

# Subjective Syndromes, Physiological Changes and After-Effects of the Acute $\Delta$ 9-Tetrahydrocannabinol-Intoxication\* Two Double-Blind Studies in Volunteers

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Received September 7, 1972

**Summary.** Two different double-blind trials with  $\Delta$ 9-Tetrahydrocannabinol were performed on altogether 73 normal volunteers.

Factoranalyses yielded the following three dimensions of the  $\Delta$ 9-THC experience:

- a) "derealization of self and surroundings",
- b) "anxious-depressive state" and
- c) "euphoric-stimulated state".

An oral dosage of 23.5 mg  $\Delta$ 9-THC caused the following physiological changes:

1. The variance of changes from the predrug level of the diastolic blood-pressure was significantly increased by  $\Delta$ 9-THC.
2. The pulse-rate did not change significantly which was probably due to the very high predrug pulse-rate of the subjects.
3. The body temperature decreased under  $\Delta$ 9-THC.
4. The pH of saliva was significantly lowered by  $\Delta$ 9-THC.

Anxious-depressive states during the  $\Delta$ 9-THC intoxication were correlated with a relative increase in systolic blood-pressure.

25 subjects completed a semantic differential on their mood daily for 9 days after the experiment. Those subjects who had received  $\Delta$ 9-THC felt ill at ease and constrained on the day after the experiment. No such after-effects were found on the following days.

**Key words:**  $\Delta$ 9-Tetrahydrocannabinol — Double-Blind Studies in Volunteers — Subjective Syndromes — Physiological Changes — After-Effects.

**Zusammenfassung.** An insgesamt 73 gesunden Versuchspersonen wurden 2 Doppelblindversuche mit delta-9-Tetrahydrocannabinol durchgeführt.

Die unter delta-9-THC aufgetretenen subjektiven Veränderungen ließen sich auf Grund faktorenanalytischer Berechnungen den folgenden 3 Syndromen zuordnen:

- a) „Derealisation von Ich und Umwelt“,
- b) „ängstlich-depressives Zustandsbild“ und
- c) „euphorisch-angeregtes Zustandsbild“.

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\* Based on a paper presented at the C.I.N.P. congress in Copenhagen, August 1972.

23,5 mg delta-9-THC per os bewirkte folgende physiologische Veränderungen:

1. Die Varianz der Veränderungen des diastolischen Blutdruckes im Vergleich zur Ausgangslage wurde signifikant vergrößert.

2. Die Pulsfrequenz stieg nicht signifikant an, was vermutlich auf den hohen Ausgangswert unserer Probanden zurückzuführen ist.

3. Die Körpertemperatur nahm ab.

4. Der pH-Wert des Speichels wurde signifikant erniedrigt.

Ängstlich-depressive Zustandsbilder während der delta-9-THC-Intoxikation gingen mit einem relativen Anstieg des systolischen Blutdruckes einher.

Die Stimmung von 25 Probanden an 9 dem Experiment folgenden Tagen wurde mit einem semantischen Differential erfaßt. Diejenigen Probanden, die delta-9-THC erhalten hatten, fühlten sich am Tage nach dem Experiment beeinträchtigt. An den folgenden Tagen konnten keine Nachwirkungen beobachtet werden.

*Schlüsselwörter:*  $\Delta^9$ -Tetrahydrocannabinol — Doppelblindversuche am Gesunden — Subjektive Syndrome — Physiologische Veränderungen — Nachwirkungen.

## 1. Introduction

Two double-blind trials were performed on the acute effects of delta-9-THC in man. The main aims of these studies were as follows:

In order to assess the subjective delta-9-THC effects reliably it seemed useful first of all to construct self-rating scales for the dimensions of the delta-9-THC experience based on factoranalytical results. As a next step we thought it of interest to correlate these psychological dimensions with physiological changes during the cannabis intoxication.

Furthermore, as several of our subjects at the beginning of our experiments complained spontaneously of a hang-over on the day after receiving delta-9-THC, we began to study these after-effects systematically.

## 2. Methods

### *a) Design of Study I*

In the first double-blind study on average 23.5 mg delta-9-THC (i.e. 350 mcg/kg) dissolved in olive oil were administered orally to 18 normal volunteers with no prior experience of cannabis. The control group of 18 subjects received pure olive oil as placebo. All subjects were students, 27 were male and 9 female. Each subject was tested alone in a neutral but relatively comfortable setting.

### *b) Design of Study II*

In the second double-blind trial 37 normal volunteers, again students, were treated together with 15 mg delta-9-THC, placebo and "no drug" in a cross-over design. The substance was administered orally too, the solvent this time being ethyl alcohol. 15 of the subjects had taken cannabis before, but only four of them more than 25 times. 19 students of this trial were male and 18 female. The study was performed in a lecture room.

### *c) Assessment of Drug Effects*

Drug effects were assessed by the use of several psychometric tests given before, during or after the intoxication of those who had received delta-9-THC.

Only those methods will be reported here which are relevant to the main aims of the studies as mentioned above.

When drug effects in most subjects had diminished, i.e. at a minimum of three hours after application, all subjects of both trials were required to compare their own experience during the experiment with 54 statements likely to be descriptive of delta-9-THC effects. They had to use a four point scale ranging from "exactly like my own experience" to "not at all like my own experience".

The 54 statements describing subjective cannabis effects best had been selected from the 156 items of Ditman's DWM-Scale [6-8] by two psychiatrists and a clinical psychologist, one of whom had had personal experiences with cannabis himself. The items were translated literally into German. Furthermore, in the first trial only, the following physiological variables were measured before and twice at hourly intervals after drug administration:

- a) pulse-rate,
- b) systolic and diastolic blood-pressure,
- c) sublingual body temperature and
- d) pH of saliva.

Blood-pressure and body temperature were assessed as reports in the literature on the effects of cannabis in man on these variables are inconsistent [5]. The pH of saliva seemed of interest as several investigators [3,4,15,16] have reported correlations between the acidity of saliva and certain aspects of mood in normals. The pulse-rate was included in our first study to find out, whether the consistently reported increase proves true also for subjects with no prior experience of cannabis receiving a rather high dosage of delta-9-THC [5].

In addition, most of the subjects of the first study were asked to fill in a semantic differential on their mood daily for several days after the experiment in order to assess after-effects.

## **3. Results**

### *a) Dimensions of the Subjective Delta-9-THC Experience*

To find the dimensions of the subjective delta-9-THC experience, firstly a principal component analysis was performed with the results of the 54 statements from the 55 subjects who had received delta-9-THC in both trials. Cattell's scree test suggested a three factor solution [2]. Secondly a principal factor analysis was computed with subsequent rotation to simple structure according to the Varimax criterion [10].

Based on the results, three scales were constructed according to the classical theory of mental testing [12]. This procedure yielded scales which can be described as measuring the following syndromes:

- a) "derealization of self and surroundings",
- b) "anxious-depressive state" and
- c) "euphoric-stimulated state" [9].

The first scale consists of the following 21 items, retranslated into English (Table 1).

Table 1. Dimension I: "Derealization of self and surroundings"

Item No.	Statement
4	Words had strange new meanings
7	I felt hot or flushed at times
11	I found I could just sit and look at something for hours
12	I saw people and animals in motion who weren't really there
14	People thought what I said was not important
15	It was an experience of great beauty
17	I felt cold or had chills
18	Hours went by like seconds—or one second seemed to last forever
23	I was able to influence people and objects with my thoughts
29	I felt as if I were several different people, only one of which was the usual "me"
31	I had levels of thought I can't express in words
33	I felt separated from everyone and everything
34	I felt as if I were floating in space
35	I had trouble understanding what was being said
37	I kept seeing things after I'd stopped looking at them
38	I felt paralyzed
40	My "I" or "self" seemed to leave my body
41	I felt as if I had no body at all
43	Solid objects changed their shapes and even disappeared
51	Sounds seemed to affect what I saw
54	The experience was very unusual

The reliability of the scale was estimated by Cronbach's  $\alpha$  [13]. An  $\alpha = 0.94$  was found.

The second scale is characterized by the following items (Table 2).

The reliability of the scale is  $\alpha = 0.87$ .

The third dimension of subjective delta-9-THC effects, the "euphoric-stimulated state" is defined by the following items (Table 3).

The reliability of the scale is  $\alpha = 0.88$ .

We attempted to establish the validity of the scales by comparing the delta-9-THC to the placebo effects in both studies. For the first trial we

Table 2. Dimension II: "Anxious-depressive state"

Item No.	Statement
5	I felt unsteady and uneasy
8	I felt depressed
13	I felt anxious or tense
19	I had nausea, headache or other physical pain which dominated the experience
24	I felt remorse over things in the past
36	I became afraid I might die
42	At times I felt as if I were being persecuted
46	I had a feeling of complete despair
47	Everything seemed hopeless
50	I felt I might become permanently insane

Table 3. Dimension III: "Euphoric-stimulated state"

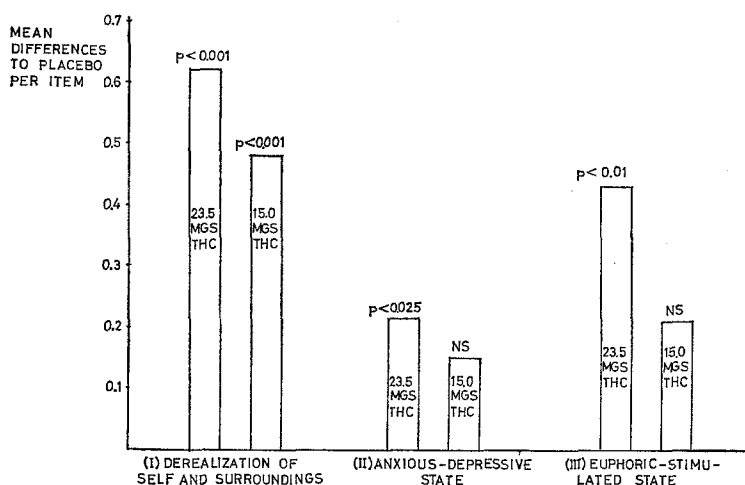
Item No.	Statement
1	I felt more alert and alive than I have in a long time
2	I had wonderful sexual feelings
3	I felt a tremendous energy
9	I felt more free
10	I felt more creative than usual
21	I had a craving for food
25	I felt a sense of wonder, joy, and peacefulness in the world
30	I enjoyed what happened to me
32	I felt as if I had been reborn
52	I enjoyed being in this state so much that I will want it to last for days
53	I have been greatly helped by the experience

found statistically significant differences for all three scales. Thus, a dosage of 23.5 mg delta-9-THC causes a derealization of self and surrounding and anxious-depressive as well as euphoric-stimulated states, in subjects with no prior cannabis experience.

In the second study a statistically significant difference between delta-9-THC and placebo was found only in the first dimension.

The results of both studies are compiled in Fig. 1.

The intercorrelations between the scales "anxious-depressive state" and "euphoric-stimulated state" were not significantly negative, as one might expect ( $r = 0.02$ ). This indicates that delta-9-THC like LSD [11] may produce strong but opposing emotions at approximately the same time and/or at different times during one intoxication.

Fig. 1. Subjective Effects of  $\Delta 9$ -THC in the DAE-scale I

### b) Physiological Changes and Correlations with Subjective Experiences

In respect to the physiological variables measured in the first trial, differences from the predrug-level were computed for each subject and the delta-9-THC and placebo-group compared by the Mann-Whitney U-test [14]. The following tables show the means and standard deviations of the actual scores at the three testing occasions.

While no significant difference between the mean changes in systolic and diastolic blood-pressure were found, the variance of changes was significantly higher ( $p < 0.02$ ) for the diastolic blood-pressure under delta-9-THC (Table 4 and 5) after two hours.

The pulse-rate under delta-9-THC was decreased one hour after and increased two hours after drug administration, without however reaching statistical significance (Table 6). That the consistently reported

Table 4. Systolic blood-pressure

		Hours after application		
		0	1	2
$\Delta 9$ -THC (N = 18)	$\bar{x}$	126.7	118.1	118.3
	s	20.2	18.2	20.4
PLA (N = 18)	$\bar{x}$	125.0	119.4	116.7
	s	11.9	17.0	13.2

Table 5. Diastolic blood-pressure

		Hours after application		
		0	1	2
$\Delta 9$ -THC	$\bar{x}$	83.3	78.9	81.4
( $N = 18$ )	$s$	15.0	14.3	14.4
PLA	$\bar{x}$	81.7	79.4	79.2
( $N = 18$ )	$s$	6.4	9.8	7.5

Table 6. Pulse-rate

		Hours after application		
		0	1	2
$\Delta 9$ -THC	$\bar{x}$	89.8	82.0	90.7
( $N = 18$ )	$s$	13.5	16.5	17.5
PLA	$\bar{x}$	81.4	77.4	75.2
( $N = 18$ )	$s$	11.8	12.0	12.7

Table 7. Body temperature in °C

		Hours after application		
		0	1	2
$\Delta 9$ -THC	$\bar{x}$	36.9	36.9	36.6
( $N = 18$ )	$s$	0.43	0.44	0.51
PLA	$\bar{x}$	36.9	37.0	36.8
( $N = 18$ )	$s$	0.38	0.41	0.37

increase was not found in our cannabis-naïve subjects is probably due to their relatively high predrug pulse-rate.

The body temperature decreased as shown in Table 7 under delta-9-THC. While the decrease is rather small the difference to placebo is significant two hours after drug-application ( $p < 0.01$ ).

The pH of saliva was significantly lowered two hours after application of delta-9-THC as compared to placebo ( $p < 0.05$ ) (Table 8).

The correlations between the changes of these physiological variables and the psychological dimensions of the subjective delta-9-THC experience were generally rather low. The only statistically significant correlation found indicates that anxious-depressive states correspond to a

Table 8. pH of saliva

		Hours after application		
		0	1	2
$\Delta 9$ -THC	$\bar{x}$	6.59	6.43	6.31
( $N = 18$ )	$s$	0.32	0.35	0.40
PLA	$\bar{x}$	6.66	6.54	6.68
( $N = 18$ )	$s$	0.29	0.33	0.31

relative increase of systolic blood-pressure two hours after application ( $r = -0.47$ ,  $p < 0.05$ ). The same tendency was found for the diastolic blood-pressure ( $r = -0.39$ ) without however reaching statistical significance.

### *c) After-Effects of the Delta-9-THC Experience*

According to our instructions 14 of 16 subjects of the delta-9-THC group and 11 of 16 subjects of the placebo group of the first study completed the semantic differential given daily for an average of more than 9 days after the experiment.

This enabled us to estimate the average mood of each subject in respect to the three mood dimensions this semantic differential measures in the German version [1], that is to say "not lively, passive vs. vivid, activ" (avital-vital), "composed, calm vs. agitated, tense" (ruhig-erregt, gespannt) and "constrained, ill at ease vs. unconstrained" (beengt-harmonisch).

Deviations of the mood on the day resp. the next days after the experiment in these three dimensions from the individual average were computed.

The comparison of the delta-9-THC and the placebo group in respect to the mood deviations on the day after the experiment yielded a statistically significant difference in the second dimension of the semantic differential; the subjects who had received delta-9-THC felt on average more ill at ease and constrained than those of the placebo group.

For the second day after the experiment no such after-effects were found.

Furthermore, the intercorrelations between the three dimensions of the subjective delta-9-THC experience and the deviations from the average mood were computed for the delta-9-THC group. It was found that the more anxious and depressive the subjects felt during the actual delta-9-THC intoxication, the more tense, agitated, constrained and ill at ease they were on the next day.



The correlations between the other two dimensions of the delta-9-THC experience and after-effects were not statistically significant.

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