs on the CDC website (www.cdc.gov/diabetes/prevention/find-a-program.html). If participating in a program is not an option, I would discuss referral to a dietitian, using low-cost food and activity tracking technology, or if appropriate, a commercial weight loss program.

No matter what treatment Ms. B chooses, I would engage in regular follow-up to discuss her progress, review her goals, and emphasize the importance of lifelong healthy lifestyle for optimal health and well-being at any weight.

Viewpoint: Melanie R. Jay, MD, MS

Question 1: How effective are lifestyle interventions for the treatment of obesity?

Lifestyle change is extremely important for the prevention and management of all chronic diseases, including obesity. Unfortunately, there is little evidence that brief, infrequent counseling is effective for obesity (14). Attending intensive, multicomponent behavioral programs (such as DPP) recommended by the USPSTF (14) is challenging given competing demands on patients' time, as well as the poor access to and low insurance coverage of weight management programs. Even when programs are available, free, and widely promoted (such as the MOVE! program through the Department of Veterans Affairs), only 3% to 50% of eligible patients attend 1 or more visits (38).

Further, these programs are not effective for everyone. In Look Ahead, only a little over half of participants achieved their 7% weight loss goal at 1 year despite attending more than 35 treatment sessions on average (39). One reason for this is that the homeostatic pathways that signal hunger and satiety are often dysregulated in patients with obesity. When they lose weight, their hunger hormones (for example, ghrelin) increase, their satiety signals (for example, via leptin) are blunted, and metabolic adaptations lead to lower energy expenditure, which can all lead to weight plateaus and regain (40). When this happens, patients often blame themselves and/or are blamed by health care providers despite their sustained effort. These experiences of weight bias can further emotional eating and stress, creating more barriers to health and weight loss (41). Thus, health care providers need to be aware of their own weight biases and support patients when lifestyle interventions alone do not work.

Question 2: How effective are pharmacologic interventions for the treatment of obesity?

The GLP-1RA–containing medications that are currently FDA approved for the treatment of obesity are liraglutide (daily injection) and weekly semaglutide and tirzepatide injections (3). The mean weight loss of the weekly injectables is 15% to 20%, and 8% for liraglutide. There is also an oral form of semaglutide that is currently FDA approved for diabetes treatment only. In people with obesity and cardiovascular disease, semaglutide decreases the risk for death from cardiovascular causes (3), nonfatal myocardial infarction, or nonfatal stroke (5) and it may also decrease blood pressure (42) and improve kidney function (43). Unfortunately, in real-world practice, patients may not experience the same level of weight loss (44) and other health benefits, probably due to lower adherence and lifestyle support. Further, participants in the STEP, SURMOUNT, and SELECT studies were mostly White, so it is unclear how well these medications work in minoritized populations who are more likely to experience socioeconomic disadvantage with less access to healthy food and physical activity. With global shortages, high cost ($900 to $1200 per month), and lack of coverage by Medicare and Medicaid, access to these medications has been difficult, and this may increase obesity-related health disparities. More studies are needed to understand barriers and facilitators to use of these medications.

Choosing between medications depends on patient needs and preferences, availability, cost, and ability to tolerate side effects. While there are few comparative effectiveness studies, tirzepatide had higher weight loss in clinical trials and may have fewer gastrointestinal side effects than other GLP-1RA–containing medications (3). Nausea, constipation, and other gastrointestinal side effects can sometimes be managed through dietary

changes such as avoiding spicy and fried foods, eating slowly, maintaining adequate hydration, and avoiding late night eating (45). We usually expect at least a 5% to 10% weight loss over the first 3 months; if this does not happen or if the medication is not tolerated, it should be discontinued (46) or changed to another medication.

While the SELECT study followed patients for 4 years, longer-term effects of these medications are unknown. Patients can experience weight loss plateaus while taking the medications at around 1 year (47), and weight regain (two thirds within 1 year) is expected if patients decide to stop taking them (21, 22). There is a concern for muscle loss and sarcopenia (48). Thus, the focus of lifestyle counseling may be geared more toward adequate macronutrient intake (reduced calorie diet high in fruits and vegetables and 0.8 g/kg of body weight of protein per day [45]) and resistance training to potentially prevent or offset muscle loss (45), but more research is needed.

Much of the recent focus in media coverage has been on injectables, but there are older medications that are FDA approved and can be safe, effective for long-term use, and less expensive. Studies of phentermine–topiramate, naltrexone–buproprion, and orlistat demonstrate an additional 4% to 8% weight change above and beyond lifestyle alone (5% to 10% total weight change [3]). Phentermine and diethylproprione are FDA approved for 12 weeks only, but many providers use them longer. Medications that are used off label include oral semaglutide, topiramate, buproprion, and metformin, which can be safe and effective and can have other health benefits (for example, diabetes prevention for metformin, migraine prophylaxis for topiramate).

Question 3: Given these options, how do you engage in a shared decision-making discussion to develop a mutually agreed-on treatment plan?

First, it is important to have the conversation in a respectful way and that honors the patient's preferences and priorities. Always ask permission to discuss weight management, and ask them what steps they are taking to manage their weight. Patients often tell me that they are demoralized when they are told to lose weight even though they recently lost 10 pounds through much effort. Ms. B would like to lose 14.6% of her body weight. I agree with Dr. Thorndike that I would explore the reasons for this particular goal. While this goal is probably achievable with a GLP-1RA plus lifestyle interventions, she could probably lower her HbA_{1c} level and decrease the risk for diabetes significantly with a 5% to 7% weight loss (49). Other factors such as mobility, preferred appearance, social norms, comorbid conditions, and willingness to take medications may help determine the treatment plan. Although patients and health care professionals often strive to achieve a "normal" BMI, optimal health may be different for patients at various BMIs, so BMI itself is controversial (50) and I do not use it as a target for goal setting.

Dr. Thorndike reviewed several benefits of lifestyle interventions–increasing physical activity and improving diet would be beneficial even if it does not lead to clinically significant weight loss. To do this, I would take a more detailed dietary history, work with her to set individualized behavior change goals, and recommend an intensive program. If the DPP program is available, it would be a good fit. Online commercial programs that meet USPSTF standards are another option (such as Weight Watchers).

Ms. B noted that she is interested in an AOM (that is, a GLP-RA). Given that she has prediabetes and the fact that lifestyle-based treatments often do not lead to clinically significant weight loss, I would not require her to wait if she wants to start AOMs simultaneously with lifestyle changes. If she does not have coverage or access to the GLP-1RAs, then I would discuss the other FDA-approved weight management medications. Phentermine–topiramate could be a good option for her (barring contraindications) and is associated with a 9% weight loss with lifestyle changes (51). In many states, however, prescriptions for phentermine-containing medications (which are Schedule 4 drugs) have to be renewed monthly, which may impact adherence. Metformin is also an excellent option, given that she has prediabetes; it can lead to clinically significant weight loss (52) and has been shown to decrease the risk for progression to type 2 diabetes (53).

Regardless of treatment choice, I would discuss how obesity is a chronic disease that is caused by genetic and environmental factors. I would let her know that people often gain weight back when they stop taking AOMs. I find hypertension to be a useful analogy. When people start medications to treat hypertension their blood pressure goes down, and we would expect it to go back up when the medications are discontinued. The same thing is true for obesity.

SUMMARY

In discussing the 2022 AGA guideline on pharmacologic management of obesity in adults, Dr. Thorndike noted that lifestyle modification is the foundation for obesity management, that moderate- to high-intensity multicomponent behavioral interventions can produce 5% to 10% body weight loss, and that weight loss from lifestyle interventions improves numerous health outcomes. She acknowledges that lifestyle behavioral counseling to treat obesity requires frequent and intense contact, which can be challenging in primary care. For our patient, given the potential benefit, she would advocate more intensive lifestyle modification before moving on to pharmacologic therapy. Dr. Jay agrees that lifestyle modification forms the foundation for obesity management, but she would recommend pharmacologic therapy at this time given that our patient has prediabetes and would like to proceed with an AOM. She would recommend treatment with a GLP-1RA if our patient has coverage and access. If not, she would recommend

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phentermine–topiramate (barring contraindications) or metformin as she has prediabetes and it can decrease the risk for progression to type 2 diabetes. Both our discussants noted that obesity is a chronic disease and that regardless of whether it is treated with lifestyle modification or pharmacologic therapy, it will require a lifelong commitment to follow-up and treatment.

GRAND ROUNDS CONFERENCE (VIDEO AT ANNALS.ORG)

A transcript of the audience question-and-answer period is available in the **Appendix** (available at Annals.org). To view the conference video (Video 2), including the question-and-answer session, go to Annals.org.

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Acknowledgment: The authors thank the patient for sharing her story.

Grant Support: Beyond the Guidelines receives no external support.

Disclosures: All relevant financial relationships have been mitigated. Disclosure forms are available with the article online.

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Appendix: Comments and Questions

Dr. Zahir Kanjee: I will pose my first question to both of you. I want to get a little more specific about some of the conversations that primary care physicians are having with patients when they're starting these medications; for instance, when they're starting a GLP-1. I am wondering if you can talk a little bit more—and you both touched on both of these issues—but can you talk a little bit more about the conversations you have about side effects that are coming with these medications, the sort of preemptive conversations that you're having and the advice you give to patients in those scenarios? And then also questions about how your exercise and diet recommendations may or may not differ in a person who is starting a GLP-1 versus those who are not. Maybe we can start with you, Dr. Jay.

Dr. Melanie Jay: Yeah. So, as I said, the GI [gastrointestinal] side effects are the ones that are going to be the most common. You can almost expect them. It's almost like a sign that the medications are working. I work with veterans and underserved populations that don't have as much access to healthy food, and I do find that if people are eating a really poor diet that they tolerate the medications less. For example, I had a patient who was eating Wendy's and I could not get them to be able to eat healthier because they lived in a food desert and it was very inconvenient [to find healthy food]. So, I had to take them off [the medication] because they couldn't eat the smaller portions, they couldn't avoid the fried food, they couldn't eat the fruits and vegetables, and so it really wasn't going to work well. And, of course, our trials are done in patients who have access to resources and who are mostly White, and so we have to kind of tailor the conversation given the person's circumstances. But, you know, certainly having individual conversations, finding out what they know about medications, and what their goals are, are very important.

Dr. Anne Thorndike: I totally agree about the side effects. I think as far as the lifestyle goes, I do want to emphasize that if we can work towards having ongoing conversations with our patients about lifestyle, then by the time you're talking about the medication, this is something that you have already been doing. However, if you haven't been doing that, I think my recommendation on lifestyle modification is the same whether they're starting the medication or not. I do think that if you are starting someone on the medication, you want to emphasize that it's going to work better if they make lifestyle changes, there is no question. I think anybody who is prescribing these medications knows that they don't always work. They work for a lot of people, but they don't always work. They work better if somebody is already making lifestyle changes, and that is why it sometimes might be good to give them a couple of months to start to make these changes and then start the medication when they have gotten more of a pattern going.

Dr. Kanjee: Thank you. So, we can now turn to questions from the audience.

Dr. Kimulique H. Allen: Kim Allen, Dallas, Texas. I have a question. The patient in the exam room mentioned she is on Celexa, or citalopram, and she mentioned depression, and we know that with some of the GLP-1s we have seen depression or worsening of depressive symptoms. Would that be something that we would consider for her? And if we did, how would we follow-up with her then to make sure that her mood symptoms did not worsen? Thank you.

Dr. Jay: I am so glad you asked that question because we did not address that, and the European Union was also very concerned because they were worried about suicides in participants who were on GLP-1s. There have not been, though, in the trials at least, more psychiatric symptoms in patients on GLP-1s versus placebo. I actually wrote to the author [of the SELECT Trial] and I said, "Did you look at suicide? Did you look at these things?" And they said, "yes, we'll be publishing it soon, but we didn't really see a difference." And with a lot of weight loss studies, in general, depression gets better with weight loss. But certainly with her, if she actively has depression, then yes, we screen for it [suicide], we talk about this as a potential side effect, and it is hard to know. I mean, when someone loses a drastic amount of weight, the way they walk through the world is different, people respond to them differently, their relationships might change, and so there are some major changes that happen sometimes when someone loses significant amounts of weight. So, I do think talking about those possibilities as well is really important for our patients, so I would definitely monitor that, certainly, and thank you for that.

Dr. Kanjee: Anything to add?

Dr. Thorndike: Nothing to add.

Dr. Kanjee: Okay. We'll go to our next question.

Dr. Jack Ende: Jack Ende, University of Pennsylvania. When we talk about GLP-1 receptor agonists, are we talking for the most part about the weekly injectables, which drives me and our PharmD person crazy as we do the fire walk dance, only to find that after all of that, the pharmacy doesn't have any in stock? Or might we begin to include oral agents?

Dr. Kanjee: Dr. Thorndike, do you want to start and take that one?

Dr. Thorndike: I was mostly talking about the injectables. I don't have a lot of experience with the oral medications. My impression is they are not as effective. Dr. Jay, probably—

Dr. Jay: So, they are not FDA approved yet for weight loss, which is the reason we didn't include them [oral GLP-1RAs]. They are FDA approved for diabetes, the oral semaglutide. I think they're going to end up being pretty effective. I don't know comparatively, as the studies have not fully come out. It's a little harder to take them as well, because you have to time it with medications and other things that they're taking. So, we will see more of them, but they are not FDA approved yet for weight loss, and I totally hear you about the access issues and the preauthorizations and hopefully that will get better soon. That is happening also with the daily injections as well. I mean, those are in shortage as well even though they're going to be coming out with a generic liraglutide soon.

Dr. Prentiss Taylor: Hi. Prentiss Taylor from Advocate Healthcare. Are there any advocacy organizations with a website that you can recommend that we can point our patients to? Sometimes I send them to the American

Diabetes Association because they have such great materials, but so many patients don't have diabetes or prediabetes. Anything you can recommend?

Dr. Thorndike: I would recommend the American Heart Association; it has great resources for lifestyle modification. I think the CDC website I mentioned [www.cdc.gov/diabetes/prevention/find-a-program.html], if people are actually looking for programs in their community, is really useful. You should go check it out, put your own ZIP code in, and see what's available. It's pretty surprising, and they include a lot of different programs there.

Dr. Jay: The ACP has a whole obesity resource section as well [www.acponline.org/clinical-information/clinical-resources-products/obesity-management-learning-hub], as does the Obesity Society [www.obesity.org/meetings-education/on-demand-education/], the OMA (Obesity Medical Association) [https://obesitymedicine.org/resources/obesity-algorithm/], and Stop Obesity Now [https://stop.publichealth.gwu.edu/]. There are a lot of sites, and there are a lot of great organizations.

Dr. John D. Myers: Hi, Jack Myers, Baylor Scott & White Medical Center. I appreciate this timely discussion. I had a couple questions as far as the affordability of semaglutide in particular. These weight loss clinics and compounding pharmacies have come up; can you comment a little bit about that as it is more affordable for patients, but yet not FDA regulated? And secondly, I didn't hear anything about bariatric surgery, and I was hoping you would comment on that as well.

Dr. Jay: Yeah, well, I am not an expert on compounding pharmacies, but there is not only compounding pharmacies, there are fakes out there, and with compounding pharmacies, they are not using the same salt. I don't feel comfortable recommending it because I don't know at any individual compounding pharmacy if it's going to be legitimate. Supposedly they have to send it to some lab to get it verified [if they are a 503B pharmacy; 503A pharmacies do not need verification, and they are not supposed to be providing these medications]. Also, a lot of the people using the compounding pharmacies are chiropractors or, you know, pop-up pain clinics, so I worry that we have to make sure that this doesn't become like the opioid crisis, right? Where everyone is just giving these medications out willy-nilly, because they are serious medications with serious side effects, so I don't feel comfortable, but then again, we want increased access. So, supposedly the companies are building more factories and they're going to be giving us more of these medications, and hopefully they will come down in price, but I don't know.

Dr. Hani Morcos: Hani Morcos, American University of Antigua. I slightly disagree on the point comparing hypertension to obesity. Simply, in my opinion, because hypertension is a chronic disease that is mostly controlled and not completely treated, but I had many patients who went on lifestyle modification with good diet and exercise and lost the weight and the obesity is gone, so they are not obese anymore, so they don't have the disease. Now, recently, I am saying this because I have a patient on semaglutide, and she lost 60 lb, she was very happy, and took it for 6 months. She stopped, and a month later she put back on 10 lb, and she came running in and she said, "I don't know what to do, I don't want to stay on the medication, I don't want to lose any more weight, but I don't also want to gain any more weight." So, what's the advice here? She doesn't want to stay on them for the rest of her life, on the medication, but in the meantime she started putting on a little bit of weight.

Dr. Jay: I don't think a lot of people can get themselves cured of obesity. Some people do. My father-in-law lost 70 lb with lifestyle changes and has kept it off for 30 years. Some people can. A lot of people can't. A lot of people are like our patient, or like the graphs I showed, that they lose the weight—even the Biggest Loser study—most of the people gained the weight back. So, they lose the weight and people gain it back. This illustrates the disease of obesity where you have this homeostatic pathway in the brain that is regulating your metabolism and diet, and so I think that like hypertension, a lot of people will need to be on the medication [long-term]. Now, are there going to be studies maybe where there's a maintenance dose? And maybe that will be lower? Maybe we can find other ways, maybe if they are able to ramp up their lifestyle they may require less [medication]. Maybe some people will be able to go off of it and not, you know, there are some people who also go off the medication and don't regain the weight back. So, there is this whole spectrum, and we still have a lot more to learn. Dr. Thorndike, have you had a lot of people cured of obesity? Or is it always kind of a struggle once they did the lifestyle?

Dr. Thorndike: No, I think being technically cured, to get your BMI below 25, is not the most common occurrence. I think the question is what is the end point for that particular patient? I think sometimes we are overly focused on the numbers, and I think it is important to help people to be focused on the progress—one of the things I say when I am counseling people is that I would prefer that you lose 10 lb and keep it off for the rest of your life than if you lose 50 lb and regain it all, because I think that the benefits of that 10-lb weight loss are very strong. So, I work with people to figure out what their personal goals are, and for some people, not being obese is a personal goal, but for other people it might be to lose some weight and maintain it. No matter whether weight loss is with medications or through lifestyle alone, you still need the lifestyle to help maintain it—that needs to be a piece of it no matter what.

Dr. Regan Christopoulos: Regan Christopoulos, Endeavor Health Medical Group. I also had a question about bariatric surgery, especially just with consideration of the cost benefit. Hypertension and obesity, when we're considering treating with a GLP-1, I don't think we can make the same comparison, because we're treating hypertension for about $10 a year, and the cost of a year of a GLP-1 is two thirds of the bariatric surgery price tag. And yes, you do gain weight after bariatric surgery some of the time, but it may be 5 or 10 or 20 years later, and it looks like a lot of these people who stopped their GLP-1 are gaining weight almost immediately. So, I am just wondering your thoughts on bariatric surgery given the

cost, because it's about $18 000 to $22 000 for the whole package, better insurance coverage, and actually better availability. And also I mean, I am giving some patients phentermine now, which I used to never do, because I look at them and I say, I mean, if as soon as you stop the medicine the weight comes right back, I can treat you for $5 a month for something that is only temporary. So, just, you know, for cost–benefit reasons.

Dr. Jay: I agree with all of that. Not only that, bariatric surgery is the most effective option we have still, even though other medicines might come out. We didn't talk about bariatric surgery because our patient is not a candidate right now because you have to have—yeah, you have to have the body mass index of 35 or 30 with comorbid conditions, so maybe she would be eventually a candidate. So, we haven't really talked about it, but it is [an option], yes. And even when people gain the weight back over several years, then you can put them on a GLP-1 later on because obesity is a progressive disease. Some people will have bariatric surgery and that will be it, and some people, when they start to gain the weight back, you might end up adding another medication. Just like diabetes is a progressive disease, so is obesity. And I also agree with phentermine; right now I can't get my patients at this moment in time a GLP-1 and I am putting a lot of people on phentermine–topiramate and actually it's better than—it probably has more weight loss than liraglutide. She is on an SSRI [selective serotonin reuptake inhibitor], so you do worry about serotonin syndrome [with phentermine]—although with only 1 SSRI probably you don't have to worry—but I always have to counsel the patient about that if they are on other medications that might prolong their QT interval. So, you just have a lot more thinking to do about potential side effects. But yes, I totally agree, the cheaper medications might be the way to go, especially as we are waiting for the other costs to come down.

Dr. Thorndike: I think the question about bariatric surgery is excellent. We didn't talk about it because it's actually not in the guidelines, so that's why we didn't address it. I think the cost–benefit is something that we really need to look at over time. Obviously, it is going to be very dependent on patient preference. Some people would never want to have surgery, and other people would say I don't want to take another medication for the rest of my life. But I think the cost–benefit [analysis] needs to be done, we need to get that. The cost of these drugs is, at this time, just inordinate. It is unsustainable, in my opinion.