Appetite Suppressants
A Review

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Summary

Centrally acting appetite suppressant drugs used in the treatment of obesity fall into 2 broad pharmacological categories; those which act via brain catecholamine pathways and those which act via serotonin pathways. Of the former group, amphetamine and phenmetrazine are no longer recommended because of their stimulant properties and addictive potential. The remaining drugs in this class include amfepramone (diethylpropion), phenetermine, mazindol and phenylpropanolamine. All have been shown to reduce appetite and lower food intake, thereby helping obese patients more easily keep to a low-calorie diet and lose weight. They all have some sympathomimetic and stimulant properties. Anorectic drugs which promote serotonin neurotransmission have no such stimulant or sympathomimetic properties. They are fenfluramine, together with its recently introduced dextrorotatory stereoisomer dexfenfluramine, and fluoxetine. They reduce appetite and food intake and are effective in the treatment of obesity.

Anorectic drugs should be reserved for those who are clinically at risk from being overweight, and then only as part of a comprehensive weight-reducing programme including regular dietary counselling. Although current licensing regulations only allow their use over a relatively short period (12 to 16 weeks), clinical trials have shown them to be effective over longer periods, particularly in preventing weight regain. Of the compounds currently indicated for use in obesity, dexfenfluramine appears to have the most suitable pharmacological profile, although it should not be given to patients with a history of depression.
Obesity has been said to be the most important nutritional disorder of the developed world. It has serious adverse effects on health, being associated with an increase in morbidity and mortality from diabetes, hypertension and hypercholesterolaemia (Garrow 1988; National Institutes of Health 1985; Royal College of Physicians 1983). Weight loss can significantly lower these risks. While the principle by which weight loss can be achieved is clear, the practice is difficult and treatment is frequently unsuccessful (Wing & Jeffre 1979). To lose 1kg of adipose tissue requires a negative energy balance of about 7000 kcal (29 300kJ) [equivalent to some 70 slices of bread and butter]. Those who are significantly overweight, i.e. with a body mass index (BMI) of ≥ 30 [BMI = weight (kg)/height (m²)], often need to lose well over 30kg. Thus they need to achieve an overall energy deficit of more than 200 000 kcal (840MJ). Since going on a 1000 kcal diet is likely to produce a daily deficit of about 1000 kcal (about 4200kJ), it is clear that significant weight loss will take many months of perseverance and determination to resist the many physiological and psychological pressures to eat normally.

Appetite-suppressant drugs, by reducing hunger drives, can help patients resist these pressures and thereby assist them in adhering to a reduced calorie diet. This will in turn lead to weight loss with a consequent improvement in health.

The first appetite-suppressant drug amphetamine, was introduced into clinical practice for the treatment of obesity over 50 years ago. Shortly afterwards, the dextrorotatory stereoisomer dexamphetamine was found to be the active anorectic constituent of the racemic mixture and came to supplant it. Unfortunately, not only was dexamphetamine an appetite suppressant, it was also discovered to have marked central stimulant and euphoriant properties. These attributes led it, and a similar drug phenmetrazine to become widely taken drugs of abuse. Because of this, they can no longer be recommended for use in the treatment of obesity, and in many countries their prescription is narrowly restricted.

Subsequently a number of other centrally acting appetite suppressants have been developed for use in the treatment of obesity, with less of an abuse potential than dexamphetamine, many acting through different pharmacological mechanisms.

Despite clear differences in pharmacology and in abuse potential, there is still an unfortunate tendency to refer to all centrally acting appetite suppressants as ‘amphetamine-like’, whatever their pharmacology, and to view them all with equal suspicion. This has led to ill-informed and misguided warnings against using such drugs at all in the management of obesity. They have all been ‘tarred with the same brush’ (Richard & Lasagna 1988).

The centrally acting appetite-suppressant compounds which are currently licensed for the treatment of obesity fall into 2 broad pharmacological categories, those which act on catecholamine neurotransmitter systems within the brain and those which act on serotonergic systems (Angel 1990; Leibowitz 1990) [table I].

This review describes the clinical pharmacology, efficacy and adverse effects of each of the appetite suppressants listed in table I, and discusses the place of appetite suppressants in the management of obesity, the choice of drug, and how long treatment should be continued.

1. Drugs Acting on Central Catecholamine Pathways

Amphetamine, the first centrally acting appetite suppressant to be introduced in the treatment of obesity was found to act by enhancing catecholamine neurotransmission in experimental animals (Carlsson 1970). It is likely that it, and related
<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended daily dose (mg)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amfepramone (diethylpropion)</td>
<td>75</td>
<td>Can be given intermittently; may cause insomnia</td>
</tr>
<tr>
<td>Phentermine</td>
<td>15-30</td>
<td>Mildly stimulant; can be given intermittently</td>
</tr>
<tr>
<td>Mazindol</td>
<td>1-3</td>
<td>Sympathomimetic properties; mildly stimulant</td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td>27-75</td>
<td>Mildly stimulant</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>60-120</td>
<td>Slightly sedative; may cause gastrointestinal symptoms, and depression if stopped abruptly</td>
</tr>
<tr>
<td>Dextfenfluramine</td>
<td>15-30</td>
<td>Occasional drowsiness and/or gastrointestinal symptoms, but less than the racemate fenfluramine</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>40-60</td>
<td>Can cause drowsiness and gastrointestinal symptoms</td>
</tr>
</tbody>
</table>

*Table 1. Centrally acting anorectic drugs for use in obesity*

None of these drugs should be given concurrently with a monoamine oxidase inhibitor.

Compounds, act via a similar mechanism in humans as its anorectic activity is attenuated by catecholamine receptor blocking drugs (Silverstone & Kyriakides 1982).

### 1.1 Amfepramone (Diethylpropion)

#### 1.1.1 Pharmacology

Amfepramone is a phenylethylamine with minor sympathomimetic properties and much less stimulant activity than amphetamine (Hoekenga et al. 1978). It is well absorbed from the gastrointestinal tract with peak plasma concentrations occurring some 2 hours after administration. Metabolism within the liver gives active metabolites which have an elimination half-life ($t_{1/2}$) of 8 hours.

It has clear appetite-suppressant activity. In healthy human subjects single doses of 50 to 75mg of amfepramone lowered subjective hunger ratings and reduced food intake over an 8-hour period (Silverstone & Kyriakides 1982). Similar effects on hunger and food intake were seen in obese women (Silverstone et al. 1968).

#### 1.1.2 Efficacy

There have been several placebo-controlled double-blind clinical trials which attest to the efficacy of amfepramone in helping obese patients lose weight, at least in the short term (Hoekenga et al. 1978; Sullivan & Comai 1978).

In 3 placebo-controlled comparisons each lasting 12 weeks, the mean weight loss during amfepramone treatment (75mg daily) ranged from 9.7 to 17.5kg, compared with 3.4 to 10.7kg with placebo (Allen 1977; Bolding 1974; McQuarrie 1975). In each of the 3 trials the mean weight loss in the group receiving amfepramone was greater than that in the group receiving placebo. However, as Munro (1979) pointed out, within these studies there was wide individual variation in response, with some amfepramone recipients losing as much as 16kg while others lost no weight at all. However, such individual variation in response is not peculiar to amfepramone, it occurs with all appetite suppressants, and indeed with all the many dietary and behavioural treatments which have been recommended for use in obesity.

McKay (1973) conducted a double-blind placebo-controlled parallel group trial of amfepramone 75mg sustained release daily for 23 weeks in 20 obese patients. All 10 patients receiving amfepramone completed the trial, whereas 6 of the 10 on placebo failed to complete, 3 because of inefficacy. Among those completing the study, amfepramone had a clear advantage; by 23 weeks there...
was a mean weight loss of 11.7kg in the amfepramone group compared to 2.4kg in the placebo group.

Intermittent treatment, with alternate months on amfepramone is as effective as continuous medication in uncomplicated obesity (Munro 1979; Munro & Ford 1982; Silverstone 1974) and in obese diabetic patients (Silverstone & Buckle 1966).

Direct comparison with fenfluramine (Silverstone et al. 1970) and mazindol (Allen et al. 1977) revealed no significant differences in efficacy between these compounds over the short term.

1.1.3 Adverse Effects

Adverse effects with amfepramone are relatively uncommon, and appear to be reported less frequently than with other appetite suppressants acting via catecholamine pathways (Sullivan & Comai 1978). Some patients do nevertheless experience insomnia, particularly if they take amfepramone in the afternoon. Although cases of abuse have been reported, the risk of this occurring in obese patients taking the drug under medical supervision appears to be small (Carabilllo 1978).

1.2 Phentermine

1.2.1 Pharmacology

Phentermine is a phenylethylamine derivative with a pharmacological profile similar to amfepramone. It has significantly less sympathomimetic and stimulant activity than amphetamine. Given as an oral sustained release resin complex, it is well absorbed from the small intestine, with peak plasma concentrations within 8 hours of oral administration, therapeutic concentrations persisting for at least 20 hours, and $t_{1/2}$ of 20 to 24 hours.

Phentermine given as a single 30mg sustained release dose significantly reduced hunger ratings and food intake in nonobese subjects (Silverstone & Kyriakides 1982) and in overweight women (Silverstone 1972).

1.2.2 Efficacy

In double-blind trials, phentermine was found to be more effective than placebo in promoting weight loss in patients with uncomplicated obesity (Truant et al. 1972; Tuominen et al. 1990) and in obese diabetics (Campbell et al. 1977).

In a crossover study where obese diabetic patients received either phentermine resinate 30mg ($n = 34$) or placebo ($n = 32$) daily for 6 months, the mean weight loss among the patients when receiving phentermine was 5.3kg compared to 1.5kg on placebo ($p < 0.001$ between treatments) [Campbell et al. 1977]. 14 of the 32 patients who had been allocated to the placebo group in the parallel phase of the trial (having lost 1.2kg on average) were then prescribed phentermine in an open fashion for a further 6 months. During this period they lost a mean of 6.5kg, but despite this gratifying weight loss there was no significant change in diabetic status.

In another study of 50 patients with what the authors called ‘refractory obesity’, weight loss did not appear to be related to the plasma drug concentrations (the drug was administered at breakfast and blood taken later that day) [Douglas et al. 1983]. It was therefore concluded that there is little point in increasing the dose of phentermine above 30 mg/day, since patients who did not lose weight on that dose would be unlikely to do so with a higher dose.

Intermittent treatment on alternate months with sustained release phentermine resinate 30mg daily and placebo during the intervening months was as effective as continuous treatment (Steel et al. 1973; Truant et al. 1972). In 2 comparative trials, phentermine was found to be equal in efficacy to fenfluramine (Steel et al. 1973; Tuominen et al. 1990).

1.2.3 Adverse Effects

These are mainly minor and rarely require stopping treatment. They reflect the mild sympathomimetic and stimulant properties of the drug and include insomnia, nervousness, irritability and headache (Douglas et al. 1983). Phentermine has been given successfully to patients with moderate hypertension and to diabetics (Campbell et al. 1977).
1.3 Mazindol

1.3.1 Pharmacology

Despite having a different chemical structure from most other anorectic compounds, mazindol has a pharmacological profile in animals similar to that of amphetamine (Samain & Garattini 1982), although it acts more as a blocker of noradrenaline (norepinephrine) synaptic reuptake rather than a promoter of release. In human subjects it has less stimulant activity (Hedges 1972) and is not recognised as amphetamine-like by amphetamine abusers (Gotestam & Gunne 1972).

Mazindol is a potent appetite suppressant; 1mg reduced food intake significantly more than placebo in healthy nonobese subjects over an 8-hour period (Silverstone & Kyriakides 1982).

Mazindol is well absorbed from the gastrointestinal tract, with the peak plasma concentration reached 2 hours after oral administration. The t<sub>1/2</sub> of mazindol (and its metabolites) ranges from 33 to 55 hours, but it is likely that clearance of parent drug is more rapid, as no evidence of accumulation was found in patients receiving 6mg daily for up to 6 months.

1.3.2. Efficacy

In short term placebo-controlled trials, mazindol was significantly more effective than placebo in helping obese patients lose weight. In a study involving 90 patients (80 of whom were women), mazindol 3mg daily in divided doses led to a mean weight loss of 2.8kg over 6 weeks compared to 1.4kg on placebo (Grapin & Cohen 1974). In a rather complex study comparing mazindol to placebo, with the treatment being administered by one of 12 therapists, mazindol similarly appeared to be more useful than placebo (Atkinson et al. 1977). In a 12-week trial conducted in Japan and involving 228 obese patients, the mean weight loss on mazindol was 4.2kg compared to 1.2kg on placebo, a highly significant difference (Onishi 1990).

A crossover trial of mazindol 2 to 3 mg/day or placebo for 20 weeks also showed a clear superiority for mazindol, especially in the group receiving mazindol before placebo (Miach et al. 1976).

1.3.3 Adverse Effects

The moderate stimulant properties of mazindol can cause nervousness, irritability and insomnia. In addition dry mouth, sweating, nausea and constipation have been reported (Munro 1979). When given to patients with preexisting heart disease, dysrhythmias and a worsening of angina were reported (Bradley et al. 1974). Because mazindol may potentiate the pressor effects of catecholamines, it should not be given in conjunction with sympathetomimetic drugs, monoamine oxidase inhibitors (MAOIs) or with antihypertensive agents of the adrenergic neuron-blocking type such as guanethidine and debrisoquine. It should not be prescribed in patients with hyperthyroidism.

Mazindol has little potential for causing dependence and is rarely used as a drug of abuse (Chait et al. 1987).

1.4 Phenylpropanolamine

1.4.1 Pharmacology

Phenylpropanolamine is a phenylethylamine derivative, being the racemic mixture of the isomers of norephedrine. It is a constituent of a number of nonprescription remedies for coughs and colds, as well as being marketed as an anti-obesity agent.

It is well absorbed from the gastrointestinal tract (see Lasagna 1988 for review of pharmacology). Its t<sub>1/2</sub> is 3.9 to 4.6 hours, with most of the drug being excreted unchanged. As a consequence of its sympathomimetic properties it can increase heart rate and elevate blood pressure.

There is little direct quantitative data concerning the effect of phenylpropanolamine on hunger and food intake in human subjects, although some 45% obese patients prescribed phenylpropanolamine for weight reduction reported decreased appetite (Kalb 1942). Hoebel et al. (1975) conducted a series of double-blind placebo comparisons of a single dose of phenylpropanolamine 25mg in nonobese subjects, and demonstrated a significant decrease in liquid nutrient intake.
1.4.2 Efficacy

A number of short term placebo-controlled clinical trials of phenylpropanolamine have been carried out in obesity. In some, the active drug was given in a preparation in which it was combined with caffeine (see Lasagna 1988 for review). Only one of these studies lasted longer than 8 weeks (Weintraub et al. 1986), in which 106 obese patients received either phenylpropanolamine 75mg daily or matching placebo. The mean weight loss on active drug was 6.1kg, compared with 4.3kg on placebo (p < 0.05 between groups). In an 8-week comparison with amfepramone the mean weight loss during treatment with the 2 drugs was equivalent; 3.1kg on phenylpropanolamine plus caffeine, and 3.61kg on amfepramone (Altschuler et al. 1982).

More recent placebo-controlled clinical trials have confirmed the efficacy of phenylpropanolamine in helping obese patients lose weight (Altschuler & Frazer 1986; Greenway 1989; Schtein- gart 1990). In one of these studies, a clear appetite-suppressant effect was noted, with a mean difference in weight loss of 0.9kg over 6 weeks in 54 overweight patients (Altschuler & Frazer 1986). However, in a slightly longer term study lasting 8 weeks, an appetite questionnaire focusing on meal frequency and overall impression of 'appetite' control failed to reveal any difference from placebo, despite a corresponding difference in weight loss of 1.5kg in favour of phenylpropanolamine (Schtein- gart 1990). This failure to detect any subjective anorectic effect may have been because the questions asked were too vague to detect such differences.

1.4.3 Adverse Effects

Although phenylpropanolamine has mild stimulant properties, its abuse potential seems low (Lasagna 1988). In normal volunteers, no euphoriant effect was detected using the Addictive Research Centre Inventory (Liebson et al. 1987; Morgan et al. 1989).

The risk of other adverse effects is also low (see Lasagna 1988 for review). Even though it is a sympathomimetic compound, it has little effect on blood pressure in healthy volunteers when given at the recommended dose (Blackburn et al. 1989; Goodman et al. 1986; Liebson et al. 1987). Overweight patients with hypertension receiving phenylpropanolamine 25mg 3 times daily for 6 weeks experienced no adverse effects on blood pressure compared to placebo, although there was a greater weight loss with phenylpropanolamine (Bradley & Raines 1989). It should be avoided in patients taking monoamine oxidase inhibitors.

2. Drugs Acting on Central Serotonin Pathways

Drugs affecting serotoninergic neurotransmission have been shown to affect food intake and bodyweight in experimental animals (Angel 1990) and in humans (Silverstone & Kyriakides 1982). This anorectic action is attenuated by serotonin receptor blocking compounds such as m ergoline (Goodall & Silverstone 1988).

2.1 Fenfluramine

2.1.1 Pharmacology

Fenfluramine is the racemic mixture of the enantiomers d- and l-fenfluramine. While chemically a phenylethylamine like most of the centrally acting drugs considered in section 1, it has a markedly different spectrum of pharmacological activity. In particular, its anorectic action appears to be mediated through activating serotoninergic rather than catecholaminergic pathways in the brain (Samann & Garattini 1982). As a consequence it has no stimulant activity; if anything it has slight depressant effects (Fink et al. 1971). In addition to its central action, there is evidence that fenfluramine has a peripheral effect on muscle glucose uptake (Turner 1979).

It is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations achieved within 4 hours, and is rapidly metabolised into an active metabolite, norfenfluramine. Fenfluramine and norfenfluramine have a t½ of approximately 20 hours, and after multiple dosage steady-state plasma concentrations are reached within 4 to 5 days (Campbell 1971). Both fenfluramine and norfenfluramine are excreted in the urine, the rate of
excretion is pH-dependent, being greater when the urine is acidic.

Fenfluramine has a marked anorectic action. In healthy volunteers, hunger ratings were reduced in a dose-related manner following administration of single doses of 20, 40 and 80mg (Silverstone et al. 1975). The degree of anorexia closely paralleled the plasma drug concentration of fenfluramine. Subsequent studies have confirmed this effect on subjective hunger ratings (Holmstrand & Jonsson 1975; Kyriakides & Silverstone 1979). Food intake was significantly suppressed by single doses of 40, 60 and 80mg of fenfluramine given to healthy subjects, following an overnight fast (Silverstone & Kyriakides 1982). No difference between fenfluramine 60mg and dexamphetamine 10mg could be detected on the latency to start eating or on the rate of eating (Kyriakides & Silverstone 1979). Others have reported a similar suppression of food intake following single dose administration, persisting for up to 24 hours after an 80mg dose (Blundell et al. 1979).

2.1.2 Efficacy

A considerable number of placebo-controlled trials investigating fenfluramine in obesity have been carried out which attest to its efficacy in helping these patients lose weight (e.g. Munro & Ford 1982; Pinder et al. 1975), including patients with ‘refractory’ obesity who had failed to respond to conventional dieting treatment (Munro et al. 1966). Given as a sustained release formulation at a daily dose of 60mg, fenfluramine led to greater weight loss than placebo in 1 study, even though all patients received regular dietary advice and supervision and all entered a behavioural modification programme (Weintraub et al. 1983).

In a direct comparison of fenfluramine up to 120 mg/day plus group counselling, behaviour modification, and a combination of the 2, fenfluramine with or without behaviour modification proved superior over a 6-month treatment period (Craighead et al. 1981). However, after treatment was stopped, the drug-treated patients regained more weight than patients who had been given behaviour modification alone.

In a 20-week study in women with ‘refractory’ obesity, a direct relationship was found between the plasma fenfluramine plus norfenfluramine concentrations and weight loss (Innes et al. 1977). The mean weight loss in patients whose plasma concentration did not reach 100 μg/L was 2.1kg, compared to 5.1kg among those whose plasma concentration was between 100 and 199 μg/L, and 8.8kg in those with a concentration of 200 μg/L or over. However, others have failed to detect such a clear relationship between plasma concentrations and weight loss (Petrusko et al. 1982). In comparative studies, fenfluramine has been shown to be as effective as amfepramone (Silverstone et al. 1970), dexamphetamine (Stunkard et al. 1973) and phentermine (Steel et al. 1973).

2.1.3 Adverse Effects

The often reported gastrointestinal disturbances (nausea or diarrhoea) are likely to be a direct consequence of the serotoninergic-enhancing action of fenfluramine. Drowsiness and lethargy are often experienced during the initial stages of treatment. Although devoid of any stimulant properties, abrupt withdrawal of fenfluramine can lead to severe depression; the dose should therefore always be reduced gradually. It is less likely to suppress REM sleep than other anorectic drugs (Oswald et al. 1968), but can increase inrasleep restlessness, leading to an increase in reported dreaming and nightmares (Gagnon et al. 1969).

The incidence of adverse effects can be minimised by increasing the dose gradually over several weeks to the maximum tolerated dose. As it is devoid of stimulant properties, fenfluramine has not been used as a drug of abuse.

2.2 Dexfenfluramine

2.2.1 Pharmacology

The pharmacokinetics of d-fenfluramine (i.e. dexfenfluramine) and l-fenfluramine when given as the racemic mixture are similar in human subjects (see McTavish & Heel 1992 for review). Maximal plasma concentrations are reached within 4 hours, and the \( t_{1/2} \) is 24 hours for both enantiomers (Caccia et al. 1982). However, administration for 10
days leads to greater accumulation of the $\textit{l}$-form of fenfluramine and norfenfluramine.

In laboratory animals, dexfenfluramine has a more selective action in serotonin release and reuptake than the racemic compound, whereas the $\textit{l}$-enantiomer has a significant effect on dopaminergic neurotransmission (Garattini et al. 1988). The overall anorectic effect of dexfenfluramine is greater than that of $\textit{l}$-fenfluramine in experimental animals (Garattini et al. 1988) and humans (Goodall et al. 1992).

Dexfenfluramine was found to possess twice the anorectic potency of the racemic mixture fenfluramine when directly compared in a group of 16 human subjects. Dexfenfluramine 30mg suppressed food intake to the same degree as fenfluramine 60mg, suggesting that the greater part of the anorectic activity of the racemic mixture (see previous section) lies in the $\textit{d}$-isomer (Silverstone et al. 1987). In keeping with the view that dexfenfluramine is acting via central serotoninergic pathways, its anorectic activity is markedly attenuated by the serotonin receptor-blocking drug metergoline in laboratory animals (Garratini et al. 1988) and humans (Goodall & Silverstone 1988).

Examination of the effect of dexfenfluramine on nutrient selection in nonobese humans reveals that, compared to dexamphetamine, it tends to reduce the intake of foods high in carbohydrate content more than that of foods containing a greater proportion of protein (Goodall et al. 1991). This is consistent with the observation that dexfenfluramine reduces the frequency of snacking in obese patients prone to consume a lot of carbohydrate-containing snacks, sometimes referred to as ‘carbohydrate cravers’ (Wurtman et al. 1987). In our study, a greater differential effect was seen between sweet and nonsweet food than between carbohydrate- and non-carbohydrate-containing foods (Goodall et al. 1991). The intake of sweet foods of varying carbohydrate content was significantly more resistant to the anorectic effect of dexfenfluramine suggesting that it acts differently on foods of differing taste more than on foods of different nutrient composition. This finding has important clinical implications. Women with self-diagnosed premenstrual syndrome tend to consume more sweet foods in the premenstrual phase of their cycle than at other times of the month (Goodall et al. 1988). Probably as a consequence of dexfenfluramine having less effect on the intake of sweet food, it was found to have less of an anorectic effect when given premenstrually (Hill & Blundell 1989). Thus, women who are prescribed dexfenfluramine to help them lose weight may need to adopt additional strategies to reduce their intake of sweet food premenstrually.

Obese subjects have been shown to be as responsive to the anorectic action of dexfenfluramine as nonobese volunteers (Hill & Blundell 1990). However, there was little specificity regarding carbohydrate-containing foods. The question of the degree to which dexfenfluramine has a selective action on carbohydrate-containing foods remains open. There are those (Wurtman et al. 1987) who are convinced that it does, while others are less certain. Our own findings implicate sweetness rather than carbohydrate content; many carbohydrate-containing snacks are also sweet.

As well as suppressing appetite, single doses of dexfenfluramine increase the energy expenditure induced by a meal (dietary thermogenesis) in normal-weight men (Munger et al. 1988) and in obese men (Scafff et al. 1989). However, after discontinuing dexfenfluramine which had been given continuously for a year to 10 obese woman, there was no significant change in 24-hour energy expenditure or in dietary thermogenesis (Breum et al. 1989). This finding suggests that over the longer term dexfenfluramine exerts no clinically relevant thermogenic effect. The implication is that its efficacy in helping obese patients lose weight is entirely due to its anorectic effect. Nevertheless, a short term thermogenic effect may cause the rapid improvement in diabetic tolerance which occurs before significant weight loss with dexfenfluramine administration.

2.2.2 Efficacy

Table II summarises some of the well controlled trials investigating the efficacy of dexfenfluramine in obesity.
Dexfenfluramine proved superior to placebo in 4 shorter term (12-week) trials in uncomplicated obesity, in obesity associated with hypertension and in neuroleptic-induced obesity. In all but one, the dose of dexfenfluramine was 15mg twice daily, the exception being 30mg twice daily (Enzi et al. 1988). Weight loss during active dexfenfluramine was uniformly at least twice as much as that on placebo. Where dexfenfluramine 30mg twice daily was given, weight loss was higher in both the active treatment and the placebo group than in the other studies, suggesting that it was not merely the increased dose of dexfenfluramine which led to a mean weight loss of 0.68kg per week while taking dexfenfluramine in this study. In 2 studies weight loss was attributable to a clear appetite-suppressant effect. Finer et al. (1985) noted that 28 of the 35 patients (80%) receiving dexfenfluramine ‘reported a decrease in hunger and/or food intake’ compared to 14 of the 41 on placebo (34%). Striawanakul et al. (1989) similarly remarked that ‘patients receiving dexfenfluramine reported a significant decrease in hunger’ assessed using a visual analogue scale. Finer et al. (1987) extended their observations for a further 3 months on an open-label basis in 31 patients. Weight loss continued throughout the whole 6-month observation period, although the rate appeared to slow during the last 2 or 3 months.

### Table II. Double-blind placebo-controlled trials of dexfenfluramine (DFL) in obesity

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Number of patients</th>
<th>dose</th>
<th>Diet</th>
<th>Mean weight loss at completion (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>men</td>
<td>women</td>
<td>mg</td>
<td></td>
</tr>
<tr>
<td><strong>3-month trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Finer et al. (1985)</td>
<td>&gt; 115% ideal weight</td>
<td>48</td>
<td>81</td>
<td>15 bid General advice</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>Unresponsive to dieting/lifestyle counselling</td>
<td>(39 hosp)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzi et al. (1988)</td>
<td>Mean BMI = 32</td>
<td>30</td>
<td>103</td>
<td>30 bid Low calorie [16 kcal/kg (67 kJ/kg) ideal bodyweight]</td>
<td>8.1</td>
</tr>
<tr>
<td>Striawanakul et al. (1989)</td>
<td>120-150% ideal weight</td>
<td>4</td>
<td>48</td>
<td>15 bid General advice</td>
<td>4.9</td>
</tr>
<tr>
<td>Kolanowski et al. (1988)</td>
<td>Obesity and mild hypertension</td>
<td>18</td>
<td></td>
<td>30 daily 1200-1500 kcal (5000-6250kJ)</td>
<td>5.1</td>
</tr>
<tr>
<td>Giordano et al. (1990)</td>
<td>130-190% ideal weight</td>
<td>35</td>
<td>98</td>
<td>15 bid ‘Moderate hypocalorie’</td>
<td>33%</td>
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<tr>
<td>Goodall et al. (1988)</td>
<td>Neuroleptic-induced obesity, BMI &gt; 27</td>
<td>33</td>
<td></td>
<td>15 bid Dietary advice</td>
<td>5.5</td>
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<td><strong>6-month trials</strong></td>
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</tr>
<tr>
<td>Van Gaal et al. (1989)</td>
<td>Mean BMI = 34: android; gluteofemoral</td>
<td>39</td>
<td>15 bid 1000 kcal (4200kJ)</td>
<td>13.7</td>
<td>8.4</td>
</tr>
<tr>
<td>Noble (1990)</td>
<td>‘Partially successful dieters’ &gt; 110% ideal weight</td>
<td>13</td>
<td>47</td>
<td>15 bid 1200-1500 kcal (5000-6250 kJ)</td>
<td>6.2</td>
</tr>
<tr>
<td><strong>1-year trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guy-Grand et al. (1989)</td>
<td>&gt; 120% ideal weight</td>
<td>160</td>
<td>662</td>
<td>15 bid Low (but not very low) calorie diet</td>
<td>9.8</td>
</tr>
<tr>
<td>Tauber-Lassen et al. (1990)</td>
<td>NIDDM</td>
<td>40</td>
<td></td>
<td>15 bid 1200-1400 kcal (5000-6000kJ) diabetes diet</td>
<td>6.3</td>
</tr>
</tbody>
</table>

**Abbreviations:** hosp = hospital clinic; GP = general practice; bid = twice daily; BMI = body mass index; PL = placebo; NIDDM non-insulin-dependent diabetes mellitus.
In a 6-month placebo-controlled study involving 39 obese women, only those whose obesity was of the android type (‘apples’) appeared to benefit from dexfenfluramine whereas those whose obesity was gluteofemoral (‘pears’) did not (Van Gaal et al. 1989). Overall there was gratifying weight loss on both active and placebo treatments, probably due to more strict adherence to the dieting regimen than is usually the case, allowing less room for a drug effect to be seen.

A group of 66 overweight women who had lost some weight on a dietary regimen but who wanted to lose more, or to maintain their weight loss, were given either dexfenfluramine 15mg twice daily or placebo for 6 months while being seen regularly and counselled on a restricted calorie diet [1500 kcal/day (6300 kJ/day) for men and 1200 kcal/day (5000 kJ/day) for women]. As with the shorter term trials, the mean weight loss was twice as great with active medication than with placebo.

In the most comprehensive long term (1-year) study of any anorectic drug published to date, Guy-Grand et al. (1989) enlisted 822 obese patients (160 men, 662 women) from 24 centres in 9 European countries. The patients, who were all at least 20% above their ideal bodyweight, were randomly allocated to receive either dexfenfluramine (15mg twice daily) or placebo; all were prescribed a calorie-restricted diet. They were seen monthly for the first 2 months, and 2-monthly thereafter. By the end of 12 months, 189 placebo recipients (45%) had withdrawn, 84 (44%) because they were dissatisfied with their weight loss, compared with 49 of the 150 patients receiving dexfenfluramine (33%) who failed to complete. By the end of the trial, weight loss was significantly greater on active treatment, with more than twice as many patients losing at least 10% of their initial bodyweight. However, the time course of mean weight loss in the 256 dexfenfluramine recipients and the 227 receiving placebo who completed the trial was similar. Both groups showed a plateau effect, no weight being lost on average after the first 6 months, with a tendency to regain weight in the placebo group. After 6 months, the action of dexfenfluramine was more one of preventing weight regain than of promoting further weight loss; in the 2 months after the trial ended, patients who had been receiving dexfenfluramine gained more weight (2kg) than those given placebo (1kg) [Guy-Grand et al. 1989].

In a subgroup of obese diabetics, those receiving dexfenfluramine not only lost more weight but also achieved better diabetic control (Tauber-Lassen et al. 1990). Dexfenfluramine may have a direct effect on glucose utilisation and insulin sensitivity; after 1 week it has been shown to reduce insulin resistance independently of weight reduction (Scheen et al. 1988). Dexfenfluramine is also effective in neuroleptic-induced obesity (Goodall et al. 1988).

2.2.3 Adverse Effects

These appear to be relatively minor and short-lived (Turner 1990). In the 12-month placebo-controlled trial involving 882 patients (Guy Grand et al. 1989), dexfenfluramine was more often associated than placebo with tiredness (28 vs 20% of patients), diarrhoea (15 vs 9%), dry mouth (12 vs 4%), increased urinary frequency (7 vs 3%), and drowsiness (5 vs 2%).

There appears to be no risk of drug dependence with this compound.

2.3 Fluoxetine

2.3.1 Pharmacology

Fluoxetine is an antidepressant drug which, unlike the tricyclic antidepressants, was noted to cause weight loss rather than weight gain in depressed patients. Fluoxetine acts by enhancing central serotonergic neurotransmission through inhibiting the reuptake of serotonin into presynaptic neurons (Fuller & Wong 1989).

Fluoxetine is well absorbed orally. It has a long t₁/₂ of some 5 days and that of its active metabolite norfluoxetine is even longer, 7 to 13 days.

In nonobese healthy human volunteers fluoxetine 60mg daily for 2 weeks caused a statistically significant decrease in food intake and bodyweight in a placebo-controlled double-blind crossover trial (McGuirk & Silverstone 1990a). A subsequent 1-month placebo comparison in obese subjects revealed an even greater appetite suppressant effect
(McGuirk & Silverstone 1990b). Its effect on nutrient selection is variable. In animals it appears to be more active in suppressing the intake of carbohydrate-containing food (Fuller & Wong 1989), but this nutrient selectivity is less clear in humans. While some (McGuirk & Silverstone 1990b; Pijl et al. 1989) have found that fluoxetine curtailed the intake of carbohydrate more than protein, others have not (Breum et al. 1990).

2.3.2 Efficacy

A dose-ranging parallel study has been carried out comparing fixed doses of fluoxetine 10, 20, 40 and 60mg and placebo. Each dose was given for 8 weeks to 131 obese patients who were at least 20% in excess of their ideal bodyweight (Levine et al. 1989). The greatest mean weight loss (3.91kg) occurred in the group who received 60mg daily. There was a clearcut dose-response with those receiving lower doses losing less weight. Fluoxetine 60 to 80mg daily was shown to be as effective as the stimulant anorectic benzphetamine and superior to placebo in another 8-week trial involving 150 patients (Ferguson & Feighner 1987).

In a trial lasting 52 weeks involving obese patients who were binge eaters (n = 22) and those who were not (n = 23), both types of patient responded better to behaviour therapy plus fluoxetine than to behaviour therapy plus placebo (mean weight change an increase of 0.6kg) [Marcus et al. 1990]. Weight loss with fluoxetine plateaued after 20 weeks in the binge eaters but not in the other group.

Obese individuals with non-insulin-dependent diabetes (NIDDM) show an improvement in glucose tolerance as well as weight loss after relatively short term treatment (8 to 12 weeks) with fluoxetine but not placebo (Kutnowski et al. 1990; Rosenstock et al. 1987; Wise 1989).

2.3.3 Adverse Events

In obese patients the adverse events profile of fluoxetine is different from that seen when the drug is given to patients with depressive illness (Zerbe 1987). In the dose-ranging study of Levine et al. (1989), side effects more commonly reported with higher fluoxetine doses than with placebo were insomnia, drowsiness and diarrhoea; in depressed patients nausea is experienced more frequently.

Serious adverse effects other than drug-related allergic rashes are uncommon (Zerbe 1987) and there appears to be little risk of drug dependence. Fluoxetine has no detectable effect on psychomotor performance.

3. The Place of Appetite Suppressants in the Management of Obesity

3.1 Indications

There is no consensus on the use of anorectic drugs in clinical practice. On the contrary, views range widely from a total rejection through grudging acceptance to a clear recommendation in appropriate patients. The British National Formulary (1991) dismisses appetite suppressants out of hand as being ‘of no real value in the treatment of obesity since they do not improve the long-term outlook’. The American Medical Association (1990), while less extreme in its condemnation, remains clearly unenthusiastic: ‘Occasionally, adjunctive use of anorexants will help patients who respond unsatisfactorily.’ The Royal College of Physicians (1983) adopts a more measured tone: ‘Anorectic drugs may be a useful adjunct to dietary and behaviour therapy... but should not be used on their own.’

In order to place anorectic drugs in perspective, it should be recognised that most obese patients do not eat more than their contemporaries, therefore what they need is help in reducing their dietary intake below the norms of their society. Unfortunately, despite evidence to the contrary, obese patients are frequently viewed as self-indulgent gluttons totally lacking in willpower for whom moral exhortation rather than pharmacological assistance is required.

When given as part of an integrated dietary programme to patients thought to be medically at risk, anorectic drugs can, as we have seen, be of real benefit in helping them lose weight. The major charges levelled against anorectic drugs are: (a) the rate of weight loss slows with time (this is usually
attributed to tolerance developing); (b) when the patient stops taking the drug, he or she regains the lost weight; (c) anorectic drugs do not re-educate patients to adopt 'good' eating habits; and (d) they may lead to drug dependence and abuse and are therefore dangerous (as well as useless). I shall examine each of these charges in turn.

While it is true that the rate of weight loss plateaus after 5 to 6 months of continuous treatment, this happens with most weight loss regimens, including surgery. It occurs partly because the body adapts to a lowered calorie intake by reducing the resting metabolic rate; thus there comes a time when the lowered energy intake is matched by the reduced energy output and weight loss ceases. This is hardly the fault of the drug; in fact, true drug tolerance rarely develops. In a study designed to investigate this point, we allocated a series of obese patients into 3 groups: one group received amfepramone 75 mg/day continuously for 4 months, another group received amfepramone in the first and third months and placebo in the remaining months, and the third group received amfepramone during the second and fourth months with placebo in months 1 and 3 (Silverstone 1974). If tolerance was the predominant cause of the decreasing rate of weight loss observed over time, then the patients in the third group who received amfepramone for the first time in month 2 should have shown a greater drug effect than those in the first group who had been receiving it continuously. We found that they did not, the weight lost was almost identical. The same was true in the fourth month; those who had been receiving the drug continuously during the previous 3 months lost no less weight in month 4 than those who had only taken amfepramone during the second month.

Weight regain after stopping anorectic drug treatment reflects the release from the continuing anorectic effect which these drugs exert for as long as they are taken, despite no further weight loss occurring. That the drugs cease to work when they are no longer being taken is hardly surprising; this is a totally unrealistic expectation of any drug.

Finally, the only evidence for physical dependence with consequent withdrawal symptoms relates to the nonstimulant anorectic fenfluramine. Suddenly stopping fenfluramine can occasionally lead to a depressive syndrome. The risk of this happening is minimised by gradual dose reduction. Psychological dependence is similarly uncommon; most patients prescribed anorectic drugs have little or no difficulty in stopping treatment. The term 'drug abuse' refers to the self-administration of a substance taken for nontherapeutic purposes, usually in greater than therapeutic doses, by nonpatients. Such abuse has really only occurred with amphetamine, dexamphetamine and phentermine, drugs which are no longer recommended for the treatment of obesity and which are the subject of rigid restriction and control in most countries. For the anorectic compounds considered in this review, examples of abuse are rare.

Anorectic drugs can play a useful role in the overall management of obesity provided it is recognised that the rationale of such treatment is to provide assistance with keeping to a restricted calorie diet. Therefore, they should only be given in conjunction with appropriate dietary information and advice, which itself should be reinforced at frequent intervals and accompanied by instruction in the range of strategies which have been found to assist patients avoid overeating and losing weight (i.e. behaviour modification). Further, such drugs should be restricted to those medically at risk either through the severity of their obesity (i.e. BMI ≥ 30) or those with a serious complication of being overweight such as having NIDDM or hypertension. The place of drug therapy in promoting weight loss purely for cosmetic purposes is questionable. Appetite suppressants should not be used in childhood obesity as they may suppress growth.

When to start treatment with anorectic drugs depends on the individual preferences of doctor and patient. A good case can be made for starting anorectic drug treatment (combined with dietary instruction and behavioural advice) when the patient first presents, provided such treatment is appropriate on clinical grounds. It is likely that he or she has tried to lose weight before, either unaided or using some other dietary aid such as attending a slimming group. The greater immediate
weight loss together with the reduced discomfort of dieting associated with appetite suppressant treatment is likely to provide a much needed boost to morale and increase motivation. On the other hand, there are those who think that anorectic drugs should be held in reserve to be used only when the patient's resolution is flagging and weight loss waning. It is a matter which should largely be left to the patient to decide after full discussion of the advantages and disadvantages of drug treatment and the relative merits of starting earlier or later in the comprehensive treatment programme (which should include graded exercise). By and large, patients find anorectic drugs helpful (Ashwell 1973).

3.2 Duration of Treatment

Obesity is a lifelong condition; the great majority who lose weight regain it. Thus, it follows that treatment necessarily should similarly be long term. Even modest weight loss, provided it is maintained, brings advantages in terms of health. In the case of NIDDM, improved glucose tolerance occurs quite early on in treatment. Longer term treatment with anorectic drugs maintains greater weight loss than placebo; weight loss is reversed when therapy is stopped (Guy-Grand et al. 1990; Lawson et al. 1970; Miach et al. 1986). Continuing treatment for several years, if not for life, therefore may appear appropriate. Such a view flies in the face of the usual recommendations that if anorectic drugs are to be used at all, they should only be given for a short time, say 3 to 4 months.

My own view accords closely with that of Munro and Ford (1982) who recommend short term use (up to 6 months) in selected patients with significant obesity, in whom there is a well-defined short term objective. Longer term use may be justified to prevent weight regain (often referred to as weight maintenance). There is as yet insufficient information on prolonged use (> 1 year) either in terms of efficacy of safety. Until we have this, caution is advisable in prescribing these drugs continuously over the longer term, although there is no evidence to suggest they are likely to be harmful.

As obesity is a lifelong problem, a much longer term view of management than is usually taken needs to be adopted at the outset. It is unlikely that any single tactic will work over the long term. What is required is a range of therapeutic interventions which can be combined and/or alternated over years. Such a policy of 'ringing the changes' is likely to be more effective in maintaining motivation and prolonging success. Although in one study weight loss was less well maintained following the combination of fenfluramine and behaviour modification than with behaviour modification alone (Craighead et al. 1981), others have found a combination of anorectic and behaviour therapy (Marcus et al. 1990) more effective. Alternating treatments can help; giving dexfenfluramine, following successful weight loss on a very low calorie diet, was much more successful than placebo in preventing weight regain (Finer & Finer 1989). Thus, for the management of severe obesity, a short period (1 to 2 months) on a very low calorie diet followed by a more lenient diet accompanied by anorectic drug treatment for, say 4 to 6 months, followed by an active exercise programme together with regular behavioural modification instructions, followed in turn by attendance at a slimming group for a while may be more effective over the long term than relying on any one of these approaches alone. Imaginative choreography of all these various treatments is what is required. Anorectic drugs can play a useful role in such a programme.

3.3 Choice of Drug

The choice lies first of all between the catecholaminergic and the serotoninergic compounds. For patients with a history of depression the catecholamine-mediated drugs are preferred, although it should be stated that in a longer term trial of dexfenfluramine depression did not feature highly (Feeney & Silverstone, unpublished data). Of the catecholamine drugs, amfepramone, phentermine and mazindol are equally effective, with a similar side effect profile (see section 1), and intermittent treatment is as good as continuous with all 3 drugs (Munro 1979). For the more anxious patient a serotoninergic drug is preferable. The dextrorota-
tory isomer of fenfluramine (i.e. dexfenfluramine) is preferable to the racemic mixture because it has greater potency with fewer side effects (Silverstone et al. 1987). Fluoxetine is not yet licenced for the treatment of obesity in many countries and the number of clinical trials published thus far is limited.

The combination of a catecholaminergic and serotonin anorectic may be more effective than either alone (Weintraub et al. 1981); this approach is relatively untried and requires further study.

4. Conclusions

Anorectic drugs have the property their name implies: they suppress appetite. This results in a reduction in food intake which over time leads to a loss in weight. All the compounds licensed for use in obesity (Table 1) are more effective than placebo in helping obese patients lose weight when taken in conjunction with a calorie-restricted diet. Although the rate of weight loss falls with time, they continue to exert some effect on food intake as weight regain occurs when they are stopped. They may also have a role in weight maintenance. There is little to choose between them in terms of efficacy, all are relatively safe and unlikely to give rise to dependence, and they are very rarely used as drugs of abuse by obese patients taking them under medical supervision.

Anorectic drugs can play a useful role in an overall weight reduction programme, and should only be prescribed as part of such a programme. In many cases short term use is sufficient, but longer term administration, either intermittently or in combination, may be of benefit. The indications and disadvantages of long term administration warrant further study.

Obesity poses a serious health hazard. Obese patients need all the help they can get in the difficult task of losing weight and maintaining a lower bodyweight; anorectic drugs should not be denied them on the basis of prejudice and misconceptions.

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