The anorectic and hypotensive effect of fenfluramine in obesity

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SUMMARY. A trial is reported of the hypotensive and anorectic effect of fenfluramine in general practice when combined with Yudkin's modification of the Marriott diet. The results confirm the anorectic effect and show that the maximum reduction of blood pressure occurs during the first four weeks of treatment.

Introduction

THE medical management of obesity is often difficult. The causes are multifactorial, the patient's motivation to reduce weight may not be strong, and the physician needs to encourage constantly, explain carefully, and follow up all patients assiduously.

Most authorities have defined obesity as an excess weight at least ten per cent above the desired weight for height, age, sex, and skeletal frame. In 1960 the Metropolitan Life Insurance Company of New York published tables of desirable weights based upon these criteria which have gained general acceptance.

Apart from the adverse psychological effects of fatness, obesity may be associated with the development of significant physical disease. The Framingham Study (Kannel *et al.*, 1967) has shown that sudden death is markedly increased in men who are more than 20 per cent overweight, and, conversely, that those who reduce weight live longer. Marks (1960) quoted six reports which demonstrate that there is an increased incidence of hypertension among obese patients. Pincherle and Wright (1967) found that in 567 obese men 84 (15 per cent) had a diastolic pressure above 100 mm Hg compared with only 70 (six per cent) of 1,225 men of average weight. The hypertensive tendency may be apparent even in the second decade of life (Christakis *et al.*, 1968). Berlyne (1958) showed that the extra effort required to move the diaphragm against the impediment of a thorax and abdomen burdened by excess fat could bring about cardiorespiratory failure, but the effects of obesity in the production of coronary heart disease should not be overemphasized in comparison with the effects of raised plasma cholesterol, high blood pressure, and cigarette smoking (Royal College of Physicians and British Cardiac Society, 1976). Long-standing obesity is reported to be associated with an increased incidence of maturity onset diabetes, glucose intolerance, and hypertension (Marble *et al.*, 1971).

The management of obesity

Patients who seek advice about obesity are more often distressed by the psychosocial aspects than by the physical effects. Usually they have failed with self-imposed dietary control and the reasons for this should be determined. The direct question, "Why do you want to lose weight?", will often provide a revealing answer.

The management of an obese patient must take account of the patient's previous medical history, general physical condition, and any psychosocial factors which may have been instrumental in the production of the obesity. Obesity may be an expression of an underlying neurosis; for example, Nicholson (1946) showed that dietary advice alone was often less effective than when combined with psychotherapy. It is important to achieve a good rapport and the patient may need to be encouraged frequently.

Many patients have an unrealistic concept of the rate at which weight loss by diet may be expected; an average loss of about 0·45 kg (one pound) a week must be rated excellent. Some patients fail to appreciate that obesity may be the result, rather than the cause, of unhappiness and the practitioner should be aware of the possible presence of a psychological disorder and of the need to include psychotherapy when appropriate.

Some obese patients may seek advice for symptoms attributable to another disease, for example, ischaemic heart disease, diabetes mellitus, or hiatus hernia, to which the obesity is contributory.

Weight reduction may be achieved by dietary control alone or by dietary control plus an appetite suppressant.

The indications for an appetite suppressant have been summarized by Craddock (1973) and include:

1. To enable a co-operative patient to adhere strictly to a diet once the initial motivation has worn off.
2. As a temporary measure at the start of treatment.
3. In short courses at six or 12-monthly intervals, to enable patients who have relapsed to regain normal weight.

The place of fenfluramine

Fenfluramine is an appetite suppressant which is believed to act by stimulating the satiety centre of the hypothalamus (Anand, 1971). It has a mild sedative effect and is slowly excreted, especially if the urine is alkaline (Beckett and Brooks, 1967). Fenfluramine has little effect on metabolism; such effects as have been noticed are mainly associated with changes resulting from the previous adaptation to an abnormally high food intake (Garrow *et al.*, 1972; Hipkin and Davis, 1976). Some investigators have reported that fenfluramine has caused reduction of blood pressure in most hypertensive patients (Waal-Manning and Simpson, 1969; General Practitioner Research Group, 1971).

In vitro experiments have shown that fenfluramine inhibits pancreatic lipase (Dannenburg and Ward, 1971) and lipid synthesis (Wilson and Galton, 1971). Sapeika and Zwarenstein (1971) demonstrated that fenfluramine inhibited phosphoglucomutase and pyruvate kinase activity by the removal of magnesium ions, thereby altering carbohydrate metabolism. Lewis and his colleagues (1971) reported an increase in the production of growth hormone during sleep, and Pawan (1969) showed that in normal individuals there was an increase in free glycerol, free fatty acids, and blood ketones, with a reduction in plasma triglycerides. Bliss and his colleagues (1972) demonstrated that in patients with peripheral arterial disease fenfluramine raised serum glucose, serum cholesterol, and beta-lipoproteins.

Fenfluramine is marketed as 'Ponderax' and is available in tablets of 20 mg and capsules of 60 mg. The tablets are usually taken twice daily, half an hour before meals. The starting dose may be one or two tablets daily, increasing to a maximum of four tablets, though up to 12 tablets a day have been used. Adverse effects include lethargy, diarrhoea, and other gastrointestinal disturbances. Occasionally, vivid dreams and reversible alopecia have been reported. The major adverse effect is depression, which is most likely to occur if the drug is withdrawn rapidly, even in patients without a history of depression. Fenfluramine should not, therefore, be prescribed intermittently and should always be withdrawn gradually. Individual response is variable, but it appears to be most effective in the tense, anxious patient. It is best avoided if the patient is already depressed.

Aims

I decided to compare the effects of treating obese patients by diet alone and by diet plus fenfluramine, and to measure the hypotensive effect in normotensive and hypertensive patients. I also sought to examine the effect of fenfluramine on depression.

Method

The Metropolitan Life Insurance Company tables were used to define obesity. All patients were asked to attend a special clinic arranged to take place at the same time each week and, at each attendance, to wear as nearly as possible the same clothing. Thus, they were weighed whenever possible at the same time on the same day of the week, and wearing the same clothing. Before being weighed patients were requested to evacuate the bladder and bowel.

At the first consultation, the age, sex, height (without shoes), build and weight (in indoor clothing and without shoes) were noted for each patient. Enquiries were made about any previous history of pre-eclamptic toxaemia, hypertension (whether treated or not), depression, previous attempts at weight reduction, and women were asked whether or not they had been using an oral contraceptive. Previous treatment with hypotensive drugs was noted, but patients who were already on treatment for any other condition were excluded from the trial. The blood pressure, using a Rapid Manuel sphygmomanometer, and pulse rate were recorded before and after a general physical examination. These two blood pressure readings were averaged and regarded as the 'resting blood pressure'.

Patients were informed of their actual weight and of their 'ideal' weight as derived from the Metropolitan Life Insurance Company tables. They were divided into three groups Group A (86 patients) consisted of normotensive patients, who were treated with fenfluramine plus diet. Six patients defaulted from this group. Group B (100 patients) included hypertensive patients, who were treated with fenfluramine plus diet. Four defaulted. Group C (16 patients) included both normotensive and hypertensive patients who were treated by diet alone. Only one person in this group defaulted.

Yudkin and Carey's (1960) modification of the Marriott diet was used for all patients.

Of the 202 patients aged 15 to 75 years who were admitted to the trial (Table 1), 11 patients defaulted. Of the remaining 191 patients, 37 (19·4 per cent) were men and 154 (80·6 per cent) were women.

For the first month each patient was seen at weekly intervals and, thereafter, at four-weekly intervals for 12 months. All patients were followed up for a further 12 months after treatment ceased. Most of the patients for whom fenfluramine was prescribed needed four tablets a day, but a few required six tablets.

Results

Weight reduction

Of the 176 patients in Groups A and B (excluding

Table 1. Age of patients admitted to the trial.

	Patients	
Age (years)	Number	Percentage
15-24	16	*7.9*
25-34	38	*18.8*
35-44	50	*24.8*
45-54	57	*28.2*
55-64	33	*16.3*
65-75	8	*4.0*
Total	202	*100.0*

Table 2. Average weight loss by patient groups.

	Average weight		*Average weight loss*	
	At beginning (lbs)	At end (lbs)	lbs	Percentage
Group A	168.92	152.11	16.81	*9.95*
Group B	188.42	169.30	19.12	*10.15*
Group C	159.59	149.59	10.00	*6.27*

defaulters), 36 (20·5 per cent) reached their target weight, compared with only two (13·3 per cent) of the 15 patients in Group C. Four patients in Group A abandoned fenfluramine therapy because of pregnancy, loss of libido, lethargy, or marital disharmony. In Group B, three patients stopped fenfluramine: one developed severe headache, another general malaise, and the third developed hypertension which proved difficult to control.

The rate of weight reduction in all groups was greater during the first three months of treatment (Figure 1). The average weight reduction in each group was not only greater when fenfluramine was used, but was also greater in groups with higher initial average weight (Table 2).

The rate of weight gain in Groups A and B after stopping treatment is shown in Figure 2.

Figure 1. *Average weight loss during treatment by patient group.*

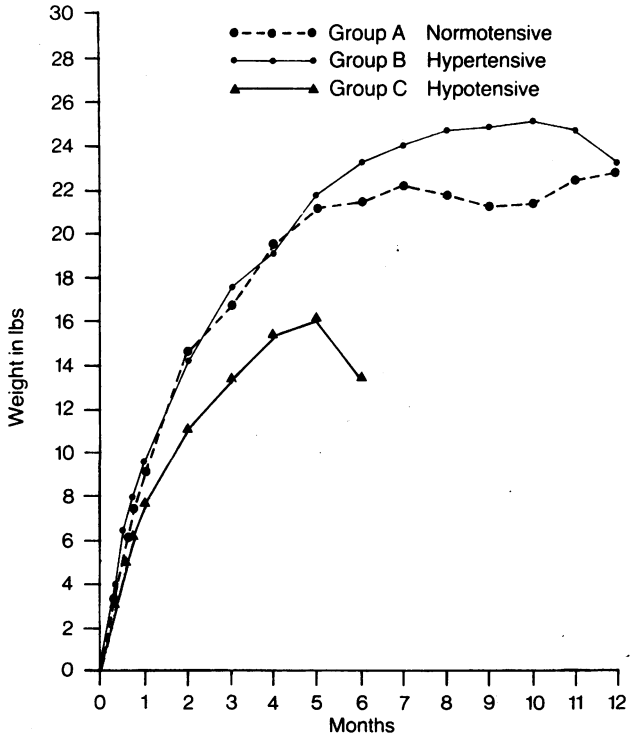
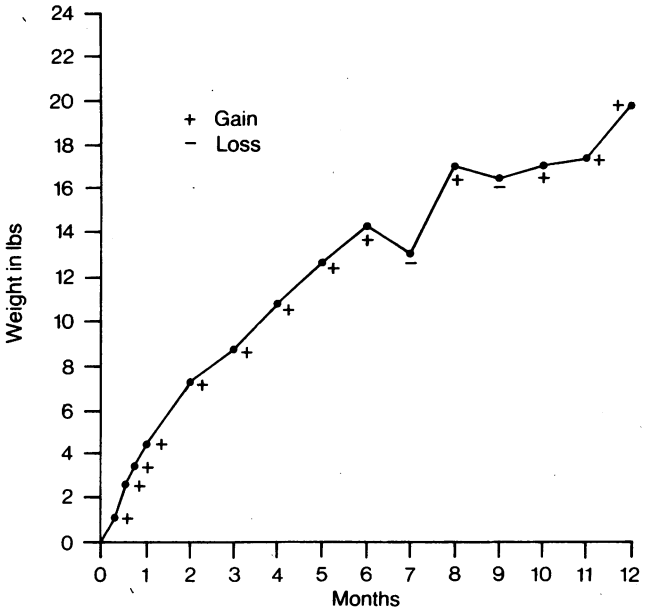


Figure 2. *Average weight change in Groups A and B after cessation of treatment.*



Blood pressure

Blood pressure fell during treatment in all three groups; there was a greater proportionate fall in patients treated with fenfluramine (Table 3). Figures 3 and 4 show that the rate of fall was greatest during the first four weeks of treatment. Blood pressure rose again when treatment ceased. Of the patients treated with fenfluramine, the average rate and amount of blood pressure gain was greater in previously normotensive patients (Figure 5).

Depression

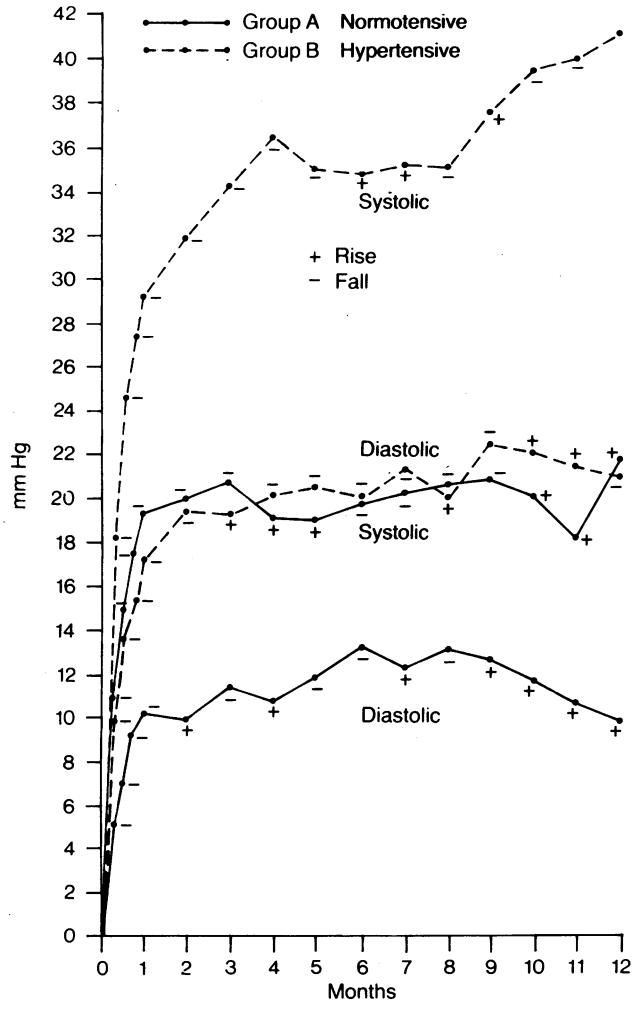
Of the 176 patients treated with fenfluramine, 39 (22·2 per cent) were suffering from depression before treatment began. Twenty-five (64·1 per cent) experienced no change in their depression before or after treatment; 11 (28·2 per cent) said that their depression improved during treatment; and three (7·7 per cent) ceased treatment because of continuing depression.

Of the 137 patients who were not depressed initially, 16 (11·7 per cent) became depressed or anxious during

Table 3. Average blood pressure loss by patient groups.

Average blood pressure (mm Hg)	*Patient group*		
Systolic	*A*	*B*	*C*
At beginning	124.71	164.68	140.00
At end	106.50	128.02	127.54
Fall	18.21	36.66	12.46
Percentage	*14.6*	*22.3*	*8.9*
Diastolic			
At beginning	73.88	98.39	89.90
At end	64.14	77.39	82.44
Fall	9.74	21.00	7.46
Percentage	*13.2*	*21.3*	*8.3*

Figure 3. *Average change in systolic and diastolic blood pressure in Group A (80 patients) and Group B (96 patients).*



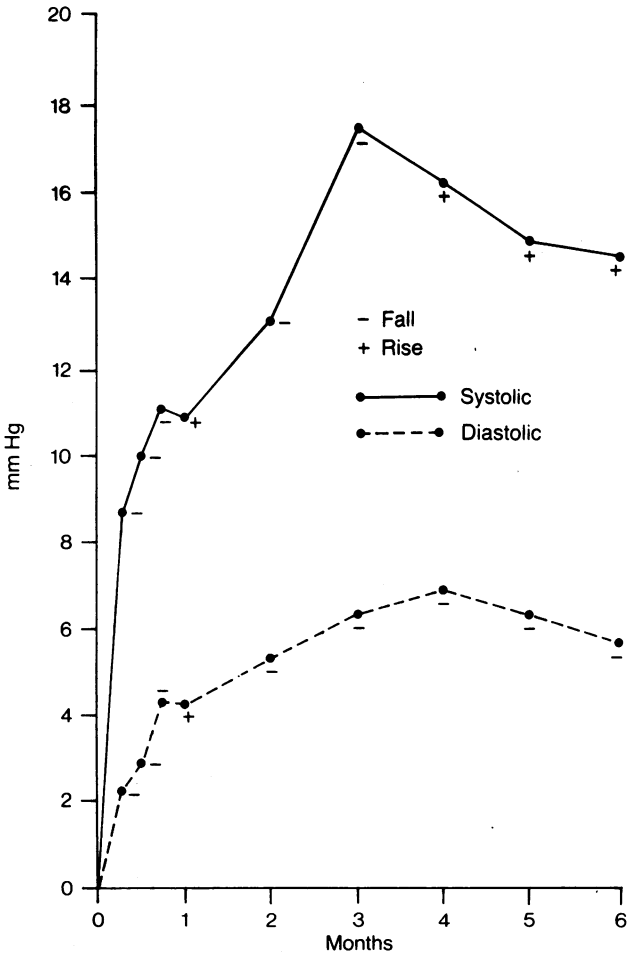


Figure 4. *Average change in systolic and diastolic blood pressure in Group C (15 patients).*

treatment and four (2·9 per cent) became depressed after stopping fenfluramine.

Other adverse effects of fenfluramine

The adverse effects most commonly experienced during fenfluramine therapy were a feeling of tiredness and giddiness, water retention, and increased 'energy' (Table 4). After ceasing to take fenfluramine, headache was complained of once, a bloated feeling twice, and facial paraesthesiae and tiredness once each.

Discussion

This trial confirms the well known tendency for a reduction in weight to be associated with a fall of blood pressure and demonstrates that there is a greater hypotensive effect when dietary control is combined with fenfluramine therapy, as has been shown by Waal-Manning and Simpson (1969), the General-Practitioner Research Group (1971) and Steele and Briggs (1972). Moreover, the findings show that the hypotensive effect is achieved more quickly than was reported by the General-Practitioner Research Group.

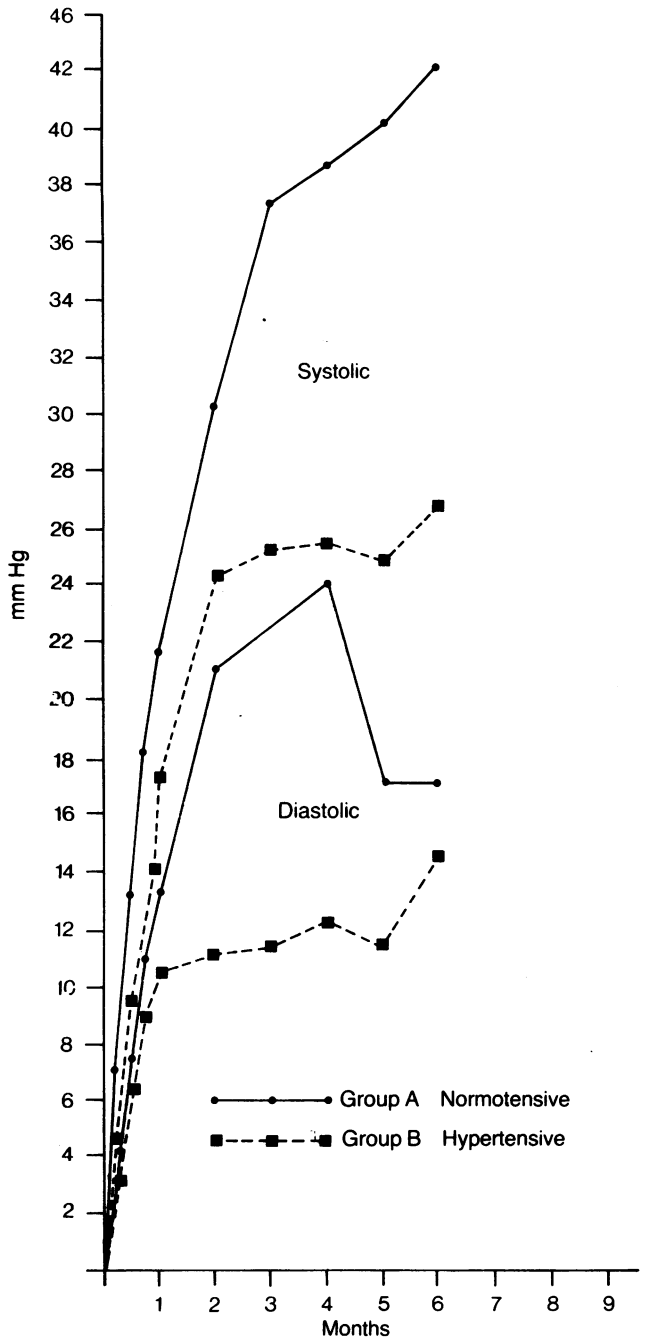


Figure 5. *Average change in blood pressure after treatment stopped in Groups A and B.*

Fenfluramine is a suitable drug to use in combination with Yudkin's modification of the Marriott diet for the treatment of obesity in tense or irritable patients, though care should be taken when depression is present. This combination treatment not only encourages such patients to lose weight but also relieves tension and reduces mild hypertension when present. High blood pressure is more common in obese patients and reduction of weight should lessen the incidence of hypertension.

Table 4. Effects of fenfluramine.

Adverse effects		*Beneficial effects*	
Tired and giddy	9	Increased 'energy'	8
Water retention	9	Increased libido	1
Diarrhoea	3	Hayfever improved	1
Headache	2		
Stiff neck	1		
Muscular irritability	1		
Excessive hangover after alcohol	1		
Total	26		10

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