GUIDELINE SYNTHESIS

Pharmacological Management of Obesity

Guidelines Being Compared:

1 Department of Veterans Affairs (VA)

VA/DoD clinical practice guideline for screening and management of overweight and obesity.

2014 Jan 01

View Summary >

2 The Endocrine Society (Endocr Soc)

Pharmacological management of obesity: an Endocrine Society clinical practice guideline.

2015 Feb 01

View Summary >

Areas of Agreement and Difference

A direct comparison of recommendations presented in the above guidelines for the pharmacological management of obesity is provided. The VA/DoD guideline also provides recommendations for screening and other management interventions, which are beyond the scope of this synthesis.

TES and VA/DoD emphasize that weight loss programs consisting of diet, exercise and behavioral modification should be the first-line approach in patients who are overweight or obese. When lifestyle interventions alone have not achieved the desired weight loss, TES and VA/DoD agree that pharmacological therapy can be considered as an **adjunct** intervention for patients with a BMI ≥30 kg/m^2, and for patients with a BMI ≥27 kg/m^2 who also have obesity-associated comorbidities (e.g., type 2 diabetes, hypertension, dyslipidemia).

Medication Selection

Both developers recommend that only FDA-approved medications be used for the pharmacological management of obesity. In eligible patients, VA/DoD recommends treatment with phentermine/topiramate extended release [ER], orlistat or lorcaserin. According to the developer, while a number of medications have been approved for short-term use (e.g., diethylpropion and phentermine), data on their effectiveness or safety following long-term exposure is lacking. The evidence of efficacy beyond one year of treatment is limited to orlistat, lorcaserin, and to the combination phentermine/topiramate ER.

TES addresses all of the FDA-approved weight loss medications (i.e., those approved for both short- and long-term use). This includes two medications that had not yet been approved by the FDA for chronic weight management at the time the VA/DoD guideline was published—liraglutide and combination naltrexone/bupropion. With regard to choosing a particular drug, TES discusses clinical circumstances in which a particular agent may be preferable, such as uncontrolled hypertension and a history of cardiovascular disease. In this context, the developer recommends against the use of the sympathomimetics phentermine and diethylpropion, which are associated with elevations in mean blood pressure and pulse rate in treated populations. Agents without cardiovascular signals (e.g., orlistat and lorcaserin) should be used preferentially in these patients, states TES. In patients with T2DM who are overweight or obese, TES suggests the use of antidiabetic medications that have additional actions to promote weight loss (such as GLP-1 analogs [e.g., liraglutide] or SGLT-2 inhibitors), in addition to the first-line agent for T2DM and obesity, metformin.

disease states—alone or in combination—for the sole purpose of promoting weight loss. VA/DoD states that such off-label use is often limited by dose-related weight loss and side effects, modest or inconsistent effect, or safety concerns and they cannot endorse it. TES suggests against off-label use of medications but does note that a trial of off-label therapy can be attempted in the context of research and by healthcare providers with expertise in weight management dealing with a well-informed patient.

Follow-Up

TES suggests assessing the efficacy and safety of weight loss medications at least monthly for the first three months, then at least every 3 months. If a patient's response is deemed effective (weight loss ≥5% of body weight at 3 months) and safe, the TES recommends that the medication be continued. If deemed ineffective, or if there are safety or tolerability issues at any time, the developer recommends that the medication be discontinued and alternative medications or referral for alternative treatment approaches be considered.

VA/DoD recommends that patients undergoing any comprehensive weight loss program be offered contact at least once a month, and that adherence to the program be assessed 1-2 times per month by measuring the patient's weight and providing feedback and ongoing support. For patients who achieve their weight loss goal, VA/DoD recommends a weight maintenance program that includes continued medication use. An average weight loss of less than 0.5 pounds per week should prompt reevaluation of the treatment plan, notes the developer.

Areas of Difference

Pharmacotherapy for Non-Obesity Indications

In addition to addressing how medications can be used as an adjunct to lifestyle interventions to promote weight loss and maintenance in obese patients, the TES guideline also addresses how prescribers can prevent or attenuate weight gain in the management of conditions other than obesity, but which are often associated with it (e.g., diabetes). The VA/DoD guideline does not address pharmacotherapy for non-obesity indications.

TES (2015)	**Care of the Patient Who is Overweight or Obese** The Task Force recommends 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 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|++++**) In order to promote long-term weight maintenance, the Task Force suggests the use of approved* 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 ≥30 kg/m^2 or in individuals with a BMI of ≥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|++OO**) In patients with uncontrolled hypertension or a history of heart disease, the Task Force recommends against using the sympathomimetic agents phentermine and diethylpropion. (**1|+++O**) The Task Force suggests 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|++OO**) If a patient's response to a weight loss medication is deemed effective (weight loss ≥5% of body weight at 3 mo) and safe, the Task Force recommends that the

that the medication be discontinued and alternative medications or referral for alternative treatment approaches be considered. (1|++++)

If medication for chronic obesity management is prescribed as adjunctive therapy to comprehensive lifestyle intervention, the Task Force suggests initiating therapy with dose escalation based on efficacy and tolerability to the recommended dose and not exceeding the upper approved dose boundaries. (2|++OO)

In patients with T2DM who are overweight or obese, the Task Force suggests 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|+++O)

In patients with cardiovascular disease who seek pharmacological treatment for weight loss, the Task Force suggests using medications that are not sympathomimetics such as lorcaserin and/or orlistat. (2|+OOOM)

*Approval in the United States is based on Food and Drug Administration (FDA) determination. Approval in Europe is based on European Medicines Agency (EMA) determination.

Drugs That Cause Weight Gain and Some Alternatives

The Task Force recommends 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|+++O)

In obese patients with T2DM requiring insulin therapy, the Task Force suggests adding at least one of the following: metformin, pramlintide, or GLP-1 agonists to

or insulin with sulfonylurea. The Task Force also suggests that the insulin therapy strategy be considered a preferential trial of basal insulin prior to premixed insulins or combination insulin therapy. (2|+++O)

The Task Force recommends 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|++++)

When antidepressant therapy is indicated, the Task Force recommends 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|+++O)

The Task Force recommends 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|+++O)

The Task Force recommends 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|+++O)

In women with a BMI >27 kg/m^2 with comorbidities or BMI >30 kg/m^2 seeking contraception, the Task Force suggests oral contraceptives over injectable medications due to weight gain with injectables, provided that women are well-informed about the risks and benefits (i.e., oral contraceptives are not contraindicated). (2|+OOO)

	redistribution, and associated cardiovascular risk. (**2|+++O**) The Task Force suggests 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|+++O**) The Task Force suggests the use of antihistamines with less central nervous system activity (less sedation) to limit weight gain. (**2|++OO**) **Off-Label Use of Drugs Approved for Other Indications for Chronic Obesity Management** The Task Force suggests 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**)
VA/DoD (2014)	**Pharmacotherapy** **Recommendations** • Offer pharmacotherapy with the combination phentermine/topiramate extended-release to patients with a BMI ≥30 kg/m^2 and to those with a BMI ≥27 kg/m^2 who also have obesity-associated conditions, as an adjunct to comprehensive lifestyle intervention, when lifestyle interventions alone do not produce the desired weight loss. **[A]** • Offer pharmacotherapy with orlistat or lorcaserin to patients with a BMI ≥30 kg/m^2 and to those with a BMI ≥27 kg/m^2 who also have obesity-associated conditions, as an adjunct to comprehensive lifestyle intervention, when lifestyle interventions alone do not produce the desired weight loss. **[B]**

	lifestyle intervention, to patients with obesity-associated conditions, for its beneficial effects on type 2 diabetes, hypertension, and/or dyslipidemia. **[B]** • Offer patients who achieve their weight loss goal, a program that includes continued medication use for weight maintenance. **[B]**

Strength of Evidence and Recommendation Grading Schemes

TES (2015)	**Quality of the Evidence** **+OOO** Denotes very low quality evidence **++OO** Denotes low quality evidence **+++O** Denotes moderate quality evidence **++++** Denotes high quality evidence **Strength of Recommendations** **1** - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends." **2** - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."
VA/DoD (2014)	The recommendations in this Clinical Practice guideline are rated according to the U.S. Preventive Services Task Force (USPSTF) rating scheme and are based on two main dimensions: 1) **net benefit** of an intervention and 2) **certainty** of evidence association with that net benefit. **USPSTF Recommendations** **Grade** | **Grade Definitions** | **Suggestions for Practice**

	recommends the service. There is high certainty that the net benefit is substantial.	service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.

	recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be measured.	If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Grade of **EO** was added for "Expert Opinion."

USPSTF Levels of Certainty Regarding Net Benefit

Definition: The USPSTF defines certainty as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.

	includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by factors such as: • The number, size, or quality of individual studies • Inconsistency of findings across individual studies • Limited generalizability of findings to routine primary care practice; and • Lack of coherence in the chain of evidence As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.

		to assess effects on health outcomes. Evidence is insufficient because of: • The limited number or size of studies • Important flaws in study design or methods • Inconsistency of findings across individual studies • Gaps in the chain of evidence • Findings not generalizable to routine primary care practice; and • A lack of information on important health outcomes More information may allow an estimation of effects on health outcomes.

Methodology

Click on the links below for details of guideline development methodology	
TES **(2015)**	**VA/DoD** **(2014)**
Both guidelines are based on systematic reviews of the evidence that included evidence tables. To collect the evidence, both developers performed searches of electronic databases and provide relevant details of the process including the specific databases searched, keywords used and date ranges applied. Details of the selection process, such as the inclusion and exclusion criteria that were applied, are also provided by both groups. To assess the quality and strength of the selected evidence, TES and VA/DoD weighted it	

conducted a meta-analysis of randomized controlled trials (RCTs). The groups describe the evidence analysis processes. To formulate the recommendations, the developers employed expert consensus and provide details of the process. Both TES and VA/DoD rate the strength of the recommendations according to a scheme. The guideline developers sought peer review (TES specifies both internal and external) as a method of guideline validation.

Benefits and Harms

Benefits

TES (2015)	Appropriate pharmacological management of patients with obesity
VA/DoD (2014)	There is strong evidence that weight loss resulting from comprehensive lifestyle interventions significantly impacts hypertension, type 2 diabetes, and pre-diabetes in the overweight population. There is also moderate evidence that weight loss has beneficial effects for dyslipidemia. It is hoped that weight loss induced improvements in cardiovascular risk factors (i.e., hypertension, type 2 diabetes, and dyslipidemia) will ultimately result in improved cardiovascular morbidity and mortality.

Harms

TES (2015)	Adverse side effects of the weight loss medications (see Table 4 in the original guideline document for common side effects of specific weight loss medications)
VA/DoD (2014)	Adverse effects, precautions, and drug interactions of anti-obesity agents are described in Appendix J of the original guideline document.

TES (2015)	See Table 4 in the original guideline document for contraindications of specific weight loss medications.
VA/DoD (2014)	• The use of weight loss drugs (orlistat, phentermine and topiramate extended-release, lorcaserin) during pregnancy is contraindicated. • Phentermine is contraindicated during or within 14 days following administration of a monoamine oxidase inhibitor (MAOI) (see Appendix J in the original guideline document for more information on specific drug contraindications). • Bupropion has a black box warning for suicidality and is contraindicated in patients with a seizure disorder, bulimia, or anorexia.

Abbreviations

BMI, body mass index

FDA, U.S. Food and Drug Administration

GLP, glucagon-like peptide

SGLT, sodium-glucose-linked transporter

T2DM, type 2 diabetes mellitus

TES, The Endocrine Society

VA/DoD, Department of Defense/Department of Veterans Affairs/Veterans Health Administration

Status

This synthesis was prepared by ECRI Institute on May 31, 2016. The information was verified by TES on May 31, 2016.