

PHARMACOLOGIC EFFECTS OF MARIJUANA

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There is an unnecessary aura of uncertainty and confusion in the discussions of the pharmacology of marijuana and its various preparations and constituents.

Part of the uncertainty is generated by the bias of those occupying the poles of thought that must be repeatedly referred to: the dominant feeling that marijuana is a frighteningly dangerous drug in no way comparable to any accepted social drug, and the often equally emotional claim by groups of increasing size that it is a purely beneficent drug in no way comparable to any acceptable social drug.

Additional reluctance to summarize the pharmacology of marijuana stems from the assumption that research on its pharmacology is scant, dated and of poor quality. Certainly huge amounts of research remain to be done. However, the inability to present a consistent formulation of the pharmacology of marijuana may not be due so much to lack of data as to the failure to apply some unifying concept to the fragmentary information available.

Most drugs can be put into classes or categories. When this is done, information derived from the previous study of other drugs in the class can be used to predict and understand the drug under scrutiny. The period of study is shortened and an organizing concept provided. For example, the study of the latest barbiturate to be synthesized is simplified by the exhaustive studies on the prototypes of the class of drugs.

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There is a class of drugs made up of the sedative-hypnotics (alcohol, barbiturates) and the general anesthetics (ether, halothane and other "Freons" including those in hair spray, nitrous oxide, the "peace pill" or PCP^(a), the solvents in glue, et cetera). If the effects of large doses of a sedative -- eg., a dose of barbiturate taken with suicidal intent or an anesthetic dose of Pentothal -- are examined, it is apparent that all of the drugs listed have qualitatively similar effects differing mostly in their physical state. Gases and volatile liquids are selected for use as general anesthetics because their transfer across the alveoli of the lungs allows for rapid onset of action, minute-to-minute control of dose and rapid recovery. The sedatives are given to achieve a longer, less intense effect and, if solids such as barbiturates are selected, they are more easily dispensed.

Having defined one drug class, let us examine the following hypothesis: marijuana has all of the properties of a sedative-hypnotic. It appears distinctive mostly because our experience is limited to its use by smoking which provides for a rapidly appearing effect but also for a rapid decay of the effect as the absorbed drug is redistributed in the body. That with the oral use of hashish or synthetic equivalents, the apparent distinctiveness from alcohol or barbiturates disappears.

To establish that the above hypothesis is correct almost beyond question, this paper will list the properties of a sedative-hypnotic (Table I) and then discuss the observations establishing that the constituents of Cannabis have the same actions.

Throughout the discussion the following cautions should be remembered.

1. Effects are described which aid in the classification of the drug. It does not follow that these effects appear regularly in the ordinary use of marijuana in our culture where the usual pattern is smoking rather than ingestion and comparatively weak "grass" is the mode.

2. The assumption is made that hashish, grass, THC and synhexyl exert qualitatively similar effects. (Synhexyl or pyrahexyl differs from the THC assumed to be the most important active component by one CH₂ group. It has been available in adequate amounts and has been studied far more thoroughly than other natural or synthetic THC's. See the review of the chemistry of marijuana that follows.)

Effects of graded doses: If marijuana is a sedative-hypnotic, the administration of progressively larger doses should lead to a sequence of changes comparable to the stages of general anesthesia. It can be shown in animals that large doses do produce anesthesia and that after huge doses the animal does die from respiratory depression.

The interpretation of the effects of smaller doses, however, appear controversial to some observers because the "high" is assumed to be a manifestation of stimulation by the drug.

(a) Available commercially as Sernyl^R

To understand the effect of smaller doses of marijuana, one must differentiate between manifest behavior - i.e. excitement or depression - and the underlying pharmacologic effect of stimulation or depression. Marijuana, like alcohol, is a depressant in its effects on the nervous system, and the "high" is a result of depression of the higher centers and consequent release of lower centers from chronic inhibitory influences. Increasing the dosage, whether of marijuana, alcohol or ether, leads to a picture of pure depression as the excitement stage is passed. There are other laboratory evidences for the depressant effect of the tetrahydrocannabinols, for example, the ability to prolong the sleep induced by other sedatives.

As marijuana is used in this country, the period of disinhibition or drunkenness is quite brief. Psychomotor ability and probably judgment are impaired during this period. The disinhibition also causes euphoria and relief of anxiety and explains the social use and possible misuse of all of the drugs of this class.

An additional area of confusion or controversy is introduced when marijuana is characterized as a "mild hallucinogen." The effect referred to is better described as a dreamy state with an increased tendency to fantasize and to accept suggestion. Such a dreamy, hypnogogic state can be induced with almost any one of the sedatives or anesthetics under favorable conditions. The use of nitrous oxide to produce such a state was described by Humphry Davy almost as soon as he isolated the gas. The Pentothal interview or the recent use of PCP (Peace Pill) are additional examples, and a transient "hallucinatory" state has also been described during the therapeutic use of chlordiazepoxide (Librium).

Effects of continuous use:

1. Physical dependence and withdrawal - Physical dependence as a factor maintaining drug misuse has undoubtedly been greatly over-emphasized. Alcohol, for example, undoubtedly provides the number 1 drug problem in our culture, but only rarely causes the D.T.'s. Nevertheless, if a drug is to be classified as a sedative-hypnotic, it must be demonstrated that the abrupt discontinuance of large doses results in a state of hyperexcitability.

Clinic observations of hashish smokers suggest that withdrawal symptoms are unusual or mild. Experimentally - i.e., for purposes of classification -- a withdrawal state can be shown. For example, - subjects were given large doses of pyrahexyl orally for 26-31 days. On the third day following discontinuation of the drug, most patients were restless and slept poorly. One subject experienced agitation progressing to dis-orientation and the symptoms were abolished within 4-5 hours by the administration of pyrahexyl. Another passed through a hypomanic state on the fourth day. Under the same experimental conditions, subjects were allowed free access to marijuana cigarettes for 39 days. The average patient smoked 17 cigarettes per day but no withdrawal state was demonstrated.

2. Liability for misuse - The question of whether the use of marijuana as a social drug can, like the use of alcohol as a social drug, sometimes leads to the development of a compulsive pattern of use is, of course, an emotionally loaded question. Certainly the hazards of smoking the weak marijuana preparations available in this country are minimal. If one looks outside of our culture to the Muslim world it appears that a compulsive pattern of use with results comparable to those of chronic alcoholism is indeed possible.

3. Other effects - There are other pharmacologic actions of Cannabis preparations which are useful in classifying the drug but which are of interest primarily to the laboratory investigator. For example, the tetrahydrocannabinols are anti-convulsant and depress polysynaptic transmission within the spinal cord.

None of the preparations of Cannabis have therapeutic applications, and none of the questions associated with its use as a social drug would be altered if it did. The use of synhexyl as an "anti-depressant" is, however, often mentioned. Review of the paper by Stockings usually cited in this regard will establish that he actually used the drug for the relief of anxiety. He clearly characterizes his ambulant patients as neurotic and describes the development after the administration of synhexyl of mild intoxication, euphoria and dreamy apathy.

Mechanism of action: The ability of a sedative or anesthetic to cause loss of consciousness is due to the sensitivity of the reticular activating system to their depressant effects. When electrodes are implanted into the reticular formation and several functionally related areas in the brain, the effect of synhexyl cannot be distinguished from that of pentothal.

Conclusion: Thus the effects of marijuana, both operationally and in its mechanism of action, correspond exactly to those of other sedatives and anesthetics, especially alcohol. The apparent distinctiveness of marijuana is due mostly to the use of a route of administration that permits the rapid development of an effect and to properties of the active components that lead to rapid decrease in the effects. One is driven to the conclusion that the differences between the dominant attitudes and consequent laws toward marijuana and alcohol are unrelated to the pharmacologic effects of the drugs but are due to a conflict between the mores of the dominant and one or more subcultures in this country.

TABLE 1 – ACTIONS THAT CHARACTERIZE SEDATIVE-HYPNOTICS
AND GENERAL ANESTHETICS

Mechanism of Action

Ascending reticular activating system specifically depressed

Descriptive

A. Effect of graded doses (stages of anesthesia)

1. Sedation and relief of anxiety
2. Disinhibition or excitement
3. Anesthesia
4. Respiratory and vasomotor (medullary) depression

B. With chronic administration

1. Anticonvulsant
2. Spinal cord depression (voluntary muscle relaxation)
3. Physical dependence (withdrawal state)
4. Liability for abuse
5. Therapeutic effect, relief of anxiety, induction of sleep

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