Pharmacologic options for the treatment of overweight and obesity

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The field of antiobesity pharmacotherapy is rapidly evolving. FDA-approved medications, such as orlistat, phentermine/topiramate, bupropion/naltrexone, and liraglutide, have significantly improved weight-loss outcomes. Agents such as semaglutide and tirzepatide are setting new standards, achieving weight-loss outcomes comparable to bariatric surgery. These medications not only aid in weight reduction but also offer additional health benefits, including improved cardiometabolic health and reduced cardiovascular risk. Antiobesity medications require long-term use because discontinuation often causes weight regain. Such as other chronic diseases, overweight and obesity require ongoing management. Patient education and support are key to maintaining results and preventing weight recidivism.

(*Menopause* 2025;32:000–000)

WEIGHT GAIN IN MIDLIFE WOMEN

Midlife is marked by physiologic, physical, and psychosocial changes because of aging and menopause, predisposing women to gain weight. Although aging, rather than menopause, is the primary driver for weight gain in midlife women, declining estrogen levels in menopause lead to increased abdominal subcutaneous and visceral fat. Midlife weight gain contributes to the rising rates of overweight and obesity in aging women and sets the stage for adiposity-related health risks. Weight gain during midlife increases the risk for cardiometabolic diseases, cancer, obstructive sleep apnea, osteoarthritis, cognitive decline, and mental health disorders.[1] Excess adiposity also worsens menopause symptoms including vasomotor symptoms (VMS) and urogenital symptoms and can affect sexual function. Addressing weight management during midlife is therefore critical for reducing these risks and improving the quality of life of aging women. Lifestyle interventions—diet, exercise, and behavioral therapy—are fundamental, but many persons experience weight regain because of metabolic and behavioral adaptations. Thus, additional treatments, including antiobesity medications and bariatric procedures, may be needed.

Released March 4, 2025.
From the Mayo Clinic, Jacksonville, Florida.
Disclosures: Dr. Hurtado Andrade reports Advisory Board/Consultant from Novo Nordisk and Research Support from the National Institutes of Health, and from Phenomix Sciences.

eISSN: 1530-0374
DOI: 10.1097/GME.0000000000002573

ANTIOBESITY MEDICATIONS

The field of antiobesity pharmacotherapy is rapidly evolving. The recognition of obesity as a chronic and multifactorial disease has deepened the understanding of its pathophysiology, leading to the development of drugs that target specific energy balance pathways. These are the FDA-approved medications for long-term weight management:

Orlistat is a pancreatic and intestinal lipase inhibitor that reduces dietary fat absorption. Available in 60 mg (over the counter) and 120 mg (prescription) doses, it is taken by mouth with meals and leads to 5% to 6% weight loss over 12 months. Adverse events include oily stools, fecal urgency, and fat-soluble vitamin (A, D, E, K) deficiencies.[2]

Phentermine/Topiramate extended release (ER) combines a sympathomimetic with an antagonist to α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainic acid (KA) receptors, an agonist to gamma-aminobutyric acid, and a carbonic anhydrase inhibitor to suppress appetite. This oral medication, starting at 3.75 mg/23 mg and up to 15 mg/92 mg daily of phentermine/topiramate, achieves a 9% to 11% weight loss over 12 months. Adverse events include paresthesia, dry mouth, insomnia, dysgeusia, and palpitations. Contraindications include cardiovascular disease (CVD), untreated hyperthyroidism, uncontrolled hypertension, monoamino oxidase (MAO) inhibitor use, and closed-angle glaucoma.[3]

Naltrexone/Bupropion sustained release (SR) combines an opioid receptor antagonist and a dopamine agonist and a norepinephrine reuptake inhibitor to suppress appetite. Starting with one 8/90 mg tablet of naltrexone/bupropion, dosing increases weekly to two tablets twice daily, achieving a 5% to 6% weight loss over 12 months. Adverse events include nausea, headache, insomnia, constipation, dry mouth, and mood changes; it is contraindicated with opioids or MAO inhibitor use.[4]

The **glucagon-like peptide-1 receptor agonists** (GLP-1 RA) liraglutide and semaglutide are subcutaneous injections that slow gastric emptying and promote satiety. Liraglutide, taken daily (0.6-3.0 mg) leads to an 8% weight loss over 13 months, whereas weekly semaglutide (0.25-2.4 mg) achieves a 15% weight loss over 16 months.[5,6] Adverse events include nausea, diarrhea, constipation, and dyspepsia. They are contraindicated for persons with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2.

Tirzepatide is a dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) RA. It has the same mechanism of action, adverse events, and contraindications as GLP-1 RA. This weekly subcutaneous injection (2.5-15 mg) achieves an average 21% weight loss over 16 months.[7]

INDICATIONS FOR ANTIOBESITY MEDICATIONS

Antiobesity medications are indicated for persons with a body mass index (BMI) between 27 kg/m^2 and 29.9 kg/m^2 in the presence of adiposity based-diseases or for persons with a BMI of 30 kg/m^2 or greater, irrespective of the presence of adiposity-based comorbidities. The choice of antiobesity medication depends on the person's weight loss goals, the presence of comorbidities that may favor or preclude the use of a specific medication, insurance coverage, and the patient's values and preferences.

APPROACH FOR THE USE OF ANTIOBESITY MEDICATIONS

There are no head-to-head trials comparing the medications to one another. However, evidence suggests that the newer GLP-1 RA-based antiobesity drugs tirzepatide and semaglutide are the most effective, with weight loss outcomes nearing those of bariatric surgery. Notably, GLP-1 RA-based antiobesity medications have effects that extend beyond weight loss because they help prevent the progression from prediabetes to diabetes; improve diabetes control, metabolic dysfunction-associated liver disease, and obstructive sleep apnea; and reduce cardiovascular events.[8] Remarkably, semaglutide is the first and only antiobesity medication approved for CVD risk reduction based on its cardiovascular outcomes data showing that, in persons with obesity and preestablished cardiovascular disease, it reduces cardiovascular events by 20%.[9] As such, although tirzepatide may be associated with better weight loss outcomes, women with preestablished CVD may benefit from semaglutide for now.

Tirzepatide and semaglutide are excellent but expensive medications ($1,000 USD/month if they are not covered by insurance). The 2022 analysis by the Institute of Clinical and Economic Research determined that phentermine/topiramate ER was the most cost-effective antiobesity medication, with a monthly cost of $100 USD.[10] This analysis did not include the Semaglutide Cardiovascular Outcomes Trial data. Although naltrexone/bupropion SR and orlistat have a similar cost to phentermine/topiramate ER, given their modest weight loss outcomes, they are usually not considered first-line medications. Furthermore, gastrointestinal adverse events associated with orlistat limit its use in clinical practice, and it is rarely used. Notably, although FDA has approved phentermine for short-term use only (12 wk or fewer), it is the least expensive antiobesity medication, and data support its safety with long-term use, with an average weight loss of 7% over 12 months.[11]

It is crucial to recognize that antiobesity medications are required for long-term or even lifelong use because discontinuation leads to significant weight regain in most people.[12,13] Similar to hypertension or diabetes, where ongoing medication is needed to maintain control of these diseases, obesity is a chronic disease requiring sustained treatment. Proper counseling regarding the chronic nature of obesity and the role of medication can help set realistic expectations for patients.

SPECIAL CONSIDERATIONS IN RELATION TO MENOPAUSE

Research on antiobesity medications in midlife women, especially in relation to menopause, is limited. A study of semaglutide in postmenopausal women showed greater weight loss in those using hormone therapy, but causation remains unclear, requiring more research.[14] Additionally, concerns exist about the effect of antiobesity drugs on muscle mass and physical function in at-risk persons. As menopause- and age-related changes in body composition make midlife women more vulnerable to sarcopenia and physical dysfunction, further research in this population is essential. Finally, VMS and excess adiposity are linked: VMS may lead to weight gain, whereas central adiposity is associated with increased VMS severity. Although weight loss via lifestyle intervention has been associated with decreased frequency and severity of VMS, research on antiobesity medications is limited. Only one small study using lorcaserin, an antiobesity medication that has since been discontinued, showed improvement in VMS.[15] Further research is needed to explore the effect of other antiobesity medications on VMS.

PEARL

In midlife women, antiobesity medications can be effective adjuncts to lifestyle changes. Newer GLP-1 RAs offer substantial weight loss and additional benefits such as improved metabolic health and reduced cardiovascular risk. When prescribing, tailor medication choice to individual health profiles, potential adverse events, and patient preferences. Emphasize the importance of long-term use, because stopping medication often leads to weight regain.

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Made possible by donations to The Menopause Society Education & Research Fund.