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REVIEW ARTICLE

Pharmacotherapy for Obesity: Past, Present and Future

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The prevalence of obesity has rapidly increased in all industrialized countries in the past few decades, most likely due to dietary and lifestyle changes. Since 1980, the prevalence of obesity has increased threefold or more worldwide. Obesity is associated with a number of diseases and metabolic abnormalities, many of which have high morbidity and mortality rates. These diseases include type 2 diabetes, hypertension, dyslipidemia, coronary heart disease, gallbladder disease, and some cancers. Even relatively modest decreases in body weight (5–10% of the initial body weight) lead to marked improvements in blood pressure, and sugar and lipid control in obese patients. Obesity treatment should begin with lifestyle changes that focus on behavioral modifications, diet control, and regular exercise. Pharmacotherapy provides an adjunct for obesity treatment, but should be used in conjunction with non-pharmacological approaches such as reduced caloric intake and increased exercise. The history of pharmacotherapy for obesity is no great success story because most anti-obesity drugs have been withdrawn from the market based on the US Food and Drug Administration warnings of serious adverse reactions. At present, only orlistat and sibutramine have been approved by the US Food and Drug Administration for long-term use, but sibutramine was withdrawn from sale in the European Union in January 2010. Rimonabant was approved for use in the European Union in 2006 but officially withdrawn in 2009. There are still many compounds under clinical development, including a new cannabinoid-1 receptor antagonist, a 5-HT_{2c} receptor agonist, ghrelin receptor antagonists, and inhibitors of gastrointestinal lipases. All of these compounds are still in preclinical or early clinical development stages. It will take time to tell whether these compounds can be used as anti-obesity drugs in the near future.

1. The History of Drug Treatment for Obesity

It has been demonstrated that even relatively modest decreases in body weight will result in significant health benefits for obese patients.^{1,2} The consensus on obesity treatment is that clinical therapy should start with

lifestyle changes that focus on behavioral modifications, diet control, and regular exercise.³ Pharmacotherapy provides an alternative approach to treat obesity, but should only be used when lifestyle changes have failed. Obesity guidelines currently recommend that drug therapy be considered for patients with a body mass index (BMI) ≥ 30 kg/m² or a BMI of 27–30 kg/m² with one or

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more obesity-related disorders, such as type 2 diabetes, hypertension, or coronary heart disease.^{1,4}

The use of anti-obesity drugs has become increasingly common in the last 30 years. Khan et al, who utilized 1998 Behavioral Risk Factor Surveillance System data, estimated that 4.6 million American adults used prescription weight loss pills between 1996 and 1998.⁵ The US Department of Health and Human Services estimated that between 1995 and 1997, 1.2–4.7 million residents in the United States used fenfluramine or dexfenfluramine for weight loss.⁶ Meanwhile, Stafford and Radley⁷ determined that 2.5 million Americans used anti-obesity medications in 1997, a fourfold increase over the figure for the previous 2 years. Furthermore, Blanck et al⁸ identified that 7% of Behavioral Risk Factor Surveillance System respondents used nonprescription weight loss products, 2% reported using phenylpropanolamine, and 1% used ephedra between 1996 and 1998. Despite the increasing use of prescription weight loss pills, the history of drug treatment for obesity is no great success story because many anti-obesity drugs, including fenfluramine-phenentermine,^{9,10} phenylpropanolamine¹¹ and ephedra,¹² were withdrawn by the US Food and Drug Administration (FDA) because of serious adverse reactions. For many years, only two drugs, orlistat (Xenical, F. Hoffmann–La Roche Ltd., Basel, Switzerland; Alli, GlaxoSmithKline PLC, London, England) and sibutramine (Meridia, Reductil, Abbott Laboratories, Abbott Park, IL, USA), have been approved for long-term use. The third, rimonabant (Acomplia, Sanofi-Aventis, Paris, France), was approved in the European Union in 2006 but officially withdrawn on January 16, 2009 by the European Medicines Agency. A few new drugs are currently undergoing clinical trials.¹³

2. Currently Available Drugs for Treating Obesity

At present, there are only two medications approved for long-term use worldwide, orlistat and sibutramine. However, sibutramine's marketing authorizations were suspended by the European Medicines Agency in January 2010 due to concerns that it could lead to an increased risk of developing heart problems. The FDA also added a history of cardiovascular disease as a contraindication to the use of sibutramine. In the following sections, the pharmacological profiles of these two drugs are discussed in detail.

3. Orlistat

3.1. Pharmacology and mechanisms of action

Orlistat, first isolated from soil bacteria (*Streptomyces toxytricini*) and approved in 1998, is a hydrogenated

derivative of lipstatin. Orlistat is a gastric and pancreatic lipase inhibitor that can decrease dietary fat absorption by about 30%.⁶ The drug works in the gut by blocking gastrointestinal lipase activity. Only a small fraction of the drug is actually absorbed after oral intake, which means that this drug is relatively safe. Many papers have shown that the bioavailability of orlistat is <1% because of its low systemic absorption rate and first-pass metabolism.¹⁴ Orlistat is excreted almost unchanged in the feces. The standard dose given is 120 mg three times per day with meals; half-strength orlistat (Alli) is also approved by the FDA for over-the-counter use in the United States.

3.2. Efficacy

Sjostrom et al¹⁵ conducted a trial on 743 obese patients to assess the efficacy of orlistat, and found that orlistat stimulated weight loss and prevented subsequent weight gain. The XENDOS study (Xenical in the Prevention of Diabetes in Obese Subjects), a placebo-controlled double-blind randomized study of 3305 obese Swedish patients spanning 4 years, showed a mean weight loss of 5.8 kg with orlistat compared with 3.0 kg in the control group, and a reduction in the occurrence of type 2 diabetes from 9.0% to 6.2%.¹⁶ Orlistat has also been studied in several placebo-controlled, double-blind trials for periods of up to 2 years. There was a mean reduction in body weight of 2.89 kg (corrected for weight changes in the control group) after treatment for 12 months. Most body weight loss occurred within the first 6 months of treatment and the body weight stabilized and remained lower if treatment continued.¹⁷ A randomized controlled trial of 120 mg orlistat three times a day as treatment for maintaining weight loss with a very low calorie diet also reduced weight regain after 3 years (4.6 kg vs. 7 kg, $p < 0.02$).¹⁸ This effect on body weight maintenance was significant in improving several metabolic parameters. A retrospective study showed that orlistat reduced the levels of triglycerides and cholesterol in blood, improved oral glucose tolerance, and decreased systolic and diastolic blood pressure.¹⁹

Some studies have focused on the effects of orlistat in adolescents. Chanoine et al conducted a 54-week multicenter trial to compare orlistat with a placebo for obese adolescents, and showed a BMI reduction of 0.55 kg/m² in the orlistat group and an increase of 0.31 kg/m² in the placebo group. Waist circumference also decreased in the orlistat group and increased in the control group.²⁰ Nevertheless, the findings were less consistent than expected. In another 6-month, double-blind, randomized, placebo-controlled trial that recruited 40 adolescents, orlistat failed to significantly reduce BMI.²¹ The effects of orlistat on childhood obesity are still equivocal and further studies are needed.

3.3. Adverse reactions

Most of the reported side effects of orlistat are gastrointestinal. Around 15–30% of patients treated with orlistat have symptoms that include fatty and oily stools, fecal urgency, and oily spotting. Meanwhile, 7% of patients treated with orlistat experienced symptoms of fecal incontinence, compared with 1% of placebo-treated patients. Malabsorption of fat-soluble vitamins, including vitamins A, D, E and K, was also noted, so it is recommended that patients using orlistat take vitamin supplements.²² Systemic adverse reactions are extremely rare due to the lack of systemic absorption. These adverse reactions are enhanced by a high-fat diet, which could be used as a part of behavioral feedback therapy. These gastrointestinal side effects appear in the early stage of treatment and generally disappear over time.

There is some concern that orlistat may be associated with an increased risk of colon cancer. A preliminary study in rats revealed an association between orlistat and increases in colonic preneoplastic markers.²³ Clearly, further studies in humans are needed. Furthermore, increasing the free fatty acid level in the lower gastrointestinal tract using lipase inhibitors to inhibit uptake of fats from a fatty diet is expected to enhance oxalate absorption, which increases the risk of kidney stones and renal impairment.²⁴

4. Sibutramine

4.1. Pharmacology and mechanisms of action

Sibutramine, originally developed as an antidepressant, is an inhibitor of noradrenaline, serotonin and dopamine reuptake. Sibutramine, the first centrally acting anti-obesity drug, has been approved for use in most countries, including the United States in 1997 and the European Union in 1999. Most of the drug and its active metabolites are excreted renally. Sibutramine mainly suppresses the appetite, but may also stimulate thermogenesis to increase energy expenditure. At a 30-mg dose, sibutramine-induced hypophagia was accompanied by inhibition of hunger.²⁵

4.2. Efficacy

Sibutramine shows greater efficacy when combined with lifestyle modifications and regular and frequent follow-up visits. The use of sibutramine promotes body weight loss, most of which occurs within the first 6 months. Thereafter, however, further treatment only helps to maintain the loss of body weight. In the STORM (Sibutramine Trial of Obesity Reduction and Maintenance) study, patients who were prescribed 10 mg sibutramine with a low calorie diet lost 11.3 kg in 6 months. The group that continued with 10 mg sibutramine seemed to show little weight

regain, while the control group appeared to regain weight in the following 12 months.²⁶ Arterburn et al performed a systematic review of sibutramine and found that the mean weight loss was 4.45 kg after 1 year, with improvements in several metabolic parameters.²⁷ In another randomized study with a 1-year follow-up, sibutramine reduced body weight by around 4.6%.²⁸

Two studies have tested whether sibutramine might be useful for obese adolescents.^{29,30} Berkowitz et al reported that 10–15 mg of sibutramine per day decreased body weight by 8.4 kg and BMI by 2.9 kg/m² in 498 obese adolescents after 12 months.²⁹ They also reported that the addition of sibutramine induced more weight loss than traditional behavior therapy alone.³⁰

4.3. Adverse reactions

Common side effects of sibutramine include dry mouth, headaches, insomnia and constipation, all of which are associated with increased adrenergic activity.³¹ Sibutramine was shown to increase heart rate by 3–7 beats per minute and to increase blood pressure by 2–3 mmHg. These adrenergic side effects are of great concern for patients with poorly controlled hypertension, tachycardia or a preexisting cardiovascular disease. Patients using sibutramine should not use monoamine oxidase inhibitors or serotonergic drugs because of the risk of serotonin syndrome.

The cardiovascular side effects of sibutramine include increasing systolic and diastolic blood pressures, and tachycardia, vasoconstriction and palpitations. These effects may be associated with its mechanism of action or possibly its peripheral effects. The SCOUT (Sibutramine Cardiovascular Outcome Trial) study revealed that blood pressure decreased during sibutramine treatment for 6 weeks, even in hypertensive patients whose body weight remained unchanged. Small increases in pulse rates were also seen regardless of the weight change status or blood pressure.^{32,33} A possible association between sibutramine treatment and QT interval prolongation was found recently. This could lead to cardiac arrest and ventricular fibrillations in rare cases. Thus, regular electrocardiographic monitoring might be recommended when using sibutramine. Furthermore, the use of sibutramine in combination with other medications, including certain antipsychotics, antidepressants and antiarrhythmic agents that may prolong QT should be avoided.³⁴

5. Comparisons and Clinical Applications of Available Drugs

There are no definitive data showing the benefits of one anti-obesity drug over another.¹ Therefore, at the start of treatment, the initial choice is largely based on the preferences of each patient, adverse effect profiles, and clinical experience. Orlistat might be beneficial for patients

Table 1 Comparison of the available anti-obesity drugs

	Orlistat	Sibutramine
Pharmacology	Inhibits gastric and pancreatic lipase	Inhibits noradrenaline, serotonin and dopamine reuptake
Target organ	Gut	Central nervous system
Mechanisms of action	Decreases dietary fat absorption by about 30%	Reduces reuptake of serotonin, norepinephrine and dopamine
Bioavailability	<1%; low systemic absorption rate and first-pass metabolism	Well absorbed from GI tract (77%); first-pass metabolism reduces its bioavailability
Excretion	Almost unchanged in feces	Original form and active metabolites excreted renally
Dosage	Standard dose: 120 mg each time, thrice daily with meals; half-strength Orlistat (Alli): over-the-counter use in USA; recommended that it be taken with vitamin supplements	Standard dose: 5–20 mg, once daily with or without meals; not recommended to combine with antipsychotics, antidepressants and antiarrhythmic agents
Weight loss	Mean body weight loss of 2.89 kg after 1-yr treatment; most weight loss occurs within first 6 mo of treatment	Mean weight loss of 4.45 kg or around 4.6% over 1 yr; most weight loss occurs within first 6 mo of treatment
Additional benefits	Reduces blood triglyceride and cholesterol levels; improves oral glucose tolerance and reduces occurrence of type 2 diabetes; decreases systolic and diastolic blood pressures	Mainly suppresses appetite; stimulates thermogenesis to increase energy expenditure; lifestyle modification and regular, frequent follow-up visits; improves several metabolic parameters
Adverse effects	Enhanced by high-fat diet; rare systemic adverse reactions; 15–30% of patients experience fatty and oily stools, fecal urgency, and oily spotting; 7% experience fecal incontinence; malabsorption of fat-soluble vitamins A, D, E and K	Associated with increased adrenergic activity resulting in dry mouth, headache, insomnia and constipation; cardiovascular effects include elevated systolic and diastolic blood pressures, tachycardia, vasoconstriction and palpitations
Notable concerns	Possibly associated with increased risk of colon cancer; may lead to higher risk of kidney stones and renal impairment	Cardiac arrest and ventricular fibrillation in rare cases; combined use with antipsychotics, antidepressants, and antiarrhythmic agents may prolong QT interval

GI=gastrointestinal.

with high levels of low-density lipoprotein cholesterol, and cardiovascular disease, or those at high risk for developing type 2 diabetes. Patients taking orlistat long-term should also take vitamin supplements. Sibutramine might reduce the rate of food intake among patients who experience a lack of satiety or who frequently snack. However, sibutramine is not recommended for patients with poorly controlled hypertension, preexisting cardiovascular disease, or tachycardia (Table 1).

6. Drugs in Clinical Development

To suppress appetite, Pfizer is developing a new CB-1 receptor antagonist that may alter the balance between the central and peripheral systems. The agent reduces

adverse effects such as anxiety and depression, but it may also have a lower efficacy for suppressing appetite (e.g., CP-945,598 by Pfizer, <http://www.clinicaltrials.gov>). Another appetite-suppressing drug currently in clinical trials is APD356 (Arena Pharmaceuticals Inc., San Diego, CA, USA). APD356 is a 5-HT_{2c} receptor agonist and may have anorexigenic effects. However, because APD356 targets a specific 5-HT receptor subtype, it may induce fewer adverse effects.³⁵ Leptin is secreted from adipose tissue and informs the brain about the amount of energy reserves, and its pathway has been broadly studied.³⁶ So far, there is clinical development of agonists or antagonists for these reaction sites. Nevertheless, many clinical studies have shown that the melanocortin system is very important in regulating food intake and energy expenditure.³⁷

Ghrelin is the only gut hormone that stimulates appetite, according to prior studies.^{38–40} Ghrelin receptor antagonists could be the newest and most efficient anorexigenic agents to suppress appetite. Another pharmacologic target is uncoupling protein 3, a protein found in skeletal muscles that produces heat.⁴¹ Another target for treating obesity is to reduce gastric emptying. Pramlintide is an analog of amylin and is used to treat type 2 diabetes. It may lead to $8.4 \pm 0.9\%$ weight loss after 20 weeks of treatment.⁴² Other gastrointestinal lipase inhibitors, such as cetilistat, may offer alternatives to orlistat with fewer adverse effects.⁴³ These compounds are still in the preclinical or early clinical development stages for the treatment of obesity. It will take time to confirm whether these compounds can be used as anti-obesity drugs in the future.

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