Using Cannabis as Medicine

The author, a general practioner in California,
has recommended cannabis to some 3,000 patients
and monitored its use in treating a wide array of conditions

By Jeffrey Hergenrather, MD

This article is based on and includes slides from a 'grand rounds' presentation to doctors at St. Rose Hospital in Hayward, California, February 7, 2018. It has been updated to reflect the rescheduling of Epidiolex.

I would like you to come out of this with an epiphany: "This is wonderful, I would like to incorporate cannabis into my practice!"

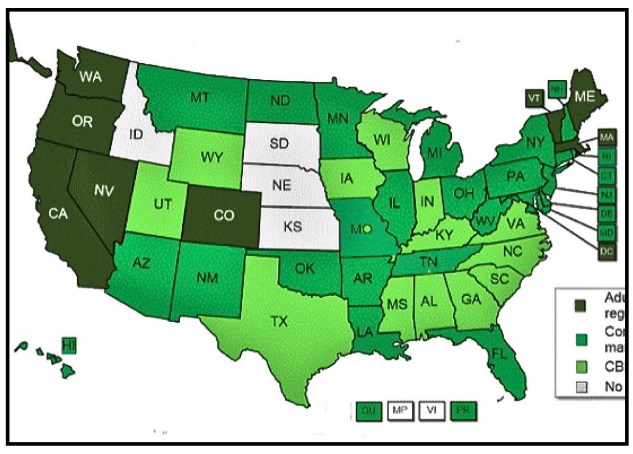
For most of my career —more than 20 years— I was an ER doc and had a small general practice. For almost the last 20 years I have been an independent doctor doing solely cannabis consultations.

You might have heard through the media about 'potdocs' who are conducting five-minute evaluations and issuing approvals. Less well known are the practioners with real expertise who are helping seriously ill patients develop treatment plans incorporating cannabis.

Since 2008 I've been president of The Society of Cannabis Clinicians, a group of physicians who meet quarterly to talk about our clinical cases and political issues arising from practicing cannabinoid medicine. The group was founded in 2000 by Tod Mikuriya, MD, who died in 2007.

Our role as doctors is to "recommend" or "approve" the use of cannabis —not to prescribe it. A prescription is an instruction to a pharmacist to provide a drug. The First Amendment protects doctors who discuss cannabis with their patients, but when the patient then obtains cannabis it's a violation of federal law. If a doctor advised the patient how to obtain it, he or she would be aiding and abetting a federal crime. So physicians are in a bind, because patients obviously want to know what brands are trustworthy and where to get them.

Although the federal government still classifies marijuana as a Schedule I drug —harmful, and with no medical benefit— public attitudes have changed. Some 70 percent of Americans live in states that have reformed their marijuana laws. Polls show that 60 percent of Americans support making marijuana legal for recreational use as we have done in California. And 90% support allowing the medical use of marijuana.



At this point we have six states that allow "adult use" of cannabis. There are 24 states that allow medical marijuana. Fifteen have limited access to CBD-rich strains which are minimally psychoactive. Only four states allow no marijuana use at all.

One of the pivotal points came in 2013 when Sanjay Gupta, CNN's chief medical officer, said to the country, "We have been terribly and systematically misled for nearly 70 years in the United States and I apologize for my role in that."

Dr. Gupta focused on a child in Colorado with Dravet Syndrome, Charlotte Figi. "Charlotte's Web" was the cannabidiol-rich strain of cannabis that her parents gave her and she did very well. Gupta's opinion was changed by what he observed —and suddenly the medical benefits of-marijuana became something people could talk about.

Some of you, I'm sure, have had questions from patients about medical cannabis.

Sanjay Gupta, M.D.
Chief of Neurosurgery
Grady Memorial Hospital,
Atlanta, Georgia

… It (marijuana) doesn't have a high potential for abuse, and there are very legitimate medical applications…. **We have been terribly and systematically misled for nearly 70 years in the United States, and I apologize for my own role in that."**

Irvin Rosenfeld and Elvy Musikka have been supplied with cannabis by the US government since the 1980s.

A rare exception to federal marijuana prohibition was the investigational new drug program begun in 1978 when a patient named Robert Randall, who was losing his eyesight to glaucoma, won the right to cultivate from a Washington, DC, judge. A year later the court instructed the federal government to supply Randall with marijuana. For the next 20 years he would get a tin of rolled cigarettes containing marijuana grown at the University of Mississippi for the National Institute on Drug Abuse (NIDA).

The program stopped enrolling patients as the AIDS crisis escalated in the early 1990s. Two survivors are still receiving tins from NIDA. But the government never investigated how they have fared. (Irvin Rosenfeld, who has a severe bone tumor disorder, has not had to use any narcotics. Glaucoma patient Elvy Musikka has not experienced further loss of vision.)

In 2014 the federal government gave Investigational New Drug status to Epidiolex, a plant extract that is 99% CBD and 1% other nonpsychoactive cannabinoids. It is made by a British company, GW Pharmaceuticals. Epidiolex is nearing FDA approval as an adjunct in the treatment of two very severe forms of epilepsy, Dravet and Lennox-Gastaut Syndromes.

[Epidiolex was approved by the FDA on June 25, 2018. On Oct. 2 the DEA placed it in Schedule V —without moving CBD from Schedule I. See story on page 10.]

I have been treating people with seizure disorders with high-THC cannabis for decades. We clinicians know that THC is a great anti-convulsant. So if we're not getting the effects we want with CBD-rich strains, we add THC to get better control. Parents of epileptic children, sharing information on the internet, also report benefit from THC and THC-acid extracts. This is an example of how cannabis consultants —and concerned citizens— are far ahead of the medical establishment in terms of understanding the range of applications and best practices.

Brief Review of Cannabis Laws

Federal: Marijuana cannot be prescribed

Controlled Substances Act, Schedule 1: Marijuana and its cannabinoid constituents, including CBD (cannabidiol), can't be prescribed, possessed, cultivated or studied without the permision of the federal government (FDA, DEA, NIA, NIH, H&HS, ONDCP).

Cannabis has been available in rare exceptions through Compassionate Investigational New Drug programs. The first, established in 1978 with glaucoma patient Robert Randall, ended in 1992 with 30 patients. In 1992 public health officials concluded "there was no scientific value to it." Three patients remain in the program; two are still receiving tins of joints from NIDA.

• 1986: FDA approves Marinol (synthetic THC) as an anti-emetic and appetite stimulant.

• 2014: Compassionate Investigational New Drug programs for Epidiolex (a 99% CBD extract) in treating two severe epilepsies.

• 2018 FDA approves Epidiolex for Dravet's and Lennox Gastaut syndromes. DEA moves Epidiolex, which is 99% CBD, to Schedule V. CBD remains on Schedule 1.

State of California:

Compassionate Use Act (CUA), 1996

By passing Proposition 215, voters legalized the medical use of marijuana. Patients may legally grow and/or possess an amount of marijuana consistent with their needs when approved by a physician.

Adult Use of Marijuana Act (AUMA), 2016

Voters passed Proposition 64 to "Control, Regulate and Tax Adult Use of Marijuana." Without changing the CUA, AUMA creates a legal right for adults 21+ to possess up to an ounce of cannabis, share and carry small amounts of cannabis and concentrates, and to grow discreet home gardens (6 plants).

The (Changing) Laws

California law changed in 1996 when voters passed the Compassionate Use Act, enabling Californians to use cannabis with the approval of a physician. The first sentence makes the law applicable to "any... illness for which marijuana provides relief."

In 2016 California passed the Adult Use of Marijuana Act, which applies to adults over age 21 —more than 29 million people.

Local jurisdictions can change the rules. There are 114 jurisdictions in the Bay Area alone. You won't know what the rules are in a given city unless you go to the internet. Here in Hayward there are no medical dispensaries and no recreational stores allowed, but you can grow plants in your garden —outdoors. The rules are all over the place.

California doctors should know about the *Ross v. Ragingwire* case. Gary Ross was a contract technician who tested positive for marijuana at a random drug test. The company, RagingWire, fired him. Ross sued to get his job back, arguing that he had used a legal medication at home and was unimpaired at work. The state Supreme Court ruled that the Compassionate Use Act did not protect patients' rights to use medical marijuana under California's Fair Employment and Housing Act.

So, in California you can lose your job —or not be hired— if you test positive for cannabinoids. California NORML is promoting a bill in the state legislature that would protect unimpaired employees. *[It failed, but will be reintroduced in 2019.]*

In any case, your patients should know not to go to work impaired and not to drive impaired.

Only the marijuana grown for NIDA can be used in clinical trials that will be approved by institutional review boards.

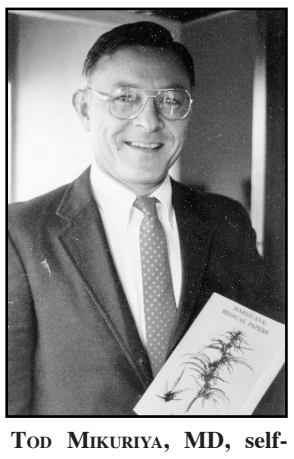
One aspect of the new law is detrimental to medical users who require heavy doses. No dose can exceed 10 milligrams, and no product can exceed 100 mgs. But many cancer patients and others are ingesting 1,000 milligrams per day. A three milliliter syringe of concentrated oil typically contains about 2,000 milligrams of cannabinoids. We are told that revised legislation will exempt patients from the dosage limits.

The State of the Evidence

The federal government contends that there aren't enough studies to justify moving marijuana off Schedule 1. That's a bit disingenuous. There has been a surge of publications since 1993, when the elements of the endocannabinoid system were fully elucidated.

A Pubmed and Google Scholar search for "cannabis and cannabinoids" turns up 3,530 citation for the years 1980-1993, and 40,500 citations since then.

If there is a dearth of randomized, placebo-controlled clinical trials it's because the federal government has obstacles to research. Only the marijuana grown for NIDA can be used in clinical trials that will be approved by institutional review boards. Except for GW Pharmaceuticals, there is no one with deep pockets trying to get plant-based cannabis medicines approved by the FDA and other regulatory authorities.



Tod Mikuriya, MD, self-published Marijuana Medical Papers in 1973

The endocannabinoid system had yet to be discovered when most of us were in medical school. The history of *Cannabis*, the plant, had been thoroughly suppressed. None of us was taught that a physician named William Brooke O'Shaughnessy published a paper describing the use of cannabis extracts by doctors in Calcutta to successfully treat epilepsy and other conditions for which Western medicine had no remedies.

The pre-prohibition medical

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Cannabis as Medicine *from previous page*

literature was recovered and republished by Tod Mikuriya in his 1973 anthology, Marijuana Medical Papers.

The cannabis plant produces cannabinoids – 21 carbon, three-ring oily molecules that are unique in nature and heavily expressed in cannabis female flowers. The predominant cannabinoids in the cannabis plant in the wild – and in cannabis-based medicines— are CBD (cannabidiol) and THC (tetrahydrocannabinol). More than 100 other cannabinoids have been identified, many of which have been shown to have medicinal effects in lab studies.

Endocannabinoids and plant cannabinoids exert similar effects when tested on lab animals: reduction of pain, body temperature, spontaneous activity, and motor control.

Endogenous ("endo-") cannabinoids are made in our bodies for sending signals from one nerve cell to another. Endocannabinoids and plant cannabinoids exert similar effects when tested on lab animals: reduction of pain, body temperature, spontaneous activity, and motor control.

The existence of cannabinoid receptors in the brain was established in 1988 by Alynn Howlett and William Devane at St. Louis University. They used a radioactively labelled synthetic cannabinoid to determine where the receptors were located.

CB1 receptors are concentrated primarily in the central nervous system but they are also found associated with nerve cells throughout the body.

These receptors, later called CB1 receptors, are concentrated in the cerebellum and basal ganglia (areas responsible for motor control); in the hippocampus (storage of short-term memory); and in the limbic system (emotional control). Cannabinoids acting through the CB1 receptors play a role in the processes of reward, cognition, and pain perception, as well as motor control.

In 1992 a second cannabinoid receptor was found in immune cells of the tonsils, thymus, bone marrow, spleen, macrophages, monocytes, and other "peripheral" areas of the body.

Also in '92, Devane and Raphael Mechoulam at Hebrew University, identified the first endogenous cannabinoid — arachidonoyl ethanolamine (AEA). They named it "anandamide" after the Sanskrit word for "bliss." Anandamide works at the CB1 and CB2 receptors. Its effects are more or less duplicated by THC.

Mechoulam's lab would find another endogenous cannabinoid, 2-AG (2-arachidonoyl glycerol), which also binds to both the CB1 and CB2 receptors.

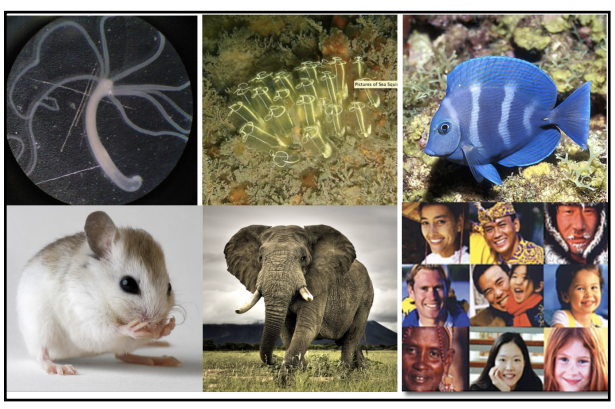
The endocannabinoids are neuromodulators, not neurotransmitters. They are produced "on demand" in the post-synaptic neuron and sent back across the synapse to tell the sending cell to fire less —or more— intensely. This process is called "retrograde signaling." *(See illustrations on page 6.)*

The "endocannabinoid system" includes the compounds from which anandamide and 2-AG are synthesized, the receptors to which they bind, the transporter molecules that bring them (and exogenous cannabinoids) from the receptor into the cell, and the enzymes that break them down

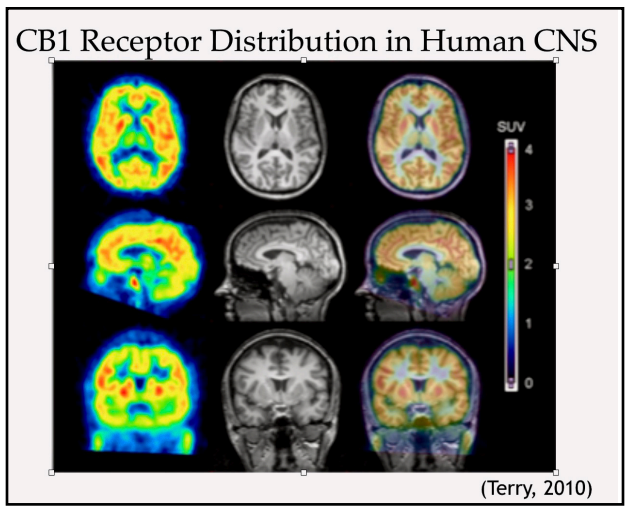
The Endocannabinoid System

• The Endocannabinoid System (ECS) is an endogenous signaling system found throughout the animal kingdom that influences multiple metabolic pathways that provide homeostasis.

• Components:
—trans-membrane endocannabinoid receptors (CB1, CB2, TRPV-1, PPAR and other targets.
—endogenous ligands, endocannabinoids
—proteins involved in synthesis, transport, and metabolism of the receptors and ligands.



The animal kingdom is designed with an endocannabinoid system.

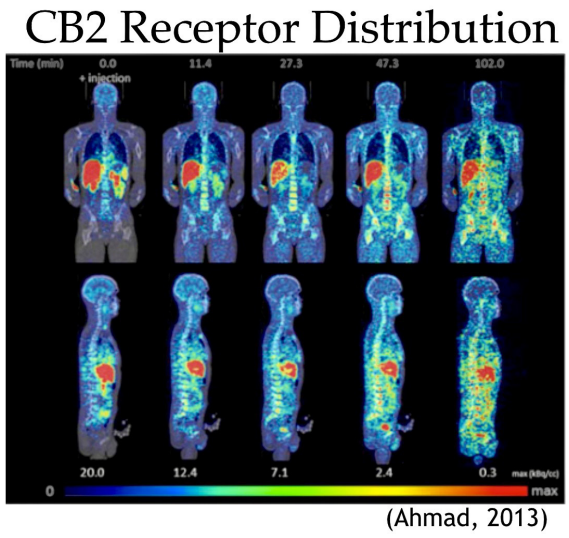


—FAAH and MAG-Lipase.

Creatures throughout the animal kingdom, down to hydras —but excepting the insects— rely on endocannabinoids to bring about homeostasis. The endocannabinoid system is a built-in system to keep us in balance.

In the above illustration, uptake of radioisotope-labelled synthetic cannabinoids reveals the location of CB1 receptors in the three brain-scan images in the column at left. Normal MRI brain images are shown in the middle column. Images in the column at right were made by a fusion of the MRI and radioisotope images.

The CB2 receptors are primarily located in the immune system. In the set of scans below, radioactively labelled THC was injected at zero minutes (*images at left)* and concentrations were measured at invervals over the course of 102 minutes. We can see CB2 receptors being activated in the liver, spleen, gut, pelvic organs, bones, lymph glands, tonsils. CB2 receptors circulate in monocytes, macrophages, T-cells and B-cells.

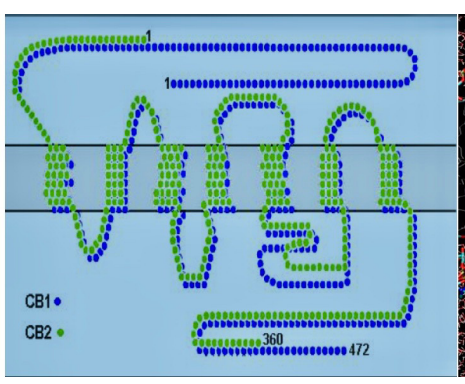


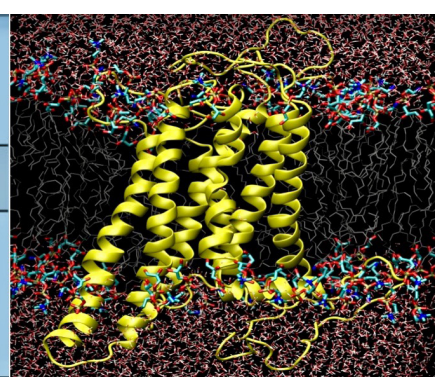
The endocannabinoid system enables us to eat, sleep, relax, and to forget. Forgetting is sometimes perceived as a negative, but ability to extinguish or diminish painful memories and fear is crucial to coping with post-traumatic stress and other disorders.

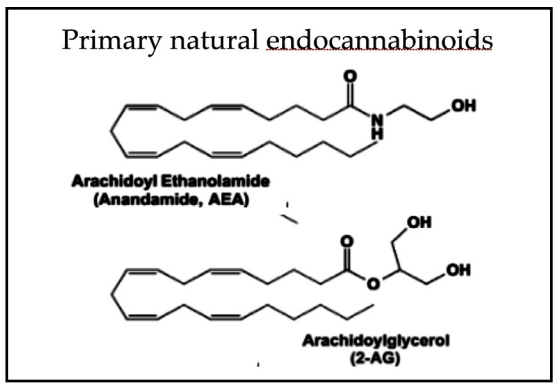
The endocannabinoid system also plays a role in cytoprotection, neuroprotection, immunomodulation, metabolic regulation, neural plasticity, embryological development and cancer control.

The US Department of Health & Human Services recognized the protective role when it applied for a patent on "Cannabinoids as Antioxidants and Neuroprotectants" in 1999. It was granted in 2003. Investigators at NIH laboratories found that when stroke was induced in test animals (by occluding arteries to the brain), animals given a simultaneous infusion of cannabinoids had a greatly reduced area of the brain affected by the stroke. Hence, this unique and powerful cannabinoid role as a neuroprotectant was discovered and patented.

The CB1 and CB2 receptors, are seven-transmembrane G-protein-coupled receptors, as shown graphically below. On the left, amino acid sequences are matched between CB1 (blue dots) and CB2 (green dots), with the smaller, mobile CB2 receptor represented as a 360 amino-acid sequence, whereas the CB1 receptor is a 472 amino-acid long sequence. These receptors are made inside the cell, migrate to the cell membrane represented by the dark zone, where they function as a pocket or receptor ready for







activation by the natural cannabinoids. THC fits into the same receptor pocket where it augments and mimics the natural receptor activation.

The computer-generated image is a guess at what the CB1 receptor looks like. THC fits into the same receptor and activates it more or less in the same way as anandamide.

There are other compounds in the body that fit into the , cannabinoid receptors, but suffice it to say: Anandamide is the principal ligand for the CB1 receptor and 2-AG is the primary endogenous ligand for the CB2 receptors.

Anandamide (AEA)

• Primary endogenous ligand at CB1receptor.
—Weaker CB2 ligand
—Spinal cord (pain cessation)
—Hippocampus (short-term memory)
—Hypothalamus (pleasure associated with food)
—Limbic System (response to stressors)
—Nucleus Accumbens (reward associated with food)
—Basal Ganglia (sleep onset)
—Cortex (sensation and response to stressors)
Degraded by Fatty Acid Amide Hydrolase (FAAH)

2-AG

• Primary endogenous ligand of the CB2 receptor.
—High levels in the brain
—Full agonist of CB1 and CB2 receptors.
—Modulates spinal cord pain transmission
• Suppresses immune response
—Decreases mast cell activation
• Protective role in nervous system
—Spinal cord injury patients with higher levels of 2-AG had better outcomes
• Hydrolyzed by Mono-AcylGlycerol Lipase (MAGL)

That's the story: THC (and other plant cannabinoids) fit into the receptor and activate it, with the effect of bringing the organism back into balance or homeostasis.

Cannabis is uniquely non-toxic, safe, and effective. An overdose might make you sleep for a day, but it's not going to kill you. You can kill yourself with too much water, salt, aspirin, or alcohol, you name it. But you can't kill yourself with cannabinoids.

On the page at right is an image of the plant cannabinoids THC and CBD, along with THCV. The difference between THC and CBD is slight —move a hydrogen atom from the methyl group in THC over to the oxygen and you've got CBD. The shape of the molecule is changed just enough so that it's not a ligand activating the CB1 receptor. It fits into the receptor, but doesn't activate it. So its net effect is to soften the effect of THC and make it much less psychoactive.

THCV has a three-carbon side-chain as opposed to the five-carbon chain of THC. (All the varins are characterized by three-carbon side-chains.) THCV also gets into the CB1 receptor, but because of the short tail, it doesn't turn the receptor on.

Cannabis cultivators have developed many varieties whose cannabinoid content is around 25% of the flowers' dry weight. It seems remarkable that a bud can be one quarter ligand (whose function is activating receptors).

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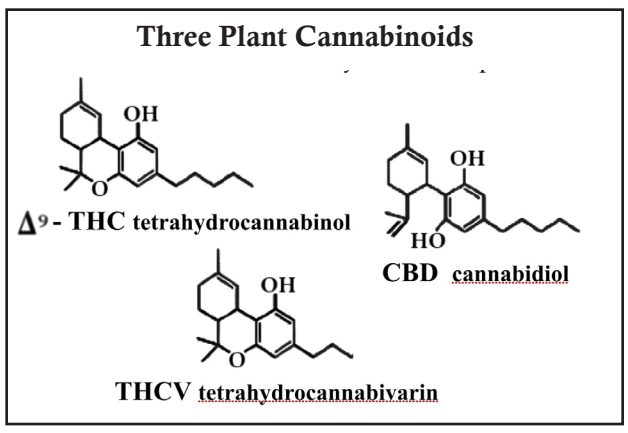
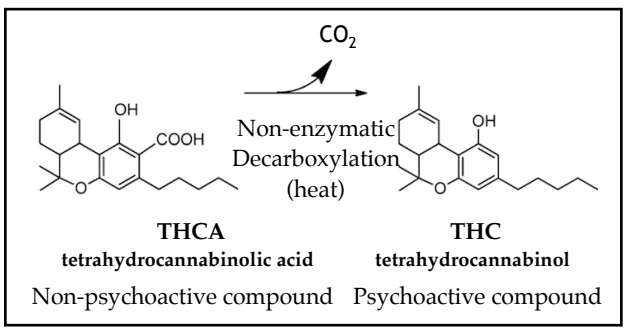
Cannabis as Medicine *from previous page*



You may hear references to THC being "activated." In a live marijuana plant, THC is in the acid form —as are almost all the cannabinoids. THCA is not psychoactive. So if you take a bud fresh off a marijuana plant and blend it into a smoothie and ingest it, you're not going to get high.

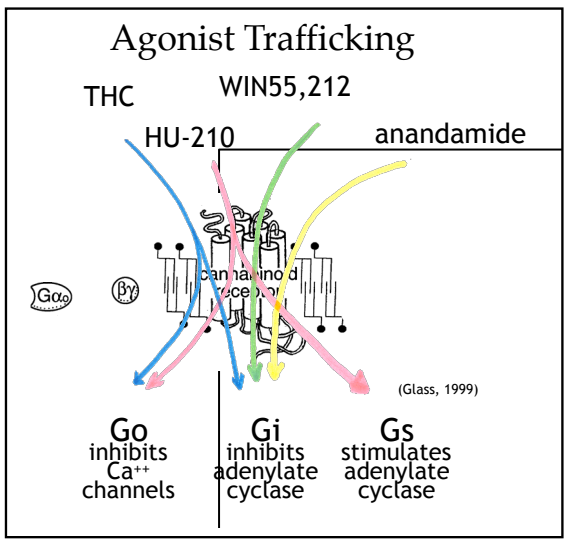


But the same bud, after it's been dried and decarboxylated with time and heat, will have had its THCA converted to THC, which will get you high when ingested. So a dried bud will get you high, but a green bud will not. Clinicians take advantage of this when we recommend medicines prepared fresh in order to avoid psychoactivity.

The mechanism by which THC and other agonists activate the CB1 receptor is complex, involving not just two receptors and two ligands, but multiple receptors and several minor cannabinoids. For example endocannabinoids activate TRPV1 receptors —also known as capsaicin receptors— which are involved in the sensing of heat.

Cannabinoids can also activate PPAR receptors on the nuclear surface inside the cell. PPAR activation regulates the expression of genes.

Given different agonists, acting at different receptors, resulting in different activities, it is not surprisng that the cannabinoids exert a multitude of effects. Many of the pharmacological actions we can expect from cannabinoid activation have been elucidated in the 20 years that I have been a cannabis specialist. They are beneficial —promoting homeostasis and well-being.



AGONIST TRAFFICKING is complex. THC (blue arrows) activates the receptor to inhibit adenylate cyclase and calcium channels. Anandamide (yellow) only inhibits adenylatecyclase. WIN55,212 and HU-210, synthetics being used in research, produce different results.

Pharmacologic effects of cannabinoids

Analgesic	Antiparasitic	Anti-diabetic
Antispasmodic	Anti-inflammatory	Bone stimulant
Anti-emetic	Immunosuppressive	Antipsychotic
Neuroprotectant	Anti host vs graft	Anxiolytic
Anti-cancer	Dermatologic	Antidepressant
• Antiproliferative	• Anti-psoriatic	Vasorelaxant
• Anti-metastatic	•Anti-eczema	Anti-ischemic
• Anti-angiogenesis	•Anti-keratotic	Anticonvulsant
Antioxidant	• Anti-pruritic	Induces sleep
Antibacterial	• UV light reducing	•Appetite
(vs MRSA!)	Bronchodilatory	Reduces GI motility
Antifungal	Anti-glaucoma	• GI secretions

Conditions often seen in clinical practice

- Pain (acute, chornic inflammatory, neuropathic)
- Mental disorders (all kinds)
- Cancers
- Gastrointestinal disorders
- Insomnia
- Migraine headaches
- Addictions (including Alcoholism)
- Spastic disorders
- Autoimmune disorders and host vs. graft reactions
- Neurodegenerative disorders
- Glaucoma
- Skin diseases
- Epilepsy, Autism, Tourette's, ADD, Dystonia, Dementia

In my practice I have seen people benefitting from each of the effects listed in column at right. About 50 percent of my patients use cannabis to treat pain. About 30 percent are treating mental health problems such as depression, anxiety, post-traumatic stress, and attention deficit disorder.

A benefit worth noting is harm reduction —using cannabis to cut down or eliminate use of drugs with adverse effects, such as alcohol. I would not exclude somebody because they have problems with addiction. Cannabinoids are valuable drugs to help people get off other drugs.

I use ICD-10 codes in my practice. For classification purposes I've created a couple of ICD-10 codes for use in tracking patients. Harm reduction is: 304.99 and polypharmacy, a common problem in the elderly: 977.9. At the bottom of this page is a complete list of the conditions for which I have approved treatment with cannabis.

Cannabis clinicians have posited that certain conditions are caused by a malfunctioning endocannabinoid system. Just one substitution of one of these amino acids *(blue or green dots on page 4 illustration)* results in a measurable change in the function of the receptor.

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ICD-10 Codes

Conditions for which the author has approved treatment with cannabis.

Achalasia K22.0
Acoustic Neuroma, benign D33.3
Acquired Hypothyroidism E03.9
Actinic keratosis L57.0
ADD w/o hyperactivity F90.0
ADD w hyperactivity F90.9
AIDS related illness B20
Alcohol abuse F10.1
Alcohol dependence F10.20
Allergic rhinitis J309
Alzheimer's dementia G30.9
Amyloidosis, unspecified E85.9
Amyotrophic lateral sclerosis G12.21
Ankylosing spondylitis M45.0
Anorexia R08.02
Anorexia nervosa F50.0
Anorexia, wasting syndrome R63.0
Anoxic brain injury G93.1
Anxiety F41.9
Anxiety with depression F41.8
Arthritis, rheumatoid M05.10
Arthritis, psoriatic, unspecified L40.50
Arthopathies, unspecified M02.80
Asthma J44.9
Autism disorder F84.0
Autoimmune, disease, undifferentiated E31.0
Autoimmune hepatitis K75.4
Autoimmune thyroiditis E06.3
Barrett's esophagus K22.7
Benign prostatic hypertrophy N40.0
Bipolar disorder, unspecified F31.9
Borderline Personality Disease F60.3
Brain trauma, unspecified S09.90
Cachexia R64

Cancer
- Adrenal C74
- Anus, unspecified C21.0
- Basal cell carcinoma, unspecified C44.00
- Biliary tract, unspecified C24.9
- Bladder, unspecified C67.9
- Bone, unspecified C41.9
- Brain unspecified C71.9
- Breast, female, unspecified C50.91
- Breast, male, unspecified C50.92
- Cervical, unspecified C53.9
- CholangiocarcinomaC22.1
- Colon, unspecified C18.9
- Duodenum C17.0
- Endocrine, unspecified 194.9
- Esophagus C15.9
- Gallbladder C23
- Larynx, unspecified C32.9
- Leukemia, lymphoidC91.10
- Leukemia, myeloid C92.10
- Lip, unspecified C00.9
- Liver, hepatocellularC22.0
- Lung, unspecified C34.9
- Lymphoma, Hodgkins C81
- Lymphoma, MALT C88.4
- Lymphoma, NonHodgkins C82
- Melanoma, unspecified C43.9
- Meningioma D32.9
- Mesothelioma, unspecified C45.9
- Mouth, unspecified C06.9
- Multiple myeloma C90.0
- Myelofibrosis D75.81
- Nasopharynx C11
- Neuroblastoma C74.90
- Neuroendocrine C7A
- Oropharynx C10.9
- Ovary C56.9
- Pancreas C25.9
- Parathyroid C75.0
- Parotid C07
- Pharynx C14.0
- Pituitary adenoma D35.2
- Prostate C61
- Rectum C20
- Renal C64.9
- Sarcoma unspecifiedC49.9
- Small intestine C17.9
- Stomach C15.9
- Squamous, HNSCC C10.9
- Squamous carcinoma, in situ D04.9
- Testicular C62.90
- Thymus C37
- Thyroid C73
- Throat C32.9
- Tongue, unspecified C01.9
- Tonsil C09.9
- Ureter, unspecified C66.9
- Urothelial, unspecified C67.9)
- Urethra C68.0
- Uterus C54.1
- Wilm's / Unspecified Urinary 189.9

Carpal tunnel syndrome G56.00
Celiac disease K90.0
Cerebral palsy, unspecified G80.9
Cerebrovascular insufficiency, acute I67.81
Cervical neck pain M54.2
Charcot Marie Tooth Disease M14.60
Chronic Atrial Fibrillation I48.2
Chronic pain syndrome G89,4
Chronic fatigue syndrome R53.82
Colitis, unspecified K51.919
Complex Regional Pain Syndrome G90.59
Constipation, unspecified K59.00
COPD J44.9
Coronary Artery Disease CAD I25
Creutzfeld,Jacob Disease A81.00
Crohn's disease, w/o comp K50.00
Crohn's disease, with complications K50.01
Cubital Tunnel Syndrome G56.20
Cyclical Vomiting Syndrome G43.A0
Deafness, complete H91.90
Depression, major F32.9
Depression, recurrent F33.9
Depression, situational F43.21
Diabetes mellitus, type 2 E11.9
Diabetes mellitus, type 1 E10.9
Diarrhea, unspecified R19.7
Diverticulosis of colon K57.30
Doulourex, Tic G50
Duodenal ulcer K26.9
Dumping syndrome K91.1
Dupuytren's contractions M72.0
Dysmenorrhea, unspecified N94.6
Dysthymic disorder F34.1
Dystonia, unspecified G24.9
Eczema, unspecified L20.9
Electric feet syndrome E53.8
Endometriosis N80.9
Epilepsy, grand mal G40.909
Epilepsy, partial complex G40.209
Epilepsy, petit mal, unspecified G40.9
Erythromelalgia I73.81
Familial adenomatous polyp D12.6
Fibromyalgia M79.7
Gallstones, colic w/o K80.2
Gastric ulcers K25.9
Gastritis, w/o bleeding K29.00
Gastroparesis K31.84
GERD, with esophagitis K21.0
GERD, w/o esophagitis K21.9
Glaucoma H40.9
Gout, unspecified M10.00
Grave's disease E05.00
Guillain Barre Syndrome G61.0
Hailey Hailey Disease Q82.8
Harm reduction 304.99*
Hashimoto's thyroiditis E06.3
Headache, cervicogenic R51
Hypertension I10
Hepatic insufficiency K72.90
Hyperacusis H93.23)
Hypothyroidism, unspecified E03.9
Inflammatory bowel disease, unspecified K75.9
Insomnia F51.04
Interstitial cystitis N30.10
Irritable bowel syndrome K58.9
Juvenile rheumatoid Arthritis M08.011
Kidney hemodialysis Z99.2
Kidney failure, unspecified N19
Lactose intolerance, unspecified E73.0
Lennox Gastaut syndrome G40.811
Liver transplant status Z94.4
Lower back pain, unspecified M54.5
Lupus erythematosis M32.10
Lyme disease A69.20
Macular degeneration, unspec H35.30
Menopausal, symptomatic N95.1
Migraine G43.9
Multifocal polyneuropathy G61.82
Multiple sclerosis G35
Muscle spasms M62.838
Myasthenia gravis w/o acute G70.00
Myasthenia gravis w acute G70.01
Nausea R11.0
Neurofibromatosis Type1 Q85.01
Neurofibromatosis Type2 Q85.02
Neurologic disease, unspecified R29.818
Neuromyelitis optica G36.0
Neuropathy peripheral, idiopathic G60.9
Obesity, unspecified E66.9
Obesity, morbid E66.01
Opioid dependence F11.20
Optic neuritis, unspecified H46.9

Osteoarthritis, primary M19.0
- Ankle and Foot M19.079
- Elbow, OA, unspecified M19.029
- Hand, OA, unspecified M19.049
- Hip OA, unspecified M16.9
- Knee OA, unspecified M17.9
- Shoulder, OA, unspecified M19.90
- Thumb, OA M18.10
- Wrist, OA, unspecified M18.039
- Polyosteoarthropathy, unspec M15.9

Osteoarthritis, post-traumatic arthropathy
- Ankle and Foot, unspecified M19.179
- Elbow, unspecified M19.129
- Hand, unspecified M19.149
- Hip, unspecified M16.50
- Knee, unspecified M17.30
- Shoulder, unspecified M12.519
- Thumb, unspecified M18.30
- Unspecified site M19.92
- Wrist, unspecified M19.139

Osteopenia M85.80
Pancreas Transplant Z94.83
Pancreatitis K85.9
Panic disorder F41.0
Paraplegia, unspecified G82.20
Parkinson's disease G20
Peptic Ulcer disease K27.9
Pelvic vaginal pain, chronic R10.2
Polymyalgia rheumatic M35.3
Polypharmacy 977.9*
Post laminectomy Syndrome M96.1
Post herpetic neuralgia B02.22
Post polio syndrome G14
Prostate enlargement N40.1
Primary Sclerosing Cholangiitis K83.0
Pruritis, unspecified L29.9
Psoriasis, unspecified L50.9
Psoriatic arthropathy L50.59
Psychosis, unspecified F29
PTSD, unspecified F43.10
Pulmonary fibrosis J84.10
Quadriplegia, C5-7 complete G82.53
Quadriplegia, C5-7 incomplete G82.54
Quadriplegia, C1-4 complete G82.51
Quadriplegia, C1-4 incomplete G82.52
Raynaud's syndrome I73.00
Renal Failure N19
Restless legs syndrome G25.81
Rheumatoid arthritis, unspecified M06.9
Rheumatic disease, unspecified M02.89
Rotator Cuff Syndrome M75.100
Sarcoidosis, unspecified D86.9
Schizoaffective, depressed F25.1
Schizophrenia, unspecified F20.9
Scleroderma, unspecified M34.0
Scoliosis M41
Sleep Apnea G47.30
Sinusitis, chronic J32.9
Spasms M62.838
Sjogren's (Sicca) syndrome M35.00
Tarsal tunnel syndrome G57.50
Thoracic back pain M54.6
Thoracic Outlet syndrome G54.0
Thrombocythemia, essential D47.3
Tinnitus, unspecified H93.19
TMJ Syndrome, unspecified M26.60
Tobacco depend/ unspecified F17.20
Torticollis M43.6
Tourette's syndrome F95.2
Tremors, essential G25.0
Tremors, unspecified R25.1
Trigeminal neuralgia G50.0
Ulcerative colitis K51.80
Ureteral calculus N20.1
Urticaria, unspecified L50.9
Uveitis, unspecified H20.0
Vater syndrome Q87.2
Vertigo, benign, unspecified H81.10
Viral Hepatitis B, chronic B19.10
Viral Hepatitis C, chronic B19.20
Vomiting, unspecified R11.10
Von Hippel Lindau Disease Q85.8

* Personal use only, not ICD-10

Cannabis as Medicine *from previous page*

The altered receptor doesn't work the same —doesn't work as well. This gives rise to our understanding of clinical endocannabinoid deficiency diseases, in which people with similar genetic patterns of their cannabinoid receptor genes have similar diseases such as migraine, depression, Parkinson's disease, irritable bowel syndrome, fibromyalgia, seizure disorders, and many others.

Endocannabinoid systems don't all work the same

Genetic variability in the endocannabinoid receptors, or polymorphisms, affect the functionality of the ECS... resulting in a spectrum of clinical endocannabinoid deficiency syndromes that may be implicated in:

- Schizophrenia subtypes (Ujike, 2002)
- Migraine headache w/ nausea (Juhasz et al., 2016)
- Multiple sclerosis (De Filippo 2008)
- Huntington's disease (Allen 2009, Van Laere, 2010)
- Parkinson's disease (Pisani 2010)
- Irritable bowel syndrome (McPartland, 2014)
- "Failure to Thrive" Syndrome, NOFTT, (Fride, 2002)
- Anorexia (Gerard, 2011)
- Chronic motion sickness (Chouker 2010)
- Fibromyalgia (Dunnett, 2007)
- Menstrual symptoms (Dunnett, 2007)
- Seizure disorders
- Happiness (Matsunaga, 2014)
- Depression, melancholic, (Hill 2005)
- Alcohol Dependence, (Schmidt, 2002)
- Obesity, (Jaeger, 2008)
- ADHD and PTSD (Lu, 2008)
- Serum lipid profiles (de Luis et al., 2016)
- Response to a Mediterranean hypocaloric diet (de Luis et al, 2016)
- Risk of cyclic vomiting syndrome (Wasilewski et al., 2017)
- Marijuana demand (Aston et al., 2017)•
- Mood disorders, depression and happiness

Retrograde Signaling

Cannabinoids diffuse from post-synaptic to pre-synaptic cells to modulate the rate of neurotransmitter release *(as illustrated in box at right)*. Whether the neurotransmitter is adrenaline, noradrenaline, dopamine, serotonin, acetylcholine... excitatory like glutamate or inhibitory like GABA... cannabinoids modulate traffic at the synapse.

Understanding that cannabinoids are involved in a multitude of metabolic processes explains the wide range of medical applications we have observed.

In 1996 after California voters legalized medical use, Tod Mikuriya was ridiculed by federal officials for authorizing patients to use marijuana to treat any condition for which it provided relief. The Drug Czar said Mikuriya was practicing "Cheech and Chong medicine."

Understanding that cannabinoids are involved in a multitude of metabolic processes explains the wide range of medical applications we have observed.

By 2013, two researchers held in highest esteem by the biomedical establishment, Pal Pacher and George Kunos, published a paper, "Modulating the eCB system in health and disease: successes and failures," Apr 2013, NIH, NIAAA. In the abstract they say that "modulating endocannabinoid activity may have therapeutic potential in almost all diseases affecting humans, including obesity/metabolic syndrome, diabetes and diabetic complications, neurodegenerative, inflammatory, cardiovascular, liver, gastrointestinal, skin diseases, pain, psychiatric disorders, cachexia, cancer, chemotherapy induced nausea and vomiting among many others."

In effect these researchers are inviting the pharmaceutical industry to bring to the public the next generation of cannabinoid medicines.

Cannabis clinicians on the other hand are using the plant in its various forms to meet our patients' needs today.

What gives us the confidence to go ahead is the safety profile of cannabis.

Risks posed by cannabis

What gives us the confidence to go ahead is the safety profile of cannabis. My feeling as a practitioner with many years' experience is: cannabis essentially does no harm. Now and then somebody will say, "It's not for me.' That happens and it is to be expected and respected.

About the worst thing that can happen is an overdose —with unpleasant lethargy, sometimes vomiting, and dysphoria that can last up to eight hours. Some people find the experience so unpleasant that they swear off cannabis: "I'm not going there again." But you have not been harmed. If you're lucky you can sleep it off.

The way patients who need large cannabinoid doses can avoid overdosing is by starting with subclinical doses and building up slowly. As people get used to it they can use more, and eventually you build up to the therapeutic levels.

For many years NIDA warned that smoking cannabis causes lung cancer. Much of the evidence had been provided by UCLA pulmonologist Donald Tashkin, who showed that cannabis smoke contained slightly higher levels of benzene and other known carcinogens than cigarette smoke. Tashkin also published photomicrographs of bronchial tissue damaged by cannabis smoke.

In 2005 Tashkin reported the results of a study comparing more than 1,200 Los Angeles residents who had cancers of the lung and upper airways with controls of corresponding age, gender and neighborhood. Analyzing everyone's history of marijuana, tobacco, alcohol and other drug use, as well as occupational exposure, family history and other risk factors, Tashkin concluded that marijuana use does *not* cause these cancers. His data even suggested a slight protective effect.

It has since been determined that cells damaged by heat and tar from cannabis will undergo apoptosis —"commit suicide"— instead of metastasizing and causing cancer. This is very likely due to the cannabinoids being there in a protective role..

Tashkin subsequently reported that cannabis use does not cause or exacerbate COPD and emphysema. "There is no evidence of clinically significant alterations in pulmonary function tests," he concluded.

Smoking causes irritation, inflammation, edema and increased mucous production in the respiratory tract mucosa. But there is *no* evidence of "clinically significant alterations in pulmonary function tests in heavy chronic cannabis smokers... There is no evidence of an increase in the incidence of cancers in the lungs, trachea, larynx, pharynx, and esophagus even in the heavy smokers."

Vaporizers effectively deliver cannabinoids without the smoke, so there are no tars, it's less irritating.

Question: "What do you tell a patient who already has COPD?"

Hergenrather: I would advise using a non-smoked method. Vaporizers effectively deliver cannabinoids without the smoke, so there are no tars, it's less irritating. California NORML asked the federal government for permission to study the effects of vaporized versus smoked cannabis, but they were denied.

Often I'll advise using cannabis as a tincture or an oil, an ingested product.

Cannabinoids are bronchodilators. I do have asthmatic patients who are using smoked cannabis. I might suggest that they vaporize but they're going to do what they're going to do. (*Knowing laughter from MDs in the audience.)*

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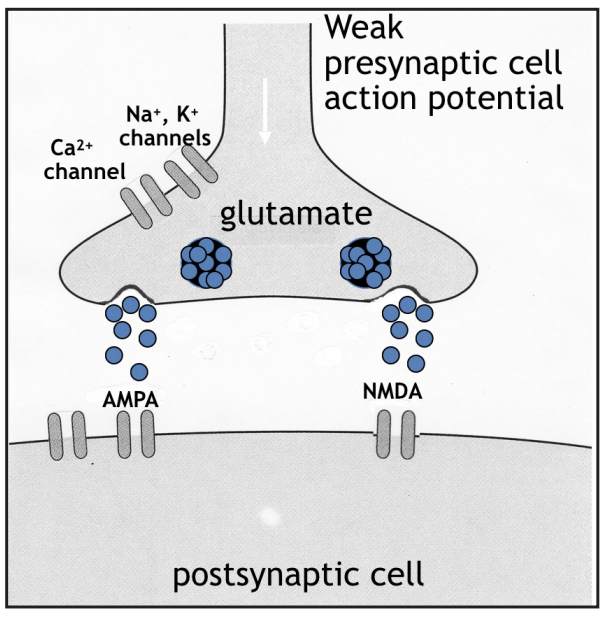
Risks of smoked cannabis on respiratory tract

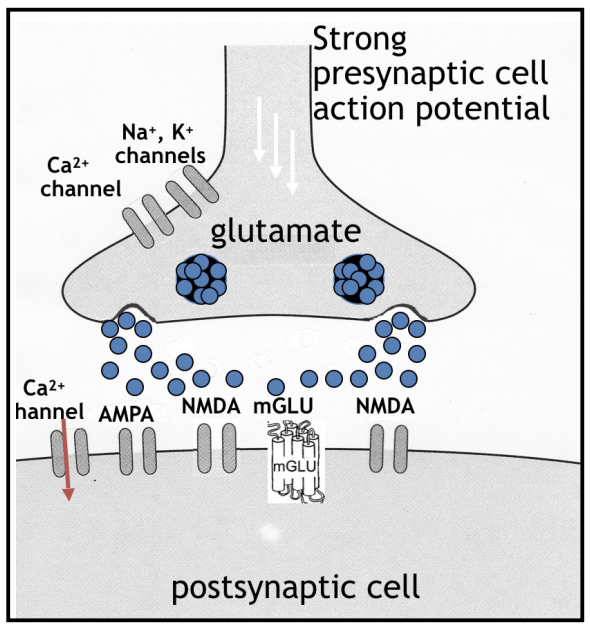
Donald P. Tashkin, MD, Professor Emeritus of pulmonary medicine at UCLA, was supported by NIDA for 45 years in efforts to find harm in smoking cannabis. Tashkin ultimately found:

- Smoking causes irritation, inflammation, edema, and increased mucous production in the respiratory tract mucosa.
- There is no evidence of clinically significant alterations in pulmonary function studies. No COPD or emphysema.
- There is no substantive evidence of an increase in the incidence of cancers in the lungs, trachea, larynx, pharynx, or esophagus, even in heavy cannabis smokers.

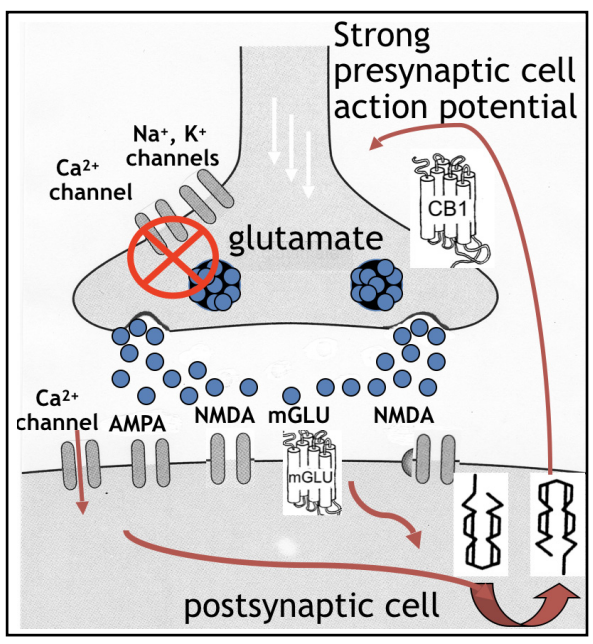
Retrograde Signaling —How cannabinoids promote homeostasis



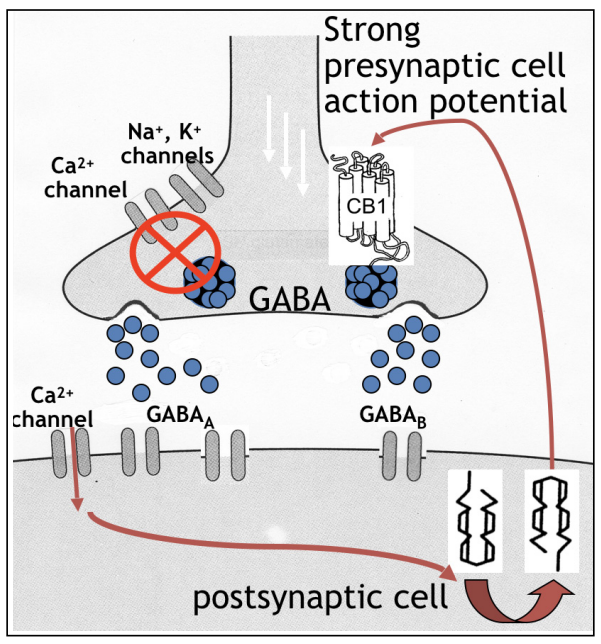
Weak action potential from depolarized neuron arrives at presynaptic axon and opens voltage-gated calcium channels... Ca^{2+} influx releases glutamate vesicles. Glutamate, an excitatory neurotransmitter, diffuses across the synaptic cleft to activate receptors in the postsynaptic cell. NMDA and AMPA are names of receptors on post-synaptic cell.



Strong stimulus of presynaptic cell increases glutamate release, which upregulates other glutamate receptors in the post-synaptic cell... Upregulated glutamate receptors open Ca^{2+} channels in the post-synaptic cell. Excitation is suppressed... Graphics are based on Wilson and Nicholl, 2002.



Suppression of excitation by glutamate: Ca^{2+} influx into post-synaptic cell stimulates synthesis and release of 2-AG (sketched molecules)... 2-AG diffuses retrograde to the presynaptic cell, where it activates CB1 receptors, which close pre-synaptic Ca^{2+} channels and stop production and release of glutamate.



Suppression of inhibition by the neurotransmitter GABA: Ca^{2+} influx into post-synaptic cell stimulates the synthesis and release of 2-AG... 2-AG diffuses retrograde to presynaptic CB1, which closes pre-synaptic Ca^{2+} channels and stops vesicle release of GABA

Cannabis as Medicine *from previous page*

Children have a variety of conditions that should be treated with cannabinoids. Dosing cannabis in children is actually easier than in adults. For seizure disorders children can use very high doses – up to 25 milligrams of CBD per kilogram of body weight per day in 2 or 3 divided doses. I seldom go higher in CBD than 5 mg/kg/day before adding some THCA or THC because it is a more efficacious medicine.

Harm is the recurring theme from most federally funded cannabis research. Damage to the brain, especially when cannabis is used by adolescents, has been widely reported in the media, but the studies don't confirm it.

Short-term memory impairment has been observed after heavy chronic recreational cannabis usage but virtually disappears after a few weeks of abstinence, according to a study by Pope et al in 2001. More recent studies are similarly encouraging with regards to the reversibility of any cannabis-associated cognitive sequelae.

In an often quoted paper by Gilman, 2014, adolescent cannabis smoking was shown to be the cause of shape and volume changes in gray matter structures in the brain, an ominous finding, though without functional evidence of harm. Recognizing that the cannabis smoking cohort was drinking more alcohol than the controls, the research was expanded and better controlled a year later by Weiland, et al. 2015. When controlling for alcohol there were no differences seen in the gray matter structures of cannabis smoking adolescents compared with their controls.

Changes associated with cannabis usage are apparently reversible with either abstinence or administration of cannabidiol.

In subsequent studies hippocampal volume changes in the youth using cannabis have been studied. No gray matter changes were observed in heavy cannabis users by Koenders et al (2016). Changes associated with cannabis usage are apparently reversible with either abstinence or administration of cannabidiol (Yucel et al, 2016).

Lower grade-point averages associated with persistent cannabis usage in high school pupils lost statistical significance when controlling for concomitant alcohol and tobacco usage (Meier et al, 2015). Cannabis usage alone was not found responsible for IQ or performance differences in teens compared to cigarette smoking or other confounds (Mokrysz et al, 2016).

The NIDA director often cites a surmised neurotoxic effect of cannabis on the developing brain that permanently lowers IQ. This small study failed to account for important confounding factors, including socioeconomic status, according to a University of Oxford review. Again and again the assertions of harm misinform and frighten physicians and the public who are weighing whether cannabis is a safe and effective medicine.

I am not seeing problems. The kids I'm treating are going off to school and not showing impairment. They're showing improvement.

I am not seeing problems. The kids I'm treating are going off to school and not showing impairment. They're showing improvement. Whether it's ADD, or cancer, or seizure disorders, they all seem to be thriving in school.

An association between cannabis use and psychosis is widely alleged, but there is nothing in the literature that shows causality. A UK study showed that cannabis use increased fourfold between 1972 and 2002, increasing 18-fold among the under-18-year- old population (Hickman et al., 2007). But incidence and prevalence of schizophrenia and psychoses were either stable or declining during the decade 1996-2005.

Though it was not in my practice I know of one young woman who had an acute psychotic reaction to a large oral dose of high THC cannabis. She was treated in a hospital setting where she fully recovered within a week. The mental aberration resolved on its own and has not recurred. Throughout my practice this is the only acute psychosis I've seen, so, yes it may occur but it is an exceedingly rare event.

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Health Concerns —Assertions and Evidence

- Pulmonary harm
- Brain development harm
- Addiction
- Psychosis and schizophrenia
- Impairment (driving, memory loss)
- Fetal and/or neonatal harm

Actual Adverse Effects

- Dry mucous membranes, injected conjunctiva, unsteady gait, short-term memory loss.
- Irritant to airway when inhhaled —smoke > cough and mucus > bronchitis
- Syncope and/or fall risk, especially with high dose "dabs" and oral overdose.
- Anxiety and panic in the neophyte or THC sensitive
- Dysphoria > paranoia > Rarely, acute psychosis
- Hyperemis syndrome —uncommon and rapidly reversible.
- Drug-drug interaction: CYP450 and 3A families; high dose CBD
- Contaminants —Pesticides, fungicides, toxic metals, other.

Marijuana and Maternity Studies

1. Maternal Marijuana Use and Adverse Neonatal Outcomes: A Systematic Review and Meta-analysis

CONCLUSIONS: Maternal marijuana use during pregnancy is not an independent risk factor for adverse neonatal outcomes after adjusting for confounding factors. Thus, the association between maternal marijuana use and adverse outcomes appears attributable to concomitant tobacco use and other confounding factors. (OSTET GYNECOL Vol 128, p 713-723.)

2. The impact of cocaine and marijuana use on low birth weight and preterm birth: A multicenter study

CONCLUSIONS: In this population of women receiving prenatal care, cocaine use was uncommon and was not related to most adverse birth outcomes. Marijuana use was relatively common and was not related to adverse pregnancy outcomes. Tobacco is still the most commonly abused drug during pregnancy, 15% of all cases of low birth weight in this study could have been prevented if women did not smoke cigarettes during pregnancy. (AM J OBSTET GYNECOL 1995;172:19-27.)

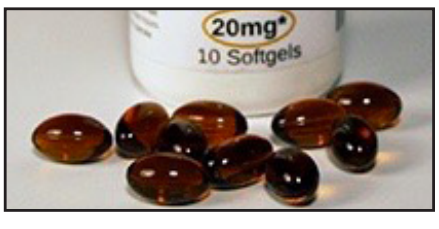
CONCLUSIONS: Maternal marijuana use during pregnancy is not an independent risk factor for adverse neonatal outcomes after adjusting for confounding factors. Thus, the association between maternal marijuana use and adverse outcomes appears attributable to concomitant tobacco use and other confounding factors. (OSTET GYNECOL Vol 128, p 713-723.)

3. Prenatal Marijuana Exposure and Neonatal Outcomes in Jamaica: An Ethnographic Study, Melanie C. Dreher, PhD, et al., Pediatrics, February 1994, Volume 93, Number 2, pp. 254-260.

CONCLUSIONS: The absence of any differences between the exposed and nonexposed groups in the early neonatal period suggest that the better scores of exposed neonates at 1 month are traceable to the cultural positioning and social and economic characteristics of mothers using marijuana that select for the use of marijuana but also promote neonatal development.

Although no positive or negative neurobehavioral effects of prenatal exposure were found at 3 days of life using the Brazelton examination, there were significant differences between the exposed and nonexposed neonates at the end of the first month. Comparing the two groups, the neonates of mothers who used marijuana showed better physiological stability at 1 month and required less examiner facilitation to reach an organized state and become available for social stimulation. The heavily exposed neonates were more socially responsive and were more

Diverse Delivery Systems



INGESTION METHODS ARE DIVERSE. At left: harvested female flowers, papers for rolling cigarettes, a Volcano vaporizer, a vape pen. In center: a balm for topical application, suppositories for rectal or vaginal use, gel caps to be swallowed. At right, kief (trichomes from the flowers), chocolate-covered blueberries, Sativex (to be sprayed under the tongue) and concentrated cannabis oil in a syringe (extruded into olive oil to show consistency). Cannabis clinicians recommend using the plant and medicinal products made from it.

Cannabis as Medicine *from previous page*

To complete the psychosis / schizophrenia issue, I would point out that association and causality of cannabis use and schizophrenia will continue to be debated in the future. I think it is compelling to recognize that there is no epidemiologic evidence that shows a significant risk for cannabis causing schizophrenia. What association there is may be attributed to individuals destined to become schizophrenic finding cannabis very comforting for their anxious and troubled mentation.

Question: As a parent of a teen: Is there any issue with motivation?

Hergenrather: It's a fair question. It depends on your perspective. I think we have to be careful to not blame the ills of our society on marijuana. The biggest problem I've seen is in kids who are under-parented. These are often kids with a lot of anxiety. Often they're living in homes without any parents.

In a healthy household, I'm feeling confident that we're doing no harm by approving cannabis use. Kids will experiment. It might not look pretty. But if it came to injected drugs or alcohol or tobacco or amphetamines or cocaine or any other number of drugs, I would much rather have them experimenting with cannabis.

Question: What about cannabis being a gateway drug?

Hergenrather: The patients I work with, now numbering more than 3,000, tend to laugh about that. If they try marijuana and like it, they stick with it as their drug of choice. Most cannabis users have no interest in other drugs. I think this idea has been overblown.

NIDA continues to portray cannabis as addictive. A cannabis dependency syndrome has been postulated with an often quoted incidence of nine percent of "ever" cannabis users becoming dependent at some point (Budney et al 2004).

This figure must be tempered by the fact that the majority of patients admitted to substance abuse treatment programs are there by legal mandate as an alternative to prosecution or incarceration, and not always because of an actual addiction to cannabis (Russo, 2016).

Studies show that cannabis has a drug-abuse liability lower than that of other legal and illicit agents (Hilts, 1994; Roques, 1998; Nutt et al., 2007).

The vast majority of my patients consistently report that they have neither addiction nor any withdrawal syndrome associated with cannabis use and cessation. They comfortably come and go from cannabis use as they wish. (Hergenrather personal observations) .

Your patients should know not to drive when impaired. Driving impaired cannot be established by a blood test. For a novice, five nanograms-per-milliliter in the blood can be associated with impairment. But someone very experienced with cannabis might be able to drive perfectly with a 100-nanogram level.

Methods of Administration

Smoke and Vapor Bioavailability: 2-56%, 10-25%. Avoids first pass metabolism

Oral forms Bioavailability: 4-20%, 6% cookies

Rectal & vaginal (Hemisuccinate) Bioavailability: twice oral route Lower first-pass metabolism

Topical Bioavailability: minimal

Transdermal Bioavailability: unknown (Huestis 2007) Avoids first-pass metabolism

THC:CBD ratio

Δ-9-tetrahydrocannabinol (THC), the main psychoactive ingredient of *Cannabis sativa* has numerous pharmacologic actions though it can also induce anxiety, paranoia, and impair memory. THC is a moderate agonist at CB1, CB2, TRPV1, and other receptors. Common marijuana has a ratio of THC:CBD of about 100:1. THC-rich cannabis may be preferred for pain control, muscle spasms, and sleep.

Cannabis grown for cannabidiol (CBD) may range from 1:1 CBD:THC to 25:1 CBD:THC.

Driving impaired cannot be established by a blood test.

Blood level does not correlate with impairment. This complicates things for law enforcement, who have to street test people for impairment. If a driver is acting spaced out, or unsteady on their feet, or not able to pay attention, they're impaired and we should get 'em off the road.

Question: Do you advise people to use cannabis to reduce opiod use?

Hergenrather: I usually recommend that people stay on the opioid dose they're on, start using cannabis until they feel an effect.When they recognize that it's working well for pain or sleep or mood, they should work with their primary doctor or prescribing doctor on tapering opioids. That can be done rather quickly. I think you can taper a fairly significant opioid use in a month or so.

The patients on benzodiazepines usually go much more slowly. Tapering off benzos might take months.

Cannabinoid receptors are not in the brainstem affecting heart rate or breathing. So even with massive overdoses, you're not going to disrupt the basic bodily functions.

Question: Why do you think cannabinoids have such a high therapeutic index?

Hergenrather: The location of the receptors. They're not in the brainstem affecting heart rate or breathing. So even with massive overdoses, you're not going to disrupt the basic bodily functions.

Cannabis is a vasodilator, so people who get a massive dose might get light-headed or faint. Dabbing, which involves inhaling a cannabis concentrate, is like inhaling a whole joint in one puff. People have fallen over and there have been reports of cracked skulls and broken shoulders.

Another concern is the Hyperemesis syndrome. Once relatively rare, the condition is being seen more frequently in big city emergency rooms. In a rare few regular cannabis users there is an acute onset of intractable vomiting, only comforted by a hot shower. Patients have to stop using cannabis for a couple days and the syndrome resolves without other treatment. Most people can resume therapeutic use of cannabis in a short time. It seems that the CB1 receptors need to re-set. Whether this represents a genetic variation in the cannabinoid receptor making this occur is unknown at this time.

Drug-drug interactions of cannabinoids and conventional medications are rare and generally not a problem. There is one worth mentioning: Both CBD and the anti-epileptic drug clobazam are metabolized by the same CYP-450 metabolic pathway, resulting in elevated levels of clobazam in the presence of high doses of CBD. This may reach toxic concentrations of clobazam. It is best to follow all anti-epileptic drugs' blood levels when using high doses of CBD. (Friedman et al, 2014).

FDA-approved cannabinoid drugs are also a treatnent option. Dronabinol (marketed as Marinol by Solvay and as Syndos by Insys) is synthetic THC. Nabilone is a THC analog developed by Eli Lilly in the 1980s and now made by Valeant. People generally prefer cannabis.

Doctors in the Society of Cannabis Clinicians recommend use of the flowering plant and medicinal products made from it —oils, tinctures, salves and all kinds of foods, beverages and chocolates.

A strain that is 20-to-1 CBD to THC will be effective pharmacologically with hardly any psychoactive effect.

Question: Why wouldn't synthetic THC be just as good at activating the receptors? If it's a lock and key...

Hergenrather: There are more than 150 terpenes — some activate the CB receptors— and more than 140 cannabinoids in the plant. Some of them might be partial agonists or antagonists. There is such a blend of molecules that when they're there together it sort of softens the impact and makes it a more effective medicine.

Some of these other molecules, the terpenes in particular, have vast therapeutical value. They might be anything from antimalarial to pain relievers to anticancer drugs in and of themselves. The entourage of all these compounds together seems to work better than the individual molecules.

In recent years cannabis strains have been identified mainly in terms of THC and CBD content. Cannabidiol is the non-psychoactive component. It has been bred up in plant strains designed for medical use. A strain that is 20-to-1 CBD to THC will be effective pharmacologically with hardly any psychoactive effect.

One of these CBD-dominant strains was being used in Israel for kids with autism. These kids were getting 300 milligrams of CBD per day and their behavior had greatly

continued on next page

Endocannabinoid metabolism

- Natural endocannabinoids are synthesized on demand as an adaptive response to cellular stress, aimed at re-establishing cellular homeostasis.
- Endocannabinoids are rapidly metabolized mostly near their site of action.
  Anandamide principally by FAAH
  2-AG principally by MAGL

Phytocannabinoid metabolism

- Phytocannabinoids are metabolized in the liver by the CYP-450 metabolic pathways.
- Genetic variations in the hepatic CYP-450 metabolic pathways are manifest as slow, intermediate, and fast metabolizers.
- Cannabidiol (CBD) potently inhibits CYP3A isoforms and CYP2C19.
- There are no other significant drug-drug interactions between cannabinoids and other medications.

A wide range of phytocannabinoid blood levels and duration of action can be expected when developing a treatment plan.

Entourage Effect

The constituents in whole plant cannabis combined are more effective in many clinical situations than are the individual molecules.

Cannabinoids: >140 in cannabis

THC is a cannabinoid receptor agonist. It has actions at the CB1, CB2 and other receptor sites in addition to non-receptor targets providing a long list of pharmacologic properties.

CBD is a non-psychotropic cannabinoid, softening the effects of THC. 2nd most prevalent in plant. Pharmacologic properties closely resemble THC.

THCV is a CB1 partial antagoist or an agonist at higher doses. Utility in metabolic syndrome and as anorectant.

Other cannabinoid constituents such as THCA, CBG, and CBDV will follow as more is understood about their dose reponse / clinical effects.

Terpenes: 150-200 in cannabis

Possess numerous therapeutic properties, including: neuroprotection, bone stimulation, anxiolytic, anti-epileptic, antibacterial, antimalarial, antidiabetic, vasorelaxant, antinausea, analgesic, antispasmodic.

Effects of a few dominant terpenes:

α-Pinene: bronchodilating, anti-inflammatory, AChE inhibitor
Limonene: anxiolytic, antidepressant, apoptosis in breast cancer.
Linalool: sedative, anti-anxiety, analgesic, anticonvulsant
β- Myrcene: sedating, muscle relaxant, hypnotic, analgesic
β-Caryophyllene: gastric cytoprotection, antimalarial, CB2 agonist
Nerolidol: sedative, potent antimalarial
Humulene: anti-inflammatory, anti-cancer

Dosing and Frequency

Highly dependent on variables of 1) cannabinoid constituents, 2) individual metabolism, 3) tolerance, and 4) condition being treated.

Dosing quantities
- 1 mg to 1000 mg daily in divided doses

Frequency of dosing
- Episodic use pattern
- Daily administration: morning, evening and/or bedtime
- Multiple or frequent administrations daily

Cannabis as Medicine *from previous page*

improved. Until one day caregivers started reporting that the medicine had stopped working.

Meiri concluded, "THC and CBD are not the only players."

Dr. David Meiri found that all these kids were using a new batch of extract made from a strain with an identical CBD-to-THC ratio, but a different profile of "trace" cannabinoids and terpenes. Meiri concluded, "THC and CBD are not the only players."

The message for cannabis clinicians and patients is: if a strain doesn't seem to be meeting the clinical needs, try a different one. That's about all we can do at this point. We don't know enough, there are too many variables to sort this out, probably in our lifetime. Some physicians, including Drs. Joe D. Goldstrich and Sunil Aggarwal, advise using two or more strains in hopes of finding a beneficial minor cannabinoid or terpene.

The various delivery systems affect the bioavailability of cannaabinoids and the onset and duration of their effects. Cannabis can be inhaled as smoke (from a pipe, waterpipe, cigarette, or dab), or vapor from a device that heats it to a point below combustion. Both smoke and vaporized cannabis enter the bloodstream by way of the lungs, thereby avoiding first-pass metabolism by the liver.

Selection of Cultivars

- Common names are fraught with inaccuracy.
- Dependable lab analysis for cannabinoids, terpenes and contaminants is essential in the cannabis marketplace.
- Use what feels best. Change strains when not finding desired effects.
- Importance of preserving any / all varietals. Cannabis is not a fungible crop.

Smoking and vaporizing remain the preferred method of administration for many users. Rapid onset, short duration of action, and ease of titration are recognized benefits. Use the inhaled forms when you want a quick response: to put out the pain, to ward off the seizure.

An underappreciated fact about inhaled cannabis is that the achieved blood levels may dwarf the blood levels achieved by a comparable dose of orally ingested cannabis. Though the oral dose has a long duration of action, a benefit in those seeking round-the-clock coverage, the inhaled dose can be expected to have a far higher blood level since it avoids the first pass metabolism in the liver.

Cannabinoids in edibles go through the portal vein into the liver where they get metabolized efficiently into 11-hydroxy and still other cannabinoids. The effects can last between six and 12 hours. Duration will vary from patient to patient.

When a patient comes through the door, I don't know if they're a fast metabolizer or a slow metabolizer. We caution people about what they might expect from edibles. I'll say 'Take a dose at bedtime If you still feel it the next morning, you're probably a slow metabolizer."

With oral tinctures and sprays it is common to hear that by holding the medicine under your tongue the medicine will enter your bloodstream avoiding first-pass metabolism. There have been no studies to confirm this notion, and, in fact most users of Sativex, the GW Pharmaceuticals drug with a 1:1 ratio of THC and CBD, report that they don't feel the drug until 30 minutes after use. This fact suggests intestinal absorption rather than buccal mucosa absorption (which would be almost instantaneous). Consider that any orally administered medicine will begin to take effect in about 30 minutes, peak at two hours, and last for 5-10 hours depending on dose, concommitant meal, and metabolism variations.

Suppository forms are useful but we don't know how well the cannabinoids are absorbed. Lab tests done in the '90s showed that THC was not absorbed via suppositories. But the whole-plant extracts now in use are full of other beneficial compounds. The terpenes are solvents and would facilitate getting through the rectal mucosa into the bloodstream.

Transdermal patches are being developed. There are several patents pending using DMSO and various terpenes as vehicles to facilitate absorption,

Natural cannabinoids are synthesized at their point of use in the body. Plant cannabinoids are metabolized in the liver.

Dosing frequency can vary from one milligram to a thousand milligrams a day, You can use large amounts in treatments of cancer, epilepsy, and other conditions.

Natural cannabinoids are synthesized at their point of use in the body. Plant cannabinoids are metabolized in the liver.

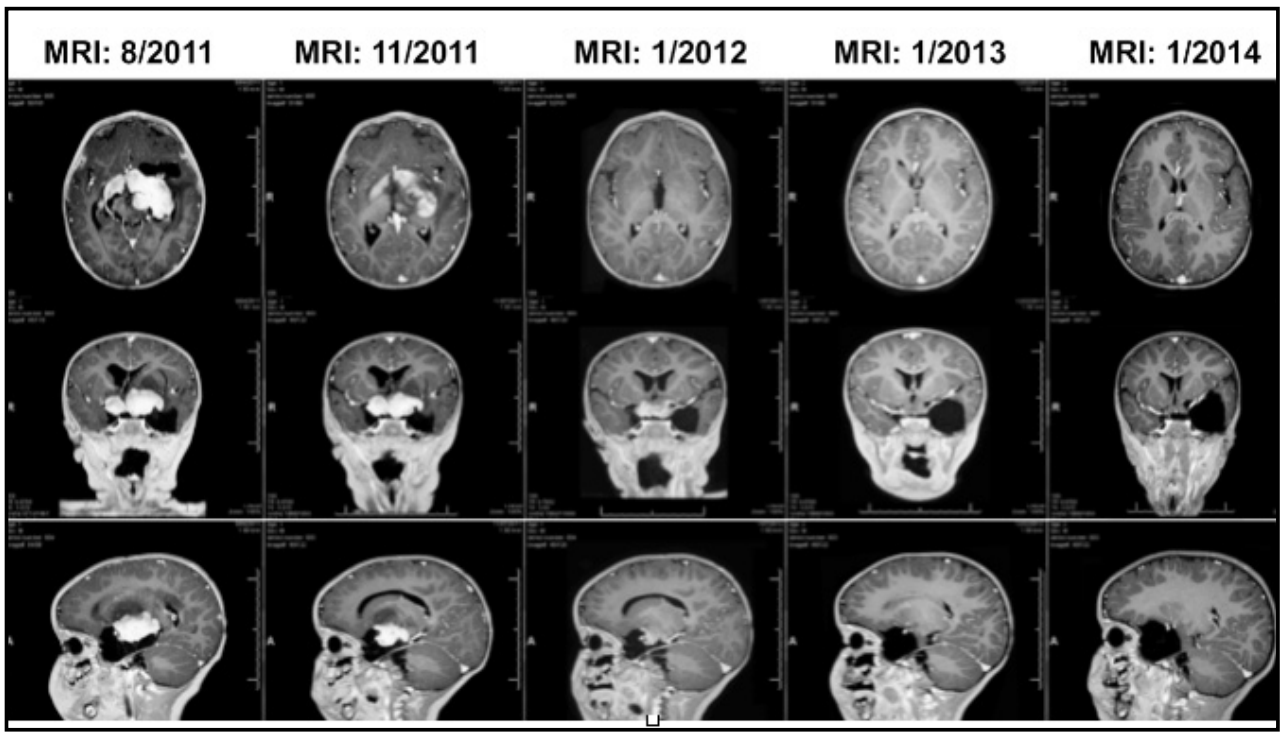
Synergism: The whole plant provides more benefit than the single molecules. There is an entourage effect of all these different molecules.

Cannabis is an adaptogen. You get what you need. Used at night it might help put you to sleep. But used in the morning it won't make you sleepy because you've already slept, your body doesn't need. sleep.

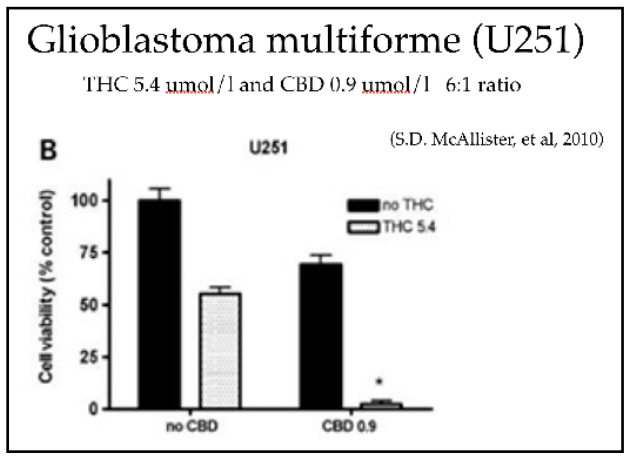
It's the same with eating. You might improve your appetite by using cannabis, but if you've already eaten and use it, it's not going to drive you back to the refrigerator. You get what you need.

Tolerance and auto-regulation is a very interesting phenomenon. Regular users are not going to get high after a while. It doesn't take long. You can develop tolerance in about a week so that an effective dose doesn't get you high. You say "I'm feeling relaxed now but I don't feel high."

What happens is an internalization of cannabinoid receptors coming out of the cell membrane and back into the cell. So the body is auto-regulating the population of cannabinoid receptors when you're using high doses on a regular basis. The receptors are rapidly restored when you stop using it. After a couple of days those receptors are back in the cell membranes and working again.



Optic Tract Glioma: 16-month old at time of Diagnosis
Treatment: Solo therapy, Full extract cannabis oil initiated within days of diagnosis. Droplet of oil placed on pacifier for twice-a-day administration. No adverse effects.



The synergism between THC and CBD is illustrated in the bar graph above. Tumor cells from UCSF patient number 251 were grown in a test tube (bar at left) and treated with cannabinoids at very low concentrations. The second bar shows the level to which addition of THC alone knocked down cell survival. The third bar shows the level to which CBD alone knocked down cell survival. The fourth bar shows that adding THC and CBD together has an effect that's much more than additive. THC and CBD work better together. They each kill cancer cells.

A point to realize is that these bar graphs are representing cannabinoid concentrations that are visible. A bigger dose and you'll kill all of the cells –a smaller dose and you might not see an effect. When dealing with cancers we tend to over-treat because the bigger the dose the bigger the effect.

The set of MRI scans at the top of the page show the progress of a child I started treating several years ago. He's now eight years old and in the second grade. He recently scored 135 on an IQ test.

At 16 months he had some nystagmus and was taken to Children's Hospital in Oakland where they found the tumor —an optic tract glioma. His parents opted for treatment with cannabis oil.

The sole treatment modality was putting the concentrated oil on his pacifier twice a day. He had a nice morning nap, giggled for a while. The evening dose helped him sleep all night. As the scans show, it took about five months for the tumor to almost completely disappear.

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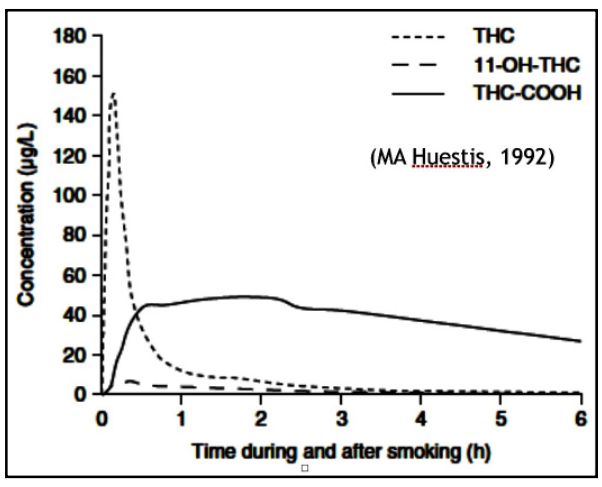
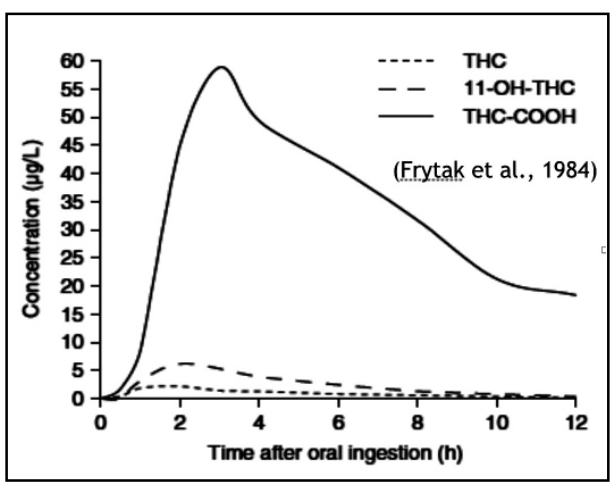
Metabolism of smoked vs orally ingested cannabis



Inhalation via the lungs provides rapid onset of a high dose with short duration. Graph shows levels of cannabinoids in the bloodstream while —and for six hours after— subjects smoked cannabis containing about 34 milligrams of THC. Vertical scale shows mean plasma level in nanograms per liter. The study involved six subjects. Δ^9THC is seen to peak at about 150 ng/ml five to 10 minutes after inhalation; it is then rapidly metabolized. Only minuscule amounts of 11-OH-THC are produced via inhalation.



Oral ingestion resulted in metabolite concentrations for 12 hours after cancer patients ingested 15 milligrams of THC. Levels of 11-OH-THC, produced in the liver, peak between two and three hours and are detectable for eight hours. First pass metabolism of ingested cannabis results in lower concentrations in the blood. THC-COOH, an inactive metabolite, breaks down slowly and can take weeks to reach undetectable levels —a boon to the drug-testing industry.

Cannabis as Medicine *from previous page*

On our annual visits he sits at the table and talks to me, just a delight to be around, a brilliant little kid. He has continued to have negatives scans up to the present time. He is staying on a maintenance dose of cannabis oil with about 2 mg/kg/day of balanced THC:CBD with no recurrence of tumor.

Question: What is the rate of auto-remission on these cancers?

Neurosurgeon in the audience: Zero.

Hergenrather: I did have a GBM patient who went nine years without a recurrence. Decided he didn't need it anymore, stopped, and he had a full recurrence within a year

Neurosurgeon: Getting nine years from a GBM patient is fantastic.

Hergenrather: Yes. And no recurrence. Since then I've treated many other GBM patients successfully, with no recurrence.

Hospice doctor: I do hospice and palliative care. Unfortunately, we see a fair number of these glioblastomas. I've seen more and more of these patients using cannabis oil. Is this something being widely used at UCSF, where these patients often go?

Hergenrather: The UCSF docs are referring out to cannabis specialists. Their reluctance usually has to do with a threatened cut-off of federal funds. The oil is the most cost-effective way to use these concentrated forms.

Question: Are extended care facilities involved in distributing cannabis?

Hergenrather: Yes, they are beginning to. I'm working in a facility in Santa Rosa, an Alzheimer's dementia center. We're taking them cannabinoid chocolates. They push off other pills.

Question: What about reimbursement?

Hergenrather: A few private insurers will make payments if a doctor referred a patient to me as a specialist . As far as Medicare and other third parties —none. That's the long arm of the drug war. If you're an ER doc treating someone for pain and the conversation includes cannabis, you're probably okay. But if you're in business as a cannabinoid specialist giving a treatment plan to somebody, you can't get reimbursement for that from Medicaid or Medi-Cal.

They're protecting the pharmaceutical industry. The drug companies are going to lose market share in many classes of medicines.

Neurosurgeon: Why is there so much resistance from the federal government? All the data is there, they would make millions of dollars taxing marijuana.

Another MD: Lobbying!

Hergenrather: I think t's all about money when we really get down to it. They're protecting the pharmaceutical industry. The drug companies are going to lose market share in many classes of medicines. This is a medicine people can grow in their garden.

Another MD: Who else would lobby to keep it on Schedule One?

Hergenrather: The alcohol industry. The incarceration industry, The gaming industry. They've done their research. When people smoke pot at the gaming tables they say, "This is stupid, I'm heading for home."

Hospice doctor: Many hospice patients are already using some form of cannabis and I find myself wondering what to tell family members. Am I right in telling them whatever combination works is okay because the cannabinoids are non-toxic? If patients are taking them in addition to opioids there shouldn't be any additive effect. Is that right?

Hergenrather: You can actually get by with less opioids. There is some cross-talk between cannabinoid receptors and opioid receptors. So you get a little better effect, a little stronger pain relief with the two together. I advise people: work your dose up on cannabinoids and then start tapering your opioids if you need to or want to.

We've gone way over time. One thing you should know is that the names of plant strains are all over the place. Sour Diesel at one dispensary could contain very different compounds than Sour Diesel at another. And as the example from Israel showed, the amounts of THC and CBD can be identical and a strain will have different effects based on its terpenes and so-called minor cannabinoids.

We really need to identify the chemovars — which molecules are there. That will guide us as we go forward with cannabis medicine.

We really need to identify the chemovars —which molecules are there. That will guide us as we go forward with cannabis medicine.

Lab testing is coming to California in July 2018. We'll be able to look at cannabis in dispensaries and know at least what the dominant cannabinoids are. The state government did not want to have a test for terpenes. I find that a shortcoming because the terpenes really do offer some significant benefits. Myrcene, for example is sedating. Limonene is energizing. So it would be useful to know terpene content when you're recommending a strain for daytime use or nighttime use.

It's important that we preserve all the cannabis varietals. The Meiri lab in Israel is pursuing the very ambitious and very logical goal of figuring out which cannabinoid ratios and which other components of the plant work best in treating certain tumors. We are a long way from understanding the best ways to use cannabis in oncology.

There are social limitations and employment issues that your patients will face. Risk of discovery. Cost can be a problem for many patients who can't grow it in a garden. If you buy a half ounce of a tincture at a dispensary and need a dropper full a day, two weeks might be $30. But if you're using massive doses in cancer chemotherapy, you would be spending at least $20 a day.

You were a great audience. Thanks for the great questions.

Doctor in the audience: I feel I could use another year of medical school.

Hergenrather: There's a lot of material.

The author thanks St. Rose Hospital, Hayward, California, for the invitation to make a grand rounds presentation (the basis of this article) in February 2018.

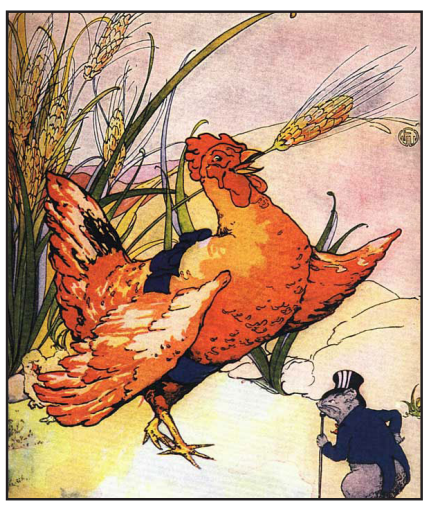
DEA puts Epidiolex in Schedule 5 but keeps CBD in Schedule 1

After conducting extensive hospital-based clinical trials tracking some 516 children with two severe forms of epilepsy —Lennox Gastaut Syndrome and Dravet Syndrome— GW Pharmaceuticals submitted its Epidiolex data to the US Food & Drug Administration on October 30, 2017.

Epidiolex is 99% CBD and one percent other cannabinoids (including 0.25% THC). Terpenes are eliminated during the CO2 extraction process.

An FDA staff review confirmed in April 2018 that Epidiolex reduced the frequency and severity of seizures by about 40%. Benefit outweighed safety concerns involving drug metabolism in the liver.

It had been 20 years since Drs. Geoffrey Guy and Brian Whittle received approval from the British Home Office to grow Cannabis in the UK to develop plant-extract medicines. And five years since the FDA allowed GW to conduct "Investigational New Drug" studies of their purified CBD as an anti-seizure medication.



The Little Red Hen planted the seed, watered the wheat, cut down the wheat, and carried the wheat to the mill —tasks the pig, the cat, and the rat declined. She ground the wheat, kneaded the dough and baked the bread —solo all the way. And when it was time to eat the bread, the pig, the cat, and the rat wanted some. GW Pharmaceuticals is the Little Red Hen of Cannabidiol.

FDA approval to market Epidiolex was granted on June 25, 2018. In an interview with *O'Shaughnessy's* Guy said the FDA approved Epidiolex for the same reason he committed his company to making it: "the sense of urgency conveyed by the families of children living with these terrible syndromes who have tried all the available anti-epilepsy drugs."

Guy credited GW's Etienne DeMeier for breeding the CBD-rich variety that is the basis for Epidiolex.

"It is impossible to completely eliminate THC," he noted.

California cannabis clinicians have patients who report that THC is useful in treating epilepsies, and will add it —or THCA, or other "minor" cannabinoids, or various terpenes— to CBD-rich medicines, to reduce seizures, improve mood, and help with sleep.

Guy said: "There is no doubt that THC is an anti-convulsant. But I don't believe there is room for any large amounts of THC in young children. Their brains are extremely plastic. Their ability to overcome epilepsy and their ability to develop cognitively depend on neuroplasticity.

"My concern is that THC reduces that capacity. That is why we designed Epidiolex the way we did."

Acknowledgment by the FDA that Epidiolex is medically useful impelled the DEA to assign it a Schedule under the federal Controlled Substances Act. On October 3 the DEA placed Epidiolex in Schedule V.

"There is no doubt that THC is an anti-convulsant. But I don't believe there is room for any large amounts of THC in young children." —Geoffrey Guy

which they define thus: "The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule IV." (Are Roman numerals supposed to confer gravitas? Like with the Super Bowl?)

The Schedule 5 status applies only to CBD products approved by the FDA. CBD preparations not approved by the FDA remain in Schedule 1 (due, supposedly, to their potential for abuse).

The price of Epidiolex will be comparable to that of other anti-epileptic drugs such as Onfi —typically $32,500/year for a child with Dravet or Lennox Gastaut Syndrome.

Dale Gieringer of California NORML did a back-of-the-envelope calculation: "At $32,500 per year, Epidiolex is a costly medication. The standard dosage of Epidiolex is from five to 25 mg of CBD per kilogram of body weight per day, which works out to 250-to-1,250 mg of CBD per day for a 100-pound patient (on the heavy side for pediatric cases).

"Using high-potency flowers of 15% CBD, this works out to 1.67 to 8.33 grams of cannabis per day, or 1.2 to 6 pounds of cannabis per year. At a price of $150/ounce, an equivalent amount of 15% CBD cannabis flowers would cost $2,880, which comes to $14,400 per year.

Physicians can now prescribe Epidiolex for any medical condition it might beneficially treat; but insurance companies will not reimburse for "off-label" uses.

According to the *Wall St. Journal,* "Out-of-pocket costs for patients taking Epidiolex could range from $5 to $10 a month for those in state Medicaid programs to as high as $200 a month for some private insurance plans."

Although US producers of cannabis medicines see GW Pharmaceuticals as a business rival, and patients may seek better pricing, all concerned owe a debt of gratitude to Geoffrey Guy and company for carrying out and sharing the research that established the safety and efficacy of CBD. Also, for alerting us to the potential benefits and synergistic effects of other "minor" cannabinoids. And for sponsoring "N-of-1" trials —a research model that cannabis clinicians and their patients can emulate.

"Without Geoffrey Guy there would be no CBD," says Rosie B., an activist who has followed the CBD saga closely since 1998.

In early October, California Gov. Jerry Brown vetoed a bill that would have given a tax break to cannabis growers who donate CBD-rich trim to Caladrius Network, Sweetleaf, WAMM and other saintly collectives that provide CBD-rich medicine free to patients with severe epilepsies. —*Fred Gardner*