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Marijuana and Medicine: The Endocrine Effects of Cannabis

By John M. McPartland, DO, MS

CANNABIS IS USED AS A RECREATIONAL DRUG, A MEDICINAL HERB, and the original source of the pharmaceutical drug dronabinol, an appetite stimulant and antiemetic. The active constituents in cannabis are cannabinoids. Although, the best-known cannabinoid is tetrahydrocannabinol (THC), there are many types, including some that are in chocoate (see *Alternative Therapies in Women's Health*, March 1999, pp. 28-29). Cannabinoids affect women's health in several ways. This article will clarify the definition of cannabinoids and address a few concerns regarding endocrinology and reproductive physiology.

History

Initially, cannabinoids were defined as a group of C_{21} terpenophenolic compounds uniquely produced by cannabis plants.[1] Later, chemists at Lilly, Pfizer, and Sterling created synthetic cannabimimetic analogs, some of which are 800 times more potent than THC. These super-THCs proved useful as powerful research tools. Devane, Howlett, and colleagues probed marijuana's psychoactivity using the super-THC CP55940, and they proved that THC fits into a selective, high-affinity neuron receptor.[2] Prior to Devane's discovery, researchers thought THC worked as a nonspecific cell membrane solvent, "sloshing" neurons in the same manner as ethanol.

After Devane discovered cannabinoid receptors, he moved to the lab of Raphael Mechoulam, the Israeli scientist who discovered THC nearly 30 years ago. The discovery of specific cannabinoid receptors was exciting, and these investigators knew that it was implausible that receptors in human tissue could only be filled by an exogenous substance. Together they searched for the "endogenous ligand" that our bodies make to fit the cannabinoid receptor. The "endocannabinoid" molecule they isolated was quite surprising; it looked nothing like THC and turned out to be an amide of

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arachidonic acid.[3] They named the molecule "anandamide," derived from the Sanskrit word *ananda* for "bliss." (Anandamide is one of the cannabinoids found in chocolate.)

The next big discovery was a cannabinoid antagonist, SR141716A, synthesized by Sanofi Labs. SR141716A blocks the effects of marijuana, and reverses the effects of THC—it improves short-term memory; makes rats more sensitive to pain; and inhibits "the munchies," thus causing weight loss. Researchers found that the cannabinoid receptors indirectly affect numerous other neurotransmitters and their receptors (including serotonin, dopamine, norepinephrine, acetylcholine, the endorphins, GABA, NMDA, and glutamate).

The identification of a second type of cannabinoid receptor ("CB2") led to the discovery of additional endocannabinoids. CB2 receptors occur on white blood cells, splenocytes, and tissues associated with immune function. Thus the cannabinoid system weaves between the mind and body.

The cannabinoid receptor is a G protein-coupled, seven-helix transmembrane nucleotide, similar to receptors of other neurotransmitters. The distribution of cannabinoid receptors correlates with the effects of THC. Dense receptor concentrations are found in the hippocampus (affecting short-term memory), the limbic system (controlling mood and emotions), and the cerebellum and basal ganglia (involved in coordination of movement). Low receptor concentrations in the brain stem help explain the lack of lethal effects from marijuana overdose.

Reproductive Tract Effects

Outside the CNS, dense concentrations of cannabinoid receptors appear in the ovaries and endometrium.[4] Although the discovery of receptors in the female reproductive tract is relatively recent, the use of cannabis to treat reproductive tract problems has a long history; many physicians (including Sir Russell Reynolds, physician to Queen Victoria) have prescribed cannabis for dysmenorrhea.[5]

This may well have been an effective treatment; THC exerts significant anti-inflammatory effects by blocking the synthesis of prostaglandin E2 from arachidonic acid. To wit, cannabinoids act as selective COX-2 inhibitors, similar to celecoxib.[6] Anti-prostaglandin activity may also account for some of the negative effects of cannabinoids on reproduction in rats, ranging from poor embryo implantation[7] to post-term delivery and an increase in the frequency of stillbirths.[8]

Cannabis is an effective antiemetic and has been used to treat nausea and vomiting of pregnancy. Given the reproductive toxicity shown in animal studies, neither marijuana nor its derivatives should be used for pregnancy-related morning sickness.

Endocrine Effects

Cannabinoids have complex actions on the endocrine system, with conflicting reports appearing in the literature. In rats, THC and anandamide stimulate the hypothalamic-pituitary-adrenal axis. This cascade begins in the receptor-rich hypothalamus, where cannabinoids quickly stimulate the secretion of corticotropin-releasing factor (CRF), which causes the pituitary to produce ATCH, resulting in the release of corticosterone from the adrenal cortex.[9] Cells in the limbic system also produce CRF, but these neurons increase CRF production during cannabinoid withdrawal from chronic use.[10]

Other pituitary hormones in rats are affected by cannabinoids. No changes are seen in serum levels of follicle stimulating hormone (FSH); but cannabinoids suppress luteinizing hormone (LH), growth hormone (GH), and thyrotropin. The prolactin response is biphasic; early stimulation is followed by suppression.[11,12] Based on a study of 56 women and 93 men who used cannabis at least once weekly for the two previous years (women averaged 5.8 uses/week; men averaged 8.2 uses/week), cannabinoids appear to have fewer endocrine effects in humans.[13] The study results indicate

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that humans who smoke marijuana on a chronic basis, compared to non-smoking controls, exhibit no differences in cortisol, prolactin, LH, or FSH.[13]

Estrogenic Effects and Breast Cancer

THC and other cannabinoids do not exhibit direct estrogenic activity in estrogen receptor assays,[4] but marijuana smoke interacts weakly with estrogen receptors in vitro.[14] Apparently, marijuana contains phytoestrogens, including the estrogenic flavonoid apigenin, and volatilized apigenin retains pharmacological activity.[14] Is the estrogenic effect of apigenin worrisome? Probably not, but this may contribute to gynecomastia that sometimes arises in males who are heavy smokers of marijuana. Apigenin has a high affinity for estrogen receptors (especially beta-estrogen receptors), but low estrogenic activity in estrogen-binding assays.[15] In vitro, apigenin actually inhibits estradiol-induced proliferation of breast cancer cells.[16]

Cannabinoids also inhibit the growth of human breast cancer cells in vitro.[17] Apparently cannabinoid receptors in breast cells suppress the synthesis of prolactin receptors and subsequently prolactin action, thus resulting in the down-regulation of the breast cancer *BRCA* 1 gene.[18] Thus, the anti-proliferative action of cannabinoids is due to inhibition of DNA synthesis rather than to cytotoxicity or apoptosis. These characteristics have interested researchers who are designing and testing cannabinoids as potentially novel breast cancer treatments.

IOM Report

The Institute of Medicine (IOM) just released a report on medical marijuana.[18] Because the report was funded by the White House Office of National Drug Control Policy, it is not surprising that the IOM endorsed pharmaceutical cannabinoids, but criticized the delivery of cannabinoids through smoked marijuana. The objections to the latter delivery system were both cultural (as Eric Voth, one of the panel of reviewers, stated, "We do not smoke medicine anywhere in our society")[19] and medical (unfiltered marijuana smoke is very high in tars).

Tars can be avoided, however, by utilizing vaporizer technology. Vaporizers heat marijuana to 180-190° C, which is sufficiently high to vaporize THC, but is below the burning point of combustible plant materials, so no smoke is generated.[20] Although vaporizers have been used with marijuana for 20 years, the IOM panel ignored this technology.

In addition to cannabinoids and phytoestrogens, marijuana contains dozens of terpenoids, which are volatilized and inhaled, cross the blood-brain barrier, and may modulate the effects of THC.[21] Limonene, carvacrol, and pulegone, for instance, inhibit acetylcholinesterase (a mechanism shared by tacrine), so these terpenoids reverse the cholinergic deficit created by THC. Tacrine has blocked THC-mediated memory loss behavior in rats, and the same may be true of acetylcholinesterase inhibitors intrinsic to cannabis plants.[21] The modulating effect of non-cannabinoids may be why many patients claim that utilizing the polypharmaceutical herb marijuana is superior to pure, synthetic THC (dronabinol).[21]

In summary, as noted by the IOM report, marijuana and cannabinoids are not completely benign substances. They are powerful drugs with a variety of pharmacological effects. Some of these effects are potentially therapeutic, but the subject of medical use of marijuana (as opposed to the use of isolated cannabinoids) remains embedded in a web of social concerns. ❖

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Myths and Mistakes About Herb-Drug Interactions

Abstract & Commentary

Source: Miller LG. Herbal medicinals: Selected clinical considerations focusing on known or potential drug-herb interaction. *Arch Intern Med* 1998;158:2200-2211.

Synopsis: *Herbal medicinals are being used by an increasing number of patients who typically do not advise their clinicians of concomitant use. Known or potential drug-herb interactions exist and should be screened for.*

COMMENT BY DENNIS AWANG, PhD, FCIC AND ADRIANE FUGH-BERMAN, MD

HERBS DO CONTAIN PHARMACOLOGICALLY ACTIVE ingredients, some of which can potentially interact with medications. However, this article contains numerous errors, and thus is not a credible source of information. In our analysis, the publication of this review indicates deficiencies in both editorial judgment and the peer review process. What follows is a limited discussion of misleading statements in the abstract.

"*If used beyond 8 weeks, Echinacea could cause hepatotoxicity and therefore should not be used with other known hepatoxic drugs, such as anabolic steroids, amiodarone, methotrexate, and ketoconazole. However, Echinacea lacks the 1,2 saturated necrine ring associated with hepatotoxicity of pyrrolizidine alkaloids.*"

This assertion is not referenced in the text, for good reason. There are no reports of hepatotoxicity associated with echinacea alone, in combination with any of the drugs listed, or in combination with any pharmaceutical drug. There is one report of hepatotoxicity with a product purportedly containing echinacea and skullcap (*Scutellaria lateriflora*). Products purportedly containing skullcap have been implicated in several cases of hepatitis, and even here skullcap may not be the culprit. Some "skullcap" products have been found to contain germander (*Teucrium chamaedrys*),[1] sometimes mistaken for skullcap. Germander has demonstrated hepatotoxicity in both rodents[2] and humans.[3,4] There is no evidence implicating echinacea as a contributing factor to hepatotoxicity.

It is not the "1,2 saturated necrine ring" but rather the 1,2-unsaturated necine ring that is associated with hepatotoxicity of pyrrolizidine alkaloids. While echinacea does not contain the dangerous unsaturated form of pyrrolizidine alkaloids, it does contain extremely low levels (0.006%) of isotussilagine and tussilagine, which are non-toxic saturated pyrrolizidine alkaloids.[5] There are of course other mechanisms of hepatotoxicity, but echinacea causes none of them.

"*Feverfew, garlic, Ginkgo, ginger, and ginseng may alter bleeding time and should not be used concomitantly with warfarin sodium.*"

There is a case report of ginseng reducing the international normalized ratio (INR) in a patient on warfarin.[6] Garlic intake has been associated with excessive

postoperative bleeding and spontaneous spinal hematoma but specific drug interactions have not been reported. Ginkgo alone[7,8] and in combination with anticoagulants[9,10] has been linked to bleeding episodes. Although both ginger and feverfew contain anticoagulant substances, there are no reports in the medical literature of bleeding episodes or alterations in bleeding time with feverfew or ginger. (*See retated article on p. 46.*)

"*Ginseng should also not be used with estrogens or corticosteroids because of possible additive effects.*"

No such interactions have been reported. Ginseng has complex actions, including effects on corticosteroid action, so a theoretical interaction with corticosteroids is possible. Ginseng does not contain phytoestrogens (although interestingly, several cases of postmenopausal bleeding have been linked to ginseng ingestion[11,12]).

"*Kyushin, licorice, plantain, uzara root, hawthorn, and ginseng may interfere with either digoxin pharmacodynamically or with digoxin monitoring.*"

Kyushin is a Chinese medicine containing dried toad venom, which does have cardiac glycoside activity. Toad venom, however, is not an herb. High chronic doses of licorice can cause hypokalemia, which of course can cause or contribute to cardiac arrhythmias, but there are no in vitro, in vivo, or clinical reports of licorice-digoxin interactions. The warning against plantain is apparently based on a plantain product that was contaminated with woolly foxglove (*Digitalis lanata*),[13] a source of cardiac glycosides (and the original source of the digoxin we use in practice). Plantain itself has never been associated with cardiotoxicity or any interaction with digoxin.

Uzara root contains cardiac glycosides but is rarely used in herbal medicine today. There are no clinical reports of hawthorn interacting with digoxin, and the reference for the statement in the text that "Hawthorn berries purportedly potentiate the action of digoxin" actually states that hawthorn may be combined with digitalis.[14]

Ginseng (*Panax* species) has not been associated with elevated digoxin levels. The reference to this statement in the text of the article is incorrect; it refers to an article on sesquiterpene esters in echinacea. Perhaps the author meant to refer to an article about eleuthero (*Eleutherococcus senticosus*), which is also called "Siberian ginseng." Siberian ginseng is not ginseng, but belongs to an entirely different genus.

The eleuthero-digoxin case is interesting. A 74-year-old man whose digoxin levels had been maintained in a consistent range for many years experienced a sudden rise in digoxin levels to 5.2 nmol/L after taking capsules purportedly containing Siberian ginseng (concurrent medications included acetaminophen, cimetidine, oxazepam, aspirin, and magaldrate).[15] Considering that the therapeutic range for digoxin is 0.6-2.6 nmol/L, the fact that this patient was completely asymptomatic with digoxin levels of 5.2 nmol/L (EKG was unchanged, and there were no other signs or symptoms of digoxin poisoning) suggests that the herb interfered with the assay for digoxin rather than actually increasing serum digoxin levels.

Although the implicated capsules were tested for the presence of digoxin and digitoxin (neither was found), the capsules were not tested to confirm that they actually contained eleuthero. Another herb known as Chinese silk vine (*Periploca sepium*) is commonly substituted for *Eleutherococcus senticosus*; periploca does contain cardiac glycosides.[16]

"*Evening primrose oil and borage should not be used with anticonvulsants because they may lower the seizure threshold.*"

The text of the article states that "evening primrose oil contains gamolenic acid (GLA) that lowers the seizure threshold" and that "Neither evening primrose oil nor borage should be used with other drugs known to lower the seizure threshold (e.g., tricyclic antidepressants and phenothaizines [sic])." Miller's own reference[17] to the first statement (the second is unreferenced) states that epileptic events were reported only in patients treated with phenothiazines.

"*Kava when used with alprazolam has resulted in coma.*"

There is no reported association between kava and coma. It is true that the reference for this statement is misleadingly titled, "Coma from the health food store: Interaction between kava and alprazolam,"[18] but surely it is reasonable to expect the author of a review article to read beyond the title of a referenced article. The case actually reports only lethargy and disorientation, not unconsciousness.

"*Numerous herbs (e.g., karela and ginseng) may affect blood glucose levels and should not be used in patients with diabetes mellitus.*"

While it is true that a number of herbs have hypoglycemic effects, in diabetics this effect may be an advantage, not a disadvantage. In fact, a double-blind, placebo-controlled, eight-week study of 36 newly-diagnosed NIDDM patients found that 100 mg or 200 mg ginseng extract reduced fasting blood glucose (the higher dose also significantly reduced HbA1c).[19] Although Miller states in the text "that ginseng…has been associated with hyperglycemic properties," it is the opposite that is true (as her own reference states). Obviously blood glucose levels should be monitored carefully when herbs with hypoglycemic activity are used. ❖

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Herbs and Anticoagulant Medication

By Tieraona Low Dog, MD

ONE QUESTION PHYSICIANS FREQUENTLY ASK IS: "CAN this herb be taken if a patient is on warfarin?" This is difficult to answer with any degree of certainty because very little published research on the subject exists.

Any substance that alters the uptake or metabolism of warfarin; the uptake or metabolism of vitamin K; the synthesis, function, or clearance of any factor or cell involved in hemostasis or fibrinolysis; or the integrity of any epithelial surface, can be potentially dangerous for those taking oral anticoagulants.[1]

Herbal medicines are quite complex, containing hundreds of constituents that produce numerous changes in our physiology. A number of herbs contain constituents that have some inhibitory action upon platelet aggregation. Ginkgolides found in ginkgo leaves inhibit platelet activating factor (PAF) and thus reduce platelet aggregation. Numerous in vitro studies have shown that garlic and ginger may also inhibit platelet aggregation.

Although inhibition of platelet aggregation does not alter the prothrombin time (PT), the risk of serious bleeding increases. Combining warfarin with aspirin or other NSAIDS increases the risk of gastric ulceration and bleeding. As a rule, when two substances with similar therapeutic effects are combined, there is an additive effect. Thus, herbs that inhibit platelet aggregation, taken concurrently with warfarin, may increase anticoagulation.

Antibiotics can also prolong bleeding time, increasing the international normalized ratio (INR) by reducing the number of bacteria in the gut that synthesize vitamin K. Many plants are rich in phenolic compounds and other antimicrobial substances that can reduce the number of bacteria in the gut. Thyme, large doses of garlic, and goldenseal (to name a few) have antibacterial effects and there is no way to predict their effect on gut bacteria.

The list of possible interactions with oral anticoagulants grows larger everyday. We used to think that acetaminophen and warfarin were safe when taken together. However, when combined with warfarin, acetaminophen is associated in a dose-dependent manner with an INR greater than 6.0.[2] There is simply no way to

say with absolute confidence whether an herb will interact with warfarin in a specific patient.

So what does this all mean? Physicians should counsel their patients about the risks and benefits of oral anticoagulation medication and stress the need to inform the health care provider of changes in diet or the use of supplement, botanical, or other over-the-counter medication. Draw the PT/INR four to six days after the patient begins the new therapy and adjust the warfarin as necessary. If there is concern about bleeding time, have this checked as well. Be watchful, adjust warfarin as necessary, and monitor bleeding times in those who are exploring their many health options with natural medicine. ❖

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Reader Questions

Are there any effective alternative treatments for fibroids?

Response: *None that have been documented in the medical literature. There are many unproven treatments popular for fibroids, including individualized traditional Chinese herbal mixtures, chiropractic, natural progesterone cream (see* Alternative Therapies in Women's Health*, April 1999, pp. 33-36), and castor oil packs (warm castor oil on flannel applied to plastic-wrap protected abdomen).*

In my clinical experience, women with symptomatic fibroids sometimes obtained temporary relief of symptoms with individualized Chinese herbal mixtures or chiropractic. Relief was often only temporary and was not accompanied by a reduction in the size of the fibroids. I have had several patients with symptomatic fibroids who tried every conceivable alternative treatment unsuccessfully for years. Surgery proved very successful as an "alternative" to alternative therapy.

Adriane Fugh-Berman, MD

CME Questions

21. High levels of cannabinoid receptors are found in all of the following except:
a. basal ganglia.
b. brain stem.
c. ovaries.
d. endometrium.

22. Tetrahydrocannabinol (THC):
a. increases prostaglandin E2 synthesis.
b. decreases prostaglandin E2 synthesis.
c. has no effect on prostaglandin E2 synthesis.

23. Which of the following statements are true?
a. Echinacea causes hepatotoxicity.
b. Echinacea contains unsaturated pyrrolizidine alkaloids.
c. Echinacea is hepatotoxic in combination with certain drugs.
d. Echinacea contains saturated pyrrolizidine alkaloids.

24. Bleeding episodes have been reported in patients taking which of the following herbs?
a. Garlic and ginkgo
b. Feverfew and ginger
c. Garlic, feverfew and ginkgo
d. Ginger

25. A clinical study of ginseng in newly diagnosed NIDDM patients found that ginseng:
a. raised fasting blood glucose levels.
b. lowered fasting blood glucose levels.
c. had no effect on fasting blood glucose levels.

Editor's Note

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Note to Readers

We invite you to submit product labels for review or questions about articles in or issues relevant to *Alternative Therapies in Women's Health*. Please send your questions or product labels (and any available promotional material) to: *Alternative Therapies in Women's Health*, c/o American Health Consultants, P.O. Box 740056, Atlanta, GA 30374. Or you may contact the staff via e-mail at leslie.coplin@medec.com or paula.cousins@medec.com

Clinical Abstracts

With Comments from Adriane Fugh-Berman, MD

Yoga and Carpal Tunnel Syndrome

Source: Garfinkel MS, et al. Yoga-based intervention for carpal tunnel syndrome. *JAMA* 1998;280:1601-1603.

Design and Setting: Randomized, single-blind, controlled trial in a geriatric center and an industrial site.

Subjects: Forty-two individuals, age range 24-77, with carpal tunnel syndrome.

Treatment: Modified Iyengar yoga classes (11 yoga postures designed to strengthen, stretch, and balance joints in the upper body along with relaxation) for eight weeks. Patients in the control group were offered a wrist splint.

Dose/Route/Duration: Twice-weekly, 1- to 1½-hour Iyengar yoga classes for eight weeks.

Outcome Measures: Changes in grip strength, pain intensity, sleep disturbance, Phalen sign, Tinel sign, and median nerve motor and sensory conduction time.

Results: Compared to the control group, subjects in the yoga group experienced significant improvements in grip strength, pain reduction, and Phalen sign; no significant differences were found in sleep disturbance, Tinel sign, or median nerve motor and sensory conduction time.

Funding: Grant 91-07-14 from the Commonwealth of Pennsylvania.

Comments: This is a reasonable study showing the benefit of modified yoga postures in reducing symptoms associated with carpal tunnel syndrome. ❖

Steroids Common in Chinese Herbal Creams

Source: Keane FM, et al. Analysis of Chinese herbal creams prescribed for dermatological conditions. *BMJ* 1999;318:563-564.

Materials and Methods: Eleven Chinese herbal creams used for chronic skin disorders (primarily eczema) in adults and children were obtained from patients (or parents) attending an outpatient dermatology clinic in London. Five suppliers of creams were identified but the original source of the creams is unknown. Creams were analyzed for the presence of steroids by high resolution gas chromatography and mass spectrometry.

Results: Eight of 11 creams tested contained dexamethasone in a mean concentration of 456 mg/g (range 64-1500 mg/g). The concentration of steroid in creams used for children was 5.2 times higher than the creams used for adults. Most containers were glass jars that were unlabeled or labeled only with directions and the name of the cream or supplier. The two preparations that were labeled with a list of herbs did not contain dexamethasone. None of the creams was labeled as containing steroids and patients were unaware that these preparations contained steroids.

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Comments: Although this study was performed in the U.K., it would not be surprising if the same situation exists in the U.S. There have been a number of cases in the U.S. in which imported patent Chinese herbal medicines have been found to contain conventional pharmaceutical drugs as well as herbs. This is not malicious adulteration; combined use of drugs and herbs is well accepted in China, Taiwan, and Hong Kong. However, drugs should be labeled (and regulated) as drugs.

The dearth of labeling of creams in this study indicates that they were probably not patent medicines but may have been made (or packaged) locally. Whatever their origin, it is of great concern that these preparations were not appropriately labeled as steroid creams. According to the study's authors, the mean dose found in these creams is roughly equivalent to 0.05% betamethasone valerate. Because patients were unaware that these creams contained steroids, appropriate precautions for high-potency topical steroids were not followed. Creams were applied to face and flexures (sometimes several times a day); the highest concentration of dexamethasone was found in a cream applied to the face of a four-month-old baby with eczema. ❖

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