Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline

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Objective: To formulate clinical practice guidelines for the pharmacological management of obesity.

Participants: An Endocrine Society-appointed Task Force of experts, a methodologist, and a medical writer. This guideline was co-sponsored by the European Society of Endocrinology and The Obesity Society.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence.

Consensus Process: One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of the Endocrine Society, the European Society of Endocrinology, and The Obesity Society reviewed and commented on preliminary drafts of these guidelines. Two systematic reviews were conducted to summarize some of the supporting evidence.

Conclusions: Weight loss is a pathway to health improvement for patients with obesity-associated risk factors and comorbidities. Medications approved for chronic weight management can be useful adjuncts to lifestyle change for patients who have been unsuccessful with diet and exercise alone. Many medications commonly prescribed for diabetes, depression, and other chronic diseases have weight effects, either to promote weight gain or produce weight loss. Knowledgeable prescribing of medications, choosing whenever possible those with favorable weight profiles, can aid in the prevention and management of obesity and thus improve health. **(*J Clin Endocrinol Metab* 100: 342–362, 2015)**

Summary of Recommendations

1.0 Care of the patient who is overweight or obese

1.1 We recommend that diet, exercise, and behavioral modification be included in all obesity management approaches for body mass index (BMI) ≥ 25 kg/m^2 and that other tools such as pharmacotherapy (BMI ≥ 27 kg/m^2 with comorbidity or BMI over 30 kg/m^2) and bariatric surgery (BMI ≥ 35 kg/m^2 with comorbidity or BMI over 40 kg/m^2) be used as adjuncts to behavioral modification

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Abbreviations: ACE, angiotensin-converting enzyme; AED, antiepileptic drug; ARB, angiotensin receptor blocker; BID, twice a day; BMI, body mass index; BP, blood pressure; CCK, cholecystokinin; CI, confidence interval; DPP-4, dipeptidyl peptidase IV; ER, extended release; GLP-1, glucagon-like peptide-1; H1, histamine; HbA1c, glycated hemoglobin; POMC, proopiomelanocortin; PYY, peptide YY; QD, every day; RCT, randomized controlled trial; SC, subcutaneous; SGLT, sodium-glucose-linked transporter; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; T2DM, type 2 diabetes; TID, three times a day.

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to reduce food intake and increase physical activity when this is possible. Drugs may amplify adherence to behavior change and may improve physical functioning such that increased physical activity is easier in those who cannot exercise initially. Patients who have a history of being unable to successfully lose and maintain weight and who meet label indications are candidates for weight loss medications. (1|⊕⊕⊕⊕)

1.2 In order to promote long-term weight maintenance, we suggest the use of approved[1] weight loss medication (over no pharmacological therapy) to ameliorate comorbidities and amplify adherence to behavior changes, which may improve physical functioning and allow for greater physical activity in individuals with a BMI $\geq$ 30 kg/m^2 or in individuals with a BMI of $\geq$ 27 kg/m^2 and at least one associated comorbid medical condition such as hypertension, dyslipidemia, type 2 diabetes (T2DM), and obstructive sleep apnea. (2|⊕⊕◯◯)

1.3 In patients with uncontrolled hypertension or a history of heart disease, we recommend against using the sympathomimetic agents phentermine and diethylpropion. (1|⊕⊕⊕◯)

1.4 We suggest assessment of efficacy and safety at least monthly for the first 3 months, then at least every 3 months in all patients prescribed weight loss medications. (2|⊕⊕◯◯)

1.5 If a patient's response to a weight loss medication is deemed effective (weight loss $\geq$ 5% of body weight at 3 mo) and safe, we recommend that the medication be continued. If deemed ineffective (weight loss $<$ 5% at 3 mo) or if there are safety or tolerability issues at any time, we recommend that the medication be discontinued and alternative medications or referral for alternative treatment approaches be considered. (1|⊕⊕⊕⊕)

1.6 If medication for chronic obesity management is prescribed as adjunctive therapy to comprehensive lifestyle intervention, we suggest initiating therapy with dose escalation based on efficacy and tolerability to the recommended dose and not exceeding the upper approved dose boundaries. (2|⊕⊕◯◯)

1.7 In patients with T2DM who are overweight or obese, we suggest the use of antidiabetic medications that have additional actions to promote weight loss (such as glucagon-like peptide-1 [GLP-1] analogs or sodium-glucose-linked transporter-2 [SGLT-2] inhibitors), in addition to the first-line agent for T2DM and obesity, metformin. (2|⊕⊕⊕◯)

1.8 In patients with cardiovascular disease who seek pharmacological treatment for weight loss, we suggest using medications that are not sympathomimetics such as lorcaserin and/or orlistat. (2|⊕◯◯◯)

2.0 Drugs that cause weight gain and some alternatives

2.1 We recommend weight-losing and weight-neutral medications as first- and second-line agents in the management of a patient with T2DM who is overweight or obese. Clinicians should discuss possible weight effects of glucose-lowering medications with patients and consider the use of antihyperglycemic medications that are weight neutral or promote weight loss. (1|⊕⊕⊕◯)

2.2 In obese patients with T2DM requiring insulin therapy, we suggest adding at least one of the following: metformin, pramlintide, or GLP-1 agonists to mitigate associated weight gain due to insulin. The first-line insulin for this type of patient should be basal insulin. This is preferable to using either insulin alone or insulin with sulfonylurea. We also suggest that the insulin therapy strategy be considered a preferential trial of basal insulin prior to premixed insulins or combination insulin therapy. (2|⊕⊕⊕◯)

2.3 We recommend angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers rather than β-adrenergic blockers as first-line therapy for hypertension in patients with T2DM who are obese. (1|⊕⊕⊕⊕)

2.4 When antidepressant therapy is indicated, we recommend a shared decision-making process that provides patients with quantitative estimates of the expected weight effect of the antidepressant to make an informed decision about drug choice. Other factors that need to be taken into consideration include the expected length of treatment. (1|⊕⊕⊕◯)

2.5 We recommend using weight-neutral antipsychotic alternatives when clinically indicated, rather than those that cause weight gain, and the use of a shared decision-making process that provides patients with quantitative estimates of the expected weight effect of the alternative treatments to make an informed decision about drug choice. (1|⊕⊕⊕◯)

2.6 We recommend considering weight gain potential in choosing an antiepileptic drug (AED) for any given patient, and the use of a shared decision-making process that provides patients with quantitative estimates of the expected weight effect of the drugs to make an informed decision about drug choice. (1|⊕⊕⊕◯)

2.7 In women with a BMI $>$ 27 kg/m^2 with comorbidities or BMI $>$ 30 kg/m^2 seeking contraception, we suggest oral contraceptives over injectable medications due to

[1] Approval in the United States is based on FDA determination. Approval in Europe is based on EMA determination.

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weight gain with injectables, provided that women are well-informed about the risks and benefits (ie, oral contraceptives are not contraindicated). (2|⊕◯◯◯)

2.8 We suggest monitoring the weight and waist circumference of patients on antiretroviral therapy due to unavoidable weight gain, weight redistribution, and associated cardiovascular risk. (2|⊕⊕⊕◯)

2.9 We suggest the use of nonsteroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs when possible in patients with chronic inflammatory disease like rheumatoid arthritis because corticosteroids commonly produce weight gain. (2|⊕⊕⊕◯)

2.10 We suggest the use of antihistamines with less central nervous system activity (less sedation) to limit weight gain. (2|⊕⊕◯◯)

3.0 Off-label use of drugs approved for other indications for chronic obesity management

3.1 We suggest against the off-label use of medications approved for other disease states for the sole purpose of producing weight loss. A trial of such therapy can be attempted in the context of research and by healthcare providers with expertise in weight management dealing with a well-informed patient. (Ungraded Best Practice Recommendation)

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed the pharmacological management of obesity a priority area in need of practice guidelines and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research evidence to develop the recommendations. The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕◯◯◯ denotes very low quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each *recommendation* is a description of the *evidence* and the *values* that panelists considered in making the recommendation; in some instances, there are *remarks,* a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.

The Endocrine Society maintains a rigorous conflict-of-interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which are reviewed before they are approved to serve on the Task Force and periodically during the development of the guideline. The conflict-of-interest forms are vetted by the CGS before the members are approved by the Society's Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflicts of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline, but they must have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (eg, stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through the Endocrine Society office.

Funding for this guideline was derived solely from the Endocrine Society, and thus the Task Force received no funding or remuneration from commercial or other entities.

A systematic review was commissioned by the Endocrine Society to quantify weight gain and weight loss associated with a discrete list of drugs chosen a priori by this guideline Task Force (3). The systematic review compared a list of 54 commonly used drugs chosen a priori by the Task Force (drugs suspected of having weight implications) that were compared to placebo in randomized controlled trials. For trials to be included, the length of treatment had to be ≥ 30 days. The outcome of interest for the review was weight change (expressed in absolute and rel-

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ative terms). The Task Force also used evidence derived from existing systematic reviews, randomized trials, and observational studies on the management of medications for other conditions that may result in weight gain. Economic analyses and cost effectiveness studies were not reviewed or considered as a basis for the recommendations. Drugs associated with weight gain and suggested alternatives are presented in Supplemental Table 1.

In several of the recommendations, we used evidence derived from randomized clinical trials about the benefits of shared decision making in terms of improving patients' knowledge, reducing decisional conflict and regret, and enhancing the likelihood of patients making decisions consistent with their own values (4). Although there is abundant evidence for the value of shared decision making across several clinical scenarios, specific evidence for obesity management is scant. This highlights a limitation of the existing literature and poses a challenge for implementing a specific strategy for shared decision making in managing obesity.

Medical management of the disease of obesity

The Task Force agrees with the opinion of prominent medical societies that current scientific evidence supports the view that obesity is a disease (5).

Weight loss produces many benefits including risk factor improvement, prevention of disease, and improvements in feeling and function. Greater weight loss produces greater benefits, but modest (5 to 10%) weight loss, such as that produced by lifestyle modifications and medications, has been shown to produce significant improvements in many conditions (5, 6).

Medications used for the management of conditions other than obesity can contribute to or exacerbate weight gain in susceptible individuals. Many of these conditions are also associated with obesity. Healthcare providers can help patients prevent or attenuate weight gain by appropriately prescribing medications that would promote weight loss or minimize weight gain when treating these conditions. Healthcare providers can help selected patients successfully lose weight by appropriately prescribing weight loss medications or in some cases surgical intervention as an adjunct to lifestyle change.

This guideline will target how providers can use medications as an adjunct to lifestyle change therapy to promote weight loss and maintenance. It will also address how prescribers can prevent or attenuate weight gain when prescribing for diabetes, depression, and chronic diseases often associated with obesity. The evidence review addresses medications with a weight loss indication, as well as those medications that affect weight when prescribed for a nonobesity indication, ie, that have been associated with significant weight gain and increase in risk of comorbidities or with weight loss.

Clinical encounter with the patient who is overweight or obese

There are a number of steps a clinician should take in the clinical encounter.

- Annual and symptom-based screening for major chronic conditions associated with obesity in all adult patients with a BMI of 30 kg/m^2 or above. These include T2DM, cardiovascular disease, hypertension, hyperlipidemia, obstructive sleep apnea, nonalcoholic fatty liver disease, osteoarthritis, and major depression.
- Timely adherence to national cancer screening guidelines with the understanding that individuals who are obese are at increased risk for many malignancies (7).
- Identification of contributing factors, including family history, sleep disorders, disordered eating, genetics, and environmental or socioeconomic causes.
- Identification of and appropriate screening for secondary causes of obesity (Table 1). These need not be automatically screened for unless the history and/or physical examination suggests the diagnosis or suspicion of the diagnosis.
- Adherence to the AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults (8), which was updated in 2013 and includes recommendations for assessment and treatment with diet and exercise, as well as bariatric surgery for appropriate candidates.
- Identification of medications that contribute to weight gain. Prescribe drugs that are weight neutral or that promote weight loss when possible.
- Formulation of a treatment plan based on diet, exercise, and behavior modifications as above.

Rationale for pharmacological treatment of obesity

The challenge of weight reduction

If permanent weight loss could be achieved exclusively with behavioral reductions in food intake and increases in energy expenditure, medications for obesity would not be needed. Weight loss is difficult for most patients, and the patient's desire to restrict food and energy intake is counteracted by adaptive biological responses to weight loss (9–12). The fall in energy expenditure (out of proportion to reduction in body mass) and increase in appetite that are observed after weight loss are associated with changes in a range of hormones (12–14). Some of these changes represent adaptive responses to weight loss and result in al-

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Table 1. Causes of Obesity

Primary Causes
Genetic causes
Monogenic disorders
Melanocortin-4 receptor mutation
Leptin deficiency
POMC deficiency
Syndromes
Prader-Willi
Bardet-Biedl
Cohen
Alström
Froehlich
Secondary Causes
Neurological
Brain injury
Brain tumor
Consequences of cranial irradiation
Hypothalamic obesity
Endocrine
Hypothyroidism[a]
Cushing syndrome
GH deficiency
Pseudohypoparathyroidism
Psychological
Depression[b]
Eating disorders
Drug-Induced
Tricyclic antidepressants
Oral contraceptives
Antipsychotics
Anticonvulsants
Glucocorticoids
Sulfonylureas
Glitazones
β blockers

[a] Controversial whether hypothyroidism causes obesity or exacerbates obesity.

[b] Depression associated with overeating or binging.

tered physiology that promotes weight regain. Other changes reflect improvements in dysfunctional hormonal systems that occur as a patient moves from being obese to being closer to a healthy weight. These latter changes underlie many of the health benefits of weight loss.

No approved weight loss medication appears to promote long-term thermogenesis. These medications promote weight loss through effects on appetite, increasing satiety, and decreasing hunger, perhaps by aiding in resisting food cues or by reducing caloric absorption (14).

As discussed above, weight loss is usually associated with a reduction in total energy expenditure that is out of proportion to changes in lean body mass; the primary determinant of resting energy expenditure appears to persist indefinitely as long as the reduced weight is maintained. Clinically, this means that the individual must reduce energy intake or increase energy expenditure indefinitely to sustain weight loss.

Neuroendocrine dysregulation of energy intake and energy expenditure in obesity

Signals to appetite and controlling centers within the central nervous system and in particular the hypothalamus and the brainstem come from the gut, adipose tissue, liver, and pancreas (Figure 1). Distention of the gastrointestinal tract is communicated to the brain. In the process of food intake, gut hormones are secreted that signal satiety in the hindgut primarily; these include most notably peptide YY (PYY; secreted in ileum and colon) and cholecystokinin (CCK; in duodenum), but also gastric inhibitory polypeptide (K cells in duodenum and jejunum) and GLP-1 (L cells in ileum), which are primarily secreted in response to glucose and promote insulin release from the pancreas as well as satiety. Ghrelin is produced in the stomach, and it is unique among gut hormones in that it is orexigenic and levels increase with time since the last meal. These hormones signal areas in the hindbrain and arcuate nucleus, as do insulin and leptin. Leptin is secreted from adipose tissue, and circulating levels are proportional to fat mass. It is an anorectic hormone, which exerts its effects by inhibiting neuropeptide Y/Agouti-related peptide neurons and activating pro-opiomelanocortin (POMC)/cocaine amphetamine-related transcript neurons in the arcuate nucleus, resulting in decreased food intake and increased energy expenditure, although the increase in energy expenditure has been disputed in leptin-deficient humans treated with leptin (15).

Obesity in humans is almost universally associated with high leptin levels and failure to respond to exogenous leptin; thus, leptin analogs have not been found to be useful so far in the treatment of obesity. In humans, many other cues such as reward and emotional factors play a role in food intake aside from hunger, and another pathway is responsible for reward-associated feeding behavior. Increased hunger and decreased satiety after weight loss are associated with an increase in the 24-hour profile of circulating levels of the orexigenic hormone ghrelin and reductions in the levels of the anorexigenic hormones PYY, CCK, leptin, and insulin. These changes in appetite-related hormones appear to persist for at least 1 year after weight reduction and may remain altered indefinitely in a manner that promotes increased energy intake and ultimately weight regain (14, 16–23)

Mechanisms of action of pharmacological agents

With the exception of orlistat, medications indicated for obesity target appetite mechanisms. The medications available for obesity treatment work primarily in the arcuate nucleus to stimulate the POMC neurons, which promote satiety. Some of the medications discussed in Section 1.0 are serotoninergic, dopaminergic, or norepinephrine-

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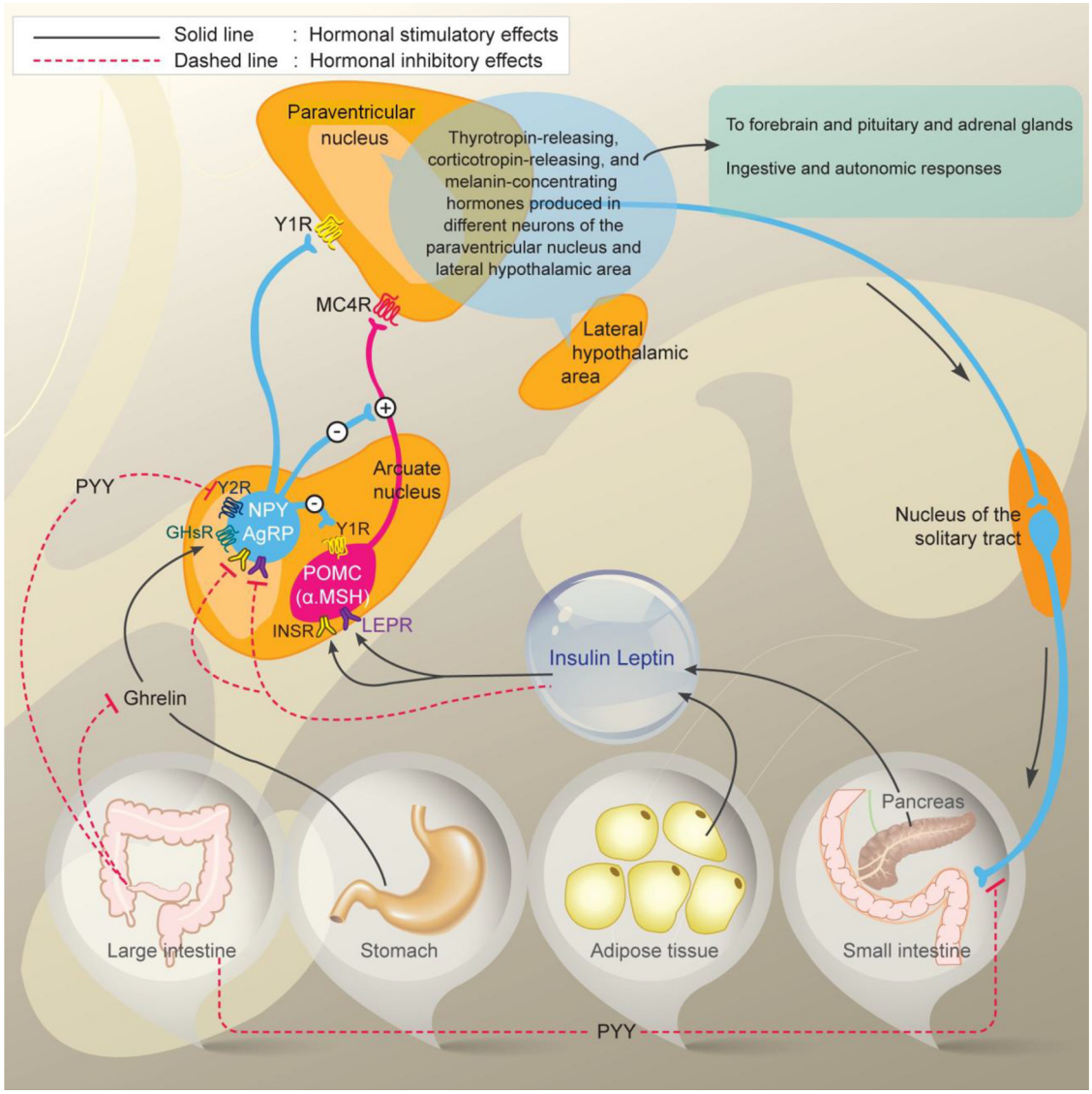

Figure 1. Interactions among hormonal and neural pathways that regulate food intake and body-fat mass. α-MSH, α-melanocyte-stimulating hormone; GHsR, GH secretagogue receptor; INSR, insulin receptor; LEPR, leptin receptor; MC4R, melanocortin receptor type 4; Y1R, Y1 receptor; Y2R, Y2 receptor. [Adapted from J. Korner and R. L. Leibel: To eat or not to eat - how the gut talks to the brain. *N Engl J Med*. 2003;349:926–928 (24), with permission. © Massachusetts Medical Society.]

releasing agents/reuptake inhibitors (Figure 2) (24). Phentermine is primarily a noradrenergic and possibly dopaminergic sympathomimetic amine. Lorcaserin is a serotonin agent specifically stimulating the serotonin type 2c receptor (25). The combination of phentermine and topiramate, which is a neurostabilizer and antiseizure medication, seems to be additive (26); however, it is unclear how topiramate enhances appetite suppression. Bupropion is a dopamine and norepinephrine reuptake inhibitor (27), which stimulates POMC neurons. In combination with naltrexone, buproprion enhances efficacy due to the release of feedback inhibition of POMC neurons that naltrexone potentiates. GLP-1 agonists also affect the POMC neurons and cause satiety (18). Orlistat blocks absorption of 25 to 30% of fat calories and is not appreciably absorbed systemically (28, 29). Another class of medications is associated with weight loss without an effect on appetite. This class is the SGLT-2 inhibitors for T2DM, which promote weight loss by preventing the reabsorption of glucose as well as water in the renal tubules (30).

1.0 Care of the patient who is overweight or obese

1.1 We recommend that diet, exercise, and behavioral modification be included in all overweight and obesity management approaches for BMI ≥ 25 kg/m^2 and that other tools such as pharmacotherapy (BMI ≥ 27 kg/m^2 with comorbidity or BMI over 30 kg/m^2) and bariatric surgery (BMI ≥ 35 kg/m^2 with comorbidity or BMI over

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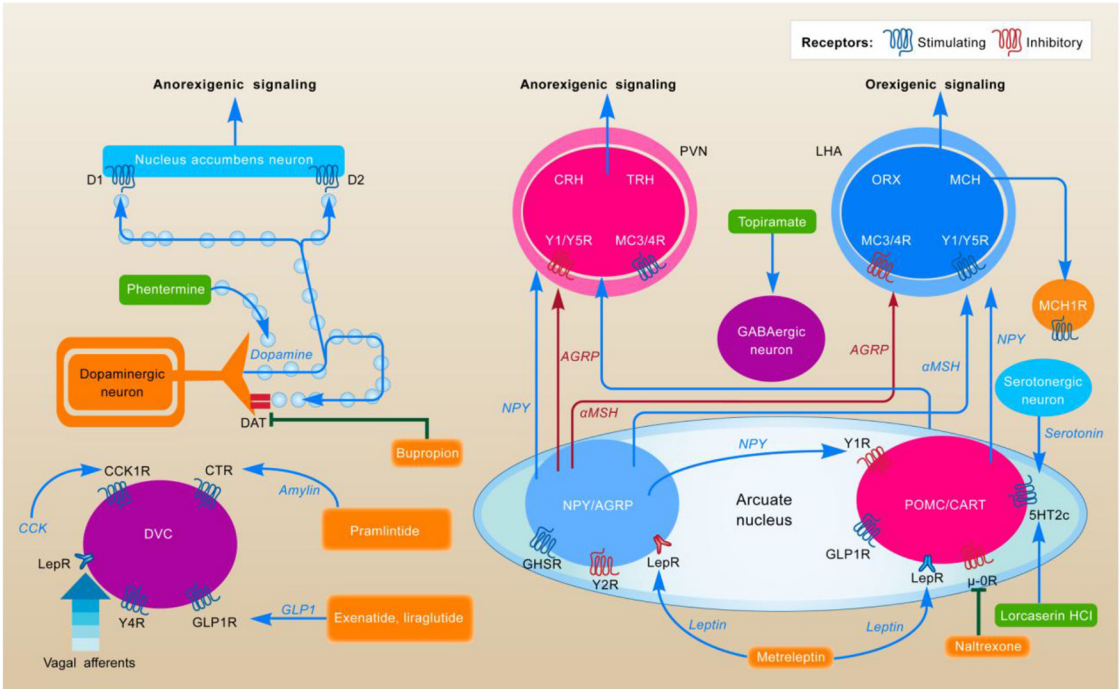

Figure 2. Antiobesity agents and their mechanism of action. AGRP, Agouti-related peptide; CART, cocaine amphetamine-related transcript; CCK1R, CCK1 receptor; GLP1R, GLP-1 receptor; CTR, calcitonin receptor; D1, dopamine 1 receptor; D2, dopamine 2 receptor; DAT, dopamine active transporter; DVC, dorsal vagal complex; GHSR, GH secretagogue receptor; LepR, leptin receptor; MC3/4R, melanocortin receptor type 3/4; MCH1R, melanin-concentrating hormone 1 receptor; NPY, neuropeptide Y; PVN, paraventricular nucleus; Y1/Y5R, Y1/Y5 receptor; Y2R, Y2 receptor; Y4R, Y4 receptor; αMSH, α melanocyte-stimulating hormone; μ-OR, μ-opioid receptor. [Adapted from G. W. Kim et al: Antiobesity pharmacotherapy: new drugs and emerging targets. *Clin Pharmacol Ther*. 2014;95:53–66 (25), with permission. © American Society for Clinical Pharmacology and Therapeutics.

40 kg/m^2) be used as adjuncts to behavioral modification to reduce food intake and increase physical activity when this is possible. Drugs may amplify adherence to behavior change and may improve physical functioning such that increased physical activity is easier in those who cannot exercise initially. Patients who have a history of being unable to successfully lose and maintain weight and who meet label indications are candidates for weight loss medications. (1|⊕⊕⊕⊕) (Table 2 and Supplemental Table 1)

Evidence and relevant values

Weight loss medications reinforce behavioral strategies to create negative energy balance. Most weight loss medications affect appetite and, as a result, promote adherence

Table 2. Advantages and Disadvantages Associated with Weight Loss Medications

Drug	Advantages	Disadvantages
Phentermine	Inexpensive ($) Greater weight loss[a]	Side effect profile No long-term data[b]
Topiramate/phentermine	Robust weight loss[a] Long-term data[b]	Expensive ($$$) Teratogen
Lorcaserin	Side effect profile Long-term data[b]	Expensive ($$$)
Orlistat, prescription	Nonsystemic Long term data[b]	Less weight loss[a] Side effect profile
Orlistat, over-the-counter	Inexpensive ($)	Less weight loss[a] Side effect profile
Natrexone/bupropion	Greater weight loss[a] Food addiction Long-term data[b]	Side effect profile Mid-level price range ($$)
Liraglutide	Side effect profile Long-term data[b]	Expensive ($$$) Injectable

[a] Less weight loss = 2–3%; greater weight loss = >3–5%; robust weight loss = >5%.

[b] Long term is 1–2 years.

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Table 3. Comorbid Conditions in Obesity and Evidence for Amelioration With Weight Reduction

Comorbidity	Improvement After Weight Loss	First Author, Year (Ref)
T2DM	Yes	Cohen, 2012 (132); Mingrone, 2012 (133)[a]; Schauer, 2012 (134); Buchwald, 2009 (135)
Hypertension	Yes	Ilane-Parikka, 2008 (136); Phelan, 2007 (137); Zanella, 2006 (138)
Dyslipidemia and metabolic syndrome	Yes	Ilane-Parikka, 2008 (136); Phelan, 2007 (137); Zanella, 2006 (138)
Cardiovascular disease	Yes	Wannamethee, 2005 (139)
NAFLD	Variable outcomes	Andersen, 1991 (140); Huang, 2005 (141); Palmer, 1990 (142); Ueno, 1997 (143)
Osteoarthritis	Yes	Christensen, 2007 (144); Fransen, 2004 (145); Huang, 2000 (146); Messier, 2004 (147); van Gool, 2005 (148)
Cancer	Yes	Adams, 2009 (149); Sjöström, 2009 (150)
Major depression	Insufficient evidence	
Sleep apnea	Yes	Kuna, 2013 (151)

Abbreviation: NAFLD, nonalcoholic fatty liver disease.

[a] This study showed that weight gain within the normal-weight BMI category (ie, increase from 23 to 25 kg/m^2) increased risk of T2DM 4-fold.

to the diet. The medication that blocks fat absorption reinforces avoidance of high-fat (energy-dense) foods, in addition to promoting malabsorption of fat calories. Medications act to amplify the effect of the behavioral changes to consume fewer calories. They do not "work on their own." To get maximal efficacy, obesity drugs should be used as adjuncts to lifestyle change therapy, and in some cases weight loss is limited without lifestyle change. Whatever baseline behavioral treatment is given, the effect of the drug will be static (33, 34). Just as increasing the dose of medication increases weight loss, increasing the intensity of behavioral modification increases weight loss (33). Patients should be made aware that lifestyle changes are needed when using a weight loss medication and that the addition of a weight loss medication to a lifestyle program will likely result in greater weight loss (6, 35–38).

In making this recommendation, the Task Force acknowledges the variation in the strength of evidence for the different lifestyle interventions and pharmacological interventions for obesity. However, the strong recommendation for reserving pharmacological interventions as an adjunct therapy also depends on values and preferences, with an emphasis on avoiding the side effects, burden, and cost of medications while promoting a healthier lifestyle that has benefit beyond weight loss.

1.2 In order to promote long-term weight maintenance, we suggest the use of approved (see Footnote 1) weight loss medications (over no pharmacological therapy) to ameliorate comorbidities and amplify adherence to behavior changes, which may improve physical functioning and allow for greater physical activity in individuals with a BMI $\geq$ 30 kg/m^2 or in individuals with a BMI of $\geq$ 27 kg/m^2 and at least one associated comorbid medical condition such as hypertension, dyslipidemia, T2DM, and obstructive sleep apnea. (2|⊕⊕◯◯)

Evidence

Caloric restriction through diet and behavior modification has been shown to produce modest but effective weight loss for controlling comorbid medical problems such as diabetes, hypertension, and obstructive sleep apnea (39, 40) (Table 3). Moreover, the adjunctive use of weight loss medication can produce even greater weight loss and cardiometabolic improvements (36, 37, 41–45). Although all of these medications and others have been shown to be effective as adjunctive treatment, none have been shown to be effective on their own. The systematic reviews conducted to support the 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults (8) evaluated the observational literature about the association of various BMI cutoffs and the incidence of death and cardiovascular disease. That guideline adopted the arbitrary BMI cutpoints of $\geq$ 30 kg/m^2 ($\geq$27 kg/m^2 with medical related comorbidity) that had been determined by the U.S. Food and Drug Administration (FDA) and listed on the package inserts of FDA-approved obesity medications. Our Task Force adopted these cutpoints, realizing that they are arbitrary and only low-quality evidence supports associations determined by these cutpoints. Nevertheless, we had to use cutpoints to provide patients and clinicians with specific implementable and practical recommendations.

The only medication available in the European Union for chronic obesity management is orlistat. We encourage additional scrutiny of medications available in the United States by the European Medicines Agency (EMA) and the

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funding of additional long-term clinical trials in the European Union and elsewhere to study the safety and efficacy of these medications, with the goal of providing access to medications for chronic obesity management to patients in need across the world.

1.3 In patients with uncontrolled hypertension or a history of heart disease, we recommend against using sympathomimetic agents phentermine and diethylpropion. (1|⊕⊕⊕◯) (Table 4)

Evidence

The product labels for medications approved for chronic weight management (46–49) include contraindications and cautions based on clinical data submission on > 1500 individuals treated with each medication before approval. These contraindications are detailed in Table 4. Prescribers should be familiar with these product labels in order to avoid contraindications and to judiciously choose patients based on product cautions.

For the sympathomimetic agents phentermine and diethylpropion, regulatory approval was given based on a smaller clinical profile and without a cardiovascular outcomes study. There is thus a lack of evidence on safety for these products across broad populations. In making a strong recommendation, the panel placed a high value on avoiding harm and a lower value on potential short-term weight loss.

Implementation remarks

Because phentermine and diethylpropion are associated with elevations in mean blood pressure (BP) and pulse rate in treated populations, we do not advocate their prescription in patients with a history of cardiovascular disease, and we suggest caution and careful monitoring in patients with hypertension history. Thus, caution is advised in prescribing these agents in patients with hypertension, history of cardiac arrhythmia, or seizures. A serotonin receptor agonist such as lorcaserin would be a better choice in a patient with these conditions.

Another example is the patient with obesity and depression on a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI). In these patients, lorcaserin would not be the best choice due to the potential for serotonin syndrome. A better choice would be phentermine/topiramate or phentermine alone. Orlistat is likely to be safe in all instances due to its mechanism of action. Other cautionary instances are outlined in Table 4.

1.4 We suggest assessment of efficacy and safety at least monthly for the first 3 months, then at least every 3 months in all patients prescribed weight loss medications. (2|⊕⊕◯◯)

Evidence

Diet, behavior modification, and, if appropriate, pharmacotherapy have been shown to be safe and effective in producing modest but effective weight loss and amelioration of comorbid medical problems. To promote maximum effectiveness, frequent assessments are indicated to assess effectiveness of the treatment, ensure accountability, and monitor safety and efficacy of the weight loss medications. The more accountable patients are to weight loss programs, the better the outcomes that are expected. Moreover, any adverse side effects of the weight loss medications can be detected early and rectified (8). The AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults reviewed randomized clinical trials on weight loss interventions and determined that the best weight loss outcomes occur with frequent face-to-face visits (16 visits per year on average) (8, 38).

1.5 If a patient's response to a weight loss medication is deemed effective (weight loss ≥ 5% of body weight at 3 mo) and safe, we recommend that the medication be continued. If deemed ineffective (weight loss < 5% at 3 mo) or if there are safety or tolerability issues at any time, we recommend that the medication be discontinued and alternative medications or referral for alternative treatment approaches be considered. (1|⊕⊕⊕⊕)

Evidence

Weight loss medications do not change the underlying physiology of weight regulation in any permanent way. Trials of weight loss medication that have used a crossover design have demonstrated that the weight loss effects of these medications are only sustained as long as they are taken and these same benefits occur on introducing the medication in patients previously treated with lifestyle alone. Historically, patients and providers thought that weight loss medications could be used to produce an initial weight loss that could subsequently be sustained by behavioral means. The available evidence does not support this view. Much as antihypertensive medications lower BP to a new steady state with BP rising to baseline levels upon discontinuing medication, weight loss medications promote weight loss to a new steady state with gradual weight gain typically occurring when medications are stopped (50, 51).

1.6 If medication for obesity management is prescribed as adjunctive therapy to comprehensive lifestyle intervention, we suggest initiating therapy with dose escalation based on efficacy and tolerability to the recommended

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Table 4. Pharmacotherapy for Obesity in the United States (December 2014)

Drug (Generic)	Dosage	Mechanism of Action	Weight Loss Above Diet and Lifestyle Alone, Mean Weight Loss, % or kg[a]; Duration of Clinical Studies	Status	Common Side Effects	Contraindications
Phentermine resin	AdipexP (37.5 mg), 37.5 mg/d Ionamin (30 mg), 30–37.5 mg/d	Norepinephrine-releasing agent	3.6 kg (7.9 lb); 2–24 wk	Approved in 1960s for short-term use (3 mo)	Headache, elevated BP, elevated HR, insomnia, dry mouth, constipation, anxiety Cardiovascular: palpitation, tachycardia, elevated BP, ischemic events Central nervous system: overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache, psychosis Gastrointestinal: dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances Allergic: urticaria Endocrine: impotence, changes in libido	Anxiety disorders (agitated states), history of heart disease, uncontrolled hypertension, seizure, MAO inhibitors, pregnancy and breastfeeding, hyperthyroidism, glaucoma, history of drug abuse, sympathomimetic amines
Diethylpropion	Tenuate (75 mg), 75 mg/d	Norepinephrine-releasing agents	3.0 kg (6.6 lb); 6–52 wk	FDA approved in 1960s for short-term use (3 mo)	See phentermine resin	See phentermine resin
Orlistat, prescription (120 mg)	120 mg TID	Pancreatic and gastric lipase inhibitor	2.9–3.4 kg (6.5–7.5 lb), 2.9–3.4%; 1 y	FDA approved in 1999 for chronic weight management	Decreased absorption of fat-soluble vitamins, steatorrhrea, oily spotting, flatulence with discharge, fecal urgency, oily evacuation, increased defecation, fecal incontinence	Cyclosporine (taken 2 h before or after orlistat dose), chronic malabsorption syndrome, pregnancy and breastfeeding, cholestasis, levothyroxine, warfarin, antiepileptic drugs
Orlistat, over-the-counter (60 mg)	60–120 mg TID	Pancreatic and gastric lipase inhibitor	2.9–3.4 kg (6.5–7.5 lb), 2.9–3.4%; 1 y	FDA approved in 1999 for chronic weight management	See Orlistat, prescription	See Orlistat, prescription
Lorcaserin (10 mg)	10 mg BID	5HT2c receptor agonist	3.6 kg (7.9 lb), 3.6%; 1 y	FDA approved in 2012 for chronic weight management	Headache, nausea, dry mouth, dizziness, fatigue, constipation	Pregnancy and breastfeeding **Use with caution:** SSRI, SNRI/MAOI, St John's wort, triptans, buproprion, dextromethorphan
Phentermine (P)/ topiramate (T)	3.75 mg P/23 mg T ER QD (starting dose) 7.5 mg P/46 mg T ER daily (recommended dose) 15 mg P/92 mg P/T ER daily (high dose)	GABA receptor modulation (T) plus norepinephrine-releasing agent (P)	6.6 kg (14.5 lb) (recommended dose), 6.6% 8.6 kg (18.9 lb) (high dose), 8.6%; 1 y	FDA approved in 2012 for chronic weight management	Insomnia, dry mouth, constipation, paraesthesia, dizziness, dysgeusia	Pregnancy and breastfeeding, hyperthyroidism, glaucoma, MAO inhibitor, sympathomimetic amines
Naltrexone/ bupropion	32 mg/360 mg 2 tablets QID (high dose)	Reuptake inhibitor of dopamine and norepinephrine (bupropion) and opioid antagonist (naltrexone)	4.8%; 1y (Ref. 79)	FDA approved in 2014 for chronic weight management	Nausea, constipation, headache, vomiting, dizziness	Uncontrolled hypertension, seizure disorders, anorexia nervosa or bulimia, drug or alcohol withdrawal, MAO inhibitors
Liraglutide	3.0 mg injectable	GLP-1 agonist	5.8 kg; 1 y (Ref. 30, 31)	FDA approved in 2014 for chronic weight management	Nausea, vomiting, pancreatitis	Medullary thyroid cancer history, multiple endocrine neoplasia type 2 history

Abbreviations: GABA, γ-aminobutyric acid; HR, heart rate; MAO, monoamine oxidase (Ref. 46–49).

[a] Mean weight loss in excess of placebo as percentage of initial body weight or mean kilogram weight loss over placebo.

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dose and not exceeding the upper approved dose boundaries. (2|⊕⊕◯◯)

Evidence

For the medications approved for long-term treatment for obesity, the recommended doses are as follows: orlistat, 120 mg three times a day (TID); phentermine/topiramate, 7.5 mg/46 mg every day (QD); lorcaserin, 10 mg twice a day (BID); naltrexone/bupropion, 8 mg/90 mg, 2 tablets BID; and for liraglutide, 3.0 mg SC QD (46–49).

For orlistat, the drug is available over the counter at a dosage of 60 mg TID. This dosage has been shown to produce greater weight loss than placebo (52). The recommended prescription dosage is 120 mg TID. Given the favorable safety profile and weight loss efficacy of orlistat at 120 mg TID, it is the preferred dose for prescription (47). There is no evidence from clinical trials using dosages higher than 120 mg TID that efficacy is greater at higher dosages, and prescribers should not exceed 120 mg TID. Orlistat, 120 mg TID, has been studied and approved for treatment of adolescents with obesity (58–60).

For phentermine/topiramate extended release (ER), it is necessary to escalate the dose when starting the medication. The clinical trial data support starting at a dosage of 3.75 mg/23 mg QD and maintaining this for at least 2 weeks. If the patient tolerates the medication, an increase to 7.5 mg/46 mg is in order. Because of the more favorable tolerability profile in clinical studies of the 7.5 mg/46 mg dose, further escalation is only recommended for patients who have not lost 3% of their body weight at 12 weeks. In that case, the dose can be increased to 11.25 mg/69 mg, and then to 15 mg/92 mg. The product label recommends a gradual reduction of dose over 3–5 days because of the observation of seizures occurring when topiramate was stopped abruptly in patients with epilepsy (41, 43, 61).

For lorcaserin, the recommended dosage is 10 mg BID. In clinical trials, lorcaserin 10 mg QD produced nearly as much weight loss as 10 mg BID (42, 44, 45).

Naltrexone/bupropion is available in 8mg/90mg combination tablets. One tablet should be started in the morning and in 1 week 1 tablet added before dinner. As tolerated, the dose should be increased to 2 tablets in the morning the 3rd week, and 2 tablets before the evening meal the 4th week to the maximum of 2 tablets twice daily. If side effects such as nausea develop during dose escalation, the dose should not be increased further until tolerated. If a patient has not lost more than 5% of body weight at 12 weeks, naltrexone/bupropion should be discontinued (79, 93).

Liraglutide should be initiated at a dose of 0.6 mg daily by SC injection. The dose can be increased by 0.6 mg per week up to a maximum of 3.0 mg. If side effects such as nausea develop during dose escalation, the dose should not be increased further until tolerated (31).

There are no comparative data of different doses of phentermine and other sympathomimetics used as a single agent. Therefore, the once-daily doses of 30 mg phentermine (37.5 mg as resin) or 75 mg tenuate should not be exceeded.

1.7 In patients with T2DM who are overweight or obese, we suggest the use of antidiabetic medications that have additional actions to promote weight loss (such as GLP-1 analogs or SGLT-2 inhibitors) in addition to the first-line agent for T2DM and obesity, metformin (63). (2|⊕⊕⊕◯)

Evidence

Individuals with obesity and T2DM may have the dual benefit of weight loss and glycemic control while prescribed a regimen including one or more of three currently available drug classes: metformin, the GLP-1 agonists (exenatide, liraglutide), and the new class of SGLT-2 inhibitors. For the goal of clinically significant weight loss, trials comparing GLP-1 agonists and other antihyperglycemic agents have shown weight loss in some subjects in higher ranges between 5.5 and 8 kg (62). Although other agents including metformin and SGLT-2 inhibitors produce more modest weight loss, ie, in the 1- to 3-kg range in most studies, these agents have not been studied in the setting of concomitant behavioral therapy, and the full weight loss potential is therefore not yet known. In summary, because a subset of diabetes patients may have substantial weight loss on certain diabetes agents that also lower blood glucose, most patients with diabetes should try one or more of these before being considered for additional medications designed for the specific goal of weight loss. The most substantial evidence supports a trial of GLP-1 agonists (see recommendation 2.1).

1.8 In patients with cardiovascular disease who seek pharmacological treatment for weight loss, we suggest using medications that are not sympathomimetics, such as lorcarserin and/or orlistat. (2|⊕◯◯◯)

Evidence

Because patients with a prior history of cardiovascular disease may be susceptible to sympathetic stimulation, agents without cardiovascular signals (increased BP and pulse) should be used preferentially. For patients with established cardiovascular disease who require medication for weight loss, orlistat and lorcaserin should be used. These drugs have a lower risk of increased BP than phentermine and topiramate ER. Lorcaserin showed a reduc-

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tion in pulse and BP greater than placebo in randomized placebo-controlled trials (44).

2.0 Drugs that cause weight gain and some alternatives

A variety of prescription medications have been associated with weight gain. Drug-induced weight gain is a preventable cause of obesity. For all patients, and particularly for patients who have a BMI > 27 kg/m^2 with comorbidities or BMI > 30 kg/m^2, the desired level of clinical efficacy for a chosen therapy should be balanced against side effects, including the likelihood of weight gain. In cases where there are no acceptable therapeutic alternatives, the minimal dose required to produce clinical efficacy may prevent drug-induced weight gain. Patients' initial weight status, the presence of risk factors for cardiovascular disease, diabetes, and other obesity-related health complications, as well as the benefits of pharmacological therapies warrant careful consideration when prescribing a first-line therapy or change in medication.

2.1 We recommend weight-losing and weight-neutral medications as first- and second-line agents in the management of a patient with T2DM who is overweight or obese. (1|⊕⊕⊕◯)

Evidence

The effect of metformin for promoting mild weight loss is likely due to multiple mechanisms (63). However, in animal models, metformin mediates a phenotypic shift away from lipid accretion through AMP-activated Protein Kinase-Nicotinamide phosphoribosyltransferase-Sirtuin 1-mediated changes in metabolism supporting treatment for obesity (64). GLP-1 agonists such as exenatide and liraglutide have also been shown to promote mild weight loss. Pramlintide is an amylin analog that promotes weight loss by increasing satiety and decreasing food intake (65, 66). Dipeptidyl peptidase IV (DPP-4) inhibitors appear to be weight neutral or may lead to minimal weight change. α-Glucosidase inhibitors such as acarbose and miglitol may be weight neutral or lead to a small change in weight (152, 153).

Clinicians should discuss possible weight effects of glucose-lowering medications with patients and consider the use of antihyperglycemic medications that are weight neutral or promote weight loss.

Weight gain is often associated with many diabetes therapies. Patients can gain as much as 10 kg in a relatively short period (3 to 6 mo) after initiating treatment with insulin, sulfonylureas, and other insulin secretagogues like glitinides and thiazolidinediones. Participants in the Diabetes Prevention Program with impaired glucose tolerance who took metformin (850 mg BID) lost 2.1 kg compared with a weight loss of 0.1 kg in the placebo group (69). A recent study comparing sitagliptin plus metformin with pioglitazone in drug-naive patients with T2DM showed that the sitagliptin-metformin combination resulted in weight loss (-1.4 kg) whereas pioglitazone led to weight gain (3.0 kg) (70). A retrospective analysis of exenatide (n = 6280), sitagliptin (n = 5861), and insulin (n = 32 398) indicated that exenatide-treated subjects lost an average of 3.0 kg, sitagliptin-treated subjects lost 1.1 kg, and insulin-treated subjects gained 0.6 kg (71).

In a 1-year trial comparing two doses of liraglutide (1.2 and 1.8 mg) with glimepiride 8 mg, subjects lost 2.05 and 2.45 kg in the 1.2- and 1.8-mg groups, respectively, compared with a 1.12-kg weight gain in the glimepiride group. Glycated hemoglobin (HbA1c) significantly ($P = .0014$) decreased by 0.84% with liraglutide 1.2 mg and by 1.14% with liraglutide 1.8 mg ($P < .0001$) compared to 0.51% with glimepiride (72). An analysis of 17 randomized placebo-controlled trials showed that all GLP-1 agonists reduced HbA1c levels by about 1% (62). The DPP-4 inhibitors sitagliptin and vildagliptin have also been shown in a meta-analysis of 25 studies to lower HbA1c by approximately 0.7 and 0.6%, respectively, in comparison with placebo (73).

A recent review of direct comparisons with active glucose-lowering agents in drug-naive patients demonstrated that DPP-4 inhibitors reduce HbA1c slightly less than metformin (by approximately 0.28) and provide similar glucose-lowering effects as a thiazolidinedione. DPP-4 inhibitors have better gastrointestinal tolerability than metformin yet are weight neutral (74, 75). Another meta-analysis found that an increase in body weight (1.8 to 3.0 kg) was observed with most second-line therapies, the exceptions being DPP-4 inhibitors, α-glucosidase inhibitors, and GLP-1 analogs ($+0.6$ to -1.8 kg) (76). Pramlintide, indicated as an adjunct to insulin, may also aid with weight loss. A meta-analysis demonstrated a weight loss of -2.57 kg for those taking pramlintide vs the control groups (77).

The SGLT-2 inhibitors dapagliflozin and canagliflozin are a new class of antidiabetic drugs that reduce renal glucose reabsorption in the proximal convoluted tubule, leading to increased urinary glucose excretion (78). A recent systematic review and meta-analysis (79) looks at not only the effect of these medications on glycemic indices but also their effects on body weight. Compared with placebo, the mean percentage change in body weight from baseline in eight studies of > 12 weeks comparing the SGLT-2 inhibitor to placebo was -2.37% (95% confidence interval [CI], -2.73 to -2.02). Canagliflozin appears to produce slightly more weight loss on average because three studies with dapagliflozin vs placebo showed mean loss of -2.06% of initial body weight (95% CI, -2.38 to

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−1.74), and five studies of canagliflozin vs placebo showed −2.61% loss (95% CI, −3.09 to −2.13); however, this was not statistically significant. This analysis may underestimate the weight loss effects of these drugs because studies of 12 weeks were included. In 52-week observations, there is no weight regain after maximal loss at 24 weeks.

In addition, because weight-sparing medications are unique in that they do not independently cause hypoglycemia, they have a lower potential for hindering an exercise program. Exercise adjustment is generally necessary only with insulin and with medications that can promote endogenous insulin secretion despite decreasing glucose levels, such as the sulfonylurea and glinide classes of agents (80). Hence, prioritizing metformin, incretin-based medications, and SGLT-2s as therapeutic strategies can reduce exercise-related hypoglycemia and potentially increase the safety and efficacy of exercise in patients with diabetes, thus supporting this important weight-reduction strategy (67, 68).

2.2 In obese patients with T2DM requiring insulin therapy, we suggest adding at least one of the following: metformin, pramlintide, or GLP-1 agonists to mitigate associated weight gain due to insulin. The first-line insulin for this type of patient should be basal insulin. This is preferable to using either insulin alone or insulin with a sulfonylurea. We also suggest that the insulin therapy strategy be considered a preferential trial of basal insulin prior to premixed insulins or combination insulin therapy. (2|⊕⊕⊕◯)

Evidence

Insulin remains the most effective agent to control serum glucose (81). However, multiple large studies typically show weight gain associated with insulin use, either as monotherapy or in combination with oral antidiabetic agents (82–85). Treatment with both metformin and insulin, or when metformin is prescribed in addition to an insulin program, yields similar glycemic benefit to insulin alone without excessive additional weight gain, as shown by meta-analyses and randomized trials (86–88).

Amylin analogs are FDA approved for use in combination with existing insulin treatment. A dose-finding study with pramlintide added to a variety of insulin regimens showed weight loss (−1.4 kg) in treatment groups (89), with HbA1c reductions of 0.62 to 0.68% in the 120-μg dose group. Additionally, weight gain was prevented when pramlintide was added to the basal insulins glargine or detemir. Other studies have found more substantial weight loss of over 3 kg with the use of pramlintide (90).

Other weight-sparing regimens have been studied, including the combination of basal insulin with the weight-neutral DPP-4 inhibitor sitagliptin (91) and weight-reducing combination therapy with liraglutide and metformin. Buse et al (92) investigated the addition of exenatide or placebo to regimens of insulin glargine alone, or in combination with metformin or pioglitazone or both, in adult T2DM patients with HbA1c of 7.1 to 10.5%. Despite superior HbA1c reduction, weight also decreased by 1.8 kg in the exenatide group compared with an increase of 1.0 kg in the placebo group (between-group difference, −2.7 kg; 95% CI, −3.7 to −1.7).

Finally, some weight benefits have been seen with the basal insulin analogs relative to biphasic and prandial insulin analog regimens. The Treating To Target in Type 2 Diabetes trial in patients receiving metformin/ sulfonylurea compared the initiation of basal insulin detemir (twice daily, if required) to that of biphasic insulin aspart BID or prandial insulin aspart TID. Basal insulin use was associated with the least weight gain at 1 year (+1.9 vs +4.7 vs +5.7 kg, detemir vs biphasic vs prandial, respectively) (93), and the weight advantage persisted during the 3-year trial (94).

2.3 We recommend ACE inhibitors, ARBs, and calcium channel blockers rather than β-adrenergic blockers as first-line therapy for hypertension in patients with T2DM who are obese. (1|⊕⊕⊕⊕)

Evidence

Angiotensin is overexpressed in obesity, directly contributing to obesity-related hypertension, providing support for the use of an ACE inhibitor as a first-line agent. Calcium channel blockers are also effective in the treatment of obesity-related hypertension and have not been associated with weight gain or adverse changes in lipids. ACE inhibitors and ARBs have not been associated with weight gain or insulin resistance and provide renal protection in diabetes (95).

If required, selective or nonselective β-blockers with a vasodilating component such as carvedilol and nebivolol are recommended because these agents appear to have less weight gain potential and less of an impact on glucose and lipid metabolism than other nonselective β-blockers (96, 97).

A study in patients taking metoprolol tartrate compared with those taking carvedilol for hypertension showed a mean weight gain of 1.19 kg, suggesting that weight gain is not a class effect of the β-adrenergic blockers (98). A meta-analysis of body weight changes in a series of randomized controlled hypertension trials of at least 6-month duration showed that body weight was higher in the β-blocker group, with a median difference of 1.2 kg between the β-blocker group and the control group (97). The Second Australian National Blood Pressure Trial re-

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ported slightly better cardiovascular outcomes in hypertensive men treated with a regimen that began with an ACE inhibitor compared with a regimen starting with a diuretic (95).

2.4 When antidepressant therapy is indicated, we recommend a shared decision-making process that provides patients with quantitative estimates of the expected weight effect of the antidepressant to make an informed decision about drug choice. Other factors that need to be taken into consideration include the expected length of treatment. (1|⊕⊕⊕◯)

Evidence

The antidepressants vary considerably with respect to their long-term weight gain potential. Serretti and Mandelli (99) evaluated the relative risk of weight gain associated with drugs within the major classes of antidepressant medications in a recent meta-analysis. Paroxetine is considered to be the SSRI associated with the greatest long-term increase in body weight (100), amitriptyline is the most potent inducer of weight gain among the tricyclic antidepressants (99), and mirtazapine (a noradrenergic and specific serotoninergic antidepressant) is also associated with weight gain in the long term (101). Other specific tricyclics that have been associated with weight gain include nortriptyline (102), whereas the effect of imipramine seems to be neutral (99). SSRIs such as fluoxetine and sertraline have been associated with weight loss during acute treatment (4–12 wk) and with weight neutrality in the maintenance (>4 mo) phase (99). No significant effect could be observed for citalopram or escitalopram on body weight (99). Among the serotonin and norepinephrine reuptake inhibitors, venlafaxine and duloxetine have been reported to slightly increase body weight over long-term treatment, although long-term data for venlafaxine are scarce (99). Bupropion selectively inhibits reuptake of dopamine and, to a lesser extent, norepinephrine. It is the only antidepressant that consistently causes weight loss (103). It was originally approved both for treating depression and for inducing smoking cessation. During clinical trials, it suppressed appetite and food cravings and significantly decreased body weight (103). The commissioned systematic review accompanying this guideline (3) was only able to demonstrate weight gain with amitriptyline (1.8 kg) and mirtazapine (1.5 kg) and weight loss with bupropion (−1.3 kg) and fluoxetine (−1.3 kg). The evidence for weight changes with other antidepressants was of lower quality.

2.5 We recommend using weight-neutral antipsychotic alternatives when clinically indicated, rather than those that cause weight gain, and the use of a shared decision-making process that provides patients with quantitative estimates of the expected weight effect of the alternative treatments to make an informed decision about drug choice. (1|⊕⊕⊕◯)

Evidence

Although better tolerated than the older antipsychotics, many of the new atypical antipsychotic agents have weight gain as a side effect (104). This weight gain is of clinical concern because it impedes patient compliance and has deleterious health consequences (104, 105) in patients who are often overweight or obese to begin with. The differential effect of atypical antipsychotics on histamine (H1) receptors, anticholinergic effects, and serotonin type 2C antagonistic effects may explain differences in weight gain among the drugs. Henderson et al (106) demonstrated that weight gain associated with clozapine treatment continued for as long as 46 months and was accompanied by a significant increase in triglyceride levels and a 37% increase in the incidence of T2DM over the 5-year period of observation. A randomized trial investigating the effectiveness of five antipsychotic medications found that a weight gain of > 7% from baseline occurred in 30% of those taking olanzapine, 16% for quetiapine, 14% for risperidone, 12% for perphenazine, and 7% of those taking ziprasidone (107). Allison and Casey (104) noted that patients lost weight when switched from olanzapine to ziprasidone, and this weight loss was associated with improvements in their serum lipid profile and glucose tolerance. In a 6-week, double-blind trial, patients were randomly assigned to receive ziprasidone (n = 136) or olanzapine (n = 133). Body weight increased significantly in those taking olanzapine (3.6 kg) compared with those taking ziprasidone (1.0 kg) (108). A review of nine randomized controlled trials comparing ziprasidone with amisulpride, clozapine, olanzapine, quetiapine, and risperidone showed that ziprasidone produced less weight gain than olanzapine (five RCTs; n = 1659; mean difference, −3.82; 95% CI, −4.69 to −2.96), quetiapine (two randomized controlled trials [RCTs]; n = 754; relative risk, 0.45; 95% CI, 0.28 to 0.74), or risperidone (three RCTs; n = 1063; relative risk, 0.49; 95% CI, 0.33 to 0.74). Ziprasidone was also associated with less cholesterol increase than olanzapine, quetiapine, and risperidone (109). Finally, a review of 34 trials of antipsychotics in youth with psychotic and bipolar disorders found that weight gain ranged from 3.8 to 16.2 kg with olanzapine, 0.9 to 9.5 kg with clozapine, 1.9 to 7.2 kg with risperidone, 2.3 to 6.1 kg with quetiapine, and 0 to 4.4 kg with aripiprazole (110). Despite the variable effects on weight gain among the antipsychotic agents, the prediabetes ef-

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fect may be similar via weight-independent mechanisms (111).

2.6 We recommend considering weight gain potential in choosing an AED for any given patient, and the use of a shared decision-making process that provides patients with quantitative estimates of the expected weight effect of the drugs to make an informed decision about drug choice. (1|⊕⊕⊕◯)

Evidence

AEDs associated with weight loss are felbamate, topiramate, and zonisamide. AEDs associated with weight gain are gabapentin, pregabalin, valproic acid, vigabatrin, and carbamazepine. Weight-neutral AEDs are lamotrigine, levetiracetam, and phenytoin. In clinical practice, it is critical to weigh patients regularly, and AED selection should be based on each patient's profile without sacrificing therapeutic efficacy (112).

Valproic acid has been shown to cause weight gain in both adults and children (113). A retrospective study of long-term weight gain in adult epileptic patients on valproic acid mono- or polytherapy showed that mild-to-moderate weight gain (5 to 10% of baseline weight) was shown in 24% of patients, whereas marked weight gain (>10% gain of baseline weight) was shown in 47% of patients (114). A study of patients taking gabapentin for 12 months or more showed that of 44 patients, 57% gained more than 5% of their baseline body weight; of these, 10 patients (23%) gained more than 10% of their baseline weight (115). Our commissioned systematic review (3) suggested weight gain with gabapentin (2.2 kg after 1.5 mo of use) and divalproex (relative risk for weight gain, 2.8; 95% CI, 1.30, 6.02). Carbamazepine is an older AED and has also been associated with weight gain, although not as significant as valproic acid or gabapentin (116). A study of 66 patients taking AEDs showed that 66.7% of those on carbamazepine had gained an average of 1.5 kg at a 6- to 8-month follow-up visit (117).

2.7 In women with a BMI > 27 kg/m^2 with comorbidities or BMI > 30 kg/m^2 seeking contraception, we suggest oral contraceptives over injectable medications due to weight gain with injectables, provided that women are well-informed about the risks and benefits (ie, oral contraceptives are not contraindicated). (2|⊕◯◯◯)

Evidence

Contraceptive drugs are available in different dosages and formulations and are composed of progestins alone or in combination with estrogens. Some progestins have androgenic/antiandrogenic properties. The research on contraceptives and weight gain is conflicting, and the studies conducted so far are difficult to compare because of the different formulations of contraceptives containing variable doses of estrogens, and with the progestins having different androgenic/antiandrogenic profiles. Moreover, randomized controlled trials comparing hormonal contraceptive methods with a placebo usually raise ethical issues. As recently documented by Gallo et al (118), only four trials included a placebo group or no intervention group, and no evidence has been found to support the association between combination (estrogen plus a progestin) hormonal contraception and weight change. In addition, the same authors, by examining 79 trials of combination contraceptives, concluded that no substantial difference in weight could be found. Moreover, discontinuation of combination contraceptives because of weight change did not differ between groups where this was studied (118).

There is limited evidence of weight gain when using progestin-only contraceptives. Mean gain was less than 2 kg for most studies up to 12 months (119). However, it should be noted that most of the trials were conducted in normal-weight women and excluded obese subjects.

Remarks

Selected studies have reported an increase in contraceptive failure in women with a BMI > 27 kg/m^2. Data on this issue are conflicting but should be discussed with the appropriate patients on an individual basis.

2.8 We suggest monitoring the weight and waist circumference of patients on antiretroviral therapy due to unavoidable weight gain, weight redistribution, and associated cardiovascular risk. (2|⊕⊕⊕◯)

Evidence

Treatments for human immunodeficiency disease include administration of antiretroviral therapy and protease inhibitors. Although effective for suppressing HIV viral activity, which should be associated with appropriate weight gain, such treatments are associated with increased deposition of visceral adipose tissue (120) and lipodystrophy (121). One study of 10 HIV patients treated with protease inhibitor-containing regimens found that patients gained an average of 8.6 kg (P = .006) after 6 months (120).

2.9 We suggest the use of nonsteroidal anti-inflammatory drugs and disease-modifying antirheumatic drugs when possible in patients with chronic inflammatory disease like rheumatoid arthritis because corticosteroids commonly produce weight gain. (2|⊕⊕⊕◯)

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Evidence

When possible, chronic steroid therapy should be avoided in the treatment of chronic inflammatory disease to avoid weight gain in individuals who are overweight or obese. Weight gain and its effects on comorbidities should be considered among the commonly known side effects of glucocorticoid therapy. This is particularly important in rheumatic diseases because, for example, obesity in the setting of osteoarthritis leads to more severe disability and reduced exercise capacity, ambulatory capacity, and quality of life (122). A systematic review reported that, based on data from four RCTs in rheumatoid arthritis, glucocorticoids cause a weight increase of 4 to 8% (123, 124). An additional study showed that, when compared with sulfasalazine, glucocorticoid therapy was associated with a 1.7-kg weight gain after 1 year of treatment (125, 126), and another showed a 2.0-kg weight gain after 24 weeks in patients taking prednisone (127).

2.10 We suggest the use of antihistamines with less central nervous system activity (less sedation) to limit weight gain. (2|⊕⊕◯◯)

Evidence

Research is inconclusive regarding differences in the weight gain potential of sedating vs nonsedating antihistamines because weight has rarely been an outcome in studies of antihistamines, but it appears that the more potent the antihistamine, the greater the potential for weight gain (128). A recent study demonstrated that the odds ratio for being overweight was increased in prescription H1 antihistamine users (129). Furthermore, a study using data from the 2005–2006 National Health and Nutrition Examination Survey found that prescription H1 antihistamine users had a significantly higher weight, waist circumference, and insulin concentration than matched controls (129).

3.0 Off-label use of drugs approved for other indications for chronic obesity management

3.1 We suggest against the off-label use of medications approved for other disease states for the sole purpose of producing weight loss. A trial of such therapy can be attempted in the context of research and by healthcare providers with expertise in weight management dealing with a well-informed patient. (Ungraded Best Practice Recommendation)

Evidence

A variety of drug classes approved for other uses have been utilized off-label by some prescribers to promote weight loss in patients who are obese. Categories of drugs used may include the antiseizure medication topiramate as well as zonisamide, metformin, GLP-1 agonists such as exenatide and liraglutide, the antidepressant bupropion, as well as drugs for attention deficit hyperactivity disorder such as methylphenidate, and thyroid hormones. Combination treatments of these drugs also represent off-label use, although they have been utilized by some practitioners. Physicians without expertise in weight management or endocrinology are advised against prescribing off-label medications.

If a provider chooses to prescribe a medication for weight loss that is not FDA approved for this indication or is not approved for chronic administration, at minimum they should advise patients that this approach has not been evaluated for safety and efficacy and is not approved by the FDA. This discussion as well as details of the risks and benefits of the treatment approach that were presented to the patient should be documented in the medical record. The provider should discuss medications that are FDA approved for weight loss with the patient and document why an off-label medication was chosen over one of these. Practices such as selling weight loss medications out of the office should be avoided because they could be interpreted as representing a conflict of interest for the provider.

Long-term prescribing of phentermine

Although phentermine is FDA approved for weight loss, it is not approved for long-term use. This presents a conundrum for clinicians because it is clear that weight regain will likely occur once the medication is stopped. One approach that has been tried to avoid this situation is intermittent therapy (130). Although this approach appears to work and might be appropriate when a patient is intermittently exposed to environmental factors that promote weight gain, it is not a logical way to prescribe given what is understood about the effects of weight loss medications on weight regulation. The question then is whether or not it is reasonable to prescribe phentermine off-label long term. In making this decision with a patient, direction and guidance provided by State Medical Boards and local laws always take precedence. However, in the many locations where these sources have not provided clear advice, clinicians are left to make their own best professional judgments.

Phentermine is currently the most widely prescribed weight loss medication, and it is likely that much of this prescribing is off label. This is likely a reflection of the low cost of phentermine as compared to other weight loss medications. There currently are no long-term data on safety or efficacy, although recent data on 269 patients treated long term with phentermine suggest that the addiction potential is low (131). In addition, recent data on single and combination agents for weight loss document phen-

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termine 15 mg alone as able to induce over 7% weight loss at 6 months (26). There currently is minimal evidence of any serious long-term side effects when phentermine is used alone for weight loss. Given the wide clinical prescribing of phentermine for more than 20 years and the lack of evidence of serious side effects, even in the absence of long-term controlled safety and efficacy data, it seems reasonable for clinicians to prescribe phentermine long term as long as the patient: 1) has no evidence of serious cardiovascular disease; 2) does not have serious psychiatric disease or a history of substance abuse; 3) has been informed about weight loss medications that are FDA approved for long-term use and told that these have been documented to be safe and effective whereas phentermine has not; 4) does not demonstrate a clinically significant increase in pulse or BP when taking phentermine; and 5) demonstrates a significant weight loss while using the medication. These aspects of care should be documented in the patient's medical record, and the off-label nature of the prescribing should be documented at each visit. Medication should be started at 7.5 or 15 mg/d initially and only increased if the patient is not achieving clinically significant weight loss. Patients should be followed at least monthly during dose escalation and then at least every 3 months when on a stable dose.

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