JAMA Internal Medicine | Review

Approach to Obesity Treatment in Primary Care
A Review

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IMPORTANCE More than 40% of US adults have obesity, which increases the risks for multiple chronic diseases and premature mortality. Historically, nonsurgical interventions often have not led to sufficient weight loss and maintenance to improve health, but highly effective antiobesity medications (AOMs) have recently become available, and additional effective therapeutics are under development. Given that most medical care for adults with obesity is delivered in primary care settings, guidance for integrating weight-management approaches is needed.

OBSERVATIONS Lifestyle interventions can lead to a mean weight loss of 2% to 9% of initial weight at 1 year and increase the likelihood of weight loss of 5% or more, but weight regain over time is common even with continued treatment. Adjunctive treatments, including AOMs and surgical approaches, can lead to larger, more sustained weight loss and improvements in numerous obesity-associated medical conditions. Highly effective AOMs, including nutrient-stimulated hormone-based therapies, induce mean weight loss of 15% or more. Barriers to intervention, including access to care, have a disproportionate influence on populations most affected by obesity and its consequences.

CONCLUSIONS AND RELEVANCE Primary care clinicians play a vital role in the assessment, management, and support of patients with obesity. With careful clinical assessment and shared decision-making, a flexible treatment plan can be developed that reflects evidence of treatment efficacy, patient preference, and feasibility of implementation. Adjunctive therapies to lifestyle interventions, including more effective pharmacotherapeutics for obesity, offer hope to patients and the potential for considerable improvements in health and quality of life.

JAMA Intern Med. 2024;184(7):818-829. doi:10.1001/jamainternmed.2023.8526
Published online March 11, 2024.

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More than 40% of US adults have obesity,[1] defined as a body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 30 or greater. In the US, obesity disproportionately affects those from some racial and ethnic minority populations[1] and is associated with increased risk for premature mortality[2] and numerous serious diseases, including type 2 diabetes (T2D), cardiovascular disease (CVD), and some forms of cancer.[3-5]

Although clinicians recognize the negative consequences of obesity for physical and psychological health, they may lack guidance on how best to help patients with obesity beyond recommending changes in diet and physical activity and managing obesity-related medical conditions. With more effective treatments now available, there is growing interest in incorporating obesity care, including prescription of antiobesity medications (AOMs), into primary care practice. In this Review, we provide guidance on treatment of obesity in adults.

Methods

We conducted a search on PubMed for systematic reviews and meta-analyses, Cochrane reviews, and professional society and government guidelines published between 2013 and November 2023, supplemented by a manual review of the bibliographies. The search terms *obesity treatment* plus *lifestyle*, *behavior*, *drugs*, *pharmacotherapy*, *primary care*, and *bariatric surgery* were used. We reviewed identified articles by title and/or abstract for relevance.

Obesity: A Chronic Disease

Medical, governmental, and scientific organizations recognize that obesity is a chronic disease, like diabetes or CVD, that requires long-term management.[6] The dramatic increase in obesity prevalence in the US over the past 4 decades is likely due to exposure of genetically susceptible individuals to the increasingly obesogenic environment, with multiple contributing factors that vary among individuals.[7] Once obesity is established, specific physiological changes make both losing weight and sustaining weight loss challenging.[8]

Improving Patient-Clinician Communication About Obesity

Obesity is a stigmatized condition. People with obesity are often incorrectly considered to lack willpower.[9] Patients frequently

Box. A Patient-Centered Approach to Discussing Weight at Clinical Visits

- When a patient is there for an acute problem, address that problem first.
- If obesity may be contributing to their medical conditions, ask the patient if you have their permission to talk about their weight.
- Ask patients their language preference for discussing weight.
- If patients indicate that they do not want to discuss their weight, focus on treating their current medical conditions and indicate availability to further discuss their weight if and when they wish to do so.
- Discuss whether, how often, and under what circumstances they want to be weighed during office visits.
- If the patient is amenable to talking about their weight, ask if they would like to make a separate appointment to discuss their weight, including potential options for weight management.

internalize this bias,[9,10] believing that they are at fault for their inability to lose weight or maintain weight loss. Health care professionals are not immune from weight bias.[11] Patients report experiencing weight stigma from medical professionals,[12] and this contributes to poor outcomes in multiple domains.[9] In addition, potentially serious but treatable conditions may be dismissed as solely consequences of obesity.

Frequently, patients have made multiple previous attempts to lose weight, and even if temporarily successful, weight regain has occurred. They may be discouraged and believe that further attempts at weight loss would be futile. Acknowledging these challenges can position clinicians as allies in their pursuit of improved health. Online resources are available to help health care professionals reduce weight bias and stigma and improve patient-physician communication.[13,14] Because patients report avoiding or delaying medical care due to perceived negative experiences during health care visits, including embarrassment at being weighed,[9] a patient-centered approach to discussing weight may be helpful (**Box**).

Determining Treatment Type and Intensity

Overweight and obesity are currently defined using BMI (**Table 1**).[15] BMI should be considered a screening tool that correlates reasonably well with high body fat at a BMI of 30 or higher, but it has considerable interindividual variability, particularly in the "overweight" range.[16] Adiposity at a given BMI varies by sex, age, and ancestry.[17] Body-fat distribution also confers differential health risk, with more central body fat associated with greater risk for cardiometabolic disease.[4] Moving beyond BMI as the primary metric for determining the need for and intensity of obesity treatment to using a more comprehensive evaluation incorporating medical and psychosocial assessment and shared decision-making[18,19] may lead to a more individualized approach to management of patients with obesity.[6]

Many resources offer recommendations for clinical evaluation of patients with obesity to assess health risk, identify secondary contributors to obesity, and guide treatment decisions.[4,20-25] For example, almost 40% of patients with obesity take obesity-promoting medications for other medical conditions[26]; changing to medications that are weight neutral or associated with weight loss may support weight-loss treatment. Often, inadequate attention is given to social drivers of health, such as food and housing insecurity, which can interfere with patients' ability to engage in recommended treatment. Brief screening instruments and other tools can help identify and address social needs that influence care.[27,28]

Table 1. Classification of Body Weight Using Body Mass Index (BMI)[a]

Category	BMI
Underweight	<18.5
Healthy weight	18.5 to <25
Overweight	25.0 to <30
Obesity	
Class 1	30.0 to <35
Class 2	35.0 to <40
Class 3	≥40.0

[a] BMI (calculated as weight in kilograms divided by height in meters squared) is a screening tool for overweight and obesity and does not directly measure body fatness or health.[15]

Lifestyle intervention is a fundamental tenet of obesity management, regardless of adjunctive therapies such as medications or surgery. The US Preventive Services Task Force recommends that clinicians offer or refer adults with obesity to intensive, multicomponent behavioral interventions.[29] These interventions typically include multiple behavioral strategies with a goal of improving diet and physical activity.[30] High-intensity behavioral lifestyle intervention, which we refer to as intensive lifestyle intervention (ILI), is generally defined as at least 12 to 16 sessions delivered by a trained interventionist over 6 months to 1 year.[4,24,29,30]

A US Preventive Services Task Force systematic review of behavioral weight-loss interventions[31] found that participants had a modestly greater (2.4 kg) mean weight loss at 12 to 18 months than controls. However, there was considerable heterogeneity in the studies, from low-intensity remote interventions to in-person ILI.[32] ILI is associated with an increased likelihood of losing 5% or more of starting weight.[4,33] Although in-person ILI has been shown to be most effective, lifestyle treatments delivered remotely are increasingly used and have the advantages of convenience and accessibility. Remote interventions that include high-frequency contact and individual feedback are associated with more weight loss than those with lower intensity (about 2 kg at 1 year).[34] Although highly motivated participants in efficacy trials receiving ILI can lose up to 9% of baseline weight at 1 year, some weight regain occurs over time even with continued intervention.[35,36]

Because behavioral weight-loss interventions delivered in the primary care setting generally result in only modest weight loss, referral to comprehensive weight-management programs is recommended where they are available, accessible, and affordable.[37] These can include specialist-based or community programs, counseling by a trained interventionist, or commercial weight-loss programs with evidence of efficacy.

The superiority of high-frequency lifestyle interventions compared with less frequent brief supportive interactions among patients taking AOMs is not yet established but is an active area of study. The mean weight loss of 15% or more seen in clinical trials of newer AOMs was achieved with approximately monthly brief lifestyle counseling visits conducted by registered dieticians or other qualified professionals, suggesting that less intensive lifestyle interventions may be sufficient.[30]

Dietary Recommendations

For weight loss, reduction in calories below that required for weight maintenance is needed. There are many healthful dietary patterns through which this may be achieved,[38] and both patient preference and the presence of other medical conditions can affect recommendations.[24] Although some dietary patterns lead to greater short-term weight reduction, longer-term randomized clinical trials (RCTs) have not shown that diets focused on altering macronutrient composition result in superior weight loss and maintenance.[39] For patients undergoing treatments that can lead to large and rapid weight loss, including AOMs and the surgical procedures now referred to as metabolic and bariatric surgery (MBS), referral to a registered dietitian may be useful to help the patient develop an individualized plan for a nutrient-dense diet that ensures adequate intake of protein and other important nutrients.[30,40]

Physical Activity

Although physical activity (PA) alone, in the absence of caloric reduction, is usually not sufficient to promote meaningful weight loss, it is very important for overall metabolic and mental health and is one of the most important factors in promoting long-term maintenance of weight loss.[41,42] Although guidelines[43] recommend 5 or more days per week of moderate-intensity PA, such as brisk walking and 2 or more days per week of muscle-strengthening exercises for health, weight-loss maintenance may require greater amounts of PA.[4] Strength training and other strategies to preserve lean body mass are likely to be particularly important in patients using AOMs or undergoing MBS,[42] as well as older adults who may have sarcopenic obesity.[44]

Adjunctive AOMs

Patient Selection for AOMs

US Food and Drug Administration (FDA) indications for AOM use in adults include BMI of 30 or higher or BMI of 27 or higher with obesity-related comorbid conditions.[45] However, not everyone with a BMI at or above these thresholds is an appropriate candidate for AOMs, and certain individuals accrue risks at a lower BMI.[21]

For patients who report that they have previously received lifestyle counseling or participated in at least 1 lifestyle intervention program but have been unable to lose or sustain a sufficient amount of weight loss to improve health, adjunctive AOMs can be prescribed without requiring additional trials of lifestyle treatment alone.[4] Presence of associated medical conditions or contraindications, other medications, cost, medication efficacy, availability, and patient preferences can help to determine whether a trial of an AOM is warranted and which medication to select initially.

FDA-Approved AOMs

Information on AOM dosing, contraindications, and common adverse events are summarized in **Table 2**,[46-54] and weight loss results from trials using AOMs are given in **Figure 1**.[55-76] Differences in intensity of concomitant behavioral interventions can affect total weight loss in both drug and placebo groups, and placebo-subtracted weight loss provides a clearer picture of medication efficacy.

Adrenergic AOMs

Older adrenergic agonists, such as phentermine, were labeled for short-term use (a few weeks), reflecting the prevailing belief that AOMs should be prescribed for a brief time to "jump-start" weight loss. Despite this short-term indication, phentermine is frequently prescribed off label for much longer[21,23] and has been by far the most prescribed AOM in the US,[77,78] primarily because of its low cost. Small studies suggest total weight loss is approximately 8% and mean 6-month placebo-subtracted weight loss is approximately 5%.[58,79] Guidance from professional societies provide qualified endorsement of long-term prescription of phentermine for patients without contraindications, such as uncontrolled hypertension or CVD, but note a paucity of research on long-term treatment.[25] In addition, as a Drug Enforcement Administration–scheduled medication, some states prohibit long-term use.

Combination of Adrenergic and GABAergic Agonist

Phentermine plus topiramate extended release at the highest dose (phentermine, 15 mg, and topiramate, 92 mg) leads to mean total weight loss of approximately 10% and placebo-subtracted weight loss of approximately 8%,[59,60] which is greater than observed for either drug administered alone.[58] To reduce cost, clinicians sometimes use concurrent prescription of both immediate-release medications instead of the extended-release combination, although this is an off-label use and, to our knowledge, there are no placebo-controlled trials showing outcomes with such combinations.

Combination of Opioid Antagonist and Dopamine/Norepinephrine Reuptake Inhibitor

Naltrexone plus bupropion extended release reduces weight on average by approximately 7% (approximately 5% placebo-subtracted)[61-64] and also more than either agent administered alone.[80] As with phentermine plus topiramate, some clinicians prescribe the immediate-release forms of naltrexone and bupropion off label to reduce costs.

Gastrointestinal Lipase Inhibition

Orlistat 3 times daily[55-57,81] was found in long-term trials to have potential benefits for both weight (mean total loss of approximately 7%) and cardiovascular risk factors. However, placebo-subtracted weight losses were approximately 3%, and adverse effects such as oily stools limit its use.

Nutrient-Stimulated Hormone-Based Therapies

Nutrient-stimulated hormone-based therapies (NuSH-BTs)[82] supply long-acting analogs of gut-secreted incretin hormones such as glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide, or other hormones like glucagon. They are the most efficacious AOMs currently available (Figure 1).

GLP-1 Receptor Agonists

The GLP-1 receptor agonists (GLP-1 RAs) liraglutide[65-67,83] and semaglutide[68-73,83] are approved for treatment of both T2D and obesity, with higher maximum doses for obesity. Prescribed for T2D for more than a decade, they reduce the risk of major adverse cardiovascular events in this population.[84-86] In adults without

Table 2. Antiobesity Medications Approved by the US Food and Drug Administration for Use in Adults[a]

Medication	Wholesale cost per mo, $[b]	Mechanism of action	Route of administration and dosage	Contraindications	Warnings[c]	Common (≥5%) adverse events in prescribing information[d]
Phentermine	16.65	Noradrenergic agonists approved as short-term adjuncts (a few weeks) but frequently administered off label long term	Oral, 8-37.5 mg daily	History of cardiovascular disease, including coronary artery disease, stroke, arrhythmias, congestive heart failure, or uncontrolled hypertension; administration during or within 14 d of taking an MAOI; hyperthyroidism; glaucoma; agitated state; and history of drug misuse	Discontinue in case of unexplained symptoms of dyspnea, angina pectoris, syncope, or lower extremity edema	Insomnia, elevation in heart rate, dry mouth, taste alterations, dizziness, tremors, headache, diarrhea, constipation, vomiting, gastrointestinal distress, anxiety, and restlessness[46]
Diethylpropion	134.57		Oral, 25-75 mg daily			
Phendimetrazine	12.29		Oral, 17.5-108 mg daily			
Phentermine plus topiramate extended release	115.90	Noradrenergic plus GABA-receptor activator and kainate/AMPA glutamate receptor inhibitor	Oral, starting at 3.75 mg/23 mg daily, then 7.5 mg/46 mg daily, escalating to a maximum of 15 mg/92 mg daily	Pregnancy (must perform monthly pregnancy testing), hyperthyroidism, glaucoma, and administration during or within 14 d of taking an MAOI	May cause acute myopia and secondary angle closure glaucoma, not recommended in severe hepatic impairment, GFR <30 mL/min/1.73 m^2 (kidney clearance), monitor creatinine, monitor pulse, monitor for depression/suicidal thoughts, consider dosage reduction or discontinuation for considerable mood sleep disorder symptoms, and monitor for metabolic acidosis and reduced kidney function	Paresthesia, dizziness, dysgeusia, insomnia, constipation, and dry mouth[47]
Naltrexone plus bupropion extended release	637.70	Opioid receptor antagonist plus dopamine/ norepinephrine reuptake inhibitor	Oral, starting at one 8-mg/90-mg tablet daily and escalating to a maximum of two 8-mg/90-mg tablets twice daily for a maximum total daily dose of 32 mg/360 mg	Uncontrolled hypertension; seizure disorder; anorexia or bulimia nervosa; long-term opioid use; undergoing abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs; glaucoma; and administration during or within 14 d of taking an MAOI	Monitor pulse and blood pressure, monitor for depression/suicidal thoughts, and monitor for hepatotoxicity and hypoglycemia	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth, and diarrhea[48]
Orlistat	60 mg: 77.99; 120 mg: 676.75	Gastrointestinal lipase inhibitor	Oral, 60 or 120 mg 3 times daily within 1 h of fat-containing meals, plus a daily multivitamin	NA	May cause severe hepatic injury, may cause nephrolithiasis due to calcium oxalate stones, and GFR <30 mL/min/1.73 m^2	Oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, and fecal incontinence[49]
Liraglutide (obesity indication)	905.02	GLP-1 receptor agonist	Subcutaneous injection, starting at 0.6 mg/d and increasing weekly by 0.6 mg/d to a maximum of 3 mg daily	Pancreatitis, patients with a personal or family history of MTC or in patients with MEN2, or severe hepatic impairment	Monitor for worsening diabetic retinopathy, hypoglycemia from concomitant insulin secretagogue, monitor kidney function in patients with preexisting kidney impairment or who report severe gastrointestinal reactions, rapid weight loss may acutely worsen gall bladder disease, monitor pulse, and monitor for depression/suicidal thoughts	Nausea, d iarrhea, constipation, vomiting, abdominal pain, headache, fatigue, dyspepsia, upper abdominal pain, increased lipase, dizziness, injection-site reactions, hypoglycemia, pyrexia, pancreatitis, ileus, and gastroenteritis[50]

(continued)

Table 2. Antiobesity Medications Approved by the US Food and Drug Administration for Use in Adults[a] (continued)

Medication	Wholesale cost per mo, $[b]	Mechanism of action	Route of administration and dosage	Contraindications	Warnings[c]	Common (≥5%) adverse events in prescribing information[d]
Semaglutide (obesity indication)	902.36	GLP-1 receptor agonist	Subcutaneous injection, starting at 0.25 mg weekly and escalating to a maximum of 2.4 mg weekly	Pancreatitis, patients with a personal or family history of MTC or in patients with MEN2, or severe hepatic impairment	Monitor for worsening diabetic retinopathy, hypoglycemia from concomitant insulin secretagogue, monitor kidney function in patients with preexisting kidney impairment or who report severe gastrointestinal reactions, rapid weight loss may acutely worsen gall bladder disease, monitor pulse, and monitor for depression/suicidal thoughts	Nausea, diarrhea, constipation, vomiting, abdominal pain, headache, fatigue, dyspepsia, flatulence, gastroenteritis, pancreatitis, ileus, gastroesophageal reflux disease, abdominal distension, eructation, dizziness, hypoglycemia in patients with type 2 diabetes, and nasopharyngitis[51]
Tirzepatide (obesity indication)	1081.07	GLP-1 and GIP receptor agonist	Subcutaneous injection, starting at 2.5 mg weekly and escalating to a maximum of 15 mg weekly	Patients with a personal or family history of MTC or in patients with MEN2; tirzepatide causes dose-dependent and treatment duration–dependent thyroid C-cell tumors in rats	Pancreatitis; monitor pulse; rapid weight loss may acutely worsen gall bladder disease; monitor for worsening diabetic retinopathy; avoid in patients with severe gastrointestinal disease, including severe gastroparesis; monitor kidney function in patients who have preexisting kidney impairment or who report severe adverse reactions that could lead to volume depletion; and monitor for depression/suicidal thoughts	Nausea, diarrhea, vomiting, constipation, abdominal pain, dyspepsia, injection-site reactions, fatigue, hypersensitivity reactions, eructation, hair loss, gastroesophageal reflux disease, and increases in serum amylase and lipase; may cause hypoglycemia in patients using insulin or insulin secretagogues[52]

Abbreviations: GABA, gamma-aminobutyric acid; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide 1; GIP, glucose-dependent insulinotropic polypeptide; MAOI, monoamine oxidase inhibitor; MEN2, multiple endocrine neoplasia type 2; MTC, medullary thyroid carcinoma; NA, not applicable.

[a] Medication approved only for rare genetic obesity syndromes is not included.

[b] Wholesale prices for prescription medications that were available to the National Institutes of Health Clinical Center Pharmacy were obtained on December 13, 2023 (Fortin Georges, PharmD, written communication), and the retail price for over-the-counter orlistat, 60 mg, was obtained from CVS[53] on November 2, 2023. Wholesale prices are generally lower than the retail prices patients pay at a pharmacy.

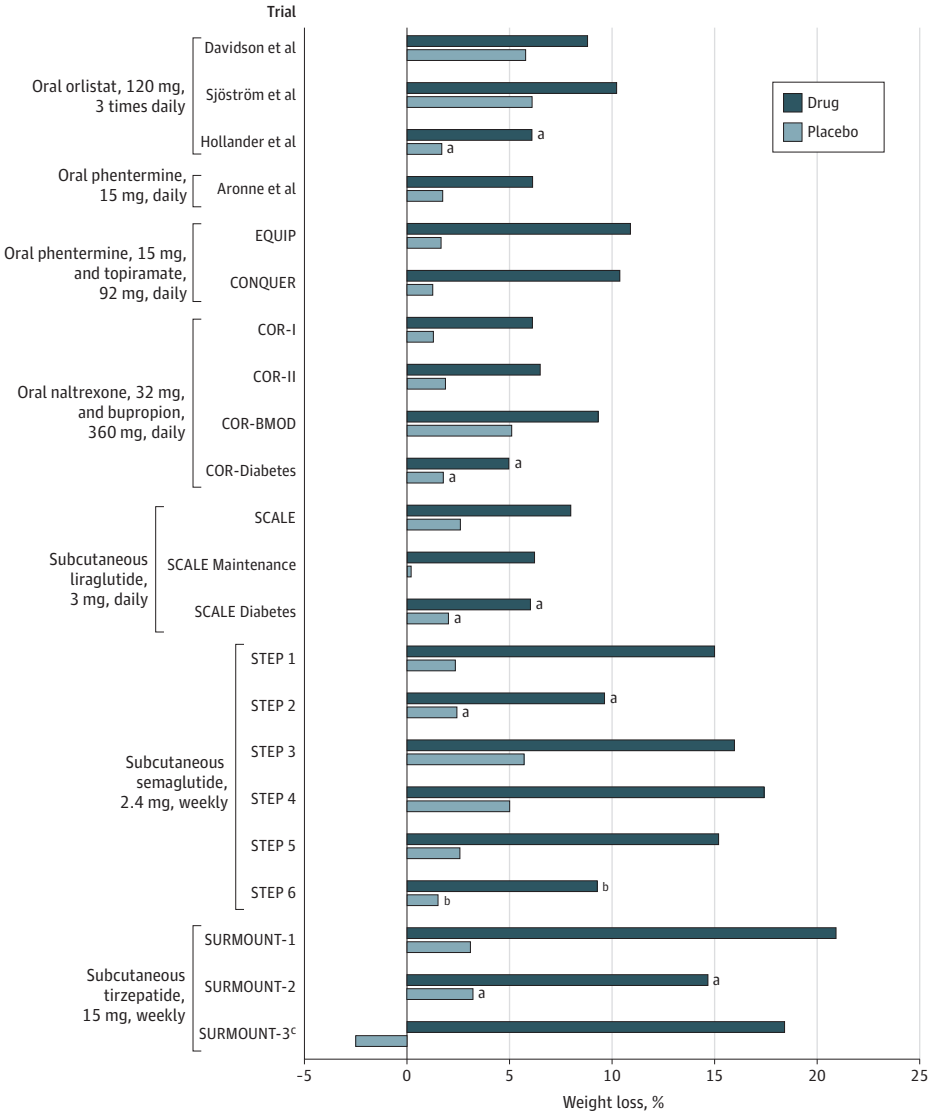
[c] All of the medications have warnings regarding hypersensitivity reactions. Effective contraception is recommended for all female individuals with reproductive potential who use antiobesity medications but is particularly essential for those using phentermine plus topiramate because of the known embryo-fetal toxic effects of topiramate (including craniofacial defects such as cleft lip/palate)[54]; thus, monthly pregnancy testing is required to prescribe this agent, as specified in the US Food and Drug Administration–required Risk Evaluation and Mitigation Strategy. There are insufficient data to recommend any of the medications for those who are supplying breast milk for infants.

[d] Frequency of adverse events for phentermine and the other noradrenergic agonists is not given in prescribing information, but common events were listed in a prior systematic review.[46]

T2D, weekly injectable semaglutide, 2.4 mg (mean total weight loss, approximately 16%; placebo-subtracted, approximately 12%),[68,70-72] is more effective for weight reduction than daily liraglutide, 3.0 mg (mean total weight loss, approximately 7%; placebo-subtracted, approximately 5%)[65,66]: more than 70% of patients lose 10% or more initial weight (vs <26% with liraglutide), and more than 50% lose 15% or more of initial weight (vs <15% with liraglutide).[83] GLP-1 RA adverse events are primarily gastrointestinal (Table 1) and often remit if the dose is titrated slowly, although some patients continue to have nausea or vomiting long term.

The dual GLP-1 plus glucose-dependent insulinotropic polypeptide RA tirzepatide was approved for treatment of T2D in 2022 and for treatment of obesity with the same dose range in November 2023.[87] The maintenance dose of tirzepatide ranges from 5 mg to 15 mg and should be titrated slowly over several months. RCTs[74-76] suggest weight-loss efficacy greater than GLP-1 RAs, with mean weight loss of approximately 20% (placebo-subtracted of approximately 18%) in adults without T2D, and with 36% losing 25% or more of initial weight. A study that randomized adults who achieved 5% or more weight loss with a 12-week ILI before taking tirzepatide vs placebo found that those who added tirzepatide lost an additional 18.4% of their initial weight by week 72, vs regain of 2.5% in the placebo group, leading to a total weight loss from start of intervention of 24.3% with tirzepatide vs 4.5% with placebo.[76] This suggests that, even among patients who can achieve more than 5% weight loss with ILI, tirzepatide can induce substantial additional weight reduction. Tirzepatide's contraindications, warnings, and adverse events are similar to those for the GLP-1 RAs, with primarily gastrointestinal adverse events.[52]

Figure 1. Weight Loss Effects of Antiobesity Medications Approved by the US Food and Drug Administration



Weight loss results, expressed as a percentage of initial body weight after at least 12 months of treatment (28 weeks for phentermine), are reported from trials of oral orlistat (Davidson et al,[55] Sjöström et al,[56] and Hollander et al[57]), oral phentermine (Aronne et al[58]), oral phentermine and topiramate extended release (EQUIP[59] and CONQUER[60]), oral naltrexone and bupropion extended release (COR-I,[61] COR-II,[62] COR-BMOD,[63] and COR-Diabetes[64]), subcutaneous liraglutide (SCALE,[65] SCALE Maintenance,[66] and SCALE Diabetes[67]), subcutaneous semaglutide (STEP 1,[68] STEP 2,[69] STEP 3,[70] STEP 4,[71] STEP 5,[72] and STEP 6[73]), and subcutaneous tirzepatide (SURMOUNT-1,[74] SURMOUNT-2,[75] and SURMOUNT-3[76]).

[a] Study was conducted only among participants with type 2 diabetes.

[b] Data from the STEP 6 trial are shown only for the subgroup of participants who had type 2 diabetes.

[c] Results shown represent additional weight loss (tirzepatide) or regain (placebo) in those who achieved a 5% or more weight loss with a 12-week intensive lifestyle intervention prior to tirzepatide or placebo initiation; total weight loss including the nondrug run-in was 24.3% for tirzepatide and 4.5% for placebo.

Selection of an AOM

All AOMs that are FDA approved for long-term use reduce weight on average by 5% or more than placebo after 1 year; the proportion achieving weight loss of 5% or more is also considerably greater than that achieved by the placebo group, and several AOMs also prevent progression of prediabetes to diabetes and improve quality of life (QOL).[88-90] Current obesity guidelines[4,20] typically recommend a weight-loss goal of 5% or more. However, a 5% weight reduction is insufficient to improve many aspects of health, and greater weight losses confer greater benefits,[24,91,92] with some data suggesting that there may be a threshold effect for reduction in some important comorbidities such as CVD and diabetes remission.[93-95] We consider highly effective AOMs to be those with mean placebo-subtracted weight loss of 10% or more or where the proportion of medication-treated patients losing 10% or more of baseline body weight is 50% or higher.

Independent of average weight loss with a medication, there is considerable variability in individual response for both weight and health outcomes. Some patients lose 10% or more using an AOM with modest efficacy, while a minority experience little to no weight loss even with highly effective medications. Currently, there are no well-established predictors of response prior to treatment initiation.

Among AOMs currently approved, tirzepatide, 15 mg, and semaglutide, 2.4 mg, have the greatest efficacy (Figure 1).[68,70,96] In most trials, patients with T2D lost somewhat less weight than those without T2D (Figure 1), but the medications' high efficacy for both glycemic control and weight loss suggests that they should be preferentially considered to support weight management in patients with obesity and T2D.[97]

Other patient factors may also guide AOM choice (Table 2).[21] Results from SELECT, a cardiovascular events trial of semaglutide, 2.4 mg, in 17 604 adults, indicate that semaglutide reduced the risk for major adverse cardiovascular events by 20% in patients with obesity and CVD but without diabetes, even though most were already taking cardioprotective medications such as statins.[98] Semaglutide, 2.4 mg, also improved symptoms and exercise tolerance in

patients with heart failure with preserved ejection fraction,[99] with greater effects among those with higher baseline BMI.[92] Semaglutide thus becomes a logical choice for patients with CVD or heart failure with preserved ejection fraction. For those who also need to start an antidepressant, naltrexone/bupropion may have potential advantages. Although individual reports of suicidal thoughts or behaviors with use of GLP-1 RAs raised concerns from regulatory agencies, a very large retrospective cohort study, which compared patients with obesity using semaglutide with matched patients taking AOMs from other classes, found no evidence that semaglutide increases risk of suicidal ideation, with similar findings for those taking semaglutide for diabetes.[100] Phentermine/topiramate might be attractive to those with insufficiently treated migraine headaches, since topiramate is FDA approved for this condition. NuSH-BTs appear to confer an elevated relative risk of serious gastrointestinal complications, including pancreatitis, gastroparesis, and ileus,[101] although absolute risk is low. Therefore, they should be used with caution in patients with a history of these disorders. Compounded versions of semaglutide and tirzepatide have recently become popular due to their lower cost, but these are not recommended because their source is often unknown and the FDA does not approve compounded medications for safety or efficacy.[102]

Strategies for Use of AOMs

Figure 2 offers a general approach that incorporates AOMs into an obesity treatment strategy. Dose titration is necessary to maximize benefits and reduce adverse effects. Some patients reduce weight successfully at doses below the maximum allowed and should be encouraged to use the lowest effective dose. Regardless of medication, clinicians must carefully monitor patients for adverse effects, weight-loss efficacy, improvement in obesity-associated medical conditions, and effect on QOL. For more potent AOMs, such as semaglutide and tirzepatide, slow titration and monitoring for excessively large or rapid weight loss is crucial. Because GLP-1 RAs delay gastric emptying,[103] patients undergoing elective anesthesia are recommended to hold GLP-1 RA therapy on the day of surgery for those taking daily medications and discontinue for 1 week before surgery for those using weekly medication.[104]

It is not advisable to discontinue an AOM based solely on reduction in BMI to the "normal weight" range given the high likelihood of weight regain after discontinuation.[66,71,105,106] For example, in an extension of a clinical trial of semaglutide, 2.4 mg, in which participants lost 17.3% of their initial weight, discontinuation of the drug and associated lifestyle intervention led to regain of two-thirds of the lost weight in the ensuing year, with similar reversion in improvements of cardiometabolic variables.[107] The SURMOUNT-4 trial—in which participants lost an average of 21% with tirzepatide after 36 weeks and were then randomized to continued drug or placebo for an additional 52 weeks—demonstrated additional weight loss of 5.5% between weeks 36 and 88 with continued treatment vs regain of 14% in the group switched to placebo.[108] This reinforces the recommendation for continued treatment, although the medication dose may need to be reduced to support weight maintenance. The concept of "treating to target" using weight loss as a biomarker for reduced risk of complications[95] is parallel to the use of drugs for hypertension or dyslipidemia, where drugs are not discontinued when the blood pressure or cholesterol reaches the normal range. However, loss of lean muscle mass and bone in addition to fat mass, which is seen with all interventions that lead to large weight losses, may be a particular concern for older adults. Therefore, treating to a target BMI threshold of 25 or less will not be appropriate for every patient, and approaches must be individualized to maximize health benefit while minimizing risk. Although evidence-based recommendations are not yet available for weight maintenance using AOMs or for discontinuation due to adverse effects, patient concerns, or costs, practical strategies incorporating shared decision-making may be helpful.[30]

There are few studies reporting maintenance of medication-induced weight loss for more than 2 years, although there is evidence for weight regain of 1% to 3% between years 1 and 2 for those taking orlistat,[109] naltrexone plus bupropion,[110] phentermine plus topiramate,[111] liraglutide,[112] and semaglutide.[72] Importantly, because of the greater magnitude of weight loss at 1 year, the total weight loss at 2 years is considerably greater with semaglutide than prior agents.

An insufficient response (<5% weight loss) after 3 months at a full dose should generally lead to discontinuation of that medication and consideration of other AOMs, along with a review of potential contributing factors, including use of obesity-promoting medications and barriers to medication adherence.[20,24] For patients who lose 5% or more but less than 10% of initial weight but still have obesity and health conditions that might be responsive to greater weight loss, switching to a different AOM with greater weight-loss efficacy or with a different mechanism of action may be appropriate. Some patients may achieve additional weight loss by combining AOMs or adding medications approved for other indications; however, consultation with or referral to a specialist with obesity-management expertise is advised when using nonapproved drug combinations.[20]

MBS

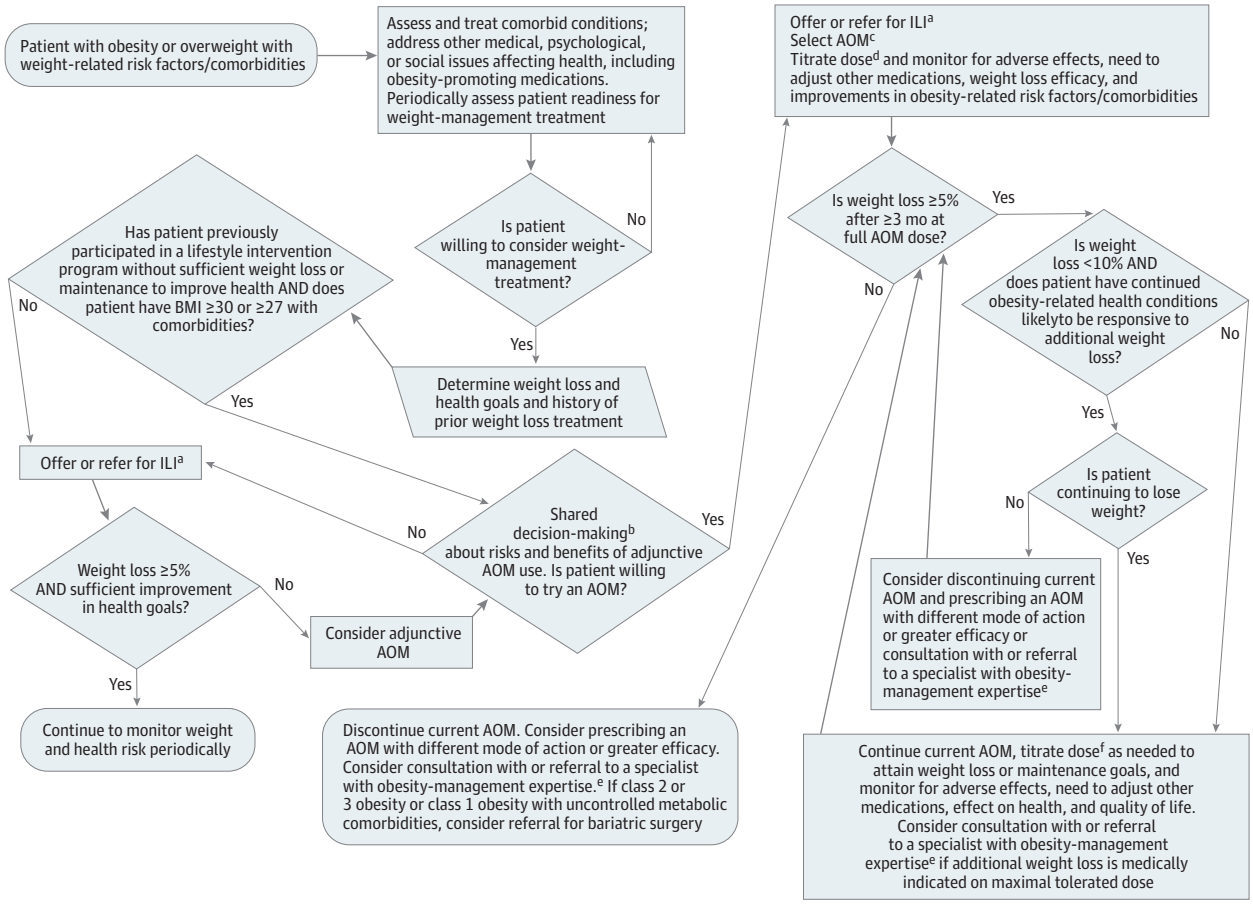
MBS refers to surgical procedures performed to induce weight loss and improve metabolic health. The most common procedures performed in the US are the vertical sleeve gastrectomy (SG) and the Roux-en-Y gastric bypass (RYGB).

Efficacy and Safety of MBS

RCTs show superior outcomes with MBS compared with lifestyle intervention or usual care on weight, cardiometabolic risk factors, and T2D outcomes,[113,114] while high-quality observational studies show greater remission of T2D, lower cancer incidence, reduced CVD morbidity and mortality, and all-cause mortality compared with matched nonoperated controls.[115] RCTs suggest that RYGB and SG have similar efficacy for weight loss and diabetes remission for up to 5 years,[116] although a very large comparative effectiveness study found meaningfully greater weight loss with RYGB at up to 5 years (RYGB, −25.5%; SG, −18.8%).[117] Insufficient weight loss or substantial regain is more likely with SG than RYGB, but regain to within 5% of preoperative weight occurs in only 2% to 4% of patients receiving RYGB and 10% to 15% of patients receiving SG at 5 to 10 years.[116,118-121] Health-related QOL improves following both procedures.[119]

SG has a lower cumulative incidence of hospitalizations, endoscopy, and reoperations than RYGB,[122] but mortality with both is low. RYGB appears to increase risk of later alcohol-related problems, although it is uncertain whether SG confers similar risk.[123] In observational studies, MBS was associated with an increased risk of self-harm and

Figure 2. Flowchart for Integrating Adjunctive Antiobesity Medication (AOM) in Obesity Management



BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); ILI, intensive lifestyle intervention.

[a] ILI is preferred and can include community-based or commercial programs with evidence of efficacy. These can include remote options, although they may have lower efficacy than in-person programs. Lower-intensity lifestyle intervention programs or counseling are options if ILI is not available, accessible, and affordable.

[b] Shared decision-making for interventions involving great degrees of risk or cost may allow full exploration of the patient's knowledge, concerns, values, and preferences.

[c] Initial selection of an AOM may be based on medication efficacy, presence of other medical conditions or contraindications, concomitant medications, cost, availability, and patient preference. For off-label prescription of medications approved for other diseases solely for obesity treatment or for nonapproved combinations, consultation with or referral to a specialist with obesity management expertise is advised.[20]

[d] Slow titration of dose as per labeling instructions is advised, particularly for nutrient-stimulated hormone-based therapies. Upward titration to an effective dose may need to be even slower in some patients to minimize gastrointestinal and other adverse effects.

[e] Change in medication and/or addition of other treatment to increase weight loss may be considered based on the patient's response to current medication, including adverse effects, effect on physical and mental health, and quality of life. Some patients may benefit from adding or combining medications; however, consultation with, or referral to, a specialist with obesity management expertise is advised when considering off-label prescription of medications approved for other diseases solely for obesity treatment or for nonapproved combinations.

[f] Dosage may need to be titrated up to full dose or down to a lower dose, based on patient response, using the lowest effective dose that achieves weight and physical and mental health goals, including weight maintenance.

suicidality.[124] Nutritional deficiencies are more likely with RYGB than SG, but micronutrient supplementation and monitoring is recommended for all patients.[125]

Patient Selection and Post-MBS Care

Guidelines have previously advised offering referral to a bariatric surgeon for adults with BMI of 40 or higher or 35 or higher with obesity-associated comorbidities.[4,126] However more recent guidelines from some professional societies suggest consideration of MBS at BMI thresholds as low as 27.5, based on the presence of comorbidities, response to nonsurgical treatments, or ancestry.[24,125,127]

Guidelines do not support requiring participation in a formal lifestyle-intervention program before referral for MBS in patients who have previously undertaken such programs and have been unable to lose or sustain an amount of weight loss sufficient to improve health.[4] However, given the availability of highly effective AOMs, it is reasonable to consider a medication trial before referral for MBS.

Primary care clinicians play an important role in identifying patients who might benefit from MBS and referring them to a trusted

surgical program.[32] Although multiple MBS practice follow-up visits are generally scheduled during the first postoperative year, primary care clinicians will be the main source of continued follow-up. There are several resources for long-term management of patients after MBS, including recommendations for laboratory evaluation and management of postsurgical complications.[40,128,129] Although evidence-based strategies for assisting patients with inadequate weight loss or weight regain after MBS are few, adjunctive treatment with AOMs may provide benefit.[130,131]

Limitations

Although we searched the published literature, this is not a systematic review, and some relevant publications may not have been included. Most professional society, governmental, and other guidelines have not yet incorporated research findings or recommendations for newly approved or investigational medications. Long-term data for newer and investigational AOMs are not yet available.

Conclusions

Every primary care practice provides medical care to patients with obesity. Lifestyle interventions are often insufficient to help patients achieve weight loss–related goals. Adjunctive treatments, including AOMs and MBS, lead to larger and more sustained weight loss and improvements in numerous obesity-associated medical conditions. Highly effective AOMs, including NuSH-BTs, induce mean weight losses of 15% or more (≥10% placebo-subtracted) and categorical weight losses approaching those seen with some forms of MBS.

Research is needed to identify patients most likely to benefit from AOMs, determine which lifestyle interventions best support weight loss and maintenance in patients taking AOMs, formulate best practices for use of AOMs, and generate strategies to address barriers to treatment in populations disproportionately affected by obesity and its complications. Policies that rectify disparities in social drivers of health, such as food and housing insecurity and access to health care, are also vital to promote equitable treatment and prevention of obesity.

With careful clinical assessment and shared decision-making, primary care clinicians can develop a flexible treatment plan that reflects evidence of treatment efficacy, patient preference, and feasibility of implementation. Adjunctive therapies to lifestyle intervention, including more effective pharmacotherapeutics for obesity, offer hope to patients and the potential for considerable improvements in health and QOL.

ARTICLE INFORMATION

Accepted for Publication: December 21, 2023.

Published Online: March 11, 2024. doi:10.1001/jamainternmed.2023.8526

Conflict of Interest Disclosures: Dr J. Yanovski reported grants from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) during the conduct of the study, as well as grants from Soleno Therapeutics and Rhythm Pharmaceuticals (both to NICHD) and nonfinancial support from Hikma Therapeutics (drug and placebo for a clinical trial) and Versanis Bio (antibodies for mouse obesity studies) outside the submitted work. No other disclosures were reported.

Funding/Support: The conduct of this research was supported in part by the Intramural Research Program of NICHD (grant 1ZIAHD000641 to Dr J. Yanovski).

Role of the Funder/Sponsor: NICHD had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The opinions and assertions expressed herein are those of the authors and are not to be construed as reflecting the views of the National Institutes of Health or the US Department of Health and Human Services.

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