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## Dose-effect relations of marijuana smoking on various physiological parameters in experienced male users

### Observations on limits of self-titration of intake

*The effects of smoking three different grades of marijuana (0, 0.5, and 2.9%  $\Delta^9$  tetrahydrocannabinol [THC]) were determined on various physiological subjective end points in experienced users tested blind at intervals of at least one week. The largest amount of  $\Delta^9$  THC equivalent taken by self-titration was 31 mg. After 2.9%  $\Delta^9$  THC marijuana, clear thinking was significantly reduced, dizziness increased, palpebral fissures narrowed, and pupils slightly decreased. There was dose-related increase in the amplitude of the patellar reflex and heart rate, significant at both dose levels. The 2.9%  $\Delta^9$  THC-containing marijuana also slightly elevated systolic and diastolic blood pressure. Pulse rate changes were found to be correlated with subjective estimates of the marijuana "high." Of the 18 subjects smoking the strongest material, 2 had panic reactions and 3 visual distortions and hallucinations. One subject became semicomatose. The majority of subjects found their experience satisfying and reinforcing. One extremely heavy marijuana user tended to show less effects than one less experienced user taking the same dose.*

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There is now an extensive literature on the pharmacological and behavioral effects of marijuana smoking in man.<sup>15, 19, 20, 24</sup> In spite of this it is surprising that there is relatively little information on dose-effect in man.<sup>12, 13, 16, 17</sup> This study was initiated

in part to provide more basic information on the dose-effect relationships of smoking marijuana of different THC content on various physiological end points: subjective estimates of the marijuana "high," subjective measures of mood, pupil size, palpebral fissure size, patellar reflex, systolic and diastolic blood pressure, and heart rate. This study was done as an introduction to other psychopharmacological investigations.<sup>21, 22</sup>

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### Methods

The subjects were 30 adult male experienced volunteer users of marijuana.

The approximate number of times each had used marijuana in the preceding year varied widely, ranging from several to as many as once or twice daily. All were young adults, from 21 to 33 years old. Most were university students. Subjects were selected on the basis that they were physically healthy and mentally normal with the exception of drug experimentation. Most were habitual users of marijuana and generally did not take other drugs. Obvious exceptions were coffee drinking, tobacco smoking, and occasional alcohol. In addition to medical and psychiatric examinations, all subjects were given the MMPI.\*<sup>4</sup> All subjects passed all tests.

The marijuana was obtained from the National Institute of Mental Health.† Two active grades containing 0.5% and 2.9%  $\Delta^9$  THC were used. The placebo material consisted of marijuana from which all of the  $\Delta^9$  THC had been extracted without significant alteration of taste, texture, and smell. In a small pilot experiment, the extracted material was given first under double-blind conditions. Experienced marijuana users had difficulty distinguishing the extracted marijuana from other material they smoked. However, once they were given the most potent marijuana, no one had any difficulty identifying the extracted product at a later session. All subjects smoked the marijuana cigarettes prepared by the staff pharmacist at the Lafayette Clinic. The study was approved by the Human Use Committees of both the Lafayette Clinic and the University of Michigan.

**Initial experimental session.** Eighteen subjects participated in an initial experimental session in which individual dosage level was determined. During this session the subject was asked to smoke as much 2.9%  $\Delta^9$  THC marijuana as he could to a maximum of 8 300 mg cigarettes. The subjects were aware of the quality of

marijuana and were encouraged to continue smoking until they actually refused to smoke any more. Generally, the user decided to stop smoking because he was "too high" in spite of vigorous urging on the part of the experimenters. Both the subject and the experimenters knew prior to the beginning of this session that active marijuana was used. However, the users did not know the precise concentration of  $\Delta^9$  THC in the cigarettes (2.9%). They were told that in this session it was important to establish the total dose level of marijuana that they would take and that in subsequent sessions the total amount smoked in this initial experimental session would be given. The subjects subsequently returned to the laboratory for 2 or 3 visits, a week or more later, and were given the same amounts of extracted marijuana. Twelve subjects were given 0.5%  $\Delta^9$  THC marijuana under the same circumstances with similar instructions. They received a similar number of cigarettes. The variable number of subjects for each test is due to the fact that, for a variety of reasons, all did not participate.

Physiological parameters were measured before and at various times after smoking. Each subject was asked to smoke as rapidly as he could. Great care was taken to ensure that all would inhale deeply and retain the smoke in the accepted social manner. Subjects exhaling large amounts of smoke were instructed to inhale properly to ensure maximal absorption of the pyrolysis products. Heart rate (Lead II) was recorded on a Grass polygraph. Blood pressure from the dominant arm was obtained by auscultation using a mercury manometer. Pupils were measured from a Polaroid color print under standard lighting conditions with the subject looking at a fixed point approximately 5 feet away. A Polaroid CU-5 camera was used with a lens adapter. The patellar reflex was recorded automatically on the polygraph as was the electromyogram (EMG) of the quadriceps femoris muscle. The patellar reflex was elicited with a mechanical rubber-tipped hammer every 2 seconds. The iso-

\*Minnesota Multiphasic Personality Inventory.

†Supplied by Dr. Monique Braude, Center for Studies of Narcotic and Drug Abuse, National Institute of Mental Health, Rockville, Md. 20852.

**Table I.** *Effects of smoking marijuana cigarettes of varying  $\Delta^9$  THC content on Clyde Mood test scores in normal human volunteers*

Mood	$\Delta^9$ THC content					
	0%		0.5%		2.9%	
	Before	After	Before	After	Before	After
Friendly						
Mean	50.0	48.0	51.0	55.0	55.0	53.0
S.E.	1.8	3.4	3.3	1.7	8.9	13.0
Aggressive						
Mean	51.0	49.0	48.0	49.0	52.0	52.0
S.E.	2.3	0.9	2.2	1.9	1.9	2.1
Clear-thinking						
Mean	51.0	47.0	48.0	45.0	50.0	44.0*
S.E.	2.4	1.5	1.8	2.9	1.9	2.1
Sleepy						
Mean	50.0	52.0	56.0	54.0	50.0	48.0
S.E.	2.5	2.3	2.8	1.7	1.9	2.9
Unhappy						
Mean	39.0	39.0	41.0	41.0	41.0	44.0
S.E.	1.5	2.3	2.3	2.5	1.2	1.8
Dizzy						
Mean	48.0	50.0	47.0	45.0	47.0	54.0*
S.E.	0.9	1.8	1.8	1.5	1.2	3.1

In this and all subsequent tables a paired comparison Student *t* test was used to determine the *p* value.

Scores are expressed as mean number of points on a 0 to 4 scale for each adjective.

\**p* < 0.05; a total of 9 subjects smoked 0%, 10 smoked 0.5%, and 18 smoked 2.9%  $\Delta^9$  THC marijuana.

metric muscle contraction was recorded simultaneously with a Grass FT 10 strain gauge. The apparatus is similar to that used previously<sup>7</sup> in tobacco smoking experiments. Subjects were also asked to score themselves on a subjective 0 to 10 scale with 10 as the maximal "high" they had in their lives. In addition, they took the Clyde Mood scale.<sup>3</sup> This entire sequence of measurements was done before and at approximately 15 minute intervals throughout the entire experiment, which lasted about 2 to 3 hours.

**Amount of marijuana smoked.** A total of 18 subjects were given 2.9%  $\Delta^9$  THC marijuana during the initial experimental session to determine the point of refusal. A total of eight 300 mg cigarettes was offered. Actually, no subject smoked more than 4 of them. The reasons given for refusing additional marijuana were complex, but most subjects simply said that they were as "high" as they felt comfortable and did not wish to get "higher." On a 0 to 10 scale

of which 0 was no "high" and 10 was the maximal "high" they had ever had in their lives, most subjects reported a "high" of 10 or more. Only 2 subjects said they had ever had stronger marijuana in their lives. The mean subjective "high"  $\pm$  S.E. for all subjects was  $9.8 \pm 0.5$ . The amount of marijuana each subject smoked varied widely, ranging from 1 to a maximum of 4 cigarettes. The mean ( $\pm$  S.E.) of the total amount of marijuana smoked was 673.8 ( $\pm$  61.7) mg. This multiplied by 2.9% gives a mean  $\Delta^9$  THC of 19.5 ( $\pm$  1.8) mg total. Assuming that 50% of the material was destroyed during smoking, this would mean that the subjects received an average total of 9.8 mg. This amount is consistent with other literature reports<sup>9-11</sup> of the amount of  $\Delta^9$  THC taken either by inhalation or orally that would give a rather marked subjective effect. Subjects smoked the marijuana cigarettes over a period of approximately 15 to 30 minutes. It was very difficult to have every subject smoke at a

**Table II.** Effects of smoking marijuana cigarettes of varying  $\Delta^9$  THC content on palpebral fissure in normal human volunteers

$\Delta^9$ THC content (%)	N	Mean palpebral fissure $\pm$ S.E.		$\Delta$ Palpebral fissure	p Value
		Before	After		
0	8	8.7 $\pm$ 0.5	9.6 $\pm$ 0.8	+ 0.9	> 0.05
0.5	9	10.0 $\pm$ 0.7	9.5 $\pm$ 0.6	- 0.5	> 0.4
2.9	9	9.3 $\pm$ 0.7	6.3 $\pm$ 0.8	- 3.0	< 0.001

Units are in mm.

**Table III.** Effects of smoking marijuana cigarettes of varying  $\Delta^9$  THC content on pupil size in normal human volunteers

$\Delta^9$ THC content (%)	N	Mean pupil size $\pm$ S.E.		$\Delta$ Pupil size	p Value
		Before	After		
0	8	5.5 $\pm$ 0.1	5.2 $\pm$ 0.2	- 0.3	> 0.2
0.5	9	6.2 $\pm$ 0.3	6.2 $\pm$ 0.3	0.0	> 0.0
2.9	8	6.1 $\pm$ 0.2	5.4 $\pm$ 0.2	- 0.7	< 0.02

Units are in mm.

more rapid pace. Most of these subjects reported that the brand of marijuana they smoked (unknown to them it was 2.9%  $\Delta^9$  THC marijuana) was among the best marijuana that they ever had. Only 2 commented that they had previously received such an "excellent" grade of marijuana. Most of the subjects thoroughly enjoyed their "high" and were in good spirits throughout the experiment, but 2 subjects exhibited panic reactions and a third became stuporous and semicomatose. In fact, this subject, who took 30.2 mg total of  $\Delta^9$  THC, was so stuporous that he had to be placed in bed. When aroused he had periodic tremors and a transient rigidity. The neurological picture was identical to one previously seen in monkeys given the synthetic THC derivative DMHP.\*<sup>6, 8</sup> About 6 hours later this subject was able to get up and walk but he was still quite disoriented. Interestingly, another individual who had much more experience with marijuana took 31.0 mg total of  $\Delta^9$  THC and showed no stuporous reaction. Although he was quite "high," he could play a guitar very well. Both subjects were observed to

inhale their marijuana equally well so that this represents either extremes in individual differences or tolerance in the more frequent marijuana user.

**Effects on mood.** The Clyde Mood test was given before and immediately after smoking marijuana. Difference scores were then calculated. The categories friendly, aggressive, clear-thinking, sleepy, unhappy, and dizzy were then analyzed for effects of 0, 0.5%, and 2.9%  $\Delta^9$  THC-containing marijuana. As can be seen in Table I, 2.9%  $\Delta^9$  THC caused a decrease in clear thinking ( $p < 0.05$ ) and an increase in dizziness ( $p < 0.02$ ). No other significant changes were observed. These findings are consistent with what was grossly apparent during the marijuana high. Subjects had difficulty concentrating, with short-term memory loss. The latter was indicated by poor performance on serial 7's. In addition, the subjects frequently wished to lie down because of mild dizziness.

**Effects on the angle of the palpebral fissure and pupil size.** Increasing doses of marijuana caused subjects to look and act "stoned." This was manifested by drooping eyelids. As can be seen in Table II, 2.9%  $\Delta^9$  THC marijuana causes a narrowing of the palpebral fissure ( $p < 0.001$ ). This

\*1-Hydroxy-3(1,2-dimethylheptyl)-6,6,9-trimethyl-7,8,9,10-tetrahydro-6-dibenzopyran.

**Table IV.** Effects of smoking marijuana cigarettes of varying  $\Delta^9$  THC content on patellar reflex in normal human volunteers

$\Delta^9$ THC content (%)	N	Mean amplitude $\pm$ S.E. in % of original		$\Delta$ Patellar reflex in %	p Value
		Before	After		
0.0	8	100 $\pm$ 0	137 $\pm$ 25	37	> 0.1
0.5	8	100 $\pm$ 0	233 $\pm$ 39	133	= 0.01
2.9	7	100 $\pm$ 0	236 $\pm$ 74	136	> 0.1

**Table V.** Effects of smoking marijuana cigarettes of varying  $\Delta^9$  THC content on heart rate in normal human volunteers

$\Delta^9$ THC content (%)	N	Mean heart rate $\pm$ S.E.		$\Delta$ Heart rate	p Value
		Before	After		
0.0	12	71 $\pm$ 1.3	73 $\pm$ 1.9	+ 2	> 0.1
0.5	10	81 $\pm$ 2.6	96 $\pm$ 3.2	+ 15	< 0.01
2.9	18	71 $\pm$ 2.4	128 $\pm$ 5.7	+ 57	< 0.001

Units are in beats per minute.

apparently contributes to their "stoned" look. A surprising finding was that there was a very small but consistent decrease in pupil size after smoking 2.9%  $\Delta^9$  THC, which was not evident upon gross inspection but was significant by pupillography ( $p < 0.02$ ). (Table III).

**Effects on the patellar reflex.** In contrast to smoking extracted marijuana (0%  $\Delta^9$  TMC) cigarettes in which a slight increase in patellar reflex was observed, 0.5% and 2.9%  $\Delta^9$  THC marijuana caused a marked facilitation of the patellar reflex, approximately 133% to 136% increase. Strangely, this effect plateaued at the lower dose of  $\Delta^9$  THC and there was no further enhancement of the patellar reflex with 2.9%  $\Delta^9$  THC marijuana. In fact, with the larger dose of marijuana there was marked variability between subjects in which some showed a marked increase and others no change or even decrease. The facilitating effect on the patellar reflex was most consistent ( $p < 0.01$ ) with the low dose of  $\Delta^9$  THC marijuana (Table IV).

**Cardiovascular effects of marijuana.** As has been reported by several groups,<sup>12, 13</sup> smoking marijuana produces dose-related increase in heart rate. This finding was

reconfirmed by data summarized in Table V. It can be seen that 0.5%  $\Delta^9$  THC produced a 15 beat per minute increase over control levels ( $p < 0.01$ ), while smoking 2.9%  $\Delta^9$  THC-containing marijuana caused an increase of 57 beats per minute over control levels ( $p < 0.001$ ). In contrast, 0%  $\Delta^9$  THC marijuana caused no significant change in heart rate.

Although 0% and 0.5%  $\Delta^9$  THC marijuana caused no significant change in blood pressure, 2.9%  $\Delta^9$  THC marijuana caused a slight but significant ( $p < 0.01$ ) increase in both systolic and diastolic blood pressure (Table VI).

### Discussion

The present study confirms and extends previous findings in the literature concerning the clinical, pharmacological, and behavioral effects of marijuana smoking in young adult volunteers. In general, no subject voluntarily smoked more than four 300 mg 2.9%  $\Delta^9$  THC-containing cigarettes. No subjects testing this concentration of  $\Delta^9$  THC took more than 31 mg. This dose is calculated on the assumption that there was a steady 50% delivery of  $\Delta^9$  THC throughout the smoking session, which is

**Table VI.** Effects of smoking marijuana cigarettes of varying  $\Delta^9$  THC content on systolic and diastolic blood pressure in normal human volunteers

$\Delta^9$ THC content (%)	N	Systolic blood pressure				Diastolic blood pressure			
		Mean $\pm$ S.E.		$\Delta$ Blood pressure	p Value	Mean $\pm$ S.E.		$\Delta$ Blood pressure	p Value
		Before	After			Before	After		
0.0	8	120 $\pm$ 1.0	122 $\pm$ 1.3	+ 2	> 0.1	78 $\pm$ 2.0	79 $\pm$ 2.4	+ 1	> 0.05
0.5	10	122 $\pm$ 1.9	122 $\pm$ 4.0	0	> 0.9	76 $\pm$ 1.4	79 $\pm$ 2.2	+ 3	> 0.05
2.9	14	123 $\pm$ 2.5	138 $\pm$ 4.9	+ 15	< 0.01	81 $\pm$ 1.4	89 $\pm$ 2.1	+ 8	= 0.01

Units are in mm Hg.

by no means certain. This is a relatively large amount by inhalation compared to the usual doses of  $\Delta^9$  THC given by mouth in most studies.

It should be emphasized that our subjects did not know that they were smoking the strongest marijuana available to us. They were urged repeatedly by the experimenter to smoke more cigarettes to a maximum of 8. Why did they stop when they actually anticipated taking all that was offered of "government grass?" The findings of Isbell and associates<sup>11</sup> that 50  $\mu$ g per kilogram of  $\Delta^9$  THC injected into a tobacco cigarette produced in their subjects a "social high" while 250  $\mu$ g per kilogram was "hallucinogenic" may provide a partial answer. If one takes 80 kg as the mean weight of our subjects, that is (0.05  $\times$  80) 4.0 mg total of  $\Delta^9$  THC for a "social high" dose; a hallucinogenic dose would be 20 mg (0.25  $\times$  80) total  $\Delta^9$  THC by inhalation. Many of our subjects easily achieved and possibly exceeded this dose of  $\Delta^9$  THC. The incidence of hallucinations was much lower than reported by Isbell and associates.<sup>11</sup> The role of nicotine-containing tobacco spiked with  $\Delta^9$  THC in their study is unknown, but one would not expect a higher incidence of hallucinations. Inasmuch as many of our subjects were frequent marijuana users, one would suspect that tolerance is a factor (as observed in animals<sup>1, 5, 18</sup>). In any event, one is forced to conclude that in large amounts  $\Delta^9$  THC becomes more dysphoric and hence less reinforcing. Our subjects did not wish to go beyond the psychological and physical states they were in. The rea-

sons given were vague but the fact was clear.

The pharmacological changes observed in the present study are consistent with some reported in the literature. The subjective mood changes of less clear thinking and dizziness would be expected of the larger doses of marijuana. The finding of a narrowed palpebral fissure further supports our previous report.<sup>5</sup> The slight constriction of the pupils after marijuana as measured by pupillography was unexpected but is consistent with the lack of gross pupillary changes observed clinically. The dose-related increase in heart rate following marijuana smoking as well as  $\Delta^9$  THC administration to man has now been observed by many. The slight increase in the patellar reflex and arterial blood pressure after marijuana smoking was unexpected but a significant finding compared to THC extracted marijuana.

Recently Cappell, Kuchar, and Webster<sup>2</sup> have offered evidence that psychosocial variables may be more significant than pharmacological variables in determining the "recreational" intake of marijuana. The fact that our subjects given 0.5%  $\Delta^9$  THC marijuana tended to limit themselves to 4 cigarettes also supports this hypothesis. However, the pharmacological effects of the lower dose of  $\Delta^9$  THC were much less obvious compared to the 2.9%  $\Delta^9$  THC material.

The present study indicates the importance of dose effect in marijuana smoking. Depending on the amount smoked, several different conclusions could be drawn. No serious side effects were ob-

served with the lower  $\Delta^9$  THC-containing marijuana cigarettes other than the usual mild reversible organic brain syndrome previously reported<sup>23</sup> and the tachycardia. It should be noted that occasional subjects have been observed to show electrocardiogram (EKG) abnormalities, including premature ventricular contractions.<sup>12, 14</sup> Except, of course, for the tachycardia, most of our subjects showed only slight EKG changes.

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