Present and future pharmacological approaches

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There is evidence that drugs altering food intake such as dexfenfluramine, sibutramine and orlistat have useful therapeutic effects, with an acceptable side effect profile. 'Thermogenic' drugs, such as ephedrine and caffeine, are also effective, but less well tolerated and may, in any case, work by producing anorexia. The state of drug treatment for obesity now is similar to the early days of anti-hypertensive treatment in the 1960s when reserpine, ganglion blockers and non-selective adrenergic blocker were all that was available. There is considerable reason for optimism that the next 10 years will bring better treatments for the obese.

Concepts of pharmacological management

Previous chapters have highlighted the health risks and diseases that result from obesity. In such circumstances one would expect pharmacological treatment to be welcomed as a useful adjunct to other treatment modalities. Yet, for many years, drug treatment of obesity has been regarded as a hallmark of poor clinical practice. Until recently the British National Formulary stated: 'drugs can play only a limited role and should never be used as the sole element of treatment; their effects tend to be disappointing'. In 1995, the Medicines Control Agency proposed to restrict the use of 'medicinal products which act upon the central nervous system so as to suppress the appetite' to those with a new definition of 'severe obesity based up a definition of a body mass index of greater or equal to 35 kg/m$^2$', because 'the products are recognised as having the potential for creating dependency and have a range of severe side effects'. A recent paper auditing prescribing performance of general practitioners, marked the prescription of appetite suppressants as poorly as prescribing more than 60% of drugs non-generically.

Why are anti-obesity drugs held in disrepute? The reasons for this appear to arise, in part, because many fail to recognise the importance of obesity both as a disease, and as a cause of disease. In part there has also been a long-standing mis-evaluation of the pharmacology of anti-obesity drugs. The medical establishment has been slow to accept the health implications of obesity and has shown many of the same prejudices as...
the public in stigmatising obese patients. Doctors are more likely regard obese people as 'weak-willed... and awkward' than lean counterparts. With this background, in which obesity is the patient's 'own fault', it is easy to conclude that the obese are not 'worthy of drug treatment' and thus undervalue drug intervention. Accepting obesity as disease, and recognising the limitations of non-drug treatments such as diet, exercise and behaviour modification, inevitably leads to the conclusion that effective drug treatments are needed. There is nothing unusual about such a conclusion, since a similar one has existed concerning many other chronic diseases, such as hypertension and diabetes mellitus. Both these require pharmacological intervention for long-term control. The spectrum of body weight from serious disease (obesity), medical risk (overweight), healthy (normal), to underweight (thin), opens it to the pressures of fashion and desire for cosmetic change (slimming). The use of drugs for 'treating' normal or thin people is widespread and clearly undermines the value of the same drugs when used to treat obesity. The pejorative and dismissive collective noun of slimming pills reflects such a prejudice against this therapeutic area.

It is encouraging that the recent greater understanding of the physiological basis, and the health implications of obesity, together with recognition of the limitations of existing non-drug treatment, is gradually dispelling this era of negativity. A number of consensus statements—from bodies such as the North American Association for the Study of Obesity (NAASO) and the UK Association for the Study of Obesity (ASO)—have recognised the need and logic of drug treatment. In Scotland, the Scottish Intercollegiate Guidelines Network (SIGN) has highlighted the need for drug treatment 'in selected patients'. Official and regulatory bodies are also increasingly adopting more realistic attitudes to drug treatment. The UK Medicines Commission recently concluded in its review of anorectic medication, that 'the criteria applied to the use of appetite suppressants should be similar to those applied to the treatment of other chronic relapsing disorders'. In the US, the Food and Drugs Administration (FDA) has issued guidance concerning the standards of clinical efficacy they wish to see for registering new anti-obesity treatments (Table 1). The FDA has recently licensed or approved two centrally acting anorectic drugs, dexfenfluramine and sibutramine. These changes have lead to an explosion of interest and research by the pharmaceutical industry, such that a large number of anti-obesity drugs are in development.

A traditional methodology of drug development applied to obesity might hypothesise that a single molecule, with a well defined mechanism of action at the appropriate molecular or biochemical target, would reverse the causes of excessive weight gain and restore a healthy body weight. The inherent complexity of body weight regulation makes such a
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Table 1  FDA guidance on the development of drugs for treating obesity

- Encourage development of new drugs that will be efficacious, safe, for specific aetiology
- Foster development for long-term or indefinite use
- Demonstrate benefit greater than with diet, exercise, behaviour modification alone
- Weight loss on drug treatment at 12 months exceeds placebo by at least 5% of baseline weight
- Significant improvement in co-morbid conditions and/or quality of life
- Exhibit safety commensurate with efficacy and projected duration of use

goal unrealistic, and it seems that a drug to ‘cure’ obesity is much less likely than a cure for diabetes mellitus or hypertension. In obesity treatment, drugs should be seen not as ‘magic bullets’, but as an adjunct to behavioural change. Treatment should aim to control or ameliorate the disease, relieve symptoms and enhance life quality and expectancy. To achieve these goals, a drug must at least induce, accelerate or help maintain weight loss; preferably it will do all three. Since patients present with a wide range in the severity of their obesity, an ideal anti-obesity drug would produce dose-related weight loss with a wide dose-response range. There has, however, been a common tendency to misinterpret the effects of anti-obesity drugs. Figure 1 shows schematic graphs of the fall in weight with an anti-obesity drug, and the fall in blood glucose with an anti-diabetic medication. Table 2 shows how misinterpretation of these outcomes can bias against recognising the worth of an anti-obesity drug. Thus there is no requirement for an anti-hypertensive drug to lower blood-pressure progressively and indefinitely, nor for it to be effective after it is discontinued. Asking whether it is better that an obese person takes a drug and stays 10% lighter, or not take the drug and remain 10% heavier is a simple way of demonstrating the logic of drug treatment. At present, there is a reliance of surrogate measures of benefit (weight loss, reduction in risk factors such as blood-pressure, dyslipaemia, etc.) rather than hard outcome measures, such as mortality and morbidity. Evidence does exist, however, for the benefits of modest weight loss insufficient to normalise body weight\textsuperscript{10-13}. However, in the quest for hard measures of therapeutic efficacy, softer measures of benefit, such as improved quality of life, must not be discounted or ignored. As for any treatment to be given long-term, there is a need for long duration studies of efficacy and safety, and this does pose considerable practical difficulties both in designing controlled trials, and in funding them\textsuperscript{14}.

The principles of treating obesity with drugs, and the onus to prescribe wisely, therefore do not differ from any other disease. Drugs must be shown to be safe and effective with a high benefit to risk ratio\textsuperscript{15}. At an individual level, treatment efficacy must be established and monitored. with the patient being seen regularly. Since the goal of treatment is
weight loss maintenance, treatment will need to be continued long-term, although periods of drug withdrawal are likely to be helpful in establishing that treatment really does need to be continued.

In developing drug treatments for obesity, it would be rational to look for drugs that act on those components of physiology or pathophysiology that are perturbed. Epidemiological evidence suggests that it is, in population terms, the combination of low activity levels with a ready food supply, high in fat, that has lead to the rapid increase in
Table 2  Interpretation of patterns of weight loss and blood-glucose lowering (Fig 1A,B)

<table>
<thead>
<tr>
<th></th>
<th>Anti-obesity drug</th>
<th>Anti-obesity drug</th>
<th>Anti-diabetic drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual misinterpretation</td>
<td>Drug started unnecessarily because patient failed to alter lifestyle. Patient doesn't need or deserve drug treatment.</td>
<td>Drug treatment needed to reduce risks of obesity.</td>
<td>Drug treatment needed because life-style changes inadequate to correct disease and unsafe to leave blood glucose at this level.</td>
</tr>
<tr>
<td>Correct interpretation</td>
<td>Worthwhile effect of drug, despite failure to normalise weight. Plateau shows continued efficacy of drug. Level of weight loss maintenance may or may not be sufficient to justify long-term drug continuation.</td>
<td>Worthwhile effect of drug, despite failure to normalise blood glucose. Plateau shows continued efficacy of drug. Desirable that blood glucose does not fall lower and lower.</td>
<td></td>
</tr>
<tr>
<td>Usual interpretation</td>
<td>Regain of weight shows that drug did not work.</td>
<td>Regain of weight shows that drug was still effective, and that long-term treatment is necessary.</td>
<td>Regain of elevated blood glucose shows that drug treatment must be continued.</td>
</tr>
</tbody>
</table>

However, at the individual level, the causes for obesity, or for that matter leanness, are less clear. This lack of knowledge means that, to some extent, drug treatment remains empirical and any drug that reduces energy intake, increases energy expenditure or alters energy storage could be of potential benefit. Table 3 classifies anti-obesity drugs and lists some of those available or under development.

Evaluating drug therapy

The bedrock of assessing anti-obesity drugs, randomised controlled trials, does not differ from any other area of medical intervention. Trials must be designed to allow clinically meaningful questions to be answered, and be of sufficient statistical power to give valid positive or negative answers. The disease of obesity, as a disease, usually presents with specific clinical complications such as diabetes mellitus, ischaemic heart disease, stroke, cancer, etc. Measures of body weight, therefore, act only as a surrogate for the real end-points of clinical interest. Surrogate end-points are useful because they allow studies to be conducted more cheaply and easily. For example, compared to measuring body weight, measuring body fat is time consuming, expensive and may involve exposing the subject to ionising radiation. Other advantages of surrogate measures include the use of smaller sample sizes and the ability to measure outcomes more quickly (e.g. body weight loss rather than infarction rates). However, it is always important to be aware that the quality of a surrogate measure diminishes the further it is from the endpoint of interest. Thus a study measuring...
Table 3  Classification of anti-obesity drugs by main mode of action. Drugs licensed or in Phase III development are listed in bold. Those of questionable efficacy are in brackets.

<table>
<thead>
<tr>
<th>Energy intake</th>
<th>Energy storage</th>
<th>Energy Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Fat</td>
<td>Brain</td>
</tr>
<tr>
<td>Behaviour modifier</td>
<td>Decreased lipid storage</td>
<td>Stimulant</td>
</tr>
<tr>
<td>serotonergic</td>
<td>GHR</td>
<td>noradrenergic</td>
</tr>
<tr>
<td>dexfenfluramine</td>
<td>Y leptin</td>
<td></td>
</tr>
<tr>
<td>sibutramine</td>
<td>insulin sensitizers</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>serotonergic</td>
<td>Ro 23-7637</td>
<td>Muscle + BAT</td>
</tr>
<tr>
<td>dexfenfluramine</td>
<td>Troglitazone</td>
<td>Thermogenic</td>
</tr>
<tr>
<td>sibutramine</td>
<td></td>
<td>β3 agonists</td>
</tr>
<tr>
<td>noradrenergic</td>
<td></td>
<td>Thyroid hormones</td>
</tr>
<tr>
<td>Phenetermine</td>
<td>Increased lipid oxidation</td>
<td>Ephedrine</td>
</tr>
<tr>
<td>Mazindol</td>
<td>α2 antagonists</td>
<td>Caffeine</td>
</tr>
<tr>
<td>Dietethypropion (PPA)</td>
<td>(Yohimbine)</td>
<td></td>
</tr>
<tr>
<td>sibutramine</td>
<td></td>
<td>Aspirin</td>
</tr>
<tr>
<td>peptidergic</td>
<td></td>
<td>Serotonergic</td>
</tr>
<tr>
<td>NPY antagonists</td>
<td></td>
<td>(Dextrophanol)</td>
</tr>
<tr>
<td>Y leptin</td>
<td></td>
<td>Noradrenergic</td>
</tr>
<tr>
<td>enterostatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Tract</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>CCK promoters</td>
<td></td>
</tr>
<tr>
<td>CCK promoters</td>
<td>Butabindide</td>
<td></td>
</tr>
<tr>
<td>chlorocitic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relay to brain</td>
<td>CCK promoters</td>
<td></td>
</tr>
<tr>
<td>Nausea/aversive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malabsorption</td>
<td>orlistat</td>
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</table>

weight loss alone could fail to recognise that a drug could produce weight loss through adverse events such as sedation and nausea, rather than anorexia or increased energy expenditure; a fall in body weight due to loss of lean tissue could be harmful rather than beneficial.

Obesity presents particular problems for clinical trials. Although the disease is easy to diagnose, it is heterogeneous and methods for defining different phenotypes are poor. Subjects recruited tend to be women who represent only half of the obese population at risk. There is a long lag time for the development of obesity to its complications, and weight loss remains poorly validated as a surrogate measure for events such as ischaemic heart disease or cancer. Weight loss maintenance over years rather months is the desired aim of any treatment but, in clinical trials, there is often a high drop-out rate (about 40% in most studies) and often poor or partial compliance. The reasons for the high attrition rates in trials are not clear, but relate in part to a patient’s own perception of obesity as a cosmetic and life-style problem rather than a disease.
Although there is evidence to suggest that a loss of 10% from baseline will give medical benefit\textsuperscript{10,13}, and reduce the costs of health care of the co-morbid conditions\textsuperscript{6}, we do not really know how much weight loss is optimal. Since visceral fat loss provides the greatest risk to health, measures of regional fat loss may be more important than total weight loss when treatment benefits are evaluated.

The US FDA has given guidance on standards of evidence necessary to achieve registration for a new compound (Table 1). The philosophy is that drugs should be developed for long-term or indefinite use, and demonstrate benefit greater than can be achieved with diet, exercise and behaviour modification alone. Anti-obesity drugs must exhibit safety commensurate with their efficacy and projected duration of use. Safety and toxicology studies will precede initial short term studies (12–24 weeks) to establish dosage and efficacy. Double-blind studies of 1 year duration are needed, and 2 years in special situations. Efficacy would be judged as loss of 5% of body weight with improvement in co-morbid diseases or risk factors, or 10% if there is no co-morbidity. Since anti-obesity drugs can be expected to be used widely and for long periods of treatment, Phase IV, post-marketing surveillance studies, must be designed and implemented. The issuing of such guidance in the US, achieved by a NAASO task force and the FDA and Federal Trade Commission, has had a galvanising effect on industry. Pharmaceutical companies and researchers, in the US, now know the standard of evidence needed to achieve new drug registration.

**Drugs that predominantly reduce food or energy intake**

In order to maintain the obese state, energy intake must be sustained sufficiently high to meet the increased metabolic demands of the large body mass. Control of food intake is complex, and has evolved to favour increased consumption; only weak mechanisms (mainly cognitive) exist to protect against the high fat, high palatability foods and low energy life-style of developed societies\textsuperscript{17}. Early drugs to be used for treating obesity were amphetamine or amphetamine derivatives. A meta-analysis of 200 controlled trials included nearly 10,000 patients in trials of 4–20 weeks duration. In 90% of trials, active drug was superior to placebo with weight loss on average 0.23 kg/week greater\textsuperscript{18}. Scoville noted that although drugs ‘do not provide complete cures,... [there] is no reason to reject them out of hand; partial success is clearly better than failure’. Despite this, his report has often be misinterpreted as suggesting anorectics were ineffective. The more recent development of serotonergic drugs,
such as fenfluramine and dexfenfluramine, without stimulant properties, has gone some way to renew interest in appetite suppressants.

**Amphetamines**

The discovery of ephedrine from the Chinese plant *Ephedra sinica*, led to the synthesis of the amphetamines in 1933\(^1\). Initially used as stimulants, it soon became apparent that these drugs also suppressed appetite and food intake\(^2\), useful not only for the obese but also for logistical military advantage in World War II. The potent abuse and addictive potential of these drugs makes them unsuitable for use.

**Phenylethylamines and other catecholaminergic ‘stimulant’ drugs**

These were developed to preserve the anorectic actions of amphetamines, but have weaker stimulant activity thanamphetamine and no addictive potential. In rodents these drugs increase sympathetic activity and stimulate thermogenesis\(^21\), but not in man where the anti-obesity action is mediated through central nervous system anorexia. Diethylpropion (amfepramone) has less stimulant activity than amphetamine\(^22\) and reduces subjective ratings of hunger. The risks of abuse appear to be small\(^23\)-\(^24\). A trial of 200 patients receiving diethylpropion for 24 weeks showed weight loss of between 6.6 and 11.3 kg, although only 18% of patients completed the trial\(^25\). Another, smaller, trial over 23 weeks showed weight loss of 11.7 kg with the active drug compared to 2.4 kg in those given placebo\(^26\). A strategy of intermittent treatment (1 month on, 1 month off) proved as effective as continuous treatment\(^27\). Despite these findings, the drug's stimulant properties made it poorly tolerated by patients (and their prescribers), and in a recent climate of disapproval of stimulant anorectic drugs, has been voluntarily withdrawn from the UK. Phentermine has similar properties and in one trial showed about 8 kg more weight loss than placebo over 36 weeks, regardless of whether the drug was given continuously or intermittently\(^28\). Mazindol (an imidazoisoindole) has a longer half-life than the phenylethylamines (33–55 h) and also is superior to placebo at producing weight loss\(^29\). The pitfall of trying to evaluate an anorectic drug in combination with a highly restricted diet was shown in one study in which Mazindol or placebo was giving together with a 260 kcal/day semi-synthetic diet\(^30\). Clearly with such a restricted diet, there was little or no room to measure any additional efficacy from the anorectic drug; nor was dietary compliance enhanced by Mazindol which had to be withdrawn in 6/25 patients.
because of side effects. This group of drugs is little used as sole agent, but may be usefully combined with other drugs (see later).

**Phenylpropanolamine**

This racemic mixture or norephedrine esters is available over the counter in the US and is a component of many 'cold cures'. These drugs release noradrenaline throughout the body, which can act at a wide variety of adrenergic receptors. The predominant action is to stimulate hypothalamic adrenoreceptors so to reduce appetite, rather than increase thermogenesis\(^3^1\). Phenylpropanolamine has a low abuse potential and has no adverse effects on blood pressure at recommended doses\(^2^9,3^2\). It is superior to placebo at producing weight loss, but the difference in weight is modest, 0.7–1.8 kg over 4–12 weeks\(^3^3\). It is widely used as an OTC preparation in the US.

**Serotoninergic drugs**

Fenfluramine was synthesised in the 1960s by the introduction of a trifluoromethyl group into the phenylethylamine ring\(^1^9\). Although for many years it was classified as a catecholaminergic drug, it was clear from animal and human clinical studies that the drug had no stimulant activity, and that its mechanism of action differed from the other phenylethylamines\(^3^4\). While amphetamines release dopamine and noradrenaline within the lateral hypothalamus, fenfluramine acted as a releaser and re-uptake inhibitor of serotonin in presynaptic neurones terminating within the paraventricular nucleus of the hypothalamus. Serotonin anorexia differs from that caused by amphetamines; it is characterised by a decreased rate of eating and early termination of meals, rather than an inhibition of eating\(^3^5\). These anorectic effects of serotonin are mediated by 5HT\(_{2B}\) and 5HT\(_{2C}\) receptors (stimulation of 5HT\(_{1A}\) receptors increases food intake; stimulating 5HT\(_{3}\) receptors has no effect on food intake)\(^3^6\). A large literature on fenfluramine exists and was reviewed in 1975\(^3^7\). Fenfluramine is a mixture of two racemic compounds, l-fenfluramine and d-fenfluramine, which are metabolised to active, but pharmacologically distinct, products l-norfenfluramine and d-norfenfluramine. The d-isomer (dexfenfluramine) was found to have greater activity at reducing food intake in rats, and have a greater specificity for serotonin release and reuptake inhibition, while the l-isomer had greater dopaminergic activity\(^1^9,3^8\).
Dexfenfluramine was developed during the 1970s, and licensed in Europe in the 1980s, and in North America in 1996. Several reviews have been published\textsuperscript{39-41}. Tables 4 and 5 detail some of the many clinical trials of dexfenfluramine in uncomplicated obesity, and obesity associated with non-insulin dependent diabetes. Randomised controlled trials of dexfenfluramine 15 mg twice daily, with or without dietary intervention, support its efficacy at producing clinically significant weight loss superior to placebo. Longer term studies show continued efficacy for up to 1 year, the longest trial period so far reported. The International Dexfenfluramine study (INDEX)\textsuperscript{42} included 822 patients, from 24 centres in 9 European countries. Patients were included if their body weight was 120\% ideal, stable to within 3 kg over the preceding 3 months, and within 85\% of their highest recorded weight. Each centre added dexfenfluramine to their usual treatment protocol (varying from formula diets, lifestyle advice or simple dietetic management). This study demonstrates important lessons on how to interpret the results of anti-obesity trials. Judged by weight loss of completing patients, the difference between active drug and placebo, while significant, appears small (Fig. 2). However, these data bias against the drug effect, because significantly more placebo-treated patients dropped out because of dissatisfaction at their lack of weight loss (84) compared to dexfenfluramine-treated patients (49). Figure 3 presents the results on the numbers of patients achieving, arbitrary, but clinically valid weight-loss targets. Taking dexfenfluramine, approximately doubled the chances of an individual reaching more than 10\% or 10 kg loss. More recent analysis of the INDEX data has allowed the prediction of long-term results from the early response to treatment\textsuperscript{43}. A loss of 1.8 kg or more after 4 weeks of treatment positively predicted 48\% of patients who achieved a loss of 10\% or more at 1 year. Failure to lose 1.8 kg after 1 month, had a negative predictive value of 90\%. A weight loss of 10\% or more after 4 months predicted 84\% of those achieving a similar weight loss at 1 year; failure to lose 10\% weight by month four predicted 90\% of those failing to achieve this target at 1 year. These figures have been incorporated into the prescribing indications in North America.

Unwanted effects of dexfenfluramine are relatively minor and short-lived\textsuperscript{40,44}. A review of 1159 patients treated with dexfenfluramine and 1138 with placebo over 3 months showed diarrhoea (17.5\% vs 7.3\%) and dry mouth (12.5\% vs 5\%) to be the most common side effects\textsuperscript{45}. Withdrawal rates from trials were similar between dexfenfluramine and placebo treated patients (6.6\% and 5.2\%). Pulmonary hypertension (PPH), a potentially fatal condition, has been associated with the fenfluramines\textsuperscript{46}. A large case control study, the IPPHS\textsuperscript{47}, collected all cases of PPH (95) from 220 hospitals over 25 months to investigate the association with anorectic medication. Obesity itself, and systemic
### Table 4  Summary of trial data of dexfenfluramine in treating uncomplicated obesity

<table>
<thead>
<tr>
<th>Trial</th>
<th>BMI/IBW</th>
<th>Duration/diet/exercise</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finer et al. 1985&lt;sup&gt;56&lt;/sup&gt;</td>
<td>89 A and P</td>
<td>BMI ~ 32</td>
<td>12 weeks</td>
<td>A: - 4.1 kg (4.8% init bw), P: 0 kg</td>
</tr>
<tr>
<td></td>
<td>30% decrease energy</td>
<td>12 weeks</td>
<td>A: - 8.1 kg (9.8% init bw)</td>
<td></td>
</tr>
<tr>
<td>Enzi et al. 1988&lt;sup&gt;97&lt;/sup&gt;</td>
<td>64 A and P</td>
<td>BMI ~ 32</td>
<td>Hypocaloric diet</td>
<td>P: - 3.5 kg (3.8% init bw)</td>
</tr>
<tr>
<td></td>
<td>24 weeks</td>
<td>30% decrease energy</td>
<td>A: - 6.0 kg</td>
<td></td>
</tr>
<tr>
<td>Finer et al. 1988&lt;sup&gt;98&lt;/sup&gt;</td>
<td>29 Active</td>
<td>IBW ~ 147%</td>
<td>12 weeks</td>
<td>A: - 10.7 kg (11.2% init bw)</td>
</tr>
<tr>
<td></td>
<td>70% caloric needs assessed from RMR</td>
<td>24 weeks</td>
<td>A: - 6.2 kg</td>
<td>Patients had already lost 13.9 kg on a VLCD</td>
</tr>
<tr>
<td>Noble 1990&lt;sup&gt;100&lt;/sup&gt;</td>
<td>42 A and P</td>
<td>BMI ~ 37 kg</td>
<td>24 weeks</td>
<td>A: - 6.2 kg</td>
</tr>
<tr>
<td></td>
<td>1200–1500 kcal/day</td>
<td>52 weeks</td>
<td>A: - 9.8 kg (10.3% init bw) Higher completion in A group</td>
<td></td>
</tr>
<tr>
<td>Guy-Grand et al. 1989&lt;sup&gt;22&lt;/sup&gt;</td>
<td>822 A and P</td>
<td>IBW ~ 158%</td>
<td>52 weeks</td>
<td>P: - 7.2 kg (7.3% init bw)</td>
</tr>
<tr>
<td>Mathus-Vliegen et al. 1992&lt;sup&gt;101&lt;/sup&gt;</td>
<td>75 A and P</td>
<td>BMI ~ 38</td>
<td>Variable</td>
<td>A: - 10.7 kg</td>
</tr>
<tr>
<td></td>
<td>12 weeks</td>
<td>50% or 1000 kcal/day reduction</td>
<td>12 weeks</td>
<td>A: - 8.0 kg</td>
</tr>
<tr>
<td>Pfohl et al. 1994&lt;sup&gt;102&lt;/sup&gt;</td>
<td>48 A and P</td>
<td>IBW ~ 156%</td>
<td>1200 (M)–1500 (F) kcal/day</td>
<td>A: - 9.6 kg (9.1% init bw)</td>
</tr>
<tr>
<td></td>
<td>52 weeks</td>
<td>1200 (M)–1500 (F) kcal/day</td>
<td>12 weeks</td>
<td>A: - 10.9 kg (11.2% init bw)</td>
</tr>
<tr>
<td>Drent et al. 1995&lt;sup&gt;103&lt;/sup&gt;</td>
<td>112 A and P</td>
<td>BMI ~ 32</td>
<td>9 weeks</td>
<td>A: - 3.1 kg, ↓ fat, CHO, energy; ↓ standing BP P: +0.2 kg</td>
</tr>
<tr>
<td></td>
<td>no dietary advice</td>
<td>Variable dietary advice</td>
<td>9 weeks</td>
<td>No change in Hamilton D ratings</td>
</tr>
<tr>
<td>O’Connor et al. 1995&lt;sup&gt;104&lt;/sup&gt;</td>
<td>60 A and P</td>
<td>BMI ~ 35</td>
<td>26 weeks</td>
<td>A: - 9.74 kg</td>
</tr>
<tr>
<td></td>
<td>Lifestyle programme</td>
<td>1300 (M)–1200 (F) kcal/day</td>
<td>12 weeks</td>
<td>P: - 4.9 kg</td>
</tr>
<tr>
<td>Lucas et al. 1995&lt;sup&gt;105&lt;/sup&gt;</td>
<td>337 A and P</td>
<td>BMI ~ 34</td>
<td>12 weeks</td>
<td>A: - 5.8 kg</td>
</tr>
</tbody>
</table>

Abbreviations: A, active treatment; P, placebo. IBW, ideal body weight. BMI, body mass index; init bw, initial body weight. M, male; F, female. CHO, carbohydrate. BP, blood pressure. RCT, randomised controlled trial. VLCD, very low calorie diet.

Hypertension increased the risk of PPH (1.9- and 2.1-fold, respectively), and exposure to any centrally anorectic medication also increased the risk of PPH (10.1-fold for recent, and 2.4-fold for past exposure). Treatment for more than 3 months further increased the odds ratio to 23.1. However, PPH is extremely rare (1–2 cases/million) and so the
Table 5  Summary of trial data for treating obese NIDDM patients

<table>
<thead>
<tr>
<th>Obese NIDDM</th>
<th>Trial size</th>
<th>BMI/IBW</th>
<th>Duration/diet/exercise</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tauber-Lassen et al. 1990</td>
<td>35 A and P</td>
<td>BMI ~ 34</td>
<td>52 weeks 1200–1440 kcal/day</td>
<td>A: -5.7 kg  P: -2.7 kg</td>
<td>Significant fall in fasting BG and glycated in A group</td>
</tr>
<tr>
<td>Stewart et al. 1993</td>
<td>60 A and P</td>
<td>BMI ~ 35</td>
<td>12 weeks 1200 kcal/day</td>
<td>A: -3.7 kg  P: +0.4 kg</td>
<td>Significant fall in glycated Hb and fructosamine in A group</td>
</tr>
<tr>
<td>Wiley et al. 1992</td>
<td>34 A and P</td>
<td>BMI ~ 34</td>
<td>12 weeks 120 weeks</td>
<td>A: -3.8 kg  P: -0.6 kg</td>
<td>Patients assigned to dexfenfluramine for 3 months, regular clinic, group behavioural programme, home visits, or no intervention</td>
</tr>
<tr>
<td>Manning et al. 1995</td>
<td>205</td>
<td>12 + 40 weeks</td>
<td>12+40 weeks</td>
<td>DF: -2.8 kg  Clinic visits: -1.2 kg  Behaviour program: -1.8 kg  Home visits: -1.1 kg  Control: +1.2 kg</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: A, active treatment; P, placebo; IBW, ideal body weight; BMI, body mass index; BW, initial body weight; M, male; F, female; CHO, carbohydrate; BP, blood pressure; RCT, randomised controlled trial; VLC, very low calorie diet.

Absolute risk is very low—about 28 cases/million person-years of exposure. This incidence is similar to the risks of death from penicillin anaphylaxis, or oral contraceptive-induced thromboembolism and myocardial infarction.

There has been considerable interest in the potential of fenfluramines to increase energy expenditure. Results in man have been contradictory, perhaps influenced by the conditions of study. Breum et al. studied obese women over 24 h in a direct calorimeter and failed to show any effect of dexfenfluramine on energy expenditure. On the other hand, Schutz and colleagues studied normal weight men with indirect calorimetry using a ventilated hood, and showed a higher rise in metabolic rate after dexfenfluramine compared to placebo (6% vs 2%), and a greater thermic response to eating a standardised meal (22% vs 16%). A second study in obese women showed that dexfenfluramine increased post-absorptive energy expenditure by 2.5%, by extrapolation equivalent to an extra 40 kcal/24 h. A thermogenic effect could thus explain how weight loss is maintained despite the increase in energy intake after 6 months treatment in long-term trials such as INDEX.

Other serotonin agonist drugs evaluated as anti-obesity agents include the selective serotonin re-uptake inhibitors such as fluoxetine, fluvoxamine and sertraline. Normally used to treat depression, these...
drugs were recognised as producing weight loss rather than weight gain usually associated with tricyclic antidepressants. The doses of fluoxetine required to produce weight loss, however, are substantially higher than those used to treat depression\textsuperscript{54}. At these doses, the drug may no longer be acting solely on serotonin neurones, but probably has effect on dopaminergic neurones also\textsuperscript{36}. A large trial compared continued treatment with Fluoxetine 20 mg, 60 mg daily or placebo for efficacy in weight loss maintenance in 317 patients who had already lost > 3.6 kg with 8 weeks of single-blind fluoxetine treatment\textsuperscript{55}. Within 8 weeks of
the maintenance phase, all three groups of patients started to regain weight and continued to do so up to 48 weeks, findings confirmed by others\textsuperscript{56,57}.

**Sibutramine**

This drug, which is expected to receive US approval for registration in 1997, is a serotonin and noradrenaline re-uptake inhibitor (SNRI). It was developed initially as an anti-depressant and bears a close structural resemblance to viloxazine. Devoid of anti-depressant activity, it decreases food intake through $\beta_1$ and $5HT_{2A/2C}$ receptor agonist activity, and is thought to enhance metabolic rate through stimulation of peripheral $\beta_3$ receptors. Dose response trials over 12 weeks have shown weight loss of 5.2–6.9 kg at a dose of 10 mg daily, and 7.6 kg at 20 mg daily (manufacturer's data on file). In a 24 week, double-blind, dose finding, controlled trial in 173 patients, 10, 15, 20 and 30 mg daily produced similar maximal loss (6.1–8.3 kg)\textsuperscript{58}. A meta-analysis of these data suggests that the percentage of patients losing 5% of baseline body weight after 12 weeks is 19% for placebo, 49% for sibutramine 10 mg, and 55% for sibutramine 15 mg.

A 1 year trial has established long-term efficacy showing weight loss of 4.8 kg for 10 mg daily, and 6.1 kg at a 15 mg daily dose\textsuperscript{59}. Weight loss with sibutramine (10 mg daily) has been compared to dexfenfluramine 15 mg twice daily in two studies\textsuperscript{60}. Both studies showed a trend to greater weight loss over 12 weeks with sibutramine but this was not statistically significant. A short-term study in patients with NIDDM showed weight loss at 12 weeks of 2.4 kg compared to 0.1 kg in placebo-treated patients with a non-significant fall in glycated haemoglobin of 0.4%\textsuperscript{61}. Adverse effects include nausea, insomnia, dry mouth, rhinitis and constipation. However, the noradrenergic effects of the drug can cause an increase in heart rate and blood pressure in some individuals, or prevent the expected fall in these parameters with weight loss. The clinical importance of these adverse effects has not yet been established.

**Orlistat**

Orlistat inhibits pancreatic and gastric lipases, thus decreasing ingested triglyceride hydrolysis\textsuperscript{62}. It produces a dose-dependent reduction in dietary fat absorption, which is near maximal at a dose of 120 mg thrice daily\textsuperscript{63}. These actions lead to weight loss in obese subjects\textsuperscript{64}. A short-term, 12 week, study showed that together with a low fat diet, orlistat
produced a dose-dependent increase in weight loss (placebo, 2.9 kg; orlistat 30 mg daily, 3.61 kg; 180 mg daily, 3.69 kg; 360 mg daily, 4.7 kg; intention-to-treat analysis)\(^65\). A 1 year controlled trial of orlistat 360 mg daily in 267 obese patients showed weight loss of 8.5%, compared to 5.4% for placebo-treated patients. 28% of orlistat-treated patients lost more than 10% of initial body weight compared to 17% of the placebo group, judged in an intention-to-treat analysis\(^66\). Adverse effects of orlistat are predominantly related to gastro-intestinal effects due to fat malabsorption. These include loose or liquid stools, faecal urgency and oil discharge, and can be associated with fat-soluble vitamin absorption. Since the consumption of a high fat meal will inevitably lead to severe gastro-intestinal symptoms, it is possible that some of the weight loss with orlistat treatment is due an 'antabuse effect' enforcing behaviour change. Registration was applied for by the manufacturer, Hoffman-La Roche, in 1997.

**Drugs that predominantly increase energy expenditure**

Interventions that increase exercise and activity are valuable components of any weight control programme and correlate strongly with success at weight loss maintenance\(^67\). It is often difficult, however, for the severely obese patient to be physically active. Changing this area of behaviour may be as much as a problem for patients as a voluntary change in eating habits. For the past 20 years, there has been a concerted search for drug treatments that might safely increase metabolic rate in obese patients, and dissipate excessive energy stores as heat. The term thermogenic drugs has been coined to describe this mode of action. Since many obese patients have already, or are at risk from, ischaemic heart disease and hypertension, it would be essential that a thermogenic drug would have only minimal, if any, effect on raising heart rate, cardiac output, myocardial oxygen consumption, or blood pressure.

**Dinitrophenol**

Dinitrophenol was the first synthetic thermogenic drug used to treat obesity. Its thermogenic action was noticed by munitions workers at the turn of the century, and shown to result from the uncoupling of oxidative phosphorylation from ATP formation. Unfortunately, during the 1930s when it came into clinical use, there were a number of deaths from multi-system side effects, and the drug was rapidly withdrawn.
**Thyroid hormones**

Since the turn of the century, thyroid hormones (thyroxine and tri-iodothyronine) have been known to increase metabolic rate and thermogenesis. Patients with spontaneous overactivity of thyroid hormone production (thyrotoxicosis) have increased resting metabolic rate, often lose weight (in the face of increased appetite and food intake), and report increased sensations of heat and sweating. The mechanisms by which thyroid hormones (and in particular tri-iodothyronine) increase metabolic rate are not fully understood but involve uncoupling of oxidative phosphorylation, increasing Na\(^+\)/K\(^+\)-ATPase activity and increasing mitochondrial metabolism\(^68\). Since thyroid hormone-induced increases in respiration are tightly coupled to the utilisation of high energy phosphorus compounds (e.g. ATP), it seems unlikely that these biochemical processes account for the thyroid hormones' thermogenic actions; increasing the actions of catecholamines, or increasing turnover of glycogen and protein, seem more likely explanations.

In clinical practice, thyroxine and tri-iodothyronine are not useful for treatment. While they increase metabolic rate, they cause tachycardia and may provoke dysrhythmias or myocardial infarction, and are also associated with accelerated protein (fat free mass) loss. Even when used to treat hypothyroidism, weight changes are minimal\(^69,70\). Research into thyroid hormone analogues is in progress, and one animal study showed the possibility of combining thyroid hormone with a β-blocker\(^71\).

**Ephedrine and xanthines**

Phenylpropanolamines, such as ephedrine, and xanthine derivatives, such as caffeine, increase metabolic rate. The amount of caffeine contained in two cups of coffee, 100 mg, will raise metabolic rate by about 4%, but the effect is short-lived, and may be followed by a period of reduced energy expenditure. Erikson, a Danish general practitioner, noted that asthmatic patients prescribed these drugs, involuntarily lost weight\(^72\). Ephedrine and caffeine appear to act synergistically, and the combination is marketed in Denmark as the Elsinore pill\(^72\). The actions of ephedrine are mediated through sympathetically-released noradrenaline, which could act at β\(_3\) receptors (on brown adipose tissue), β\(_2\) receptors (stimulating protein synthesis and increasing lean body mass) and/or at post-synaptic α receptors involved with conversion of thyroxine to tri-iodothyronine. Xanthines (and aspirin) inhibit negative feedback of released noradrenaline, adenosine and prostaglandins on noradrenaline release from sympathetic nerve terminals\(^73\). Clinical trials
have shown these drugs alone, or in combination, are effective at producing weight loss in obese subjects. In a large 24 week trial, weight loss with a 4.2 MJ/day diet with ephedrine 20 mg and caffeine 200 mg produced more weight loss (0.13–0.14 kg/week) than diet with placebo or ephedrine or caffeine alone\textsuperscript{74}. Although in this study there was no increase in heart rate or blood pressure, the expected fall in these measures with weight loss was not seen, suggesting that some of the potential benefit of weight loss may be lost with this form of treatment. In a trial comparing the same ephedrine/caffeine combination with the centrally acting anorectic dexfenfluramine, weight loss was similar after 15 weeks (8.3 ± 5.2 kg vs 6.9 ± 4.3 kg, respectively), but there were significantly more side effects of CNS stimulation in the ephedrine/caffeine treated patients\textsuperscript{75}. Long-term treatment for up to 26 months has been reported\textsuperscript{76}, but only in a few patients and not as part of a randomised controlled trial. Interestingly, much of the effect of phenylpropanolamines on body weight may result from anorexia. One study suggested that 80% of the weight loss in patients treated with the combination could be accounted for by anorexia and decreased food consumption\textsuperscript{77}.

**Atypical beta-adrenoreceptor agonists**

The finding of atypical β-adrenoreceptor agonists in 1983\textsuperscript{78}, soon led to the discovery of atypical receptors (coined β\textsubscript{3} receptors) that mediate the thermogenic effects of sympathomimetic agents, but not the β\textsubscript{1} effects of heart rate stimulation, or β\textsubscript{2} effects on smooth muscle contraction and tremor. The existence of a novel receptor involved in energy expenditure suggested a potentially valuable approach for thermogenic drug development\textsuperscript{79}. The field of β\textsubscript{3}-adrenoceptor agonists has recently been reviewed by Arch and Wilson\textsuperscript{80}, and Goldberg and Frishman\textsuperscript{81}. In obese rodents, these compounds produce weight loss (from fat) without reducing food intake; in diabetic rodents, they have anti-diabetic effects predominantly through increasing insulin action. Receptors for β\textsubscript{3}-adrenoceptor agonists are found predominantly on brown adipocytes, and initially it was thought that the compounds acted to stimulate brown adipose tissue heat production (achieved by the uncoupling of oxidative phosphorylation). However, it seems clear that, in man, skeletal muscle is the main location for thermogenesis induced by these drugs\textsuperscript{82}, and clinical results have been disappointing. Although two Beecham compounds BRL 26830 and BRL 35135 stimulated metabolic rate and produced weight loss\textsuperscript{83,84}, the findings were not consistent\textsuperscript{85}, and the thermogenic effect could not be separated from heat produced.
by troublesome skeletal muscle tremor. The human β3 receptor was recently cloned and is known to differ from the rodent receptor. Existing compounds, with activity in rodents, appear to have only poor affinity and specificity for the human receptor. Furthermore, in adult man there is little expression of brown adipose tissue β3-receptors. At other sites, such as adipose tissue, many of the existing compounds act nonspecifically on β1 and β2-receptors. More specific compounds are being developed, but are a long way from clinical use.

**Drug combinations**

Combining drugs with different modes of action is an effective clinical strategy for diseases such as hypertension and diabetes mellitus. It is a strategy that seems logical for obesity treatment, especially since body weight is controlled by factors affecting both energy intake and output. Despite this, only few trials of drug combinations have been reported. The combination of phentermine and fenfluramine has attracted considerable medical and media attention in the US, ever since the report of a 3.5 year trial. All subjects were treated with diet, exercise and behaviour modification, and randomised to a combination of fenfluramine 20 mg + phentermine 15 to 30 mg daily. After a conventional drug versus placebo trial up to 34 weeks, a variety of cross over, drug withdrawal and drug intensification protocols were tested. Interpretation of the 3.5 year results is, therefore, not straightforward, but 26/51 patients completing 190 weeks of treatment maintained a weight loss of 10% initial body weight, with concomitant improvement in serum lipids.

An open trial of this combination involving more than 1000 patients, has been reported by Atkinson. Mean weight loss at 6 months was 16.5 kg and maintained for 18 months. In a separate study, this combination has been used as a maintenance treatment in 96 subjects treated with a very low calorie diet for between 8 and 54 weeks. Mean body weight in 96 subjects fell from 106.6 kg to 89.3 kg on the diet, and to 86.2 kg after 9 months pharmacotherapy (66% patients completing). The combination of phentermine and fenfluramine is well tolerated, although there have been reports that patients suffer from impaired short term memory.

**Future possibilities for pharmacological treatment**

The rapidly advancing knowledge of the molecular biology of body weight regulation (for example the ob gene and its product, leptin) and
the neuropharmacological control of ingestive behaviour and energy expenditure holds up the promise of new approaches to obesity treatment.

Rodent models of obesity in which adipose tissue fails to express the ob gene (with resulting low levels of leptin) can have their obesity reversed by leptin administration\(^9\). In obese man, however, leptin levels are high\(^90\), suggesting a receptor defect akin to that seen in the db/db mouse. It, therefore, seems likely that large amounts of leptin would need to be administered to achieve a degree of hyperleptinaemia necessary to ‘reset’ body weight. However, another approach has been to consider whether giving leptin to offset the fall that is seen with weight loss may be more logical and pragmatic. Human clinical trials are just starting.

Neuropeptide Y (NPY) is the most potent stimulator of food intake, and also increases energy expenditure. Data suggest that leptin, in part, exerts its actions by modulating hypothalamic NPY\(^91,92\). A number of pharmaceutical companies have developed NPY inhibitors, but it will remain problematic as to how to get such compounds across the blood-brain barrier.

Cholecystokinin (CCK) acts as a physiological satiety factor by reducing meal size\(^93\), whether administered centrally or peripherally. Peripheral CCK-A receptors in the periphery slow gastric emptying and relay to the hypothalamus via the vagus to inhibit feeding. Central CCK-B receptors are found predominantly in the brain. A number of CCK-A promoters are in early development as anti-obesity drugs, and butabindide, which blocks an enzyme that metabolises CCK, is also subject to ongoing research\(^94\). A number of other peptides that are known to regulate energy metabolism and body weight, and which are thus candidates for pharmacological agonist or antagonist development are reviewed by Levine and Billington\(^95\).

**Conclusions**

There is a spectrum of body weight from malnourishment with inadequate energy stores, through ‘ideal’ body weight, to obesity, a state of excessive stores associated with health impairment. Obesity is increasing in our society because human physiology is ill-adapted to changes that have favoured increased energy consumption and decreased energy expenditure. An understanding of the regulation of body weight and energy fluxes is needed if the precise predisposition and causes of excessive fat storage are to be elucidated, and effective treatments developed. At a practical level, it is important for doctors, dietitians and
their patients to realise that weight loss can only be achieved by a negative energy balance, and that low levels of energy expenditure do not exist or constitute a bar to achieving this therapeutic goal. The logic of treating obesity with drugs does not differ from treating any other disease or risk factor. Drug treatment should be necessary and more effective than non-drug treatment, and produce a favourable risk benefit ratio. Obesity, as a chronic disease poses particular difficulties for drug treatment. The need for long-term efficacy implies that tolerance or adaptive mechanism must lead to a loss of drug effect. Long-term trials are needed to demonstrate clinical benefit rather than reduction of risk factors or other surrogate measures. There is a growing acceptance of the need and value of drug treatment of obesity, and a growing sophistication of clinical trial design.

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