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# Dexfenfluramine as adjuvant to a low-calorie formula diet in the treatment of obesity: a randomized clinical trial

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Summary

Dexfenfluramine (dF) was compared to placebo as adjuvant to a very energy-restricted diet (1.6–4.2 MJ/24 h). The diet was continued as long as possible or until a satisfactory weight loss had been achieved, and dietary efforts were continued throughout the study. Of the 37 females and five males included, 71 per cent could be followed up for 12 months. Initial BMI ranged from 28 to 54 kg/m$^2$. The lowest body weight was reached 1 month earlier in the dF group ($P = 0.037$). Throughout the study, the reduction of excess weight (REW) was greater in dF patients ($P < 0.05$ only at 4 and 6 months). At 6 months, excess weight had declined by 15 per cent more in the dF group than in the placebo group (95 per cent confidence limits of the median being 1–31 per cent). Between 6 and 12 months, both groups regained weight significantly, the rates of regain differing only insignificantly. At 12 months, excess weight showed a net decrease of only 8 per cent more in the dF group than in the placebo group (95 per cent confidence limits being −7 to +24 per cent). Therefore, REW showed no significant group difference after 12 months. Type of obesity (android or gynoid) as determined by waist to hip ratio had no significant impact on either weight loss, REW, reductions of waist and hip circumferences, or on waist to hip ratio changes. S-alkaline phosphatases and s-uric acid declined significantly in the dF group only. Side-effects were all mild and their prevalence showed no group difference. In conclusion, dF safely supports weight loss in the short term even when used as adjuvant to a highly energy-restricted diet, but dF did not effectively prevent regain of weight despite continued dietary efforts.

*Keywords:* drug therapy, dexfenfluramine, dietary therapy, adipose tissue distribution.

## Introduction

In most investigations of the efficacy of anorectics, the diets prescribed have supplied more than 1000 kcal (4.2 MJ). The use of anorectics as adjuncts to diets providing less than 1000 kcal can be questioned because a satisfactory weight loss can be expected even if energy intake exceeds to some degree the energy frame prescribed. However, in some patients on low-calorie diets, compliance problems threaten a satisfactory weight loss outcome. Further, patients obtaining large weight losses are at high risk of regaining considerable amounts of weight shortly after cessation of a very restrictive diet. While fenfluramine is a racemic mixture of D and L stereoisomers influencing serotonergic as well as dopanergic systems, dexfenfluramine (dF) is a selective serotonin agonist apparently associated with few and mild side-effects. Against this background the present placebo-controlled study tested the potency of dF during treatment with a low-calorie formula-based diet and subsequently during follow-up until 1 year after start of treatment.

Table 1 Basal clinical data (median and range) on study groups

| Group | Sex m/f | Age (years) | Height (cm) | Body weight (kg) | Overweight (%[a]) | BMI (kg/m²) |
|---|---|---|---|---|---|---|
| dF | 1/20 | 28 (18–69) | 167 (154–184) | 92.5 (77.2–122.5) | 61 (26–102) | 35.7 (28.0–45.6) |
| Placebo | 4/17 | 31 (23–68) | 166 (142–186) | 106.6 (75.7–159.8) | 71 (23–137) | 37.8 (27.5–54.4) |
| Significance of group difference ($P$) | n.s.[b] | n.s. | n.s. | 0.044 | 0.045 | 0.080 |

[a] Per cent of the 1983 Metropolitan Life Insurance Company Tables for medium frame.
[b] For group comparison of sex distribution the $\chi^2$ test was used.

## Patients and methods

### *Patients*

The report comprises the Danish study group of the international INDEX multicenter trial on dF[1]. Criteria for entry were: age ≥ 18 years; body weight > 20 per cent above ideal body weight for height (IBW) according to the 1983 Metropolitan Life Insurance Company tables for medium frame; and availability for long-term follow-up. Criteria for exclusion were: obesity due to any endocrinological disorder; history of depression necessitating treatment; evidence of severe somatic or psychiatric disease or alcohol abuse; pregnancy or desire to be pregnant; weight loss of > 3 kg within the 3 preceding months; current body weight < 85 per cent of maximum weight; unrealistic weight loss expectation; and administration of any drug which might interfere with dF or the patient's metabolism or of any other investigational drug in the previous 3 months.

The final study group comprised 42 patients (37 females and five males) as described in Table 1. After informed consent, the patients were randomly assigned to either dF ($n$ = 21) or placebo ($n$ = 21), using balanced blocks of six patients. To improve the comparability of the two treatment groups with respect to degree of excess weight, patients having a body weight < 135 per cent and patients having a body weight > 135 per cent of their IBW were randomized in separate blocks.

### *Test medication*

The investigation was conducted as a double-blind placebo-controlled study. Tablets were distributed by us in identical, coded packets. Patients were asked to take 15 mg of dF or of an identical placebo formulation twice daily (one capsule in the morning and one in the evening during meals) throughout the study.

### *Diets*

Diet A was used from start. As a mandatory part it consisted of a formula delivered as five sachets of nutrition powder (NUPO®, Oluf Mørk Ltd, Copenhagen). The formula provided 388 kcal (1.6 MJ) and fulfilled current recommendations[2] for very low calorie diets; a detailed list of contents has been published previously[3]. The patients were encouraged to use the formula as the sole source of nutrition, but they were allowed to have an additional free intake of no more than 612 kcal (2.6 MJ). To help patients keep account with this possible free intake, we used our educational system of isoenergetic and freely exchangeable units illustrated on cards[4]. This system was also used for the teaching of diets B and C.

We changed from diet A to diet B if weight loss had been < 3 kg for each of two consecutive months. We regarded these patients as being unable to comply with a very energy restricted formula-based diet. Therefore, diet B consisted of conventional foods only and provided 1250 kcal (5.2 MJ).

Diet C was an individual diet calculated for weight maintenance. Patients were shifted from diet A or diet B to diet C when a satisfactory weight loss had been achieved.

### *Patient assessment*

Patients were seen at preselection and selection visits ($T_0$), and monthly thereafter ($T_1$, $T_2$, . . ., $T_{12}$) in groups. A written and verbal patient education programme was provided.

### *Measurements*

Body weight was determined using an electronic scale (Seca 707, Seca, Copenhagen) to the nearest 0.1 kg. In the standing position the waist circumference was measured midway between the lower rib margin and the iliac crest, and the hip measure was taken at the widest circumference over the great trochanters[5].

Blood pressure was determined in the sitting position after at least 10 minutes of rest. A large cuff (15 × 43 cm bladder) was used when the overarm circumference exceeded 35 cm; otherwise a normal cuff (12 × 35 cm bladder) was used. At $T_0$, $T_6$ and $T_{12}$ the following determinations were performed using routine methods: blood haemoglobin, leucocytes, thrombocytes, serum sodium, potassium, creatinine, prothrombine, albumin, bilirubin, alkaline phosphatases, ASAT, uric acid, cholesterol, blood glucose, and erythrocyte sedimentation rate.

*Ethics*

The Helsinki Declaration 2 was observed, and the study protocol was approved by the Copenhagen Municipal Ethical Committee.

*Statistics*

As no effective surveillance of drug compliance could be performed in this long-term study, data were analysed on an intention-to-treat basis. Data on drop-out patients were included in the analyses for the period of participation. The Mann–Whitney rank sum test or the $\chi^2$ test were used for comparison of unpaired data. Paired data were tested for significant changes using Friedman's test. Detailed testing with Wilcoxon's signed rank test was only performed if Friedman's test showed significant differences. $P$ values below 0.05 (two-tailed) were considered significant.

## Results

*Course*

Seventeen patients (81 per cent) of the dF group and 13 patients (62 per cent) of the placebo group adhered to the programme throughout the 12 months ($P = 0.306$). Two patients of the placebo group were withdrawn due to intercurrent diseases (gall stone disease and asthma), and one dF treated patient became pregnant. The remaining drop-outs were caused by failure to attend the scheduled visits at the clinic. The individual shift from diet A to diet B took place between 2 and 7 months after start of treatment. Median duration of diet A was 4 months and 4.5 months in the dF and placebo groups respectively ($P = 0.439$). The lowest weight was registered significantly earlier ($P = 0.037$) in the dF group (median 5 months, range 1–10 months) than in the placebo group (median 6 months, range 3–12 months).

*Weight loss*

Weight loss was considerable in both groups (Figure 1, upper graph). No group difference between the absolute weight losses was observed

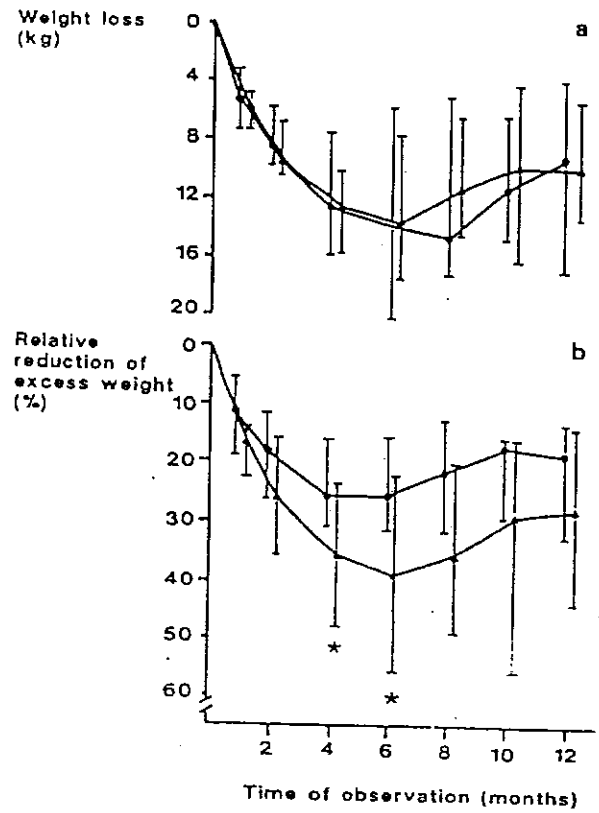


Figure 1 a, Absolute weight loss during 12 month treatment with either dexfenfluramine (triangles) or placebo (circles). Medians with bars indicating 50 per cent central observations. b, Relative reduction of excess weight during the same trial. Medians with bars indicating 50 per cent central observations. Asterisk indicate a significant ($P < 0.05$) group difference at the time of observation.

($P > 0.05$). However, the randomization had resulted in a placebo group significantly heavier and more overweight than the dF group. As rate of weight loss is positively associated with resting metabolic rate and therefore with degree of overweight[6], assessment of drug efficacy under these circumstances is not valid when based on absolute weight losses. Therefore, drug efficacy was assessed as the percentage reduction of excess weight (REW (per cent) = weight loss (kg) × 100/absolute initial excess weight (kg) ). Throughout the trial, REW was higher in the dF group than in the placebo patients, the difference reaching significance at $T_4$ and $T_6$ ($P < 0.05$; Figure 1, lower graph). At $T_6$ the median group difference of REW was 15 per cent (95 per cent confidence limits 1–31 per cent).

*Regain*

As seen from Figure 1, weight was regained in both groups after 6 months. At $T_{12}$ the median group difference of REW was only 8 per cent (95

per cent confidence limits −7 to +24 per cent). Thus, REW showed no significant group difference at $T_{12}$. Regain of weight between 6 and 12 months of treatment was significant among dF-treated ($P = 0.001$) as well as among placebo treated patients ($P = 0.043$). Weight regain rate did not differ significantly between dF and placebo groups (0.7 kg/month (range 0–2.9 kg/month) versus 0.9 kg/month (range 0–3.7 kg/month), $P = 0.447$).

*Waist to hip ratio*

Before the treatment, waist to hip ratio did not differ significantly between the dF and the placebo groups (median 0.89 (range 0.69–1.04) versus 0.88 (range 0.71–1.05), $P = 0.880$). During the weight loss period (0–6 months) changes of waist to hip ratio showed no group difference (median of dF group −0.03 (range +0.12 to −0.16), placebo group −0.03 (range + 0.05 to −0.12), $P = 0.971$), and consistently the ratio did not differ significantly between groups at any examination. Thus, treatment with dF did not seem to influence changes in waist to hip ratio. With this finding in mind, dF and placebo groups were pooled for the following calculations concerning waist to hip ratios. Using a cut-off point of 0.8 for females and 1.0 for males, the waist to hip ratio grouped nine patients (seven females and two males) as having a gynoid fat distribution and 33 patients (30 females and three males) as having an android obesity. Using observations between 0 and 6 months, median changes in body weight, percentual reduction of overweight, waist and hip circumferences, and waist to hip ratio are given in Table 2. It will be seen that type of obesity (gynoid or android) did not significantly influence the changes of any of these variables.

*Heart rate and blood pressure*

No major changes were observed in heart rate and blood pressure. The individual changes in heart rate and systolic, diastolic and mean blood pressures showed no significant group differences between dF and placebo treated patients.

*Biochemical determinations*

The biochemical surveillance pointed to no adverse drug effects. Of variables associated with obesity complications, serum alkaline phosphatases and uric acid declined significantly during the first 6 months only in the dF group ($P$ values 0.001 and 0.047, respectively), while serum glucose and cholesterol changed only insignificantly in both treatment groups, probably due to very few raised values before treatment. A decline of serum albumin in the dF and the placebo groups may reflect dietary factors common to the two groups.

*Clinical side-effects*

The number of patients reporting various side-effects is given in Table 3. There was no significant difference between the number or severity of reports in the dF and the placebo group.

## Discussion

This report describes the outcome of a controlled, double-blind clinical trial which was a part of the international INDEX multicentre study[1]. The present separate report is warranted by the fact

Table 2 Changes (median and range) in body weight, excess body weight, waist and hip circumferences, and in waist to hip ratio during the first 6 months of treatment, in patients with either android or gynoid type of obesity

| *Changes in* | *Android obesity (n = 27)* | *Gynoid obesity (n = 8)* | *Significance of difference* |
|---|---|---|---|
| Body weight (kg) | −12.0** (+1.0 to −30.0) | −16.2* (−7.7 to −22.7) | n.s. |
| Excess weight (%*) | −30** (+6 to −84) | −33* (−24 to −66) | n.s. |
| Waist (cm) | −11.0** (+11.0 to −24.0) | −9.5 (+6.0 to −18.0) | n.s. |
| Hip (cm) | −9.0** (+4.0 to −21.0) | −12.0* (−6.0 to −21.0) | n.s. |
| Waist/hip | −0.03 (+0.12 to −0.16) | −0.03 (+0.05 to −0.07) | n.s. |

* Per cent of excess weight at $T_0$.
Significance of differences between observations at $T_0$ and $T_6$: * $P < 0.05$; ** $P < 0.01$.

Table 3 Number of patients reporting various side-effects

| *Side-effect* | *dF (n = 21)* | *Placebo (n = 21)* |
|---|---|---|
| Fatigue | 2 | 1 |
| Dizziness | 2 | 1 |
| Depression | 2 | 1 |
| Irritability | 2 | 1 |
| Headache | 3 | 2 |
| Orthostatic hypotension | 1 | 0 |
| Dry mouth | 1 | 3 |
| Constipation | 3 | 2 |
| Diarrhoea | 3 | 1 |
| Myosis | 1 | 0 |
| Back pains | 2 | 2 |
| Joint pains (knees) | 1 | 1 |
| Menstrual irregularities | 1 | 1 |
| Pneumonia | 1 | 0 |
| Loss of hair | 1 | 0 |

Only side-effects reported by one or more patients of the dF group have been included.

that our dietary recommendations and supporting programme were different from programmes run at other centres involved in the multicentre study. In particular, our patients were offered a nutrition powder making possible a diet providing 388 kcal (1.6 MJ)/24 h for many weeks. Hitherto no clinical dF trial has used energy levels below 1000 kcal (4.2MJ)/24 h[7]. Accordingly, our patients assigned to placebo lost an average of about 1.5 times as much as did all patient groups of the INDEX study. Furthermore, our patients were overall 10 years younger than the mean of the entire group.

Our study has demonstrated that dF leads to a somewhat faster and somewhat larger reduction of excess weight even when used as an adjunct to a severely energy restricted diet in a patient education programme that has previously proved very effective[4,8].

From our study it also seems clear that dF does not always prevent significant weight regain between 6 and 12 months after the start of treatment. A tendency to weight regain, although not statistically significant, was found within the dF group, and also in the entire INDEX population of 822 patients[1], but Guy-Grand and co-workers do not report a group comparison of the weight changes between 6 and 12 months of treatment. Compared to placebo, dF has been shown to prevent regain (and even cause some further weight loss) in patients having lost weight during an initial 8 week treatment with a very low calorie diet, but the dF treatment lasted only 28 weeks[9].

From the clinical studies it may be suggested that dF has a somewhat prolonged effect on body weight when compared to other anorectics, but long-term clinical trials are needed to verify this suggestion. Thus, so far it has not been documented that dF can prevent relapse of overweight during true long-term treatment. Such an efficacy should be due either to a prolonged anorectic effect or to thermogenic properties[7]. To our knowledge, no study has been published investigating the influence of dF on food intake after months of treatment. A thermogenic effect of *dl*-fenfluramine has been demonstrated in a short-term animal study[10] and also found in a human single-dose study[11], suggesting a stimulation of the thermic effect of food. Recently preliminary data indicated that dF possesses a thermogenic effect when determined in animal[12] or human[13,14] single-dose studies. However, Breum and co-workers[15] found no overall thermogenic effect and no effect of dF on the post-prandial heat loss when measuring energy expenditure repeatedly during and after cessation of a 1-year treatment with the drug. A true long-term efficacy of dF may still be hoped for, but can hardly be expected.

Side-effects of dF are few and mild. In the INDEX study as a whole, dF was associated with slightly more complaints and side-effects than placebo[1]. In our population we found no significant difference. Neither did screening blood tests point to adverse effects, which is in accordance with unpublished results of the total INDEX study (B. Guy-Grand, personal communication). Falls in serum alkaline phosphatases and uric acid during continued energy restriction have been observed previously[16,17]. Any specific explanation of the fact that these variables decreased significantly only in the dF group cannot be given; the better REW in the dF group after 6 months is a possible cause.

The total INDEX study including 822 patients may offer further information on any influence of dF on waist to hip ratio. We found a decrease of the waist to hip ratio of the same order of magnitude as previously found in patients reducing their weight comparably[18], but the change was not significant in this study, with its lower number of patients. As discussed by Wadden and co-workers[18], it is currently unknown whether changes in waist to hip ratio reliably reflect changes in the risk of future obesity complications. In our patients, dF did not seem to influence changes in fat distribution. It has been a matter of debate whether or not fat distribution influences the ability to lose weight. Our finding of equally good weight reductions in patients with android and gynoid types of obesity is in

accordance with previous reports[19,20] However, Wadden and co-workers[18] found a better reduction of body fat in patients having a gynoid type of obesity. As it grows increasingly clear that the risk of developing obesity complications seems to be related to the intra-abdominal fat mass in particular[21], future clinical weight reduction studies should focus on the obtained decrease of the intra-abdominal fat deposit.

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