Prescription and Over-the-Counter Options for Weight Loss

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Prescription drugs have been available as weight loss aids in the United States for more than a century. Many different modes of action have been tried to effect weight loss. Most of the drugs require the patient to also initiate a low-calorie diet while on the medication. Mechanisms of action include centrally acting compounds that affect brain centers involved in mood, satiety, and hunger. Others act within the gastrointestinal tract to block fat absorption. Recently, use of several weight loss drugs has been associated with increased risk and adverse cardiovascular events, resulting in the removal of 1 approved drug from the market and the rejection of another compound from the Food and Drug Administration approval process. Nevertheless, the Food and Drug Administration did approve 2 new centrally acting drugs in 2012. Thus, today, there are a few new prescription drug choices for the physician treating an obese patient. Nutr Today. 2013;48(2):76–78

As of May 2012, there was only 1 US Food and Drug Administration (FDA)–approved prescription drug (Rx drug) for long-term weight loss, Xenical (Genentech, San Francisco, California), and this same drug, at a lower dosage, was also the only FDA-approved over-the-counter (OTC) drug for weight loss. Alli (GSK, Brentford, Middlesex, United Kingdom) is an example of an Rx to OTC "switch" from prescription to OTC at a lower dose. Its mechanism of action is to compete with lipase and reduce the absorption of fat in the intestine (Figure). On June 27, 2012, the FDA approved the use of lorcaserin (to be sold as Belviq, Arena Pharmaceuticals, Zofingen, Switzerland) for weight loss in obese patients. This was the FDA's first approval of a drug for weight loss in 13 years. On July 17, 2012, the FDA approved the use of Qsymia (formally known as Qnexa; Vivus, Inc, Mountain View, California) for weight loss. Qsymia is composed of phentermine and topiramate in an extended-release form and was approved as an addition to a reduced-calorie diet and exercise for chronic weight management.

There are many dietary supplements that claim to increase weight loss; however, the FDA has issued many warning letters with regard to the lack of evidence of efficacy and overstatement of expected weight loss. The FDA has taken legal action to remove a number of weight loss dietary supplements because they contained illegal and harmful substances. In summary, there are few choices for patients and consumers that are effective in weight reduction, and none have been proven to prevent obesity.

For Rx drugs for weight loss to be effective, dieters must also follow a low-calorie diet.

Historical Perspective

The history of the FDA is intimately linked to the marketing of weight loss drugs. As described by FDA's Dr Coleman, "In the early 1930s, the industrial chemical dinitrophenol found widespread favor as a weight-loss drug, due principally to the work of Maurice Tainter, a clinical pharmacologist from Stanford University. Unfortunately the compound's therapeutic index was razor thin and it was not until thousands of people suffered irreversible harm (e.g. the difference between the dose that is efficacious and that which is toxic) that mainstream physicians realized that dinitrophenol's risks outweighed its benefits and abandoned its use. Yet, it took passage of the Food, Drug, and Cosmetic Act's amendments in 1938 before federal regulators had the ability to stop patent medicine men from selling dinitrophenol to Americans lured by the promise of a drug that would safely melt one's fat away."[1] The Food Drug and Cosmetic Act was passed in 1906, and as time went on, the FDA gained greater regulatory powers after the passage of the 1938 amendments to the Food, Drug, and Cosmetic Act. Table 1 reviews the long history of Rx drug approvals followed by removal from the US market either directly by the FDA or by the company marketing the product. All of the drugs now on the market share a common systemic mode of action, except for Xenical (orlistat), which is not absorbed into the bloodstream and acts locally in the small intestine.[2] Some of the other centrally acting drugs were in the marketplace for 40 years before being withdrawn as data became more available about related adverse cardiovascular effects. For

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The author has no conflicts of interest to disclose.

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DOI: 10.1097/NT.0b013e318288140a

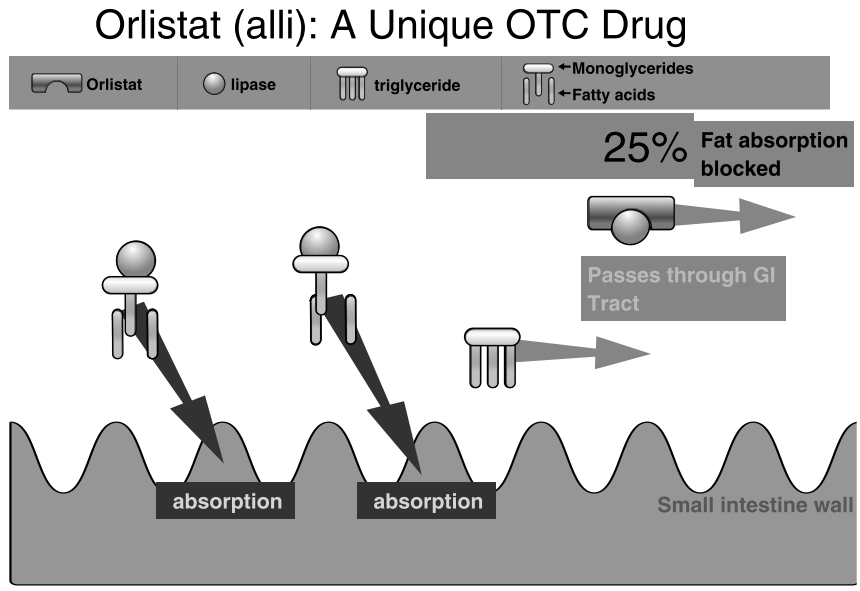

FIGURE. Mechanism of action of orlistat, the active ingredient in Xenical and Alli. Abbreviations: GI, gastrointestinal; OTC, over-the-counter.

example, phentermine combined with fenfluramine was prescribed for weight loss for several years until the FDA was able to demonstrate that the combination had adverse cardiac effects, and it was withdrawn. Other drugs such as Acomplia (rimonabant) were approved in Europe and other countries but not approved in the United States. One other currently FDA-approved Rx drug is phentermine (Apidex-P). It is a centrally acting norepinephrine-releasing drug that is approved for short-term (eg, for a few weeks) treatment of obesity. Phentermine is a cardiovascular stimulant (increases heart rate and elevated blood pressure, as examples). It is also an appetite suppressant, and after short-term use, tolerance to the appetite-suppressing effects is often seen and long-term use of this drug has been associated with rebound weight gain (Table 2).[3]

Lorcaserin (Belviq)

All of the Rx weight loss drugs were approved in studies where the placebo and the active groups followed low calorie diets. Lorcaserin, prescribed in addition to a low-calorie healthy diet and physical activity/exercise, was recently approved by the FDA for weight loss in obese patients. This drug was rejected by the FDA in 2010 because of insufficient cardiovascular safety data. However, further testing provided the FDA with sufficient clinical data to permit FDA's approval of this drug. Lorcaserin acts by activating a serotonin receptor in the brain that results in a feeling of fullness. It will be very important for patients taking the drug to adhere to the label instructions and recommendations to ensure that risks of any potential adverse cardiac effects that may occur with drugs that have similar modes of action are avoided.

TABLE 1 Historic Perspective of Food and Drug Administration (FDA)–Approved Weight Loss Drugs Subsequently Removed by the FDA From the Market

Centrally Acting Agents for Long-term Weight Loss			
Drug	**Year FDA Approved**	**Year Taken Off Market**	**Serious Adverse Effects**
Thyroid hormone	1893	1949	Hyperthyroidism (which includes cardiac effects)
Amphetamine	1937	1971	Known cardiovascular toxicity
Aminorex	1967	1972	Pulmonary hypertension
Fenfluramine	1973	1997	Heart valve insufficiency and primary pulmonary hypertension
Phenylpropanolamine	1960	2000	Hemorrhagic stroke
Sibutramine (Meridia)	1997	2010	Myocardial infarction and stroke

TABLE 2 Mechanisms of Action of Drugs for Weight Loss

Drugs for Weight Loss: Mechanisms of Action
Brain—centrally acting agents
Norepinephrine mimics
Serotonin mimics or reuptake inhibitors
Opioid receptor mimics
Combinations of drugs that act on the brain
Gut—peripherally acting agents
Block fat absorption
Reduce efficiency of starch digestion

Qsymia (Formally Known as Qnexa)

Qsymia was also recently approved by the FDA as a weight loss drug for obese patients. Qsymia is a combination of 2 existing drugs—the stimulant phentermine (discussed above) and the antiseizure drug topiramate. Topiramate use has been linked to cleft palate in neonates. Thus, Qsymia must not be used during pregnancy because of its teratogenic potential. The labeling of Qsymia includes a warning that those at risk of becoming pregnant should avoid Qsymia and that those who become pregnant while taking Qsymia should stop taking it immediately. Those at risk of becoming pregnant should have a negative pregnancy test before starting Qsymia and again every month while using the drug and should use effective contraception consistently while on the drug. Because women of reproductive age are the group that has the greatest number of dieters, it is critical to clearly warn women who may become pregnant about this very serious potential adverse effect.[4] The average weight loss with this drug was 14% over 1 year, and a longer study published in the *New England Journal of Medicine* in 2011 reported a 10% weight loss over 2 years.[5] Patients on the drug also had improved cardiovascular and metabolic risk factors, such as lower cholesterol and a lower risk of type 2 diabetes.

Dietary Supplements for Weight Loss

Over the past decade, hundreds of dietary supplements have been marketed with weight loss claims. Some of the most common bioactive substances in these supplements include high concentrations of caffeine and, in the past, before it was banned, ephedra. Of great concern is the surreptitious inclusion of very high doses of Rx drugs or other banned, dangerous, and even illegal products in the dietary supplements claiming to help in weight loss. In 2008 and subsequently, the FDA issued nationwide alerts about tainted weight loss products containing undeclared, active pharmaceutical ingredients. The alert listed more than 70 weight loss products that might be harmful. Some of the products claimed to be "natural" or to contain only "herbal" ingredients. The risks posed by these products included high blood pressure, seizures, rapid heartbeat, palpitations, myocardial infarction, and stroke. The substances found in these supplements included sibutramine, fenproporex (a controlled substance that is not approved for marketing in the United States that can cause arrhythmia and possible sudden death), fluoxetine (a prescription-only antidepressant), bumetanide and furosemide (potent Rx diuretics), cetilistat (an experimental obesity drug not approved for marketing in the United States), phenytoin (a prescription-only antiseizure medication that is associated with severe birth defects), and phenolphthalein (a suspected cancer-causing agent that is not approved for marketing in the United States).[6] As can be clearly seen in this list, some very dangerous compounds have been found in certain dietary supplements making weight loss claims. Moreover, there are very few dietary supplements that have been tested in well-controlled clinical studies to determine their consistent efficacy as weight loss aids.

CONCLUSIONS

Obese and overweight patients have very few pharmacological agents that are FDA-approved Rx drugs to help them lose weight. Older systemically acting Rx drugs did more than simply reduce weight gain, and their adverse effects resulted in their removal from the US market. Today, there are only 3 FDA-approved Rx drugs for chronic weight loss in the United States: Xenical (orlistat), which works to reduce fat absorption in the intestine; Belviq (lorcaserin), which is centrally acting, working in the brain; and Qsymia (phentermine and topiramate), which is also centrally acting. There is only 1-FDA approved OTC drug for weight loss, Alli (orlistat). Dietary supplements that appear to work may contain potentially harmful substances.

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