A brief review of drugs for weight loss

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Abstract

Achievement of weight loss via pharmaceutical means has a long history. Amphetamines represent the most commonly prescribed class of agent taken for weight loss, but in the recent past much attention has been paid to a new class of drug that stimulate glucagon receptors in brain, causing the release of insulin. Marketed primarily for control of diabetes, these are now widely prescribed both on and off label for weight control. This brief review covers classes of drugs used in weight control, with commentary on their side effects and other factors affecting usage.

The entry of a new class of medication for pharmacologically assisted weight loss provides an opportunity to review the history and current status of drugs in this important and highly lucrative market. While some new drugs are receiving a tremendous amount of attention in the popular press and social media, it's important to recall that pharmacologically assisted weight loss has a long history. Amphetamines or amphetamine-related compounds remain the most commonly prescribed weight loss agents, largely due to their appetite suppressant effects, and have been a mainstay of treatment for most of the past century. Three classes of drug now exist for weight control: amphetamines and amphetamine-like agents, incretin mimetics, and agents that block the absorption of fats.

There are 10 currently approved agents in the US, four are approved for use in Canada (see Table). Most US approved medications are amphetamines or closely related central nervous system stimulants. Several of these exist in combination with other drugs. Approved amphetamines and

amphetamine-like agents include phentermine, diethylpropion, benzphetamine and phendimetrazine. Combination agents include naltrexone and bupropion (Contrave), and phentermine/topiramate (Qsymia). The exact mechanism of action of these drugs remains somewhat elusive. For the amphetamines, their noradrenergic properties are probably responsible for their appetite-suppressant effects. Naltrexone is an antagonist at opiate receptors in brain, in the past such antagonism has been observed to reduce craving for non-opiate substances such as alcohol. It has also been used with variable success in compulsive behaviors in which a neurobiological reward mechanism is presumed to exist. Its combination with the amphetamine derivative bupropion is empirical, as is the combination of the psychostimulant phentermine and the anticonvulsant topiramate. It is questionable whether either of these agents is more efficacious in weight reduction than an amphetamine alone.

Amphetamines remain among the most widely used pharmaceuticals of any class. Primarily employed to manage attention deficit hyperactivity disorder, they are frequently misused for their euphoriant properties or to increase mental acuity in people without ADHD type diagnoses. They are associated with insomnia, appetite suppression/weight loss, dependence and in rare cases amphetamine induced psychoses.

Phentermine is an amphetamine derivative that acts primarily at the Trace Amine Associated Receptor (1) (TAAR1) as an agonist. TAAR1 receptors work to modulate neurotransmission of monoamines like dopamine and norepinephrine. It has been available as a weight loss agent since the late 1950s, and is still used as an anorectant today. Readers may recall the controversy in the mid-1990s when phentermine in combination with the serotonergic agent fenfluramine was introduced as the prescription weight loss agent Fen-Phen. Due to numerous reports of cardiac valve injury, Fen-Phen had a short and litigious history. While it is still available in the US, numerous restrictions largely based on liability concerns limit its use. Phentermine as a single agent remains available, as does a

combination of the antiseizure medication topiramate and phentermine, marketed in the US and Canada as Qysmia. It should be noted that this combination is purely empirical. After the introduction of topiramate as an anticonvulsant, weight loss was observed in clinical populations, so it began to be used off-label as a weight management agent in patients with no history of seizure disorder.

Amphetamine-based drugs are effective weight loss agents but concerns regarding abuse and dependence have long existed. Other undesirable side effects include insomnia and irritability, and prolonged use at higher doses can result in amphetamine-induced psychosis. A defined withdrawal syndrome exists upon drug discontinuation. Concerns regarding the abuse potential of amphetamines have resulted in their classification as scheduled drugs. Most amphetamines are listed as Schedule II (US) or Schedule IV agents (Canada), making their prescription cumbersome and subject to oversight. None save phentermine is approved for weight loss in Canada.

In the more recent past, a class of agents called glucagon-like-peptide(GLP-1) agonists has entered the marketplace. Although initially marketed for their ability to reduce serum glucose, a secondary effect of significant weight loss has led to both approved and off -label use in non-diabetic patients. These drugs stimulate glucagon-like-peptide-1 receptors in brain and cause the release of insulin, thereby lowering blood sugar levels. Through somewhat unclear mechanisms they also act to increase the sensation of satiety, and their ability to slow gastric emptying also contributes to their appetite suppressant effects. They are primarily of use in the management of Type 2 diabetes. A number of such agents exist, several are being considered for separate approval as weight loss agents. These are discussed below.

At present, the GLP1 agonists liraglutide (Saxenda/Xultophy) and semaglutide (Wegovy/Rybelsus) are FDA/Health Canada approved weight loss drugs. Setmelanotide (IMCIVREE) is an injectable

agent that is solely approved in the rare genetically mediated enzyme deficiencies (pro-opiomelanocortin [POMC], proprotein convertase subtilisin/kexin type 1 [PCSK1], or leptin receptor ([EPR] deficiency].

Because of observations of clinically significant weight loss with incretin mimetics, liraglutide was FDA approved in 2021 specifically for weight loss in patients without Type 2 diabetes. Wegovy is also FDA approved for obesity in high body mass index (BMI) patients aged 12 and above, it is administered in the form of a weekly subcutaneous injection. Most common side effects of the incretin mimetics are gastrointestinal (nausea) with rare instances of pancreatitis, but there is an association with thyroid cancer and some are contraindicated in patients with a history of medullary thyroid carcinoma or in patients with a rare condition called Multiple Endocrine Neoplasia syndrome.

Semaglutide is also marketed in the US and Canada as Ozempic. While currently only indicated for Type 2 diabetes, there is significant off label prescribing of this drug for weight loss, as is the case with tirzepatide,(Mounjaro) another drug also indicated only for Type 2 diabetes, although there are current trials underway that may lead to its separate approval as a weight loss agent. These drugs are costly and many insurance plans do not cover their use for weight loss purposes. Also, while randomized trials do suggest their efficacy over at least intermediate periods of time, with significant weight loss that can amount to approximately 20% of total body weight in some studies, rebound weight gain occurs upon discontinuation, as it does with the discontinuation of any pharmacological intervention for weight loss. Due to a very high degree of social and industrial interest in these drugs, expanded FDA approval for tirzepatide and semaglutide is likely in the near future.

In sum, incretin mimetics offer an attractive alternative to amphetamine based preparations for weight loss. Their use is not without risk – gastroinstestinal discomfort, pancreatitis, gall bladder and kidney disease are among reported side effects, and they can result in clinically significant hypoglycemia,

particularly when used with other drugs that increase insulin secretion. But generally their overall side effect profile is more benign than with amphetamines. As with any weight loss drug, continued use is necessary to maintain weight loss and rebound weight gain will occur on their discontinuation, but they lack the risk of dependency and misuse that is strongly present with amphetamines. A major drawback is related to their high cost, which is often not reimbursed by government or third party insurors.

Table 1. Currently approved (FDA- US) drugs for weight loss

DRUGS FOR WEIGHT LOSS	Trade names	FDA/Health Canada approved for weight loss?	Comments
Amphetamine-based agents			
Benzphetamine	Regimex, Didrex, others	Yes (US) No (CA)	Schedule I controlled substance in Canada
Phendimetrazine	Bontril, Melfiat, others	Yes (US) No (CA)	Schedule IV controlled substance in Canada
Phentermine	Adipex, Fastin, others	Yes (US) No (CA)	Schedule IV controlled substance in Canada
Diethylpropion	Tenuate and others	Yes (US) No (CA)	Schedule IV controlled substance in Canada
Naltrexone/bupropion	Contrave	Yes (US) Yes (CA)	
Phentermine/topiramate	Qysmia	Yes (US) Yes (CA)	Phentermine Schedule IV controlled substance in Canada

Incretin Mimetics			
Liraglutide	Saxenda, Victoza (US) Zultophy (CA)	Yes = Saxenda, Victoza (US) Yes = Saxenda (CA) No = Zultophy (CA)	
Semaglutide	Ozempic, Wegovy (US) Rybelsus (CA)	Yes = Wegovy (US) Yes = Rybelsus (CA) No = Ozempic (US)	
Setmelanotide	IMCIVREE	Yes (US, restricted) No (CA)	Use restricted to genetically mediated enzyme deficiencies
Tirzepatide	Mounjaro	No (US) No (CA)	
Lipid absorption blockers			
Orlistat	Xenical (prescription) Alli (non-prescription)	Yes (US) Yes (CA)	Available as prescribed agent, an OTC medication, and a dietary additive

Orlistat (Xenical, available in some doses without a prescription) has a different mechanism of action. It promotes weight loss by blocking pancreatic lipases needed for the absorption of fats in the digestive tract. Rather than being absorbed, these fats are excreted unchanged. It may be used as a food additive and can be found in specifically labelled products like potato chips (crisps?) and other processed foods. Side effects include gastrointestinal upset, oily, loose stools and fecal incontinence. Since these side effects are associated with the intake of fatty foods, orlistat acts as an adverse conditioning agent when excessively fatty foods are ingested. More rarely, liver and kidney damage have been reported.

In addition to drug-specific side effects, when prescribing any agent for weight loss the usual cautions apply: No drug for weight loss is a panacea and to be effective all must be used in combination with behavioral interventions and dietary modifications for weight control. Rebound weight gain *will* occur when use of any of these drugs is stopped and must be anticipated. No weight loss drug should be used during pregnancy, a time when weight gain may be an important issue. Some, like topiramate, are specifically associated with fetal malformations and are contraindicated in pregnancy.

Pharmacological adjuncts to well-managed behavioral weight loss programs can assist many in addressing what is often a life-long, challenging condition with numerous health-related consequences. It should be continually emphasized, however, that the weight loss observed with the use of medications alone tends to be modest and is effective only while the medication is being taken. Absent long-term behavioral and dietary changes weight gain will reoccur and this important consideration must be made clear to both patients and clinicians for whom the prescription of a medication might seem like a less effortful solution than a comprehensive psychological and behavioral regimen of which pharmacotherapy is only a part.