DOET (2,5-Dimethoxy-4-Ethylamphetamine), a New Psychotropic Drug

Effects of Varying Doses in Man

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DOET (2,5-dimethoxy-4-ethylamphetamine) is a new psychotropic agent which chemically resembles mescaline and amphetamine. It is essentially the ethyl homologue of DOM (2,5-dimethoxy-4-methylamphetamine), a psychotomimetic drug widely used by hippie populations and designated "STP." DOET was administered to normal male subjects in doses ranging from 0.75 to 4 mg and contrasted with effects of a water placebo. In all cases DOET produced subjective effects including a mild euphoria, a feeling of enhanced self-awareness, and a tendency to feel "anxious" at higher doses. Although there was some increase in subjective effects at higher doses, this was not marked. No hallucinogenic or psychotomimetic effects were observed at any dose. Thus, over a five-fold range of pharmacologically active dosage, the "enhanced awareness" produced by DOET was not associated with psychotomimetic or hallucinogenic actions.

PSYCHEDELIC drugs embrace a large number of agents of widely different chemical classes but which produce notably similar profound subjective effects.[1] Nuances of subjective effects which may vary among drugs[2] have not been well quantified.

Shulgin[3,4] has synthesized a large number of methoxylated amphetamines related to mescaline and amphetamine. One of these, DOM (2, 5-dimethoxy-4-methylamphetamine) (Fig 1), informally designated "STP," was psychotomimetic and hallucinogenic in doses larger than 5 mg, and was about 50 to 100 times more potent than mescaline.[5] In low doses, DOM consistently produced subjective effects but was not hallucinogenic or psychotomimetic.[6]

We also administered low doses of DOET 2,5-dimethoxy-4-ethylamphetamine) the ethyl homologue of DOM (Fig 1) to normal subjects and compared its effects to those of *d*-amphetamine in a double-blind experiment design.[7,8] DOET produced mild euphoria and enhanced self-awareness in the absence of psychotomimetic or hallucinogenic effects. Although both DOET and *d*-amphetamine were mildly euphoriant, their subjective effects differed. Subjects receiving *d*-amphetamine tended to feel tense, alert, and mildly uncomfortable. With DOET, subjects felt relaxed, more accepting to new ideas, and more aware of their feelings and body images.

Most psychedelic drugs such as lysergic acid diethylamide (LSD) produce psychotomimetic and hallucinogenic effects at about two to three times the minimally detectable dosages. To assess the spectrum of psychological effects of DOET, it is important to study a range of doses. In the present study we have examined in normal subjects the psychological and physiological effects of doses of DOET ranging from 0.75 mg to 4 mg as well as a water placebo.

Methods

Normal control male subjects (*Ss*) were obtained from the Financial Aid Office of the Johns Hopkins University, and were told that paid *Ss* were being solicited for an experiment at the medical school. All applicants were screened in an interview by an experienced clinical psychiatrist (L.F.). Applicants with a history of psychiatric disability or extensive use of marihuana or LSD were rejected. The 18 *Ss* accepted for the study were all white male college graduates aged between 21 and 35. They were told that they would receive a drug, DOET, which might produce subjective effects ranging from mild euphoria to a complete hallucinogenic-psychotomimetic syndrome or a water placebo.

Ss were admitted to the NIH sponsored research ward of the Johns Hopkins Hospital two days prior to receiving the drug. They received a complete physical examination including blood chemistry tests, hematological tests, chest x-ray films, electroencephalograms and electrocardiograms. There were no abnormal findings in any *Ss*.

Ss received doses of DOET varying from 0.75 mg to 4 mg as the hydrochloride dissolved in distilled water or distilled water orally at 9 AM after fasting since the preceeding midnight. Dosages were as follows: 4 *Ss* received water; two *Ss* received 0.75 mg, two *Ss* 1.25 mg, two *Ss* 2 mg, two *Ss* 2.5 mg, two *Ss* 3 mg, two *Ss* 3.5 mg, and two *Ss* received 4 mg.

Ss spent the day that they received the drug in their hospital room with a research assistant in a relaxed neutral atmosphere not designed to elicit any particular emotional set. The research assistants were blind to the drug and dose administered as were the *Ss*.

Interviews with the research assistant were tape-recorded at varied intervals during the test day. Interviews were semistructured so that initially the tape recorder was turned on and the *Ss* were instructed to describe whatever they were feeling, after which certain types of questions, eg, presence or absence of visual or mood changes, were always asked. Although the interview procedure was similar to that employed in our earlier study,[8] in the present investigation more questions were directed toward possible hallucinogenic or psychotomimetic changes. Transcripts of interviews with 17 of the 18 *Ss* were scored blindly by an independent observer with respect to certain features that might be expected to characterize the drug experience. A transcript of interviews with one *S* who received 2.5 mg of DOET was lost.

Ss were also administered a self-rating subjective drug-effects questionnaire[9] consisting of 40 items which measure mood and somatic changes and which was originally designed to measure subjective changes occurring with low doses of LSD. This questionnaire was administered the night preceding the experiment and six hours after drug ingestion, when drug effects had subsided. At this postdrug session, *Ss*

Accepted for publication March 16, 1970.

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Table 1.—Subjective Effects of Varying Doses of DOET*

Effect	Placebo (Water) (No. = 4)	Low Dose (0.75-1.25 mg) (No. = 4)	Medium Dose (2-3 mg) (No. = 5)	High Dose (3.5-4 mg) (No. = 4)
High	0.00	0	1.20 (3)	1.00 (2)
Pleasant	0.25 (1)	0.50 (1)	1.20 (2)	1.25 (2)
Unpleasant	0.00	0.25 (1)	0.80 (2)	0.25 (1)
Difficulty concentrating	0.00	0.75 (2)	1.80 (3)	0.50 (1)
Talkative	0.00	1.00 (2)	1.20 (2)	1.25 (2)
Reports insight	0.00	1.00 (2)	1.80 (3)	1.25 (2)
Thoughts faster than words	0.00	0.75 (2)	0.60 (1)	0.50 (1)
Visual effects	0.25 (1)	0.25 (1)	0.40 (1)	0.00
"Nervous" or restless	0.00	0.25 (1)	0.60 (1)	1.50 (3)
Euphoric	0.00	0.25 (1)	0.80 (2)	0.75 (1)
Relaxed	0.00	0.75 (2)	1.00 (2)	0.50 (1)
Light-headed	0.25 (1)	1.25 (4)	1.40 (3)	2.25 (4)
Aware of body image	0.25 (1)	1.00 (3)	1.80 (5)	1.50 (3)

* Transcripts of tape-recorded interviews with subjects receiving different doses of DOET or placebo were graded blindly for each effect. Scoring was as follows: 0, no effect at all; 1, slight effect; 2, moderate effect; 3, marked effect. Data are presented as the mean score per subject. Numbers in parentheses indicate the number of subjects reporting the presence of an effect.

Table 2.—Total Subjective Effect Scores of Subjects With Varying Doses of DOET*

Group	Subjective Effect Scores ± SEM
Placebo	1.00 ± 1.00† (4)
Low dose (0.75-1.25 mg)	7.00 ± 1.41 (4)
Medium dose (2-3 mg)	12.80 ± 3.43 (5)
High dose (3.5-4 mg)	11.25 ± 2.97 (4)

* Transcripts of tape-recorded interviews with subjects receiving different doses of DOET or placebo were graded blindly for different subjective effects detailed in Table 1. Scoring was as follows: 0, no effect at all; 1, slight effect; 2, moderate effect; 3, marked effect. Data are presented as the mean score per subject for all effects. Numbers in parentheses indicate the number of subjects in each group.

† Differs from all drug dose levels ($P < 0.02$).

were instructed to rate how they felt during the preceding six hours.

Subjective mood changes were measured by a symptom checklist that was originally developed by Parloff et al[10] and modified by Uhlenhuth et al.[11] The checklist contains 64 symptoms with a 4-point quantitative scale for each. Clinical clusters that have been identified in psychiatric patients with this checklist include anxiety (11 items), depression (11 items), somatic concern (15 times), and obsessive-compulsive symptoms (6 items). The symptom checklist was given immediately prior to the drug, at three hours and at six hours.

Ss also were administered tests of free associations and their reproduction,[12] multiple trial serial learning of random words, and several procedures designed to measure possible changes in perception. The perceptual tasks included tests of visual discrimination of light intensities, discrimination of graded weights, and the visual perception of Thematic Apperception Test (TAT) stimuli as slides exposed for brief periods (1/100 second, 1/50 second, and 1/10 second).

Pulse rate, blood pressure, oral temperature, and pupillary diameter were determined at hourly intervals.

Results

Subjective Effects.—Subjective effects were first noted about 1½ hours after ingestion of the drug, were most prominent at about three to four hours, and subsided by five hours. They were similar in character to those observed in our earlier study,[7,8] and included subjective feelings of mild euphoria and enhanced self-awareness. At higher doses there was some "nervousness" or "restlessness" (Table 1). *Ss* tended to be talkative and reported a sensation that thoughts were coming faster than words (Table 1). There were also some reports of difficulty in concentration although these did not appear to be dose-related. Under DOET, *Ss* felt light-headed and were very much aware of their body image. Out of 14 *Ss* receiving DOET, only two reported any visual effects and these consist-

ed solely of closed-eyes imagery. Moreover, one of the placebo *Ss* reported similar visual effects.

The lowest dose of DOET employed was readily distinguished from placebo (Table 2). The total subjective effect scores for the *Ss* receiving the lowest doses of DOET were seven times greater than those of *Ss* receiving placebo. The total subjective effects scores of *Ss* receiving medium and high doses were higher than those of *Ss* receiving the lowest doses, although the difference was not statistically significant. In no S was there any evidence of perceptual distortion or cognitive impairment. Thus, in doses five times greater than the dose at which subjective effects could be clearly discerned, DOET was neither psychotomimetic nor hallucinogenic.

Some features of the experiences of *Ss* under DOET are best illustrated by excerpts of the transcripts of the recorded interviews. Subject 1, who received 0.75 mg of DOET, reported 2½ hours after drug ingestion: "I think I'm slightly euphoric, my words are starting to come out kind of trippingly on the tongue, though I don't really feel much different than normal. I feel better able to 'feel how I feel,' perhaps like being conscious of being conscious . . . an infinite progression of consciousness . . . something that increases as I tend to get drunker."

Subject 2, who received 1.5 mg of DOET, reported three hours after taking the drug: "I feel a slight difficulty concentrating, as though my mind is trying to hurry me along all the time . . . my thoughts seems to change quite a lot; and I just seem to close my eyes and think about whatever I feel like, and it seems to come out in spurts of different things."

Subject 3, who received 2.5 mg of DOET, described his experience: "I think I was more empathic with characters in the book I was reading . . . I didn't have a terribly

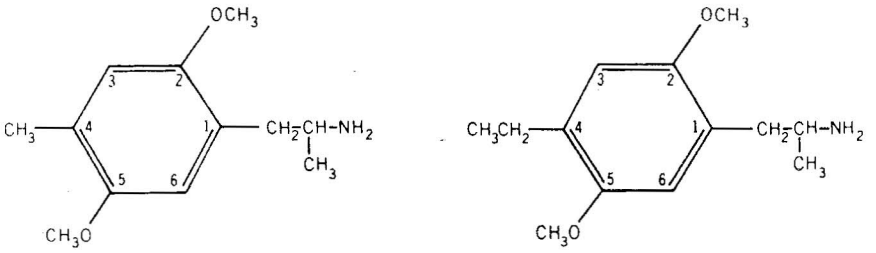

Fig 1.—Structures of DOM (2,5-dimethoxy-4-methylamphetamine) and DOET (2,5-dimethoxy-4-ethylamphetamine).

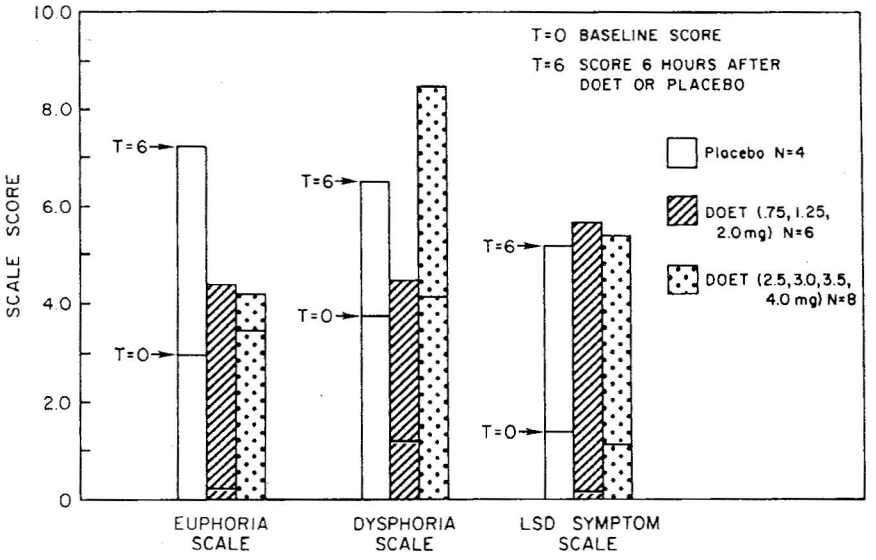

Fig 2.—Effect of DOET and placebo on the drug-effects questionnaire.

Table 3.—*Physiological Effects of Varying Doses of DOET

Effect	2 Hours			4 Hours			6 Hours		
	Placebo	Low Dose	High Dose	Placebo	Low Dose	High Dose	Placebo	Low Dose	High Dose
Pupillary diameter									
% of *Ss* with dilation	0	33	50	0	33	50	0	33	37.5
Mean dilation (mm)	−0.1	+0.4	+1.1	+0.2	+0.3	+1.0	+0.1	+0.1	+0.7
Blood pressure (systolic)									
% of *Ss* with increase > 20 mm Hg	0	0	0	0	16.7	0	0	0	12.5
Mean change (mm Hg)	+2.0	+1.0	+4.0	+3.0	+2.0	+3.0	+4.0	+8.0	+6.0
Blood pressure (diastolic)									
% of *Ss* with increase > 20 mm Hg	0	0	0	0	0	0	0	0	0
Mean change (mm Hg)	+2.0	+3.0	+2.0	+4.0	+2.0	+1.0	+1.0	+2.0	+3.0
Pulse rate									
% of *Ss* with increase > 20/min	0	16.7	0	25	0	12.5	0	16.7	12.5
Mean change	+2	+4	+2	+5	+2	+3	+2	+5	+3
Temperature (oral)									
% of *Ss* with increase > 2 F	0	0	0	0	16.7	0	0	0	12.5
Mean change (F)	+0.4	+0.2	+0.5	+0.8	+0.5	+0.2	+0.2	+0.3	+0.1

* Four subjects received water placebo, six subjects received the "low" dose of DOET (0.75 to 2 mg), and eight subjects received the "high" dose of DOET (2.5 to 4 mg).

large mental effect other than being impatient with the tests . . . on the other hand, I was quite aware that I was impatient, but to my own satisfaction I still wanted to do well. I guess I was more aware than usual. I was thinking more of how I was thinking and trying to compensate, you know, knowing that I was impatient and consciously trying not to rush through just to get it done with, whereas if I had taken LSD I would have just said to hell with everything."

Subject 4, four hours after receiving 3.0 mg of DOET, said: "I feel fairly pleasant. I am trying to judge whether I got a drug or not. If I did, I think it was a very low dose because I haven't felt and don't feel much different than I do normally."

Subject 5 received 4.0 mg of DOET and described his experience four hours after receiving the drug: "Since maybe two hours ago I was feeling a little nervous or jittery but at the same time I began to feel my reactions were loosening up and I've had more desire to talk and take things less seriously. Now I feel like I am relaxing. My body has felt a little bit lighter. I seem to be worrying about things less than normal. Nothing looks any different than normal."

Physiological Effects.—DOET produced pupillary dilation which was more marked at high doses with effects most prominent at four hours (Table 3). There were no changes in systolic or diastolic

Table 4.—*Analysis of Variance for Drug-Effects Questionnaire Scores After DOET or Placebo*

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square	*F* Value
Times	1	906.51	906.51	17.530*
Factors	2	206.06	103.03	7.091†
Groups	7	1797.88	256.83	2.370
Ss	8	865.79	108.22	
T × G	7	517.03	73.86	1.430
T × F	2	19.08	9.54	0.814
F × G	14	374.31	14.52	
T × S	8	413.62	51.70	
F × S	16	232.45	26.73	
T × F × G	14	387.87	27.70	2.365
T × F × S	16	187.37	11.71	
Total	95	5908.00	62.18	

* $P<0.01$.
† $P<0.05$.

Table 5.—*Response to Symptom Check-list After DOET or Placebo**

Time (hr)	F_1	F_2	F_3	F_4	F_5
Placebo (No. =4)					
0-3	−0.25	−0.32	−0.18	−0.13	−0.13
3-6	+0.13	+0.31	0.00	0.00	+0.19
Low Dose (0.75, 1, 2 mg) (No. = 6)					
0-3	−0.41	−1.25	−0.41	−0.17	−0.41
3-6	−0.25	+0.25	−0.33	−0.08	+0.90
High Dose (2.5, 3, 3.5, 4 mg) (No. = 8)					
0-3	+1.31	−0.83	−0.83	−0.19	+1.19
3-6	−1.20	−0.38	−0.13	+0.07	−0.44

* The changes in scores from 0 to 3 hours and from 3 to 6 hours were computed for symptoms of anxiety (F_1), depression (F_2), obsessive-compulsive symptoms (F_3), anger (F_4), and somatic symptoms (F_5). Data are expressed as the mean increase (+) or decrease (−) in scores for groups receiving placebo and low or high doses of DOET.

Table 6.—*Analysis of Variance for Symptom Checklist Scores After DOET or Placebo*

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square	*F* Value
Time	1	5.02	5.010	.4598
Factors	4	24.39	6.100	6.4800*
Groups	6	20.16	3.360	1.2730
Ss	7	18.46	2.630	
T × G	6	140.04	23.340	2.1410
T × F	4	59.63	14.910	2.8990†
F × G	24	36.60	1.520	1.6206
T × S	7	76.36	10.900	
F × S	28	26.35	0.941	
T × F × G	24	182.86	7.610	1.4820
T × F × S	28	143.95	5.140	
Total	139	733.84	5.270	

* $P<0.01$.
† $P<0.05$.

blood pressure, pulse rate, or oral temperature at any dose.

Drug-effects Questionnaire and Symptom Checklist.—The results of the drug-effects questionnaire were subjected to an analysis of variance (Table 4 and Fig 2). This analysis shows that DOET did not produce a simple effect or a significant state of *Ss*. Placebo *Ss* were generally as responsive to the euphoria, dysophria, and LSD symptom scales as were the *Ss* on the highest doses of DOET.

Ss' responses to the 50-item symptom checklist were scored and then examined in terms of change scores from time zero to three hours and three hours to six hours on each of the five factors that are intrinsic to the check list (Table 5). Data were then subjected to an analysis of variance (Table 6), which again showed that DOET did not produce a simple increase in psychiatric symptoms. DOET tended to decrease "depressive" symptoms and produced a rise in "anxiety." These effects diminished at six hours. The decrease in depressive symptoms was most marked at lower doses, while the enhancement of "anxiety" was apparent predominantly at higher doses.

Perceptual Tasks.—On the tasks of discriminating light of different intensities and in distinguishing weights of different masses, there was almost no impairment regardless of the dose of DOET. This indicates no impairment of perceptual discrimination, and also suggests a maintenance of ability to concentrate on a task, even after the highest doses of DOET, since the weight discrimination tasks requires strategy in problem solving as well as the ability to discriminate weights. There also was no deficit in the perception of TAT cards exposed for brief intervals (1/100, 1/50, or 1/10 seconds at any dose, although low doses of DOM (2.7 to 3.3 mg) produced impairment in this task (Snyder et all and Weingartner et al, unpublished data). In free association tasks, results resembled those in our earlier study with DOET.[7] There were the same decreases in high frequency associations with an increase of highly reproducible low-medium frequency associates. Results of these studies will be reported in detail separately.

Comment

In this study, DOET produced subjective effects over a fivefold range of doses in the absence of marked impairment of perceptual or cognitive performance. In an evaluation of the types of subjective effects produced by varying doses of DOET, reports of "nervousness" or restlessness tended to increase with higher doses, as did a light-headed feeling. This may have been reflected in the increased "anxiety" scores on the symptom check list with the subjects receiving higher doses of DOET. For other subjective effects, there was not as marked an enhancement of intensity of

effect with increasing doses. Interestingly, there was no statistically significant increase in total subjective scores with the medium and high doses of DOET as compared to the low dose.

DOET did not effect scores on the euphoria, dysphoria, or LSD subscales of the drug effects questionnaire, regardless of dose. In our earlier study,[7,8] DOET had produced a small but significant increase in the euphoria and the LSD scores on the same drug-effects questionnaire. The reason for the difference in the result of these two studies is unclear. DOET also failed to impair performance on the cognitive task of serial anticipated learning or on the tasks of discrimination of light intensities or weights (Weingartner et al, unpublished data). DOET at all doses did not affect the perception of thematic apperception cards exposed for brief intervals (Weingartner et al, unpublished data). DOM, which appears to be less potent than DOET in terms of the minimal dose required to produce subjective effects.[5,7] (Shulgin, personal communications), did alter the perception of tachistiscopically exposed TAT cards with doses of about 3 mg, lower than some of the doses used in the present study. Although it is difficult to compare results obtained with different drugs in different studies, these results suggest that at equivalent doses DOET affects perceptual processes less than DOM.

In summary, DOET, in doses ranging from 0.75 mg to 4 mg produced mild euphoria and a subjective feeling of enhanced self-awareness. The effects were fairly similar in quality at all the dosages with some enhancement of effects at higher doses. The absence of perceptual distortion or cognitive disfunction at doses of DOET five times greater than the minimal dose for subjective effects indicates that DOET may produce a distinctly different spectrum of effects from the well-known "psychedelic drugs." Thus, the lowest dose of LSD whose subjective effects can be regularly detected is about 25μg to 50μg. At five times this level, ie, 125μg to 250μg; LSD is consistently hallucinogenic and psychotomimetic. Although DOET's unique dose-response characteristics reported here differ markedly from other "psychedelic" drugs, further studies at higher dose levels of DOET would be needed before one could ascertain whether DOET is qualitatively rather than only quantitatively different from other psychedelic agents.

This research was supported by Clinical Research Facilities grant FR-35 from the Public Health Service. Dr. Snyder is a recipient of NIMH Research Career Development Award K-3-MH-33128.

Dr. Joel Elkes advised us during the course of this study.

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