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Drug Treatment for Obesity in the Post-Sibutramine Era

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Contents

Abstract

Obesity is a major health problem worldwide. It is associated with cardiovascular diseases, diabetes mellitus and decreased longevity. In managing obesity, diet and exercise are essential; pharmacological therapy may be added for obese patients or overweight patients with cardiovascular risk factors. Sibutramine is a serotonergic and adrenergic drug that reduces food intake and increases thermogenesis. It reduces bodyweight by about 4.2 kg after 12 months, and improves blood glucose and lipids; however, it can increase heart rate and blood pressure. In the SCOUT (Sibutramine Cardiovascular OUTcomes) study, sibutramine increased serious cardiovascular events, such as stroke or myocardial infarction, compared with placebo, and was consequently withdrawn from the market. The lesson learnt from this is the importance of patient selection, limiting the duration of treatment and stopping treatment in non-responders. Currently, phentermine and amfepramone (diethylpropion) are approved for short-term treatment of obesity (up to 3 months) and orlistat is approved for longer-term treatment; however, the gastrointestinal adverse effects of orlistat may be intolerable for some patients.

There is now a clear need to find anti-obesity drugs that are effective and safe in the long term.

Obesity is a major health problem worldwide and its prevalence has been increasing in the US, where two-thirds of adults are now either overweight or obese.[1,2] Obesity is not just a cosmetic problem; it is a medical problem as it is associated with hypertension, dyslipidaemia, type 2 diabetes mellitus and increased cardiovascular risk.[3-5] Obesity is also associated with obstructive sleep apnoea, osteoarthritis and some cancers, such as cancers of the colon, breast and endometrium. The Nurses' Health Study showed that mortality was significantly higher among those who were obese.[6]

Modest weight reduction, in the range of 5–10% of the initial weight, is beneficial in terms of reducing mortality.[7] Weight loss achieved through diet and regular physical activity has been shown to reduce the risk of developing type 2 diabetes.[8]

If obesity is as much a cause of cardiovascular disease as hypertension and diabetes, then addressing this condition should be accorded the same importance and priority.[3] Treatment of obesity should not be for the short term, but should be a long-term aim directed at attaining and maintaining normal bodyweight and composition.[9-12] In this review, a current perspective is offered on the long-term management of obesity in the aftermath of the withdrawal of sibutramine.

1. Management of Obesity

1.1 Lifestyle Changes

Management of obesity should always include lifestyle and behavioural modifications, including appropriate diet and exercise.[13-15] There is some debate over which type of diet is the most effective;[16-18] for instance, the DASH (Dietary Approaches to Stop Hypertension) diet has changed over the years.[19-21] In general, most diets involve calorie restriction and can lead to weight loss in the short term, but few diets can prevent long-term regain of weight.[22,23] What is needed is a change in eating habits that is sustainable. Regular exercise is important, but is limited by the exercise capacity of the individual. Unfortunately, many obese people who need to lose weight for medical reasons are unable to exercise because of poor cardiorespiratory function or musculoskeletal problems. Even so, everyone can and should exercise and perform physical activity. Indeed, the most sedentary individuals stand to benefit even from a minimal increase in activity.

For obese children, non-pharmacological treatment is especially preferable over pharmacological treatment.[10] Apart from managing obese children, environmental pressures leading to obesity should be considered. These include food portion sizes, energy-dense fast foods and drinks, and lack of physical activity. Parents and schools can also play a role in promoting healthy eating and lifestyle.[24]

1.2 Pharmacological Treatment

Drugs to treat obesity should not be prescribed for purely cosmetic reasons.[11] They are recommended for persons with obesity (body mass index [BMI] $\geq 30\ kg/m^2$) or those with increased BMI ($>27\ kg/m^2$ for sibutramine or $>28\ kg/m^2$ for orlistat) with co-morbidities such as type 2 diabetes, cardiovascular diseases and obstructive sleep apnoea.[11-13] To potentiate the effects of pharmacological treatment, it should be combined with lifestyle changes, such as restricted calorie intake and increased physical activity.[15]

Indeed, drugs for obesity are not very efficacious on their own. On average, they tend to reduce bodyweight by <5 kg after 1 year of treatment.[9,13,25,26] Nevertheless, this modest amount of weight loss in those who are overweight is potentially beneficial as there are improvements in insulin sensitivity, glucose, lipids and blood pressure.[27,28] These changes are expected to lead to reductions in cardiovascular morbidity and mortality, although this remains to be demonstrated in large outcome trials. For this reason, some experts believe that drugs for the treatment

Table I. Drugs that have been used for obesity

Drug	Mechanism of action	Adverse effects	Current status
Thyroxine	Increases metabolic rate	Hyperthyroidism, palpitations, anxiety, insomnia, diarrhoea	Not indicated for obesity
Dinitrophenol	Uncouples oxidative phosphorylation in mitochondria	Cataracts, neuropathy, sensation of warmth, sweating	Withdrawn
Amphetamine	Increases the neurotransmitters dopamine, noradrenaline (norepinephrine) and serotonin in brain	Addiction, headache, nausea, dry mouth, nervousness, anxiety, hypertension, tachycardia	Banned as an anti-obesity drug
Phentermine	Sympathomimetic amine	Headache, insomnia, irritability, palpitations and increased blood pressure	Short-term use (<12 wk)
Amfepramone (diethylpropion)	Sympathomimetic amine	As above	Short-term use (<12 wk)
Aminoxaphen (aminorex)	Indirect sympathomimetic action	Pulmonary hypertension	Withdrawn
Phenylpropanolamine	Central α_1-adrenergic receptor agonist	Haemorrhagic stroke, psychosis	Banned in the US
Fenfluramine, dexfenfluramine	Selective serotonin reuptake inhibitor	Pulmonary hypertension, valvulopathy	Withdrawn
Sibutramine	Noradrenaline and serotonin reuptake inhibitor	Headache, insomnia, dry mouth and constipation	Withdrawn
Rimonabant	Cannabinoid receptor antagonist	Depression, nausea, dizziness, arthralgia and diarrhoea	Withdrawn
Orlistat	Lipase inhibitor	Diarrhoea, flatulence, bloating, abdominal pain and dyspepsia	Marketed

of obesity have to show long-term benefits in terms of cardiovascular outcomes and overall mortality before they can be recommended without reservation.[9]

Table I shows the various drugs that have been used for the treatment of obesity. It is immediately apparent that many drugs have been used at one time or another but most have now been withdrawn, the latest being sibutramine.

1.3 Sibutramine

1.3.1 Pharmacological Properties of Sibutramine

Sibutramine was approved by the US FDA in 1997 for the long-term (>12 months) management of obesity.[29] Sibutramine undergoes extensive first-pass metabolism and is converted to two active metabolites, N-desmethyl and N-bisdesmethyl sibutramine, which are more stable.[30] The conversion to N-desmethyl sibutramine is influenced by cytochrome P450 (CYP) 2B6.[31] Sibutramine and its two active metabolites inhibit serotonin and noradrenaline (norepinephrine) reuptake, and may also have some effect on brain peptides such as neuropeptide Y and pro-opiomelanocortin.[32]

Sibutramine reduces food intake, and enhances satiety without causing sedation or markedly changing behaviour.[30,33] It also increases basal metabolic rate and oxygen consumption.[30,34] Meta-analyses suggest that sibutramine significantly reduces bodyweight,[9,25] i.e. by about 4.2 (95% CI 3.6, 4.8) kg after 12 months of treatment.[26] In a 12-month study, sibutramine improved plasma glucose, triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein cholesterol.[30] Moreover, there is a reduction in waist circumference.[35,36] In obese patients with type 2 diabetes, sibutramine reduces glycosylated haemoglobin;[37-39] however, once treatment stops there is some regain of weight.[40] The STORM (Sibutramine Trial of Obesity Reduction and Maintenance) study compared sibutramine with placebo in maintaining bodyweight over a period of 18 months after an initial treatment period of 6 months with sibutramine.[41] While there was substantial regain of bodyweight

in the placebo group, there were also small increases in the sibutramine group; however, in one study, sibutramine reduced bodyweight further in patients already on a very low calorie diet.[42]

1.3.2 Adverse Effects of Sibutramine

The most common adverse effects of sibutramine are headache, insomnia, dry mouth and constipation.[30] Unlike the amphetamines, sibutramine is not a drug of abuse[43] and, unlike fenfluramine, it has not been associated with pulmonary hypertension or valvulopathy.[44] However, sibutramine increases heart rate, and systolic and diastolic blood pressure by about 2 mmHg at a dose of 10–15 mg daily in some studies,[30] but not in other studies.[45,46] Meta-analysis suggests a small increase in diastolic blood pressure,[47] which can potentially increase the risk of stroke and myocardial infarction in susceptible patients.

Sibutramine stimulates peripheral sympathetic activity, but also inhibits centrally sympathetic outflow.[48] The balance between peripheral activation and central inhibition determines the net change in blood pressure, which may vary in different circumstances. The chronic effect of sibutramine is also tempered by any weight loss that accompanies such treatment.[39]

1.3.3 SCOUT (Sibutramine Cardiovascular OUTcomes) Trial

At the time of its approval by the European Medicines Agency (EMA), it was already known in some studies that sibutramine increased blood pressure.[47] Thus, there was a need to investigate the safety of this drug in patients with cardiovascular disease. The SCOUT (Sibutramine Cardiovascular OUTcomes) trial was therefore initiated to study the long-term effects of sibutramine treatment on cardiovascular outcomes in subjects with high cardiovascular risk. This was a randomized, double-blind, placebo-controlled study with a treatment duration of 5 years involving 10 742 overweight or obese patients with known coronary heart disease or type 2 diabetes, plus one additional cardiovascular risk factor such as hypertension. In the 6-week, single-blind phase of SCOUT, sibutramine treatment led to a 2.2 kg reduction in bodyweight, a 2.0 cm reduction in waist circumference, a 3.0 mmHg decrease in systolic blood pressure, a 1.0 mmHg reduction in diastolic blood pressure and a 1.5 beats per minute (bpm) decrease in pulse rate.[49] However, the final results of SCOUT showed that sibutramine significantly increased the risk of serious non-fatal cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, resuscitation after cardiac arrest or cardiovascular death) compared with placebo (11.4% vs 10%) [table II].[50] There was no significant increase in cardiovascular or all-cause mortality, and no significant increase in risk in diabetic patients without a history of cardiovascular disease (table III).

1.3.4 Controversy Over the Withdrawal of Sibutramine in the EU

In January 2010, the Committee for Medicinal Products for Human Use (CHMP) of the EMA suspended marketing authorization for sibutramine or medicines containing sibutramine across the EU,[51] and in October 2010 the FDA requested the withdrawal of sibutramine.[52] These recommendations were based on the results of the SCOUT trial, despite the proven benefits of the drug over a decade of clinical use. They were

Table II. Primary endpoints and all-cause mortality in SCOUT[50]

Analysis	Placebo [n (%)] (n = 4898)	Sibutramine [n (%)] (n = 4906)	Hazard ratio (95% CI)	p-Value
Primary endpoint	490 (10.0)	561 (11.4)	1.16 (1.03, 1.31)	0.02
non-fatal MI	159 (3.2)	200 (4.1)	1.28 (1.04, 1.57)	0.02
non-fatal stroke	95 (1.9)	127 (2.6)	1.36 (1.04, 1.77)	0.03
resuscitated cardiac arrest	7 (0.1)	11 (0.2)	1.58 (0.61, 4.08)	0.34
cardiovascular death	229 (4.7)	223 (4.5)	0.99 (0.82, 1.19)	0.90
All-cause mortality	404 (8.2)	418 (8.5)	1.04 (0.91, 1.20)	0.54

MI = myocardial infarction.

Table III. Cardiovascular events[a] in SCOUT (Sibutramine Cardiovascular OUTcomes) by predefined subgroups[50]

Study group	Placebo [number of events/ number of subjects (%)]	Sibutramine [number of events/ number of subjects (%)]	Hazard ratio (95% CI)	p-Value
All patients	490/4898 (10.0)	561/4906 (11.4)	1.16 (1.03, 1.31)	0.02
History of DM only	77/1178 (6.5)	79/1207 (6.5)	1.01 (0.74, 1.38)	0.95
History of CVD only	66/793 (8.3)	77/759 (10.1)	1.28 (0.92, 1.78)	0.15
History of DM and CVD	346/2901 (11.9)	403/2906 (13.9)	1.18 (1.02, 1.37)	0.02

a Cardiovascular events were defined as heart attack, stroke, resuscitated cardiac arrest or cardiovascular death.

CVD = cardiovascular disease; **DM** = diabetes mellitus.

controversial for a number of reasons.[53] Patients randomized to placebo experienced less weight loss and this might have prompted them to adopt a healthier lifestyle. It is of interest to note that an intention to lose weight is a better determinant of poor outcome than the amount of weight lost.[54]

The patient population and drug regimen in SCOUT did not conform to the licensed use of sibutramine. Thus, the drug was not for use in patients with known cardiovascular diseases, was to be discontinued if there was a lack of response and was not to be used for longer than 2 years.[55] Five years of treatment in SCOUT amounted to five times the licensed duration of treatment. Most weight loss occurs during initial treatment; therefore, benefit-risk profile is less favourable with prolonged use. Moreover, as any effect on heart rate and blood pressure is mitigated by weight loss, patients who do not lose weight while taking sibutramine may be at increased risk from these cardiovascular adverse effects.

While obesity puts people at risk of cardiovascular disease and renal failure, paradoxically people with these conditions fare better if they are obese.[56] Sibutramine is usually used, both in clinical trials and in clinical practice, in obese patients as primary prevention of cardiorenal disease. In SCOUT, sibutramine was tested for secondary prevention in those participants with known cardiovascular disease.

In practice, it may be impossible to avoid prescribing sibutramine to patients with cardiovascular disease because obese people may have clinically unapparent or undiagnosed cardiovascular disease. However, the increase in cardiovascular risk in SCOUT, although statistically significant, was of the order of 10–20%. This is a small increase, relative to the risk due to smoking, for example. Stronger warnings might have been sufficient. Moreover, in young female patients, the absolute risk of cardiovascular events may be so low that even a statistically significant increase may be unimportant in absolute terms. The withdrawal of sibutramine may deprive them of an effective treatment for obesity. Subgroup analysis showed that in patients with diabetes but no known cardiovascular disease, the hazard ratio was close to unity (table III).

1.3.5 The Lesson of Sibutramine

The lessons learnt from the withdrawal of sibutramine are the importance of patient selection, limiting the duration of treatment and stopping treatment in non-responders. Indeed, a major trend in the future is to identify, for every treatment, patient groups that may benefit more and have fewer adverse effects, as well as non-responders or those more prone to adverse effects. This is one of the central aims of personalized medicine. About 7.6% of patients receiving sibutramine experienced an increase in blood pressure of >10 mmHg and an increase in heart rate >10 bpm.[57] Data from Taiwan suggested that certain genotypes might influence whether a person would respond to sibutramine or not.[58]

While the safety profile of sibutramine is controversial, it is the devil we know. It may be even more hazardous if obese patients turn to Internet pharmacies to purchase obsolete anti-obesity drugs, and unproven treatments.[59] The antidepressants sertraline, fluoxetine and reboxetine, and the antiepileptic drug topiramate have been used in an off-label manner to aid weight loss. The long-term consequences of these drugs used in

this unlicensed indication are unknown. Sibutramine has been found in adulterated non-prescription medicines and health foods.[60] Surgical treatment for obesity, such as bariatric surgery, is associated with greater risks (but, arguably, also greater benefits).[61,62] Liposuction to remove large volumes of fat carries a hazard and has little proven value in reducing cardiovascular risk.[63]

2. Current Perspective of Drugs for Obesity

2.1 Phentermine and Amfepramone (Diethylpropion)

Currently, only phentermine and amfepramone (diethylpropion) are approved for the short-term treatment of obesity (up to 3 months) and orlistat is approved for longer-term treatment (table I). Phentermine and amfepramone are old, off-patent drugs that have not undergone the rigorous evaluation modern drugs have to undergo.[29] Phentermine was part of the Fen-Phen combination that caused cardiac valvular abnormalities, but as this adverse effect was thought to be due to fenfluramine or dexfenfluramine, phentermine was not banned. Phentermine is a derivative of amphetamine and is potentially addictive, therefore it is only approved for short-term use.

Amfepramone, a prodrug of ethylpropion (ethcathinone), is another noradrenaline-releasing agent like amphetamine that has been abused as a party drug. Both phentermine and amfepramone can increase blood pressure and heart rate, and are thus contraindicated in patients with cardiovascular disease. In the UK, these drugs can only be prescribed on a named-patient basis.

2.2 Orlistat

When sibutramine was withdrawn, orlistat became the only medication approved for the management of obesity for periods longer than 3 months. Orlistat is a gastrointestinal lipase inhibitor that blocks hydrolyzation of fat in the gut and reduces its absorption.[64] Calorie intake is thus reduced, leading to weight loss. A meta-analysis of 29 studies showed that orlistat reduced bodyweight by 2.59 kg after 6 months of treatment and 2.89 kg after 12 months of treatment.[65]

Orlistat-treated patients had significant reductions in waist circumference, total- and LDL-cholesterol and blood pressure, and significant improvements in blood glucose levels and insulin resistance compared with those receiving placebo diet.[66-68] In practice, the use of orlistat is limited by its adverse effects, mainly due to unabsorbed fat in the intestine, which leads to diarrhoea, flatulence, bloating, abdominal pain and dyspepsia. These troublesome adverse effects may reduce patient compliance and cause patients to discontinue treatment. Vitamin supplementation may be needed to replenish the fat-soluble vitamins (vitamins A, D, E and K).[69] It should also be remembered that orlistat has not been shown to improve hard cardiovascular endpoints in large clinical trials.

2.3 Incretins

Incretins, such as glucagon-like peptide-1 (GLP-1), are a class of hormones secreted in the gut in response to glucose.[70] They delay gastric emptying and stimulate insulin secretion. Such increased insulin secretion is dependent on the blood glucose level, such that this response is blunted when a patient shows signs of hypoglycaemia. Exenatide and liraglutide are two synthetic GLP-1 analogues that have been marketed for treating type 2 diabetes and, although they cause nausea and need to be injected, they do reduce appetite and facilitate weight loss.[71]

Circulating levels of incretins can be increased by inhibiting dipeptidyl peptidase IV (DPP-4). Gliptins, such as sitagliptin, vildagliptin and saxagliptin, are all DPP-4 inhibitors that can be taken orally.[72] While the oral route of administration is an advantage, their effect on bodyweight is neutral. At present, these drugs acting on the incretin system are not indicated for obesity but for glycaemic control in patients with type 2 diabetes who are already receiving metformin therapy.

2.4 Pramlintide

Pramlintide is an analogue of amylin that is approved for use in addition to insulin in patients

with diabetes. Amylin, like insulin, is secreted from pancreatic β cells, but in reduced amounts in type 2 diabetes. Subcutaneous injection of pramlintide lowers blood glucose, reduces glucagon secretion, slows gastric emptying and promotes satiety. It lowers bodyweight by 2.1 kg after 6 weeks of therapy[73] and 3.7 kg after 16 weeks of therapy.[74]

2.5 Rimonabant

Antagonists of the cannabinoid type 1 receptor suppress appetite and induce weight loss.[75] Rimonabant was the first drug in this new class that was marketed. In clinical studies, it was well tolerated, induced weight loss and improved the metabolic profile.[76-78] Rimonabant has never been approved by the FDA, but in April 2006 the EMA approved its use as an adjunct to diet and exercise in treating obesity. After marketing, there were many reports of psychiatric adverse effects such as depression, which eventually led to its withdrawal in October 2008.[79] There are other cannabinoid receptor antagonists, such as taranabant, that have been developed but, at present, the potential and future of this drug class remain unclear.

3. The Future of Drugs for Obesity

There are currently a large number of drugs for the treatment of obesity undergoing research and development. New drugs being evaluated in clinical trials include APD-365, CD-945,598, MK-0364, ATL-962, GT 389-255, AOD9604, leptin, peptide $YY_{(3–36)}$ and TM30338.[80,81] Qnexa (combination of phentermine and topiramate) and Contrave (combination of naltrexone sustained release [SR] and bupropion SR) are currently awaiting FDA approval. It is hoped that some of these drugs will eventually prove to be efficacious and safe. It has been said that ''worldwide government regulations and treatment guidelines have been somewhat instrumental in impeding the development of these drugs''.[30] However, in light of the chequered history of anti-obesity drugs (table I), they need to be carefully evaluated for their long-term safety and efficacy.

4. Conclusions

Obesity is a major health problem worldwide. Sibutramine reduces bodyweight by a modest amount over a period of 6–12 months but causes a small increase in blood pressure and heart rate. The SCOUT study showed increased numbers of cardiovascular events in the sibutramine arm compared with the placebo arm, which prompted the drug to be withdrawn. Options for patients who have been taking sibutramine are very limited. Lifestyle changes, including diet, physical activity and behavioural modification, are critically important in the management of obesity. For those who do not respond adequately to these measures, pharmacological treatment is needed. The only anti-obesity drug for long-term use is orlistat, which is often not tolerated. There is an obvious need to develop new anti-obesity drugs, but these need to be carefully evaluated for their long-term benefits and safety.

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