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Withdrawal Depression in Obese Patients after Fenfluramine Treatment

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Summary

Measurements of subjective feeling in 20 patients receiving fenfluramine alternating with placebo and in 19 patients receiving phentermine alternating with placebo indicated that depression of mood occurred four days after fenfluramine withdrawal but no such depression was seen with phentermine.

Introduction

All the common anorexic agents in current use are amphetamine congeners having in common the phenylethylamine structure illustrated in the following examples:

As many anorexic agents have some of the stimulant properties of amphetamine there has been considerable anxiety about their possible exploitation as drugs of abuse (Duncan and Munro, 1968; Advisory Committee Report, 1970). It is sometimes implied that if no side effects are stimulated by the central nervous system the drug will be free from this hazard. Such an assumption may be unwarranted, since addiction to barbitur-

ates and tranquillizers is well documented (Isbell, 1950) and compound preparations containing both an amphetamine and a barbiturate—for example, Drinamyl—are commonly used “drugs of abuse.”

Fenfluramine is the most widely prescribed non-stimulant amphetamine derivative in this country. It has mild sedative properties and, with the exception of one unconfirmed report, has not been recognized as a drug of abuse (Brandon, 1969; Hawks, 1970) and has been successfully used to prevent withdrawal symptoms in patients dependent on methylamphetamine and dexamphetamine (Jones, 1971). However, Oswald *et al.* (1971) recorded consistent changes in mood after withdrawal of fenfluramine from patients who had taken it for the preceding 28 days or longer, depression being maximal on the fourth post-withdrawal day. Adverse or unpleasant effects on withdrawal indicate that the organism has become adapted to the drug in a manner which may lead to physical or psychological dependence on it.

The present study was undertaken to compare the effects on mood and appetite of fenfluramine and phentermine. The latter agent, having mild stimulatory effects, has been suspected of being taken for “kicks” (Duncan and Munro, 1968) though there are no confirmed reports of its abuse in this country (Advisory Committee's Report, 1970). A case has been reported from Ireland of a patient abusing several amphetamine-like drugs including phentermine (Murray, 1964) and another single case from the United States (Rubin, 1964).

Design of Study

The patients were obese women aged 20 to 60 years who were participating in a double-blind controlled trial of fenfluramine and phentermine in varying regimens as aids to weight reduction. Details of this trial will be reported elsewhere. Participants were asked to make a record, each evening, of their mood and subjective appetite during that day, using the linear self-rating record sheet described by Oswald *et al.* (1971) and discussed by Aitken (1969). At the end of the trial the records of two comparable groups of patients were analysed in detail. The first group consisted of 20 patients who received fenfluramine 20 mg thrice daily for 28 days followed by placebo for 28 days. The second comprised 19 patients who took phentermine 30 mg (as a slow-release resin preparation Duromine) each morning plus identical placebo tablets at midday and in the evening for 28 days, followed by placebo alone for 28 days.

Results

The mean ratings of mood and of appetite for the two groups over the whole 56-day period are shown in Figs. 1-4. It is clear that both agents were effective as appetite suppressants as compared with placebo. Neither caused any marked shift of mood

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FIG. 1—Effect of fenfluramine and placebo on mood of 20 patients.

FIG. 2—Effect of phentermine and placebo on mood of 19 patients.

FIG. 3—Effect of fenfluramine and placebo on appetite of 20 patients.

FIG. 4—Effect of phentermine and placebo on appetite of 19 patients.

while the drug was being taken, although there seemed to be a rise in the self-rating score during the first week of phentermine administration. On withdrawal of fenfluramine a pronounced decline in mood was apparent, the lowest value being recorded on the fourth day after stopping the drug. A correlated *t* test comparing the fourth day after withdrawal of fenfluramine with the 27th day after withdrawal showed the difference to be significant at the 1% level. There was no corresponding effect on stopping phentermine.

Discussion

This work confirms the withdrawal depression, on the fourth day after discontinuing fenfluramine, described by Oswald *et al.* (1971) and parallels the delay to a peak of withdrawal abnormality in cerebral electrophysiology (Lewis *et al.*, 1971). Campbell (1971) showed that plasma concentrations of fenfluramine reach a plateau three to four days after starting the drug, and unpublished observations showed that a similar time is taken for the drug to be removed from the body (Campbell, personal communication).

Although withdrawal depression is an indication of dependence on a drug this does not necessarily mean that the drug is or will become a drug of abuse. Oswald *et al.* (1971) felt that the abuse potential of fenfluramine is low because it has unpleasant initial side effects, but many drugs of abuse seem to many subjects to have unpleasant initial side effects. One might expect that phentermine, in view of its stimulating side effects, would be more likely to become a drug of abuse; it is interesting that it does not produce withdrawal depression.

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