

# O B E S I T Y

## *the 21st century disease*

Obesity will be the leading cause of death and disability in the 21st century. This epidemic is largely attributable to increasingly sedentary lifestyles and the abundance of tasty, high-fat foods. Obesity increases the risk of developing Type 2 diabetes, coronary heart disease, hypertension, osteoarthritis and some forms of cancer. To date, the success of prescription medicines for obesity has been limited. This article discusses the current approaches by the pharmaceutical industry in the search for blockbuster fat-busting drugs.

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Obesity will be the leading cause of death and disability this century. It has been declared by the World Health Organisation (WHO) as the largest global chronic health problem in adults which, by 2025, will emerge as a more serious world problem than malnutrition.

The health risks and economic costs associated with obesity are profound. Epidemiological data show that obesity substantially increases the risk of developing Type 2 diabetes, coronary heart disease, hypertension, osteoarthritis and some forms of cancer. **Figure 1** shows the reduced life expectancy associated with increasing severity of obesity.

The incidence of obesity is increasing markedly in developed countries, although the highest rates of increase are now in under-developed countries. It is estimated that upwards of 250 million people worldwide have reached a weight that is classified as clinically obese. While the UK has one of the highest rates of obesity in Europe, there is a much higher prevalence of obesity in the US, which is predicted to continue to increase dramatically (**Figures 2 and 3**).

If these widely quoted statistics are accurate then a significant proportion of readers should have a deep personal interest in this subject!

In December 2001 the US Surgeon General issued a warning of the significantly increased risk of death from obesity. Thus, 300,000 Americans a year die from illnesses caused or worsened by obesity, a death toll that may soon overtake tobacco as the chief cause of preventable deaths.

It is estimated that treating conditions associated with obesity costs the US healthcare system more than \$100 billion annually<sup>1</sup>. The expanding patient population associated with an increasing drive to reduce health care costs will result in massive growth of the market for obesity therapies.

Although it is predicted that the obesity market will emerge as a major global drug market in the next 5-10 years, growth to date has been relatively small compared to that seen in other markets (largely due to an absence of effective drug therapies). The market potential for obesity drugs is better reflected in the multi-billion dollar market (estimated at \$33 billion in the early 1990s<sup>2</sup>) for slimming products and diet foods, than in the modest \$870 million of prescription sales for anti-obesity drugs in 2000. IMS predicts that the obesity market will grow by >20% per year for the next seven years, representing one of the fastest growing markets for the pharmaceutical industry.

**Definition of obesity**

In simple terms, obesity occurs when an individual's food intake exceeds their energy expenditure. It is defined by WHO as a condition of abnormal or excessive fat accumulation in adipose tissue, to the extent that health may be impaired. The distribution as well as the amount of fat has health implications. Women typically collect fat in their hips and buttocks, giving them a 'pear' shape, whereas men usually build up fat around their waist, leading to the development of an 'apple' shape. Fat carried mainly around the waist is more likely to lead to obesity-related health problems.

Whether someone is classified as overweight or obese is generally determined on the basis of their body mass index (BMI), calculated by dividing body weight (kg) by height (metres) squared as outlined in Figure 4.

A potential problem of BMI is that it does not differentiate between the relative proportions of the body mass that are muscle and fat. Thus, certain athletes with a high muscle and low fat mass and a healthy lifestyle could be defined as unhealthy and obese using the BMI. Therefore, it is prudent to use more than one measure of obesity and other indicators that have been widely used are waist and neck circumference for men and hip circumference for women.

Obesity does not have a single cause and is multifactorial in nature. Factors that have been cited include dysfunctional biological mediators of weight regulation, genetic influences that predispose to weight gain, ageing, sociocultural and/or environmental influences and excessive dietary fat intake and low levels of physical activity, commensurate with affluent industrialised lifestyles.

The rapid increase of obesity to epidemic proportions has led to a significant shift in medical opinion. In the past obesity was often regarded as a 'lifestyle' disorder – a result of overeating and laziness; today, the medical community recognises obesity to be a serious disease that manifests life-threatening comorbidities if left untreated.

**Treatment of obesity**

Obesity is a particularly challenging medical condition to treat because of its complex aetiology.

There are three recognised approaches to the treatment of obesity, which can be either applied alone or in combination; these are: diet and exercise therapy, surgical intervention and drug treatment. While diet and exercise to induce weight

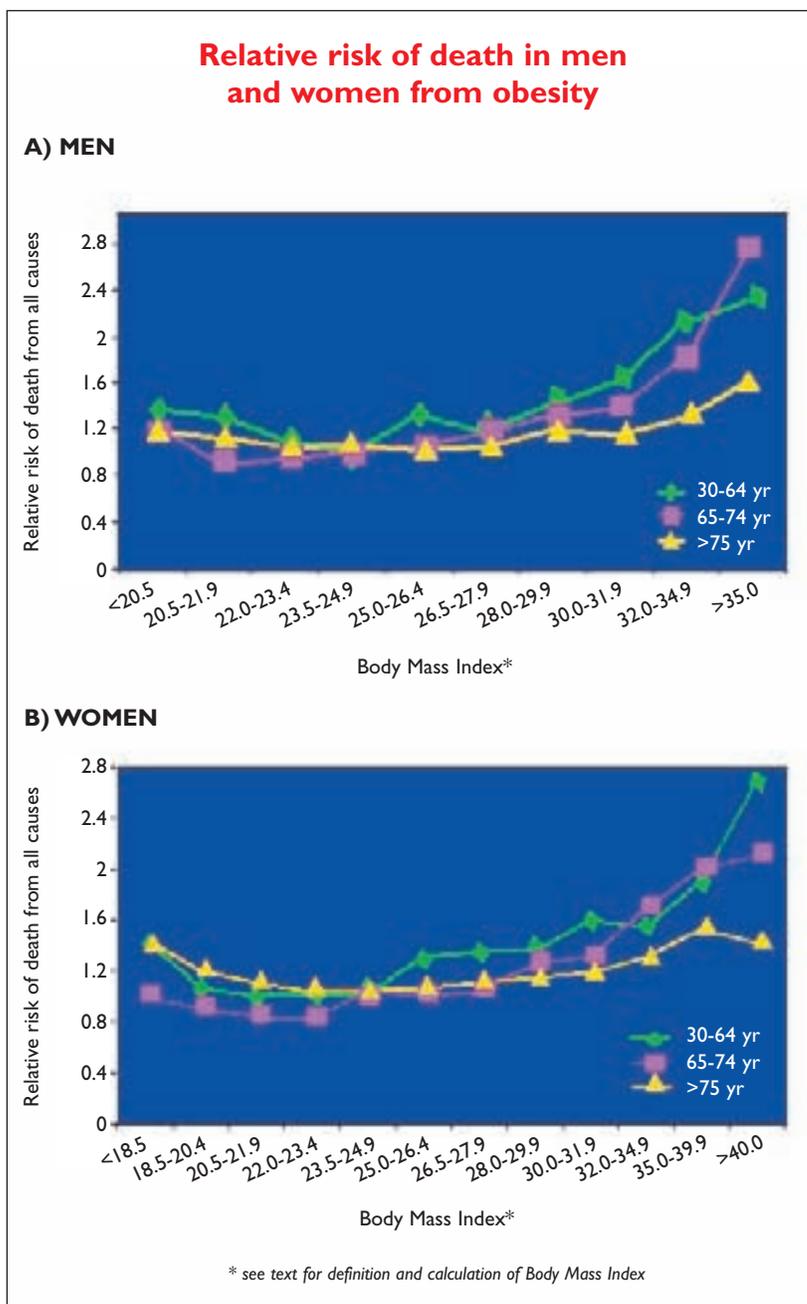


Figure 1

loss is the first-line treatment, it is generally unsuccessful for the majority of individuals in the long term. Many consumer surveys have found that at any one time a large percentage of the population is dieting; yet obesity prevalence continues to rise rapidly, as illustrated in Figure 3. Only a minority of patients succeed in maintaining their weight loss.

Surgery is an effective treatment for obesity but is considered unacceptable by most patients. Therefore drug therapies are viewed as increasingly important as an aid to dietary approaches.

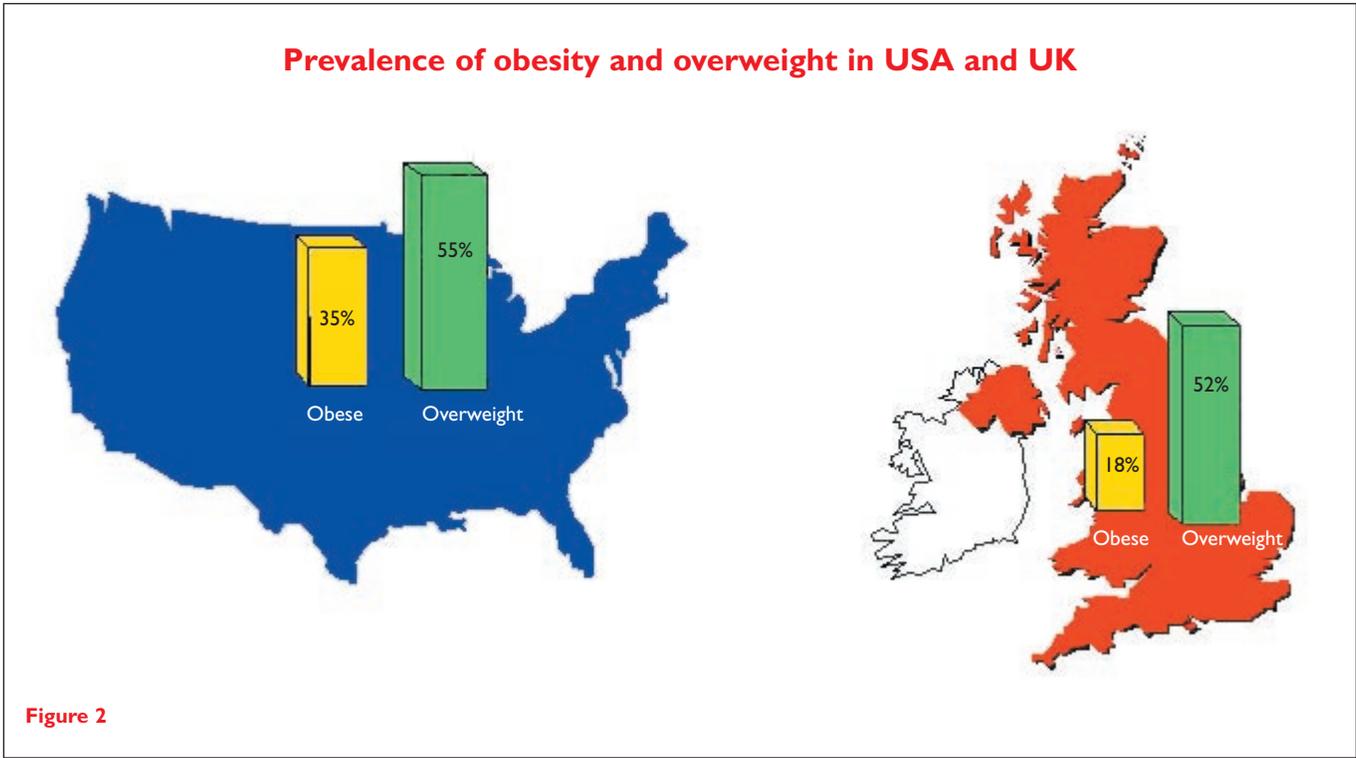


Figure 2

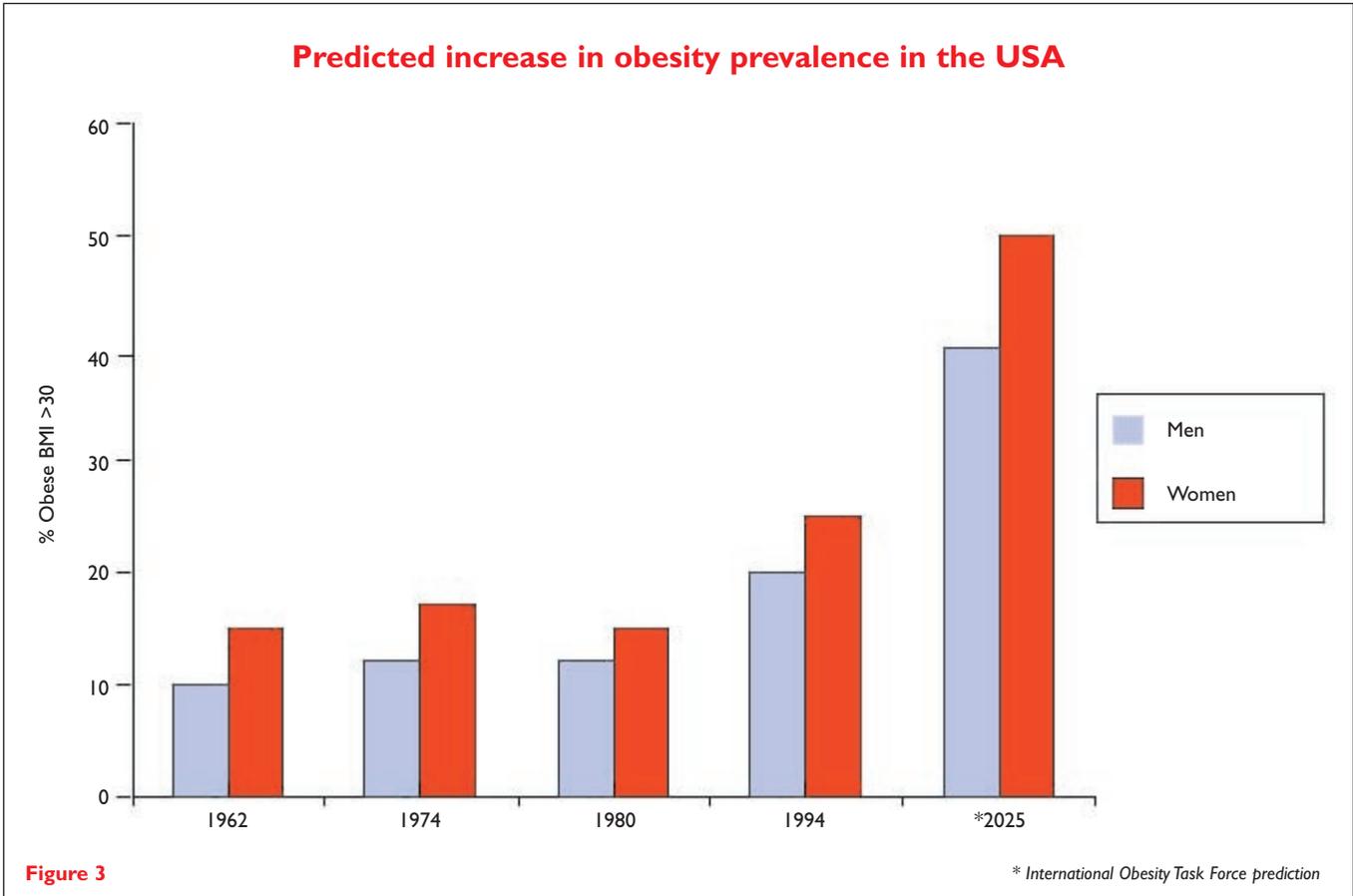


Figure 3

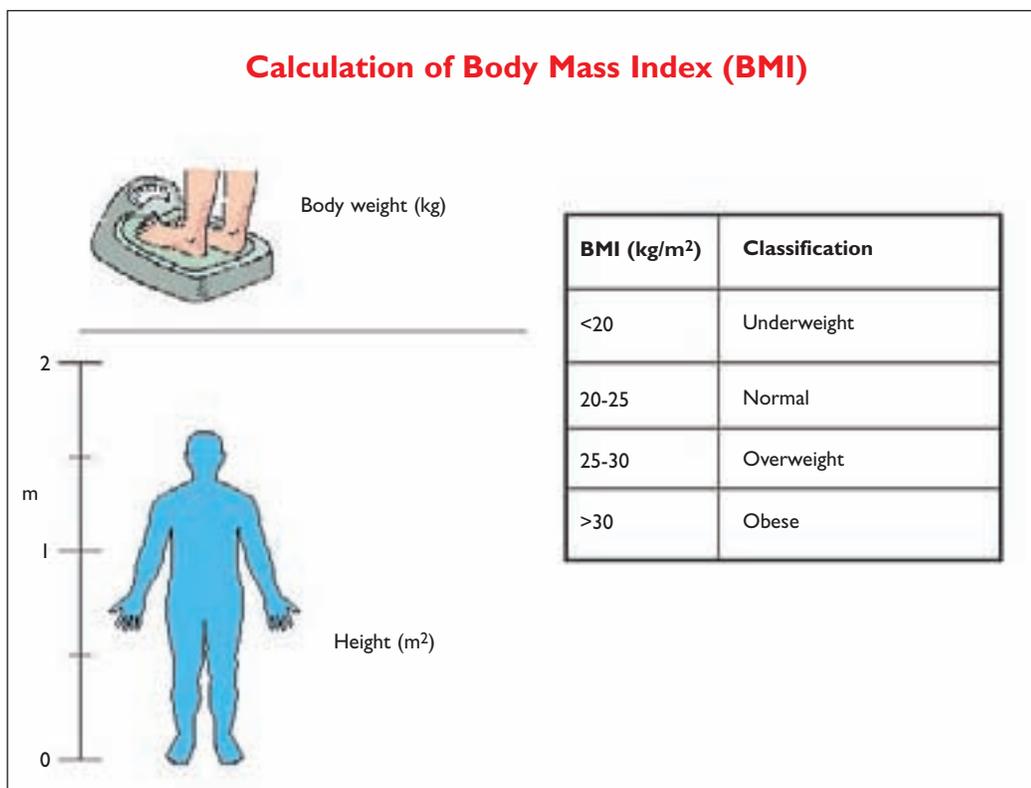


Figure 4

**Current drug treatments**

The drug treatment of obesity is in its infancy and until recently the disease has been low on the drug industry’s list of priorities, as it has tended to be viewed as a simple problem of gluttony in a time of plenty.

At present there is a paucity of drug treatment options for obesity and there is a history of past failures in trying to overcome the high regulatory hurdles of safety and efficacy that are required for an acceptable agent. Two products have recently been introduced into the market, and both have had limited success, Xenical™ from Roche and Merida™/Reductil™ from Abbott.

Orlistat (Xenical™), a lipase inhibitor, works peripherally by preventing the breakdown, and hence absorption, of fat in the gastrointestinal system. Inhibition of lipase causes about one-third of fat to pass through the gastrointestinal tract and be excreted. Xenical is the biggest selling anti-obesity product, with sales in 2001 of \$600 million, and a 50-97% market share in the seven major markets (IMS Health). However, orlistat is associated with unpleasant side-effects, including the production of oily stools, which can lead to faecal incontinence. Hence sales of the drug have yet to reach the blockbuster levels that were originally predicted.

Sibutramine (Reductil™/Meridia™), a mixed

serotonin (5-HT)-noradrenaline reuptake blocker, boosts 5-HT and noradrenaline levels by inhibiting reuptake of the neurotransmitters. The increased levels of 5-HT and noradrenaline decrease food intake by their action on brain mechanisms of appetite and satiety. The inhibition of the reuptake of noradrenaline also increases resting energy expenditure, so patients burn more calories. However, sales of sibutramine have also been modest (\$200 million in 2001), due mainly to its side effects of increased heart rate and blood pressure associated with increased levels of noradrenaline in the cardiovascular system. The Italian regulatory authorities have recently suspended all sales of sibutramine after reports of serious cardiac side-effects, including two deaths, in patients taking the product.

**Past failures**

The 5-HT releaser and reuptake inhibitor, d-fenfluramine (Redux™), was launched in the USA in 1996 by American Home Products (AHP) and attracted huge media interest as it was the first new anti-obesity agent approved by the FDA for more than 20 years. Initially there were strong sales, but in a dramatic development, Redux was withdrawn from the market in September 1997 following reports of a causal link with pulmonary hypertension and heart valve defects. AHP agreed to settlements, for the

class action litigation over Redux, which cost the company billions of dollars.

Another high profile disappointment in the obesity field has been leptin, a protein hormone secreted by fat cells that acts centrally on receptors in the hypothalamic region of the brain. It was identified in 1994 as a critical mediator in the regulation of body fat and body weight in mice<sup>3</sup>, and its discovery is viewed as a landmark finding in obesity research. Leptin levels rise as body fat increases, leading to a reduction in food intake and an increase in metabolism, and hence weight loss. The biotechnology company, Amgen, paid \$25 million upfront for the rights to leptin before knowing whether it had any application in humans. In initial clinical trials, the effect of leptin on body weight was minimal, which led to a reassessment of its role in weight regulation in humans. It is now known that most obese people have high levels of leptin, suggesting that they may have developed a form of resistance mechanism. Amgen are, however, still targeting the leptin pathway through small molecular weight leptin analogues (Table 1).

### Potential new treatments

As Table 1 shows, there is a relative paucity of new agents in clinical development for obesity as compared to other indications. For example, in Parkinson's disease, a market of similar value to

current sales of obesity prescription products, there are 24 novel entities in clinical development, yet the predicted market growth in Parkinson's disease is much smaller than obesity.

The limited number of compounds in clinical development is partly due to the previous negative industry view of the indication. In addition, the disappointment of product withdrawals, failures of drugs in development and the limited sales of sibutramine and orlistat have had a significant influence on progress. Thus the competitive position for new agents is very good, provided they meet the high standards of safety and efficacy that will be required.

A number of compounds currently in development for obesity were originally investigated in other indications and were switched to obesity following the observation that patients lost weight during clinical studies. Axokine was originally in development for the treatment of amyotrophic lateral sclerosis (ALS), NNC-90-1170 for Type 2 diabetes and ecopipam for schizophrenia. Indeed, orlistat and sibutramine were also originally developed in alternative indications, as anti-infective and anti-depressant agents respectively. Prozac<sup>TM</sup> was in development for obesity but failed after a 12-month trial. Pfizer has also investigated its anti-depressant, Zoloft<sup>TM</sup>, in obesity but development is believed to have been halted.

**Table 1**  
**Compounds in development for obesity**

COMPOUND	MECHANISM	COMPANY
<b>Phase III</b> SR141716 Axokine <sup>TM</sup>	Cannabinoid receptor 1 (CB <sub>1</sub> ) antagonist Ciliary neurotrophic factor (CNTF)	Sanofi-Synthelabo Regeneron
<b>Phase II</b> NNC-90-1170 Not disclosed Ecopipam P57 BVT.933	Glucagon-like peptide 1 (GLP-1) Leptin analogue Dopamine (D <sub>1</sub> /D <sub>5</sub> ) receptor antagonist Not disclosed 5-HT <sub>2C</sub> receptor agonist	Novo Nordisk Amgen Schering-Plough Phytopharm/Pfizer Biovitrum
<b>Phase I</b> ATL-962 GI181771 SB418790	Lipase inhibitor Cholecystokinin-A (CCK-A) receptor agonist B3 adrenoceptor agonist	Alizyme GSK GSK
<b>Pre-clinical</b> VR 1065 Not disclosed Not disclosed Not disclosed	5-HT <sub>2C</sub> receptor agonist Melanocortin 4 (MC-4) receptor agonist Neuropeptide Y antagonist Neuropeptide Y antagonist	Vernalis/Roche Millennium BMS Pfizer

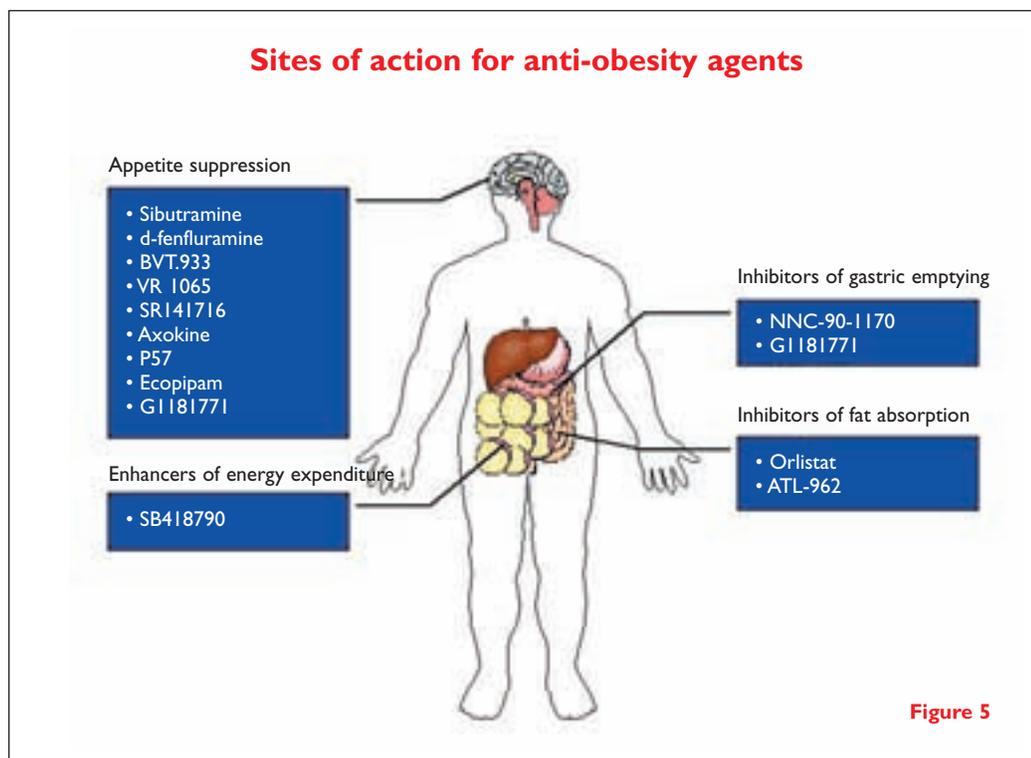


Figure 5 outlines the site of action of compounds in development for obesity. Axokine receptors are located in the same area of the brain as leptin receptors and are thought to trigger a similar set of mechanisms to reset the feeding/satiety balance. There were reported instances of toxicity associated with the trials of Axokine in ALS, which the company has dismissed as irrelevant to the obesity indication.

Cannabis and endogenous cannabinoids are appetite stimulants and cannabinoid receptor (CB<sub>1</sub>) antagonists decrease food intake in animals. Sanofi-Synthelabo is investigating the use of CB<sub>1</sub> receptor antagonists for obesity and significant weight loss has been observed in patients in Phase II trials.

P57 is an oral anorectic agent derived from the African Hoodia plant being developed by Phytopharm and partnered with Pfizer in 1998. The mechanism of action of the compound has not been revealed but is claimed to be “entirely new”.

GlaxoSmithKline has two anti-obesity products in Phase I clinical trials: G1181771, a cholecystokinin-A (CCK<sub>A</sub>) receptor agonist and GW418790 a  $\beta$ 3 adrenoceptor agonist. CCK is a neuropeptide released in the gastrointestinal tract in response to food. It is thought that CCK<sub>A</sub> receptors in the gastrointestinal tract and in the brain may contribute to satiety.  $\beta$ 3 adrenoceptor agonists work by a peripheral mechanism on fat cells to stimulate fat mobilisation and thereby decrease body weight. It remains

to be determined in clinical trials whether this will be an effective long-term weight control therapy as patients may increase their food consumption to compensate for the increase in metabolic rate.

Alizyme is developing a lipase inhibitor, ATL-962, which is unlikely to inhibit fat absorption to a higher degree or be better tolerated than orlistat.

As outlined above, body weight regulation is extremely complex, with multiple pathways involved that are redundant and compensatory. The challenge is to identify individual pathways that are critical and can be manipulated to produce robust long-term weight control.

Of the numerous pharmacological strategies for appetite control investigated to date, the only one that has proven efficacy in producing weight loss, and thus appears to be a critical pathway is the brain 5-HT system. 5-HT exerts its action on food intake through different subtypes of 5-HT receptor<sup>4</sup>. Recent studies have identified the 5-HT<sub>2C</sub> receptor as a critical mediator of satiety induced by 5-HT. Transgenic mice with a targeted deletion of the 5-HT<sub>2C</sub> receptor (‘knockout’ mice) overeat and become obese, and are resistant to the effects of the anorectic, d-fenfluramine<sup>5</sup>. Similarly the decrease in food intake of rats given d-fenfluramine is attenuated by administration of selective 5-HT<sub>2C</sub> receptor antagonists<sup>6</sup>, as illustrated in Figure 6.

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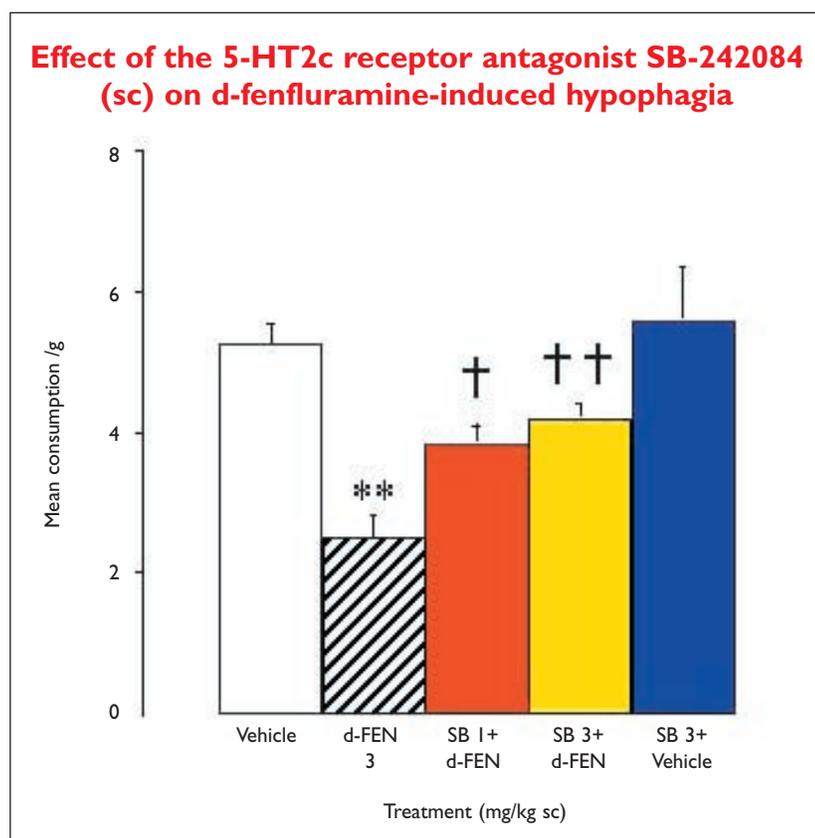
Therefore, selective 5-HT<sub>2C</sub> receptor agonists are being investigated by a number of companies as potential novel anorectic agents. The Swedish company Biovitrum and the UK company Vernalis, in partnership with Roche, have the most advanced programmes in the field. Biovitrum recently announced positive Phase IIa results for BVT.933 in a double-blind placebo-controlled study in 154 obese patients.

The spectre of valvular heart disease associated with serotonergic mechanisms means that any novel 5-HT treatment will be subject to particular scrutiny by the regulatory authorities. However, selective 5-HT<sub>2C</sub> receptor agonists are likely to have an improved cardiovascular side-effect profile compared to d-fenfluramine and sibutramine since 5-HT<sub>2C</sub> receptors are found only in the brain and not in the heart and lung.

### Early stage research

The genomics revolution has led to a fresh wave of research in obesity and significant progress in the identification of novel targets for anti-obesity agents. The question to be answered over the next few years is which of these novel mechanisms (often initially found in obese rodents) are relevant to human obesity.

Figure 6



Although genomically derived drugs are probably some way off, there are a large number of approaches to appetite control in late preclinical research derived from classical pharmacology. These include neuropeptide Y antagonists<sup>7</sup> and melanocortin receptor agonists<sup>8</sup>. New targets for drugs that increase energy expenditure are uncoupling protein 2 (UCP2) and 3 (UCP3)<sup>9</sup>. These proteins are expressed peripherally and when activated increase thermogenesis leading to reduced storage of fat.

Whether these targets will translate into new therapies remains to be seen as they are only a single component of complex signalling pathways that control food intake, energy stores and hunger/satiety, with a number of counter-regulatory mechanisms and feedback loops.

### Conclusion

Obesity is now generally recognised as a life-threatening disease, which is growing at a rate that poses a significant threat to healthcare systems worldwide. The renewed interest in obesity from the pharmaceutical industry has made the search for novel therapies one of the most exciting and challenging areas for drug discovery.

Long-term weight loss is never likely to be as simple as popping a pill, but the ultimate therapeutic goal in obesity is not just weight loss but a reduction in mortality and morbidity from associated diseases.

While a clear winner has yet to emerge in the race to develop a safe and effective anti-obesity agent, a company successful in doing so will have billions of dollars in sales almost guaranteed. **DDW**

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