



Sibutramine: gone, but not forgotten

The licence for the anti-obesity drug sibutramine has been suspended in Europe: a decision that casts considerable doubt on the ability of the European Medicines Agency (EMA) to correctly apply scientific principles. Preliminary, unpublished data from the Sibutramine Cardiovascular Outcomes (SCOUT) trial have revealed a possible significant increase in cardiovascular events, in a group of individuals for whom the drug has always been contraindicated: those with cardiovascular disease (CVD). The assumption has been made by the EMA that everyone with a BMI of ≥ 27 must have CVD, meaning that nobody in Europe is allowed to take sibutramine, despite a decade of use in real life practice, and a full portfolio of clinical trials, which revealed no danger signals. The concept of primary versus secondary prevention has been arrogantly disregarded by the Agency. Although the possible rise in cardiovascular events in this high-risk group is troubling, and suggests that the known sporadic increases in blood pressure and pulse rate may be more sinister than was previously thought, the evidence profile for the use of sibutramine in obese individuals without CVD is still strongly favourable.

Sibutramine

Sibutramine inhibits noradrenaline and serotonin reuptake, leading to improved satiety and subsequent reduction in food intake. Additionally, it attenuates the reduction in metabolic rate which occurs with weight loss. Randomised placebo-controlled studies^{1–4} have shown that sibutramine alongside lifestyle and dietary advice can induce dose-dependent weight loss of 5–10% in most patients,² including those with type 2 diabetes.^{3,4} It increases almost four-fold the proportion of patients sustaining $>5\%$ weight loss.⁵ There is evidence for improvements in insulin resistance and lipids, some studies suggesting that it increases serum high-density lipoprotein (HDL) cholesterol independently of weight loss,⁶ and there is also evidence that sibutramine-induced weight loss causes regression of left ventricular mass independent of blood pressure.⁷ It is contraindicated in patients suffering from heart disease, congestive heart failure, cardiac arrhythmia, stroke, or uncontrolled hypertension. The summary of product characteristics (SPC) describes a mean increase in resting systolic and diastolic blood pressures of 2–3mmHg and a mean increase in heart rate of 3–7bpm.⁸

SCOUT trial

SCOUT is a multi-centre, double-blind, placebo-controlled trial⁹ designed to evaluate the potential benefits of weight management on cardiovascular outcomes in overweight and obese patients at high risk for cardiovascular events, with diabetes and/or overt cardiovascular disease. It is a post-approval commitment to the European regulatory authorities prompted by concern that sibutramine's mode of action could exacerbate hypertension, although the agent would be contraindicated in clinical practice for most patients eligible for

SCOUT. Over 9000 patients were randomised in a double-blind fashion to receive either sibutramine or matching placebo. Unlike most obesity trials, which include patients aged 18–65, SCOUT was designed to assess higher-risk patients and was restricted to less healthy, and older (aged 55 years or more), individuals. Paradoxically, data from the six-week lead-in period, when all patients received sibutramine 10mg, showed greater median falls in blood pressure and smaller increases in heart rate in the high-risk SCOUT population compared to the 'current labelled' population despite similar weight loss.¹⁰ Preliminary results of the study are said to show that patients treated with sibutramine may have experienced a 16% increased risk of cardiovascular events such as myocardial infarction and stroke compared with placebo-treated patients (hazard ratio 1.161 [95% CI 1.029–1.311]; $p=0.016$).

Suspension of sibutramine

As the obesity crisis gets bigger, the choice of methods for treating it gets smaller: effective drugs are being withdrawn and bariatric surgery rationed by postcode lottery. Ironically, the amphetamine-related drugs phentermine and diethylpropion are still available on a controlled, named-patient basis, despite adverse associations including addiction, abuse and severe side effects; their 40-year-old drug trials were under-powered and stunted, and would not be given a shred of credibility today. Because of the suspension of sibutramine and, in 2008, rimonabant, the poorly monitored use of amphetamine drugs in unaccredited private slimming clinics is likely to increase.

An estimated 86 000 people in the UK alone will have been forced to stop sibutramine, at least temporarily; most will already have tried and failed on orlistat, leaving no option but weight regain and a worsening risk profile. Although some of this cohort will undoubtedly have been prescribed sibutramine in contravention of National Institute for Health and Clinical Excellence (NICE) guidelines, most will have been free of CVD, will have settled on sibutramine, without side effects, and will have been appropriately monitored for increases in blood pressure and pulse rate. The withdrawal of rimonabant in 2008 not only robbed clinicians of a highly effective drug in obesity and diabetes (a 1.9% reduction of HbA_{1c} in patients over 8.5% in the SERENADE trial), but also brought global research into the hitherto unexplored endocannabinoid system to a shuddering halt. In the UK, rimonabant was being prescribed responsibly, for patients with complicated obesity often with overt type 2 diabetes, by clinicians with a special interest in the subjects, according to its SPC and NICE guidelines which warned against prescribing it to anyone with a history of mental health problems, thereby avoiding the majority of problems. Residual adverse events were generally limited to mood changes such as boredom or irritability. Rimonabant could have been saved by restricting its use to accredited prescribers, in the same way that



Roaccutane – a drug with a notorious side-effect profile, especially with regard to mental health – is used effectively by dermatologists. A ban on phentermine and diethylpropion was overturned in 2005, because of a legal loophole which insisted that it was not acceptable to use the same evidence to ban a drug as that which was used to license it in the first place; on the other hand, in the case of rimonabant the EMA did use the same basic information utilised to license the drug (and used by NICE to appraise rimonabant in a positive light) to ban it. With sibutramine the authorities have ignored the safety data first used to license the drug in favour of new evidence, based on the wrong cohort of patients.

The obesity paradox

Abdominal obesity is a major cardiovascular risk factor, yet overweight and obesity at the time of an event may predict more favourable outcomes. A 2009 retrospective study¹¹ illustrated the paradox, looking at patients who had suffered major coronary events and had undergone cardiac rehabilitation and exercise training (CRET), assessing the role of deliberate weight loss. It concluded that purposeful weight loss with CRET in overweight/obese coronary patients is associated with only a non-significant trend for lower mortality despite being characterised by marked improvements in obesity indices, exercise capacity and plasma lipids, and that mortality at three years was considerably lower in the baseline overweight/obese group than in patients with baseline BMI <25kg/m², as well as in those with high baseline fat compared with those with low fat. Thus, excess weight seems to be a risk factor for CVD but, after an event, excess weight might be protective. A separate 2009 paper¹² subdivided men into four categories:

- Those of normal weight in middle age whose weight remained normal into old age.
- Those with a BMI >25 in middle age who remained overweight into old age.
- Men who moved from normal weight to overweight.
- Men who moved from overweight to normal weight.

It reported that the fourth group had the highest CVD risk in mid-life, and more co-morbidities and greatest total mortality in late life, even more so than those who started overweight and remained so. The authors offered the explanation that there may be a cardiological reason for frailty and weight loss. The SCOUT interim results might appear to confirm the obesity paradox; the induction of weight loss after an event possibly being harmful, and eliminating the protective effect of excess weight in confirmed CVD patients. However, that does not alter the fact that weight reduction in an otherwise healthy person will reduce their risk of a first event. There has been considerable criticism of papers which purport to illustrate the paradox, particularly in not allowing for the possibility of weight being lost because of co-morbid or cardiological conditions, which might accentuate the link between lower weight and pathology. A 2010 paper has shed further light, concluding that overweight and obese

men had increased longevity only if they registered high levels of fitness.¹³ Another paper, published in February this year, also questions the validity of whether or not this 'reverse epidemiology' is attributable to a real protective effect of high body fat mass.¹⁴

In the US, the Food and Drug Administration has re-assessed sibutramine, and simply resorted to demanding label changes. The 'Dear Doctor' letter announcing the suspension of sibutramine in the UK stated: 'Although most of the patients enrolled within SCOUT are contraindicated from being treated with sibutramine under normal conditions of use, the Committee considered the cardiovascular risk to be relevant to normal clinical use because it is not always possible to identify underlying cardiovascular disease in patients who are obese or overweight. Therefore further restrictions on the use of sibutramine would be unlikely to reduce the risk to an acceptable level.' This was stated despite the fact that a portfolio of clinical trials, and almost a decade of real-life usage, clearly demonstrated an 'acceptable level of risk'. The EMA has failed to recognise the difference between primary and secondary prevention, designating all fat people as cardiovascular victims.

It could feasibly be that excess weight is protective after a cardiovascular event, and it could also be that sibutramine genuinely increases risk because of some unidentified covert mechanism, just as torcetrapib increases HDL massively, but is linked with excess rather than reduced mortality. However, sibutramine should not have been suspended until the conundrum has been properly dissected, in order that patient safety is foremost. The aim of the suspension was to reduce patients' exposure to risk; the unforeseen, although perfectly foreseeable, consequence has been to increase patients' risk because of the discontinuation of the agent. There are disparate results surrounding sibutramine, but the landmark five-year SCOUT study about to be presented will clarify who should be taking the drug, and who should not.

The pipeline is crammed with agents which may soon be licensed for the management of obesity: liraglutide, dapagliflozin, lorcaserin, Contrave, Empatic, tesofensine and others; but agents are needed urgently to combat the current epidemic. The rest of the world can prescribe sibutramine, but Europe cannot. Such a momentous decision as the suspension of a proven agent should have a solid evidence foundation, and not rely on unsubstantiated rumour.

David Haslam, MB, BS, General Practitioner, Physician in Obesity Medicine, Centre for Obesity Research, Luton and Dunstable Hospital, and Chair of the National Obesity Forum, UK

Conflict of interest statement

There are no conflicts of interest.

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References are available online at www.practicaldiabetesinternational.com.



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