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Rise and fall of anti-obesity drugs

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Abstract
Although it is not generally a life-threatening disease, obesity is becoming a major health problem worldwide. It can be controlled by means of drugs, and, consequently, these are required to be safe as well as effective. In this paper, we summarize the fate of various drugs that have been introduced for clinical use in the treatment of obesity. Fenfluramine and dexfenfluramine were withdrawn because of heart valve damage. Sibutramine suppresses appetite and increases heart rate and blood pressure. In the Sibutramine Cardiovascular Outcomes trial, an increase in major adverse cardiovascular events prompted its withdrawal in Europe and the United States. Rimonabant is an endocannabinoid receptor antagonist that reduces body weight and ameliorates some cardiovascular risk factors. However, adverse psychiatric side effects led to its withdrawal as well. Orlistat is approved in Europe and the United States for the treatment of obesity, but its use is limited by gastrointestinal side-effects. Ephedrine and caffeine are natural ingredients in foods and supplements that may help the person to lose weight. In the light of several failed attempts, there is a clear need to develop drugs that are effective and safe in the long term in order to successfully combat the phenomenon of obesity.

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Key words: Obesity; Anti-obesity drugs; Sibutramine; Rimonabant; Orlistat

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INTRODUCTION
Obesity, which is characterized by excess body fat, is a major public health problem in many parts of the world[1,2]. The consequences of obesity are substantial. Obesity amplifies the risks of hypertension, dyslipidaemia, type 2 diabetes, cardiovascular disease, obstructive sleep apnoea, osteoarthritis, and several cancers[3-6]. Obesity is also associated with reduced average life expectancy[7]. It is suggested that the treatment of obesity is a lifelong task, like dealing with any other complex disease[7]

In the management of obesity, lifestyle and behavioral modification, including appropriate diet and exercise, should be the initial as well as the maintenance treatment for obesity; pharmacotherapy is recommended for patients who are obese, or overweight patients with co-morbidities such as type 2 diabetes, cardiovascular disease, obstructive sleep apnoea, osteoarthritis, and several cancers[3-6]. Anti-obesity drugs are classified into three groups, according to their mechanism of action: appetite suppressants, inhibitors of fat absorption, stimulators of energy expenditure and thermogenesis[7]. Many medications have been used to treat obesity over the years. However, most of the anti-obesity drugs that have been approved by the United States Food
PHENTERMINE AND FENFLURAMINE

The combination of phentermine with fenfluramine or dexfenfluramine was once commonly used in managing obesity. Phentermine is a noradrenergic drug, which stimulates the release of noradrenaline and reduces food intake by acting on β-adrenergic receptors in the perifoncal hypothalamus[9]. Fenfluramine and dexfenfluramine (the d-isomer of fenfluramine) are serotonergic drugs, which cause the release of serotonin to suppress appetite and reduce food intake[13].

Both phentermine and fenfluramine were individually approved by the USFDA. The combination of phentermine with fenfluramine or dexfenfluramine was not thought to be more effective than either drug alone, but lower doses of each drug could be used in combination, leading to fewer side effects[14]. However, both fenfluramine and dexfenfluramine were withdrawn from market by the USFDA in 1997[15]. The decision was prompted by a preliminary report of 24 women receiving fenfluramine[15]. This study identified heart valve damage in association with the use of fenfluramine[15]. Echocardiographic and histological findings demonstrated unusual valvular morphology that resembled those in carcinoid or ergotamine-induced heart valve disease[13]. In this study, pulmonary arterial hypertension was also identified in eight women[13].

SIBUTRAMINE

Sibutramine was widely used after its approval by the USFDA in 1997[16,18]. It is a serotonergic and adrenergic drug that inhibits the reuptake of serotonin and norepinephrine[16]. Sibutramine is converted to two pharmacologically active metabolites, N-desmethyl and N-bisdesmethyl sibutramine, which are more stable and have a much longer half-life compared with sibutramine itself[16]. Sibutramine suppresses appetite, causes satiety, and increases thermogenesis mainly through its two active metabolites[16].

A meta-analysis showed that sibutramine promoted weight loss by about 4.45 kg at 12 mo in overweight and obese adults who had a BMI of 25 kg/m² or greater[17]. In a 12-mo study, sibutramine showed potential benefit by improving biochemical risk factors associated with obesity, including plasma glucose, insulin, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C)[18]. In obese patients, sibutramine was shown to reduce waist circumference, which is a strong predictor of cardiovascular disease[18,19]. Moreover, sibutramine caused a decrease in the level of glycosylated haemoglobin in obese patients with type 2 diabetes[20-22]. In studies lasting 24 wk or less, however, there was some regain of weight after the treatment of sibutramine stopped[23].

The most frequently encountered side effects of sibutramine are headache, dry mouth, insomnia, and constipation[24]. Unlike fenfluramine, the use of sibutramine has not been associated with increases in pulmonary hypertension or heart valve damage. However, sibutramine increased heart rate and caused a mean of 2 mmHg increase in both diastolic and systolic blood pressure at a dose of 10-15 mg daily in some patients[16]. The increase in blood pressure was more pronounced in patients who were younger and more obese[16]. In some other placebo-controlled trials, sibutramine did not increase blood pressure in either normotensive individuals or hypertensive patients[25]. Moreover, in a study of 6 mo in duration, the sibutramine/sustained release verapamil/trandolapril combination significantly reduced blood pressure and improved total cholesterol, HDL-C and triglycerides compared with the sustained release verapamil/trandolapril combination in obese hypertensive patients[26]. Therefore, the influence of sibutramine on the sympathetic nervous system might be more complicated than previously believed. The effect of sibutramine treatment on sympathetic vasomotor tone in obese patients has been studied[27]. It was found that the balance between peripheral stimulation and central inhibition on the sympathetic nervous system determined the net change in blood pressure, which might

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<td>Orlistat</td>
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<td>Rimonabant</td>
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vary in different circumstances\[27\]. Due to the concern over blood pressure, sibutramine is not recommended for use in patients with coronary heart disease, cardiac arrhythmias, uncontrolled hypertension, congestive heart failure, or a history of stroke.

The 5-year Sibutramine Cardiovascular OUTcomes (SCOUT) trial was a randomized, double-blind and placebo-controlled study involving 10,742 overweight or obese patients with cardiovascular disease, hypertension or type 2 diabetes\[28\]. After a 6-wk lead-in period, patients who received single-blind sibutramine had, on average, a 2.2 kg reduction of body weight, a 2.0 cm reduction of waist circumference, a 3.0 mmHg decrease in systolic blood pressure, a 1.0 mmHg decrease in diastolic blood pressure, and a 1.5 bpm decrease in pulse rate\[28\]. In addition, sibutramine was found to be efficacious, tolerable and safe in this 6-wk single-blind period\[28\]. In January 2010, a preliminary report of the SCOUT study, which showed that sibutramine was associated with an increased risk of serious, non-fatal cardiovascular events such as myocardial infarction or stroke as compared with placebo (11.4% vs 10%, hazard ratio, 1.16; 95% confidence interval, 1.03-1.31), led to the recommendation to suspend the use of sibutramine by the Committee for Medicinal Products (CHMP) for Human Use of the European Medicine Agency (EMEA)\[29,30\]. Sibutramine has subsequently been withdrawn from the European market\[30\]. The USFDA requested that healthcare professionals be notified that sibutramine should not be used in patients with known cardiovascular disease\[29\]. The full results of the SCOUT study were published in September 2010\[31\]. Long-term sibutramine treatment was shown to increase the risk of non-fatal myocardial infarction and non-fatal stroke, but not of cardiovascular death or death from any cause, in overweight or obese patients with pre-existing cardiovascular diseases. The USFDA decided that the drug might pose unnecessary cardiovascular risks to patients, and so sibutramine was withdrawn on 8 October 2010\[32\].

**RIMONABANT**

The endocannabinoid system has been identified as playing a significant role in the control of food intake and energy balance, as well as lipid and glucose metabolism\[33\]. Endocannabinoids act as endogenous ligands capable of activating two types of G protein-coupled cannabinoid receptors, the cannabinoid type 1 (CB\(_1\)) receptor and the cannabinoid type 2 (CB\(_2\)) receptor\[34\]. The CB\(_1\) receptor is expressed in the central nervous system and in peripheral tissues such as adipose tissue, the gastrointestinal tract, the liver and muscle, which are all involved in lipid and glucose metabolism\[35\]. The CB\(_2\) receptor is located in the immune and hematopoietic cells\[36\]. Prior studies have demonstrated that the endocannabinoid system is overactive in obesity, suggesting that weight loss could be induced and metabolic profiles improved if the elevated endocannabinoid tone is possibly suppressed\[37\]. Rimonabant, the first drug selectively antagonizing the CB\(_1\) receptor in the brain and in the periphery, is aimed at fighting obesity and associated risk factors\[37\]. The approval of rimonabant was recommended by the CHMP of the EMEA in April 2006\[7\].

Thus far, there have been four large human clinical trials that tested the safety and efficacy of rimonabant\[34,38-40\]. The rimonabant in obesity (RIO) Europe trial and the RIO-North America trial included obese patients or overweight patients with obesity-induced disease. The RIO-Lipids and RIO-Diabetes trials included patients with hyperlipidaemia and type 2 diabetes, respectively. All these four randomized, double-blind, placebo-controlled trials of rimonabant showed similar effects of rimonabant on weight loss and cardiovascular risk factors. Rimonabant promoted weight loss by about 4.7 kg at 1-year follow-up\[34\]. However, it was later reported that use of rimonabant was associated with psychiatric side effects including anxiety, depression and suicidal ideation. These adverse psychiatric events were observed in 26% of the participants in 20 mg rimonabant group compared with 14% of those on placebo in the same four studies\[41\]. In October 2008, despite the extensive clinical trial data, the suspension of rimonabant was recommended by the EMEA\[7\]. Permission for the use of rimonabant was also declined by the USFDA\[35\].

**ORLISTAT**

Orlistat, a reversible gastrointestinal lipase inhibitor, is approved for the long-term management of obesity. Orlistat reduces caloric intake and leads to weight loss by inhibiting hydrolyzation of dietary fat in the gut and reducing its absorption\[42\]. In a meta-analysis of 29 studies, orlistat reduced body weight by about 2.59 kg at 6 mo and about 2.89 kg at 12 mo\[43\]. When compared to treatment with placebo and diet, orlistat significantly reduced waist circumference, total cholesterol, LDL-C and blood pressure, and improved blood glucose levels and insulin resistance\[44,45\]. In practice, the most common side effects of orlistat affect the digestive system, and include diarrhea, flatulence, bloating, abdominal pain and dyspepsia\[46\]. Orlistat may not be well tolerated as a result of these side-effects which are related to the unabsorbed fat in the intestine. In addition, long-term use of orlistat can result in a deficiency of the fat-soluble vitamins (vitamin A, D, E, and K). Adequate vitamin supplementation may therefore be needed for patients on orlistat. It should be remembered that there are very limited data on the long term effects of orlistat on cardiovascular outcomes.

**EPHEDRINE AND CAFFEINE**

Ephedrine and caffeine belong to the category of drugs that increase energy expenditure and thermogenesis. In a long-term placebo-controlled clinical trial, the combination of ephedrine and caffeine showed a greater effect on weight loss than either when used alone. These substances are contained in some health supplements. How-
ever, to date, the combination of ephedrine and caffeine has not been approved as an anti-obesity treatment[2].

OTHER ANTI-OBESITY DRUGS

There are three other drugs that show promise but are not yet licensed for the treatment of obesity. Metformin has been used for many years in patients with type 2 diabetes mellitus. It is the only anti-diabetic drug that has been shown, in long term clinical trials, to reduce mortality and to prevent the development of diabetes[49]. Unlike sulphonylureas and insulin, it does not cause weight gain. In some studies, weight reduction has been observed among non-diabetic individuals. Metformin is not currently licensed for the treatment of obesity, but it is a first line treatment in patients with type 2 diabetes, especially if they are obese.

Topiramate is an anti-epileptic drug that blocks voltage-dependent sodium channels, glutamate receptors, and carbonic anhydrase, and augments the activity of gammaaminobutyrate (GABA). It remains unlicensed for the treatment of obesity because diarrhoea and leakage were observed in early clinical studies. Qnexa is a combination of topiramate and phentermine[50]. The combination is better tolerated and it causes impressive weight reduction. The USFDA has not approved it yet, the outstanding concerns being possible effects on the fetus in women of childbearing age and an increase in heart rate.

Liraglutide, like exenatide, is a glucagon-like peptide-1 (GLP-1) analogue that was first used for the treatment of type 2 diabetes mellitus. As GLP-1 suppresses appetite and delays gastric emptying, liraglutide reduces body weight, even in non-diabetic individuals[51].

CONCLUSION

Despite promising results on body weight reduction and some cardiovascular risk factors, most anti-obesity drugs developed so far have not been approved or have had to be withdrawn from the market, due to adverse side effects. As sibutramine is no longer available, orlistat is currently the only anti-obesity drug to have been approved for long-term use[52]. The development of new anti-obesity drugs is therefore urgently needed. The long-term safety and efficacy of newly-developed drugs should be carefully evaluated. It should also be mentioned that most clinical trials tested anti-obesity drugs in combination with a reduced calorie diet. Since compliance is usually better in clinical studies, the weight reduction in clinical practice might be smaller.

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