



Topic: Medications for Treatment of Obesity

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Clinical Position Statement: Medications for Treatment of Obesity

Currently Available Medications for Treatment of Obesity

Approved for weight loss	Approved for other indications, but used for weight loss
liraglutide (Saxenda®)	antidepressants (bupropion, fluoxetine, sertraline)
lorcaserin (Belviq®)	anti-epileptics (topiramate, zonisamide)
naltrexone-bupropion ER (Contrave®)	anti-diabetics [exenatide (Byetta®), liraglutide (Victoza®), metformin, pramlintide (Symlin®)]
orlistat (OTC - Alli®; Rx - Xenical®)	
phentermine-topiramate ER (Qsymia®)	
generic stimulants (benzphetamine, diethylpropion, phendimetrazine, phentermine)	

OTC = over the counter; RX = prescription only

Summary

- Most anti-obesity medications work by suppression of appetite. Orlistat alters digestion and absorption of dietary fat.
- Though anti-obesity medications may promote modest weight loss, the extent of benefit is small, on average 5 kilograms (11 lbs) in the first year above lifestyle modifications alone, such as caloric restriction, exercise, and counseling. When combined with lifestyle modification, drug treatment results in less than 5-10% weight reduction for the majority of patients. [1-6]
- There continues to be lack of evidence to support positive long term health benefits of anti-obesity medications, such as a reduction in cardiovascular morbidity and mortality, and sustained weight loss beyond one year. The majority of trials were 12 months or less in duration. [1,2,7,8]

- The risk of side effects with anti-obesity medications may outweigh their benefits. Anti-obesity medications have been associated with serious adverse effects including heart valve disorders, heart attack, stroke, and liver failure. In fact, many anti-obesity medications were initially denied approval or are no longer available due to significant cardiovascular risks. (See Appendix 1)
- The long-term clinical efficacy and safety of medications used for weight loss, but approved for other indications has not been established.
- Guidelines recommend use of non-pharmacological therapies first line, including diet, exercise, and behavior therapy. They suggest that anti-obesity medications approved for weight loss should only be used as part of a treatment program, and only when lifestyle changes do not promote weight loss after 6 months. ^[9,10]
- Anti-obesity medications are frequently excluded under most benefit contracts. In addition, orlistat (Alli[®]) is and often excluded by contract because it is available over-the-counter (OTC).

Clinical Efficacy for Weight Loss

Medications approved for weight loss

- Anti-obesity medications have not been proven in reliable clinical studies to be more effective than non-pharmacologic interventions, such as diet, exercise and behavior modification for long-term maintenance or progressive reduction in weight loss.
 - Clinical trials of lifestyle modification (diet, exercise, and behavioral counseling) show an average weight loss of approximately 5 to 8.5 kg during the first 6 months, and approximately half of this weight-loss is maintained at 24 to 48 months. ^[11]
 - The addition of anti-obesity medications to lifestyle modification has been shown to produce modest incremental weight loss (averaging 5 kilograms or 11 lbs); however, many studies for weight loss medications are flawed because patients in these studies tended to quit early (up to 50%) and never had “final” results. This means it is uncertain whether the results of these trials can be relied upon to predict how well patients will do during treatment. ^[1,2,12,13]
- There is no evidence demonstrating that one anti-obesity medication is superior to another for promotion or maintenance of weight loss. ^[1,2]
- Although weight loss of 5-10% following diet, exercise and in some cases, drug treatment has been associated with improvements in blood pressure, lipids, and blood glucose parameters, there is no reliable evidence that *medication-induced* weight loss improves health-related quality of life or obesity-related health conditions (such as diabetes, cardiovascular events or death). ^[1,2,7,14]

Medications approved for other indications, but used for weight loss

- There are currently no well-designed studies to establish the clinical efficacy of medications approved for other conditions, but used for weight loss.

- Guidelines recognize but do not specifically recommend use of any of these medications for promotion or maintenance of weight loss. ^[10]
 - Anti-diabetics ^[6,15-25]
 - Some medications used for the management of diabetes, such as glucagon-like-peptide 1 (GLP-1) receptor agonists [exenatide (Byetta[®]), liraglutide (Victoza[®])], pramlintide (Symlin[®]) and metformin, have been associated with weight loss in clinical studies.
 - In clinical trials of anti-diabetic medications, the average weight loss ranged from 0.4 to 4 kg (0.9 to 9 lbs) over 4 to 60 months. However, it is unknown if the observed weight reductions are clinically relevant and result in improved health outcomes.
 - Anti-depressants: Bupropion has been associated with weight loss (mean 2.7 kg). Neither fluoxetine nor sertraline has consistently shown promotion or maintenance of weight loss. ^[8]
 - Anti-epileptic drugs: Topiramate seems to be associated with weight loss, a varying amount of weight loss in clinical studies. However, many patients discontinued therapy due to adverse events. ^[8,26,27]

Safety

- Historically, anti-obesity medications have been associated with significant safety risks, including fatal adverse events. Those risks were not clearly understood until after FDA approval, when the medications were used by many patients. In addition, a number of anti-obesity medications were initially denied approval by the FDA because of serious safety concerns. (See Appendix 1)
- Long-term cardiovascular safety studies are currently underway for liraglutide (Saxenda), lorcaserin (Belviq), naltrexone-bupropion ER (Contrave), and phentermine-topiramate ER (Qsymia). Until the results of these trials are available, the cardiovascular safety profile of these medications is uncertain. ^[28-30]
- Long-term safety of other therapies (antidiabetic medications, antiepileptic drugs, antidepressants) for treatment of obesity is unknown. Dosing of these medications for weight loss frequently exceeds the FDA-recommended dosing, therefore, the relative risk of adverse events may be increased above what might be seen when these medications are used for other conditions.
- No obesity medication has been studied in large comparative trials; therefore, the relative safety is unknown.
- Adverse events may be under-reported, as many patients discontinued before completion of these studies.

Appendix 1: Safety Concerns with Anti-obesity Medications ^[13,31-36]

Anti-obesity Medication	FDA approval history	Serious Safety Concern
bupropion/naltrexone (Contrave®)	Initially denied in 2010, but subsequently approved in 2014	Risk of hypertension and increased heart rate. Long term cardiac safety unknown.
liraglutide (Saxenda®)	Approved in 2014	Medullary thyroid cancer (animal studies), acute pancreatitis, and tachycardia. Long term cardiac safety unknown.
lorcaserin (Belviq®)	Initially denied in 2010, but subsequently approved in 2012	Heart problems (valvular heart disease).
orlistat (OTC - Alli®; Rx - Xenical®)	Currently available	Serious liver injury
phentermine/topiramate CR (Qsymia®)	Initially denied in 2010, but subsequently approved in 2012	Possibility for major cardiovascular events. Long-term cardiac safety unknown.
generic stimulants (including phentermine)	Currently available	Heart and lung problems (including valvular heart disease and pulmonary hypertension).
fenfluramine, dexfenfluramine (Redux®)	Withdrawn from market	Heart and lung problems (including valvular heart disease and pulmonary hypertension).
sibutramine (Meridia®)	Withdrawn from market	Heart attack and stroke.
taranabant	Never approved	Serious depression and anxiety.

Cross References

Medication policy - Byetta®, exenatide, dru348

Medication policy - Victoza®, liraglutide, dru347

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