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.

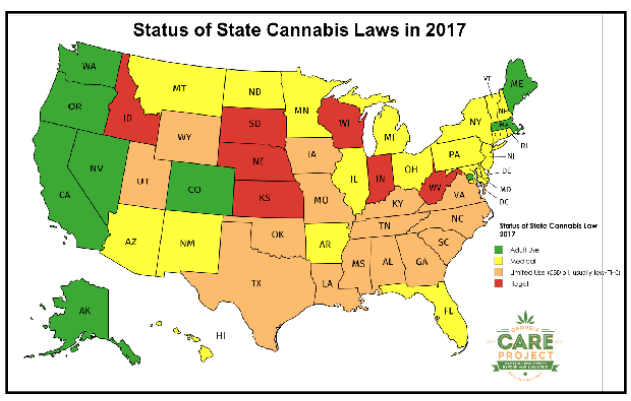
I would like you to come out of this with an epiphany: "This is wonderful, I would like to incorporate cannabis into my practice!"

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.

Sine 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 23 states that allow medical marijuana. 16 have limited access —CBD-rich strains which are minimally psychoactive are allowed (including West Virginia as of 2017). Only five 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 became something people could talk about.

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

Pivotal TV Story and Commentary - 2013

Sanjay Gupta, M.D.
Chief of Neurosurgery

… 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, and the federal government agreed to supply him 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 Lenox-Gastaut Syndromes. It is highly unlikely that insurance companies will reimburse for other uses in the near future.

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 expressed permission of the federal government (FDA, DEA, NIDA, NIH, H&HS, ONDCP).

- Cannabis is available in rare exceptions thru the Compassionate Investigational New Drug programs.
- 1978: Established in 1978 with Robert Randall and ending in 1992 with 30 patients enrolled. In 1992 public health officials concluded "there was no scientific value to it". Four patients remain in the program.
- 2014: Compassionate Investigational New Drug programs for cannabidiol (CBD cannabis extracts) for seizure disorders (Dravet's, Lennox Gastault, other intractable seizure disorders.

State of California:

Compassionate Use Act of 1996 (CUA) (Proposition 215) - Medical marijuana legalized by ballot Initiative: Patient may legally possess an amount of marijuana consistent with the patient's needs when approved by a physician

Adult Use of Marijuana Act, 2016 (AUMA) (Proposition 64) – Voter initiative to legalize cannabis in California. "Control, Regulate and Tax Adult Use of Marijuana Act". Without changing the CUA, Prop 64 creates a legal right for adults 21+ to possess up to an ounce, share and carry small amounts of cannabis and concentrates, and grow discrete home cannabis gardens (6 plants).

California's local jurisdiction marijuana laws have gotten more complicated than ever.

One one hand, the legalization initiative allows all adults 21 and over to possess up to one ounce of cannabis buds, 7 grams of extract, and to grow six plants in their homes.

But what about access to marijuana dispensaries? What about growing plants in my outdoor garden?

The answer to these questions vary from city to city and county to county. There are 114 jurisdictions in the Bay Area alone. A patchwork of conflicting cananbis laws blankets the state. Many citizens are confused about what's legal in their city limits or unincorporated county land.

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. Tod Mikuriya drafted the first sentence, which made the law applicable to "any... patient for whom marijuana provides relief."

In 2016 California passed the Adult Use of Marijuana, 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. On a site called Greenstate.com, you can type in a location and get a status report. Here in Hayward there are no medical dispensaries and no recreational stores, 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 company had a reasonable concern about the federal government raiding their facility looking for marijuana.

Your patients should know not to go to work impaired and not to drive impaired.

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, but its fate is uncertain as we go to press.

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

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 disingeuous. 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 feds have created obstacles to research. Only the marijuana grown for NIDA can be used in clinical trials that will be approved by institutional review boards. There is no one with deep pockets trying to get plant-based cannabis medicines approved by the FDA and other regulatory authorities.

The Science

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 were taught that a physician named William Brooke O'Shaughnessy published a paper describing the use of cannabis extracts by doctors in Calcutta to successfully

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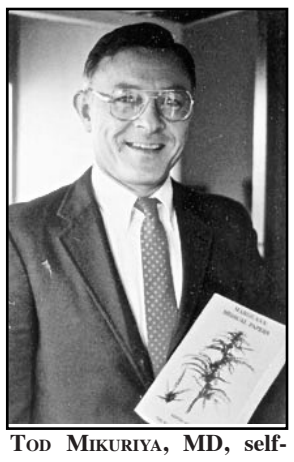


Tod Mikuriya, MD, self-published Marijuana Medical Papers in 1973

Cannabis as Medicine *from previous page*

treat epilepsy and other conditions for which Western medicine had no remedies. The pre-prohibition medical literature was recovered and republished by Tod Mikuriya in his 1973 anthology, Marijuana Medical Papers.

The *Cannabis* plant produces cannabinoids —molecules containing 21 carbon atoms in ring structures, with atoms of hydrogen and oxygen attached at different points. The predominant cannabinoids in *Cannabis* plants in the wild —and in cannabis-based medicines currently available— are CBD (cannibidiol) and THC (tetrahydrocannabinol). More than 100 other cannabinoids have been identified, including some that have shown medical potential in lab studies.

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.

These receptors, later called CB1 receptors, are concentrated in the cerebellum and basal ganglia (areas responsible for motir 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 —arachidonyl 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 endocannaboinoids 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 10.)*

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 —FAAH and MAG-Lipase.

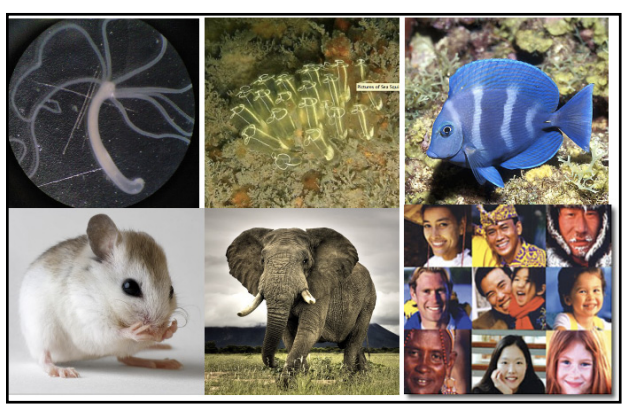
Creatures throughout the animal kingdom, down to hydras —but excepting the insects— rely on endocannabinoids to bring about homeostasis. The endocannabinoid system is a built-in system to keep us in balance.

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

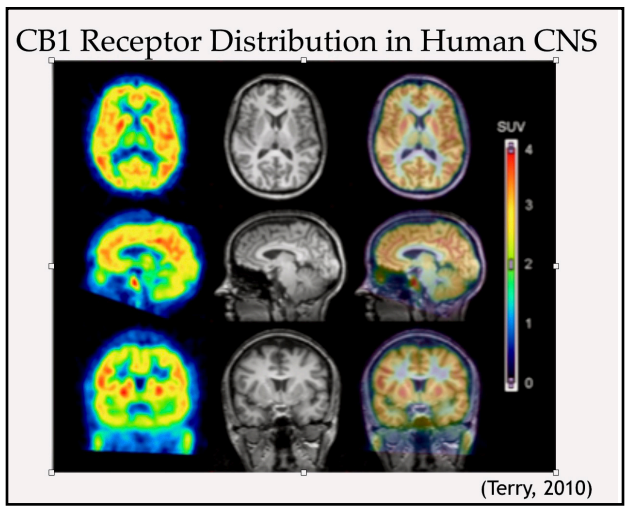
The Endocannabinoid System

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

• Components:
—transmembrane 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.

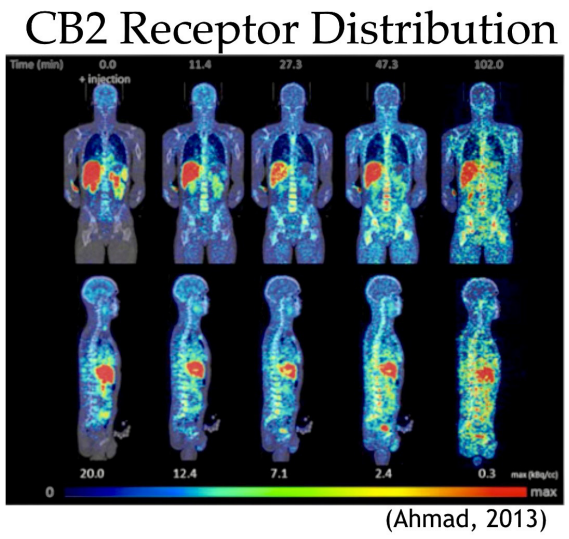


The animal kingdom is designed with an endocannabinoid system.



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. FOR WHAT PURPOSE?

The CB2 receptors are primarily located in the immune system. In the a 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.

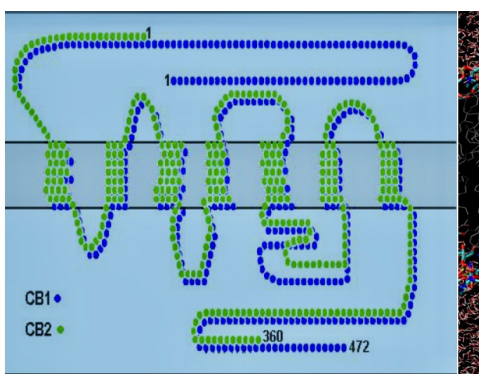


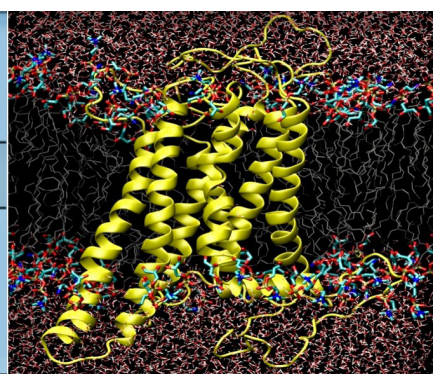
The endocannabinoid system enables us to eat, sleep, relax, and to forget. Forgetting is sometimes perceived as a negative, but ability to extinguish or diminish painful memories and fear is crucial to coping with post traumatic stress and other disorders.

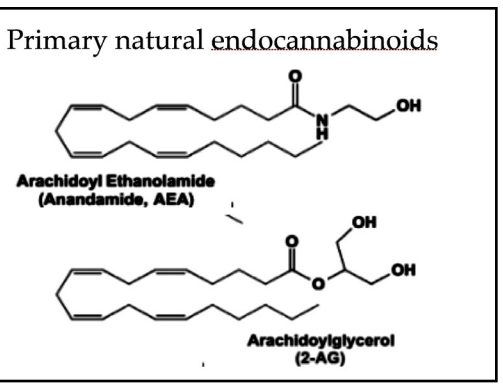
The endocannabinoid system also plays a role in cytoprotection, neuroprotection, immunomodulation, metabplic regulation, neural plasticity, embryological development and cancer control.

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 stroke volume. Hence, this unique and powerful cannabinoid role as a neuroprotectants was discovered and patented. In response to this ambulance rigs in Israel carried a synthetic cannabinoid as a first line treatment for stroke and neurotrauma for a short time, however, the trial was discontinued for lack of efficacy with the molecule and dosage tried. I DON'T THINK ISRAELI AMBULANCES CARRIED MECHOULAM'S HU-210 IN RESPONSE TO THE US PATENT.

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 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.

Anandamide (AEA)

• Primary endogenous ligand at CB1receptor.
—Weaker CB2 ligand
—Spinal cord (pain cessation)
—Hippocam[pus (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)

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 enogenous ligand for the CB2 receptors.

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.

The various roles of cannabinoid receptor activation have been summarized as helping us to eat, sleep, relax, forget, and protect. This system has been preserved for over 600 million years of evolution because it brings us into balance. People like to use cannabis because it makes them feel good through a wide range of beneficial pharmacologic effects.

It 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.

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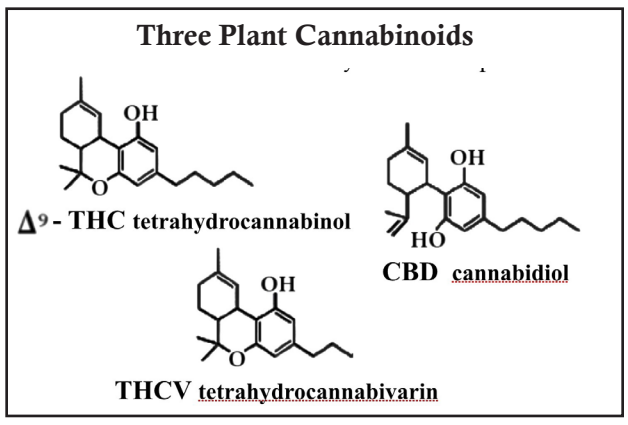
Cannabis as Medicine *from previous page*

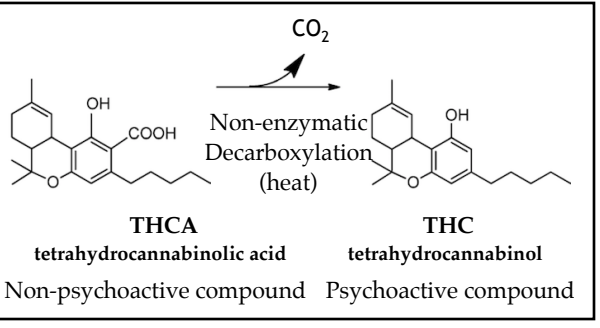


Above is an image of the plant cannabinoids THC and CBD, along with THCV. The difference between THC and CBD is slight —move a hydrogen atom from the methyl group in THC over to the Oxygen and you've got CBD. The shape of the molecule is changed just enough so that it's not a ligand activating the CB1 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.

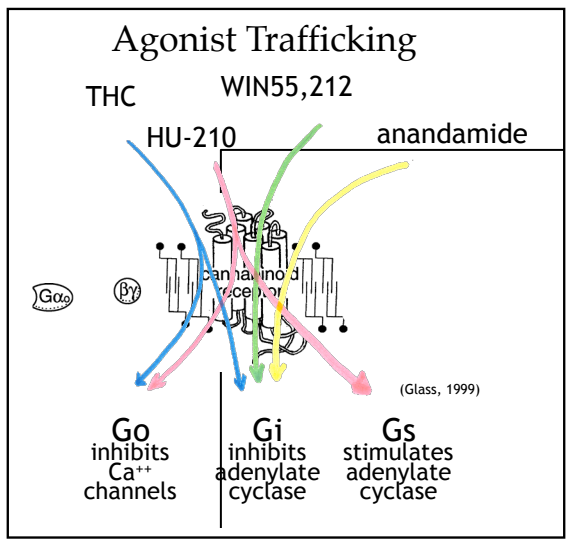
THCV has a three-carbon side-chain as opposed to the five-carbon chain of THC. (All the varins are characterized by three-carbon side-chains.) THCV also gets into the CB1 receptor, but because of the short tail, it doesn't turn the receptor on.

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).

You may hear references to THC being "activated." In a live martijuana 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 psychocactivity.



The mechanism by which THC and other agonists activate the CB1 receptor is depicted above. 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.

Cannabinoid trafficking is complex, involving not just two receptors and two ligands. Some minor cannabinoids can activate the 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. PPARs help regulate the expression of genes. DID YOU WANT THIS CUT?

Pharmacologic effects of cannabinoids

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

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 generally beneficial.

In my practice I have seen people benefitting from each of the effects listed below at left. 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

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Conditions 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

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, uncompensated
- Migraine
- Multiple Sclerosis
- Huntington's Disease
- Parkinson's, uncompensated
- Irritable bowel syndrome
- "Failure to thrive"
- Anorexia, uncompensated
- Chronic motion sickness
- Fibromyalgia
- Menstrual symptoms
- Seizure disorders

ICD-10 Codes

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
Alzheimer's dementia	G30.9
Amyotrophic lateral scler	G12.21
Ankylosing spondylitis	M45.0
Anorexia	R08.02
Anorexia nervosa	F50.0
Anorexia, wasting synd	R63.0
Anxiety	F41.9
With depression	F41.8
Arthritis, rheumatoid	M05.10
Arthritis, psoriatic, unspe	L40.50
Arthopathies, unspecified	M02.80
Asthma	J44.9
Autism disorder	F84.0
Autoimmune, dis, undiffe	E31.0
Autoimmune thyroiditis	E06.3
Basal cell carcinoma, unsp	C44.00
Benign prostatic hypertro	N40.0
Bipolar disorder, unspecif	F31.9
Borderline Personality Dis	F60.3
Brain trauma, diffuse	S06.2X0
Cachexia	R64
Cancer	
Adrenal	C74.10
Anus, unspecified	C21.0
Basal cell CA, unsp	C44.00
Biliary tract, unsp	C24.9
Bladder, unspec	C67.9
Bone, unspecified	C41.9
Brain unspecified	C71.9
Breast, female, un	C50.91
Breast, male, unsp	C50.92
Cervical, unspeci	C53.9
Cholangiocarcinoma	C22.1
Colon, unspecified	C18.9
Connective/sarcom	C49.9
Duodenum	C17.0
Endocrine, unspec	C7A.00
Esophagus	C15.9
Gallbladder	C23
Headache	R51
Larynx, unspecified	C32.9
Leukemia, lymphoid	C91.10
Leukemia, myeloid	C92.10
Lip, unspecified	C00.9
Liver, hepatocellular	C22.0
Lung, unspecified	C34.9
Lymphoma, Hodgk	C81
Lymphoma, MALT	C88.4
Lymphoma, NonH	C82
Melanoma, unspec	C43.9
Meningioma	D32.9
Mesothelioma, unsp	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
Prostate	C61
Rectum	C20
Renal	C64.9
Small intestine	C17.9
Stomach	C15.9
Squamous, HNSCC	C10.9
Squamous Ca, in situ	D04.9
Thymus	C37
Throat	C32.9
Tongue, unspecified	C01.9
Tonsil	C09.9
Uterus	C54.1
Wilm's / Unsp Urin	C64.9
Carpal tunnel syndrome	G56.00
Celiac disease	K90.0
Cerebral palsy, unspecified	G80.9
Cerebrovascular insuff acu	I67.81
Cervical neck pain	M54.2
Charcot Marie Tooth Diseas	M14.60
Chronic pain syndrome	G89.4
Chronic fatigue syndrome	R53.82
Colitis, unspecified	K51.919
Complex Regional Pain Syn	G90.59
Constipation, unspecified	K59.00
COPD	J44.9
Coronary Artery Dis CAD	I25
Crohn's disease, w/o comp	K50.00
Crohn's disease, w comp	K50.01
CRPS, unspecified	G90.50
Cubital Tunn el Syndrome	G56.20
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
Douloureux, Tic	G50.0
Duodenal ulcer	K26.9
Dumping syndrome	K91.1
Dupuytren's contractions	M72.0
Dysthymic disorder	F34.1
Dystonia, unspecified	G24.9
Eczema, unspecified	L20.9
Electric feet syndrome	E53.8
Endometriosis	N80.9
Epilepsy, grand mal	G40.6
Epilepsy, partial complex	G40.209
Epilepsy, petit mal	G40.7
Epilepsy, unspecified	G40.9
Erythromelalgia	I73.81
Familial adenom's polyp	D12.6
Fibromyalgia	M79.7
Gallstones, colic w/o it is	K80.2
Gastric ulcers	K25.9
Gastritis, w/o bleeding	K29.00
Gastroparesis	K31.84
GERD, with esoph'itis	K21.0
GERD, w/o esoph'itis	K21.9
Glaucoma	H40.9
Gout, unspecified	M10.00
Grave's disease	E05.00
Harm reduction	
Hashimoto's thyroiditis	E06.3
Headache, cervicogenic	R51
Hypertension	I10
Hypothyroidism, post...	E89.0
Inflammatory BD, unspec	K75.9
Insomnia	F51.04
Interstitial cystitis	N30.10
Irritable bowel syndrome	K58.9
Juvenile rheumatoid Arth	M08.011
Kidney hemodialysis	Z99.2
Kidney failure, unspecified	N19
Lactose intolerance, unspe	E73.0
Liver transplant status	Z94.4)
Lower back pain, unspec	M54.5
Lyme disease	A69.20
Macular degeneration, uns	H35.30
Menopausal, symptomatic	N95.1
Migraine	G43.9
Multiple sclerosis	G35
Muscle spasms	M62.838
Myasthenia gravis w/o acu	G70.00
Myasthenia gravis w acute	G70.01
Nausea	R11.0
Neuromyelitis optica	G36.0
Neuropathy peripheral, idio	G60.9
Obesity, unspecified	E66.9
Obesity, morbid	E66.01
Opioid dependence	F11.20
Osteoarthritis, primary	M19.0
Ankle and Foot	M19.079
Elbow, OA, unspe	M19.029
Hand, OA, unspec	M19.049
Hip OA, unspecified	M16.9
Knee OA, unspec	M17.9
Shoulder, OA, unsp	M19.90
Thumb, OA	M18.10
Wrist, OA, unspe	M18.039
Polyosteoarthr, un	M15.9
Osteoarthritis, post-traumatic arthrop:	
Ankle and Foot, unsp	M19.179
Elbow, unspecified	M19.129
Hand, unspecified	M19.149
Hip, unspecified	M16.50
Knee, unspecified	M17.30
Shoulder, unspec	M12.519
Thumb, unspecified	M18.30
Unspecified site	M19.92
Wrist, unspec	M19.139
Osteopenia,	M85.80
Pancreas Transplant	Z94.83
Pancreatitis,	K85.9
Panic disorder	F41.0
Parkinson's disease	G20
Peptic Ulcer disease	K27.9
Pelvic vaginal pain, chron	R10.2
Polymyalgia rheumatica	M35.3
Polypharmacy	
Post laminectomy Synd	M96.1
Post herpetic neuralgia	B02.22
Post polio syndrome	G14
Prostate enlargement	N40.1
Psoriasis, unspecified	L50.9
Psoriatic arthropathy	L50.59
PTSD, unspecified	F43.10
Pulmonary fibrosis	J84.10
Quadriplegia, C5-7 compl	G82.53
Quadriplegia, C5-7 incompl	G82.54
Quadriplegia, C1-4 compl	G82.51
Quadriplegia, C1-4 incompl	G82.52
Raynaud's syndrome	I73.00
Renal Failure	Z94.0
Restless legs syndrome	G25.81
Rheumatoid arthritis, unsp	M06.9
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
Siogren's (Sicca) syndrome	M35.00
Thoracic back pain	M54.6
Thoracic Outlet syndrome	G54.0
Tinnitus, unspecified ear	H93.19
Tobacco depend/ unspec	F17.20
Torticollis	M43.6
Tremors, essential	G25.0
Tremors, unspecified	R25.1
Trigeminal neuralgia	G50.0
Ulcerative colitis	K51.80
Ureteral calculus	N20.1
Vertigo, benign, unspec	H81.10
Viral Hepatitis B, chronic	B19.10
Viral Hepatitis C, chronic	B19.20
Vomiting, unspecified	R11.10

Cannabis as Medicine *from previous page*

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. On the previous 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 8 illustration)* results in a measurable change in the function of the receptor. 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.

Retrgrade 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.

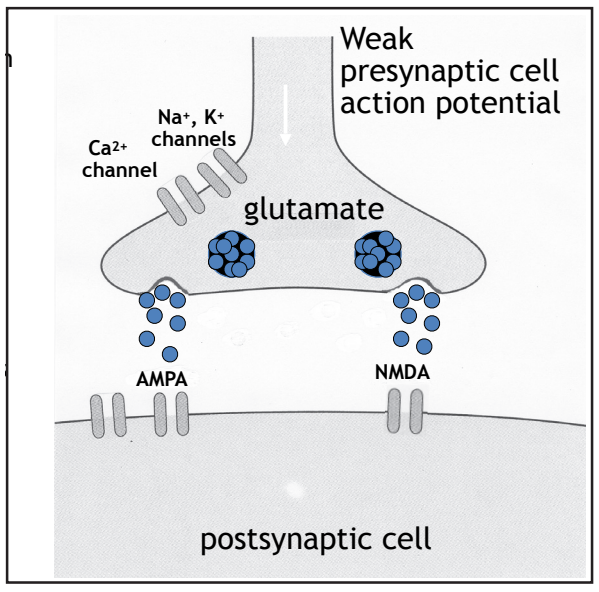
In 1996 after California voters legalized medical use, Tod Mikuriya was ridiculed by federal officials for authorizing patients to use marijuana to treat any condition for which it provided relief. The Drug Czar said Mikuriya was practicing "Cheech and Chong medicine."

By 2013, two researchers held in highest esteem bu 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 my 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."

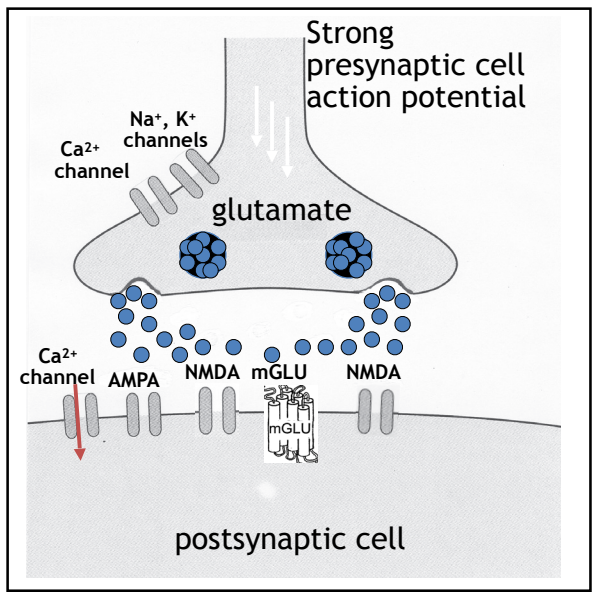
In effect these researchers are inviting the pharmaceutical industry to bring to the public the next generation of cannabinoid medicines.

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

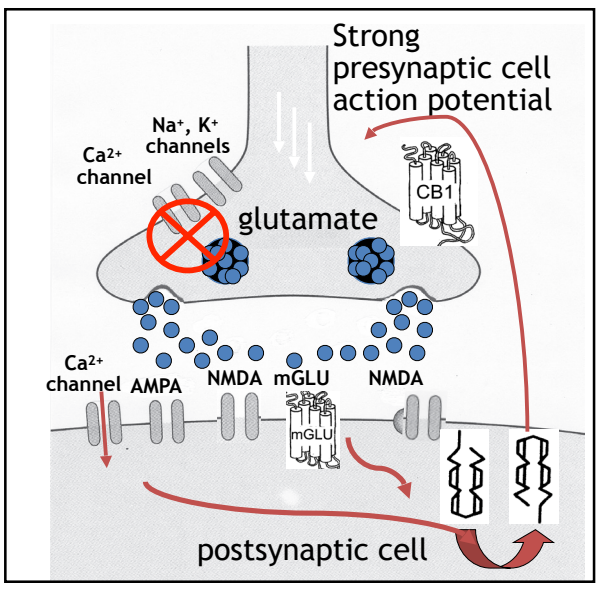
Retrograde Signaling —How cannabinoids promote homeostasis



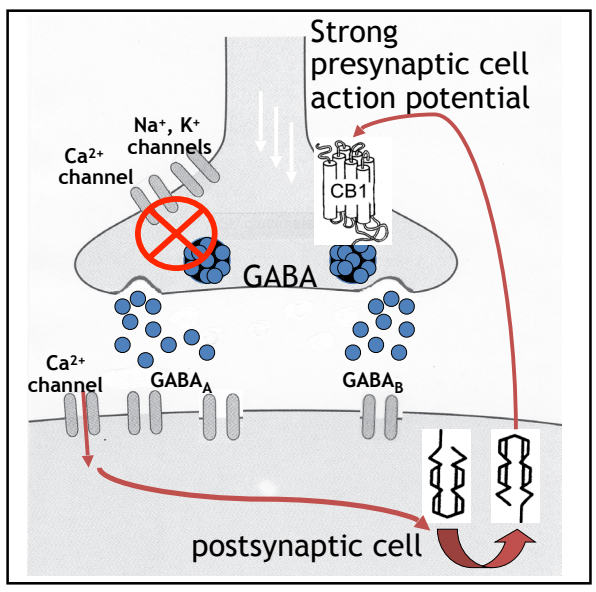
Weak action potential from depolarized neuron arrives at presynaptic axon and opens voltage-gated calcium channels... Ca^{2+} influx releases glutamate vesicles. Glutamate, an excitatory neurotransmitter, diffuses across the synaptic cleft to activate receptors in the postsynaptic cell. NMDA and AMPA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

Almost limitless therapeutic potential

"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".—*Pal Pacher and George Kunos, April 2013*

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 dysphorira 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 the National Institute on Drug Abuse 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."

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

JYH: 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.)*

Children can use very high doses —25 milligrams of CBD per kilogram of body weight. A study at UCSF showed some loose stools in children getting those massive doses. But in general, adults and children are getting benefits with more-or-less comparable doses.

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.
- 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.

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 cananbis 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.

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

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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

Cannabis as Medicine *from previous page*

Cannabis clinicians recommend using the plant and medicinal products made from it —flowers, oils, tinctures, salves and all kinds of foods, beverages and chocolates.

Lower grade-point averages associated with persisten cannabis usage in high school pupils lost statistical significance when controlling for concomitant alcohol and tobaccco 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 counfounds (Mokrysz et al, 2016).

The NIIDA director often cites a surmised neurotoxic effect of cannabis on the developing brain that permanently lowers IQ. This very small study failed to account for important confounding factors, including socioeconomic status. Its conclusions have been discredited. DISCUSS?

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.

In my practuce I know of one patient who had a severe psychosis after ingesting a massive dose. It lasted a week, resolved on its own and did not recur.

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

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?"

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 patients consistently report that they have neither an addiction nor any withdrawal syndrome associated with cannabis use (Hergenrather, 2017).

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.

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?

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 benzodiazepams usually go much more slowly. Tapering off benzos might take months.

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

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.

continued on next page

Actual Adverse Effects

- Dry mucous membranes, injected conjunctiva, unsteady gait

  short-term memory loss.
- Irritant to airway when ihhaled —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:

3. 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 autonomically stable at 30 days than their matched.

Cannabis as Medicine *from previous page*

Developing a Treatment Plan

Another concern is Hyperemesis syndrome, which is relatively rare. It's seen in the ERs occasionally —a cannabis user who started vomiting. They have to stop using cannabis. The receptors seem to re-set, and after a day they are back to feeling normal and can go rback to using cannabis therapeutically

Drug-drug interactions are rare. The only problem is with the anti-epilepsy drug clobazam, which is metabolized by the same metabolic pathway as CBD. So if your patient is on really high doses of CBD, you have to watch the blood levels of the anticonvulsant.

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.

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.

We use female flowering plants —flowers, oils, tinctures, salves and all kinds of foods, beverages and chocolates.

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

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. Distinct from industrial hemp by having more than .03%

There are 150 terpenes —some activate the CB receptors— and 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 it 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 cannabus 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 *(as explained by Dr. Meiri elsewhere in this issue)*. These kids were getting 300 milligrams of CBD per day and their behavior had greatly improved. Until one day caregivers started reporting that the medicine had stopped working. 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 clinicians advise using two or more strains in hopes of finding a beneficial minor cannabinoid or terpene. SENTENCE ADDED BASED ON WHAT I'VE HEARD FROM GOLDSTRICH AND SUNIL AGGARWAL.

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.

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.

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 sprays, cannabinoids enter the bloodstream through the buccal membrane in the mouth, avoiding metabolism by the liver (although a small amount may get swallowed).

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,

Dosing frequency can vary from one milligram to a thousand milligrams a day, You can use large amounts in treatments OF WHICH DISEASES?

Methods of Administration

Smoke and Vapor	Bioavailability: 2-56%, 10-25% Avoids first pass metabolism
Oral forms	Bioavailability: 10-20%, 4-20% 6% cookies
Rectal & vaginal. (Hemisuccinate).	Bioavailability: twice oral route Lower first-pass metabolism
Topical Administration	Bioavailability: minimal
Transdermal Administration	Bioavailability: unknown (Huestis 2007) Avoids first-pass metabolism

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 hepaticas CYP-450 metabolic pathways are manifest as slow, intermediate, and fast metabolizers.
- Cannabidiol (CBD) potently inhibits CYP3A isoforms and CYP2C19.
- There are no 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.

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

Entourage Effect

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

Cannabinoids: >100 cannabinoids 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(1).

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

THCV is a CB1 partial antagonist or at higher doses as an agonist (7). Utility in metabolic syndrome and as an anorectant.

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

Terpenes: 150-200 in cannabis

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

Effects of a few dominant terpenes:

A Pinene: bronchodilating (4), anti-inflammatory (5), AChE inhibitor (14)

Limonene: anxiolytic (6,7), antidepressant (10), apoptosis in breast cancer (15)

Linalool: sedative (8), anti-anxiety (9), analgesic (16), anticonvulsant (17)

ß Myrcene: sedating, muscle relaxant, hypnotic (11), analgesic (12)

ß Caryophyllene: gastric cytoprotection (13), antimalarial (18), CB2 agonist (19)

Nerolidol: sedative (20), potent antimalarial

Humulene: anti-inflammatory (23), anticancer

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 itnernalization of cannabinoid receptors coming out of the cell membrane and back into the cell. So the body is auto-regulating the population of cannabindo 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.

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