PAPERS AND ORIGINALS

Chronic Fenfluramine Administration: Some Cerebral Effects

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Summary

Human cerebral function was monitored electrophysiologically during sleep over a period of months before, during, and after the intake of fenfluramine, 40-120 mg/day. Effects included dose-related reduction of paradoxical sleep, increase of intra-sleep restlessness, and changes in E.E.G. slow-wave sleep. It is hypothesized that weight loss may be associated with increase of the last. Grinding of teeth (bruxism) also was noted.

Long-term studies make it possible to demonstrate changing central effects with time, including tolerance phenomena. Withdrawal abnormalities are related to the time taken for the drug to be eliminated—in the present case reaching a maximum four days after withdrawal.

Introduction

Obesity is a major health problem, in the treatment of which most drugs have been amphetamine derivatives. The B.M.A. Working Party (1968) noted central nervous system effects of these drugs and considered fenfluramine the least undesirable. In previous reports we suggested that fenfluramine was qualitatively different in its action on the human brain, for we did not find the selective suppressing effect on paradoxical (R.E.M. or "rapid eye movement") sleep that is possessed by dexamphetamine, phenmetrazine, diethylpropion, or chlorphentermine (Oswald *et al.*, 1968; Lewis, 1970). However, like Gagnon *et al.* (1969), we did find a sleep-disturbing effect—fenfluramine caused greater intra-sleep restlessness—namely, more frequent shifts to stage 1 sleep (drowsiness).

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These were acute studies. We now describe the effects of chronic administration and of withdrawal on a number of human brain functions. Parallel observations of subjective experience are described by Oswald *et al.* (1971).

Methods

Six patients aged 21-35 were studied. Four (Cases 1-4) were young men in good general health who volunteered for the study and who were considered only slightly overweight, whereas two others had an extreme degree of obesity, refractory to past treatments, and entered the study weighing 127 kg (Case 5) and 111·4 kg (Case 6). All were to refrain from alcohol and keep regular hours throughout the study.

The study was designed so that there should be a sequence of baseline, drug, and withdrawal periods. The same number of apparently identical tablets were taken daily by the patients for several months. The first four men at first received two blank (placebo) tablets at 8 a.m. and again at 6 p.m. Subsequently fenfluramine 40 mg was substituted for the afternoon dose and later for the morning dose also. Finally blank tablets were substituted during the withdrawal period. The Table shows the duration of each phase. Tablets were issued in separate packs for morning and evening, and in small, irregular batches in order to conceal the date of any change of content. The two grossly obese patients received tablets additionally at midday. Their packs contained either one fenfluramine 20-mg and one blank tablet, two fenfluramine 20-mg tablets, or two blank tablets. One patient (Case 5) was dropped from the study after 25 days on fenfluramine 60 mg/day because of drinking bouts. Case 6, unlike the others, was not subjected to abrupt withdrawal. After 101 days on the drug his evening pack of tablets was changed to blanks for 11 days, then his midday tablets also for seven days, and finally he received only blanks for the last eight days.

Cerebral function during sleep was monitored by continuous recording of electroencephalogram (E.E.G.), eye movements, and submental muscle tone, as described by Haider and Oswald (1970). The patients slept in quiet, ventilated rooms. The first two nights under full laboratory conditions were discarded as adaptation nights, after which came the first baseline nights.

The number of nights under each condition is shown in the Table for the first four patients. The different type of regimen for Case 6 is shown in Fig. 7.

The recorded data were analysed in terms of standard criteria (Rechtschaffen and Kales, 1968) for each 20-sec period. The total duration of sleep and the durations of orthodox (N.R.E.M.) and of paradoxical (R.E.M.) sleep were obtained. Orthodox sleep was divided into stage 1 (drowsiness); stage 2, characterized by E.E.G. sleep spindles; and stages 3 and 4, with increase of high-voltage E.E.G. slow waves. The hour-by-hour distribution of all these stages of sleep and of transitions between them or into wakefulness was obtained.

Results

The convenience of patients had to be considered and it was not possible to obtain laboratory data on the same drug-day for each person, though we started, changed, or stopped drug dosage just before times when more frequent recordings were possible. Consequently we present some results as illustrative graphs for individuals over the months of study.

Paradoxical Sleep.—Fenfluramine 40 mg had little effect on the proportion of sleep spent as paradoxical sleep, but on 80 mg/day the means of three of the first five *recorded* nights fell to more than 2 standard deviations (S.D.) below the baseline mean in respect of paradoxical sleep duration in the first three hours of sleep and rose to 2 S.D. above baseline after withdrawal (Fig. 1). Tolerance is suggested by the fact that the last recordings on the 80-mg dose approached baseline again. Withdrawal abnormalities in Case 2 are shown in Fig. 2. There was also a rebound in the mean whole-night paradoxical sleep, in excess of 2 S.D. above the baseline on the second and third recordings after withdrawal. Fig. 3 shows a curve fitted to the available withdrawal data for consecutive nights for the patients who stopped fenfluramine abruptly. The peak of rebound abnormality occurs at the fourth withdrawal night.

Intra-sleep Restlessness.—Spontaneous shifts to stage 1 sleep (drowsiness) or to wakefulness were more frequent during fenfluramine administration, as Fig. 4 shows for Case 1. He had sub-baseline values during the early withdrawal period. The combined data for the second three hours of sleep of Cases 1-4 indicated a rise in intra-sleep restlessness after starting the larger dose, with tolerance for this action by the time the drug was withdrawn. Spontaneous tooth-grinding in sleep (bruxism), shown as rhythmic muscle potentials in the record, were noted on the larger dose of the drug, especially in Case 2, in whom it was not observed during baseline recordings (Fig. 5).

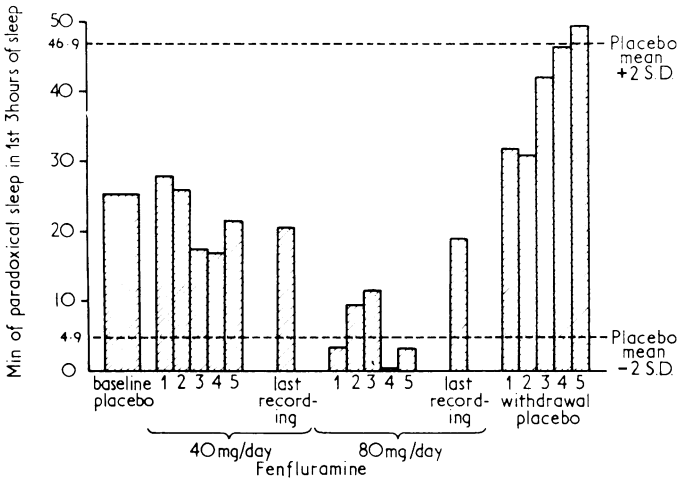

FIG. 1—Effect of chronic administration and withdrawal of fenfluramine on time spent as paradoxical sleep in the first three hours of total sleep (after falling asleep and excluding any awakenings) in Cases 1-4. The weighted mean of the patients' baseline means is shown, together with the 2 S.D. limit. The mean of the values of the first drug night, and the mean for the second night on drug that could be recorded from each man, and so on, are shown, together with the last drug night that was recorded on the low dose of 40 mg/day. Similarly the first five recorded nights and the last recorded night on 80 mg are shown, and the first five recorded withdrawal nights. On the 80-mg dose there is a suppression of paradoxical sleep at first, with three of the first five means falling over 2 S.D. from the baseline. A rebound excess occurs after withdrawal, rising to 2 S.D. above baseline on the fourth and fifth recorded withdrawal nights.

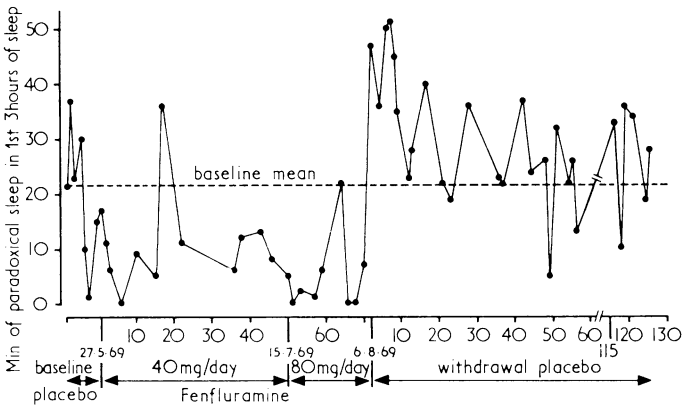

FIG. 2—In Case 2 a rebound abnormality occurred after fenfluramine withdrawal, shown by minutes of paradoxical sleep in the first three hours of sleep. A sustained peak occurred in the first 10 days after withdrawal.

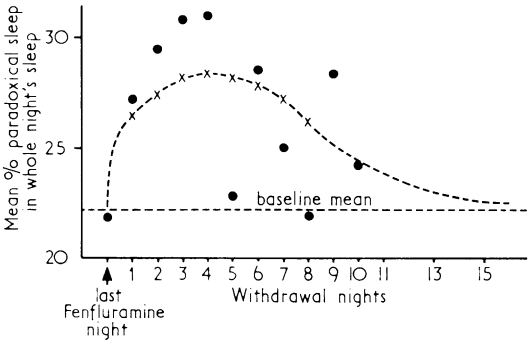

FIG. 3—Time-course of whole-night paradoxical sleep abnormality after fenfluramine withdrawal. The last fenfluramine night is the last one recorded, the withdrawal nights are all consecutive nights. The individual values are means for as many of the four patients as were recorded on the night concerned. All four patients contribute to the last fenfluramine night, and all four to the first and third withdrawal nights. The solid part of the curve is applied to calculated best-fit values (Elderton, 1938) and the broken-line parts of the curve are hand-fitted. The curve reaches a peak at the fourth withdrawal night.

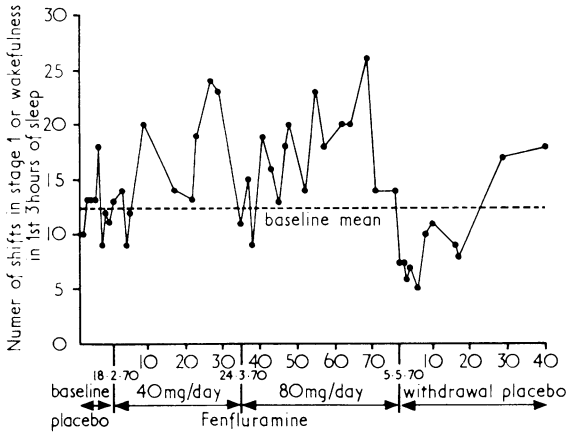

FIG. 4—Case 1. Increase of intra-sleep restlessness above the baseline mean during fenfluramine intake and a fall below baseline in the week after withdrawal of the drug.

Slow-wave Sleep.—Sleep stages 3 and 4 were at first dramatically increased by fenfluramine in Cases 2 (see Fig. 6) and 1. Stages 3 and 4 were not consistently affected in Cases 3 and 4, and appeared initially reduced in Case 6 (Fig. 7). The time of weight losses in relation to amounts of stages 3 and 4 sleep leave us with the impression that times of losing weight were associated with increased stages 3 and 4 sleep. It was also our qualitative observation that where the durations of stages 3 and 4 were increased during fenfluramine intake, the slow waves themselves appeared enhanced in voltage.

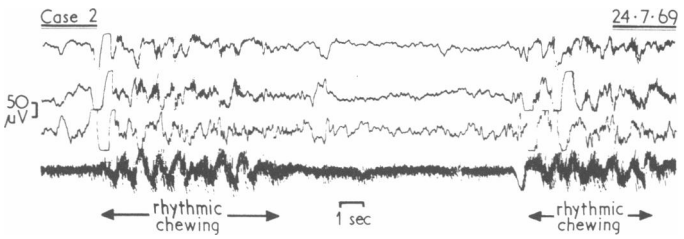

FIG. 5—Tooth-grinding during sleep (bruxism) of Case 2 on 80 mg of fenfluramine per day. Two episodes of rhythmic movement are visible in the bottom, submental electromyogram trace. The top two traces are from the outer canthi electrodes and the third trace, from the scalp, shows slow E.E.G. waves of stage 3 sleep just before the first of the two chewing episodes. E.E.G. signs of sleep persist throughout. These were 2 out of 53 such episodes, of 2-30 seconds' duration, occurring between 2.30 and 3 a.m., and among 184 such episodes during the whole of that night's sleep.

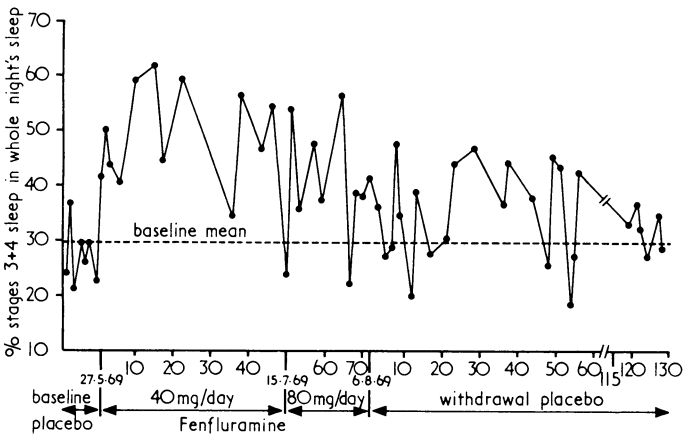

FIG. 6—Case 2. Dramatic and sustained rise above both personal baseline and normal values occurred in combined stages 3 and 4 (slow-wave) sleep as a result of chronic fenfluramine administration to this patient (who lost 3·4 kg). It appears maximal after about two weeks and seems to decline during the 71 days of administration.

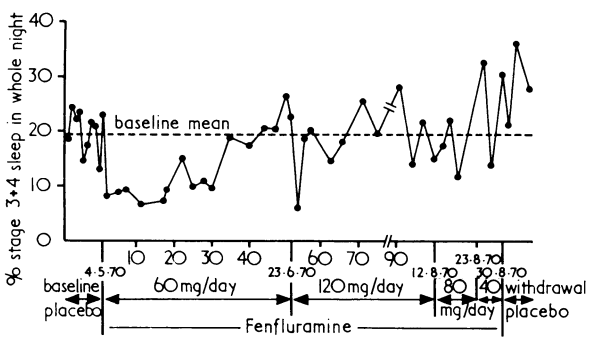

FIG. 7—In Case 6 (111 kg initial weight), who did not lose weight, fenfluramine 60 mg/day appears to cause a sustained fall in combined stages 3 and 4 sleep for the first month, with subsequent recovery to normal. His three highest values occur in the withdrawal phase, suggesting a degree of rebound.

Details of Four Cases

Case No.	Initial Weight (kg)	Weight at Withdrawal (kg)	Weight Change (kg)	Baseline Days	40 mg/day	80 mg/day	Withdrawal Days
1	82·12	76·67	−5·45	9 (9)	34 (10)	42 (15)	40 (11)
2	71·45	68·05	−3·40	10 (10)	49 (12)	22 (9)	56 (22)
3	77·93	73·94	−3·99	6 (6)	81 (16)	14 (5)	35 (12)
4	90·05	91·17	+1·12	10 (10)	49 (12)	28 (9)	50 (18)

Numbers in parentheses indicate the number of nights of all-night sleep recording. Baseline numbers include pre-drug and late (about four months) post-drug baseline nights.

Discussion

Our earlier single-dose studies had failed to show the effects of the drug on paradoxical sleep. Increase of intra-sleep restlessness, seen after single doses, is confirmed. The sub-baseline degree of restlessness, or frank inertia, after withdrawal seen in Fig. 4 has been noted after withdrawal of a drug resembling fenfluramine (Oswald, 1970). Reduction of stages 3 and 4 sleep was earlier described (Oswald *et al.*, 1968) whereas Fig. 6 now shows a striking increase to values that are, in our experience, and that of Williams *et al.* (1964), above the normal range.

Slow-wave sleep (stages 3 and 4), often considered "worth more" than stages 1 and 2 (Dement and Greenberg, 1966), is now thought to be an obligatory condition for the large nocturnal secretion of growth hormone (Sassin *et al.*, 1969a, 1969b). Growth hormone is a lipolytic agent (Fain *et al.*, 1965; Hunter, 1968), and the possibility arises that fenfluramine might partly reduce weight by an action on the brain that leads both to slow-wave sleep increase and to growth hormone secretion increase. Besser *et al.* (1969) reported that amphetamine provoked a rise of growth hormone secretion. First results of some current experiments strengthen our expectation that serial blood samples during sleep contain higher growth hormone levels during fenfluramine intake with weight loss.

Bruxism seemed to be provoked by fenfluramine. Brandon (1969) described daytime involuntary teeth-grinding and Riley *et al.* (1969) teeth-chattering after excess of fenfluramine, while Ashcroft *et al.* (1965) reported tooth-grinding as a feature of amphetamine abuse.

TIME-COURSE OF EVENTS

Withdrawal of amphetamine is followed by rebound abnormalities of cerebral function persisting many weeks (Oswald and Thacore, 1963). In the case of such drugs as tricyclic antidepressants, heroin, or phenobarbitone, the number of days between withdrawal and the peak of paradoxical sleep rebound is about equal to the time required to eliminate the drug from the brain (Lewis and Oswald, 1969; Haider and Oswald, 1970; Lewis *et al.*, 1970). In Fig. 3 above the peak of the rebound is at about four days after drug withdrawal, and in a companion paper (Oswald *et al.*, 1971) we report mood depression maximal four days after fenfluramine withdrawal. The time-course may be understood in the light of fenfluramine's long half-life and the fact that three to four days are needed to establish equilibrium blood levels on continued dosage or, conversely, to allow the blood levels to fall to zero (Campbell, 1971).

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References

Ashcroft, G. W., Eccleston, D., and Waddell, J. L. (1965). *British Medical Journal*, **1**, 57.

Besser, G. M., Butler, P. W. P., Landon, J., and Rees, L. (1969). *British Medical Journal*, **4**, 528.

Brandon, S. (1969). *British Medical Journal*, **4**, 557.
B.M.A. Working Party (1968). *British Medical Journal*, **4**, 572.
Campbell, D. B. (1971). *South African Medical Journal, Supplement* **45**, 10.
Dement, W., and Greenberg, S. (1966). *Electroencephalography and Clinical Neurophysiology*, **20**, 523.
Elderton, W. P. (1938). *Frequency Curves and Correlation*. Cambridge, Cambridge University Press.
Fain, J. N., Kovacev, V. P., and Scow, R. O. (1965). *Journal of Biological Chemistry*, **240**, 3522.
Gagnon, M. A., Tétreault, L., and Bordeleau, J. M. (1969). *Activitas Nervosa Superior*, **11**, 202.
Haider, I., and Oswald, I. (1970). *British Medical Journal*, **2**, 318.
Hunter, W. M. (1968). In *Growth and Development of Mammals*, ed. G. A. Lodge and G. E. Lamming. London, Butterworths.
Lewis, S. A. (1970). In *Amphetamines and Related Compounds*, ed. E. Costa and S. Garattini. New York, Raven Press.
Lewis, S. A., and Oswald, I. (1969). *British Journal of Psychiatry*, **115**, 1403.
Lewis, S. A., Oswald, I., Evans, J. I., Akindele, M. O., and Tompsett, S. L. (1970). *Electroencephalography and Clinical Neurophysiology*, **28**, 374.
Oswald, I. (1970). In *Amphetamines and Related Compounds*, ed. E. Costa and S. Garattini. New York, Raven Press.
Oswald, I., Jones, H. S., and Mannerheim, J. E. (1968). *British Medical Journal*, **1**, 796.
Oswald, I., Lewis, S. A., Dunleavy, D. L. F., Brezinova, V., and Briggs, M. (1971). *British Medical Journal*, **3**, 70.
Oswald, I., and Thacore, V. R. (1963). *British Medical Journal*, **2**, 427.
Rechtschaffen, A., and Kales, A. (editors). (1968). *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. Washington, D.C., U.S. Government Printing Office.
Riley, I ., Corson, J., Haider, I., and Oswald, I. (1969). *Lancet*, **2**, 1162.
Sassin, J. F., *et al.* (1969a). *Science*, **165**, 513.
Sassin, J. F., *et al.* (1969b). *Life Sciences*, part I, **8**, 1299.
Williams, R. L., Agnew, H. W., and Webb, W. B. (1964). *Electroencephalography and Clinical Neurophysiology*, **17**, 376.

Drugs of Dependence Though Not of Abuse: Fenfluramine and Imipramine

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Summary

Measures of subjective feeling used by five patients indicated that depression of mood occurred about four days after fenfluramine withdrawal. An experiment in which another 11 patients took fenfluramine 80 mg for 28 days confirmed the depression, maximal on the fourth withdrawal day. It also indicated that in the first week of administration there was some mood elevation, but with feelings of impaired ability to concentrate. The drug reduced appetite and weight. A comparison is drawn with imipramine, which was found to induce initial and withdrawal changes of subjective experience (of dreaming) in six volunteers. It is suggested that certain mood-influencing drugs may not be drugs of abuse because of some unpleasant initial effects, though they can be drugs of dependence.

Introduction

A few years ago amphetamine was not accepted as a drug of addiction because "physical" withdrawal features were supposedly absent. Nevertheless, clinicians encountered amphetamine addicts and observed inertia, sleepiness, and depression of mood following withdrawal. The brain is a "physical" organ and governs psychological function, and as techniques become mo ophisticated withdrawal signs after more drugs must be discovered. They may be traditionally physical or, since brain physiology di es mental life, of a psychological nature. Today we have drug "abuse" and drug "dependence" (W.H.O., 1969). The former implies use of a drug contrary to law or medical opinion. Dependence implies that the drug influences behaviour and that through repeated experience the organism is in some way changed, so that if the drug is stopped it is then missed and withdrawal features appear. Like other brain responses dependence could be expected to be a graded and not an absolute phenomenon.

We have found that regular intake of fenfluramine, an amphetamine derivative, leads to dependence on the drug for the maintenance of normal mood, and, for comparison, we show a minor form of dependence on imipramine.

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Measuring Instruments

A drug may influence how a man feels. Observers can make inferences about how he feels and attempt measurement, but a man's inner, subjective experience is his alone, and he alone can truly describe it. Words are often inadequate, so we used a simple thermometer-like measure, a line, 10 cm long, on which the patient could make a mark to indicate where, along a continuum of feeling, he would place himself that day. The number of mm along the line was eventually measured. Visual-analogue self-rating scales of this type have been discussed by Aitken (1969).

The principal measuring device was a sheet of paper with space for name and date and a 10-cm line running across it with, at the left-hand end, the words, "Most depressed ever," and at the right-hand end, "most cheerful ever." The instructions were: "Please indicate by a mark on the line how you felt in your spirits today. If you have felt more lively and cheery than usual you should make your mark to the right of centre, if more listless and gloomy than usual your mark should be to the left. An average day should mean a mark in the centre." It was completed at night and the measures from it are taken as measures of *mood*.

Similar 10-cm lines were used to measure appetite. They were marked "no appetitite at all" at one end, and at the other end "greatest ever relish for food." Patients were reminded that there is a difference between relish for food and amount eaten. Another sheet of paper gave a self-estimate of how well the patient had felt able to concentrate mentally and ran from "extremely difficult to concentrate" to "wonderfully alert and penetrating mind." A morning sheet gave a self-estimate of dreaming and ran from "absolutely dreamless in retrospect" to "seemed to be vivid dreaming all the time."