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# Evaluation of Phentermine and Fenfluramine, Alone and in Combination, in Normal, Healthy Volunteers

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*Recent clinical reports indicate that combined administration of phentermine and fenfluramine may have useful effects in the treatment of drug abuse. The present study was designed to evaluate the subjective and mood-altering effects of these drugs, alone and in combination, in normal healthy volunteers. Seven male and five female volunteers participated in an eight-session, double-blind study in which each subject received each of the following drug conditions:* d-*amphetamine (10 and 20 mg), phentermine (30 mg), fenfluramine (40 and 80 mg), phentermine (30 mg) with fenfluramine (40 mg), phentermine (30 mg) with fenfluramine (80 mg), and placebo. Sessions were conducted in a laboratory setting two or three days a week. Subjects completed standardized self-report questionnaires and psychomotor tests before and at regular intervals after each drug administration. Phentermine produced effects that were similar to those of* d-*amphetamine, whereas fenfluramine produced different and apparently aversive effects (e.g., it increased measures of anxiety and confusion). Phentermine reduced the apparently aversive effects of fenfluramine when the two drugs were given together. These results suggest that the combination of phentermine and fenfluramine would have a low potential for abuse.* ***[Neuropsychopharmacology 14:233–241, 1996]***

Most existing and proposed pharmacotherapies for the treatment of substance abuse consist of single drugs with a central mechanism of action that in some way decreases drug-taking behavior. An alternative approach is to develop pharmacotherapies consisting of more than one compound, acting on the same or different neurotransmitter systems. For example, Rose and Levin (1991) have pioneered the use of combining agonists and antagonists in the treatment of nicotine dependence and find that such combinations show considerable promise in laboratory and clinical studies (Rose et al. 1994a, 1994b). Another drug combination that has recently been proposed as a treatment for drug abuse is phentermine, a drug that stimulates the release of dopamine and norepinephrine, and fenfluramine, a drug that stimulates the release of serotonin. This combination has been shown in double-blind, placebo-controlled studies to be an effective treatment for obesity (Weintraub 1992a, 1992b; Weintraub et al. 1984, 1992a, 1992b), and uncontrolled studies suggest that it may also be effective in treating alcoholism and cocaine abuse (Hitzig 1993; Rothman et al. 1994). In one open-label study alcoholic patients who received the phentermine and fenfluramine combination reported that it decreased craving for alcohol and they exhibited decreased alcohol use within a short time after the initiation of treatment (Hitzig 1993). In another uncontrolled

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study, cocaine abusers who received the phentermine and fenfluramine combination reported decreases in cocaine craving and their cocaine use declined during treatment (Rothman et al. 1994). In both studies the investigators also reported that treatment with the phentermine and fenfluramine combination also decreased the psychiatric symptomatology that accompanies alcohol and cocaine abuse, such as neuroses and depression (Hitzig 1993, 1994; Rothman et al. 1994). Thus, preliminary data suggest that this drug combination may be useful for a variety of substance abuse disorders. However, before widespread use of this treatment can be implemented, its safety and efficacy should be evaluated in controlled, double-blind studies.

One issue related to safety that must be addressed before this combination can be considered as a pharmacotherapy in substance abusers is its abuse liability. Both phentermine and fenfluramine are Schedule IV drugs under the Controlled Substance Act, and the PDR (1993) warns against their use in individuals with past or current drug abuse problems. However, there is little epidemiological evidence that either of these drugs is used illicitly (U.S. DHHS 1991a, 1991b), and human behavioral pharmacological assessments of the dependence-producing effects of chlorphentermine (Griffith et al. 1976), a drug with a pharmacological profile similar to that of phentermine, and of fenfluramine (Griffith et al. 1975; Pinder et al. 1975; Chait et al. 1986) indicate that they are unlikely to be abused. To date, clinical experience suggests that the abuse potential of the combination of these two drugs is also minimal (Weintraub 1992a, 1992b; Hitzig 1993; Rothman et al 1994). However, no abuse liability assessments of phentermine or the combination have been conducted.

The participants in the present study were normal healthy volunteers who are at relatively low risk for developing drug abuse problems. Although the abuse liability of new compounds should be also assessed in individuals with histories of substance abuse who are at greater risk for abusing any drug, the acute effects of stimulant drugs in normal volunteers provide a good indication of these drugs' likelihood to be abused by drug-abusing populations (Foltin and Fischman 1991). Therefore, the present study may provide an initial indication of whether the phentermine plus fenfluramine combination has significant potential for abuse.

The purpose of the present study was to evaluate the effects of phentermine and fenfluramine, alone and in combination, on standardized measures of abuse liability. The study examined the subjective and behavioral effects of acute doses of phentermine (30 mg), fenfluramine (40, 80 mg), and phentermine (30 mg) plus fenfluramine (40 and 80 mg) compared to *d*-amphetamine (10 and 20 mg) and placebo. *d*-Amphetamine is a prototypic psychomotor stimulant with known abuse potential, and these doses of *d*-amphetamine have been shown reliably to produce subjective effects in normal volunteers (Johanson and Uhlenhuth 1981; Brauer and de Wit in press). The doses of phentermine and fenfluramine were chosen because they have been used in preliminary clinical studies for the treatment of substance abuse (Hitzig 1993; Rothman et al. 1994).

## METHODS

### Participants

Twelve subjects (7 male and 5 female) were recruited from the university community with posters, advertisements, and word-of-mouth referrals. Interested individuals were first screened over the telephone. Candidates between 21 and 35 years of age, who were high school graduates, spoke English fluently, and reported drinking at least one alcoholic beverage per week attended a face-to-face interview. Subjects who met DSM III-R criteria for a major Axis I disorder (APA 1987), including past or current substance abuse (excluding tobacco dependence), were excluded. Subjects were also screened by a physician, and individuals with major medical illnesses or abnormal electrocardiograms were also excluded. This study was approved by the University of Chicago Institutional Review Board and the National Institute on Drug Abuse Institutional Review Board.

### Procedures

Prior to participating subjects attended an orientation session to explain procedures and obtain written informed consent. Subjects were told that they might receive stimulants/appetite suppressants, sedatives/minor tranquilizers, antihistamines, and/or placebo, but they were not informed of the actual drug(s) they had received until after the study. They were instructed not to take any drugs other than those given by the experimenter (including alcohol) for 24 hours before and after a session. Subjects were allowed to consume their usual amounts of caffeine and nicotine, but not in the hour immediately prior to or during the experimental session. They were instructed not to eat anything in the hour prior to the laboratory session and to keep the amount of food consumed prior to that time stable across sessions. After completing the study subjects attended a debriefing interview and were paid for their participation.

This study utilized a within-subjects design, in which all subjects were administered all drug conditions. The study was placebo controlled, and drugs were administered under double-blind conditions. Groups of two to four subjects attended eight sessions, conducted once or twice per week. Sessions were separated by at

least 48 hours to minimize the carry-over effects of drugs between sessions (half-lives for phentermine, fenfluramine, and amphetamine are 19 to 24 hours, 13 to 30 hours, and 11 to 13 hours, respectively; Baselt and Cravey 1989). Sessions were conducted in a comfortable laboratory environment from 7:45 A.M. until 2 P.M. When subjects reported to the laboratory at 7:45 A.M., breath alcohol levels were obtained to verify that they were alcohol-free, and they completed baseline mood, physiological, and behavioral measures (see later). Then at 8 A.M., they ingested two capsules with 100 ml water. The capsules contained placebo, *d*-amphetamine (10 or 20 mg), phentermine (30 mg), fenfluramine (40 or 80 mg), or the combination of phentermine (30 mg) and fenfluramine (40 or 80 mg). The order of drug conditions was counterbalanced across subjects. All dependent measures were repeated hourly for 6 hours. At 2 P.M. subjects completed the final end-of-session questionnaire, and then they left the laboratory. When subjects were not completing mood questionnaires or behavioral tests, they were free to relax in the laboratory and to engage in leisure activities (e.g. watch television, read, play board games).

### Drugs

All drugs were administered in opaque gelatin capsules (size 00) with dextrose as filler.

### Dependent Measures

Subjective effects were measured repeatedly during the sessions using (1) an experimental version of the Profile of Mood States (POMS; McNair et al. 1971; Johanson and Uhlenhuth 1980); (2) the Addiction Research Center Inventory (ARCI; Haertzen et al.1963; Martin et al. 1971); and (3) ten 100-mm visual analog scales (VAS; Folstein and Luria 1973). Each of these subjective effects measures has been shown to be sensitive to the mood effects of a variety of psychoactive drugs, including stimulants (Fischman and Foltin 1991).

The POMS is an adjective checklist on which subjects rate themselves with respect to each of 72 adjectives describing mood states on a scale of 0 ("Not at all") to 4 ("Extremely"). The adjectives have been factor-analyzed into eight scales, including Anger, Anxiety, Confusion, Depression, Elation, Fatigue, Friendliness, and Vigor. Two additional scales have been intuitively derived: Arousal = [(Anxiety + Vigor) − (Fatigue + Confusion)] and Positive Mood = [Elation − Depression].

The ARCI consists of 49 true/false statements related to drug effects. The statements are separated into five empirically derived scales that represent subjective effects typical of specific drug classes: A (Amphetamine scale measures stimulation, high), BG (Benzedrine Group scale measures mental efficiency, cognitive effects), LSD (Lysergic Acid Diethylamide scale measures somatic complaints or dysphoria), MBG (Morphine-Benzedrine Group scale measures euphoria), and PCAG (Pentobarbital-Chlorpromazine-Alcohol Group scale measures sedation).

On the 10 VAS scales, subjects indicated the degree to which they felt "stimulated," "high (as in a drug high)," "anxious," "sedated," "down," "hungry," whether they felt any drug effects, liked the effects, felt high, and wanted more of the drug.

On a final end-of-session questionnaire subjects indicated their overall liking of these drug effects on a 100-mm visual analogue scale and identified the class of drug they received (stimulant/appetite suppressant, sedative/minor tranquilizer, antihistamine, or placebo).

Behavioral effects (i.e. psychomotor impairment) were assessed using the Digit Symbol Substitution Test (DSST; Wechsler 1958) and computerized eye-hand coordination test (Hindmarch et al. 1991; Nuotto and Kortilla 1991). The measure of interest in the eye-hand coordination test was the number of seconds (out of a total of 2 minutes) subjects spent with the cursor outside of a circle they were tracking with the mouse. These psychomotor tests have been shown to be sensitive to drug effects (Stone 1984; Hindmarch et al. 1991; Nuotto and Kortilla 1991). Physiological effects measured were heart rate, blood pressure, and temperature.

### Data Analysis

For ease of interpretation and presentation, data for each dependent variable were analyzed as mean peak change from baseline using a priori means comparisons (the time of peak effect varied across drugs). Peak change scores were calculated by subtracting baseline scores for each subject from scores at each time point, and the peak score (the largest change in either direction) for each subject in each condition was used in the analysis. Preliminary analyses revealed that the low doses of *d*-amphetamine (10 mg) and fenfluramine (40 mg) did not produce reliable effects on mood, and therefore these doses were eliminated from further analyses. Thus, the final comparisons performed were *d*-amphetamine (20 mg) versus placebo; phentermine (30 mg) versus placebo; fenfluramine (80 mg) versus placebo; and *d*-amphetamine (20 mg) versus phentermine (30 mg). Additional comparisons were conducted on those measures on which either phentermine or fenfluramine differed significantly from placebo. On those measures, the effects of the drugs alone were compared to the effects of the phentermine/fenfluramine drug combination. In addition, the effects of the combination were compared to those of the placebo. For all comparisons, $p$ values under .05 were considered significant.

**Table 1.** *F* Values for a priori Comparisons of Mean Peak Change from Baseline[a]

| Dependent Measure | AMP (20) vs. PLAC | PHEN vs. PLAC | FEN (80) vs. PLAC | AMP (20) vs. PHEN | PHEN/FEN (80) vs. PLAC | PHEN/FEN (80) vs. PHEN (30) | PHEN/FEN (80) vs. FEN (80) |
|---|---|---|---|---|---|---|---|
| ARCI A | 1.48 | 2.47 | 0.25 | 0.13 | | | |
| ARCI BG | 2.87[b] | 2.54 | 0.21 | 0.01 | | | |
| ARCI LSD | 7.70[c] | 4.24[c] | 5.42[c] | 0.51 | 1.57 | 0.65 | 1.15 |
| ARCI MBG | 2.23 | 2.37 | 0.02 | 0.00 | | | |
| ARCI PCAG | 4.25[c] | 3.05[b] | 0.01 | 0.10 | | | |
| POMS Anger | 0.05 | 0.05 | 2.10 | 0.20 | | | |
| POMS Anxiety | 2.49 | 0.46 | 11.76[c] | 0.81 | 1.90 | | 4.20[c] |
| POMS Arousal | 12.68[c] | 7.27[c] | 0.59 | 0.75 | 4.61[c] | 0.30 | |
| POMS Confusion | 1.87 | 1.32 | 4.32[c] | 0.05 | 0.00 | | 4.16[c] |
| POMS Depression | 0.51 | 0.35 | 2.03 | 0.02 | | | |
| POMS Elation | 0.92 | 0.92 | 4.17[c] | 0.00 | 0.27 | | 2.31 |
| POMS Fatigue | 5.36[c] | 3.84[b] | 0.32 | 0.13 | 2.49 | 0.15 | |
| POMS Friendliness | 0.43 | 0.03 | 0.31 | 0.67 | | | |
| POMS Positive Mood | 0.68 | 0.46 | 5.83[c] | 0.20 | 0.46 | | 3.03[b] |
| POMS Vigor | 12.17[c] | 3.23[b] | 0.03 | 2.86[b] | | | |
| VAS "Feel Drug" | 0.94 | 0.94 | 9.92[c] | 0.00 | 12.06[c] | | 0.10 |
| VAS "Feel High" | 0.43 | 1.20 | 0.00 | 0.11 | | | |
| VAS "Like Drug" | 9.22[c] | 4.03[c] | 0.99 | 1.06 | 8.73[c] | | 0.90 |
| VAS "Want More" | 5.91[c] | 3.93[b] | 0.85 | 0.20 | 10.60[c] | 1.63 | |
| VAS "Anxious" | 0.06 | 0.52 | 13.42[c] | 0.24 | 3.26[b] | | 3.46[b] |
| VAS "Down" | 0.69 | 0.30 | 3.55[b] | 0.80 | | | |
| VAS "High" | 0.39 | 0.07 | 0.13 | 0.80 | | | |
| VAS "Hungry" | 0.09 | 0.03 | 0.27 | 0.20 | | | |
| VAS "Sedated" | 1.10 | 1.28 | 1.36 | 0.00 | | | |
| VAS "Stimulated" | 1.5 | 0.20 | 0.03 | 0.61 | | | |
| Blood pressure—dias | 1.85 | 0.11 | 0.07 | 1.05 | | | |
| Blood pressure—sys | 8.21[c] | 1.45 | 0.07 | 2.76 | | | |
| Heart rate | 0.15 | 0.48 | 0.01 | 0.09 | | | |
| Temperature | 0.01 | 0.00 | 0.01 | 0.01 | | | |
| DSST | 0.05 | 0.91 | 4.54[c] | 0.53 | 3.26[b] | 0.11 | |
| Seconds outside circle | 0.85 | 0.00 | 0.60 | 0.77 | | | |

[a] df for overall *F* test = 7,77; df for each contrast = 1.

[b] Significantly different from placebo at $p < .10$.

[c] Significantly different from placebo at $p < .05$.

## RESULTS

### *d*-Amphetamine

*d*-Amphetamine produced prototypic stimulantlike effects on a number of subjective measures (see Table 1). Relative to placebo, *d*-amphetamine significantly increased scores on the Arousal and Vigor scales of the POMS and on "Like Drug" and "Want More" visual analogue scales. *d*-Amphetamine decreased scores on the ARCI LSD and PCAG scales and on the POMS Fatigue scale. Mean peak subjective ratings on representative measures are shown in Figure 1. *d*-Amphetamine also significantly increased systolic blood pressure relative to placebo but did not alter any other physiological or behavioral measures. The majority of subjects (75%) correctly identified *d*-amphetamine as a stimulant, whereas one subject identified placebo as a stimulant. End-of-session ratings of overall liking showed that subjects liked *d*-amphetamine more than placebo (mean *d*-amphetamine = 59 versus mean placebo = 42.7).

### Phentermine

Phentermine produced subjective effects that were similar to those of *d*-amphetamine (see Table 1 and Figure 1). Phentermine significantly increased POMS Arousal and Vigor scores, and VAS ratings of "Like Drug." It also decreased ARCI LSD scores. Phentermine did not significantly influence any physiological or behavioral measures relative to placebo. In contrast to *d*-amphetamine, only 45% of subjects correctly identified phentermine as a stimulant, while the rest of the subjects

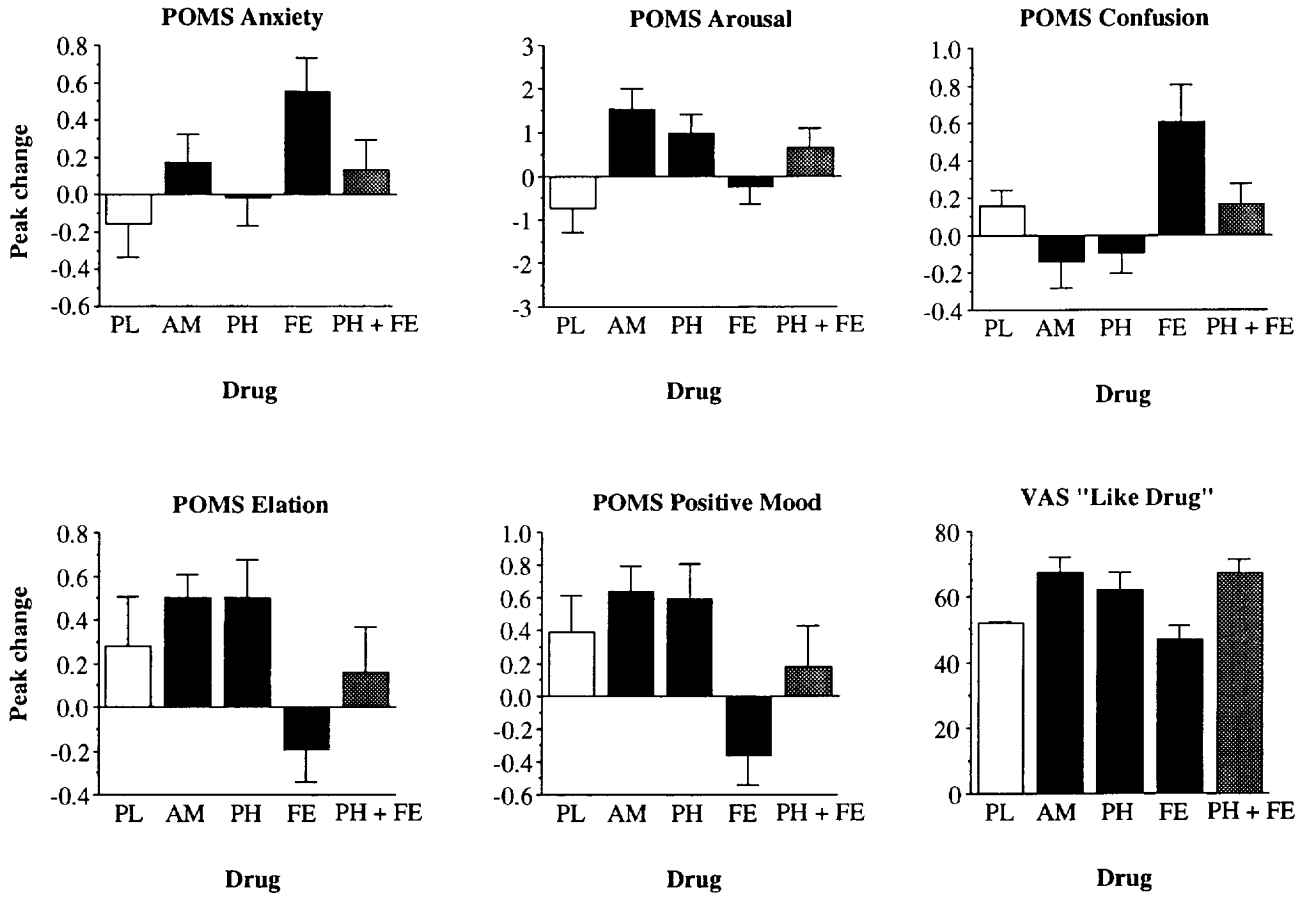


**Figure 1.** Subjective effects of placebo (PL), *d*-amphetamine (20 mg; AM), phentermine (30 mg; PH), fenfluramine (80 mg; FE), and phentermine (30 mg) + fenfluramine (80 mg; PH + FE). Data shown are mean ± SEM peak changes from baseline. Scores on the POMS factor-analyzed scales (e.g., Anxiety, Confusion) can range from 0 to 4, whereas scores on the intuitively derived scales (e.g., Arousal) can range from 0 to 8. Scores on the visual analogue "Like Drug" scale can range from 0 to 100.

identified it as either a placebo (27%), sedative (18%), or antihistamine (9%). One subject failed to complete the end-of-session questionnaire on the phentermine session. Ratings of overall liking were similar to those of *d*-amphetamine, with a mean rating of 56.5.

### Fenfluramine

Fenfluramine also produced significant subjective and behavioral effects when administered alone, but these effects were qualitatively unlike those of *d*-amphetamine and phentermine (see Table 1 and Figure 1). For example, fenfluramine increased scores on the POMS Anxiety and Confusion scales, as well as on VAS ratings of "Feel Drug." Fenfluramine also decreased scores on the ARCI LSD and POMS Elation and Positive Mood Scales and impaired DSST performance. End-of-session drug identification rating of fenfluramine were inconsistent: Three of the eleven subjects (27%) identified fenfluramine as a placebo, three as an antihistamine, two as a sedative (18%), and two as a stimulant (data missing for one). In general, subjects disliked the effects of fenfluramine. The mean end-of-session rating of drug liking for fenfluramine was 22.7, compared to 42.7 for placebo.

### Phentermine Plus Fenfluramine

The combination of phentermine and fenfluramine relative to placebo produced a subjective effects profile that resembled some of the effects of each drug alone. Like phentermine, the drug combination produced increased Arousal (POMS) and ratings of "Feel Drug," "Like Drug," and "Want More" (Table 1 and Figure 1). Like fenfluramine, the combination produced a trend toward increased anxiety (VAS; $p < .10$) and impaired psychomotor performance (DSST; $p < .08$). In general the effects of the drug combination were smaller than those of either drug alone, and in some cases the effects of the combination were opposite to those of the individual drugs. However, there were only two significant differences in the direct statistical comparison between the

phentermine/fenfluramine combination and either drug alone: Scores on the POMS Anxiety and Confusion scales were significantly higher after fenfluramine alone than after the combination (Table 1 and Figure 1). Almost half of the subjects (42%) identified the drug combination as a placebo, and only one subject identified it as a stimulant. Despite this, ratings of drug liking were similar to those of *d*-amphetamine and phentermine, with a mean of 51.4.

## DISCUSSION

The purpose of this study was to assess the relative abuse liability of the combination of phentermine and fenfluramine in normal volunteers. Twelve subjects received phentermine and fenfluramine, alone and in combination, in addition to placebo and *d*-amphetamine. The abuse potential of phentermine, fenfluramine, and the combination was determined by comparing their subjective and behavioral effects to those of *d*-amphetamine, a drug with known potential for abuse.

When administered alone, phentermine had a profile of effects similar to *d*-amphetamine (see Table 1 and Figure 1). For example, phentermine, like *d*-amphetamine, increased ratings of Arousal, Vigor, and drug liking and decreased ratings of Confusion. The magnitude of these effects was also similar to those of *d*-amphetamine. The apparently similar abuse potential of phentermine and *d*-amphetamine is not surprising, as both enhance dopamine transmission, an effect that has been associated with the rewarding effects of drugs (Wise 1984; Di Chiara and Imperato 1988; Koob and Bloom 1988). Based in part on this pharmacological effect, phentermine is under Schedule IV of the Controlled Substances Act. However, clinical experience has demonstrated scant evidence of abuse of phentermine and related drugs (Griffith et al. 1976; Weintraub 1992a, 1992b). Moreover, the results of studies assessing the reinforcing effects of phentermine and related drugs in laboratory animals have been equivocal (Griffiths et al. 1976; 1978; Corwin et al. 1987). The reasons why phentermine is not abused despite its apparent similarity to *d*-amphetamine on measures related to abuse potential are unclear but may relate to differences in the availability of the two drugs.

In contrast, fenfluramine alone appears to have little or no abuse potential, producing effects that could be viewed as aversive, such as increased scores on the POMS Anxiety and Confusion scales and decreased ratings of Arousal, Elation, and Positive Mood. In addition, fenfluramine impaired psychomotor performance, decreasing scores on the DSST. The apparently low abuse potential of fenfluramine is consistent with its actions as a drug that increases serotonin neurotransmission. Several lines of evidence suggest that enhanced serotonergic transmission may be aversive (Lyness et al. 1980; Smith et al. 1986; Yu et al. 1986; Porrino et al. 1989; Ritz and Kuhar 1989; Carroll et al. 1990a, 1990b; Roberts 1992; Brauer et al. in press). These results are also consistent with those of previous studies. In humans fenfluramine does not produce stimulant like subjective effects (Griffith et al. 1975; Chait et al. 1986), and in drug discrimination studies in animals, purportedly an animal model of human subjective effects (Schuster and Johanson 1988), fenfluramine and *d*-amphetamine have different effects (Evans et al. 1990). Furthermore, fenfluramine is not self-administered by animals (Griffiths et al. 1976) and humans do not self-administer it in laboratory-based abuse liability procedures, although they do self-administer *d*-amphetamine under the same experimental conditions (Johanson and Uhlenhuth 1980; Chait et al. 1987). Thus, these results suggest that, based on its aversive effects, fenfluramine is very unlikely to be abused when administered alone. The fact that fenfluramine produces aversive effects also suggests that it may not be acceptable to patients as a treatment medication.

When administered in combination, phentermine and fenfluramine appear to have an abuse potential somewhere between that of either drug alone. The results suggest that phentermine may dampen some of the aversive effects of fenfluramine, perhaps making it a more acceptable treatment. At the same time fenfluramine may attenuate some of the positive effects of phentermine, thus reducing its abuse potential. For example, phentermine (nonsignificantly) increased, and fenfluramine decreased, ratings of Elation and Positive Mood relative to placebo. The combination of these two drugs produced intermediate effects (see Figure 1). It should be noted, however, that this relationship did not hold for every measure. For example, phentermine increased ratings of drug liking and wanting more drug relative to placebo, but fenfluramine did not change ratings on these measures. In this case the combination of phentermine and fenfluramine produced ratings of drug liking similar to those of phentermine alone and similar to those of *d*-amphetamine. The reasons why the drug combination produced lesser effects than phentermine on some measures and similar effects on other is not clear and deserves further study.

However, it may be just this profile (e.g., reducing some effects but not others) that is responsible for the apparent efficacy of this combination as a pharmacotherapy for drug abuse. For example, the fact that the combination engenders relatively high ratings of drug liking may serve both to substitute for the drug of abuse (e.g., cocaine), thereby reducing drug taking and may also enhance compliance among patients. These effects of the drug combination may be due to the dopamine-releasing actions of phentermine (Dackis and Gold 1985). In contrast, the fact that the combination produced

some undesirable effects (e.g., decrements in psychomotor performance, decreased elation) may help to protect against the development of abuse of the drug combination. These effects may be related in part to the serotonin-releasing actions of fenfluramine, as animal studies have shown that enhancing serotonin transmission decreases the rewarding effects of *d*-amphetamine and cocaine (Lyness et al. 1980; Smith et al. 1986; Yu et al. 1986; Porrino et al. 1989; Ritz and Kuhar 1989; Carroll et al. 1990a, 1990b; Roberts 1992).

Several limitations of this study should be noted. First, this study examined the effects of phentermine and fenfluramine under acute dosing conditions, which may differ from those observed under chronic dosing conditions. For example, although we have found that acute administration of the serotonin agonist fenfluramine produced primarily aversive effects, other drugs that enhance serotonergic transmission have antidepressant and/or anxiolytic effects when administered chronically (e.g., fluoxetine; Leonard 1992). In addition, although subjects in this study reported positive subjective effects of phentermine, anecdotal reports indicate that obese patients treated chronically with phentermine do not experience mood-altering effects beyond the first few days of treatment. Second, only single doses of some of the drugs were tested. Thus, it is difficult to be sure that equivalent doses of the drugs were compared and that the drugs produce similar maximal effects at higher doses. This can only be confirmed with dose-response studies. Finally, of note is that the magnitude of some of the mood effects of the drugs were small. For instance, although scores on the POMS Elation scale can range from 0 to 4, the scores obtained in this study ranged only from −0.4 to +0.8 (change scores). Thus, although the drug effects reported in this article reached statistical significance, the clinical relevance of some of these effects may be limited.

Nevertheless, the results of this study suggest that the phentermine/fenfluramine combination has relatively low abuse potential in normal volunteers. Further studies of its abuse potential should be conducted directly in drug-abusing volunteers in advance of its widespread use as a pharmacotherapy. The results of the present study, taken with those of previous studies in drug-abusing subjects, suggest that phentermine and fenfluramine may be a safe and efficacious treatment for substance abuse.

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