



Department of Vermont Health Access

Therapeutic Class Review Weight Loss Therapy

Overview/Summary

Overweight and obesity are conditions characterized by excess body fat and are associated with increased risk of conditions such as hypertension, dyslipidemia, type 2 diabetes, cardiovascular diseases and sleep apnea.¹ The etiology of obesity is multifactorial in origin with genetic, environmental and psychologic factors contributing to various degrees among different patients.² Assessment of overweight and obese patients most commonly involves an evaluation of body mass index (BMI), a measure of total body fat composition; however, waist circumference and overall health status may also be of value. For adult obese patients, in addition to a BMI ≥ 30 kg/m² and a large waist circumference, certain obesity-related diseases place patients at a high absolute risk for subsequent death. Patients with established coronary heart disease, other atherosclerotic diseases, type 2 diabetes or sleep apnea are considered high risk and require aggressive weight loss treatment. In addition, three of the following obesity-related risk factors also confer a high absolute risk: hypertension, smoking, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, impaired fasting glucose, family history of early cardiovascular disease and age (men ≥ 45 years, women ≥ 55 years).³

Although patients may decide to lose weight for a variety of reasons, a major goal of weight loss therapy is to improve cardiovascular risks to reduce overall morbidity and mortality.² Weight loss therapy is recommended for patients with a BMI ≥ 30 kg/m² (obese) and for patients with a BMI between 25.0 to 29.9 kg/m² (overweight) or a high risk waist circumference (men >40 inches, women >35 inches) with two or more risk factors.³ Treatment of obesity is a life-long process which may require substantial lifestyle changes. It is well established that any weight loss regimen should be comprehensive and always encompass lifestyle modification, including diet and exercise as well as behavioral modification.¹⁻⁶ Pharmacotherapy may be helpful in high risk obese patients as adjunct to diet and exercise.³⁻⁶ Lifestyle modification should be tried for at least six months before considering the addition of pharmacotherapy to any weight loss regimen.³ Specifically, in adult patients, it is recommended that pharmacotherapy be limited to those with a BMI ≥ 30 kg/m² or a BMI ≥ 27 kg/m² with concomitant obesity-related risk factors or diseases.^{3,6} For obese children (BMI $\geq 95^{\text{th}}$ percentile), pharmacotherapy can be considered if intensive lifestyle modification has failed to limit weight gain.⁴ For overweight children (BMI $\geq 85^{\text{th}}$ percentile and $<95^{\text{th}}$ percentile), pharmacotherapy should be reserved for patients with severe, significant comorbidities who have not responded to lifestyle modification. Pharmacotherapy should never be used without concomitant lifestyle modification or for purely cosmetic reasons.^{1,6}

Medications used for the treatment of obesity can be classified based on the mechanism of action: medications that reduce food intake, medications that interfere with fat absorption and medications that increase energy expenditure.¹ Included in this review are agents that work by reducing food intake or interfering with fat absorption. Several drugs that increase energy expenditure, including supplements containing ephedra alkaloids, have been withdrawn from the market due to safety concerns.²

Sympathomimetic drugs reduce food intake by causing early satiety.⁷ This class of medications includes benzphetamine (Didrex[®]), diethylpropion, phendimetrazine (Bontril[®] PDM, Bontril[®] Slow Release) and phentermine (Adipex-P[®]). All of these agents share similar pharmacologic properties to amphetamines, and work by stimulating the release of norepinephrine or inhibiting its reuptake. Because of this, these agents have been designated controlled substances (Schedule III or IV) by the Food and Drug Administration (FDA) due to a potential for abuse. In addition, all of the sympathomimetics are FDA approved for short term use only.⁸⁻¹³ Currently, all of the sympathomimetics are available generically. Meridia[®] (sibutramine) was a sympathomimetic that was FDA approved for the long term treatment of

obesity but has since been pulled from the market. In October 2010, the manufacturers of sibutramine announced their voluntary withdrawal of sibutramine from the market at the request of the FDA. The withdrawal came after a review of post-marketing clinical trial results that demonstrated an increased risk for serious cardiovascular events associated with the agent.¹⁴⁻¹⁶

Alli[®] and Xenical[®] (orlistat) work by interfering with fat absorption. Specifically, orlistat works by inhibiting pancreatic lipase, resulting in the incomplete hydrolysis of ingested fat, as well as increased fat excretion. Orlistat (Xenical[®]) is the only weight loss agent FDA approved for long term treatment of obesity. Orlistat is not classified as a controlled substance and is available as a branded prescription (Xenical[®]) or over-the-counter product (Alli[®]).^{17,18}

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade Name)	Medication Class	Schedule	Generic Availability
Benzphetamine (Didrex ^{®*})	Sympathomimetic	III	✓
Diethylpropion*	Sympathomimetic	IV	✓
Orlistat (Alli ^{®†} , Xenical [®])	Lipase inhibitor	-	-
Phendimetrazine (Bontril [®] PDM*, Bontril [®] Slow Release*)	Sympathomimetic	III	✓
Phentermine (Adipex-P ^{®*})	Sympathomimetic	IV	✓

*Generic available in at least one dosage form and/or strength.

†Over-the-counter product.

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications^{8-13,17,18}

Generic Name	Management of Exogenous Obesity as a Short Term (Few Weeks) Adjunct in a Regimen of Weight Reduction Based on Caloric Restriction	Management of Exogenous Obesity as a Short Term (Few Weeks) Adjunct in a Regimen of Weight Reduction Based on Exercise, Behavioral Modification, and Caloric Restriction	Obesity Management Including Weight Loss and Weight Maintenance When Used in Conjunction with a Reduced Calorie Diet	Reduce the Risk for Weight Regain After Prior Weight Loss	Weight Loss in Overweight Adults When Used Along with a Reduced Calorie and Low-Fat Diet
Benzphetamine	✓*†				
Diethylpropion	✓*†				
Orlistat			✓‡ (Xenical®)	✓‡ (Xenical®)	✓ (Alli®)
Phendimetrazine	✓*†				
Phentermine		✓‡			

*In patients with an initial body mass index (BMI) ≥ 30 kg/m² and who have not responded to appropriate weight reducing regimen (diet and/or exercise) alone.

†Indicated for monotherapy only.

‡In patients with an initial BMI ≥ 30 kg/m² or ≥ 27 kg/m² in the presence of other risk factors.

In addition to its Food and Drug Administration approved indication, orlistat may also be used off-label for prophylaxis treatment of coronary arteriosclerosis and diabetes mellitus, and in the treatment of type 2 diabetes and hyperlipidemia.¹⁹

Pharmacokinetics

Table 3. Pharmacokinetics¹⁹

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Benzphetamine	Not reported	Not reported	Not reported	Not reported
Diethylpropion	Rapid (IR); uniform (CR)	3 to 67	N-ethylamino-propiofenone*	4 to 8
Orlistat	<5	0 to 4	None	1 to 2
Phendimetrazine	Not reported	80	Phenmetrazine	2 to 4
Phentermine	Slow (extended release resin)	70 to 80	Not reported	20

*Many of the diethylpropion's metabolites are active and may contribute to its therapeutic effects.
CR=controlled-release, IR=immediate-release

Clinical Trials

Limited significant clinical trials evaluating benzphetamine, diethylpropion and phendimetrazine for weight loss management were retrieved by a comprehensive literature search. Evidence of the effectiveness of centrally acting appetite suppressant agents on weight loss has been well documented since the 1970s.²

Results from a four year trial not only demonstrated superior weight loss with orlistat compared to placebo (both in addition to lifestyle modification) at one ($P<0.001$) and four years ($P<0.001$), but also that treatment with orlistat significantly decreased the progression to type 2 diabetes ($P=0.0032$). In this trial (N=3,305), the cumulative incidence rates of type 2 diabetes after four years of treatment were 6.2 vs 9.0% (hazard ratio, 0.627; 95% confidence interval [CI], 0.455 to 0.863); corresponding to a 37.3% decrease in the risk of developing diabetes with orlistat.²⁰

In a trial of female patients who had completed a year of sibutramine (not available in the United States) plus lifestyle modification treatment, the addition of orlistat did not significantly increase weight loss as compared to the continued use of sibutramine plus lifestyle modification.²¹ Additionally, in another trial, orlistat in combination with a low fat diet achieved similar weight loss compared to a low carbohydrate, ketogenic diet alone. In this trial both groups attended weekly group meetings and were advised to increase daily exercise and fluid consumption, as well as to take a multivitamin and to limit their consumption of alcohol and caffeine.²²

In Kang et al (N=74), controlled release phentermine achieved significant reductions in body weight and waist circumference compared to placebo ($P<0.001$ for both). Additionally, significantly greater proportions of patients reduced their baseline weight by ≥ 5 and $\geq 10\%$ with phentermine compared to placebo ($P<0.001$ for both). Patients in this trial were educated to follow a lifestyle modification, including a hypocaloric diet.²³ The CONQUER trial (N=2,487) demonstrated that phentermine in combination with topiramate was also an effective weight loss treatment. Specifically after 56 weeks, combination therapy significantly reduced bodyweight compared to placebo ($P<0.001$ for all comparisons), and again significantly greater proportions of patients receiving combination therapy were able to achieve a reduction in baseline weight by ≥ 5 and $\geq 10\%$ ($P<0.0001$ for all comparisons). In this trial, all patients received standardized counseling for diet and lifestyle modification.²⁴

Several meta-analyses have been conducted evaluating orlistat, sibutramine (not available in the United States) and other medications used for the treatment of obesity, as well as lifestyle and behavioral modification.²⁵⁻²⁹ In the analysis conducted by Li et al, sibutramine with lifestyle modification was found to be more effective than lifestyle modification alone. Patients treated with sibutramine were also 20 to 30% more likely to lose $\geq 5\%$ of their body weight compared to placebo. In general, treatment with sibutramine was associated with modest increases in heart rate and blood pressure, and small improvements in triglycerides and high-density lipoprotein-cholesterol levels. Regarding treatment with orlistat, pooled analysis demonstrated that at 6 and 12 months, the mean weight loss achieved was 2.59 (95% CI, 1.74 to 3.46) and 2.89 kg (95% CI, 2.27 to 3.51) compared to placebo. Orlistat was also associated with more

gastrointestinal-related adverse events compared to placebo. Additionally, pooled analysis of trials evaluating phentermine- and diethylpropion-treated patients demonstrated an average loss of 3.6 (95% CI, 0.6 to 6.0) and 3.0 kg (95% CI, -1.6 to 11.5) compared to placebo. These agents used in combination with lifestyle modification resulted in a modest increase in weight loss which only reached significance for phentermine-treated patients.²⁸

Clinical Trials

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Torgerson et al²⁰</p> <p>Orlistat, 120 mg TID</p> <p>vs</p> <p>placebo</p> <p>Patients incorporated lifestyle changes into management programs.</p>	<p>DB, PC, PRO, RCT</p> <p>Patients 30 to 60 years of age with a BMI ≥ 30 kg/m², who were nondiabetic based on an oral glucose tolerance test</p>	<p>N=3,305</p> <p>4 years</p>	<p>Primary: Time to onset of type 2 diabetes, change in body weight after four years of treatment</p> <p>Secondary: Change from baseline in anthropometric measurements, metabolic profile, time to onset of impaired glucose tolerance</p>	<p>Primary: Orlistat significantly decreased the progression to type 2 diabetes compared to placebo ($P=0.0032$). The cumulative incidence rates after four years were 6.2 vs 9.0% with a HR of 0.627 (95% CI, 0.455 to 0.863) corresponding to a 37.3% decrease in the risk of developing diabetes with orlistat compared to placebo.</p> <p>For patients who completed the four years of treatment (52.0 and 34.0% of orlistat- and placebo-treated patients) weight loss was significantly greater with orlistat than placebo at one (11.4 vs 7.5 kg; $P<0.001$) and four years (6.9 vs 4.1 kg; $P<0.001$). Significantly more orlistat-treated patients (72.8%) than placebo-treated patients (45.1%) achieved weight loss $\geq 5\%$ after one year of treatment ($P<0.001$).</p> <p>Secondary: Treatment with orlistat resulted in early and significant improvements in cardiovascular risk factors that were sustained throughout the trial, including BP, waist circumference and lipids. TC, LDL-C and LDL-C:HDL-C decreased significantly more with orlistat than placebo, at both one and four years of treatment. Additionally, HDL-C increased less with orlistat.</p> <p>There was no difference in the progression rate from normal to impaired glucose tolerance over four years between orlistat- and placebo-treated patients (27.6 vs 30.5%; $P=0.1521$).</p>
<p>Wadden et al²¹</p> <p>Orlistat, 1 capsule TID</p> <p>vs</p> <p>placebo</p> <p>Patients continued</p>	<p>PC, RCT</p> <p>Women who had completed 1 year of treatment that combined sibutramine 10 to 15 mg/day with different amounts of</p>	<p>N=34</p> <p>16 weeks</p>	<p>Primary: Weight loss</p> <p>Secondary: Not reported</p>	<p>Primary: Body weight was essentially unchanged with both treatments during the 16 week trial. The addition of orlistat to sibutramine did not significantly increase weight loss compared to placebo (P value not reported).</p> <p>Patients who lost $<10\%$ of weight in the previous year lost 1.2 ± 3.2 kg during the 16 week trial, independent of which medication they received. Those who had lost $>10\%$ of weight in the previous year gained 1.7 ± 2.6 kg during the 16 week trial, yielding a significant difference between</p>

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sibutramine*, 10 to 15 mg Daily and were instructed to limit their fat intake to a maximum of 20 g/meal (or snack) and 60 g/day.	lifestyle modification			<p>groups ($P<0.01$).</p> <p>Women who had lost $<10\%$ of weight in the previous year tended to lose more weight if they added orlistat compared to placebo (-2.6 ± 4.9 kg vs -0.4 ± 1.2 kg, respectively), but there was no significant difference between treatments (P value not reported).</p> <p>Patients who lost five to 14% of initial body weight in the previous year who added orlistat, had a mean weight increase of 0.2 ± 5.1 kg in the 16 week continuation trial.</p> <p>There were no significant differences in weight change during the 16 week continuation trial between patients who received 10 or 15 mg/day of sibutramine (P value not reported).</p> <p>Fifty percent of patients who added orlistat reported soft stool ($P=0.04$) and increased frequency of bowel movements ($P=0.04$) at least one day a week, as compared to only 9.1% of patients who added placebo. Additionally, 42.9% of patients who added sibutramine reported oily evacuation ($P=0.02$) and fecal urgency ($P=0.09$) at least one day of the week as compared to 0 to 9.1% of patients who added placebo.</p> <p>Secondary: Not reported</p>
<p>Yancy et al²²</p> <p>Group 1: Low carbohydrate, ketogenic diet (<20 g of carbohydrates daily)</p> <p>vs</p> <p>Group 2: orlistat, 120 mg TID plus low fat diet ($<30\%$</p>	<p>RCT</p> <p>Patients 18 to 70 years of age with a BMI 27 to 30 kg/m² plus an obesity-related disease or a BMI ≥ 30 kg/m² regardless of comorbidity</p>	<p>N=146</p> <p>48 weeks</p>	<p>Primary: Percentage change in body weight</p> <p>Secondary: BP, fasting serum lipid, glycemic parameters</p>	<p>Primary: Over 48 weeks, weight loss was significant and similar in the treatment groups. The expected mean change from baseline in Group 1 was -9.5% (95% CI, -12.1 to -6.9) or -11.4 kg (95% CI, -14.8 to -7.9) compared to -8.5% (95% CI, -11.0 to -6.1) or -9.6 kg (95% CI, -4.5 to 2.6) in Group 2.</p> <p>Waist circumference also decreased similarly in the two treatments.</p> <p>The proportions of patients in each group who achieved the following levels of weight change were similar: $<5\%$ weight loss (36 vs 41%), five to $<10\%$ weight loss (19 vs 18%), 10 to $<20\%$ weight loss (31 vs 31%) and $\geq 20\%$ weight loss (14 vs 11%) ($P=0.91$).</p>

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<p>energy from fat, 500 to 1,000 kcal/day deficit)</p> <p>Both interventions included small group meetings at an outpatient clinic every 2 weeks for 24 weeks, then every 4 weeks for 24 weeks.</p> <p>All participants were advised to exercise on their own for 30 minutes ≥ 3 times per week, take a multivitamin daily, drink 6 to 8 glasses of fluids daily, and minimize consumption of caffeine and alcohol.</p>				<p>Patients who attended $\geq 80\%$ of the group counseling sessions lost considerably more weight, regardless of treatment assignment (observed means: Group 1 [n=26], -14.9%; Group 2 [n=27], -13.9%).</p> <p>Secondary: Group 1 had greater improvements in SBP ($P=0.24$) and DBP ($P<0.001$) compared to Group 2.</p> <p>Group 1 appeared to have greater improvements initially in serum HDL-C and TG levels, whereas Group 2 appeared to have greater improvements initially in TC and LDL-C levels. At 48 weeks there were no significant differences in any of these measures between the two groups ($P=0.80$, $P=0.58$, $P=0.29$, and $P=0.14$)</p> <p>Serum urea nitrogen levels increased more in Group 1 compared to Group 2 (mean difference, 2.0 mg/dL; 95% CI, 0.4 to 3.5; $P=0.01$).</p> <p>Within Group 1, the following decreased significantly from baseline to 48 weeks: fasting glucose levels (-9.7 mg/dL; 95% CI, -16.9 to -2.6; P value not reported), fasting insulin level (-7.3 μU/mL; 95% CI, -13.5 to -1.2; P value not reported [patients without diabetes only]) and HbA_{1c} (-0.3%; 95% CI, -0.5 to -0.1; P value not reported).</p>
<p>Kang et al²³</p> <p>Phentermine CR 30 mg Daily</p> <p>vs</p> <p>placebo</p> <p>Patients were educated to follow a lifestyle modification, including a hypocaloric diet.</p>	<p>DB, PC, RCT</p> <p>Patients ≥ 19 years of age with obesity, a BMI ≥ 30 kg/m² or 27 to 30 kg/m² who are being treated for dyslipidemia, hypertension or type 2 diabetes</p>	<p>N=74</p> <p>12 weeks</p>	<p>Primary: Changes in bodyweight, waist circumference and metabolic parameters</p> <p>Secondary: Safety</p>	<p>Primary: Significant reductions in weight loss (8.1\pm3.9 vs 1.7\pm2.9 kg; $P<0.001$) and waist circumference (7.2\pm0.5 vs 2.1\pm0.6 cm; $P<0.001$) were achieved with phentermine compared to placebo. Significantly greater proportions of patients receiving phentermine achieved weight reductions of $\geq 5\%$ from baseline (95.8 vs 20.8%; $P<0.001$) and $\geq 10\%$ (62.5 vs 4.7%; $P<0.001$) compared to patients receiving placebo.</p> <p>TC ($P<0.001$) and LDL-C ($P<0.001$) were significantly improved with phentermine; however, there were no significant differences in SBP and DBP, FPG, TG or HDL-C between the two treatments.</p> <p>Secondary:</p>

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<p>Gadde et al²⁴ CONQUER</p> <p>Phentermine 7.5 mg/day plus topiramate 46 mg/day</p> <p>vs</p> <p>phentermine 15 mg/day plus topiramate 92 mg/day</p> <p>vs</p> <p>placebo</p> <p>All patients received standardized counseling for diet and lifestyle modification.</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 to 70 years of age who were overweight or obese with a BMI of 27 to 45 kg/m² and ≥2 of the following comorbidities at baseline: SBP 140 to 160 mmHg, DBP 90 to 100 mm Hg or taking ≥2 antihypertensive agents; TG 2.26 to 4.52 mmol/L or taking ≥2 lipid lowering agents; FPG >7.77 mmol/L at 2 hours after oral glucose load during glucose tolerance test or diagnosed with type 2 diabetes managed with lifestyle changes or metformin monotherapy; and a waist circumference ≥102 cm for men or ≥88 cm for women</p>	<p>N=2,487</p> <p>56 weeks</p>	<p>Primary: Percent change in body weight, proportion of patients achieving ≥5% weight loss</p> <p>Secondary: Safety</p>	<p>Dry mouth and insomnia were the most commonly reported adverse events.</p> <p>Primary: At 56 weeks, changes in bodyweight were -1.4 (LSM, -1.2%; 95% CI, -1.8 to -0.7), -8.1 (-7.8%; 95% CI, -8.5 to -7.1; <i>P</i><0.001) and -10.2 kg (-9.8%; 95% CI, -10.4 to -9.3; <i>P</i><0.001) with placebo, phentermine 7.5 mg/day plus topiramate 46 mg/day and phentermine 15 mg/day plus topiramate 92 mg/day.</p> <p>Twenty one (n=204), 62 (n=303) and 70% (n=687) of patients receiving placebo (OR, 6.3; 95% CI, 4.9 to 8.0; <i>P</i><0.001), phentermine 7.5 mg/day plus topiramate 46 mg/day (OR, 6.3; 95% CI, 4.9 to 8.0; <i>P</i><0.0001) and phentermine 15 mg/day plus topiramate 92 mg/day (OR, 9.0; 95% CI, 7.3 to 11.1; <i>P</i><0.0001) achieved ≥5% weight loss. The corresponding numbers for ≥10% weight loss were seven (n=72), 37 (n=182; OR, 7.6; 95% CI, 5.6 to 10.2; <i>P</i><0.0001) and 48% (n=467; OR, 11.7; 95% CI, 8.9 to 15.4; <i>P</i><0.0001).</p> <p>Secondary: The most commonly reported side effects were dry mouth (13 vs 21 vs 2%), paraesthesia (14 vs 21 vs 2%), constipation (15 vs 17 vs 6%), insomnia (six vs 10 vs 5%), dizziness (seven vs 10 vs 3%) and dysgeusia (seven vs 10 vs 1%). The proportions of patients who had depress-related adverse events were five, eight and 3%. The proportions of patients who had anxiety-related adverse events were five vs eight vs 3% (<i>P</i> values not reported).</p>
<p>Neovius M et al²⁵</p> <p>Orlistat 360 mg/day</p>	<p>MA</p> <p>8 head-to-head</p>	<p>N=885</p> <p>3 to12</p>	<p>Primary: Median weight loss</p>	<p>Primary: The median weight loss in sibutramine- and orlistat-treated patients was 11.7 kg (10.1 to 13.0) and 8.0 kg (5.5 to 9.5), respectively. Four of the</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs sibutramine* 10 to 20 mg/day	RCTs	months	Secondary: Not reported	<p>seven trials directly comparing sibutramine and orlistat monotherapy demonstrated that sibutramine was significantly more efficacious for weight loss, while the remaining three trials showed equivalence.</p> <p>Three trials also investigated orlistat and sibutramine as combination therapy, and two demonstrated that combination therapy was significantly more effective than orlistat alone (-10.8 vs -5.5 kg; -13.7 vs -9.4 kg), but not sibutramine alone (-10.8 vs -10.1 kg; -13.7 vs -11.7 kg).</p> <p>Pooled analysis of seven trials comparing orlistat and sibutramine monotherapy demonstrated a weighted mean difference of 2.2 kg ($P<0.001$), favoring sibutramine.</p> <p>Secondary: Not reported</p>
Czernichow et al ²⁶ Anti-obesity drugs (orlistat and sibutramine*)	MA 8 PC, RCTs of overweight/obese patients ≤ 18 years of age evaluating the effect of anti-obesity drugs on weight and cardiovascular risk factors	N=1,391 Up to 12 months with a minimum of 6 month follow-up	Primary: Impact of treatment on body weight, BMI, waist circumference and cardiovascular risk factors Secondary: Not reported	<p>Primary: The pooled mean weight decrease between active and placebo groups was 5.25 kg (95% CI, 3.03 to 7.48).</p> <p>The pooled mean BMI decrease between the active treatments and placebo was 1.89 kg/m² (95% CI, 1.06 to 2.73). The effect was not significantly greater in trials of sibutramine compared to trials of orlistat (2.28 kg/m²; 95% CI, 1.76 to 2.81 vs 1.67 kg/m²; 95% CI, 0.18 to 3.52).</p> <p>Seven trials reported on waist circumference and the pooled mean decrease between active and control groups was 4.74 cm (95% CI, 2.97 to 6.52).</p> <p>Four trials provided data on cardiovascular risk factors. Overall, there was no evidence to suggest that treatment was associated with any effect on the lipid profile, insulin concentration, or pulse rate. For BP, there was some evidence that treatment was associated with a small increase in SBP and DBP compared to placebo.</p>
Viner et al ²⁷ Anti-obesity drugs	MA 6 DB, PC, RCTs	N=1,259 6 to 12	Primary: Change in BMI	Primary: Pooled estimate of mean BMI change with orlistat and sibutramine was a reduction of 0.83 kg/m ² (95% CI, 0.47 to 1.19) and 2.20 kg/m ² (95% CI,

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<p>(orlistat, rimonabant* and sibutramine*)</p> <p>Patients receiving orlistat were administered 120 mg TID, and also received behavioral, dietary and exercise counseling.</p> <p>Patients receiving sibutramine* were administered 5 to 15 mg/day.</p> <p>No trials evaluating rimonabant* were retrieved.</p>	<p>investigating the effects and safety of anti-obesity drugs for BMI reduction in patients <20 years of age for a duration of 6 months</p>	<p>months</p>	<p>Secondary: Waist circumference, body composition, lipid profiles, glycemic parameters, BP, adverse events</p>	<p>1.57 to 2.83). Two trials evaluating sibutramine also used a behavior therapy program which produced a mean BMI reduction of 2.23 kg/m² compared to placebo and a behavior therapy program.</p> <p>Secondary: Outcomes for waist circumference, body fat and BP were only reported in one trial evaluating orlistat; therefore, were not included in the analysis. Data were unavailable on the effect of sibutramine on body composition; however, sibutramine was associated with a decrease in waist circumference of nearly 6 cm on average.</p> <p>There were no significant differences in fasting lipids, glucose or insulin between orlistat and placebo. Sibutramine was associated with significant improvements in TG and HDL-C compared to placebo.</p> <p>Sibutramine-treated patients had higher SBP, DBP and heart rate compared to placebo.</p> <p>Patients receiving orlistat were significantly more likely to experience a range of gastrointestinal side effects than placebo. Those taking sibutramine were also significantly more likely to experience dry mouth but no other adverse events.</p>
<p>Li et al²⁸</p> <p>Pharmacologic treatment of obesity (bupropion, diethylpropion, fluoxetine, orlistat, phentermine, sertraline, sibutramine*, topiramate and zonisamide)</p> <p>Only results for Food and Drug Administration approved ant-obesity</p>	<p>MA</p> <p>Patients with a BMI ≥27 kg/m²</p>	<p>N=not reported (82 trials)</p> <p>6 to 12 months</p>	<p>Primary: Weight loss between baseline and follow up, adverse events (from RCTs only)</p> <p>Secondary: Not reported</p>	<p>Primary: <i>Efficacy of Diethylpropion</i> Pooled analysis demonstrated that diethylpropion-treated patients lost an average of 3.0 kg (95% CI, -1.6 to 11.5) of additional weight compared to placebo. Diethylpropion use, in addition to lifestyle interventions, was associated with a modest increase in weight loss.</p> <p>No data on side effects or adverse events were reported.</p> <p><i>Efficacy of Orlistat</i> Pooled analysis of 12 trials reporting six month outcomes, demonstrated an estimate of the mean weight loss for orlistat-treated patients compared to placebo-treated patients was 2.59 kg (95% CI, 1.74 to 3.46). The total weight lost in the orlistat-treated patients was 5.39 kg. Pooled analysis of</p>

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agents are reported.				<p>22 trials reporting 12 month outcomes, demonstrated an estimate of the mean weight loss for orlistat-treated patients compared to placebo-treated patients was 2.89 kg (95% CI, 2.27 to 3.51). The total weight lost in the orlistat-treated patients was 8.13 kg.</p> <p>Results indicate an increase in diarrhea (RR, 3.40); flatulence (RR, 3.10); and bloating, abdominal pain and dyspepsia (RR, 1.48) in orlistat-treated patients compared to placebo.</p> <p><i>Efficacy of Phentermine</i> Pooled analysis demonstrated that phentermine-treated patients lost an average of 3.6 kg (95% CI, 0.6 to 6.0) of additional weight compared to placebo. Phentermine use, in addition to lifestyle interventions, resulted in a significant but modest increase in weight loss.</p> <p>No data on side effects or adverse events were reported.</p> <p><i>Efficacy of Sibutramine</i> Sibutramine with lifestyle modification was more effective than placebo with lifestyle modification in promoting weight loss in overweight and obese adults at all time points assessed. An average of 4.5 kg more weight was lost at one year in sibutramine-treated patients. Additionally, these patients had a 20 to 30% greater likelihood of losing ≥5% of their body weight compared to placebo.</p> <p>Treatment with sibutramine was associated with modest increases in heart rate and BP, very small improvements in glycemic control among diabetics, and small improvements in HDL-C and TG levels.</p> <p>Efficacy and safety beyond two years of treatment are unknown.</p> <p>No serious adverse events were reported.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>McGovern et al²⁹</p> <p>Nonsurgical interventions on obesity</p>	<p>MA</p> <p>61 RCTs with patients 2 to 18 years of age, with the majority of participants being overweight</p>	<p>N=not reported</p> <p>Duration not reported</p>	<p>Primary: Efficacy of nonsurgical interventions on obesity outcomes</p> <p>Secondary: Not reported</p>	<p>Primary: <i>Pharmacological Treatments</i></p> <p>Three trials assessed the effect of sibutramine on obese adolescents and the pooled effect size was large (-1.01; 95% CI, -1.28 to -0.73); this effect is consistent with a loss in BMI of 2.4 kg/m² (95% CI, 1.8 to 3.1) after six months of use.</p> <p>Three trials of orlistat demonstrated a small to moderate effect on obesity outcomes (-0.29; 95% CI, -0.46 to -0.12); this effect is consistent with a loss in BMI of 0.7 kg/m² (95% CI, 0.3 to 1.2).</p> <p>Three trials of metformin monotherapy on hyperinsulinemic nondiabetic obese adolescents demonstrated a small nonsignificant change in obesity outcomes at six months (-0.17; 95% CI, -0.62 to 0.28).</p> <p>Other trials measured the effect of sympathomimetics, dehydroepiandrosterone and fiber supplements. The results of these trials are not reported.</p> <p><i>Dietary Interventions Only</i></p> <p>Six trials evaluating different diets (reduced-glycemic-load diet, protein-sparing modified diet, low-carbohydrate diet, high-protein diet and hypocaloric diet) against control. The pooled effect across all these diets was -0.22 (95% CI, -0.56 to 0.11) with small between-study inconsistency. Trials evaluating diets focused on reducing carbohydrates estimated nonsignificant large reductions in obesity outcome.</p> <p><i>Physical Activity Interventions Only</i></p> <p>Evaluated trials yielded inconsistent results. Trials that measured the effect of physical activity on adiposity found a moderate treatment effect (-0.52; 95% CI, -0.73 to -0.30) and trials measuring the effect on BMI found no significant effect (-0.01, 95% CI, -0.21 to -0.18).</p> <p><i>Combination Lifestyle Intervention (Physical Activity and Dietary Modification)</i></p> <p>The pooled estimate across 23 trials was consistent with a small to</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				moderate treatment effect. The largest effects were associated with parental involvement in delivering the intervention, when the parents were either targeted individually or with the child. No significant interaction between age of participants and the effect of lifestyle interventions with parental involvement, but there was a trend toward a larger treatment effect in children ≤ 8 years of age (-0.70; 95% CI, -1.00 to -0.40).

*Agent is not available in the United States.

Drug regimen abbreviations: CR=controlled-release, TID=three times daily

Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, LSM=least squares means, MA=meta-analysis, MC=multicenter, OR=odds ratio, PC=placebo-controlled,

PRO=prospective, RCT=randomized controlled trial, RR=relative risk

Miscellaneous abbreviations: BMI=body mass index, BP=blood pressure, DBP=diastolic blood pressure, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, HDL-C=high-density lipoprotein-cholesterol, LDL-C=low-density lipoprotein-cholesterol, SBP=systolic blood pressure, TC=total cholesterol, TG=triglycerides

Special Populations

Table 5. Special Populations^{8-13,17,18}

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Benzphetamine	No dosage adjustment required in the elderly. Food and Drug Administration approved for use in children >12 years of age.	No dosage adjustment required.	No dosage adjustment required.	X	Yes (% not reported)
Diethylpropion	No dosage adjustment required in the elderly. Food and Drug Administration approved for use in children >16 years of age.	No dosage adjustment required.	No dosage adjustment required.	B	Yes (% not reported)
Orlistat	No dosage adjustment required in the elderly. Food and Drug Administration approved for use in children >12 years of age.	No dosage adjustment required.	No dosage adjustment required.	B	Unknown
Phen- dimetrazine	No dosage adjustment required in the elderly. Use is not recommended in children <12 years of age.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown
Phentermine	No dosage adjustment required in the elderly. Food and Drug Administration approved for use in children >16 years of age.	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use with caution.

Adverse Drug Events

Table 6. Adverse Drug Events (%)⁸⁻¹³

Adverse Event	Benzphetamine	Diethylpropion	Orlistat	Phendimetrazine	Phentermine
Allergic					
Allergic reactions involving the skin	✓	-	-	-	-
Ecchymosis	-	✓	-	-	-
Erythema	-	✓	-	-	-
Rash	-	✓	-	-	-
Urticaria	✓	✓	-	-	✓
Cardiovascular					
Arrhythmia	-	✓	-	-	-
Electrocardiography changes	-	✓	-	-	-
Elevation of blood pressure	✓	✓	-	✓	✓
Palpitation	✓	✓	-	✓	✓
Pedal edema	-	-	2.8	-	-
Precordial pain	-	✓	-	-	-
Pulmonary hypertension	-	✓	-	-	✓
Regurgitant cardiac valvular disease	-	-	-	-	✓
Tachycardia	✓	✓	-	✓	✓
Valvulopathy	-	✓	-	-	-
Central Nervous System					
Agitation	-	-	-	✓	-
Anxiety	-	✓	-	-	-
Blurred vision	-	✓	-	✓	-
Cerebrovascular episode	-	✓	-	-	-
Compulsive episode	-	✓	-	-	-
Depression	✓	✓	3.4	-	-
Dizziness	✓	✓	5.2	✓	✓
Drowsiness	-	✓	-	-	-
Dyskinesia	-	✓	-	-	-
Dysphoria	-	✓	-	-	✓
Euphoria	-	✓	-	-	✓
Flushing	-	-	-	✓	-
Headache	✓	✓	30.6	✓	✓
Insomnia	✓	✓	-	✓	✓
Jitteriness	-	✓	-	-	-

Adverse Event	Benzphetamine	Diethylpropion	Orlistat	Phendimetrazine	Phentermine
Nervousness	-	✓	-	-	-
Malaise	-	✓	-	-	-
Mydriasis	-	✓	-	-	-
Overstimulation	✓	✓	-	✓	✓
Psychiatric anxiety	-	-	2.8 to 4.7	-	-
Psychotic episode	✓	✓	-	-	✓
Psychotic state	-	-	-	✓	-
Restlessness	✓	✓	-	✓	✓
Sweating	✓	-	-	✓	-
Tremor	✓	✓	-	✓	✓
Endocrine					
Changes in libido	✓	✓	-	✓	✓
Gynecomastia	-	✓	-	-	-
Impotence	-	✓	-	-	✓
Menstrual upset	-	✓	-	-	-
Gastrointestinal					
Abdominal pain/discomfort	-	✓	25.5	-	-
Constipation	-	✓	-	✓	✓
Diarrhea	✓	✓	-	✓	✓
Dry mouth	✓	✓	-	✓	✓
Fatty/oily stool	-	-	5.5 to 20.0	-	-
Fecal incontinence	-	-	1.8 to 7.7	-	-
Fecal urgency	-	-	2.8 to 22.1	-	-
Flatus with discharge	-	-	2.1 to 23.9	-	-
Gastrointestinal disturbances	✓	✓	-	-	✓
Increased defecation	-	-	2.6 to 10.8	-	-
Infectious diarrhea	-	-	5.3	-	-
Nausea	✓	✓	3.6 to 8.1	✓	-
Oily spotting	-	-	4.4 to 26.6	-	-
Rectal pain/discomfort	-	-	3.3 to 5.2	-	-
Stomach pain	-	-	-	✓	-
Tooth disorder	-	-	2.9 to 4.3	-	-
Unpleasant taste	✓	✓	-	-	✓
Vomiting	-	✓	3.8	-	-
Hearing and Vestibular Disorder					
Otitis	-	-	2.9 to 4.3	-	-

Adverse Event	Benzphetamine	Diethylpropion	Orlistat	Phendimetrazine	Phentermine
Hematopoietic System					
Agranulocytosis	-	✓	-	-	-
Bone marrow depression	-	✓	-	-	-
Leukopenia	-	✓	-	-	-
Musculoskeletal System					
Arthritis	-	-	5.4	-	-
Back pain	-	-	13.9	-	-
Joint disorder	-	-	2.3	-	-
Myalgia	-	-	4.2	-	-
Pain lower extremities	-	-	10.8	-	-
Tendonitis	-	-	2	-	-
Reproductive (Female)					
Menstrual irregularity	-	-	9.8	-	-
Vaginitis	-	-	2.6 to 3.8	-	-
Respiratory System					
Ear, nose and throat symptoms	-	-	2	-	-
Influenza	-	-	39.7	-	-
Lower respiratory infection	-	-	7.8	-	-
Upper respiratory infection	-	-	26.1 to 38.1	-	-
Skin and Appendages					
Dry skin	-	-	2.1	-	-
Rash	-	-	4.3	-	-
Urinary System					
Urinary frequency	-	-	-	✓	-
Urinary tract infection	-	-	5.9 to 7.5	-	-
Other					
Dysuria	-	✓	-	✓	-
Fatigue	-	-	3.1 to 7.2	-	-
Hair loss	-	✓	-	-	-
Increased sweating	-	✓	-	-	-
Muscle pain	-	✓	-	-	-
Polyuria	-	✓	-	-	-
Sleep disorder	-	-	3.9	-	-

✓ Percent not specified.
 - Event not reported.

Contraindications/Precautions

Benzphetamine, phendimetrazine and phentermine are contraindicated with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to sympathomimetic amines and glaucoma.^{8,10-13} Benzphetamine is also contraindicated in women who are or may become pregnant as this agent may cause fetal harm when administered to pregnant women.⁸

Diethylpropion is contraindicated with pulmonary hypertension, advanced arteriosclerosis, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma and severe hypertension.⁹

Additionally, benzphetamine, diethylpropion, phendimetrazine and phentermine should not be given to agitated patients or who have a history of drug abuse.⁸⁻¹³ Benzphetamine and phendimetrazine should not be used concurrently with other nervous system stimulants, and diethylpropion and phendimetrazine should not be used in combination with other anorectic drugs.^{8,10,11}

When sympathomimetic agents are taken concurrently with or within 14 days of monoamine oxidase inhibitors, hypertensive crisis has occurred.⁸⁻¹³

Orlistat is contraindicated with chronic malabsorption syndrome and cholestasis and in patients with known hypersensitivity to any component of the preparation.^{17,18}

When a patient develops tolerance to the anorectic effects of benzphetamine, diethylpropion and phentermine; the drug should be discontinued. The recommended dose should not be exceeded in an attempt to increase the effect.^{8,9,12,13} Use of weight loss medications may alter insulin or hypoglycemic medication requirements in patients with diabetes. Psychological disturbances and hallucinations have been reported in patients who administer weight loss medications with the exception of orlistat.^{8-13,17,18}

Caution should be exercised when prescribing weight loss medications for patients with mild hypertension.^{8-13,17,18}

The use of sympathomimetic weight loss medications for longer than three months has been associated with a 23-fold increase in the risk of developing pulmonary hypertension.⁹ Symptoms such as the onset or aggravation of exertional dyspnea; or unexplained symptoms of angina pectoris, syncope or lower extremity edema suggest the possibility of pulmonary hypertension. If these symptoms develop the agent being administered should be discontinued immediately. The possibility of an association between pulmonary hypertension and the use of phentermine monotherapy cannot be ruled out; there have been rare cases of pulmonary hypertension in patients reportedly administering phentermine monotherapy.^{12,13}

Valvular heart disease has been reported with some anorectic drugs (dexfenfluramine and fenfluramine).⁹ Possible contributing factors for the development of valvular heart disease include use for an extended period of time, higher than recommended doses, and/or use in combination with other anorectic drugs. Valvulopathy has been rarely reported with diethylpropion monotherapy, but the causal relationship remains uncertain. No cases of valvulopathy have been reported with phendimetrazine monotherapy.^{10,11} The possibility of an association between valvular heart disease and the use of phentermine monotherapy cannot be ruled out; there have been rare cases of valvular heart disease in patients who reportedly have administered phentermine monotherapy.^{12,13}

To limit unwarranted exposure and risks, treatment with diethylpropion and phendimetrazine should be continued only if the patient has satisfactory weight loss within the first four weeks of treatment. Also, treatment with diethylpropion or phendimetrazine is not recommended in patients who have used any anorectic agents within the prior year.⁹⁻¹¹

Organic causes of obesity should be excluded before prescribing orlistat.^{17,18}

Patients who are prescribed orlistat should be advised to adhere to dietary guidelines as gastrointestinal-related adverse events may increase based on the fat content of meals. Patients should be strongly encouraged to take a multivitamin supplement that contains fat-soluble vitamins to ensure adequate nutrition because orlistat has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene. Patients should administer the multivitamin at least two hours before or after the administration of orlistat.^{17,18}

Some patients administering orlistat may develop increased levels of urinary oxalate; therefore, caution should be exercised when prescribing the agent to patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis. Additionally, as with any weight-loss agent, misuse of orlistat is a possibility in inappropriate patient populations.^{17,18}

Drug Interactions

Table 7. Drug Interactions³⁰

Generic Name	Interacting Medication or Disease	Potential Result
Weight loss therapy (benzphetamine, diethylpropion, phendimetrazine, phentermine)	Furazolidone	Increased sensitivity to central nervous system stimulants.
Weight loss therapy (benzphetamine, diethylpropion, phendimetrazine, phentermine)	Guanethidine	Central nervous system stimulants can reverse the hypotensive effects of guanethidine.
Weight loss therapy (benzphetamine, diethylpropion, phendimetrazine, phentermine)	Monoamine oxidase inhibitors	Exaggerated pharmacologic effects caused by central nervous system stimulants.
Weight loss therapy (benzphetamine, diethylpropion, phendimetrazine, phentermine)	Serotonin reuptake inhibitors	Increased sensitivity to sympathomimetic effects and risk of serotonin syndrome.
Weight loss therapy (orlistat)	Cyclosporine	Whole blood cyclosporine concentrations may be decreased, resulting in a decrease in the immunosuppressive action of the agent.

Dosing and Administration

Table 8. Dosing and Administration^{8-13,17,18}

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Benzphetamine	<u>Management of exogenous obesity as a short term (few weeks) adjunct in a regimen of weight reduction based on caloric restriction:</u> Tablet: 25 to 50 mg Daily to TID	Safety and efficacy in children <12 years of age have not been established.	Tablet: 50 mg
Diethylpropion	<u>Management of exogenous obesity as a short term (few weeks) adjunct in a regimen of weight reduction based on caloric restriction:</u> Controlled-release tablet: 75 mg Daily in midmorning Tablet: 25 mg TID, one hour before meals, and in midevening if desired to overcome night hunger	Safety and efficacy in children <16 years of age have not been established.	Controlled-release tablet: 75 mg Tablet: 25 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Orlistat	<p><u>Obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet and reduce the risk for weight regain after prior weight loss:</u> Capsule (Xenical®): 120 mg TID with each main meal containing fat</p> <p><u>Weight loss in overweight adults when used along with a reduced-calorie and low-fat diet:</u> Capsule (Alli®): initial, 60 mg with each meal containing fat; maximum, three capsules/day</p>	<p>Safety and efficacy in children <12 years of age have not been established (Xenical®).</p> <p>Safety and efficacy in children have not been established (Alli®).</p>	<p>Capsule: 60 mg (Alli®) 120 mg (Xenical®)</p>
Phen-dimetrazine	<p><u>Management of exogenous obesity as a short term (few weeks) adjunct in a regimen of weight reduction based on caloric restriction:</u> Extended-release capsule: 105 mg Daily 30 to 60 minutes before the morning meal</p> <p>Tablet: initial, 35 mg BID to TID one hour before meals; maximum, two tablets TID</p>	<p>Use not recommended in children <12 years of age.</p>	<p>Extended-release capsule: 105 mg</p> <p>Tablet: 35 mg</p>
Phentermine	<p><u>Management of exogenous obesity as a short term (few weeks) adjunct in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction:</u> Capsule (15 and 30 mg): 15 to 30 mg approximately two hours after breakfast</p> <p>Capsule (37.5 mg): initial, 37.5 mg Daily before or one to two hours after breakfast</p> <p>Tablet: initial, 18.75 to 37.5 mg Daily before or one to two hours after breakfast or 18.75 mg BID</p>	<p>Safety and efficacy in children <16 years of age have not been established.</p>	<p>Capsule: 15 mg 30 mg 37.5 mg</p> <p>Tablet: 37.5 mg</p>

BID=twice-daily, TID=three times daily

Clinical Guidelines

Current guidelines are summarized in Table 9. The guidelines addressing the management of weight loss are presented globally, addressing the role of various medication classes in the management of this disease.

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
<p>Endocrine Society Clinical Practice Guideline: Prevention and Treatment of Pediatric Obesity (2008)⁴</p>	<ul style="list-style-type: none"> The objectives of interventions in overweight and obese patients is the prevention, or amelioration of obesity-related comorbidities including glucose intolerance and type 2 diabetes mellitus, metabolic syndrome, dyslipidemia and hypertension. The use of body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, with Centers for Disease Control and Prevention-derived normative percentiles, is recommended as the preferred method for the diagnosis of an overweight or obese child.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • A child is diagnosed as overweight if the BMI is $\geq 85^{\text{th}}$ percentile but $< 95^{\text{th}}$ percentile, and obese if the BMI is $\geq 95^{\text{th}}$ percentile for age and sex. • Routine laboratory evaluation for endocrine causes of obesity in obese children or early to midpubertal obese adolescents is not recommended, unless the child's height velocity, assessed in relation to stage of puberty and family background, is attenuated. • Children whose obesity has a syndromic etiology, especially in the presence of neurodevelopmental abnormalities, should be referred to a geneticist. • Parents of children who have inexorably gained weight from early infancy and have risen above the 97^{th} percentile for weight by three years of age should be informed of the availability of MC4R genetic testing. However, a positive MC4R test occurs in only two to 4% of these patients and currently will not alter treatment. • Children with a BMI in $\geq 85^{\text{th}}$ percentile are recommended to be evaluated for associated comorbidities and complications. • Clinicians should prescribe and support intensive lifestyle (dietary, physical activity and behavioral) modification to the entire family and to the patients, in an age-appropriate manner, and as the prerequisite for all overweight and obesity treatments for children and adolescents. • Clinicians should prescribe and support healthy eating habits. • Clinicians should consider prescribing and supporting controlling caloric intake through portion control; reducing saturated dietary fat intake for children greater than two years of age; increasing the intake of dietary fiber, fruits and vegetables as well as eating timely, regular meals and avoiding constant "grazing" during the day. • Clinicians should prescribe and support 60 minutes of daily moderate to vigorous physical activity. • Clinicians should consider prescribing and supporting a decrease in time spent in sedentary activities. • Clinicians should consider educating parents about the need for healthy rearing patterns related to diet and activity and that parents should be probed and diagnosed for unhealthy intrafamily communication patterns. • Pharmacotherapy, in combination with lifestyle modification, should be considered if a formal program of intensive lifestyle modification has failed to limit weight gain or to mollify comorbidities in obese children. • Overweight children should not be treated with pharmacotherapeutic agents unless significant, severe comorbidities persist despite intensive lifestyle medication. A strong family history of type 2 diabetes or cardiovascular risk factors strengthens the case for pharmacotherapy. • It is suggested that only physicians experienced in the use of antiobesity agents and who are aware of the potential for adverse reactions offer pharmacotherapy. • Additional medications that are not Food and Drug Administration (FDA) approved for treatment of obesity that may be treatment options include metformin and topiramate. • Use of topiramate should be limited because it promotes drowsiness and interferes with cognition, and it should not be used outside of a clinical research study. • In general, children with a BMI $< 95^{\text{th}}$ percentile should not be treated with antiobesity drugs. Pharmacotherapy for overweight children (BMI $\geq 85^{\text{th}}$ percentile but $< 95^{\text{th}}$ percentile) should be reserved for those with severe, significant comorbidities who have not responded to lifestyle modification.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Bariatric surgery is suggested to be considered only in children who have attained Tanner 4 or 5 pubertal development and final or near-final adult height; with a BMI >50 kg/m² or has a BMI >40 kg/m² and significant, severe comorbidities; who have severe obesity and comorbidities persist despite a formal program of lifestyle modification, with or without a trial of pharmacotherapy; psychological evaluation confirms the stability and competence of the family unit; and there is access to an experienced surgeon in a medical center employing a team capable of long term follow-up. The patient must also demonstrate the ability to adhere to the principles of healthy dietary and activity habits. • Surgery is not recommended for preadolescent children, for pregnant or breast-feeding adolescents, those planning on becoming pregnant within two years of surgery, any patient who has not mastered the principles of healthy dietary and activity habits, any patient with an unresolved eating disorder, untreated psychiatric disorder or patients with Prader-Willi syndrome. • To prevent obesity, children should be breast-fed for a minimum of six months. Additionally, clinicians should consider promoting and participating in efforts to educate children and parents by means of ongoing anticipatory guidance about healthy dietary and activity habits. • Clinicians should encourage school systems to provide adequate health education courses promoting healthy eating habits.
<p>American Academy of Pediatrics: Recommendations for Treatment of Child and Adolescent Overweight and Obesity (2007)⁵</p>	<ul style="list-style-type: none"> • Data on optimal dietary approaches for weight management in children are lacking, and long term trials of available interventions in adults have not demonstrated efficacy. • Although evidence is limited, the increase of physical activity alone has not been shown to improve children's weight status substantially. • Particular consideration should be given to methods of increasing activity in adolescents, and studies suggest that time, cost, availability and convenience were key influencing factors to what adolescents ate and their level of physical activity. • It is recommended that all children meet the goal of 60 minutes of moderate activity per day. • It is recommended that clinicians instruct parents on techniques for increasing activity in the home environment. • Epidemiologic and experimental evidence from the past decade supports decreased television watching as a primary preventative intervention for the reduction of overweight and other chronic disease risks. • The most effective treatments for childhood obesity include both dietary and physical activity interventions. Simply providing education about needed changes is inadequate. • Behavioral therapy techniques including environmental control approaches, as well as monitoring, goal setting and contingency management, can facilitate recommended changes in a child's diet and physical activity. • Pharmacotherapy alone has not proved to be an effective obesity treatment. Medication use as part of a structured lifestyle modification produces an average weight loss of five to 10%. Weight loss typically plateaus at four to six months of therapy, after which weight regain may occur. • Pharmacologic agents may be helpful in the treatment of obesity for carefully selected patients, as part of a multimodal therapy that includes diet, exercise and behavior modification.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Few guidelines are available regarding the use of weight loss medications in the pediatric populations. Weight loss through lifestyle changes is optimal. • Medications may be used as adjunctive therapy when clear health risks are present and lifestyle changes alone have not been effective. • The 99th percentile of BMI for age may be an appropriate threshold for identifying children and adolescents who are at very high risk for biochemical abnormalities and severe adult obesity and thus may be candidates for more aggressive treatment such as pharmacotherapy. • Orlistat and sibutramine* have been approved for limited use among pediatric patients. • Preliminary research suggests that metformin may improve weight control, but this has not been tested in children and the drug is not approved for this indication. • Medication choice should be made on an individual basis, taking into account patient's weight-related health risks, the mechanism of action of the agents, the adverse events associated with the medication, patient/family preferences and, if known, the cause of obesity. • It is not possible to provide uniform guidelines regarding the duration of pharmacotherapy. • Physicians should recognize that weight gain is common once medications are discontinued. • There is limited research on the safety, efficacy and long term outcomes of bariatric surgery for adolescents; therefore, data from adult trials must be considered as surrogate evidence.
<p>National Institutes of Health: National Heart, Lung, and Blood Institute: The Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obese Adults (2000)³</p>	<ul style="list-style-type: none"> • Treatment of an overweight or obese person incorporates a two-step process; assessment, to determine the degree of obesity and health status, and management; which involves not only weight loss and maintenance of weight, but also measures to control other risk factors. • Assessment should include the evaluation of BMI, waist circumference and overall medical risk. • Classifications for BMI are the following: underweight; <18.5 kg/m², normal weight; 18.5 to 24.9 kg/m², overweight; 25.0 to 29.9 kg/m², obesity (Class 1); 30.0 to 34.9 kg/m², obesity (Class 2); 35.0 to 39.9 kg/m² and extreme obesity (Class 3); ≥40 kg/m². • It is not necessary to measure waist circumference in individuals with BMIs ≥35 kg/m² since it adds little to the predictive power of the disease risk classification of BMI. • Men who have a waist circumference >40 inches, and women who have a waist circumference >35 inches, are at higher risk of diabetes, dyslipidemia, hypertension and cardiovascular disease because of excess abdominal fat. • Diseases such as established coronary heart disease, other atherosclerotic diseases, type 2 diabetes and sleep apnea place patients at a high absolute risk for subsequent mortality. These patients will also require aggressive management. • Osteoarthritis, gallstones, stress incontinence and gynecological abnormalities increase risk but are not generally life-threatening. • Three or more of the following risk factors also confer high absolute risk: hypertension, cigarette smoking, high low-density lipoprotein-cholesterol, low high-density lipoprotein-cholesterol, impaired fasting glucose, family history of early cardiovascular disease and age (male ≥45 years and female ≥55 years).

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Patients' readiness to lose weight should also be assessed by the following items: reasons and motivation for weight loss, previous attempts at weight loss, support expected from family and friends, understanding of risks and benefits, attitudes toward physical activity, time availability and potential barriers to the patient's adoption of change (financial limitations). • Weight loss therapy is recommended for patients with a BMI ≥ 30 kg/m² AND for patients with a BMI between 25.0 to 29.9 kg/m², or a high risk waist circumference, and two or more risk factors. • Individuals at lesser risk should be counseled about effective lifestyle changes to prevent any further weight gain. • An initial weight loss of 10% of body weight achieved over a six month period is a recommended target. A rate of one to two pounds per week is recommended, as greater rates of weight loss do not achieve better long term results. • In patients in whom weight loss or a reduction in body fat is not achievable, a goal of prevention of further weight gain is appropriate. Prevention of weight gain is also an appropriate goal for people with a BMI 25.0 to 29.9 kg/m² who are not otherwise at high risk. • A combination of diet modification, increased physical activity and behavior therapy can be effective. • Caloric intake should be reduced by 500 to 1,000 calories/day (kcal/day) from current level. • Physical activity has direct and indirect benefits. • All adults should set a long term goal to accumulate ≥ 30 minutes or more of moderate-intensity physical activity on most, and preferably all, days of the week. • Including behavioral therapy; consisting of self-monitoring, stress management, stimulus control, problem-solving, contingency management, cognitive restructuring and social support, helps with compliance. • Strong evidence supports the recommendation that weight loss and weight maintenance programs should employ a combination of low calorie diets, increased physical activity and behavior therapy. • Pharmacotherapy may be helpful for eligible high risk patients. • Drugs for obesity should be used only in the context of a treatment program that includes diet, physical activity changes and behavior therapy. • If lifestyle changes do not promote weight loss after six months, pharmacotherapy should be considered. • Pharmacotherapy is currently limited to those patients who have a BMI ≥ 30 kg/m², or those who have a BMI ≥ 27 kg/m² if concomitant obesity-related risk factors or diseases exist. • If a patient has not lost 4.4 pounds after four weeks of treatment, it is not likely that this patient will benefit from that particular drug. • Surgery is an option for patients with extreme obesity.
<p>American Society for Clinical Nutrition: Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and</p>	<ul style="list-style-type: none"> • Weight loss is recommended to lower elevated levels of total cholesterol, low-density lipoprotein-cholesterol and triglycerides, and to raise low levels of high-density lipoprotein-cholesterol in overweight and obese persons with dyslipidemia. • Weight loss is recommended to lower elevated blood pressure in overweight and obese persons with high blood pressure.

Clinical Guideline	Recommendations
<p>Obesity in Adults: Executive Summary (1998)⁶</p>	<ul style="list-style-type: none"> • Weight loss is recommended to lower elevated blood glucose levels in overweight and obese persons with type 2 diabetes. • Practitioners should use BMI to assess overweight and obesity. Body weight alone can be used to follow weight loss, and to determine efficacy of therapy. • The BMI should be used to classify overweight and obesity and to estimate relative risk of disease compared to normal weight. • The waist circumference should be used to assess abdominal fat content. • For adult patients with a BMI of 25.0 to 34.9 kg/m², sex-specific waist circumference cutoffs should be used in conjunction with BMI to identify increased disease risk. • The initial goal of weight loss therapy should be to reduce body weight by approximately 10% from baseline. With success, further weight loss can be attempted if indicated through further assessment. • Weight loss should be about one to two pounds per week for a period of six months, with the subsequent strategy based on the amount of weight loss. • Low calories diets are recommended for weight loss in overweight and obese persons. Reducing fat as part of a low calories diets is a practical way to reduce calories. • Reducing dietary fat alone without reducing calories is not sufficient for weight loss. However, reducing dietary fat, along with reducing dietary carbohydrates, can facilitate caloric reduction. • A diet that is individually planned to help create a deficit of 500 to 1,000 kcal/day should be an integral part of any program aimed at achieving a weight loss of one to two pounds per week. • Physical activity is recommended as part of a comprehensive weight loss therapy and weight control program because it modestly contributes to weight loss in overweight and obese adults, may decrease abdominal fat, increases cardiorespiratory fitness and may help with maintenance of weight loss. • Physical activity should be an integral part of weight loss therapy and weight maintenance. Initially, moderate levels of physical activity for 30 to 45 minutes, three to five days a week, should be encouraged. All adults should set a long term goal to accumulate at least 30 minutes or more of moderate-intensity physical activity on most, and preferably all, days of the week. • The combination of a reduced calorie diet and increased physical activity is recommended since it produces weight loss that may also result in decreases in abdominal fat and increases in cardiorespiratory fitness. • Behavioral therapy is a useful adjunct when incorporated into treatment for weight loss and weight maintenance. • Practitioners need to assess the patient's motivation to enter weight loss therapy; assess the readiness of the patient to implement the plan and then take appropriate steps to motivate the patient for treatment. • Weight loss and weight maintenance therapy should employ the combination of low calories diets, increased physical activity and behavior therapy. • FDA approved weight loss drugs may be used as part of a comprehensive weight loss program, including dietary therapy and physical activity for patients with a BMI of ≥ 30 kg/m² with no concomitant obesity-related risk factors or diseases, and for patients with a BMI of ≥ 27 kg/m² with concomitant obesity-related risk factors or disease.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Weight loss drugs should never be used without concomitant lifestyle modifications. • Continual assessment of drug therapy for efficacy and safety is necessary. If the drug is efficacious in helping the patient to lose and/or maintain weight loss and there are no serious adverse effects, it can be continued. If not, it should be discontinued. • Weight loss surgery is an option for carefully selected patients with clinically severe obesity (BMIs ≥ 40 kg/m² or ≥ 35 kg/m² with comorbid conditions) when less invasive methods of weight loss have failed and the patient is at high risk for obesity-associated morbidity or mortality. • After successful weight loss, the likelihood of weight loss maintenance is enhanced by a program consisting of dietary therapy, physical activity and behavior therapy which should be continued indefinitely. Drug therapy can also be used; however, drug safety and efficacy beyond one year of total treatment have not been established. • A weight maintenance program should be a priority after the initial six months of weight loss therapy. • Literature suggests that weight loss and maintenance therapies that provide a greater frequency of contacts with health care professionals and are provided over the long term should be utilized whenever possible. This can lead to more successful weight loss and weight maintenance. • All smokers, regardless of their weight status, should quit smoking. • A clinical decision to forego obesity treatment in older adults should be guided by an evaluation of the potential benefits of weight reduction for day-to-day functioning and reduction of the risk of future cardiovascular events, as well as the patient's motivation for weight reduction. • The possibility that a standard approach to weight loss will work differently in diverse patient populations must be considered when setting expectations about treatment outcomes.

*Not available in the United States.

Conclusions

Overweight and obese patients are at increased risk for obesity-related morbidity and mortality. The decision to lose weight may be made for several different reasons. Weight loss therapy is recommended in patients with a body mass index (BMI) ≥ 30 kg/m² and for patients with a BMI 25.0 to 29.9 kg/m², or a high risk waist circumference (men >40 inches and women >35 inches), with at least two risk factors (hypertension, smoking, high low-density lipoprotein cholesterol, low high-density lipoprotein, impaired fasting glucose, family history of early cardiovascular disease and age [men ≥ 45 years and women ≥ 55 years]). Patients with any of the following obesity-related disease are at a high absolute risk for mortality; therefore, require aggressive weight loss therapy: established coronary disease, other atherosclerotic diseases, type 2 diabetes and sleep apnea.³

In general, any weight loss regimen should be comprehensive and incorporate lifestyle and behavioral modification.¹⁻⁶ If after six months, lifestyle modification fails to limit weight gain, pharmacotherapy may be considered as adjunct therapy. Pharmacologic agents may be helpful in the treatment of obesity for carefully selected patients, as part of a multimodal therapy that includes diet, exercise and behavioral modification.⁵ For adult patients, pharmacotherapy is typically reserved for patients with who have a BMI ≥ 30 kg/m² or those who have a BMI ≥ 27 kg/m² if concomitant obesity-related risk factors or diseases exist.³ Children with a BMI $<95^{\text{th}}$ percentile may be treated with weight loss agents if severe, significant comorbidities exist and lifestyle modification alone has not been successful.⁴

An initial weight loss of 10% of body weight achieved over a six month period is a recommended target, with a recommended rate of weight loss of one to two pounds per week.³ There are no well established guidelines regarding the appropriate duration of weight loss agents; if therapy is well tolerated it may be continued. However, the safety and efficacy of weight loss agents beyond one year of total treatment have not been established.⁶ Clinicians should be aware that if pharmacotherapy is discontinued there is a possibility of weight gain.⁵ For any specific weight loss agent, if a patient has not lost 4.4 pounds after four weeks of treatment, it is not likely that the patient will benefit from that particular agent.³

The currently available weight loss agents work by two different mechanisms of action. The sympathomimetics (benzphetamine [Didrex[®]], diethylpropion, phendimetrazine [Bontril[®] PDM, Bontril[®] Slow Release] and phentermine [Adipex-P[®]]) help decrease food intake by stimulating the release of norepinephrine or inhibiting its reuptake. These agents are Food and Drug Administration (FDA) approved for the short term treatment of obesity and have been designated controlled substances due to their pharmacologic similarity to amphetamines and potential for abuse.⁸⁻¹³ All sympathomimetics are available generically. Meridia[®] (sibutramine) was a sympathomimetic FDA approved for the long term treatment of obesity but has since been pulled by the FDA due to concerns of adverse cardiovascular effects.¹⁴⁻¹⁶ Alli[®] and Xenical[®] (orlistat) are lipase inhibitors that work by interfering with fat absorption. Based on its mechanism of action and pharmacologic structure, orlistat is currently the only FDA approved weight loss agent that has not been designated a controlled substance. In addition, orlistat (Xenical[®]) is approved for the long term treatment of obesity and is available as a branded (Xenical[®]) or over-the-counter product (Alli[®]).^{17,18}

Although head-to-head trials are rare, several meta-analyses have demonstrated that orlistat and sibutramine (not available in the United States) are effective, and neither agent has been found to consistently be more effective than the other.²⁵⁻²⁹ There is evidence to suggest that combination therapy with orlistat and sibutramine did not result in a significant amount of additional weight loss.¹⁶

Current clinical guidelines do not distinguish among any of the available weight loss agents and state that choice of medication should be made on an individual basis, taking into account patient's weight-related health risks, the mechanism of action of the medication, the adverse events associated with the medication, patient/family preferences and, if known, the cause of obesity.⁵

Appendix I: Utilization Within This Drug Class for DVHA: January 1, 2011 to June 30, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Alli	11	26	48%	\$1,240.71	\$47.72
Phentermine Hcl	11	25	46%	\$673.31	\$26.93
Xenical	2	3	6%	\$1,131.87	\$377.29
Class Total:	24	54	100%	\$3,045.89	\$56.40

Recommendations

Currently, all anti-obesity drugs are managed by the Department of Vermont Health Access (DVHA) via prior authorization. No changes to the DVHA approval criteria for anti-obesity agents (see below) are proposed at this time.

Initial Request:

- The patient is > 12 years old for Xenical/Alli, all others age > 16 years
And
- The patient's Body Mass Index (BMI) is:
 - 1) $\geq 30\text{kg/m}^2$ OR
 - 2) $\geq 27\text{kg/m}^2$ with comorbid condition of Hypertension, Obstructive Sleep Apnea, Type 2 Diabetes Mellitus, Dyslipidemia, or Coronary Heart Disease (history of MI, angina, coronary artery procedures)

And

- The patient has failed to lose weight after 6 months on a weight loss regimen of low calorie diet, increased physical activity, and nutritional counseling.
And
- The medication will be used as part of a total treatment plan including a calorie and fat restricted diet and exercise regimen.
And
- Requested agent is not to be used in combination with another anti-obesity agent
And
- If the request is for a brand name product with a generic equivalent, the patient has a documented intolerance to the generic product.
And
- If the request is for Xenical, the patient has had a 3 month trial of Alli and has not achieved at least a 5 pound weight loss.
And
- The patient does not have any contraindications to use.

Continuation of Therapy Request (Xenical/Alli only, other agents FDA approved only for short-term use)

- Xenical/Alli may be approved if weight loss of 5 or more pounds during 3 months of therapy is documented.

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