U.S. DEPARTMENT OF JUSTICE
Drug Enforcement Administration

In the Matter of MDMA Scheduling	Docket No. 84-48

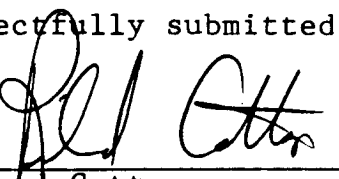
ADDITIONAL DOCUMENTS SUBMITTED ON BEHALF OF DRS. GRINSPOON AND GREER, PROFESSORS BAKALAR AND ROBERTS

The attached additional documents are submitted for inclusion in the record in this proceeding on behalf of Drs. Greer and Grinspoon, Professors Bakalar and Roberts:

41. Letter from Charlotte Johnson to Richard Cotton, dated July 16, 1985
42. Letter from Paul S. Gipe to Frank Sapienza, dated June 12, 1979
43. Letter from Stark Ferriss to Frank Sapienza, dated June 12, 1979
44. Letter from Sandra J. Stoltenow and Michael L. Rehberg to Frank Sapienza, dated June 13, 1979
45. Letter from J. W. Brackett, Jr. to Frank Sapienza, dated June 26, 1979
46. Letter from F. E. Perry to Frank Sapienza, dated August 2, 1979

47. Schuster, C.R. and Johanson, C.E., "Efficacy, Dependence Potential and Neurotoxicity of Anorectic Drugs," in Behavioral Pharmacology, The Current Status (L.S. Seiden, R.L. Balster, eds.) (1985), Proceedings of the Joint Meeting Between the Behavioral Pharmacology Division of the American Psychological Association and the American Association for Pharmacology and Experimental Therapeutics held in St. Louis, Missouri, April 2-6, 1984.

Respectfully submitted,



Richard Cotton
Dewey, Ballantine, Bushby,
Palmer & Wood
1775 Pennsylvania Avenue, N.W.
Washington, D.C. 20006

Dated: July 19, 1985

CERTIFICATION OF SERVICE

I certify that on July 19, 1985, a copy of the foregoing Additional Documents Submitted on Behalf of Drs. Grinspoon and Greer, Professors Bakalar and Roberts, was mailed postage prepaid to each of the following:

Stephen E. Stone, Esq.
Charlotte A. Johnson, Esq.
Office of Chief Counsel
Drug Enforcement Administration
1405 1 Street, N.W.
Washington, D.C. 20537

Robert T. Angarola, Esq.
Robert A. Dormer, Esq.
Hyman, Phelps & McNamara, P.C.
1120 G Street, N.W.
Washington, D.C. 20005

David E. Joranson
State of Wisconsin Department of
Health and Social Services
Controlled Substances Board
1 West Wilson Street
P.O. Box 7851
Madison, WI 53707

Lyn B. Ehrnstein, Esq.
257 North Wetherly Drive
Beverly Hills, CA 90211

Richard Cotton

U.S. Department of Justice

Drug Enforcement Administration

Washington, D.C. 20537

JUL 16 1985

Richard Cotton, Esq.
Dewey, Ballantine, Bushby, Palmer & Wood
1775 Pennsylvania Avenue, N.W.
Washington, D.C. 20006

Re: MDMA SCHEDULING
Docket No. 84-48

Dear Mr. Cotton:

This is in response to your July 8, 1985 letter concerning the documents which the agency provided pursuant to the order of Administrative Law Judge Francis L. Young. I regret the confusion and error contained in the transmittal letter of July 3, 1985. You have received all letters from forensic laboratories contained in the files of the Drug Enforcement Administration relating to MDMA.

I will explain the manner in which these letters were initiated. There were eight letters which responded to Mr. Sapienza's letter of June 6, 1979, which was sent to seventeen state and local law enforcement laboratories. Three of these letters were included in Government's Exhibit B-11. These eight letters are summarized in the list attached to your July 8, 1985 letter. There are four letters which are dated prior to June 6, 1979, which were sent in response to telephone conversations between Mr. Sapienza and the laboratory personnel. All four of these letters are included as part of Government Exhibit B-11.

The Drug Enforcement Administration recieved two letters in response to the Microgram request published in August, 1982. These letters are included as part of Government's Exhibit B-11, and are described as follows:

Robert D. Burris, Criminalist
Criminalistics Laboratory
Fort Worth Police Department
1000 Throckmorton Street
Fort Worth, Texas 76102
Dated: August 20, 1982

Don C. Taylor
Supervisor of Toxicology Laboratory
Texas Department of Public Safety
P.O. Box 3393
Abilene, Texas 79604
Dated: December 28, 1982

All other letters which are included as part of the Government's documents were either submitted in response to a telephone conversation or were unsolictied. DEA has recieved no letters to date in response to the 1985 Microgram request which was published in March, 1985.

Please note that a letter dated March 12, 1979 from the Metropolitan Dade County Crime Laboratory was attached to our July 3, 1985 letter in error. It is unrelated to MDMA, but an example of DEA's continuous efforts to obtain information from state and local law enforcement laboratories concerning non-controlled substances found in the illicit traffic.

Sincerely,

Charlotte A. Johnson

Charlotte A. Johnson
Attorney
Office of Chief Counsel

cc: Francis L. Young
Administrative Law Judge
Drug Enforcement Administration
1405 I Street, N.W.
Washington, D.C. 20537

C MONWEALTH OF PENNSYLVAN
HEADQUARTERS
PENNSYLVANIA STATE POLICE
HARRISBURG

June 12, 1979

Mr. Frank Sapienza
U. S. Department of Justice
Drug Enforcement Administration
Office of Compliance and Regulatory Affairs
1405 I Street, N.W.
Washington, D. C. 20537

Dear Frank:

In answer to your inquiry about MDMA and Ethylamphetamine, our laboratory system has had no encounter with the former. However, three of our laboratories have encountered Ethylamphetamine.

Submissions have been from the northwest, central, and southeast areas of the state and one sample consisted of one pound of material.

I hope this information is of value. Please do not hesitate to contact us anytime.

Sincerely yours,

Paul S. Gipe

Paul S. Gipe
Criminalist II

PSG/cj

JUN 15 1979

STATE OF NEW YORK

NEW YORK STATE POLICE
STATE CAMPUS
ALBANY, N. Y. 12226

SCIENTIFIC LABORATORY

June 12, 1979

Mr. Frank Sapienza
United States Department of Justice
Drug Enforcement Administration
Regulatory Control Division
Washington, D. C. 20537

Dear Sir:

In response to your letter of June 06, 1979 regarding MDMA and ethylamphetamine, this Laboratory has not encountered any exhibits of MDMA and only one (1) of ethylamphetamine in an exhibit from a clandestine laboratory.

We have, however, encountered ephedrine in tablet, capsule and powder form quite frequently during the past year. The exhibits of ephedrine were both in combination with other drugs and, less frequently, with no other drugs.

We have also encountered preparations containing phenylpropanolamine with some frequency.

I hope this information will be helpful to you.

Respectfully,

Stark Ferriss
Captain
Director

IOWA DEPARTMENT OF

PUBLIC SAFETY

Robert D. Ray
GOVERNOR

Refer To File No. _____

Charles W. Larson
COMMISSIONER

June 13, 1979

Mr. Frank Sapienza
Regulatory Control Division
United States Department of Justice
Drug Enforcement Administration
Washington, D.C. 20537

Dear Mr. Sapienza:

In response to your recent letter, our laboratory has not analyzed either MDMA or ethylamphetamine in the last three years. We have, however, encountered fenethylline in several cases in 1977.

With the exception of nitrazepam which we have discussed previously, our laboratory has not been encountering any drugs which may warrant studies about future control.

We will keep your address and telephone number, and should this status change, keep you posted.

Respectfully,

Sandra J. Stoltenow

SANDRA J. STOLTENOW, Criminalist
Division of Criminal Investigation
Criminalistics Laboratory

MICHAEL L. REHBERG,
Laboratory Administrator
Division of Criminal Investigation

SJS:pg

Office of the District Attorney: Laboratory of Criminalistics
1557 Berger Drive, Suite B-2
San Jose, California 95112
(408) 299-2224

County of Santa Clara
California

Louis P. Bergna, *District Attorney*

June 26, 1979

Mr. Frank Sapienza
United States Department of Justice
Drug Enforcement Administration
Regulatory Control Division
Washington, D.C. 20537

Dear Mr. Sapienza:

In reply to your request of June 6, 1979, this Laboratory has not yet encountered either MDMA or ethylamphetamine in its casework. Occasionally, samples of methamphetamine have produced small amounts of an impurity with the TLC characteristics of ethylamphetamine; however, this has been the limit of our exposure to date.

About ten years ago, I made about 1/10 of a mole of ethylamphetamine HCl, and passed out a number of small samples to members of the California Association of Criminalists for reference purposes.

Maxine Hutchin, of the Alameda County Sheriff's Laboratory, told me informally that she has encountered it in her controlled substances analysis casework, but otherwise I have no information.

Sincerely,

J. W. Brackett, Jr.
Director

JWB:cs

STATE OF
WASHINGTON

Dixy Lee Ray
Governor

WASHINGTON STATE PATROL
Public Safety Building, Seattle, Washington 98104

August 2, 1979

Mr. Frank Sapienza
Regulatory Control Division
Drug Enforcement Administration
U.S. Department of Justice
1405 Eye Street, N.W.
Washington, D.C. 20537

Dear Mr. Sapienza:

In response to your inquiry regarding 3,4-methylenedioxymethamphetamine and ethylamphetamine, neither our Western Laboratory in Seattle nor our Eastern Laboratory in Spokane have encountered these drugs. If we encounter these drugs in the future, we shall inform you.

Sincerely,

COLONEL R. W. LANDON, Chief

F. E. Perry.

F. E. Perry, Captain
Coordinator
State Patrol Crime Laboratory System

FEP:rgs

Behavioral Pharmacology: The Current Status
pages 263–279

EFFICACY, DEPENDENCE POTENTIAL AND NEUROTOXICITY OF ANORECTIC DRUGS

C.R. Schuster and C.E. Johanson

The Drug Abuse Research Center
The University of Chicago Pritzker School of Medici
5841 S. Maryland Avenue, Chicago, Illinois 60637

The problem of obesity is not simply cosmetic. Obesity has been associated with heart disease, hypertension and diabetes and is therefore a major public health problem. Amphetamines were widely abused when they were commonly prescribed for weight reduction. Dependence on the drug, tolerance development and escalation of dosage to toxic levels were frequent. Amphetamine prescriptions have decreased but the need for safe, effective anorectic agents for obesity treatment still exists.

For a number of years we have investigated the dependence producing properties of amphetamines and related anorectic drugs with the goal of developing methodologies capable of comparing their relative dependence potential. Three years ago we broadened our evaluation of anorectic drugs to include measures of efficacy as anorectics as well as neurotoxicity to complement the assessment of dependence potential. The goal of this resear program is to develop and validate procedures which can be utilized to develop safe anorectic agents. We will present data on seven drugs: d-amphetamine, mazindol, phenmetrazine, diethylpropion, methylphenidate, fenfluramine and phenylpropanolamine. They were selected for review because they are anorectics with varying mechanisms of action and levels of abuse.

Anorectic efficacy is determined in our evaluation by monitoring changes in food intake in rats and monkeys following the acute administration of a drug. Dose-response determinations are made and an ED_{50} dose is calculated and compared to potencies obtained on measures of dependence potential. This allows a determination of whether patients receiving a therapeutic dose of an anorectic will be exposed to a dose capable of producing dependence.

Dependence potential is assessed in both monkeys and humans by measuring the reinforcing properties of drugs. The self-administration of a drug is assumed to be evidence that it has dependence potential. Additionally, using drug discrimination procedures in pigeons and monkeys, we determine whether the drug will substitute for d-amphetamine. Thus we can predict if the drug produces dependence from the self-administration results and whether the dependence is of the "amphetamine-type" from the drug discrimination results. Similar self-administration and drug discrimination studies are conducted with humans where it is also possible to determine the correlation between mood scale predictions of dependence potential (e.g., euphoria scales) and the drug's reinforcing effects.

The third component of our assessment of the anorectics is their neurotoxicity. Our interest in the possible neurotoxic effects of anorectic agents was prompted by our observations of long-term changes in brain monoamines induced by methamphetamine in monkeys (Seiden,Fischman,Schuster 1977), rats and guinea pigs (Wagner,Seiden,Schuster 1979).

The intent of this review is to demonstrate that the evaluation of any psychotropic drug for use as an anorectic agent should include measures of dependence potential, therapeutic efficacy and possible long-term, even irreversible neurochemical consequences. By comparing all of these factors, a balanced evaluation of a drug's risk-benefit ratio can be obtained. Such evaluations provide a background for comparing new psychoactive drugs with the goal of finding safe, efficacious drugs with minimal dependence potential.

ANORECTIC EFFICACY

Rats were utilized in studies that compared the ED_{50} dose for anorexic effects with doses that produce long-term neurochemical consequences. Monkeys were utilized to compare the ED_{50} dose for suppression of food-intake with amphetamine-like discriminative stimulus effects.

Rat Studies

Rats were given 15 minutes access to a milk solution each day and their intake measured. Dose-response functions were obtained by administering drugs (S.C.) 15 mins prior to the session.

Monkeys Studies

Rhesus monkeys were given 2 hours access to food pellets each day and their intake measured. Drugs were given intra-gastrically 60 mins prior to the session. The anorectic drug effect is expressed as the change in food consumption from baseline averaged across animals.

Results

Table 1 gives the ED_{50} doses for the anorectics tested. The rank ordering of their potencies in rats and monkeys are: d-amphetamine > mazindol > fenfluramine > diethylpropion > phenmetrazine = methylphenidate. There is a marked difference in the efficacy and potency of phenylpropanolamine (PPA) in these two studies. In rats, PPA had no effect in doses up to 128 mg/kg, whereas in the monkey PPA was both a potent and efficacious anorectic. Our failure to decrease food intake in the rat is in contrast to studies by Kornblith and Hoebel (1976) in which doses of 5, 10 and 20 mg/kg of PPA produced a significant decrease in food intake in rats. Further research is necessar to determine what variables account for these differences.

Table 1: Food Intake: ED_{50} (mg/kg)

DRUG	RATS	MONKEYS	HUMANS*
d-Amphetamine	1.7	0.4	5 mg
Mazindol	3.2	1.0	1 mg
Fenfluramine	5.0	2.2	20 mg
Diethylpropion	10.0	3.0	25 mg
Phenmetrazine	12.9	3.8	25 mg
Methylphenidate	13.5	?	
Phenylpropanolamine	128	4.2	25-50 mg

*Anorectic Dose from Physician's Desk Reference

DISCRIMINATIVE STIMULUS PROPERTIES

The discriminative stimulus properties of anorectics were evaluated in pigeons, rhesus monkeys and humans. The use of three species permits predictions about the generality of findings and increases our confidence in the reliability of the results.

Pigeons

Methods. Four white Carneaux pigeons served in this experiment. Chambers with two response keys, two lamps, and a grain magazine were used. In the terminal conditions of this experiment, both keys were illuminated during the session and injections were given 10 min presession. One key was associated with cocaine injections and the alternate key was associated with saline injections. After an injection responding under a FR 30 on the appropriate key was followed by access to grain. The drug condition preceding each session was selected from a semi-random sequence. Incorrect responses reset the fixed-ratio requirement on the correct key. Each session lasted until 50 reinforcers were delivered or until 30 min had elapsed, whichever occurred first. Training continued until the percent of total responses on the

correct key was above 90% and the number of responses emitted on the incorrect key before the first reinforcer was delivered was less than 30 for seven consecutive sessions.

After the previous experiment using cocaine was completed, d-amphetamine at a dose of 2.0 mg/kg was used as the training drug. All other aspects of the experiment remained the same including the drug-key association. Criterion performance remained stable, i.e., the change in training drug did not disrupt the discrimination. The stimulus properties of seven anorectic drugs were then evaluated during test sessions. Test sessions were identical to training sessions except that both keys were activated, i.e., food was delivered following the completion of 30 consecutive responses on either key. d-Amphetamine and saline training sessions were intermixed with test sessions in a six day sequence which consisted of two amphetamine, two saline, and two test sessions. In general, three or four doses of each test compound were tested in a mixed order.

The percent of drug-appropriate responding during the overall session was used as a measure of accuracy and the overall session response rate was used as a measure of non-specific drugs effects.

Results. The previous study using the same subjects had demonstrated that the discriminative stimulus properties of cocaine were pharmacologically specific (de la Garza, Johanson in press). Other psychomotor stimulants, such as d-amphetamine and cathinone, substituted for the cocaine stimulus. Drugs, such as procaine and nicotine, showed only partial substitution whereas oxazepam and pentobarbital produced saline-appropriate responding.

Fig. 1 shows the discriminative performance for the seven drugs expressed as a percent of the animals at each dose that responded above 80% on the amphetamine-appropriate lever. For each drug except fenfluramine, there was a dose-dependent increase in drug-appropriate responding. The order of potency is: mazindol > d-amphetamine = methylphenidate = phenmetrazine > diethylpropion > PPA. With fenfluramine there were individual differences that are not well described by the composite function. Two pigeons showed substitution at criterion levels at 3-10 mg/kg, one showed a maximum of 60% drug-appropriate responding at 10 mg/kg and the fourth pigeon showed no drug-appropriate responding at any dose.

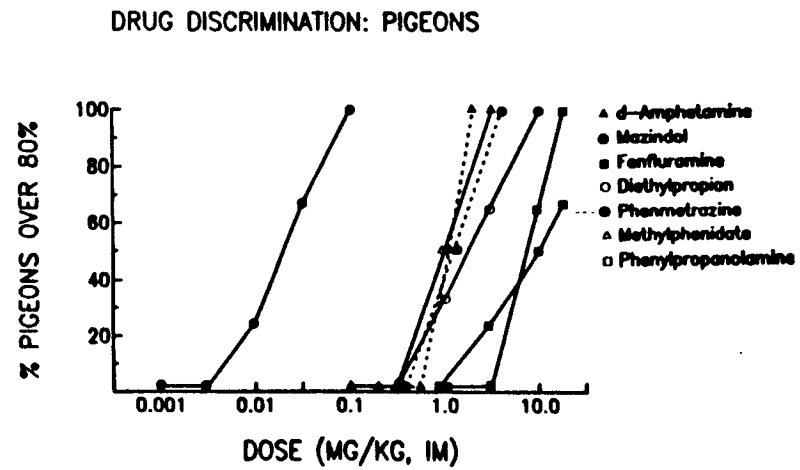


Fig. 1. The discriminative stimulus properties of anorectics evaluated using a two-key discrimination paradigm in pigeons trained to discriminate d-amphetamine from saline. The ordinate is the percent of d-amphetamine trained (2 mg/kg) pigeons responding 80% or more on the amphetamine-appropriate key during test sessions as a function of dose.

Rhesus Monkeys

The species most commonly used in drug self-administration studies is the rhesus monkey. Few studies, however, have used this species in drug discrimination studies despite the clear advantages of comparing the reinforcing and discriminati' stimulus properties of drugs within the same species.

Methods. Three monkeys participated in this experiment. During experimental sessions, the subjects were seated in a Plas-Lab restraining chair and placed in a cubicle containing two response levers and an electric shock delivery system. The monkeys were initially trained on a trial procedure to avoid or escape electric shocks. The trial was signalled by the illumination of stimulus lights. Five seconds after the initiation of the trial, a shock period began. During this period, shocks were delivered every 2 seconds until a response occurred on the correct lever (escape). Immediately after a response occurred, the stimulus lights and shocks were turned off. If the response occurred before the five second period elapsed, the stimulus lights went off and shocks were not delivered (avoidance). A 55 sec intertrial interval followed before a new trial began. During training, the operational

or correct lever alternated daily and the lever that terminated the trial was made conditional upon the presence of drug or saline. If a correct response occurred, i.e., a response on the lever associated with the drug condition, the trial was terminated. The right lever was operative after drug for one monkey, and the left lever for the other two. The opposite lever was operative after vehicle. When five consecutive sessions with more than 90% correct trials were obtained, the drug conditions were presented in a semirandom sequence. The sessions lasted until 30 trials were completed or until 40 minutes had elapsed, whichever came first. Training was considered complete when seven consecutive sessions of more than 90% correct trials were obtained. A correct trial is a trial in which no incorrect responses occurred. During testing sessions, responding on either lever terminated the trial. The percent of drug lever trials was used as a measure of drug substitution. The cumulative latency to the termination of the trial was used as a measure of non-specific effects.

During training the drug used was 0.25 mg/kg cocaine delivered intramuscularly. A study was then completed comparing the potency of the stimulus properties of cocaine and d-amphetamine given by several routes of administration (de la Garza, Johanson in press). After its completion, i.g d-amphetamine at a dose of 0.56 or 1.0 mg/kg was used as the training drug. All other procedural details remained the same (including the drug-lever association) except drug was delivered via a nasogastric feeding tube 60 min prior to the experimental session.

Results. In addition to evaluating the seven anorectic drugs, several additional drugs which are not anorectics were tested to verify the pharmacological specificity of the discrimination. None of the drugs, which included diazepam, pentobarbital and morphine, produced drug-appropriate responding above 25%. Fig. 2 shows the percent of animals that responded above 80% on the amphetamine-appropriate lever at each dose tested for the seven anorectics. All drugs except fenfluramine and PPA substituted for the drug cue with the order of potency: amphetamine > phenmetrazine > mazindol > diethylpropion > methylphenidate. None of the animals responded as if they had been given amphetamine following any of the doses of fenfluramine. Similarly, PPA only substituted for amphetamine in one monkey at a dose of 100 mg/kg. The measure of performance decrement, cumulative latency, was not affected by any of the drugs. For fenfluramine and PPA it is possible that higher doses should have been tested. However, since the food intake of the monkeys was

suppressed by the higher doses for periods of 24 hours or longer it is clear that a pharmacologically active dose was tested.

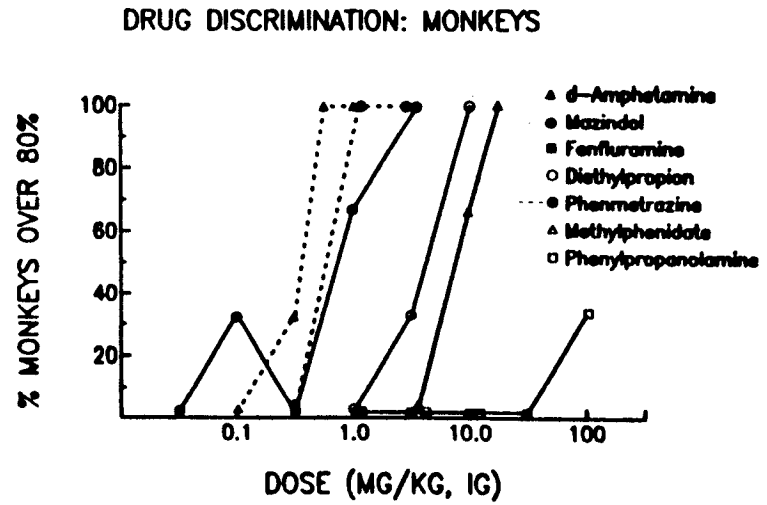


Fig. 2. This figure shows the discriminative stimulus properties of selected anorectics evaluated using a two-lever discrimination paradigm in rhesus monkeys trained to discriminate d-amphetamine from saline. The ordinate is the percent of d-amphetamine-trained (0.56 or 1 mg/kg) monkeys responding 80% or more on the amphetamine-appropriate lever during test sessions as a function of dose.

Humans

For many years experienced drug addicts were used in the evaluation of the dependence potential of new psychotropic drugs. Often they were asked whether the test drug was similar to other drugs they had experienced in the past. Essentially these experienced addicts had training in drug discrimination "on the street." It is possible to do similar studies by teaching normal human volunteers to discriminate drugs and compare their categorization of drugs to that of animals. The most desirable way to make comparisons to the animal model would be to duplicate the procedures used in animals. However, for a variety of reasons, alterations are necessary. For instance, animals are given extensive periods of training in drug discrimination and the doses that are tested may approach toxic levels. Animals once trained can be tested with a multitude of drugs using within-subject balanced designs. With humans, however, there are

limitations on time and dose, and the number of drugs which can be investigated in any one subject. Despite these limitations, our results to date have demonstrated that using humans in the study of the discriminative stimulus properties of drugs is feasible and appears to be a promising alternative to the use of experienced addicts in determining the similarity of new drugs to known drugs of abuse.

Methods. The results reported below are from two studies involving a discrimination between 10 mg d-amphetamine and placebo. In Study 1 diazepam and several doses of amphetamine were tested and in Study 2, d-amphetamine as well as two doses each of phenmetrazine and fenfluramine were evaluated. Standard procedures were used for recruitment, screening, consent and payment (Chait, Uhlenhuth, Johanson 1984a). Only healthy volunteers between the ages of 21 and 35 with no drug abuse or dependence history were selected. Subjects were told that their job was to learn to discriminate between two different drugs, "A" and "B," based on the effects produced by each. They were told that they could receive either prescription or over-the-counter appetite suppressants, sedatives or placebos. Subjects reported to the laboratory between 9 and 11 a.m., three days per week throughout the 9-week study. Upon arrival, subjects completed three subjective effects questionnaires. After filling these out, subjects received a capsule, which they ingested under observation of the experimenter. Subjects were then free to leave for the day, taking three additional sets of questionnaires to fill out 1, 3 and 6 hr later. The subjective effects questionnaires were the Profile of Mood States, the 49-item Addiction Research Center Inventory and a set of visual analog scales.

The study was divided into three sequential phases which differed slightly from Study 1 and 2. The phases were sampling, training and testing. On the first session, all subjects received Drug A, and it was identified to them as such at the time of ingestion. All subjects received Drug B on the second session, and it was also identified to them as such. For half the subjects, Drug A was placebo and Drug B was 10 mg d-amphetamine (AMP). The assignments were reversed for the other subjects. In Study 1, there were only these 2 sampling sessions but in Study 2, sessions 1 and 2 were repeated so that each drug was sampled twice. The next 6-7 sessions comprised the training period. In Study 1 there were six training days and in Study 2 there were 7 training days. On the training days, subjects received Drug A or Drug B in a mixed order but were not told which drug they received when they ingested the capsule. At 1, 3 and 6 hr after capsule ingestion, in addition to the questionnaires described above, subjects filled out a form on which they identified (as Drug A or Drug B) the drug they believed they received, and indicated on a visual analog scale how certain they were of their identification. Subjects were told that they were free to change their identification from hour to hour. There were no consequences attached to the 1- and 3-hr identifications, but the 6-hr identification was differentially reinforced as follows: After subjects filled out the final (6-hr) set of forms, they telephoned the experimenter and reported their final drug identification (Drug A or Drug B). If their response was correct, they were told so and received a bonus payment when they returned to the laboratory for the next session. If their response was incorrect, they were so informed. We arbitrarily decided that subjects had learned the discrimination if identification was correct on at least 5 the 6 training days in Study 1. In Study 2, the criterion was 6 of 7 or 5 correct in a row.

Only subjects who met the training criterion entered the test phase. The purpose of the test phase was to determine whether the discriminative stimulus properties of AMP would generalize to those of other doses of AMP (2.5 and 5) and another drug (10 mg diazepam) in Study 1, and phenmetrazine (25 and 50 mg) and fenfluramine (20 and 40 mg) in Study 2. The test phase consisted of test days intermixed with additional training days. Test days were exactly the same as training days except that subjects were not informed when they telephoned whether or not their response was correct — they were simply told that it was a "test day" and that they would receive the bonus payment. Thus, on test days both responses were equally reinforced, and subjects received no feedback as to which drug they received. Subjects were not told the purpose of test days, nor did they know when test days were scheduled until after they had reported their final identification. Additional training days were interspersed over the course of the test phase in order to determine whether subjects maintained the discrimination. These training days were exactly like the training days during the training phase. No more than two test or training days occurred in succession and the order varied across the subjects.

Results. In Study 1, 7 of the 17 subjects who began the experiment met the criterion of 5 out of 6 correct during training. In Study 2, 14 out of 27 correctly identified the capsule on 6 of 7 training days or on five in succession. Correct responding was lowest at hr 1 but was similarly high at hr 3 and 6. Certainty ratings increased over the day and were higher when the subsequent identification was correct. The subjective effects of amphetamine compared to placebo were similar to those found in a previous study for 10 mg d-amphetamine (Johanson, Kilgore, Uhlenhuth 1983).

During the testing phase the discrimination was maintained at about 80-90% correct for both amphetamine and placebo over the two studies. The number of drug-appropriate responses decreased with lower doses of amphetamine. For 2.5 mg the percent was 21 and it was 50% for 5 mg. The percent of AMP-appropriate responses was 29, 29 and 48 for 10 mg diazepam and the two doses of fenfluramine, respectively. The 25 mg and 50 mg dose of phenmetrazine produced 79% and 86% amphetamine-appropriate answers, respectively. These results are in excellent agreement with those using rhesus monkeys. In both monkeys and humans phenmetrazine produced amphetamine-like discriminative stimulus effects whereas fenfluramine and diazepam did not. It is our intention to test the remaining anorectic drugs using these same procedures.

SELF-ADMINISTRATION

Animal Studies

Rhesus monkeys have been used extensively to assess the dependence potential of new compounds (Johanson,Schuster 1981). In general drugs which are abused by humans are self-administered by monkeys (Johanson,Balster 1978) and those which are not abused, do not maintain responding in monkeys. This concordance has led to the acceptance of the self-administration paradigm as an animal model of drug dependence (Thompson,Unna 1977). The dependence potential of the anorectics reviewed in this paper has been evaluated extensively both in our own laboratory as well as others.

Several studies have demonstrated that amphetamine maintains responding in several species and under a variety of conditions (see Johanson,Schuster 1981). This is also true for methylphenidate (e.g., Wilson,Hitomi,Schuster 1971; Johanson, Schuster, 1975), phenmetrazine (e.g., Wilson,Hitomi,Schuster 1971; Griffiths, Winger, Brady, Snell 1976; Woolverton, unpublished observations), diethylpropion (e.g., Johanson, Schuster 1977), and mazindol (Wilson, Schuster 1976; Woolverton, unpublished observations) but not fenfluramine (e.g.,Woods,Tessel 1974; Griffiths,Winger,Brady,Snell 1976) or PPA (Woolverton, unpublished observations). These results are in general agreement with the actual levels of abuse of these drugs and support the use of animal self-administration studies as a means of predicting dependence potential.

Humans Studies

Many studies designed to develop a methodology for assessing dependence potential in humans have not directly measured drug-taking behavior. For instance, in research conducted at the Addiction Research Center, a profile of physiological and subjective effects of an unknown compound is determined in drug-experienced subjects. The extent to which this profile is similar to the profile of known drugs of abuse is viewed as an indication of dependence potential (Jasinski 1973; Martin 1973). While the results from animal self-administration studies and this type of human study have yielded similar conclusions, only recently have studies in humans used both measures of subjective effects and drug-taking behavior (e.g., Johanson, Uhlenhuth 1980).

Methods. The subjects in these studies were normal human volunteers between 21 and 35 years of age. Prior to acceptance, each subject was given a brief interview during which the nature of the study was explained in detail, a psychological evaluation was conducted, and a drug history was taken. Subjects were accepted if they were considered normal on the basis of this interview and a subsequent physical examination. Most subjects had some experience with psychotropic drugs, but none had a history of drug abuse or dependence.

Each subject participated in a related series of identical choice experiments each comparing a drug to placebo. Subjects typically participated in 2-4 experiments. An experiment consisted of three sessions per week over a 3-week period (total nine sessions). During the first four sessions, the subject came to the laboratory at 9-10 AM and remained there for approximately 5 min. At this time, subjective effects forms were completed and the subject received a colored capsule (i.e., drug or placebo) for immediate ingestion. Half of the subjects received drug during sessions 1 and 3 and placebo during sessions 2 and 4. The order was reversed for the other half. For each subject, drug and placebo capsules were consistently colored to facilitate identification. Each subject was instructed during the initial four sessions to note the color of the capsule and to try to associate characteristic effects with each of the two capsule colors. After ingesting the capsule, the subjects were free to leave the laboratory. They took three additional sets of questionnaires with them which they were to fill out 1, 3 and 6 h later. During the last five sessions the procedure was identical in every respect, except that the subjects were given a choice of which of the two colored capsules they would ingest, i.e., they were given a choice between drug and placebo.

Dependence potential was assessed using several measures. These included the capsule chosen during the five choice sessions, changes in mood, and ratings of liking. Mood states were evaluated prior to the ingestion of the capsule as well as 1,3 and 6 h later. The instrument used in all the studies to assess mood was an experimental version of the Profile of Mood States (POMS), a 72-item adjective checklist, which has been shown to be sensitive

to the effects of psychotropic drugs including d-amphetamine (Johanson,Uhlenhuth 1980). In the most recent studies, additional verbal reports have been used in addition to the POMS. These included the Addiction Research Center Inventory (ARCI) and a set of visual analog scales.

Results. Using this procedure preference for d-amphetamine (5 and 10 mg), diethylpropion (25 and 50 mg), phenmetrazine (25 and 50 mg), fenfluramine (20 and 40 mg), mazindol (0.5, 1 and 2 mg), and PPA (12.5, 25 and 50 mg) has been assessed in separate groups of subjects. In most cases, there were 10-13 subjects per drug except for 5 mg d-amphetamine where 31 subjects were used. As Fig. 3 shows, amphetamine, diethylpropion and phenmetrazine were preferred to placebo whereas fenfluramine and PPA were not. These results closely parallel those found in the study of the reinforcing effects of these drugs in the monkey. An exception is seen, however, with mazindol. Mazindol served as a positive reinforcer in two separate studies using monkeys but was avoided by humans.

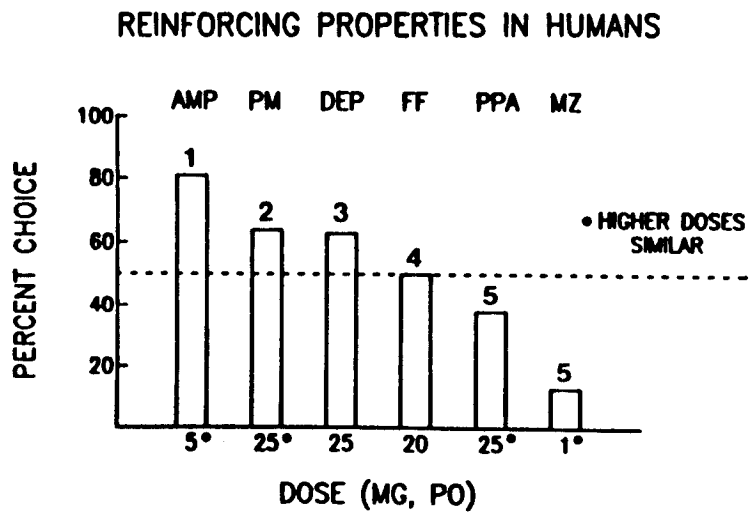


Fig. 3. Mean percent of drug choices across subjects in each of several studies where a choice was given between drug and placebo. The doses indicated on the abscissa are considered to be equitherapeutic. The number above each bar refers to the published citation. 1) Johanson, Uhlenhuth 1980; 2) Chait, Uhlenhuth, Johanson 1984b; 3) Johanson,Uhlenhuth,1978; 4) Johanson,Uhlenhuth 1982; 5) Chait,Uhlenhuth,Johanson in press.

The subjective effects produced by these drugs show a concordance between certain mood changes and reinforcing effects. Drugs which served as reinforcers produced changes in mood states that could be interpreted as positive. For instance, increases in MBG scores on the ARCI have been considered evidence of drug-induced euphoria. In several of our own studies as well as others, amphetamine, diethylpropion and phenmetrazine increased MBG scores (Jasinski,Nutt,Griffith 1974; de Wit, Uhlenhuth,Hedeker,Johanson in press; Chait, Uhlenhuth, Johanson 1984a) whereas fenfluramine (Johanson,Uhlenhuth, 1982) and PPA did not (Chait,Uhlenhuth,Johanson in press). Mazindol, in addition, to producing decreases in Elation and Positive Mood scores or the POMS increased LSD (considered a measure of dyphoria) scores on the ARCI (Chait,Uhlenhuth,Johanson in press).

NEUROTOXICITY

For the past 10 years we have worked in association with Dr. L. Seiden to investigate the possible neurotoxicity of various anorectic drugs. These studies were stimulated by initial findings that the repeated administration of high doses of d-methamphetamine to rhesus monkeys produced irreversible depletions of norepinephrine in the frontal cortex and midbrain, and dopamine in the caudate nucleus (Seiden,Fischman,Schuster 1977). Later investigations of the effects of d-methamphetamine using the rat and guinea pig found long-term depletions of dopamine in the caudate in both species (Wagner, Seiden,Schuster 1979). A review of this literature can be found in Ricaurte, Guillery,Seiden,Schuster,Moore (1982). Of primary relevance in the present context is the finding that amphetamines produce damage to DA neurons in several species which strongly suggests that such changes would also occur in humans. It becomes of importance, therefore, to determine whether the amphetamines are unique in this regard or whether other anorectic drugs produce similar effects.

Methods

A major problem in comparing drugs for their possible neurotoxic effects is the selection of appropriate doses. The data on anorectic potency in rats allowed the calculation of an ED_{50} dose for each drug which could be used as the point of comparison for the selection of doses to be tested for possible neurotoxicity. Generally, doses of 5, 10 and 20 times the ED_{50} for suppression of food intake were selected for investigation. Higher doses were tested if no neurotoxic effects were seen at these doses and a sufficient number of animals survived the four day regimen. In certain cases where the lowest dose (5 times the ED_{50} dose) produced significant depletions, lower doses were tested. In the

case of fenfluramine, for example, doses 5 and 10 times the ED_{50} produced long term depletions of serotonin and therefore lower doses of 1.25 and 2.5 times the ED_{50} dose were tested.

Toxicity testing was carried out as follows: Half of each daily drug dose was administered subcutaneously in two divided doses at 0700 and 1700 hours for 4 consecutive days to a group of male rats. Control rats were injected with the drug vehicle. Two weeks after completing the 4-day treatment period, rats that survived the drug regimen were killed for monoamine level determinations. DA and 5HT were measured in the striatum, NE and 5HT in the hippocampus and DA, NE and 5HT in the rest of brain. The selection of these regions was based upon a more detailed regional analysis of the effects of d-methamphetamine (Ricaurte, Schuster, Seiden 1980).

Results

There were marked differences in the effects obtained with the various anorectic agents tested to date. d-Amphetamine produced a decrease in the levels of DA and 5HT in certain regions of the brain including the striatum and hippocampus but had no effects on NE in any area. The minimal dose (25 mg/kg) required to produce this effect was 20 times the ED_{50} dose for suppressing milk intake. On the other hand, methylphenidate produced no effects on the levels of DA, NE or 5HT at doses up to 5 times (50 mg/kg) its ED_{50} for anorexia. Higher doses could not be tested because they were lethal. Mazindol at a dose 40 times (120 mg/kg) its ED_{50} for anorexia produced a small but significant decrease in NE levels in the hippocampus and rest of brain. Diethylpropion at a dose 10 times (100 mg/kg) its ED_{50} for anorexia produced a decrease in serotonin levels in the hippocampus and rest of brain. Fenfluramine also produced a long lasting depletion of serotonin in the striatum, hippocampus and rest of brain at a dose (6.25 mg/kg) only 1.25 times the ED_{50} dose for anorexia. In the case of the other anorectics, the minimal dose necessary to produce a prolonged neurochemical effect varied from 10 (DEP) to 40 (mazindol) times the ED_{50} dose. It would thus appear that fenfluramine is a significantly more toxic drug than the other anorectics tested. This conclusion is in accord with previous findings by Harvey (1978).

CONCLUSIONS

The present report has reviewed data on the efficacy, dependence potential and neurotoxic effects of seven anorectic drugs. Several important conclusions can be made. First, the necessity of conducting a comprehensive evaluation of a drug becomes obvious. For instance, for fenfluramine the dependence potential and efficacy studies would suggest that this drug is an

ideal anorectic. The neurotoxic effects of fenfluramine in the rat, however, are produced at dose levels in the same range as those necessary to produce anorexia. Further research in other species is needed to determine whether the neurotoxic effects of fenfluramine are limited to the rat. If they are found in other species, this would strengthen the prediction that such effects could occur in humans and would strongly argue against the use of this drug. A second conclusion is that it is important to evaluate drugs in several species. In most cases, as the present report shows, there is a striking concordance in the results with animals and humans. However, there are interesting discrepancies. For instance, mazindol which is self-administered by monk[illegible] when given intravenously is aversive in normal human volunte[illegible] when given orally. Fenfluramine and PPA are similar to d-amphetamine as discriminative stimuli in pigeons but not in monkeys. Further research, which is necessary to determine the factors responsible for these differences, may elucidate important variables contributing to the pharmacological properties of specific drugs and result in the refinement of our testing procedures.

Finally, the dependence potential testing appears to be a valid predictor of these anorectic drugs' actual abuse. Amphetamine, methylphenidate, phenmetrazine and diethylpropion which serve as positive reinforcers and produce amphetamine-like discriminative stimulus effects have all been found to be extensively abused. In contrast fenfluramine and phenylpropanolamine which do not serve as positive reinforcers or produce amphetamine-like discriminative stimulus effects are not widely abused. Therefore it appears that these procedures will be useful in the prediction the dependence potential of new anorectic drugs. Hopefully, through comprehensive assessme[illegible] we can aid in finding efficacious anorectic drugs with l[illegible] dependence potential and an absence of neurotoxicity.

Acknowledgements

The authors wish to emphasize that there were many collaborators in these studies. d-Amphetamine sulfate was obtained from the National Institute on Drug Abuse. Mazindol was furnished by Sandoz, Inc. (East Hanover, NJ), diethylpropion by Merrill-National Laboratories (Cincinnati, OH), fenfluramine by A.H. Robins Co. (Richmond, VA), phenylpropanolamine by Sigma Chemical Co. (St. Louis, MO), phenmetrazine and methylphenidate by Ciba Pharmaceutical Co. (Summit, NJ). The research was supported by National Institute on Drug Abuse grants DA 00250, DA 00085, DA 02812 and DA 00024.

References

Chait LD, Uhlenhuth EH, Johanson CE (1984a). An experimental paradigm for studying the discriminative stimulus properties of drugs in humans. Psychopharmacology 82: 272.

Chait LD, Uhlenhuth EH, Johanson CE (1984b). Drug preference and mood in humans: Effects of phenmetrazine. Fed Proc 43: 570.

Chait L,Uhlenhuth EH,Johanson CE. Drug preference and mood in humans: mazindol and phenylpropanolamine. In Harris LS (ed): "Problems of Drug Dependence, 1983," National Institute on Drug Abuse Research Monograph Series, in press.

de la Garza R, Johanson CE (1984). Discriminative stimulus properties of cocaine in pigeons. Psychopharmacology, in press.

de la Garza R, Johanson CE, Schuster CR (1984). The discriminative stimulus properties of cocaine and d-amphetamine. A comparison of three routes of administration. In Harris LS (ed): "Problems of Drug Dependence, 1983," National Institute on Drug Abuse Research Monograph Series, in press.

de Wit H,Uhlenhuth EH,Hedeker D,Johanson CE. Lack of preference for diazepam in anxious volunteers. Archives of Gen Psych, submitted.

Griffiths RR, Winger G, Brady JV, Snell JD (1976). Comparison of behavior maintained by infusions of eight phenylethylamines in baboons. Psychopharmacology 50: 251.

Jasinski DR (1973). Assessment of the dependence liability of opiates and sedative hypnotics. In Goldberg L.,Hoffmeister F (eds): "Psychic Dependence," New York: Springer-Verlag, p. 160.

Jasinski DR,Nutt JG,Griffith JD (1974). Effects of diethylpropion and d-amphetamine after subcutaneous and oral administration. Clin Pharmac Therap 16: 645.

Johanson CE, Kilgore K, Uhlenhuth EH (1983). Assessment of dependence potential of drugs in humans using multiple indices. Psychopharmacology 81: 144.

Johanson CE, Schuster CR (1975). A choice procedure for drug reinforcers: Cocaine and methylphenidate in the rhesus monkey. J Pharmacol Exp Therap 193: 676.

Johanson CE, Schuster CR (1977). A comparison of cocaine and diethylpropion under two different schedules of drug presentation. In Ellinwood EH, Kilbey MM (eds): "Cocaine and Other Stimulants," New York: Plenum Press, p 545.

Johanson CE,Schuster CR (1981). Animal models of drug self-administration. In Mello NK (ed): "Advances in Substance Abuse: Behavioral and Biological Research, Vol II," Greenwich: JAI Press, p 219.

Johanson CE,Uhlenhuth EH (1978). Drug self-administration in humans. In Krasnegor N (ed): "Self-Administration of Abused Substances: Methods for Study," DHEW Publication No. (ADM)78-727, National Institute on Drug Abuse Research Monograph No. 20: 273.

Johanson CE, Uhlenhuth EH (1980). Drug preference and mood in humans: d-Amphetamine. Psychopharmacology 71: 275.

Johanson CE,Uhlenluth EH (1982). Drug preference in humans. Fed Proc 41: 228.

Kornblith CL, Hoebel BG (1976). A dose-response study of anorectic drug effects on food intake, self-stimulation, and stimulation-escape. Pharm Biochem Beh 5: 215.

Martin WR (1973). Assessment of the abuse potentiality of amphetamine and LSD-like hallucinogens in man and its relationship to basic animal assessment programs. In Goldberg L,Hoffmeister F (eds): "Psychic Dependence," New York: Springer-Verlag, p 146.

Ricaurte GA, Guillery RW, Seiden LS, Schuster CR, Moore RY (1982). Dopamine nerve terminal degeneration produced by high doses of methylamphetamine in the rat brain. Brain Res 235: 93.

Ricaurte GA, Schuster CR, Seiden LS (1980). Long-term effects of repeated methylamphetamine administration on dopamine and serotonin neurons in the rat brain: A regional study. Brain Res 193: 153.

Seiden LS, Fischman MW, Schuster CR (1977). Changes in brain catecholamines induced by long-term methamphetamine administration in rhesus monkeys. In Ellinwood E, Kilbey M (eds): "Cocaine and Other Stimulants." New York: Plenum Press, p 179.

Wagner GC, Seiden LS, Schuster CR (1979). Methylamphetamine-induced changes in brain catecholamines in rats and guinea [illegible]. Drug Alcohol Depend 4: 435.

Wilson MC,Hitomi M, Schuster CR (1971). Psychomotor stimulant self-administration as a function of dosage per injection in the rhesus monkey. Psychopharmacologia 22: 271.

Wilson MC, Schuster CR (1976). Mazindol self-administration in the rhesus monkey. Pharmacol Biochem Behav 4: 207.

Woods JH, Tessel RE (1974). Fenfluramine: amphetamine congener that fails to maintain drug-taking behavior in the rhesus monkey. Science 185: 1067.