Denis J. Petro, M.D., is a practicing neurologist and clinical drug researcher in Arlington, Virginia. While the history of the medical uses of cannabis extends over 5,000 years, an understanding of the pharmacological properties of this most interesting plant remains a subject of intense interest. In the past ten years, new and exciting developments have emerged in cannabinoid research. Marijuana is the popular term for the group of substances derived from the herbaceous plant, Cannabis sativa. When the flowering tops and leaves of the plant are dried and rolled into cigarettes, marijuana can be smoked to deliver volatilized substances to the lungs. In addition to the psychoactive compounds unique to the cannabis plant, the smoke can contain particulate matter and tars as found in tobacco. Pathogens, such as aspergillus and salmonella can be delivered in the inhaled smoke. Transmission of contaminants can be limited with the use of a water pipe or alternative delivery system, such as use of the leaves in food for oral ingestion. The pharmacological properties of cannabis depend on the route of administration and will be discussed in relation to either the smoked form or the synthetic oral preparation, Marinol (delta-9-THC), a more recent form. Much of the clinical data obtained in the Marinol research program can be generalized to include cannabis, except for the route of administration. Chemistry Among the more than 400 chemical entities in the cannabis plant, the cannabinoids have been the group of compounds studied the most. At least 60 cannabinoids have been identified and studied. It should be noted that a particular plant has only trace amounts of most of the cannabinoids, not enough to have any clinical effect. The most thoroughly studied cannabinoids include delta-9-tetrahydrocannabinol (delta-9-THC), delta-8-tetrahydrocannabinol (delta-8-THC), cannabidiol (cBD), and cannabinol (cBN). After two decades of clinical research, a synthetic oral preparation, Marinol, has been approved by regulatory authorities for therapeutic use in the United States. The approved indications for the use of Marinol are for treatment of: (1) anorexia associated with weight loss in patients with AIDS; and (2) nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional treatments.

Cannabinoids have only limited solubility in water and are usually prepared in a vehicle such as alcohol or sesame oil. The pharmacological actions of any cannabinoid may depend on the nature of the vehicle used to administer it. For example, if serum albumin is the vehicle, the cannabinoid will bind to the albumin and subsequently limit the availability of the drug to the target tissue. Thus, studies comparing the relative potency of specific cannabinoids may not represent the true effect of cannabis when administered as a smoked cigarette. Since the clinical pharmacology of orally administered delta-9-THC (Marinol) has been extensively studied, most of the data relevant to cannabis has been obtained in studies of oral Marinol. Marinol is formulated in soft gelatin capsules containing either 2.5 mg, 5 mg or 10 mg delta-9-tHc.

Pharmacokinetics

No significant differences have been found between the sexes in the metabolism, disposition, and kinetics of delta-9-THC in humans (Wall et al. 1983). The absorption, distribution, metabolism, and secretion of cannabis depends on the method of administration and potency of the individual plant in use. In addition, the amount of cannabinoid delivered to the circulation depends on the inhalation technique of the subject. When inhaled, a standard 1-gram cigarette containing 2 percent delta-9-THC could deliver 0.4 to 10 mg of the drug to the circulation. Because of the high lipid solubility and first pass hepatic metabolism, only 10 percent to 20 percent of the dose reaches the circulation when administered orally. Plasma protein binding of delta-9- THC and its metabolites is approximately 97 percent. Plasma concentrations reach their peak within seven to ten minutes after smoking and within one to two hours after oral ingestion. The subjective and physiological effects are maximal within a half-hour after smoking and at two hours after oral ingestion.

The distribution of cannabis metabolites throughout the body is extremely rapid with uptake in liver, lung, spleen, and fat. Less than 1 percent of the administered dose reaches the brain. The elimination half-life is about 30 hours with 80 percent excreted via the intestine and liver and 20 percent excreted in the urine. At least 80 cannabinoid metabolites have been identified in man. Detectable levels of cannabinoid metabolites can be found in the blood and urine for up to one month after exposure to marijuana. Secondary exposure to cannabis smoke can result in inhalation of sufficient cannabinoids to produce positive urine test results.

The biotransformation pathways of cannabis in humans have been studied extensively. The metabolic profile includes hydroxylation, oxidation to carboxylic acids, is-oxidation, conjugation, and epoxidation. Together with the observation of wide variations in cannabinoid metabolism among species, these data may explain the differential effects of cannabis on experimental animals and man and on different human subjects.

Analytic techniques have been developed to detect the presence of cannabis metabolites in the urine. The metabolite of cannabis usually detected in the highest concentration is 11-nor-delta-THC-9-carboxylic acid (THC-cooH). This metabolite is found in urine in the free or conjugated state as a glucuronide. Most analytic techniques use THC-COOH as an indicator of cannabis use. The analysis is conducted in two steps beginning with a scitening immunoassay for THC metabolites. Confirmation of a positive test is achieved using the more sensitive gas chromatography with mass spectrophotometry (GC-MS). A positive THC-COON test is a level of 15 to 20 ng/dl using the GC-MS test.

The test can be positive for three days after a single use of cannabis. In a chronic cannabis

user, the urine test can detect residual positive levels for up to four to six weeks after last use, thus a positive urine test for a chronic user does not necessarily indicate recent or continued use (Ellis et al. 1985). Metabolite concentrations in the urine have been found to be higher following oral ingestion than after smoking cannabis (Cone 1990). Lower but still detectable concentrations in the urine have been found with ingestion by passive inhalation.

Studies by Perez-Reyes et al. (1972, 1973) demonstrated that THC metabolites are not excreted by the salivary glands. However, THC has been detected in saliva and is the result of direct absorption into the buccal mucosa as the cannabis is smoked. Amounts are highest within an hour of inhalation and drop thereafter. Although the amount of absorption is relatively small, it seems reasonable that additional small amounts are probably absorbed in the mucous membranes of the upper respiratory tract as well (Perez-Reyes 1990).

Pharmacological Effects in Humans

The two effects of cannabis that have been demonstrated to be of therapeutic value, to the extent that Marinol is marketed for treatment, are as an antiemetic and as an appetite stimulant in AIDS patients manifesting anorexia. The approval of Marinol for these indications represents de facto recognition that the risk-benefit ratio of delta-9-mc is favorable. Adequate and well-controlled studies are required for approval, and Marinol has met all standards set by the Food and Drug Administration (FDA). This fact is often forgotten by those critics who claim that cannabinoids have no therapeutic effects. In spite of lack of evidence to support any diversion of Marinol in these patients, the drug remains in Schedule II under the Controlled Substances Act.

While therapeutic effects have been demonstrated, most pharmacological studies have emphasized central nervous system (cNs) effects and other system actions that might be considered toxic. Behavioral responses in healthy subjects, at varying doses and under different conditions, have been reported. In addition, clinical experience with 474 patients exposed to Marinol has been published. In healthy subjects, CNS effects on mood, memory, motor coordination, cognition, sensorium, time sense, and self-perception are noted. The most prominent cardiovascular effect in healthy subjects is tachycardia at rest. The increase in heart rate is dose-related, and its duration correlates with concentrations of delta-9-mc in blood. Other cardiovascular effects include increased supine blood pressure, decreased blood pressure on standing and conjunctival reddening (bloodshot eyes). The respiratory effect of a single dose of inhaled cannabis is significant to induce bronchodilatation. Bronchitis and asthma have been reported in chronic cannabis smokers. This observation is not unexpected due to the presence of tars in marijuana smoke and the tendency of recreational smokers to inhale deeply.

Immunosuppression is reported in animals and in vitro. Clinical experience has not indicated an increased susceptibility to infections. Ironically, Marinol is indicated to treat the anorexia associated with AIDS with no reports of increased immunosuppression. Among the endocrine effects reported are decreased testosterone and inhibition of spermatogenesis in men and anovulatory cycles in women.

Mechanism of Action

An understanding of the mechanism of action of cannabinoids remains an exciting challenge to the neurosciences. In the past decade researchers have made discoveries that promise answers to fundamental questions about
cannabis. If the active ingredients in cannabis trigger specific receptors in the brain, what is their normal role in brain function? For the receptor theory of cannabis action to be proven, two questions must be answered: what is the nature of the THC receptor and what is the natural brain chemical (the endogenous ligand)?

Before 1988 many neuroscientists thought that since THC is a fat-soluble molecule, the logical explanation was for THC to insert itself in cell membranes. Researchers in the United States and Israel were able to extract membrane receptors from the brain cortex, hippocampus, and basal ganglia that demonstrated binding with cannabinoid compounds in a dose-dependent and pharmacologically specific manner. Isolation of the cannabinoid receptor in 1988 was a signal event in neuroscientific research. The receptor is involved in the regulation of the cellular cyclic AMP (CAMP) second messenger system and the inhibition of adenylate cyclase. The cannabinoid receptor has been cloned and binding sites have been identified (Matsuda et al. 1990; Munroe et al. 1993; Pertwee 1993).

The search for a brain chemical that binds the receptor has focused on a molecule derived from arachidonic acid, christened "anandamide," from a Sanskrit word meaning "bliss." Other candidate molecules have been proposed that, unlike anandamide, are water-soluble. The discovery of the cannabinoid receptor and the endogenous ligand has infused new energy in the field of cannabinoid pharmacology (Devane et al. 1992).

Toxicity

No drug is free of toxic effects. One of the most important roles of the clinician is to balance the risks of a potential medical treatment against the benefits to be gained from its use. After 5,000 years of use, cannabis remains a remarkably safe drug. To date, there exists no reported case of a fatal overdose. Considering that hundreds of people die each year from aspirin overdoses, one can only be impressed by the safety of cannabis. In the hearings concerning the rescheduling of marijuana in 1988, the Drug Enforcement Administration's (DEA) own administrative law judge declared that marijuana in its natural form was "one of the safest, therapeutically active substances known to man." It is often said that if aspirin were a new drug submitted to the FDA for review, regulatory approval would not be a certainty. Yet, the most psychoactive cannabinoid, delta-9-THC, is marked for two indications that are, by definition, untreatable by any other drug available to the physician.

With the marketing of Marinol in the United States, well-controlled clinical trials have been conducted that provide some indication of the safety
of Marinol. Adverse reactions to Marinol were identified in clinical trials in the United States and its territories involving 474 patients (157 patients with AIDS-related weight loss and 317 patients with nausea and vomiting associated with cancer chemotherapy). A cannabinoid dose-related "high" (easy laughing, elation, and heightened awareness) has been reported by patients receiving Marinol in both the antiemetic (24 percent) and appetite stimulant clinical trials (8 percent). Adverse reactions from these trials have been classified by frequency and body system. For those reactions that occurred while the subjects were being treated with Marinol and that were felt to be probably causally related to Marinol, the results are presented by incidence:

Incidence of events: less	Cardiovascular:	Conjunctivitis,	Nervous system:	Digestion,

In addition, other events that occurred with a frequency of less than 1 percent and had an unknown relationship to the use of Marinol include:

Body as a w

Reviewing the adverse reactions to Marinol reveals no unusual or unexpected effects of this drug, which is given to patients with the difficult medical problems of cancer and AIDS. In keeping with the restrictions placed on Marinol (Schedule II), the product labeling includes a strong warning regarding possible addiction or diversion. No evidence to support such a warning has been found in the studies of Marinol. In studies, on patients with AIDS who received Marinol for up to five months, no abuse, diversion, or systematic change in personality or social functioning were observed, despite the inclusion of a substantial number of patients with a past history of drug abuse. While abuse of Marinol has not occurred,

the drug can cause signs of an abstinence syndrome on abrupt withdrawal. Electroencephalographic changes consistent with the effects of drug withdrawal (hyperexcitation) were recorded in patients after abrupt discontinuation. Patients also complained of disturbed sleep for several weeks after discontinuing therapy with high dosages of Marinol. Volunteers receiving dosages of 210 mg/day for 12 to 16 consecutive days reported symptoms such as irritability, insomnia, and restlessness within 12 hours after discontinuation. By approximately 24 hours after discontinuation, withdrawal symptoms intensified and included "hot flashes," sweating, rhinorrhea, loose stools, hiccups, and anorexia. These withdrawal symptoms gradually dissipated over the next 48 hours.

Accidental or intentional overdose with Marinol has not occurred. Side effects are usually dose-related and improve with reduction in the daily dose. In antiemetic studies, drowsiness and other nonpsychotropic symptoms were equal in incidence in the higher and lower doses. The incidence of dysphoric effects was only 12 percent in the low-dose group as compared to 28 percent in the high-dose group. Interestingly, in the antiemetic studies the efficacy of Marinol was not reduced in the low-dose group. Thus, the use of a low dose of Marinol can minimize side effects while maintaining therapeutic benefit. The signs and symptoms of a mild Marinol overdose include drowsiness, euphoria, heightened sensory awareness, altered time perception, reddened conjunctiva, dry mouth, and tachycardia. A moderate overdose causes memory impairment, depersonalization, mood alteration, urinary retention, and reduced bowel motility. Severe intoxication includes decreased motor coordination, lethargy, slurred speech, and postural hypotension.

The estimated lethal human dose of intravenous Marinol is 30 mg/kg (2100 mg/70 kg). Using this estimation of the lethal dose, the equivalent inhaled THC would represent the smoking of 240 cannabis cigarettes with total systemic absorption of the average 8.8 mg of THC in each cigarette. Since absorption is much less than 100 percent, the amount of smoked marijuana required to reach lethality is on the order of one to two thousand cigarettes. The physical impossibility of a fatal overdose using smoked cannabis is obvious.

The safety data obtained in clinical trials of Marinol provide some insight into the potential toxicity of cannabis. Clearly, inhaled cannabis presents hazards related to this method of administration. The presence of contaminating herbicides and infectious agents is avoidable with organic cultivation techniques and sanitary cigarette production. The presence of tars and other particulate matter can be minimized using water pipes. Water pipes also can limit direct oral exposure to tars and other potential carcinogens.

A consistent response to the acute administration of cannabis is an increase in heart rate;

however, tolerance to this effect develops after approximately one week of regular use. Also seen are blood pressure changes including increased supine pressure and orthostatic hypotension. In the clinical trials of Marinol less than 3 percent of patients experienced cardiovascular adverse reactions (palpitations or tachycardia). Since Marinol has not been studied in the elderly or in patients with preexisting cardiovascular disease, caution should be exercised with these patients. In the Marinol antiemetic studies, no difference was found in efficacy or tolerance in patients over 55 years old. As always, the clinical judgment of the clinician has to balance the possible risks against the potential benefits in any population, such as the elderly or those with heart disease.

While a large body of preclinical data exists regarding the effects of cannabinoids on endocrine gland activity, studies on humans have been the subject of controversy. There are reports of cannabis-induced decreases in testosterone and hormone levels to the lower end of the normal range, but the interpretation of these results is uncertain. Likewise, the increase in anovulatory menstrual cycles in females is consistent with the suppression of LH secretion as seen in rats, but the clinical correlation in terms of fertility is unknown.

The potential for a drug to induce cancer is always studied when a new drug is considered. Animal studies are only an indirect measure of the potential carcinogenicity of a drug. Mutagenicity testing of Marinol was negative in the Ames test. Inhaled cannabis contains many of the same toxic substances found in tobacco cigarettes. Exposure to these substances can be limited or even eliminated with the use of alternative delivery systems for cannabinoids.

A potential connection between marijuana and leukemia was reported in a controlled study of 204 pairs of children. Two hundred and four children with acute non-lymphoblastic leukemia (ANLL) were matched with an equal number by age, race, and residence (area code and exchange). Marijuana use was reported by ten mothers (during or within three months prior to pregnancy) of the children with ANLL and in one control case. This observation represents a tenfold risk (P = 0.005). Marijuana use by fathers, in the year prior to conception, did not demonstrate a significant association with
increased risk. This unexpected result may have been influenced by limitations in the study design. The observed rate of cannabis use of 5 percent in study cases is lower than the rate of 10 percent seen in a group of new mothers. The 0.5 percent rate found in the control group may be due to underreporting by subjects who were contacted by telephone and were perhaps unwilling to admit to an activity that is still illegal. In addition, in any study with a large number of outcome variables, the possibility of a random, but incorrect finding, is increased.

Over the years, in vitro studies of human and animal cells have suggested that cell-mediated

immunity may be adversely affected by cannabis. If these in vitro results have any merit, one would expect to see increased opportunistic infections in AIDS patients who use Marinol to treat the cachexia (wasting syndrome) associated with AIDS. However, no increase in infections has been found. Likewise, patients undergoing cancer chemotherapy might be expected to show more problems with infections. Again, no relationship between the use of Marinol and opportunistic infection was seen.

A working definition of neurotoxicity is any adverse effect on the structure or function of the central or peripheral nervous system by a biological, chemical, or physical agent that may result from direct or indirect actions or reflect permanent or reversible changes in the nervous system. This definition includes temporary and reversible effects on the nervous system as neurotoxic. Neuroscientists have attempted to create animal models to test for neurotoxicity with cannabinoids. As with human studies, route of administration, duration, and age at exposure are variables influencing the results of the studies. In summary, prepubescent rats developed hippocampal lesions after chronic cannabis exposure. A therapeutic window for the production of an effect was seen when 40-day-old rats were more severely affected than 70-day-old rats. Periods of exposure to cannabis, shorter than three months have not demonstrated neurotoxic effects in rats. Studies on prepubescent rhesus monkeys, using up to one-year exposure to cannabis smoke, did not produce neurotoxicity as seen in rats.

The range of psychopathological effects said to be related to cannabis use is wide. However, the fact that cannabis users have experienced virtually every psychiatric illness may be an indication that cannabis is the cause of psychiatric illness, but it is no proof of causality. In many cases, reports of amotivational syndrome, marijuana-induced cerebral atrophy, or acute paranoid reactions have been published with only a minimal concern for scientific objectivity. Widespread media attention to anecdotal reports of brain damage obscure the search for scientific truth. In subjects using marijuana as a recreational drug, one can expect the usual range of mental effects coincident with their search for a "high." If the subject is paranoid or depressed, one would not expect a pleasant experience in all cases.

The effects of cannabis on driving have been extensively studied. It takes no stretch of the imagination to assume that an individual experiencing a "high" should not be on the road. The degree of impairment after cannabis use has been studied in comparison with that caused by alcohol, and both drugs produced impairment of driving performance, with the combination leading to worse results than either drug alone. The Marinol patient instruction is the standard

warning seen with many drugs, i.e., not to drive, operate machinery, or engage in any hazardous activity until it is established that patients are able to tolerate the drug and to perform such tasks safely.

Conclusion

This chapter reviewed the chemistry and pharmacology of cannabis. The past decade has seen exciting developments in cannabinoid research. Isolation of specific cannabinoid receptors and the search for the endogenous ligand active at these receptors is ongoing. The decade has seen the regulatory approval of Marinol for the treatment of anorexia in AIDS and in patients with nausea and vomiting associated with cancer chemotherapy. Future developments of other cannabinoids and more acceptable administration of cannabis to avoid the adverse pulmonary effects of smoking are exciting new areas for research. These research developments have to be balanced against the restrictive public policy decisions of governmental agencies, such as the DEA. It is hoped that a rational discussion of the issues will occur as progress in this most interesting therapeutic approach continues.

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