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Weight Loss Medications
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Introduction

The VA National Center for Health Promotion and Disease Prevention (NCP), Veterans Health Administration (VHA) Office of Patient Care Services with input from the field, developed a Weight Management Program for Veterans (MOVE!®). This program is based on the NIH Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report [1] and the United States Preventive Services Task Force (USPSTF) Screening and Interventions for Obesity in Adults: Summary of the Evidence for the US Preventive Services Task Force [2] and Screening for Obesity in Adults.[3]

The following resources provide guidance to VHA clinicians for implementation/ maintenance of weight management programs:

- Handbook 1101: Managing Overweight and/or Obesity for Veterans Everywhere (MOVE!) Program[4]
- Joint Veterans Affairs (VA)/Department of Defense (DoD) Clinical Practice Guideline for Screening and Management of Overweight and Obesity (CPG) (2006)[5]

The MOVE! Reference Manual addresses the full spectrum of weight management. The manual consists of topic-specific chapters, and each topic should be considered in relation to others.

General Information

Non-pharmacological treatments for weight loss are generally considered first-line therapy. Treatment within a behaviorally-based, high-intensity program can promote modest but clinically relevant weight loss in overweight/obese adults. For this reason, weight loss medications should be considered only as an adjunct to promoting behavior changes in diet and physical activity.[1] They should generally be used only with concurrent participation in the Weight Management Program for Veterans (MOVE!) or a similar multidisciplinary behaviorally-based weight-management program.

Because weight loss medications have risks and side effects, they should be considered only for those at significant medical risk from obesity, generally those with

BMI >30 or BMI >27 with one or more obesity-associated conditions (e.g., diabetes, hypertension, sleep apnea, hyperlipidemia).[6, 7] In Veterans who do not meet these criteria, the risk of complications from medication is usually greater than both the baseline health risk due to overweight and any potential benefit from weight loss.

Patients who take weight loss medications should be monitored closely for side effects and response to treatment.[6, 7] Therefore, medical supervision by a physician, nurse practitioner, or physician assistant is always required when using these medications.

Medication Options

Many sympathomimetic/anorectic agents are available and have been used for the treatment of obesity over the past several decades. Most of these products have unacceptably high medical risks, are not effective in the long-term, or lack sufficient evidence for safety. In addition, many have the potential for developing tolerance. Examples of such products include the following:

Dexfenfluramine	Fenfluramine
Desoxyephedrine	Mazindol
Phenmetrazine	Benzphetamine
Phentermine*	Phendimetrazine
Diethylpropion	Sibutramine

Other amphetamine derivatives

Some agents on this list are no longer available in the US, although Veterans may be able to obtain them from other countries. The products on this list that are approved by the US Food and Drug Administration (FDA) are labeled for short-term use only in the treatment of obesity*.

Sibutramine was previously approved by the FDA as a weight loss medication, but upon the recommendation of FDA, the pharmaceutical company withdrew Sibutramine from the market. VHA sent letters to patients and prescribing providers to instruct patients to discontinue the use of Sibutramine and to discuss treatment alternatives with the MOVE! team or their primary care provider.

When weight loss medications are indicated as adjunctive treatment, agents that have been approved for long-term use are preferred over short-term agents. Currently, only one agent is approved by FDA for long-term use in the treatment of obesity: orlistat (brand name Xenical®, Alli®)[8].

Metformin is a viable treatment option for patients with co-morbidities related to hyperglycemia (diabetes and prediabetes). Research has shown that metformin is efficacious in promoting glycemic control and modest weight loss and reducing the risk of diabetes, and is safe to use on a long-term basis.[9, 10]

The rest of this chapter will focus only on orlistat. Orlistat has been found to be modestly efficacious in promoting weight loss and preventing weight regain. Although orlistat is approved for "long-term" use, few studies have followed patients taking this medication for more than 2 to 4 years. We do not yet know the longer-term (>4 years) consequences of taking this medication.

Orlistat

http://www.pbm.va.gov/Clinical%20Guidance/Drug%20Monographs/Orlistat.pdf

Mechanism of Action

Orlistat blocks the enzyme lipase, preventing the digestion and absorption of dietary fat and resulting in reduced calorie intake. The fats that are not digested simply pass through the gut and are eliminated in the feces. Orlistat prevents about 30 percent of consumed fats from being absorbed, which is enough to produce a clinically significant weight loss. Veterans who are already consuming diets very low in fat will probably not benefit from orlistat.

Efficacy

Orlistat is modestly effective for losing weight. In a meta-analysis of 22 studies, patients who took orlistat over a 12-month period lost an average of 6.4 pounds (range, 4.4–11 pounds) more than those taking a placebo pill.[7] The difference between orlistat and placebo in percentage of subjects losing at least 5 percent of their body weight was 21 percent (favoring orlistat). Note that all trials included a diet and lifestyle modification in both the treatment and placebo groups, and some also included behavioral, educational, and/or psychosocial co-interventions.

Dosing

In clinical settings, orlistat is taken as a 120-mg capsule three times a day, either during or within one hour of each meal containing fat. (In 2007, orlistat became available over the counter in a 60-mg formulation, marketed under the brand name Alli®.[8]) The dose should be omitted if the meal is skipped or contains no fat.

Adverse Effects

Because the mechanism of action for orlistat is in the gut rather than the bloodstream, it has few side effects outside of the gastrointestinal system. Side effects are generally mild and transient, and typically occur within 3 months of starting therapy. About half of all GI side effects last for less than 1 week, and most last for no more than 4 weeks. Any remaining side effects decrease after the first year of treatment.

Decreased fat absorption due to orlistat may impair the absorption of the fat-soluble vitamins A, D, E, and K. Fat-soluble vitamin deficiency is perhaps the most serious consequence of taking orlistat, but reports of it are rare. Patients who take orlistat should also take a daily multivitamin that contains all four of these fat-soluble vitamins. The multivitamin should be taken either 2 hours prior to or 2 hours after orlistat to avoid impairing the absorption of the fat-soluble components.

According to the manufacturer's insert, some of the most frequently reported adverse side effects from clinical trials reported at 1 year include:

- Oily spotting: 26.6% vs. 1.3% in placebo
- Flatulence with discharge: 23.9% vs. 1.4% in placebo
- Fatty/oily stool: 20.0% vs. 2.9% in placebo
- Oily evacuation: 11.9% vs. 0.8% in placebo
- Increased defecation: 10.8% vs. 4.1% in placebo
- Fecal incontinence: 7.7% vs. 0.9% in placebo
- Fecal urgency: 22.1% vs. 6.7% in placebo
- Abdominal pain/discomfort: 25.5% vs. 21.4% in placebo

A meta-analysis[7] calculated the following "number needed to treat for harm" estimates for select adverse effects (estimates are based on data from trials with 6-month to 2-year outcomes):

- Diarrhea: 1 patient will experience diarrhea for every 2 treated.
- Flatulence: 1 patient will experience flatulence for every 7 treated.
- Bloating, abdominal pain, and dyspepsia: 1 patient will experience these effects for every 26 treated.

GI side effects are generally a result of fat that goes undigested through the GI tract; thus, meals very high in fat tend to cause more symptoms than meals lower in fat. This can serve as a negative reinforcer for the patient to consume a nutritionally-balanced, reduced-calorie diet with no more than 30 percent of calories from fat. Patients who experience unpleasant side effects despite a lower fat diet can sometimes find relief by increasing fiber intake either through their regular diet or through the use of fiber supplements (e.g., Metamucil®or Citrucel®).

Precautions and Contraindications for Use

VHA Pharmacy Benefits Management shared the following information provided by the FDA regarding "Orlistat and Severe Liver Injury." Although a cause and effect relationship of severe liver injury with orlistat use has not been established, because of the seriousness of severe liver injury, FDA has added information about reported cases of severe liver injury to the label of Xenical and Alli to educate the public about the signs and symptoms of liver injury and the need to see a physician promptly should they occur.

The signs and symptoms of severe liver injury include itching, yellow eyes or skin, fever, weakness, vomiting, fatigue, dark urine, light-colored stools, or less of appetite. People who experience these signs and symptoms should contact their health care professional immediately.

Health care professionals should be aware that post marketing cases of severe liver injury have been reported rarely with the use of orlistat. They should weigh the benefits of weight loss with the potential risks associated with Xenical and Alli before prescribing or recommending theses medications to their patients. Patients should also be educated about the signs and symptoms of liver injury.

Criteria for Use in VA

Orlistat is a non-formulary drug within VA; it's available for use only through a non-formulary drug request by the prescribing provider. The over-the-counter formulation (60 mg) is not available through the VA. The national VA Pharmacy Benefits Management (PBM) Strategic Healthcare Group has established the following criteria (summarized here) for use of orlistat[11]:

Criteria for Initial 90-Day Supply

- BMI >30, or >27 with obesity-associated condition(s)
- Participation in MOVE! or a similar weight management program
- No contraindications to orlistat, including hypersensitivity to orlistat, malabsorption syndromes, or cholestasis
- Demonstrated ability to comply with a low-fat diet
- Currently taking or prescribed a multivitamin/mineral supplement that includes vitamins A, D, E, and K

Criteria for Initial 90-Day Refill

- Attendance at all follow-up appointments (initial follow-up at 2-4 weeks after starting treatment, then monthly visits for the first 3 months.)

- At 12 weeks, a loss of at least 5% of initial body weight or an average loss of >1 lb per week
- No intolerable side effects and patient wishes to continue taking orlistat
- No hypersensitivity to orlistat, malabsorption syndromes, or cholestasis
- Currently taking a multivitamin/mineral supplement with vitamins A, D, E, and K

Criteria for Refills Every 6 Months

- Maintenance of 67% of initial weight loss or continued weight loss
- Attendance at all follow-up appointments (at least one every 90 days)
- No intolerable side effects and patient wishes to continue taking orlistat
- No hypersensitivity to orlistat, malabsorption syndromes, or cholestasis
- Currently taking a multivitamin/mineral supplement with vitamins A, D, E, and K
- Has been taking orlistat for less than 4 years (the maximum allowable duration for this drug)

These criteria can also be found on the PBM web site at http://www.pbm.va.gov/Clinical%20Guidance/Criteria%20For%20Use/Orlistat%20-%20Criteria%20for%20Use.pdf

Long-Term Use

Patients who experience no or few minor side effects while taking orlistat can continue to take these drugs as long as they continue to make progress losing weight towards their goal OR have achieved their weight loss goal and need assistance with weight maintenance AND are within the time-frame established by PBM for maximum duration of therapy. PBM has established 4 years as the maximum duration of therapy for orlistat, pending further evidence of long-term efficacy and safety in Veterans.

Use of Weight Loss Medications in Older Adults

Pharmacological treatments are only infrequently used to induce weight loss in older adults, due to the impact of existing co-morbidities, potential interactions with other prescriptions, and over-the-counter medication use. Polypharmacy in older adults is a prevalent problem and even a single additional prescription may increase economic, compliance, and/or metabolic burdens.

Research evidence for the use of orlistat in the elderly is minimal, as most relevant randomized controlled trials either excluded older adults or included them in only small numbers.[12]

Orlistat may be a more viable weight-loss treatment for older adults. One randomized controlled trial found that orlistat therapy was just as effective in older adults (≥65 years old) as younger adults. The incidence of gastrointestinal side effects did not differ by

age.[12] Older subjects treated with orlistat may be at greater risk for fecal incontinence because both external and internal sphincter functions decline with age. However, because constipation is also a common problem in older adults, orlistat therapy could have beneficial gastrointestinal effects.

In summary, the data regarding the use of pharmacotherapy for weight loss in older adults is limited. Further clinical studies are needed to evaluate the use of pharmacotherapy to treat obesity in older adults.

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Links

The links from this chapter are listed below:

VA National Center for Health Promotion and Disease Prevention (NCP)
http://www.prevention.va.gov/

Veterans Health Administration (VHA) Office of Patient Care Services
http://www.patientcare.va.gov/index.asp

Weight Management Program for Veterans (MOVE!®)
http://www.move.va.gov/

NIH Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report (1998)
http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.htm

Screening and Interventions for Obesity in Adults: Summary of the Evidence for the US Preventive Services Task Force (2003)
http://www.annals.org/content/139/11/933.full.pdf+html

Screening for Obesity in Adults (2003)
http://www.annals.org/content/139/11/930.full

Handbook 1101 - Managing Overweight and/or Obesity for Veterans Everywhere (MOVE!) Program
http://www.move.va.gov/download/Resources/1101.1HK3_27_06.pdf

Joint Veterans Affairs/Department of Defense Clinical Practice Guideline for Screening and Management of Overweight and Obesity (2006)
http://www.healthquality.va.gov/obesity/obe06_final1.pdf

Orlistat Monograph
http://www.pbm.va.gov/Clinical%20Guidance/Drug%20Monographs/Orlistat.pdf

Orlistat Criteria for Use in VA
http://www.pbm.va.gov/Clinical%20Guidance/Criteria%20For%20Use/Orlistat%20-%20Criteria%20for%20Use.pdf

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3. Screening for obesity in adults: recommendations and rationale. *Ann Intern Med.* Dec 2 2003;139(11):930-932.

4. Managing Overweight and/or Obesity for Veterans Everywhere (MOVE!) Program: NCP MOVE! Program; 2006.

5. VA/DoD Clinical Practice Guideline for Screening and Management of Overweight and Obesity: VHA; 2006.

6. Snow V, Barry P, Fitterman N, Qaseem A, Weiss K. Pharmacologic and surgical management of obesity in primary care: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* Apr 5 2005;142(7):525-531.

7. Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. *Ann Intern Med.* Apr 5 2005;142(7):532-546.

8. Orlistat (Xenical) National PBM Drug Monograph VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel; 2005.

9. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* Feb 7 2002;346(6):393-403.

10. Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet.* Nov 14 2009;374(9702):1677-1686.

11. Criteria-for-Use Checklist for Orlistat (Xenical): VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel; 2005.

12. Hauptman J, Lucas C, Boldrin MN, Collins H, Segal KR. Orlistat in the long-term treatment of obesity in primary care settings. *Arch Fam Med.* Feb 2000;9(2):160-167.