Using Cannabis as Medicine

The author, a general practitioner in California, has recommended cannabis to some 3,000 patients and monitored its use in 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. 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 Cannabinoid Physicians, a group of physicians who meet quarterly to talk about 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, 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 legalizing marijuana. For the next 20 years we will get a litany of refined legislative changes.

One aspect of the new law is detrimental to medical users. In any case, your patients should know not to go to work impaired and not to drive impaired.

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

So, in California you can lose your job — or not be hired — if you test positive for cannabinoids. California employers use a cutoff of 50 nanograms per milliliter, which is a reasonable number. Of 10,000 tests, 1,000 will be positive. Of these, 500 will be false positives. That number has been the same for 25 years. But what about access to marijuana dispensaries? On a site called Greenstate.com, you can type in a location, also report benefit from THC and CBD.

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. A patchwork of conflicting cannabis laws exist from county to county to city. There are 114 jurisdictions in the Bay Area alone. A patchwork of conflicting cannabis laws exist from county to county to city.

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...
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 (cannabidiol) 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 Alyyn 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 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—arachidonyl ethanolamine (AEA). They named it “anandamid” 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 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 hydra—excepting the insects—rely on endocannabinoids to bring us back into balance or homeostasis.

CB1 receptors are concentrated primarily in the central nervous system but they are also found associated with nerve cells throughout the body. CB2 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, TRPV1, PPAR and other targets).
  - endogenous ligands, endocannabinoids
  - proteins involved in synthesis, transport, and metabolism of the receptors and ligands.

Anandamide (AEA)

- Primary endogenous ligand at CB1 receptor.
  - 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)

Depressed 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)

The endocannabinoid system enables us to eat, sleep, relax, and 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 cyto-protection, 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 stroke volume. Hence, this unique and powerful cannabinoid role as a neuroprotectors was discovered and patented. In response to this ambulance ride 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 AMBULANCE 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 Anandamid.

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.

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.
Cannabis as Medicine

Three Plant Cannabinoids

<table>
<thead>
<tr>
<th>THC</th>
<th>CBD</th>
<th>THCV</th>
<th>CBDv</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ1-THC tetrahydrocannabinol</td>
<td>cannabidiol</td>
<td>tetrahydrocannabinolic acid</td>
<td>cannabinol</td>
</tr>
</tbody>
</table>

Decarboxylation

\[
\text{CO}_2 + \text{THCA} \rightarrow \text{THC} + \text{H}_2\text{O}
\]

The mechanism by which THC and other cannabinoids activate the CB1 receptor is depicted above. THC (blue arrows) activates the receptor to inhibit adenylate cyclase and calcium channels. Anandamide (yellow) only inhibits adenylate cyclase. 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 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 CUTF?

Pharmacologic effects of cannabinoids

Many of the pharmacological actions we can expect from cannabinoid trafficking are the result of the expression of genes. DID YOU WANT THIS CUTF?

- Analgesic
- Anti-inflammatory
- Immuno-suppressive
- Anti-emetic
- Neuroprotectant
- Antispasmodic
- Anticonvulsant
- Anti-emetic
- Induces sleep
- Anti-psoriatic
- Anti-pruritic
- Antiphlogistic
- Antidiabetic
- Antinociceptive
- Antioxidant
- Antithrombotic
- Anti-angiogenesis
- Anti-metastatic
- Antineoplastic
- Anti-cancer
- Antihypertensive
- Antihyperlipidemic
- Vasorelaxant
- Anti-angio genesis
- Anti-neoangiogenesis
- Antineoplastic
- Anti-proliferative
- Antimigraine
- Anti-parkinson's
- Anti-movement disorder
- Anti-pain
- Anti-tumor
- Anti-inflammation
- Antipyretic
- Anti-gastroesophageal
- Antipeptic
- Antiallergic
- Anti-diabetes
- Anti-glaucoma
- Antihypertensive
- Anticoagulant
- Antithrombotic
- Anti-inflammatory
- Anti-oxidant
- Anti-cancer
- Anti-inflammatory
- Anti-neuropathic
- Anti-pain
- Anti-stroke
- Anti-migraine
- Anti-convulsion
- Anti-seizure
- Anti-epileptic
- Anti-convulsion
- Anti-seizure
- Anti-epileptic
- Anti-convulsion
- Anti-seizure
- Anti-epileptic

- Acid reflux
- Stomach acid
- GI secretions
- Appetite
- Induces sleep
- Anticonvulsant
- Antipsychotic
- Anxiolytic
- Antidepressant
- Vasorelaxant
- Antihypertensive
- Anti-angina
- Anti-pain
- Anti-stroke
- Anti-migraine
- Anti-convulsion
- Anti-seizure
- Anti-epileptic
- Anti-convulsion
- Anti-seizure
- Anti-epileptic

Conditions Seen in Clinical Practice

- Pain (acute, chronic inflammatory, neuropathic)
- Meningitis (all kinds)
- Cancers
- Gastrointestinal disorders
- Insomnia
- Migraines headaches
- Addictions (including Alcoholism)
- Spastic disorders
- Autoimmune disorders and host vs. graft reactions
- Neurodegenerative disorders
- Glaucoma
- Skin diseases
- Epilepsy, Autism, Tourette’s, ADD, Dyslexia, Dementia

Endocannabinoid systems don’t all work the same

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

- Schizophrenia, uncompensated
- Bipolar
- Multiple Sclerosis
- Huntington’s Disease
- Parkinson’s, compensated
- Irritable bowel syndrome
- “Failure to thrive”
- Anorexia, uncompensated
- Chronic motion sickness
- Fibromyalgia
- Menstrual symptoms
- Seizure disorders

Given different agonists, acting at different receptors, resulting in different activities, it is not surprising that the cannabinoids exert a wide range 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
Cannabis as Medicine

Cannabis as Medicine

Cannabis Side Effects

Cannabis as Medicine

Cannabis as Medicine

Effects, such as alcohol, I would not exclude nobody because they have problems with addiction. Cannabinoids are weak drugs to help people to use 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.

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... excitation 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 medicinal 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 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 “modulating endocannabinoid activity my have therapeutic potential in all most 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.

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, vomiting sometimes, 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 off.

The way patients who need large cannabinoid dosages 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 shown 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 200 Los Angeles residents who had cancers of the lung and upper airways with controls of corre...
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 tests compared to cigarette smoking or other confounders (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 practice 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 cannabis use during pregnancy?”

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 in 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 (Hills, 1994; Rouges, 1998; Nett 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 opioid use? I usually recommend that people stay on the opioid dose they’re on, start using cannabis until they feel an effect. 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.

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.
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 can- nabis user who started vomiting. They have to stop using cannabis. Their receptors seem to re-set, and after a day they are back to feeling normal and can go back to using can- nabis therapeutically.

Drug-drug interactions are rare. The only problem is with the anti-epilepsy drug clozazine, which is metabo- lized 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 treatment option. Dronabinol (marketed as Marinol by Solvay and as Synodex by Insys) is synthetic THC. Nabulbinone 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**

-5.9-tert-hexanoxyoabinoindol (THC), the main psychoactive ingredient in Cannabis. THC has numerous pharma- cologic actions though it can also induce anxiety, paranoia, and impair memory. THC is a monotonous homolog of CBD, CBDV, 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 spasm, and sleep.

Cannabis grown for cannabinoid (CBD) may range from 1:1 CBD:THC to 25:1 CBD:THC. Distinct from industrial hemp by having more than .03% THC.

There are 150 terpenes — some activate the CB recep- tors— 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 therapeutic 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 mole- cule.

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

One of these CBD-dominant strains was being used inIsrael for kids with autism — plant strains designed for medical use. A strain that is 20-40% CBD is the non-psychoactive component. It has been bred up in strains. 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 mole- cule.

Cannabinoids can 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. Cannabis in edibles go through the portal vein into the liver where they get metabolized efficiently into 11-hy- droxy 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 cau- tion patients 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 baccal membrane in the mouth, avoiding me- talism 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 supposito- ries. 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 sev- eral patents pending using DMSO and various terpenes as vehicles to facilitate absorption, Dosing frequency can vary from one milligram to a thou- sand milligrams a day. You can use large amounts in treat- ments OF WHICH DISEASES?

**Dosing and Frequency**

Highly dependent on variables of 1) cannabinoid constituents, 2) individual metabolism, 3) toler- ance, and 4) time of day the treatment is given.

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

Dosing regimes
- **Nerolidol:** sedative (20), potent antimalarial (18), CB2 agonist (19)
- **ß Caryophyllene:** sedating, muscle relaxant, hypnotic (16), anticonvulsant (17)
- **Linalool:** anxiolytic (6,7), antidepressant (10), apoptosis in breast cancer (15)
- **Limonene:** bronchodilating (4), anti- inflammatory (3)
- **Lavandulene:** sedating, muscle relaxant, hypnotic (16)

**Terpenes**

- 150-200 in cannabis

Possess numerous therapeutic properties including: neuroprotection, bone stimulation, anxiety, antidepressant, anti-epileptic, antibacterial, antimalarial, anti- diabetic, vasorelaxant, antinausea, analgesic, antiimmunosuppressive, and other effects.

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 you won’t make you sleepy because you’ve already slept, your body doesn’t need sleep.

**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.

**Phytocannabinoid metabolism**

- Phytocannabinoids are metabolized in the liver by the CYP450 metabolic pathways.
- Genetic variations in the hepatic CYP450 metabolic pathways are manifest as slow, inter- mediate, 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 de- veloping a treatment plan.

**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-psychotoxic cannabinoid, softening the effects of THC. 2nd most prevalent in plant. Pharmacologic properties closely resembles THC.

THC 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 responses and effects such as THCA, CBG, CBDV, and others.

**Methods of Administration**

- Smoke and Vapor: Bioavailability: 2-5%, 10-25%
- Oral forms: Bioavailability: 10-20%, 4-20% 6 cookies
- Rectal & vaginal: Bioavailability: twice oral route (Hemisuccinate). Lower first-pass metabolism
- Topical: Bioavailability: minimal to nonexistent
- Transdermal: Bioavailability: unknown

Avoids first-pass metabolism

Where in this (issue). These kids were getting 300 milli- grams of CBD per day and their behavior had greatly im- proved. 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: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 need, 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 cannabinoids 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 can- nabis 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 cau- tion patients 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 baccal membrane in the mouth, avoiding me- talism 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 supposito- ries. 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 sev- eral patents pending using DMSO and various terpenes as vehicles to facilitate absorption, Dosing frequency can vary from one milligram to a thou- sand milligrams a day. You can use large amounts in treat- ments OF WHICH DISEASES?

**Natural cannabinoids**

- Are synthesized on demand as an adaptive response to cellular stress, aimed at re-establishing cellular homeostasis.
- Are rapidly metabolized mostly near their site of action.

**Suppositories**

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