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A comparison of fenfluramine and amphetamine in man

dl-Fenfluramine hydrochloride (60, 120, 240 mg), d-amphetamine sulfate (20, 40 mg), and placebo were compared in 8 postaddict volunteers, each dose given orally in random sequence at weekly intervals using a double-blind crossover design. Fenfluramine had little effect on blood pressure and temperature, but caused a marked dilation of pupils, whereas amphetamine was a potent vasopressor and a weak mydriatic. While fenfluramine produced euphoria in some subjects, its overall effects were unpleasant, sedative, and qualitatively different from amphetamine. Three subjects given 240 mg of fenfluramine experienced brief but vivid hallucinogenic episodes characterized by olfactory, visual, and somatic hallucinations, abrupt polar changes in mood, time distortion, fleeting paranoia, and sexual ideation. These observations indicate that fenfluramine is a hallucinogenic agent with a pharmacologic profile in man that is not amphetamine-like.

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Human subjects given the anorexigenic drug, fenfluramine (N-ethyl-m-trifluoromethyl phenylisopropylamine, Pondimin), often report a sense of unpleasant lethargy from the drug rather than a euphoric "high,"[8] and concomitant electroencephalographic patterns can be more characteristic of sedative agents than drugs of the amphetamine class.[3-5] Moreover, with animal paradigms of human drug-seeking behavior, fenfluramine is not reinforcing[22] and relatively devoid of amphetamine-like sympathomimetic properties.[2]

From these and other studies, one might conclude that fenfluramine is unique and not likely to lead to amphetamine-like psychotoxicity or abuse—an estimate corroborated by the very few reports of fenfluramine abuse in Europe where the drug has been available clinically for some years.[7, 20] On the other hand, Levin has reported descriptions of 60 young men from South Africa (where the drug could be obtained without prescription) who self-administered fenfluramine in doses of 80 to 400 mg on one or more occasions to obtain a euphoric effect.[15, 16] The constellation of symptoms remembered by these men included hallucinogenic, sedative, and amphetamine-like effects. Of possible concern are still other reports of dysphoria and sleep disturbance after chronic fenfluramine use and abrupt withdrawal,[12, 19] a like sequence also following amphetamine.

There is therefore the possibility that fenfluramine may have reinforcing properties (amphetamine-like or otherwise) not previously identified in controlled clinical studies. To explore this issue, the subjective and physio-

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logic effects of fenfluramine and amphetamine were compared by using methods previously described by Martin and associates[18] and Jasinski, Nutt, and Griffith.[13]

Methods

Participants were 8 men detained for federal crimes committed in connection with their narcotic use. They ranged in age from 31 to 44 and were in good health, as evidenced by medical history, physical examination, and appropriate laboratory studies, and exhibited no psychiatric impairment beyond drug abuse and concomitant antisocial behavior. All had used narcotics for an average of 18 yr before incarceration; in addition, 7 had also used amphetamine or cocaine, and 4, LSD-like hallucinogens. Participation was voluntary.

The doses of *dl*-fenfluramine hydrochloride (60, 120, 240 mg) and *d*-amphetamine (20, 40 mg) were selected following a dose run-up and on the basis of prior studies,[18] respectively. During dose run-up, 1 subject given 270 mg of fenfluramine reported transient, paranoid thoughts just prior to a euphoric episode. For this reason, and because a demonstration of psychotomimetic effects was not a purpose of this study, the largest dose of fenfluramine used in the crossover was 240 mg, an amount also well tolerated in toxicity studies done elsewhere. A cherry syrup with a trace of quinine added served as both the vehicle for the drugs and as a placebo. Each treatment was administered orally in random sequence at weekly intervals under double-blind conditions.

Subjects were admitted to the ward the evening before their test day and examined to rule out intercurrent illnesses. On the test day, they were awakened at 6:30 A.M., and baseline physiologic observations were made at 7:00 and 7:30 A.M. Treatments were given at 8:00 A.M. Physiologic observations would then be repeated at 0.5, 1, 2, 3, 4, 5, 6, 12, and 24 hr postdrug. These were: (1) duplicate 10-min supine blood pressures as determined by calibrated sphygmomanometer and auscultation; (2) pulse rate; (3) respiratory rate; (4) rectal temperature; and (5) pupil diameter (determined photographically; eye 11 inches from a back-illuminated opal glass screen and target transilluminated to 300 ft-lamberts). Two-min standing blood pressures and pulse rates were obtained at 3 and 24 hr and compared to the immediately preceding supine values. Urine pH was not controlled in this acute study.

At these postdrug intervals, subjective effects were measured by a group of questionnaires completed by both subjects and observers. These were the Single Dose Opiate Questionnaire for subjects and observers[6] and a special questionnaire for subjects that consisted of items from the following scales of the Addiction Research Center Inventory[10]: MBG (Morphine-Benzedrine Group Scale), a general measure of drug-induced euphoria; LSD (Lysergic Acid Diethylamide Group Scale), a measure of dysphoric and somatic symptoms elicited by graded doses of LSD and certain narcotic antagonists[11, 17]; and an 11-item Amphetamine Scale, a measure specific for the dose-related effects of *d*-amphetamine.[18] The Amphetamine Scale contains items that relate mainly to concepts of self-confidence and personal assertiveness.

The effects of drugs on food intake were estimated by calculating the caloric value of food actually eaten at the noon, evening, and breakfast meals (using weighed portions and standard tables). Except for noncaloric beverages, including coffee, subjects fasted from midnight until the noon meal and then again until the evening meal (5:00 P.M.).

The morning following the test day, subjects estimated their time asleep to the nearest half-hour. Sleep time was also estimated by observers who inspected subjects at half-hour intervals during the evening and night (6:00 P.M. to 6:00 A.M.).

Dose-effect relationships were determined by partitioning the treatment sums of squares from the analysis of variance for a randomized block design into components to test the significance of the regression mean square of measured total 6-hr response on each measure against dose of amphetamine and fenfluramine. In addition, mean placebo responses and 95% confidence limits of mean placebo response were calculated for each measure to allow dif-

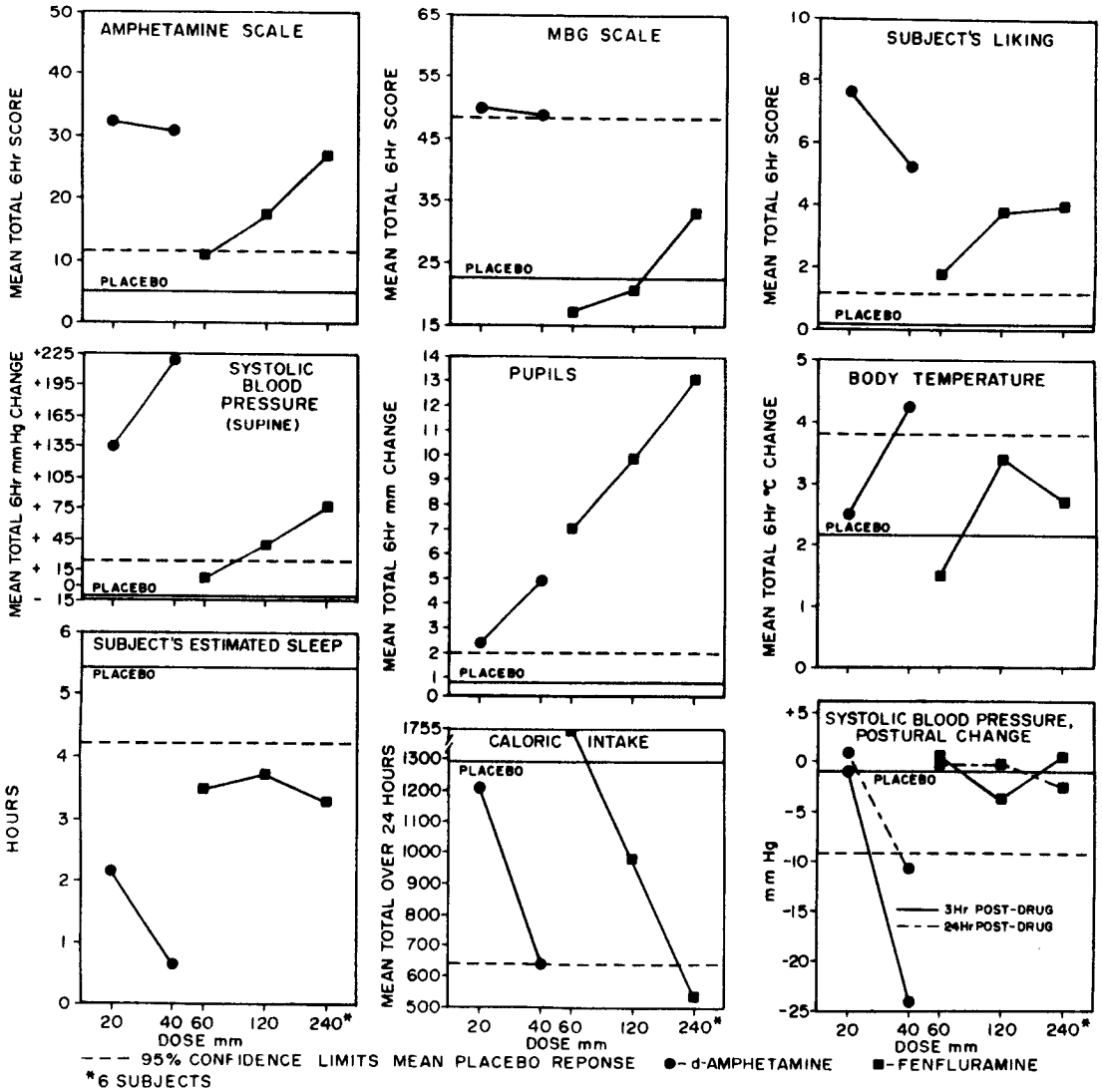

Fig. 1. Dose-response plots for placebo condition and orally administered *dl*-fenfluramine and *d*-amphetamine. Each point represents the mean group response of 8 subjects (6 subjects, 240 mg fenfluramine condition). Responses for subjective scales represent the sum of the scores for the first 7 observations (total 6-hr scores). Blood pressure and temperature responses are calculated as the sum of the changes from the mean of the predrug control for the first 7 observations (total 6-hr change). Caloric intake, sleep time, and postural blood pressure change are described in the text.

ferentiation of fenfluramine and amphetamine effects from placebo.

Results

To compare the effects of fenfluramine and amphetamine during the first few hours after administration, the responses with each measure for the first 7 observations (total 6-hr scores) were summed and the mean total 6-hr scores were used to construct dose-response as illustrated in Fig. 1. However, some effects persisted as long as 12-24 hr.

Physiological effects. The most prominent physiologic effect of fenfluramine was a dose-

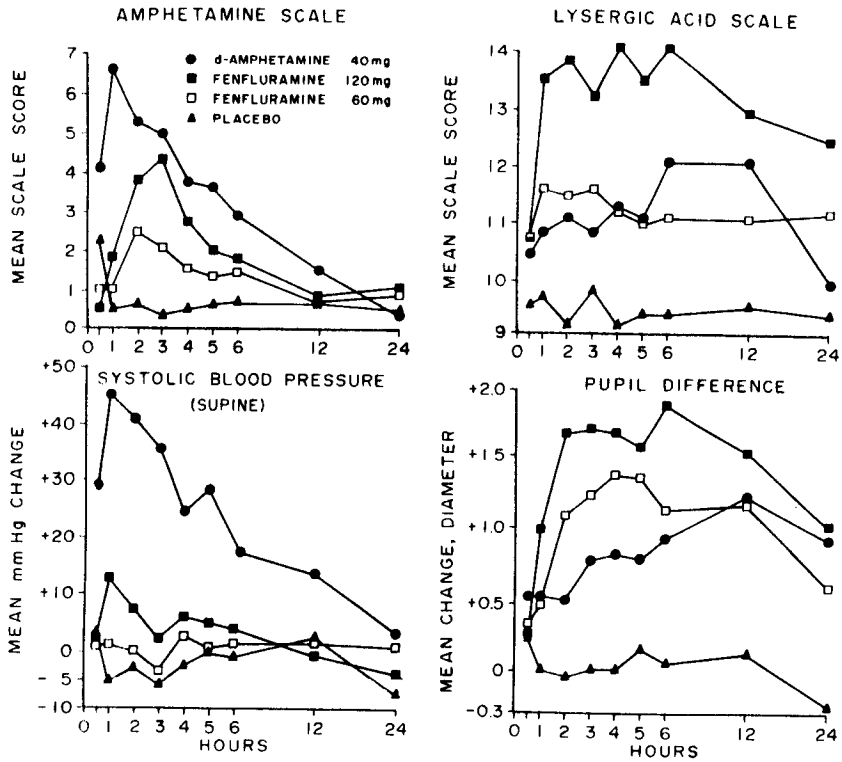

Fig. 2. Time-action curves for amphetamine and fenfluramine. Each point represents the mean change from 8 subjects. Euphoric effects (amphetamine scale) were paralleled by elevation of supine blood pressure while dysphoric effects (LSD scale) were accompanied by mydriasis.

related increase in pupil diameter; the effect of amphetamine by this measure during the first 6 hr was, by comparison, relatively slight (Fig. 1). Fenfluramine also elevated systolic and diastolic blood pressures, but less than did amphetamine. Although not statistically significant, there was a trend for pulse rate to increase with fenfluramine and to decrease with the larger dose of amphetamine. The larger dose of amphetamine caused hyperpyrexia and differences in standing and supine blood pressure, the latter being manifested 24 hr later (Fig. 1). As may be seen in Fig. 2, the pressor effects of amphetamine and fenfluramine generally assumed a time-course paralleled by the duration of euphorogenic effects (Amphetamine Scale). The mydriatic and LSD Scale responses were of much longer duration.

Appetite and sleep. Amphetamine, 40 mg, and fenfluramine, 120 and 240 mg, reduced caloric intake at the three meals following drug administration, but because of a large variability, only the effects on the noon meal were statistically significant. Valid relative potency calculations for this effect indicate 4.2 mg of fenfluramine equivalent to 1 mg of amphetamine as an anorexiant, but with admittedly wide 95% confidence limits (2-412). Both fenfluramine and amphetamine caused significant reduction in self-estimated sleep time (Fig. 1); only amphetamine, however, reduced observed sleep time.

Subjective effects. Significant degrees of euphoria were produced by amphetamine as indicated by elevated Amphetamine, MBG, and Subjects' Liking Scale scores (Fig. 2). This euphoric response tended to change gradually in a stepwise fashion during the 6-hr interval. The dysphoric items (LSD Scale) elicited by amphetamine were not significantly different from placebo in this small series. Seven of 8 subjects rated the larger dose of amphetamine as more euphorogenic than the 20-mg dose, and a significant dose relationship could be shown

Table I. *Drug identifications (single dose questionnaire) for comparison of placebo condition with* d-*amphetamine and fenfluramine**

Subjects	Placebo	d-amphetamine		Fenfluramine		
		20	40	60	120	240†
Blank	45	25	19	42	23	11
Dope	0	0	0	0	0	0
Cocaine	0	2	0	0	3	0
Marijuana	0	0	0	0	0	0
Barbiturate	0	0	0	0	0	12
Alcohol	0	0	0	0	0	0
Benzadrine (amphetamine)	3	29	36	0	5	8
LSD	0	0	0	6	10	5
Thorazine	0	0	0	0	0	0
Librium	0	0	0	0	0	0
Others	1	0	4	6	1	9

*Numbers represent total response by all subjects for the first 7 observations. Maximum response in any category, =56.
†Six subjects.

among these 7 by Amphetamine, MBG, and Liking Scale measures. One subject, however, denied both euphorogenic and dysphorogenic effects after the 40-mg dose (but not at 20 mg), which flattened the dose-response curve. These effects of amphetamine were generally categorized by subjects as "amphetamine" (Table I). Although subjective effects were accompanied by obvious behavioral changes, no relationship between behavioral change and drug condition or dose condition could be demonstrated.

The response to the 60 mg dose of fenfluramine was modest. Only 3 subjects identified this dose as psychoactive (subjects' liking, Fig. 1; Table I). The effect with the larger doses of fenfluramine was more definite; however, subjects varied considerably in their response to the same dose of fenfluramine and to different doses, and in terms of the manifestation of a particular effect over time. In contrast to amphetamine, the euphoric mood states elicited were of shorter duration, episodic, and accompanied by degrees of personal grandiosity. These euphoric changes would alternate (sometimes in a matter of minutes) with even more striking dysphoric episodes that eventually became the more prevailing and predominant effect. These polar opposites of mood and early psychotomimetic effects were reflected in simultaneous elevations of Amphetamine, Liking, and LSD Scale measures during the first 6 hr. The combined 6-hr MBG Scale response, a more general measure of drug-induced euphoria, was not different from placebo. However, a randomized block analysis of variance of peak MBG scores indicated significant dose-related increases with fenfluramine. These MBG Scale peaks were of short duration (1-2 hr) and associated with peak Amphetamine Scale and blood pressure elevations.

Five of the 8 subjects receiving the 240-mg dose of fenfluramine eventually were sedated and categorized the response as "barbiturate"-like (Table I), although their appearance more resembled that seen following a large dose of phenothiazines. Hallucinogenic phenomena were not observed in these 5. Three other subjects, however, experienced frank hallucinogenic episodes of sudden onset, but without sedative effects.

Hallucinogenic effects. Three subjects sustained clear-cut hallucinogenic syndromes during the crossover assay. This response was not expected and, except as noted, promptly antidoted with diazepam.

Only mild changes were noticed in 1 subject. Approximately 1½ hr postdrug, he became angry and demanded a conference to learn "why people were looking at his television set"—an inappropriate concern because the receiver was locked and secure in his room in another part of the building. In a matter of minutes, however, he experienced a "mellow high," denied being angry, and explained

that his preoccupation was without foundation. He thereafter continued with testing and identified other changes such as time compression and alterations of body image, which came in "waves" for about 5 hr. Because the patient was comfortable, in good contact with staff, and willing to continue, no attempts were made to terminate these symptoms.

With 2 other subjects, hallucinogenic effects were more pronounced. One man with considerable LSD experience became mute some 45 min after taking fenfluramine, and for the next half-hour communicated by making animal-like noises and gestures. Upon recovering his voice, he explained that he had been on a "beautiful trip," which began with his noticing that the shadows cast by the venetian blinds reminded him of a reptilian underbelly. Subjectively, he was very quickly transformed into a large and fearsome dinosaur, searching, during what seemed like a period of years, for his dinosaur wife and child—an experience that culminated in an ecstacy of reunion and closeness with his family group. The subject later explained that he was at all times aware that his experiences were drug-induced and unreal, but his decision to remain mute was to prolong the state as long as possible. The thematic content of his hallucinogenic state was connected by the subject to a troubled domestic relationship.

A second subject also experienced derealization, rapid, and polar alterations of mood, visual hallucinations, distortions of perspective, changes in body image, vivid sexual hallucinations and ideas, and transient paranoia. In contrast to the episodes described above, this subject evaluated his experience as mostly unpleasant, except for the sexual hallucinations. He and the above subject experienced infrequent, short-lived episodes of unreality for 3 days postdrug.

Discussion

Previous studies from the Addiction Research Center have shown the relationship between amphetamine structure and amphetamine activity in man or, more specifically, the pharmacologic profiles obtained by modifications of the isopropylamine side chain (methamphetamine, phenmetrazine, methylphenidate, ephedrine, diethylpropion, benzphetamine). These structural configurations were observed to have a profound effect on weight potencies but pharmacologic profiles were essentially unchanged. In other words, for a given effect on appetite, all drugs produced equal degrees of euphoria and vasopressor change despite differences in physical potency ranging from 1:1 to 1:20.[13, 18]

It was significant to learn whether a different type of structural modification (ring substitution), as exemplified by fenfluramine, would give qualitative alterations in pharmacologic responses and not merely qualitative differences in overall potencies. Our study indicates that the most conspicuous similarity between the effects of amphetamine and fenfluramine is an anorexigenic effect, fenfluramine being about ¼ as potent as amphetamine—an estimate in keeping with other efficacy studies in man[23] and inhibition of food intake by oral fenfluramine in the dog.[1] In rat assays, fenfluramine is relatively more potent,[2] perhaps because this animal can parahydroxylate the reference drug, amphetamine, more rapidly. This is a minor pathway in man. There is also good evidence that fenfluramine and amphetamine-induced anorexia may involve different pharmacologic mechanisms.[9, 14, 21]

In most other respects, the effects of fenfluramine were quite different. Fenfluramine, unlike amphetamine, caused substantial and generally dose-related subjective expressions of lethargy, sedation, dysphoria, and unpleasant somatic symptomatology. While fenfluramine was to some degree euphorogenic, as evidenced by elevated Amphetamine and Subjects' Liking Scale scores, this response could be differentiated from amphetamine by the transitory MBG response, subjects' drug identifications, and clinical manifestations. The physiologic profiles were also different. Fenfluramine was a weak vasopressor and a potent mydriatic, whereas amphetamine caused substantial increases in blood pressure and mild pyrexia, but effects on pupils had a rather long latency. Only amphetamine induced significant postural differences in blood pressure. These data indicate that fenfluramine is not amphetamine-

like and probably would not substitute in amphetamine-like patterns of abuse.

In support of Levin's studies,[15, 16] fenfluramine was observed to have hallucinogenic activity in 3 of 5 subjects who experienced syndromes characterized by visual hallucinations, sensory distortion, fleeting paranoia, derealization, depersonalized awareness, somatic symptomatology, labile mood, a modest increase in pulse rate and blood pressure, mydriasis, and hyperactive tendon reflexes—the last not measured systematically. This configuration resembles that produced by a number of hallucinogens, including LSD and certain ring-substituted amphetamines. This similarity, plus the cases cited by Levin, suggests that LSD-like, rather than an amphetamine-like, abuse potential should be considered. This issue aside, hallucinogenic and dysphoric symptoms may well limit the therapeutic utility of fenfluramine as an anorexiant.

While 3 subjects experienced hallucinogenic phenomena (without sedation), 5 others were moderately sedated following the largest dose of fenfluramine and denied psychotomimetic symptoms. No reasons can be given for these differences. Preliminary data suggest that the hallucinatory response may result from a rapid absorption of oral fenfluramine or its conversion to norfenfluramine.

The similarity between the effects of fenfluramine and endogenous emotional depression, both characterized by symptoms of dysphoria, hypochondriasis, insomnia, emotional lability, and anorexia, is of interest, suggesting that ring-substituted phenethylamines may be used as tools to investigate these functional states.

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