Drugs in Obesity

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SUMMARY

The principles considered in the management of obesity are discussed; they include education and motivation, diet, exercise and drugs. Drugs provide no cure but may need to be used during an initial period of dietary regulation. Amphetamine and related drugs should not be used. Fenfluramine is approved for use; it appears to have the least undesirable side-effects.

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Drugs (medicines) provide no cure for obesity. It is in fact important to decide whether they should be used at all. At best they provide a crutch to be used during an initial period of dietary regulation; some physicians never use anorectics in initial treatment. It is the basic psychological disturbance that must be treated.

The principles to be considered in the management of obesity include: education and motivation, diet, exercise and drugs.

Education and Motivation

This is the most important aspect of the long-term management of obesity.

Obesity must be considered a life-long problem involving a careful balance of food intake against energy expenditure required to achieve, and thereafter to maintain, a normal body weight. Important, therefore, is education of the patient in the basic principles of nutrition, and a modification of the incorrect eating patterns offers greater chance of successful treatment. The motivation of the patient must be strong enough to ensure acceptance of a new attitude to eating. Adjunctive measures aimed at modifying behaviour, such as psychotherapy and group therapy, may help in individual cases.

Psychological factors in response to stress would appear to be the basis of some cases of obesity, but the use of psychotropic drugs is limited and for specific indications only. There must be a good patient-therapist relationship; encouragement is a good stimulus to success.

Diet

In the long term the only factor that causes reduction in weight (mass) is a decrease in the intake of calories to a level below that of energy loss. The aim must be to re-educate the patient in correct habits of eating, and any abnormal eating patterns such as nibbling and night-eating must be corrected.

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Proprietary 'slimming' foods should be discouraged. They are expensive and, in the case of diabetic foods, rich in calories because of sorbitol content. They may mislead the patient to suppose that they may be consumed in addition to his diet and that he will still lose weight. Alcoholic beverages must be avoided; alcohol is a drug that provides calories.

Exercise

Obese patients in whom there are no medical contraindications should be advised to increase their daily activity, particularly those persons with sedentary occupations. It is a useful adjunct to dietary restriction. The benefits of exercise are difficult to demonstrate in the short-term management of obesity, but in the long term they are much more evident.

DRUGS

It must be emphasised that the role of drug therapy is not as definitive treatment but rather as supportive therapy. The medicine of choice is the one that produces the best results and causes fewest side-effects.

Diuretics

These may produce reduction in body weight, but this is due to loss of fluid and has little or no effect in the long term, where the basic problem is to produce loss of fat from adipose tissue.

Bulk Agents

Bulk preparations such as methylcellulose have been prescribed in the hope that they will produce a feeling of satiety. Many obese patients do not experience the sensation of satiety. Also, this agent does not produce loss of appetite. Bulk agents appear to be of little value, perhaps exerting a placebo effect.

Methylcellulose is a laxative. There are many objections to the use of this and other purgatives, e.g. phenolphthalein, to reduce body weight.[1]

It should hardly be necessary to mention in this context that obese persons want to eat proper food.

Thyroxine

The thyroid hormones thyroxine and liothyronine are indicated in patients who have hypothyroidism. The use of these agents in euthyroid subjects is potentially dangerous and not justified.

Biguanides

Phenformin and metformin may produce loss of weight in obese diabetic patients and they may also achieve this in non-diabetic individuals. The effect is less than that of medicines like fenfluramine, and the side-effects, especially gastro-intestinal symptoms produced by the necessary high doses, are unacceptable to most patients. They are not recommended for non-diabetic patients. They are potentially harmful when used in obese maturity-onset diabetics.[2]

Central Nervous Stimulants

Amphetamine, dexamphetamine, and certain amphetamine-like compounds such as benzphetamine, phentermine, chlorphentermine, propylhexedrine, diethylpropion, phenmetrazine and phendimetrazine (transformed to its *N*-oxide and phenmetrazine in the body)[3] are claimed to act on the appetite control centre in the hypothalamus, thus causing a decrease in physiological hunger; however, there is reason to suppose that more likely they assist in the reduction of body mass by an action on the higher centres in the central nervous system.

Amphetamine, dexamphetamine, methamphetamine and phenmetrazine are banned in South Africa but a number of other agents (mentioned above) with similar actions are available for use to control the appetite. They have not been conclusively demonstrated to differ significantly from the amphetamine compounds. In varying degree they all induce central stimulant effects with increased mental and physical activity and sometimes excitement and agitation. Many patients experience a 'lift'.

These stimulant agents are contra-indicated in patients with a history of psychiatric disorder, severe angina, and recent myocardial infarction. Great care is necessary in those with hypertension and cardiac disease; they are contra-indicated in patients who have severe hypertension. Amphetamine-like drugs, but not fenfluramine, antagonise adrenergic neurone-blocking drugs and may cause sudden rises in blood pressure in patients receiving these antihypertensive drugs (guanethidine, bethanidine and debrisoquine).[4]

These drugs should be used with caution in patients who are sensitive to the adrenergic agents. They are therefore contra-indicated in patients receiving monoamine oxidase (MAO) inhibitors. Also, interaction with tyramine in tyramine-containing foods is a potential cause of dangerous reaction. Hyperthyroidism and glaucoma are also contra-indications to the use of this type of drug.

Adverse effects produced by these amphetamine-like compounds include anxiety, tremors, dizziness, tachycardia, palpitations, headache, nausea, dry mouth, constipation, insomnia and blurred vision (mydriasis). Since they cause dilatation of the pupil in predisposed patients (with narrow iridocorneal angle), these drugs must be regarded as potential inducers of glaucoma.[5]

Continued administration leads to tolerance of the drug and loss of the anorectic effect; to continue the effect doses must be increased, which tends to produce disagreeable effects, especially nervousness and insomnia. They should be used in short courses of only a few weeks since long-term use may result in dependence and the possibility of withdrawal reactions.

These drugs have been extensively abused. There are authorities who state that not only amphetamines but also close amphetamine derivatives must never be given.

Ephedrine is a sympathomimetic agent which has a stimulant effect on the central nervous system. It is advertised directly to the public and sold over the counter, but is not mentioned in standard works as an agent to be used in the management of obesity. When given in dosage adequate for depression of appetite it causes anxiety and insomnia and other unwanted side-effects similar to those produced by the other central nervous stimulants. It is contra-indicated in hypertension and cardiovascular disease. It should not be administered concurrently with MAO inhibitors.

Mazindol is a tricyclic imidazo-iso-indole compound which suppresses the feeling of hunger. It is chemically different from the amphetamines, and its site of action in the brain is stated to be different. Nevertheless, it has a low degree of amphetamine-like effect.[6] Patients may complain of central nervous stimulation, nervousness, agitation, dizziness, insomnia, dry mouth, nausea, and constipation.[7,8] Some may complain of sexual impotence.[9] It can cause increase in the pulse rate and pupillary diameter.[10] This drug also should not be used in patients with glaucoma or with severe cardiac, renal and hepatic disease, in agitated states, or during therapy with MAO inhibitors. It potentiates adrenergic agents. It is contra-indicated in hypertensive patients.

The stimulant drugs mentioned keep the patient awake at night and may tempt him to embark on a midnight raid on the refrigerator.

Fenfluramine

Although fenfluramine is an amphetamine derivative, it possesses sedative rather than stimulant properties. It has special features. It contains a trifluoromethyl radical in the benzene ring. It is not degraded to amphetamine; it is excreted unchanged or as norfenfluramine. It lacks mood-elevating properties; it does not have the euphoriant effect of the stimulant amphetamines and derivatives which makes them potentially dangerous drugs. Its anorectic effect lasts about twice as long as that of the amphetamines; it has interesting metabolic effects as well as anorectic effects. Also, it lowers the blood pressure in patients who have mild or moderate hypertension.

The anti-obesity action of fenfluramine is not clearly understood. It would appear that factors both peripheral (metabolic) and central (cephalotropic) are involved.[10a,b,11] The site of action and effects are as follows:

Site of action	*Effect*
Cortex	Sedation
	Suggestion
Hypothalamus	
Appestat	Anorexigenic
Releasing factor	Growth hormone release
Peripheral	Metabolic changes

The sedative effect may cause a decrease in food intake in obese subjects in whom there are psychological disturbances because they are sensitive about their appear-

ance or in whom there are such symptoms as anxiety, irritability, or in whom loneliness and frustration produce an irresistible urge to eat — the 'compulsive' eaters.

The influence of suggestion may account for loss of weight in obese persons at the beginning of any new treatment or consultation with a new doctor. However, a double-blind trial of dummy and fenfluramine tablets in obese hypertensive patients has revealed a greater weight loss from fenfluramine than from the dummy tablets.[12,13]

Certain investigators state that fenfluramine exerts a controlling influence on the appestat. It is regarded as producing depression of food intake and control of eating behaviour through a direct inhibitory action on the hypothalamus or neighbouring structures.[10a,b]

Endocrine factors, such as growth hormone, may be influenced by fenfluramine which produces various central effects during sleep, and weight loss may be associated with increase of electro-encephalographic slow-wave sleep during which the large nocturnal secretion of growth hormone occurs.[14]

As far as the metabolic actions are concerned, it has been shown that the drug affects the metabolism of carbohydrate and fat directly in the tissues:[10] by diverting carbohydrate from adipose tissue to muscle; by mobilising fat and reducing lipid synthesis; and by inhibiting the activity of certain enzymes.

It has been demonstrated that in man fenfluramine inhibits lipogenesis, and that it increases lipolysis.[15] Cholesterol levels are unchanged, but when abnormally high they may be lowered. It also produces an increase in peripheral glucose utilisation: blood glucose levels have been shown to be reduced and improved glucose tolerance produced, when the drug has been given for some time.

Fenfluramine is effective in reducing weight in many obese patients. It has also proved effective in the treatment of refractory obesity.[16] It is the best of the anti-obesity drugs for obese patients who have hypertension.[17] It is also useful in obese patients with diabetes. In maturity-onset diabetes carbohydrate restriction can produce successful control in a majority of patients. For diet-unresponsive patients fenfluramine provides an effective alternative to sulphonylureas and biguanides.[10]

Another indication for the use of fenfluramine is in patients who gain weight while on long-term psychotropic drugs. These subjects should be examined for cardiac, renal or thyroid disease, and should be questioned regarding the use of other drugs. Dieting, diuretics, or a trial of fenfluramine might be appropriate in special circumstances.[18]

Tolerance, a major limitation to the long-term use of the anti-obesity agents mentioned, does not develop to fenfluramine.

Side-effects produced by fenfluramine include sedation, which is not always undesirable, but on rare occasions it may be marked in degree; this can usually be avoided by starting with low doses which are increased to full therapeutic doses over a period of 3 weeks. Looseness of the bowels, rarely frank diarrhoea, may occur, but this is minimised by the stepwise increase in the dosage regimen recommended.

Fenfluramine can cause a fall in blood pressure in patients receiving rauwolfia or methyldopa.[4] As with so many other drugs, it should not be used with MAO inhibitors.

It is not recommended that fenfluramine be administered during the first trimester of pregnancy unless the physician considers that the benefits outweigh any possible risk. *In vitro* cultures of fetal skin cells and amniotic fluid cells were not affected by concentrations of fenfluramine 100 times higher than would be found in body fluids *in vivo*. This suggests that the drug would have no adverse effects on the fetus if taken during pregnancy.

Fenfluramine is a drug of dependence but not of abuse.[19] Some dependence may occur, and sudden withdrawal followed by depression, especially marked after 4 days; it is best to withdraw the drug gradually. The drug is not subject to control by the WHO Committee on Drug Dependence. The Bureau of Narcotics and Drugs Dependence (BNDD) also accepted that the drug presents virtually no risk of abuse or dependence and has given it least restrictive scheduling. In the USA the Food and Drug Administration (FDA) has approved its use, having concluded that it is the only really effective anti-obesity agent for consistent weight loss.

In the *British National Formulary*[20] (BNF) (1974 - 76) it is stated that: 'Amphetamine and related drugs, including phenmetrazine, phentermine, and diethylpropion, should not be used to depress appetite, as the drugs in this group are liable to cause habituation and psychotic reactions in varying degrees', and 'if it is thought necessary to give a drug to help the patient in the beginning, fenfluramine appears to have the least undesirable side-effects'.

Fenfluramine is not included in the Misuse of Drugs Act (1971) in England. It is the only anti-obesity drug included in the new *British Pharmacopoeia*.

In Canada, the amphetamines and benzphetamine, phenmetrazine and phendimetrazine are banned for use in obesity. In the Netherlands, although never marketed, phendimetrazine, phenmetrazine and benzphetamine are controlled under the Amphetamine Act listed in Artikel 3 (b) in the *Nederlandse Staatscourant* of 25 January 1972.

In South Africa there is a Draft Bill, the Medicines Control Bill (*Government Gazette* No. 3997, 1973), to be called the Medicines Control Act 1974, when promulgated. The anti-obesity drugs are listed therein, as follows:

Schedule E — fenfluramine, propylhexedrine.
Schedule G — chlorphentermine, diethylpropion, phentermine.
Schedule H — benzphetamine, phendimetrazine.
Schedule J (banned drugs) — amphetamine, dexamphetamine, methamphetamine, phenmetrazine.

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