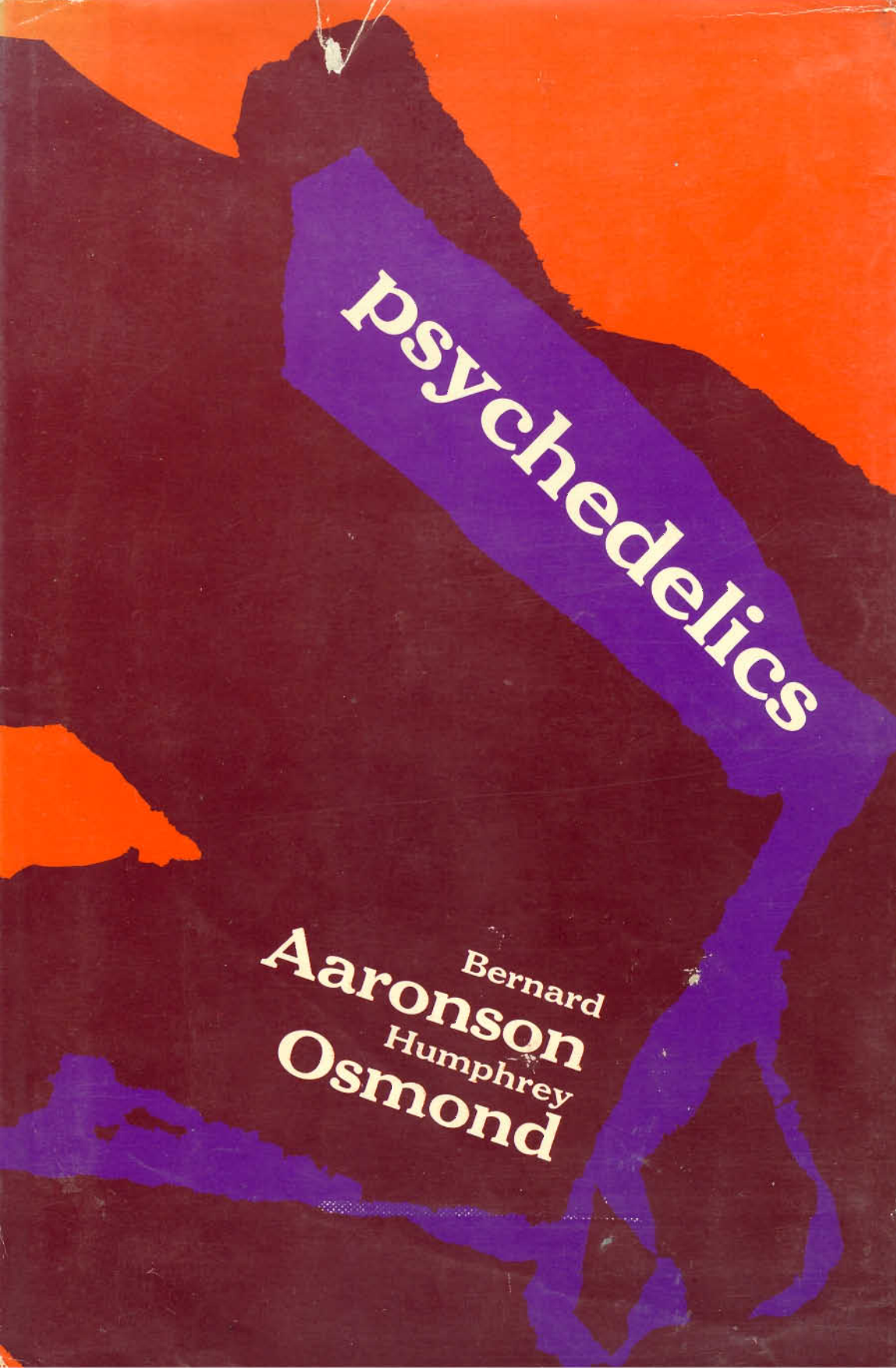
psychedelics
Bernard
Aaronson
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Osmond

Psychedelics

The Uses and Implications of Hallucinogenic Drugs

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BERNARD AARONSON AND HUMPHRY OSMOND

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DOET (2,5-DIMETHOXY-4-ETHYLAMPHETAMINE) AND DOM (STP) (2,5-DIMETHOXY-4-METHYLAMPHETAMINE), NEW PSYCHOTROPIC AGENTS: THEIR EFFECTS IN MAN

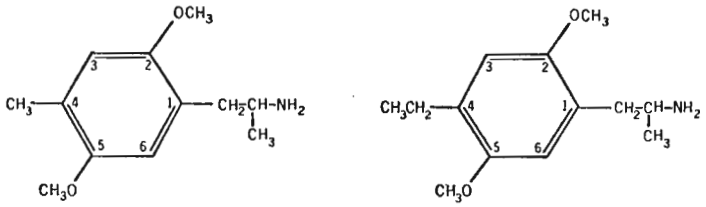
Solomon H. Snyder, M.D., Herbert Weingartner, Ph.D. and Louis A. Faillace, M.D.

Departments of Pharmacology and Psychiatry, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205

INTRODUCTION

The psychedelic drugs embrace a large number of compounds of widely varied structures, including the phenylethylamine, tryptamine, amphetamine and lysergic acid classes, which, however, produce strikingly similar subjective effects. Despite the similar effects of the psychedelic drugs as well as the cross tolerance that exists among them, differences in the nuances of subjective effects occur among the different drugs. Such differences include many reports that mescaline produces a more sensual experience than does LSD. There are also variations in onset and duration of action. Thus, dimethyltryptamine has a duration of action of only one hour, while the effects of LSD last about 8 to 10 hours.

Shulgin (1964) has synthesized a number of methoxylated amphetamine derivatives, several of which are hallucinogenic. Some of these compounds, including MMDA (3-methoxy-4, 5-methylenedioxyamphetamine) as well as MDA (3,4-methylenedioxyamphetamine), tend to produce psychotropic effects with minimal perceptual distortion (Shulgin, 1964; Shulgin *et al.*, 1967). One of the compounds synthesized first by Shulgin, DOM (2,5-dimethoxy 4-methylamphetamine) has been used extensively by "hippie" populations and informally designated "STP." In a number of experiments we have examined the effects of DOM and of its ethyl homologue, DOET (2,5-dimethoxy-4-ethylamphetamine) (Fig. 1) in normal control subjects. Although in low doses



2,5-DIMETHOXY-4-METHYLAMPHETAMINE (DOM) 2,5-DIMETHOXY-4-ETHYLAMPHETAMINE (DOET)

FIG. 1. Structures of DOM and DOET.

these compounds produce similar effects, there are notable differences in dose-response characteristics.

METHODS

The subjects for both the DOET and DOM studies were male volunteers aged 21 to 35 obtained through the Financial Aid office of the Johns Hopkins University. Applicants were screened by an interview with an experienced psychiatrist and by the administration of the Minnesota Multiphasic Personality Inventory (MMPI), and applicants with a history of extensive drug use or evidence of borderline or psychotic emotional disturbances were rejected.

COMPARISON OF DOET AND AMPHETAMINE

In our initial study, the effects of DOET were contrasted with those of *d*-amphetamine. Subjects were admitted twice to the research ward of the Johns Hopkins Hospital with a two week interval between sessions. They were informed that they would receive on separate occasions *d*-amphetamine or DOET, a test drug which might produce "psychological effects."

DOET (1.5 mg as the hyrochloride) or *d*-amphetamine (10 mg as the sulfate) were given orally at 9:00 A.M. in a double blind design to subjects (Ss) who had fasted since the preceding midnight. Ss spent the drug day in their hospital room with a research assistant in a relaxed neutral atmosphere not designed to elicit any particular emotional set. On the evening prior to receiving the drug they were administered tests of free associations and their reproductions, free recall of random and organized words, and ranking of

associations. These tests were readministered 2, 4 and 6 hours after receiving the drug.

Semistructured interviews were tape recorded at varying intervals, and transcripts of these interviews were scored blindly with respect to features which might be expected to characterize the experience of either drug. Subjects were also administered a self-rating subjective drug effects questionnaire (Katz, Waskow and Olsson, 1968) consisting of 240 items. This questionnaire is a comprehensive scale which measures the various aspects of perceptual, mood and somatic changes in subjects undergoing a drug experience. The scale was originally designed to measure the changes in Ss experience with low doses of LSD. The questionnaire contains several subscales, including a euphoria subscale, a dysphoria subscale and an LSD specific subscale.

Pulse rate, oral temperature, pupillary diameter and blood pressure were determined each hour. Urine was collected prior to drug ingestion and after 3, 6, 9 and 24 hours, and was refrigerated and assayed for unchanged DOET by a specific spectrophotofluorometric method. In this method, DOET is extracted from an alkaline urine solution saturated with salt into a mixture of heptane and isoamyl alcohol. After back extraction into 0.1 N H_2SO_4, the native fluorescence of DOET is measured (activation wave length 290mμ; fluorescent wave length 350mμ). This method can detect as little as 50mμg of DOET and is specific for the unchanged compound (Snyder and Sangavi, in preparation).

Subjective experiences: The most notable effects of DOET were a feeling of mild euphoria and enhanced self-awareness. Subjective effects were first noted about one and one half hours after drug administration and peaked in 3 to 4 hours, subsiding 5 to 6 hours after drug administration (Table I.). DOET and amphetamine shared certain subjective effects. Thus, with both drugs there were reports of euphoria and feeling "talkative." Other effects clearly differentiated these compounds. Seven out of 10 *d*-amphetamine sessions produced better than normal ability to concentrate, while 8 out of 10 DOET sessions were associated with subjective difficulty in concentrating. Only after DOET were there reports of "feels high," "reports insight," "notably pleasant experience," "aware of body image," "impatient with tests," "time passes slowly," "washed-out after drug," "thoughts faster than words," and "visual effects." The visual effects under DOET consisted only of closed eye imagery evoked upon the suggestion of the research assistant that Ss close their eyes and describe whatever happens. Only with *d*-amphetamine was there any loss of appetite.

Some features of the drug experience are best illustrated by the following excerpts from transcribed interviews: Mr. K., who received amphetamine first, reported, "I'm concentrating more. I've just been focussing on

TABLE I

Subjective effects of DOET and d-*amphetamine*

Effect	*Number of Subjects Reporting Effect*	
	DOET	*d*-amphetamine
feels high	6	0
reports insight	4	0
notably pleasant experience	7	0
aware of body image	5	0
impatient with tests	4	0
difficulty in concentrating	8	0
better concentration (than normal)	0	7
talkative	7	6
thoughts faster than words	6	0
visual effects	4	0
euphoric	6	4
time passes slowly	2	0
time passes quickly	0	1
"washed out" after drug	2	0
feels especially alert	2	6
loss of appetite	0	3

Transcripts of tape recorded interviews with subjects under DOET or *d*-amphetamine were graded blindly for the presence or absence of each effect. Data are presented as the number of subjects reporting the presence of an effect. Ten subjects received DOET and *d*-amphetamine on two separate occasions.

those cards and attending to the questions asked . . . I find this annoying. It isn't the way I like to be." On DOET, Mr. K. said, "I am more likely to have interesting or new associations of ideas. The other drug [*d*-amphetamine] helped concentration but wasn't relaxing, and didn't help me to associate at all except in a very limited sense. . . . A number of things are closer to the surface than they would normally be [on DOET] . . . I was tremendously suggestible today."

Mr. O. received DOET first and reported, "I can skip readily from one thing to another . . . but if something gets my attention I can get very involved and really focus. . . . I am more aware of myself . . . gee, I am smiling a lot." While on *d*-amphetamine he observed, "No, I am not noticing more about myself this time. . . . This time I haven't done any deep thinking. . . . I am able to concentrate more."

Physiological changes: DOET produced pupillary dilation in 8 out of 10 Ss with effects more prominent 4 hours after the drug (Table II). However, there were no marked changes in pulse rate, blood pressure or oral temperature with either drug.

TABLE II

Physiological effects of DOET and d-*amphetamine*

Parameters	2 Hours		4 Hours		6 Hours	
	DOET	AMPH	DOET	AMPH	DOET	AMPH
Pupillary Diameter						
No. of Ss with dilation	8	1	8	0	4	0
Mean dilatation (mm)	+1.1	+0.2	+1.4	+0.1	+1.1	0
Blood Pressure (Systolic)						
No. of Ss with increase > 20 mm Hg	0	2	0	1	0	0
Mean change (mm Hg)	+5.0	+8.0	+6.0	+4.0	+4.0	+2.0
Blood Pressure (Diastolic)						
No. of Ss with increase > 20 mm Hg	0	0	0	0	0	0
Mean change (mm Hg)	+2.0	+6.0	+3.0	+3.0	+2.0	+2.0
Pulse Rate						
No. of Ss with increase > 20/min	0	0	2	0	1	0
Mean change	+2	+3	+7	+5	+4	+5
Temperature (oral)						
No. of Ss with increase > 2° F	0	0	2	0	0	0
Mean change (° F)	+0.4	+0.2	+1.0	+0.5	+0.7	+0.1

Ten subjects each received DOET (1.5 mg) and *d*-amphetamine SO_4 (10 mg) on separate occasions.

Urinary excretion of DOET: In the 24 hours after administration of DOET, excretion ranged from 103 to 657 μg with a mean of 365 μg, so that between 10% and 40% of the ingested dose appeared in the urine as the unmetabolized compound. The rate of urinary excretion of DOET (Fig. 2) was greatest during the second three hour period, coinciding with the peak of subjective drug effects. If urinary DOET concentration reflects brain concentrations, this would suggest that the psychological effects of this drug are closely related to the presence of the unchanged compound, as has been shown for LSD (Aghajanian and Bing, 1964). The increased excretion of DOET in the second three hour period also suggests a retarded gastrointestinal absorption of the drug.

Drug effects questionnaire: This measure was administered to Ss on the evening prior to drug treatment as well as 2 and 4 hours after DOET and *d*-amphetamine. Both DOET and *d*-amphetamine increased the euphoria scores (Fig. 3) ($p < .05$ for 4 hours scores as compared to pre-drug scores

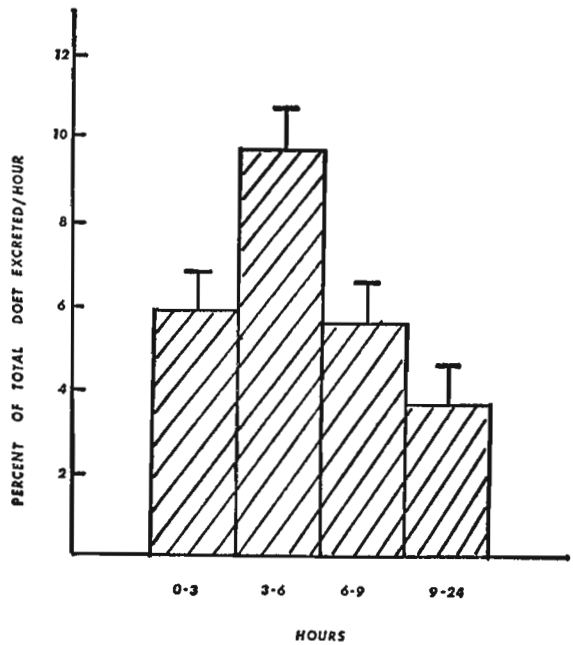


FIG. 2. Urinary excretion of unchanged DOET. Urinary excretion of DOET per hour in each collecton period was calculated as the percent of the total DOET excreted in the first 24 hours after drug administration. Bars and vertical lines show the mean and S.E.M. respectively for 10 subjects.

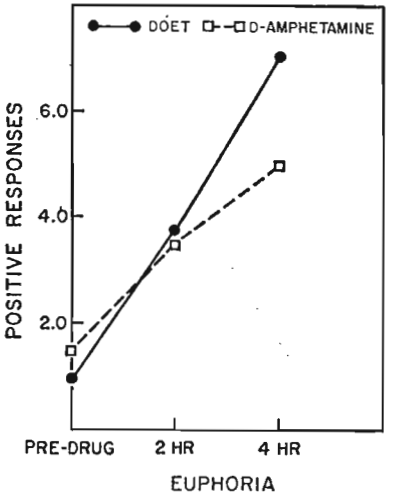


FIG. 3. Effect of DOET and *d*-amphetamine on the euphoria sub-scale of the drug effects questionnaire. Each point is the mean number of positive responses from 10 subjects.

by the *t* test for differences between correlated means). These data agree with the interview information which indicated that both drugs produced a mild euphoria. Only DOET produced an increase in LSD specific symptoms (Fig. 4) ($p < .05$ for 4 hour scores as compared to pre-drug scores by the *t* test for differences between correlated means). However, the LSD scores for the DOET Ss were considerably lower than those produced by 50 μg of LSD (Katz, Waskow, and Olsson, personal communication).

In summary, low doses of DOET consistently produced subjective effects, including a mild euphoria and feelings of enhanced self-awareness, without producing any perceptual or cognitive distortion. This dose of DOET could be clearly distinguished from the effects of 10 mg of *d*-amphetamine.

Ss receiving DOET were administered several tests to evaluate certain intellectual functions. In one task Ss were presented single stimulus words and asked to rank 7 other words in order of how closely they seem related to the stimulus words. Ranking of these words by an S was scored as correlations between his rankings and the rankings of the same words based on normative data (Snyder *et al.*, 1968). Both at baseline and after DOET and *d*-amphetamine the Ss effectively ranked associative words to their stimuli according to their free associative strength in normative data. The correlation of Ss rankings and the ranking of the same words based on their associative response strength to the stimuli used to generate them was $R = 0.50$

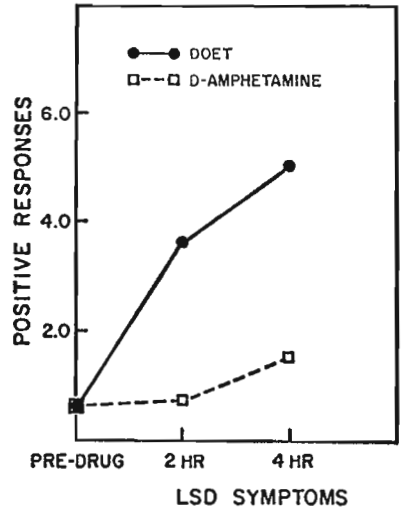


FIG. 4. Effect of DOET and *d*-amphetamine on LSD symptoms sub-scale of the drug questionnaire. Each point is the mean number of positive responses from 10 subjects.

($p < .01$), indicating that neither DOET nor *d*-amphetamine impaired performance on this task. Ss receiving DOET and amphetamine were also administered tests of free recall of words and showed no impairment in free recall of organized word sets (Snyder *et al.*, 1968).

EFFECTS OF LOW DOSES OF DOM AND WATER PLACEBO IN NORMAL SUBJECTS

DOM has been identified by chemists at the U.S. Food and Drug Administration as the active ingredient in tablets of "STP," an hallucinogenic drug used by "hippie" populations. STP was reported in the lay press to produce hallucinogenic episodes lasting up to 72 hours; its effects were *accentuated* by chlorpromazine, a drug which *decreases* the effects of other psychedelic agents. In a pilot study (Snyder *et al.*, 1967) we had examined the effects of varying doses of DOM in normal control Ss. Doses of 2.0 mg were barely perceptible. Doses between 2 and 3 mg produced subjective effects similar to those produced by 1.5 mg of DOET. Doses greater than 5 mg were hallucinogenic. The duration of action was similar to that of LSD, about 6 to 8 hours, with no reports of prolonged effects. In several Ss, chlorpromazine attenuated the effects of DOM.

In order to examine the effects of low doses of DOM in a more controlled study, the following experiment was performed. Ss were hospitalized on the John Hopkins research ward in a design similar to the experiment contrasting DOET with *d*-amphetamine, except that they were hospitalized only once and received only one drug treatment. In a double blind design, 6 Ss received water, 4 Ss received 3.3 mg of DOM and 2 Ss received 2.7 mg of DOM (all doses computed as the hydrochloride).

As in the study with DOET and *d*-amphetamine, interviews with Ss were tape recorded, Ss were administered free association tests and urinary excretion of DOM was determined. Blood pressure, pulse rate, pupil diameter and oral temperature were recorded each hour.

DOM was determined in the urine by a technique which was essentially the same as that used for the measurement of unchanged DOET. DOM had the same fluorescent spectrum as DOET and produced a fluorescence of the same intensity as DOET.

Data from the two dosages of DOM were consolidated, since statistical analysis indicated that there were no significant differences between the two drug dosages and because of the small number of Ss.

On the drug effects questionnaire, DOM produced an increase in the LSD-like symptoms (Fig. 5) ($p < .05$) similar to the score obtained by the

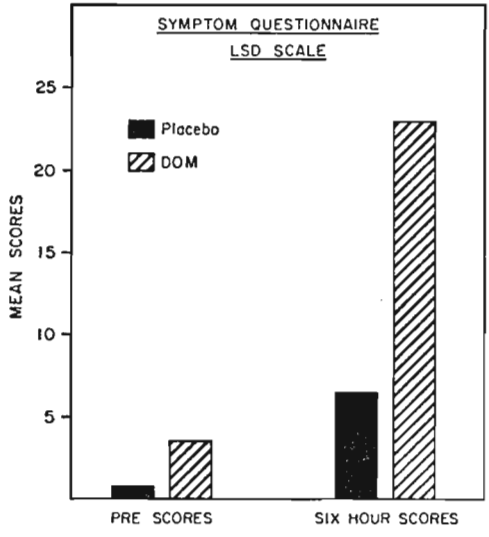


FIG. 5. Effects of DOM and water placebo. Each bar represents mean scores for 6 subjects.

Ss receiving 1.5 mg of DOET. There was a significant increase in both the euphoria and dysphoria scales (Fig. 6) for DOM as compared to placebo ($p < .05$). Interestingly, both drug and placebo groups showed significant increases ($p < .05$) in dysphoria symptoms from their pre-test scores. Apparently, both groups became somewhat uncomfortable in the hospital, complaining of a certain amount of physical symptoms during the 6 hour testing period.

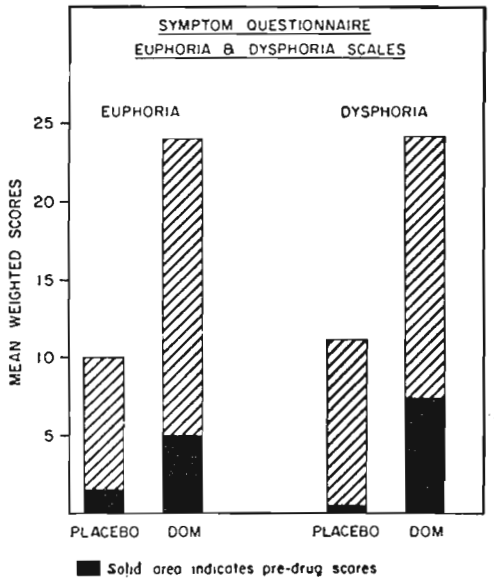


FIG. 6. Effect of DOM and water placebo. Each bar represents mean scores for 6 subjects.

In summary, DOM in doses of about 3 mg produced effects similar to the effects of 1.5 mg of DOET. Since, in an earlier study (Snyder *et al.*, 1967), 2.0 mg of DOM were barely detectable by Ss, it would appear that DOET is somewhat more potent than DOM in terms of the minimal dose required to produce subjective effects. This finding accords with the observation of Uyeno (personal communication) that DOET was almost twice as potent as DOM in impairing size discrimination in squirrel monkeys.

The subjective effects of the two dose levels of DOM resembled those of DOET and were distinguishable by blind analyses of tape transcripts from

placebo. These effects had a time course similar to those following DOET, with onset after 1 to 1½ hours, a peak effect at 3 to 4 hours and subsidence by 5 to 6 hours. As with DOET there were no hallucinogenic or psychotomimetic effects. The only perceptual effects were "closed eye imagery" occurring in 3 of the 6 Ss. As with DOET, DOM did not produce a significant change in blood pressure, pulse rate or oral temperature, but did produce a slight pupil dilation.

The time course of DOM excretion resembled that of DOET except that there was not as pronounced a peaking of urinary DOM during the 3 to 6 hour collection period, as had occurred for DOET. Also, between 5 to 10% of the ingested dose of DOM was excreted during the 24 hours after drug administration, considerably less than the excretion of DOET.

In the experiment contrasting DOET with amphetamine, Ss under the effects of DOET had shown no impairment in the structured intellectual task of ranking free associations or in the free recall of organized word sets. To evaluate such functions with DOM, Ss were administered serial learning tasks in which they were asked to learn a list of 8 random words read to them. Learning trials were continued until Ss produced one perfect list, *i.e.*, repeated all 8 words in the order that they were presented. Equivalent lists were read to the Ss prior to the drug administration 2, 4 and 6 hours after DOM. Strikingly, the Ss who received DOM learned the list in significantly fewer trials than did those who were administered placebo (Snyder *et al.*, 1968). The improved performance by the DOM Ss was maximal 4 hours after drug ingestion, coinciding with maximal subjective effects and peak urinary excretion of unchanged DOM. Thus, as with DOET, small doses of DOM did not impair cognitive functions and may have resulted in improved performance.

Although DOM did not produce any gross perceptual changes, the possibility of subtle effects on simple visual perception was examined in tasks requiring the judgment of horizontal and vertical line lengths at short exposure. Ss receiving DOM or water were required to judge the length of horizontal and vertical lines at 1/100 sec exposure (Snyder *et al.*, 1968). There were no differences in performance of this task between Ss receiving DOM or placebo, indicating that DOM did not impair simple visual perception. The effects of DOM on the perception of more complex stimuli, thematic apperception cards at short intervals, will be discussed below.

THE EFFECTS OF VARYING DOSES OF DOET IN NORMAL SUBJECTS

In the study contrasting DOET and *d*-amphetamine, 1.5 mg of DOET had produced a mild euphoria and subjective feelings of enhanced self-awareness in the complete absence of hallucinogenic or psychotomimetic effects.

This suggested that DOET may differ from related compounds in failing to produce perceptual and cognitive distortion in doses which nonetheless produced noticeable subjective effects. To determine if DOET was in fact unique in its spectrum of psychological effects, we studied a wide range of doses of DOET in normal control Ss.

In this study, subject selection, hospitalization on the research ward and experimental setting were the same as in the two previous studies with DOET and DOM, respectively. Ss were admitted to the research ward on one occasion and received DOET in doses varying from 0.75 mg to 4.0 mg as the hydrochloride dissolved in distilled water, or received distilled water alone orally at 9:00 A.M. after fasting since the preceding midnight. Dosages were as follows: 4 Ss received water; 2 Ss received 0.75 mg; 2 Ss received 1.25 mg; 2 Ss received 2.0 mg; 2 Ss 2.5 mg; 2 Ss 3.0 mg; 2 Ss 3.5 mg, and 2 Ss received 4.0 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 or dose administered, as were the Ss. Interviews were tape recorded and their transcripts analyzed blindly, as in the study with DOET and amphetamine. Ss were administered tests of visual discrimination of light intensity and tests of weight discrimination. They were also administered tests of free association that Ss had received in the other two studies, as well as the same test of perception of tachistoscopically exposed thematic apperception cards as had been used with DOM. Pulse rate, blood pressure, oral temperature and pupil diameter were determined each hour.

Subjective effects were first noted about 1½ hours after drug ingestion, were most prominent after about 3 to 4 hours, and subsided at about 5 hours. They were similar in character to those observed in the study with DOET and amphetamine, and included a relaxed feeling which, in higher doses, was associated with some nervousness or restlessness, a tendency to be talkative and a sensation that thoughts were coming faster than words (Table III). 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 2 reported any visual effects, and these consisted solely of closed eye imagery. Moreover one of the Ss receiving water reported similar effects.

The lowest dose of DOET employed was readily distinguished from placebo (Table IV). The total subjective effects scores for the Ss receiving lowest doses of DOET were 7 times greater than those of Ss receiving placebo. The total subjective effect scores of Ss receiving medium and high doses were higher than those of Ss receiving lowest doses, although the difference was not statistically significant. In no Ss was there any evidence of perceptual

TABLE III

Subjective effects of varying doses of DOET

Effect	Placebo (H_2O) (n = 4)	Low dose (0.75–1.0 mg) (n = 4)	Medium dose (2.0–3.0 mg) (n = 5)	High dose (3.5–4.0 mg) (n = 4)
high	0	0	1.20(3)	1.00(2)
pleasant	0.25(1)	0.50(1)	1.20(2)	1.25(2)
unpleasant	0	0.25(1)	0.80(2)	0.25(1)
difficulty concentrating	0	0.75(2)	1.80(3)	0.50(1)
talkative	0	1.00(2)	1.20(2)	1.25(2)
thoughts faster than words	0	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	0.25(1)	0.60(1)	1.50(3)
euphoric	0	0.25(1)	0.80(2)	0.75(1)
relaxed	0	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 IV

Total subjective effect scores of subjects with varying doses of DOET

Group	Subjective Effect Scores ± S.E.M.
placebo	1.00 ± 1.00[a] (4)
low dose (0.75–1.0 mg)	7.00 ± 1.41 (4)
medium dose (2.0–3.0 mg)	12.80 ± 3.43 (5)
high dose (3.5–4.0 mg)	11.25 ± 2.97 (4)

[a] Differs from all drug dose levels $p < .02$.

Transcripts of tape recorded interviews with subjects receiving different doses of DOET or placebo were graded blindly for different subjective effects detailed in Table I. 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.

distortion or cognitive impairment. Thus in doses 5 times greater than the dose at which subjective effects could be clearly discerned, DOET was neither hallucinogenic nor psychotomimetic.

On the tasks of discriminating lights of different intensities and weights

of different masses, there was no impairment irrespective of the dose of DOET. This indicates no impairment of perceptual discrimination. Effects of varying doses of DOET on perception of thematic apperception cards exposed for short intervals will be discussed below.

At none of the doses of DOET was there any change in systolic or diastolic blood pressure, pulse rate or oral temperature. There was mild pupil dilation with effects most prominent at 4 hours.

EFFECTS OF DOET AND DOM ON THE PERCEPTION OF THEMATIC APPERCEPTION CARDS

In the three studies described above, a large number of psychological tests were administered. Of these, tests of the perception of tachistoscopically exposed TAT cards were administered both with DOM and DOET, and indicated a differential response to the two drugs. Accordingly, the performance of Ss in the three different experiments in the tasks will be discussed together.

Eight thematic apperception (TAT) cards were projected as slides for a period during which Ss were asked to give a different associative label to each slide. The slides were then reprojected in different, random orders, successively at 1/100 sec, 1/25 sec and 1/10 sec exposures, and Ss were required to label the cards with their initial associations. All procedures, including choosing labels during long exposure time and attempting to reproduce them at short exposures, were performed prior to drug ingestion and 2, 4 and 6 hours afterwards. Ss were asked to guess if they were unsure of which stimulus had been presented. This task was administered to Ss in the DOM study and in the study using varying doses of DOET, but was not used in the study contrasting DOET and amphetamine.

In the DOM study, Ss receiving DOM mislabelled stimuli more frequently than did Ss receiving placebo (Fig. 7). This effect was maximal at 4 hours, corresponding to the time of peak subjective effects. The differences in performance between Ss receiving DOM and those receiving placebo were greatest with shortest exposure times. This difference in mislabelling tended to disappear as viewing time was increased. It is striking that DOM caused impairment in labelling TAT cards, since it had not impaired perception of line length. The TAT cards are complex stimuli that presumably contain emotionally meaningful material, while the horizontal and vertical lines are not emotionally meaningful. This suggests that DOM altered performance in the TAT tasks by affecting the associative organization of perceptual organization without affecting "simple" visual perception.

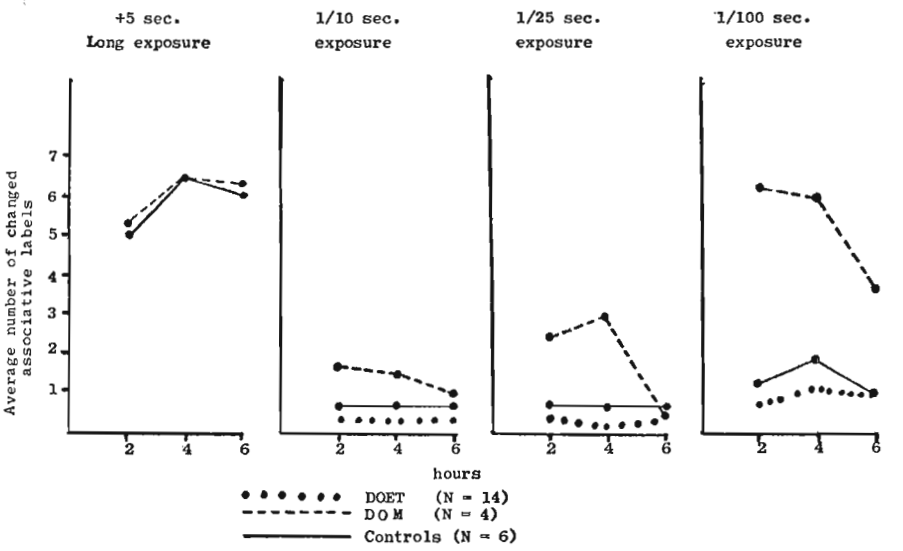


FIG. 7. The effect of DOM, DOET or water placebo on associations to thematic apperception test (TAT) cards exposed for varying time periods. Data for varying doses of DOET were combined.

In the study with varying doses of DOET, the drug had no effect on the perception of TAT cards (Fig. 7) regardless of the dose employed. The highest doses of DOET employed (4.0 mg) were higher than the absolute dose of DOM used. Moreover, if DOET is more potent in terms of threshold for subjective effects, 4.0 mg of DOET would be equivalent to a dosage of DOM considerably higher than 3.0 mg. These considerations suggest that DOET differs significantly from DOM in its paucity of disorganizing effects on perception.

SUMMARY

We have studied the effects of DOM and DOET in normal control subjects. In one study the effects of DOET were contrasted with those of *d*-amphetamine, while in the others the effects of varying doses of DOET or DOM were contrasted with those of a water placebo. Our results indicate that over a 5-fold range of dosage, DOET is able to produce significant subjective effects, the most prominent of which are a mild euphoria and enhanced self-awareness. These occur in the absence of hallucinogenic or psychotomimetic

effects. At 5 times the minimal perceptible dose of LSD or other psychedelic drugs, marked hallucinogenic or psychotomimetic changes are usually observed. This would indicate that DOET differs qualitatively in its spectrum of psychological effects from most other "psychedelic" agents. Indeed, it is possible that in terms of its subjective effects, DOET ought not to be classified along with the other psychedelic agents. Despite a chemical resemblance to amphetamine, the effects of DOET are distinctly different from those of amphetamine and were distinguishable in a double blind experiment.

DOM has previously been shown (Snyder *et al.,* 1967) to be hallucinogenic and psychotomimetic in doses exceeding 5 mg. In doses of about 3 mg. its subjective effects were similar to those of DOET. However, in a task requiring the labelling of tachistoscopically presented thematic apperception cards, DOM produced impaired performance, while DOET in higher doses was without effect. This suggests a difference in the effects produced by the two drugs. Although extensive dose-response data is not available on DOM, it appears that 2.0 mg is about the minimal perceptible dose (Shulgin, personal communication; Snyder *et al.,* 1967), while doses greater than 5.0 mg tend to be hallucinogenic. This suggests that the hallucinogenic-psychotomimetic threshold for DOM is considerably closer to the minimal perceptible dose than is the case for DOET. Indeed, there is yet no evidence that DOET is in fact hallucinogenic. The ability of DOET to produce mild euphoria and enhanced self-awareness in the absence of cognitive or perceptual distortion suggests that it may be of therapeutic utility in psychiatry.

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DISCUSSION

DR. STEIN: Do you have D- and L-isomers of DOM and DOET? Is there any difference?

DR. SNYDER: No, we don't, but you can ask Dr. Shulgin about that.

DR. SHULGIN: I know of three separate experiments in three separate laboratories. There seem to have been efforts made to resolve them into D- and L-components. All three have failed so far.

DR. LUDWIG: I am interested in possible clinical applications. What are your thoughts about this in terms of treating minor types of depression? I refer to DOET specifically.

DR. SNYDER: The use of DOET in depression seems to be an interesting possibility. The first concern would be that DOET should have a reasonably high therapeutic index, so that untoward psychotropic effects do not occur at doses close to the therapeutic levels.

From our studies in normal control subjects, we feel that DOET might also be useful as an adjunct to psychotherapy since it produced an enhancement of self awareness.

DR. DOMINO: In view of the fact that you obtained dose-effect curves with DOET, I was a little disappointed you didn't do the same with amphetamine. You implied a basic difference. Do you think that really is valid?

DR. SNYDER: I don't know. I hope I wasn't trying to imply that it was different from amphetamine in dose-response characteristics at all.

The only point I was making about the dose-response data with DOET was that we were very impressed that with a dose that was five times greater than a dose which produced definite subjective effects, DOET still was not psychotomimetic or hallucinogenic. In this way DOET seemed to differ from other psychedelic drugs.

DR. DOMINO: Is there any difference between DOET and amphetamine? I think this is an important point.

DR. SNYDER: Yes, in the double-blind comparison of DOET and amphetamine they were clearly distinguishable, both in subjective effects and in their effects on the performance of several psychological tests.

Our own impression is that there is a real difference between amphetamine and DOET. The principal subjective effect of DOET is one of feeling more relaxed, open to new insight while fully lucid. It's a very different type of effect from what is conventionally reported with amphetamine.

DR. DOMINO: My point was you only used one dose, 10 mg., and to be fair you would have to run dose-effect curves with amphetamine as well.