SMU | Dedman School of Law

SMU Law Review

Volume 24 | Issue 3 Article 6

January 1970

New Trends in Drug Research: Marihuana - A Case in Point

Leo E. Hollister

NEW TRENDS IN DRUG RESEARCH: MARIHUANA — A CASE IN POINT*

by

*Leo E. Hollister***

THE evergrowing social use of cannabis derivatives in the Western world has once again caused concern about its consequences. Following the brief interest in clinical research initiated by the La Guardia Commission over twenty years ago,[1] few subsequent studies of the effects of marihuana in man have been done.[2] Recently, such studies have been resumed, using newly available 1-Δ^1-trans-tetrahydrocannabinol (Δ^1-THC or THC), or extracts of marihuana calibrated for THC content.

I. Legal Considerations in Marihuana Research

Although some legal hobbles bothered researchers two years ago, they are not especially troublesome now. When I began my work, the state of California had a statute allowing the state division of narcotics to dispose of marihuana for purposes of research or instruction *only* to the heads of schools of medicine, pharmacology, and criminology which had been approved by the attorney general.[3] Thus, even though I met federal requirements,[4] I was apparently ineligible under the state qualifications. The Federal Bureau of Narcotics liberally construed the federal requirements. As long as I did my work at the Veterans Administration Hospital, it was considered to be federal territory and therefore beyond the jurisdiction of the state. Fortunately, no one has challenged this interpretation.

The channels for doing research on drugs of dependence are reasonably clear as far as federal requirements are concerned.[5] Under the informal administrative procedure of the National Institute of Mental Health, the experimental protocol is submitted to the Drug Dependence Section of the Institute, which is also authorized to supply materials as requested. If the protocol is approved by the Institute's scientific review committee, the

---

* This Article is based on a lecture delivered to the Short Course on Drug Abuse at Southern Methodist University, April 8, 1970.

** B.S., M.D., University of Cincinnati. Medical Investigator, Veterans Administration Hospital, Palo Alto, California; Associate Professor of Medicine, Stanford University School of Medicine.

[1] Mayor's Committee on Marihuana (New York City), The Marihuana Problem in the City of New York: Sociological, Medical, Psychological and Pharmacological Studies (1944).

[2] Most of these studies, quite possibly because of legal difficulties in obtaining natural marihuana preparations, employed the synthetic tetrahydrocannabinol homolog, synhexyl. This material was used for several medical purposes. *See, e.g.*, Himmelsbach, *Treatment of the Morphine-Abstinence Syndrome with a Synthetic Cannabis-Like Compound*, 37 S. Med. J. 26 (1944); Parker & Wrigley, *Synthetic Cannabis Preparations in Psychiatry: (I) Synhexyl*, 96 J. Mental Sci. 276 (1950); Stockings, *A New Euphoriant for Depressive Mental States*, 1947 Brit. Med. J. 918; Thompson & Proctor, *The Use of Pyrahexyl in the Treatment of Alcoholic and Drug Withdrawal Conditions*, 14 N.C. Med. J. 520 (1953).

[3] Cal. Health & Safety Code § 11655 (West 1964), *as amended*, § 11655 (West Supp. 1969).

[4] Int. Rev. Code of 1954, §§ 4751, 4753.

[5] 26 C.F.R. §§ 152.66-.71 (1970).

Food and Drug Administration is notified so that a separate application for investigation of a new drug need not be filed. As most research is based in some institution, it is implicit that additional review has been done by institutional research committees, as well as committees on human studies, if humans are involved. Materials are provided the investigator in amounts required to do his proposed experiment. Under federal regulations, he must report on the progress of the experiment at least annually, and keep records of the disposition of the materials which have been provided.[6]

Unfortunately, the state may become involved. California requires an investigator to submit his proposal to a state review board of mixed disciplines to determine whether or not the research should be continued.[7] Besides being a duplication of effort, this could lead to the contretemps in which federal approval was given and state approval withheld. Obviously, states should not pass laws controlling research with drugs of dependence without full awareness of federal regulations. Such a principle might also be applied to laws regulating the possession, distribution, and sale of drugs, as well as the implementation of treatment programs.

II. Problems with Materials and Dosage

The older clinical studies were far less quantitative than would ordinarily be demanded of pharmacological studies. These older inquiries usually expressed doses as so many milliliters of cannabis extract produced in some standard fashion, or as the equivalent of so many milligrams of cannabis material. Unless the components of such materials are known, such bases for dosages are extremely uncertain.

My associates and I obtained from the Bureau of Narcotics two samples of marihuana. One was a potent material that was grown in Turkey and labeled "hashish." Our assay indicated that its content of Δ^1-THC was slightly more than 2%. In addition, it contained amounts of other cannabinoids: cannabidiol, the precursor of THC, and cannabinol, the product of THC decomposition. The same agency provided us with a "brick" of marihuana which had been seized and held for evidence. This sample contained no detectable tetrahydrocannabinol, a good quantity of cannabinol, and an unidentified material which may have been cannabidiolic acid or its ester. The difficulties in identifying some of the components arise because adequate standards of marihuana constituents are difficult to obtain. Even a sample of the United Nations Reference Standard of cannabis obtained with considerable difficulty from the U.S. Department of Justice contained no THC, despite having some cannabinol and cannabidiol. Enormous variations in content of active materials exist in any natural product, and certainly cannabis is no exception.

Obviously, before clinical experiments with extracts of the natural product, or marihuana itself, may be performed, careful quantitative assays for THC content must be done and doses in terms of equivalence of THC

[6] *Id.* § 152.100.

[7] Cal. Health & Safety Code § 11333 (West Supp. 1969).

specified. While it is still argued whether or not THC is the sole active material in cannabis, it seems reasonably certain that it accounts for the major amount of activity, and thus qualifies as a reasonable basis for dosage. The extraction of cannabis and the quantification of THC content by gas-liquid chromatography is not especially difficult, because the extracts hold chemical stability for considerable periods of time when kept under refrigeration. However, the greatest objection is the noxious taste. Fortunately, almost complete extraction of the cannabinoids still leaves a residue which can then be re-extracted to provide a foul-tasting material which can be used as a placebo.

Giving oral doses of extracts, or THC itself, is advantageous in that the components of the doses are known with some precision. However, the amount absorbed in an active form is uncertain. The smoking of cannabis which has been quantified for THC content raises even more questions: (1) How much of the putative dose is absorbed? (2) What is the difference in potency between materials absorbed directly into the blood through the lungs, as opposed to gastrointestinal absorption and a pass through the liver where it could be metabolized in part before reaching the brain? (3) Does smoking change the activity of cannabis, forming new or additional active materials? (4) Can one rely on reports of "getting high" from smoking to use as an end-point in dosage? In regard to the latter question, I would have some doubts based on conflicting reports from volunteer smokers of our THC-free marihuana. When three subjects smoked in a group, all reported some degree of activity, but when one sophisticated user smoked alone, he reported none. The latter observation was consistent with the failure of the material to produce effects in another subject when a sizable amount of extract of the material was given orally.

III. Studies Using Synthetic Δ^1-THC Orally

Researchers at the Addiction Research Center of the U.S. Public Health Service Hospital, Lexington, Kentucky, and ourselves have both published on the effects in man of oral doses of synthetic THC.[8] The Lexington group employed a dosage of 10 to 30 milligrams, or 120 to 480 micrograms per kilogram. We used doses of 30 to 70 milligrams, or 341 to 946 micrograms per kilogram. Thus, the two studies were complimentary in exploring a wide range of dosage. It should be emphasized that this range is still more than the effective dose received from smoking an ordinary marihuana cigarette. However, it is not greater than the amount one might get from smoking several cigarettes of reasonable quality, or from smoking the stronger preparation, hashish.

Briefly stated, the results are as follows:

(a) *Physiological changes.* No changes in pupil size, respiratory rate, deep

[8] Hollister, Richards & Gillespie, *Comparison of Tetrahydrocannabinol and Synhexyl in Man*, 9 Clin. Pharmacol. Ther. 783 (1969); Isbell, Gorodetzsky, Jasinski, Claussen, Spulak & Korte, *Effects of (-)Δ^9-Trans-Tetrahydrocannabinol in Man*, 11 Psychopharmacologia 184 (1967).

tendon reflexes, or oral temperature were observed. Pulse rate rose constantly. Systolic and diastolic blood pressures tended to fall; orthostatic hypotension may have accounted for two faints. Conjunctival injection paralleled the clinical course. Finger ergograph tracings revealed the development of muscular weakness which was progressive.

(b) *Perceptual and psychic changes.* Euphoria was a predominant and persistent symptom, followed by the development of sleepiness. Time sense was altered, hearing less discriminant, vision apparently sharper with many visual distortions. Depersonalization, difficulty in concentrating and thinking, and dream-like states were prominent. Many of these symptoms were similar to those produced by psychotomimetics of the LSD-mescaline-psilocybin class. On self-reporting scales, the subjects initially became more friendly, but less so with the passage of time; they became less aggressive, especially late in the course; they began to get sleepy, especially after three hours; and they became persistently less clear-thinking, euphoric, and dizzy.

(c) *Psychometric tests.* Repetitive psychometric measures of arithmetic ability (Number Facility: NF) or drawing freehand (Flexibility of Closure: FC) showed differing kinds of impairment. The NF test, a familiar and simple task, showed a slowing of performance against time, with maintained accuracy. The FC test, less familiar and more difficult, showed reduced accuracy with no slowing of performance, probably indicating some loss of finer judgment.

(d) *Biochemical determinations.* Plasma-free, fatty acids remained unchanged, unlike the case with drugs of the LSD-type. Blood glucose values were also unchanged. Both creatinine and phosphorus clearance were temporarily decreased. This is a phenomenon which has been observed with LSD.

We compared Δ^1-THC with synhexyl, a synthetic THC-like material. The latter has been studied rather extensively in the past for possible clinical utility. On the whole, the changes reported above were also produced by synhexyl, but the Δ^1-THC was three times more potent than the synhexyl. The latter drug was slower in initial action by about one hour, but longer-lasting in equivalent doses.

The Lexington group has compared the effect of taking THC orally with the effect of smoking cigarettes containing known quantities of THC. They estimate that potency is increased approximately three-fold by smoking as compared with taking the same material by mouth. As might be expected, effects arise much quicker, but are of briefer duration, when the material is smoked. They have compared the effects of smoked THC (75 to 225 micrograms per kilogram) with those of LSD given intramuscularly in doses of 0.5 to 1.5 micrograms per kilogram.[9] Subjective effects between the two drugs were not readily distinguishable, but objective differences were marked: LSD increased body temperature, systolic and diastolic blood pressure, deep tendon reflexes, and dilated the pupils, while

[9] Isbell & Jasinski, *A Comparison of LSD-25 with (-)Δ^9-Trans-Tetrahydrocannabinol (THC) and Attempted Cross Tolerance Between LSD and THC*, 14 PSYCHOPHARMACOLOGIA 115 (1969).

THC had none of these effects. We made a retrospective comparison of the effects of LSD and THC taken orally and came to similar conclusions regarding the objective differences.[10] Subjectively, we thought that THC produced less total impairment with more euphoria and dreamlike states than LSD at comparable doses, and that, unlike the latter drug, sedation was a prominent feature with THC as most subjects fell asleep. In general, we have seen less psychotomimetic effects than the Lexington group. They have used patients formerly addicted to narcotics as subjects, while we have used primarily graduate students. This may explain the different reports of subjective effects.

IV. Studies with Quantified Marihuana Extracts Orally

We have completed additional experiments using extracts of marihuana, gauging doses on the basis of THC content. We have used doses ranging from 5 to 60 milligrams, as well as making comparisons between these and the placebo extract. Even with the smaller doses, all subjects had appreciable clinical effects as compared with placebo. With the larger doses, psychotomimetic effects were observed. Generally, the effects produced by these extracts were comparable to those which would have been produced by similar doses of synthetic THC. None of these studies has yet been published, but the results of some are known.

A number of psychological tests have been done. The most conspicuous result has been the fact that even relatively small doses of marihuana disrupt short-term memory, such as used in keeping track of a task. Long-term memory is not impaired. The same division between tests that are impaired and those which are not was seen with regard to a number of other such psychological functions. But with most sizable doses at any given time, subjects would be likely to show impairment of a considerable number of intellectual and motor functions. We have also studied the effects of marihuana on appetite, hunger, and food consumption, comparing it to alcohol, dextroamphetamine, and placebo. Although marihuana is reputed to stimulate appetite, it did so under experimental conditions only some of the time; *i.e.*, seven of twelve subjects consumed more food with more gusto after marihuana than after the other comparison treatments. We still don't know the extent to which these differences represent variations between subjects, or variations within subjects over repeated testing.

A group at the University of Utah has also made use of marihuana extracts for clinical studies.[11] They, too, have been impressed with the disruptive effects of marihuana on sequential thought, suggesting impairment of rapid decision-making and short-term memory. As have others, they have noted a great variability in performance during marihuana intoxication, which may be related to the fact that subjects go "in-and-out"—the effects seeming to come and go in cycles and waves.

---

[10] Rutgers Symposium on Drug Abuse, Drugs and Youth 208-11 (1969).

[11] Clark & Nakashima, *Experimental Studies of Marihuana*, 125 Am. J. Psychiatry 379 (1968).

V. Studies with Smoked Marihuana

As marihuana is more commonly smoked than taken orally, some investigators feel that proper studies can be done only by utilizing this particular method of administration. The major argument is that native marihuana may include other active materials which are not found in synthetic THC or extracts, or that the process of combustion may create new active materials. No proof for either assertion is available. One great disadvantage of this method of administration is that the dose, even when the amount in the cigarette is known, is impossible to judge, as variations in technique of smoking may create tremendous variations in delivery of the dose.

The first study provided marihuana in cigarettes with the putative doses being 4.5 and 18 milligrams, which were compared with a placebo smoke.[12] Naive smokers experienced few subjective effects, although they showed an increased heart rate and conjunctival injection. Experienced smokers of marihuana reported a typical "high," which was not elaborated upon. Performance on the digit-symbol substitution test and the pursuit rotor test was impaired, but curiously, the continuous performance test, which is usually more sensitive, was unchanged. No changes in blood sugar were found. In general, the effects of the drug smoked in this fashion were found to be relatively mild and innocuous, leading the investigators to take a sanguine view of the social use of the drug.

Using a driving simulator, another study tested driving skill in untreated subjects who smoked marihuana cigarettes until "high" and consumed large doses of alcohol.[13] Under marihuana conditions, speedometer errors were increased, suggesting that the subjects did not monitor the speedometer as carefully as they might have normally. Driving was otherwise little impaired. As might have been expected, marked impairment was observed from the high doses of alcohol. Such highly controversial findings have elicited criticism directed at the fact that the doses of the two drugs were disproportionate, that a dose-response curve was not obtained, and that simulated driving might not be an adequate model for real life.[14] My own objections are that the study could have scarcely been better designed to provide a miniscule dose of marihuana or to miss the effects when testing. Smoking to a "high" is imprecise enough, but if it really took thirty minutes to smoke the cigarette (as the paper states), then it was scarcely smoked at all. Proper smoking technique usually consumes a cigarette within five to ten minutes. The first study mentioned, which used relatively small doses of marihuana, but still probably larger than used in the simulated driving study, found that most effects of the drug had dissipated by the end of one hour. This was precisely the time the subjects were tested for their driving ability. Although the authors were careful to refrain from stating that marihuana did not affect the ability to drive a

[12] Weil, Zinberg & Nelsen, *Clinical and Psychological Effects of Marihuana in Man*, 162 Science 1234 (1968).

[13] Crancer, Dille, Delay, Wallace & Haykin, *Comparison of the Effects of Marihuana and Alcohol on Simulated Driving Performance*, 164 Science 851 (1969).

[14] Kalant, *Marihuana and Simulated Driving*, 166 Science 640 (1969).

car, it is unfortunate that many lawyers and courts may draw this conclusion. Sometimes it is better not to be so scientific. Since our first experiments, we have simply asked subjects when they were "high": "Do you think you could drive a car now?" Without exception the answer has been, "No!"

VI. Some Possible Implications for the Law

The social use of marihuana under most circumstances is based upon relatively weak doses of THC, and is consequently a mild intoxication. In part, this is due to the very low THC content of much of the marihuana available for social use, as well as to the intrinsic difficulty in administering a dose efficiently by means of smoking. Consequently, generalizations about the social desirability of the drug on such limited experience should be cautiously made. The higher doses of drug given orally in the two studies thus far completed indicate that the full range of psychotomimetic effects and their complications can be expected when stronger materials become more generally available.[15] The present comparison of marihuana with alcohol is based on a dose similar to beer with a 2% alcoholic content, rather than gin with a 43% alcoholic content.

From the legal point of view, it may be desirable to distinguish several different forms of marihuana, rather than to lump cannabis derivatives together. To return to the analogy with alcoholic beverages, the degree of potency of the various products may be considered. Native marihuana ranges in THC content from very small amounts, such as 0.05%, to somewhere between 1.0 and 1.5%. Just as there are vintages wines, so there are vintage grasses, with some species and some growing areas producing higher yields. Nonetheless, native, American-grown grass might be regarded as relatively mild. When it is in the possession of, and being used by, untold millions of our citizens, it may be most realistic at least to eliminate the penalties for possession of amounts of this material appropriate for personal use. I would judge that amounts less than one kilogram of dried natural material could be presumed for personal use, just as would possession of three cartons of cigarettes. We would, in effect, be encouraging the equivalent of beer-drinking. Such a change could hardly make matters any worse than they now are.

By the same token, we should like to discourage the use of more potent material. Imported marihuana plant materials,[16] resin,[17] or extracts[18] might be included in a separate category. Penalties might still be retained for their

[15] Despite the relative weakness of most available marihuana preparations, an increasing number of reports of adverse reactions appear in the medical literature. However, these represent only a small fraction of the total number. *See, e.g.*, Baker & Lucas, *Some Hospital Admissions Associated with Cannabis*, 1969 THE LANCET 148; Leonard, *Cannabis: A Short Review of its Effects and Possible Dangers of its Use*, 64 BRIT. J. ADDICTION 121 (1969); Perna, *Psychotogenic Effect of Marihuana*, 209 J.A.M.A. 1085 (1969); Talbott & Teague, *Marihuana Psychosis: Acute Toxic Psychosis Associated with the Use of Cannabis Derivatives*, 210 J.A.M.A. 299 (1969).

[16] Imported plant materials from Mexico or Vietnam may be much more potent in THC than those from domestic sources.

[17] This would include hashish, which is usually prepared outside the United States.

[18] I have examined one extract that had 70% THC content. This is relatively simple to make.

possession, and such penalties might be similar to those deemed appropriate for hallucinogenic drugs.

In still another category, synthetic analogs of THC or their precursors might be included. Although the synthesis of THC is not at all easy at the moment (this has slowed down research with this material), it may be feasible for illicit laboratories to undertake this business in the next few years. The cost will remain high, and, therefore, synthetic THC will have only a limited market, but we should probably still want to discourage use of synthetics by some appropriate penalties.

In short, in terms of legal definitions, a blanket grouping together of all cannabis preparations and synthetics of THC is less suitable than making distinctions based on the potency of the materials and the severity of their intoxicating effects. Precedents for such differential labeling of intoxicants can be found in some of our licensing procedures regarding beer and wines, as opposed to spiritous liquors, or on the alcohol tax structures of other countries (for example, Finland) where an attempt is being made by using markedly different levels of taxation to alter drinking habits from spiritous liquors to beer. The law can be used to implement social goals if we can define what these should be.

As the law has shown remarkable responsivity to social needs in the recent past,[19] it seems ridiculous that it should still be a matter of great concern that the law may impede research on drugs of dependence. If one matter can be agreed upon in this whole controversial field, it is that we need more research. Yet many sober individuals are greatly concerned that present laws at the state level and even the legislation presently under consideration by the Congress[20] will seriously impair research. Surely no law should be passed which affects research on drugs of dependence without ample consultation with those who are actively involved in this area. Seldom has it been more necessary that legislators, law enforcement people, and courts work closely with medical and social scientists to come to grips with a common problem.

[19] An excellent example of such responsivity is the vast changes in state abortion laws in the past several years.

[20] S. 3246, 91st Cong., 1st Sess. (1969).

Southwestern Law Journal

VOLUME 24 | August 1970 | NUMBER 3