Effects of marihuana-dextroamphetamine combination

Under a double-blind, randomized, complete block design, subjects were given either placebo or 10 mg/70 kg dextroamphetamine sulfate (A) orally followed 1½ hr later by a marihuana cigarette (M) prepared to deliver 50 μg/kg delta-9-tetrahydrocannabinol (THC). Statistical analyses suggested that heart rate and blood pressure increased in an additive manner when both drugs were given. Electrocardiogram changes, when present, were nonspecific in character and appeared to be associated with marihuana. In a second study, psychomotor performance was evaluated by a similar design using doses of 10 mg/70 kg of A and M prepared to deliver 25 μg/kg THC. Impairment was related to smoking of M, and no difference could be distinguished between M alone and M-A combination. Subjective evaluation, as measured by the modified Cornell Medical Index (CMI) demonstrated only additive effects for the combination.

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The social use of marihuana has been shown to be associated with the use of other drugs such as alcohol, amphetamines, and barbiturates. Recently Carlin and Post[2] surveyed 107 marihuana users and found that over 74% experimented with other drugs and that 60% had taken amphetamines. In 1973 Fisher and Brickman[9] studied 1,100 subjects and categorized them into six groups with reference to marihuana smoking. Their report suggested that over 60% of the active marihuana smokers occasionally used stimulant drugs. Animals investigations of marihuana-amphetamine interaction have shown that moderate doses of either marihuana extract or 95% pure delta-9-tetrahydrocannabinol (THC) enhanced amphetamine-induced hyperactivity in mice.[3, 10]

Studies with cannabis in man have reported an initial stage of excitement and stimulation after smoking,[21] but measurement of such parameters as psychomotor function has demonstrated only impairment.[6, 13] Cardiovascular investigations in man with THC and 11-hydroxy-THC have shown that following intravenous administration both induce a prominent dose-related increase in heart rate.[15, 20] The prevention of the marihuana-induced tachycardia by propranolol, a β-adrenergic blocking drug, and failure of atropine to block suggest sympathoadrenal involvement.[1, 4] Since am-

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Table I. *Protocol for the marihuana-dextroamphetamine cardiovascular study*

Time (min)	*Procedure*
−30	Breathalyzer test, blood pressure, ECG
−15	Blood pressure, ECG
00	Blood pressure, ECG, subjective questionnaire, administration of amphetamine
30	Blood pressure, ECG, subjective questionnaire
60	Repeat 30 min
90	Repeat 30 min, administration of marihuana cigarette
100	Blood pressure, ECG (30-sec rhythm strips—1 per min)
105-165	Blood pressure, ECG, subjective questionnaire, 15-min intervals
195-375	Blood pressure, ECG, subjective questionnaire, 30-min intervals

Table II. *Protocol for the marihuana-dextroamphetamine psychomotor study*

Time (min)	*Procedure*
−15	Breathalyzer test for ethanol
0	Heart rate and blood pressure, administration of amphetamine
90	Heart rate and blood pressure, administration of marihuana cigarette
100	Termination of smoking
100-105	Heart rate and blood pressure
105-120	Wobble Board I-IV and Pursuit Meter I-IV
120-135	Delayed Auditory Feedback I, III, V, VI, IX
135-155	Pegboard, reaction time, tremor test, tapping count
155-170	Fatigue-Pursuit Meter V and VI
170	Modified Cornell Medical Index

phetamine also induces cardiovascular as well as central nervous system effects, a pharmacologic interaction between marihuana and amphetamine is possible. The purpose of this investigation was to evaluate the cardiovascular, psychologic and psychomotor effects of marihuana and amphetamine alone and in combination, and to investigate the possibility and nature of an interaction between them.

Methods

Healthy male medical and graduate students between the ages of 21 and 30 were selected from among those who volunteered. All subjects admitted prior casual use of marihuana but denied habitual drug use. Each subject's complete medical history was taken, and each had a physical examination, blood chemistry (SMA 12/60), complete blood count (CBC), and electrocardiogram (ECG) before being admitted. All subjects were overtly normal. During the study, subjects were asked to refrain from the use of all drugs, including alcohol and caffeine-containing beverages, for 18 hr prior to testing. Prior to each session, subjects were tested with a Breathalyzer for the presence of alcohol. No alcohol was detected in breath sample from any of the subjects.

Experimental design. The complete investigation was partitioned into two separate studies. The first was concerned with the cardiovascular and psychologic effects of a marihuana-amphetamine combination; the second evaluated the psychomotor effects following administration of both drugs. Each study was conducted in a double-blind manner with all treatments assigned to each subject according to a randomized complete block design. Subjects were tested individually at the same time of the day at all sessions. Each subject session was separated by one week. Both studies consisted of four experimental sessions: (1) placebo-dextroamphetamine and placebo-marihuana, (2) placebo-dextroamphetamine and marihuana, (3) dextroamphetamine and placebo-marihuana, and (4) dextroamphetamine and marihuana. The marihuana cigarettes were smoked 1½ hr after ingestion of the dextroamphetamine. The cigarettes were prepared according to the method of Manno and colleagues[16] and were prepared to deliver predetermined dose of THC. The subjects were instructed to smoke the entire cigarette over a 10-min period, inhaling deeply and holding each inhalation for approximately 20 sec.

Experimental protocol. The experimental protocol for the first study is shown in Table I. Six experienced marihuana smokers were selected. Subjects were maintained in an upright sitting position on a hospital bed for the

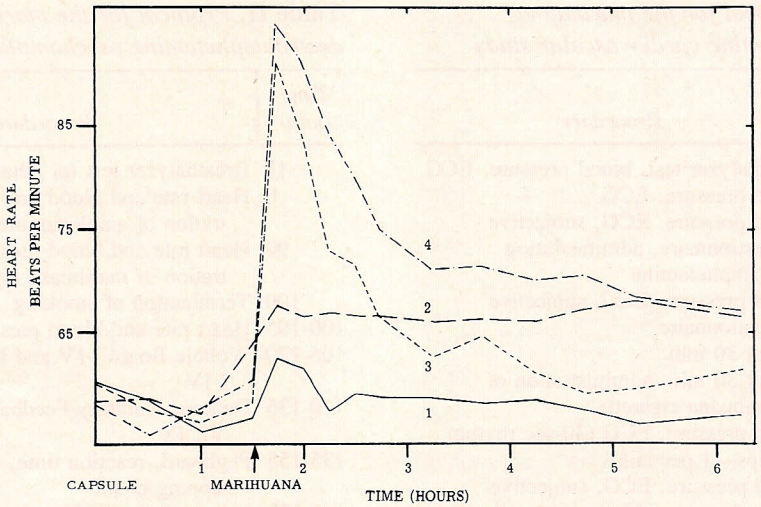

Fig. 1. Mean heart rate for 6 subjects following dextroamphetamine-marihuana. The marihuana cigarettes, designed to deliver either 0 or 50 μg/kg THC, were smoked 1½ hr after dextroamphetamine (0 or 10 mg/70 kg). The four curves represent the following treatment schedules: (1) dextroamphetamine, 0 mg/70 kg; marihuana, 0 μg/kg THC; (2) dextroamphetamine, 10 mg/70 kg; marihuana, 0 μg/kg THC; (3) dextroamphetamine, 0 mg/70 kg; marihuana, 50 μg/kg THC; and (4) dextroamphetamine, 10 mg/70 kg; marihuana, 50 μg/kg THC.

duration of each session. Baseline cardiac function measurements were made at 30 and 15 min and immediately prior to amphetamine administration to ensure stabilization of cardiac functions. Either one capsule of dextroamphetamine, 10 mg/70 kg, or a placebo capsule was administered at time zero. A marihuana cigarette, prepared to deliver either 0 or 50 μg/kg THC, was smoked 90 min later. After smoking, ECG rhythm strips were recorded every minute for the first 5 min to more closely monitor the appearance of any ECG abnormalities. Total session time was 6 hr, 45 min.

Heart rate was monitored by means of a lead II ECG tracing. The tracing was also used to detect any possible cardiac irregularities.

Arterial blood pressure was determined by routine noninvasive auscultatory methods. The same observer was used for each subject throughout the study to ensure uniformity.

Subjects were asked to rate their impressions of the "high" on a 0 to 10 scale (0 being no "high," 10 being the highest they have ever been). In addition, subjects were also given a modified Cornell Medical Index (CMI), a printed list of diverse symptoms that are scored on a 0 to 4 intensity scale. Included in the symptoms were questions pertaining to stimulation or depression of either mental or physical function.

The experimental protocol for the second study is shown in Table II. Twelve subjects, each having prior experience with marihuana, were selected, but one withdrew because of schedule difficulties. The dose of dextroamphetamine remained at 10 mg/70 kg, but the marihuana dose was reduced to 25 μg/kg THC. The Wobble Board (WB), Pursuit Meter (PM), and Delayed Auditory Feedback (DAF) tests were conducted at each session to evaluate psychomotor and mental performance. These have been described elsewhere in detail.[7] Several tests measuring manual dexterity, reaction time, and finger tremor were also used. Being built into a single portable box which resembles a suitcase, this group of tests has been termed the "suitcase" test. At the end of each session, subjects were administered the modified CMI for psychologic evaluation of drug effect. The analysis of variance was used to evaluate the variability attributable to subjects, session, and treatment.

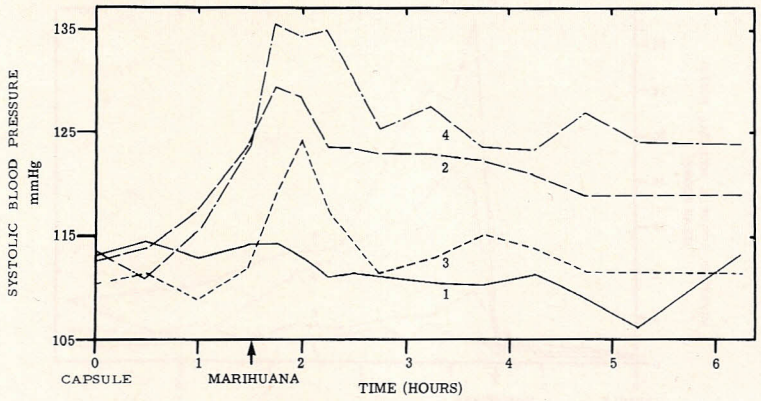

Fig. 2. Mean systolic blood pressure for 6 subjects following dextroamphetamine-marihuana. The marihuana cigarettes, designed to deliver either 0 or 50 μg/kg THC, were smoked 1½ hr after dextroamphetamine (0 or 10 mg/70 kg). See Fig. 1 for treatment schedule.

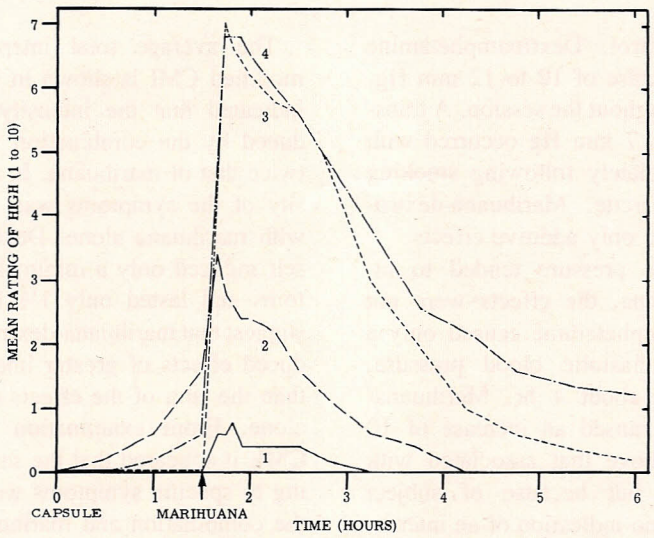

Fig. 3. Mean subjective "high" for 6 subjects following treatment with dextroamphetamine-marihuana. The marihuana cigarettes, designed to deliver either 0 or 50 μg/kg THC, were smoked 1½ hr after dextroamphetamine (0 or 10 mg/70 kg). See Fig. 1 for treatment schedule.

Results

Effects on blood pressure, heart rate, and CMI. Mean heart rate for the four treatments over the 6-hr time period is shown in Fig. 1. Dextroamphetamine induced an increase of approximately 10 bpm within 2 hr; this increase persisted for the duration of the session. Marihuana was also associated with a heart rate increase to an average of 91 bpm within the first 15 min, which returned to the baseline of 60 to 65 bpm within 3 hr. Marihuana-dextroamphetamine produced an acceleration compatible with additive effects characterized by the rapid onset of tachycardia of marihuana and the sustained effect of amphetamine.

Systolic blood pressures for the four treatments are shown in Fig. 2. A slight but consistent increase in systolic blood pressure was associated with marihuana for 1 hr. Peak systolic pressure after marihuana was about 10

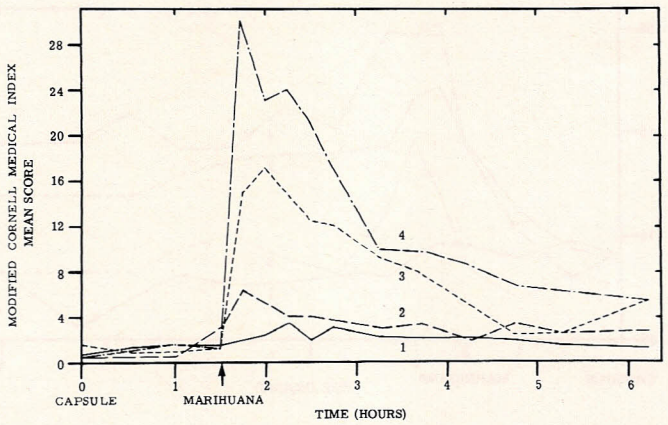

Fig. 4. Mean responses checked on the modified CMI for 6 subjects following dextroamphetamine-marihuana. The marihuana cigarettes, designed to deliver either 0 or 50 μg/kg THC, were smoked 1½ hr after dextroamphetamine (0 or 10 mg/70 kg). See Fig. 1 for treatment schedule.

mm Hg above control. Dextroamphetamine also induced an increase of 10 to 12 mm Hg, which persisted throughout the session. A transient increase of 5 to 7 mm Hg occurred with amphetamine immediately following smoking of the placebo cigarette. Marihuana-dextroamphetamine showed only additive effects.

Although diastolic pressure tended to increase after marihuana, the effects were not consistent. Dextroamphetamine caused only a slight increase in diastolic blood pressure, which persisted for about 4 hr. Marihuana-dextroamphetamine caused an increase of 10 mm Hg diastolic above that associated with either drug alone, but because of subject variability provided no indication of an interaction between the two.

Due to the nature of the questionnaire used and the dose of THC, the rating effectively reflected only the marihuana effect. Thus, marihuana-dextroamphetamine combination could not be distinguished from marihuana alone (Fig. 3). Factors that could have caused this result were that subjects were limited by their own previous experience with marihuana and probably were not accustomed to the doses used in this study, and that the nature of the rating scale limited scores to a maximum of 10, which was approximated by the marihuana alone. Although the combination did show a slight prolongation of the "high," the prolongation was not consistent among all subjects.

The average total intensity score of the modified CMI is shown in Fig. 4. The results indicated that the intensity of symptoms induced by the combination was approximately twice that of marihuana. In addition, the intensity of the symptoms was 1½ hr longer than with marihuana alone. Dextroamphetamine itself induced only a minimal increase in symptoms and lasted only 1½ hr. Thus, the data suggest that marihuana-dextroamphetamine produced effects of greater intensity and duration than the sum of the effects of each drug given alone. From examination of the individual CMI, it appeared that the same questions relating to specific symptoms were scored for both the combination and marihuana alone, but the intensity of symptoms associated with the combination was approximately twice that of marihuana alone.

Psychomotor effects. The effects of the drugs on the Wobble Board Scores are given in Table III. All scores for dextroamphetamine alone were slightly lower than after placebo (indicating an increase in standing steadiness), but only in test III, eyes open and motor on, was the difference from placebo significant. Marihuana alone resulted in an ($p < 0.001$) increase in score for tests I, II, and III, indicating decrease in standing steadiness. The effect of marihuana-amphetamine was indistinguishable from the sum of the two drugs alone.

The results of the Pursuit Meter tests are

Table III. *Summary of the effects of marihuana-dextroamphetamine for Pursuit Meter and Wobble Board (means and SD)*

Procedure	Treatment				
	Placebo-placebo	*Amphetamine-placebo*	*Marihuana-placebo*	*Marihuana-amphetamine*	*SD*
A. Wobble Board					
I	1,146	986	1,600	1,624	170
II	1,448	1,287	2,167	1,959	320
III	2,299	2,131	2,947	2,652	305
IV	3,825	3,659	3,769	3,720	428
B. Pursuit Meter test					
I	25,605	28,036	40,993	37,109	8,076
II	31,090	29,940	42,456	43,635	8,454
III	24,605	23,985	30,345	31,857	5,239
IV	27,161	28,738	43,045	36,948	8,098
C. Pursuit Meter–RNX time in sec					
I	1.12	1.22	1.34	1.29	0.18
II	1.22	1.21	1.32	1.28	0.23
III	1.19	1.14	1.17	1.31	0.26
IV	1.11	1.15	1.28	1.24	0.22
D. Pursuit Meter-fatigue					
I	78,541	72,833	111,428	103,951	29,609
III	74,809	64,763	80,779	80,180	10,096

summarized in Table III. The data reveal that the mean digital scores for tests I through IV following treatment with marihuana increased ($p < 0.001$), indicating a decrease in attentive motor performance. Mean scores following dextroamphetamine differed little from placebo, and both drugs in combination resulted in an increase similar to that of marihuana alone.

Reaction time to the secondary task of interfering lights indicated no consistent change after administration of dextroamphetamine. Marihuana was associated with an increase ($p < 0.05$) in reaction time for test I. Reaction times for test II and IV also appeared to increase following treatment with marihuana, but due to the large variation in individual scores, there were no significant differences. Treatment with both drugs had no effect above the single effects of marihuana on reaction time. The mean scores were consistent with those for marihuana alone.

After marihuana, mean scores for the Fatigue Pursuit Meter I, a test designed to measure attentive motor performance for 300 sec, were significantly increased above placebo, although the difference from placebo score calculated on a time basis was indistinguishable from the 100-sec Pursuit Meter test. The 100-sec placebo score test was 256 cts/sec; placebo score for the 300-sec test was 261 cts/sec. With marihuana, the respective scores for the tests were 410 cts/sec and 371 cts/sec. There were no significant effects on the Pursuit Meter Fatigue Test II after any treatment.

Mean scores for the "suitcase" test are shown in Table IV. For the pegboard test, the analysis of variance indicated that marihuana caused an increase in time needed to perform all three procedures. No difference from additivity could be concluded for the combination. Simple reaction time and tapping ability were not significantly affected by either drug (Table IV). Tremor, however, increased following marihuana. Dextroamphetamine-marihuana caused an increase in tremor suggestive of addition. No treatment effects were found with any of the five Delayed Auditory Feedback tests.

Subjective impressions were assessed as in Study I for the four treatments. Marihuana increased the intensity of subjective response symptoms checked on the modified CMI. Dextroamphetamine, although causing an increase

Table IV. *Summary of the effects of marihuana-dextroamphetamine for the "suitcase" test (means and SD)*

Procedure	Treatment				
	Placebo-placebo	*Amphetamine-placebo*	*Marihuana-placebo*	*Marihuana-amphetamine*	*SD*
A. Peg Board					
I	23.30	21.93	23.95	23.90	2.1
II	23.99	23.35	25.52	25.09	2.3
III	25.95	25.12	29.49	27.84	4.0
B. Reaction time	4.95	4.67	4.97	5.10	0.4
C. Tapping	66	73	60	66	12
D. Tremor, ¼"	5.4	6.5	10.1	10.8	6.9

Table V. *Summary of subjective impressions for marihuana-dextroamphetamine combination (means and SD)*

Procedure	Treatment				
	Placebo-placebo	*Amphetamine-placebo*	*Marihuana-placebo*	*Marihuana-amphetamine*	*SD*
A. CMI intensity score	5.7	12.0	18.8	20.0	9.1
B. Driving impaired	1/11	3/11	7/11	8/11	
C. Drug identification					
Amphetamine	1/11	6/11	1/11	8/11	
Marihuana	1/11	4/11	9/11	11/11	
D. Subjective high	0.4	2.3	5.3	7.0	2.1

in mean score, did not do so as consistently as marihuana. On the CMI test, the combination showed only addition of marihuana and dextroamphetamine effects. There were similar results with the subjective impression of the "high" associated with the treatments. Marihuana increased subjective "high" rating from 0.4 for placebo to 5.3. Although increasing the mean score to 2.3, dextroamphetamine could not be distinguished from placebo with assurance. The effect of the combination on subjective "high" was additive (Table V).

The subjects' ability to discriminate drug treatment is illustrated in Table V. Subjects were able to identify the combination as being active drug with some degree of certainty. When marihuana was given alone, subjects were also able to identify the treatment as active drug. However, identification of dextroamphetamine treatment differed little from what would be expected from random guessing. Eight of the 11 subjects felt their driving would be impaired after marihuana-dextroamphetamine and 7 subjects felt so for marihuana alone. The difference, however, was not large enough to distinguish these two treatments with confidence on this question. With dextroamphetamine alone, 3 subjects felt that the drug would impair driving, while 1 subject on placebo indicated his driving would be impaired. It was not established, therefore, that dextroamphetamine had an apparent effect on subjective impression of driving ability.

Discussion

The purpose of our investigation was to evaluate the effects of dextroamphetamine on the cardiovascular, psychologic, and psycho-

motor changes produced by smoking marihuana. Animal investigations have shown that THC, particularly in low concentrations, can heighten and prolong amphetamine-induced hyperactivity, but that treatment with higher doses of THC reverses this effect.[5]

The doses selected for our investigation were based on the results of previous investigations from this laboratory[8, 13] and were designed to reflect the minimal dose necessary to induce the effects of interest. A 1½-hr time period was allowed between the administration of dextroamphetamine and the marihuana smoking to approximate simultaneous peak activity for both drugs. Although the rate of amphetamine excretion is dependent on pH, previous dose-response studies by Martin[17] and Evans[8a] and their co-workers demonstrated that the effects of dextroamphetamine in normal subjects are dose-related and after ingestion are optimal in approximately 1 to 2 hr. Previous investigation of the psychologic and physiologic effects of dextroamphetamine and marihuana with testing 1½ hr later revealed only the activity of each drug.[22] The results of our study indicate that when marihuana and dextroamphetamine are given together the resultant effects cannot be distinguished from the simple addition of the effects of each component alone.

The increase in heart rate after the combination reflected the prompt tachycardia induced by THC and the small sustained elevation by amphetamine. ECG changes, when present, were nonspecific in character and appeared to be associated with marihuana. The most common alterations were irregularity of pulse and flattened T waves. Premature ventricular beats were observed on some occasions. There was no consistency between treatment and ECG changes. All of these observations are similar to those described by Kochar and Hosko.[14]

Blood pressure changes after marihuana-amphetamine combination reflected the sustained pressor effects of amphetamine and a transient increase due to THC. This increase in blood pressure did not prevent the tachycardia associated with THC. Since the change in blood pressure with THC was synchronous with THC tachycardia, it may be possible that the increased pressure with THC is a reflection of its chronotropic effect. Although the mean increase in systolic blood pressure was about 20 mm Hg with the combination, it is possible that the use of much higher doses of each drug might cause a more striking increase.

The psychomotor performance study failed to reveal any significant interaction between marihuana and amphetamine. Little difference was observed between the combination of marihuana and amphetamine and marihuana alone with respect to their effects on psychomotor performance (WB, PM, and "suitcase"). Amphetamine, at 10 mg/70 kg, neither inhibited nor enhanced the impairment caused by marihuana smoking. This suggests that the impairment from THC is not due strictly to fatigue or sedative effects, since previous studies have indicated that amphetamine can alleviate impairment due to fatigue or sedative drugs.[19] The THC may induce alterations in sensory input and impairment in fine coordination. None of the subjects exhibited any gross impairment of physical functions, although several could be considered to be in a state of intoxication. Amphetamine itself had no consistent distinguishable effect on performance scores, as already reported from this laboratory.[8]

The report to the Mayor's Committee on Marihuana[18] demonstrated that ataxia is present up to 3 hr after marihuana smoking and parallels the disappearance time of subjective symptoms. This suggests that the two effects may be related and are perhaps partially due to alterations in sensory perception. Other studies have demonstrated that marihuana smoking causes difficulty in fine movement or coordination, which is related to the associated ataxia.[12] In our study, however, no gross impairment in motor function was observed, and simple reaction on the "suitcase" test and reaction time on the Pursuit Meter did not reveal any consistent difference from placebo. Attentive motor performance following marihuana smoking was impaired, indicating that fine motor control is affected.

One study has suggested that central stimulants can acutely block THC effect.[11] Our results do not support such a conclusion, but indicate that the two drugs are additive in behavioral and

neurophysical effects. There was no evidence of interaction between marihuana and amphetamine. Dextroamphetamine did not reduce observed marihuana effects. The subjective response as assessed by modified CMI in Study I indicates both heightened and prolonged drug effects following the combination. This effect was less evident when the dose of marihuana was decreased (Study II).

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