Therapeutic Cannabis

What Clinicians Need to Know…

And Other Fun Facts

Internal Medicine Grand Rounds
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Steven L. Leach, MD
Division of General Internal Medicine

This is to acknowledge that Steven Leach, MD, has disclosed that he does not have any financial interest or other relationships with commercial concerns related directly or indirectly to this program. Dr. Leach will be discussing off label uses in his presentation.

Steven L. Leach, MD
Professor of Internal Medicine
Associate Vice Chair for Clinical Operations
Holder of the Irene Wadel and Robert I. Atha
Professorship in Internal Medicine
In Honor of John W. Burnside, MD

Steven Leach, MD, is a Professor of Medicine in the Division of General Internal Medicine. Dr. Leach attended medical school at the University of Chicago-Pritzker School of Medicine, where he graduated in 1993. He then completed his internship and residency training in Internal Medicine with an emphasis in Primary Care at the UT Southwestern Affiliated Hospitals. He joined the faculty of UT Southwestern in 1996. Dr. Leach has served in a number of administrative capacities, including Medical Director of the University's General Internal Medicine Clinic, Chief of Staff for University Hospital Zale Lipshy from 2006-2007 and the Chief Medical Officer for UT Southwestern University Hospitals from 2009-2015. He currently serves an Associate Vice Chair for Clinical Operations in the Department of Medicine, as the Medical Director for the Multispecialty Clinic and as the Medical Director for Student Health Services. In addition to his administrative responsibilities, he maintains a robust clinical practice.

Interests: Preventive Medicine, Quality Improvement

Objectives:

- Provide an introduction to the Endocannabinoid System
- Provide a context for reading the medical literature regarding therapeutic cannabis
- Provide a foundation for having an informed discussion with patients, families and colleagues

At the conclusion of this presentation the listener should be able to:

- Describe the regulatory history of cannabis in the United States
- Understand the fundamentals of the Endocannabinoid System
- Recognize the different types of cannabis products, how they are produced and their basic pharmacokinetics
- Articulate some of the common uses of therapeutic cannabis and the data on effectiveness

The use of medicinal and recreational cannabis is rapidly expanding in the United States. Twenty-nine states, plus Washington DC, Guam and Puerto Rico, have legalized cannabis for medicinal purposes[1]. Another 16 states have legalized non-psychoactive forms of cannabis (so called low THC cannabis). Eight states have legalized recreational use. The most recent National Survey of Drug Use and Health estimated that 22.2 million Americans (12 years of age and older) reported using cannabis in the past 30 days, and between 2002 and 2015 the percentage of past month cannabis users in this age range has steadily increased.[2] Medical providers are not uncommonly faced with questions about the safety and efficacy of these products.

Definitions

Cannabis refers to any plant of the genus *cannabis*. Botanists disagree about whether there are multiple species of cannabis, such as *C. sativa*, *C indica* and *C. ruderalis*, or if each of these is merely differing phenotypes of a single species*, C. sativa*. Hemp, or "industrial hemp" as it is often referred to, is a subset of cannabis characterized by certain physical and chemical properties. Hemp fiber is widely used for industrial purposes, such as fiber for paper, linen and brake pads. It is also used for medicinal purposes as well as its nutritional value (hemp seed oil). In common vernacular, marijuana is the subset of cannabis with psychoactive properties used for recreational and medicinal purposes. The physical attributes of hemp and marijuana are not mutually exclusive. For regulatory purposes the distinguishing feature is the content of Δ^9-tetrahydrocannabinol (THC), the psychoactive component of cannabis. Hemp is cannabis yielding ≤0.3% THC[3].

Over 100 organic substances are derived from cannabis. These derivatives and related synthetic analogues are collectively referred to as "cannabinoids." The most widely known of the naturally occurring agents are THC and cannabidiol (CBD or cannabis oil).

History

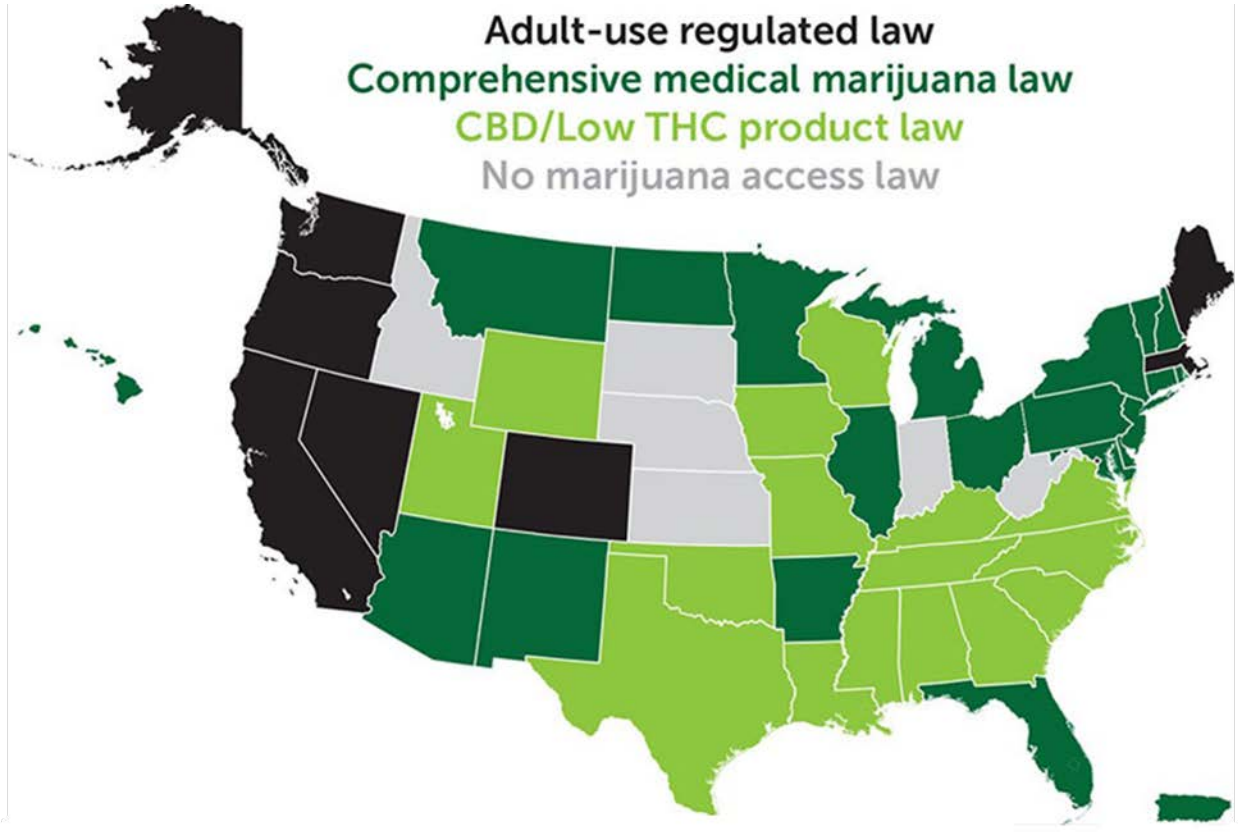
There is evidence that cannabis was used for medicinal purposes as early as 2700 BC in China. Indications for the use of cannabis included rheumatic pain, constipation, disorders of the female reproductive system, malaria, and others. In India, cannabis was used for both medicinal and psychoactive purposes from at least 1000 BC[4].

In America, industrial hemp was a colonial cash crop. Cannabis was introduced for medicinal purposes in the US in 1840 by William O'Shaughnessy as a treatment for tetanus and by Jean-Jaques Moreau de Tours for the treatment of mental disorders in 1845[5],[6]. It was rapidly adopted in the medical community and was included in the third edition of the US Pharmacopeia published in 1854[4]. But it did not take long for the psychoactive properties to become exploited. In 1853 the New York Times described cannabis extract as a "fashionable narcotic." A Harper's Magazine article in 1883 described oriental-style hashish parlors in New York City. By 1905 some states were regulating it as "poison" and began requiring a prescription.

At the same time, the Mexican Revolution of 1910 resulted in approximately 890,000 legal immigrants to the United States. Although recreational use of cannabis was not introduced by this group, smoking cannabis was common among laborers as a form of relaxation. These immigrants referred to cannabis as "mariguana." This new term, the practice of smoking marijuana and the associated stigma became tightly associated with this immigrant group and subsequently other minority groups.

The 1920's saw rapid expansion of state laws regulating cannabis use. In 1930 the US created the Federal Bureau of Narcotics and Harry Arslinger was appointed the first commissioner. He initiated the first federal war on drugs in the US. As a result of his efforts, the Marihuana Tax Act of 1937 was passed, essentially making the possession and transport of cannabis a federal crime. Although opposed by the AMA, cannabis was removed from the US Pharmacopeia in 1942.

Figure 1. Legalization of cannabis in the US in 2016[1].



The Boggs Act of 1952 and the Narcotics Control Act of 1956 imposed mandatory sentencing for possession of cannabis, with first time offenses resulting in a sentence of 2-10 years in prison and up to a $20,000 fine.

In 1970 the Marihuana Tax Act was ruled unconstitutional. Congress repealed that Act and passed the Comprehensive Drug Abuse Prevention and Control Act (Controlled Substances Act)

of 1970[7]. The Act created the "scheduling" of drugs as we know them today. Marijuana was classified as schedule 1 meaning it was not only dangerous but had no therapeutic value. By the mid 1980's, federal enforcement of drug crimes reached a climax with the three strikes you're out, resulting in up to 25 years in prison for repeat offenders and the death sentence for drug kingpins.

In spite of intensified criminalization, interest in cannabis for therapeutic purposes never disappeared. Synthetic THC received FDA approval as a therapeutic drug in 1985. Sold under the name dronabinol, it was approved for the treatment of chemotherapy-induced nausea and vomiting, as well as HIV-associated anorexia. In the ultimate act of irony, it was classified as a schedule 3 substance.

The last 20 years have been described as the era of decriminalization of cannabis. In 1996 California passed Proposition 215, otherwise known as The Compassionate Use Act, the first "medical marijuana" law. Since that time all but 5 states have now legalized at least some form of medicinal cannabis. In 2012 Colorado and Washington became the first states to legalize cannabis for recreational purposes. (Figure 1)

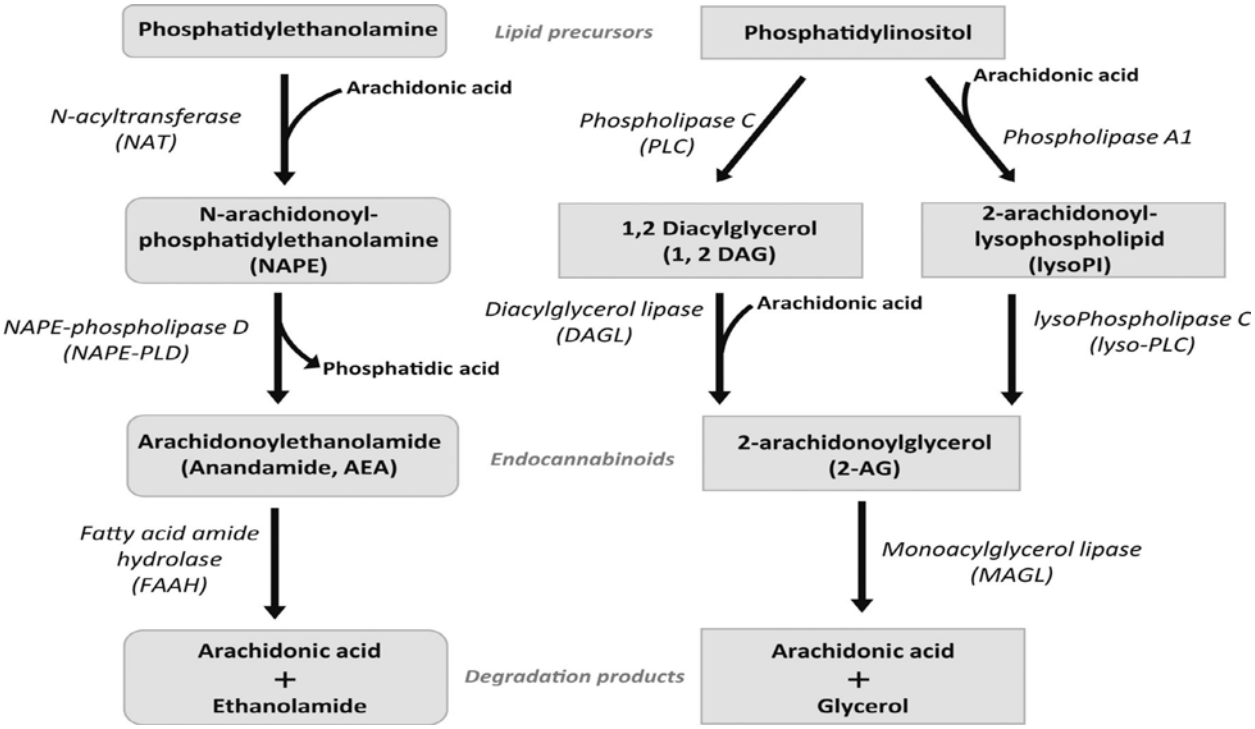
The Endocannabinoid System

The full chemical structure of THC was characterized in 1964 by Mechoulam and Gaoni [8]. But it was not until 1990 that the first cannabinoid receptor, CB1, was cloned, its DNA sequence was identified, and its location in the brain was determined by Matsuda [9] and Herkenham [10]. A number of discoveries rapidly followed, including the identification of a naturally occurring endocannabinoid in the brain, N-arachidonoylethanolamide, or AEA, (surnamed anandamide after the Sanskrit "Ananda," meaning "bliss or happy")[11], the identification of a second cannabinoid receptor, CB2[12], and the characterization of another endogenous cannabinoid, 2-Arachidonoylglycerol (2-AG)[13]. Collectively, the endogenous cannabinoids (endocannabinoids), cannabinoid receptors and the enzymes that synthesize and degrade endocannabinoids were labeled the Endocannabinoid System (ECS). The characterization of the ECS led to a massive expansion in cannabinoid research.

Endocannabinoids

The choreography of the Endocannabinoid System is remarkable in its complexity and its ubiquity. In the brain, endocannabinoids originate from membranes of post-synaptic neurons. They derive from phospholipids in response to activation of post synaptic cells. Unlike most neurotransmitters that are stored in advance in vesicles, endocannabinoids are produced on demand. In a relatively simple two-step process, both 2AG and anandamide are produced when combined with arachidonic acid. (Figure 2) The endocannabinoids then cross the synapse and activate presynaptic receptors on axon terminals. The production of these transmitters is tightly regulated, with degradation in both presynaptic and postsynaptic cells. In the brain they primarily function in retrograde signaling. Peripherally, they affect the regulation of metabolic pathways and inflammatory processes.

Figure 2. Synthesis and degradation of endogenous cannabinoids[14].



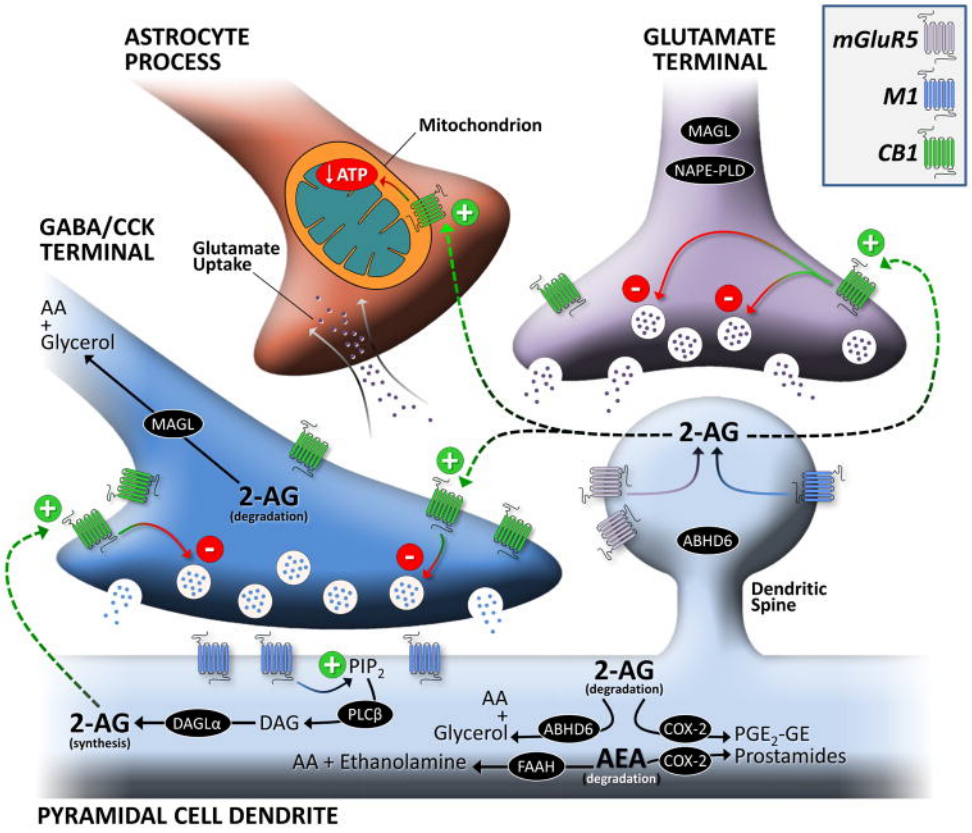
Anandamide is a low efficiency agonist of CB1 and a very low efficiency agonist for CB2. Under certain circumstances, anandamide can function as a competitive CB receptor antagonist. Anandamide is rapidly degraded and therefore found in low concentrations in the brain other tissues, but its activity can be prolonged by the inhibition of fatty acid aminohydrolase (FAAH). 2-AG is considered a high efficacy agonist of CB1 and CB2 receptors. It is present in the brain in much higher concentrations than anandamide, in part due to slower degredation.

In addition to 2AG and anandamide, additional endocannabinoids include 2-Arachidonoyl glycerol ether (noladin ether), O-Arachidonoyl ethanolamine (virodhamine) and N-Arachidonoyl dopamine (NADA). The effect of these endogenous ligands is less well understood. A number of synthetic cannabinoids have also been developed. The most well known of these is nabilone, which is commercially available. In addition, there are research agents such as (-) HU-210, (+) HU-211, WIN 55,212-2, (-) CP55,940.

Cannabinoid Receptors

CB1 and CB2 are G-protein coupled receptors (GPCR's). CB1 receptors are extraordinarily abundant in the brain—10 times more abundant in the brain than μ-opioid receptors[15]. CB1 receptors are also widely dispersed in peripheral tissues, including lung, liver, GI tract, pancreas, adipose tissue and muscle [14],[16],[17]. In fact, it is one of the most abundant mammalian GPCR's. CB2 receptors were first isolated from promyelocytic cell lines and are most abundant in cells derived from macrophages, such as microglia, osteoclasts and osteoblasts[17].

Figure 3. The Endocannabinoid System in the Brain[18]

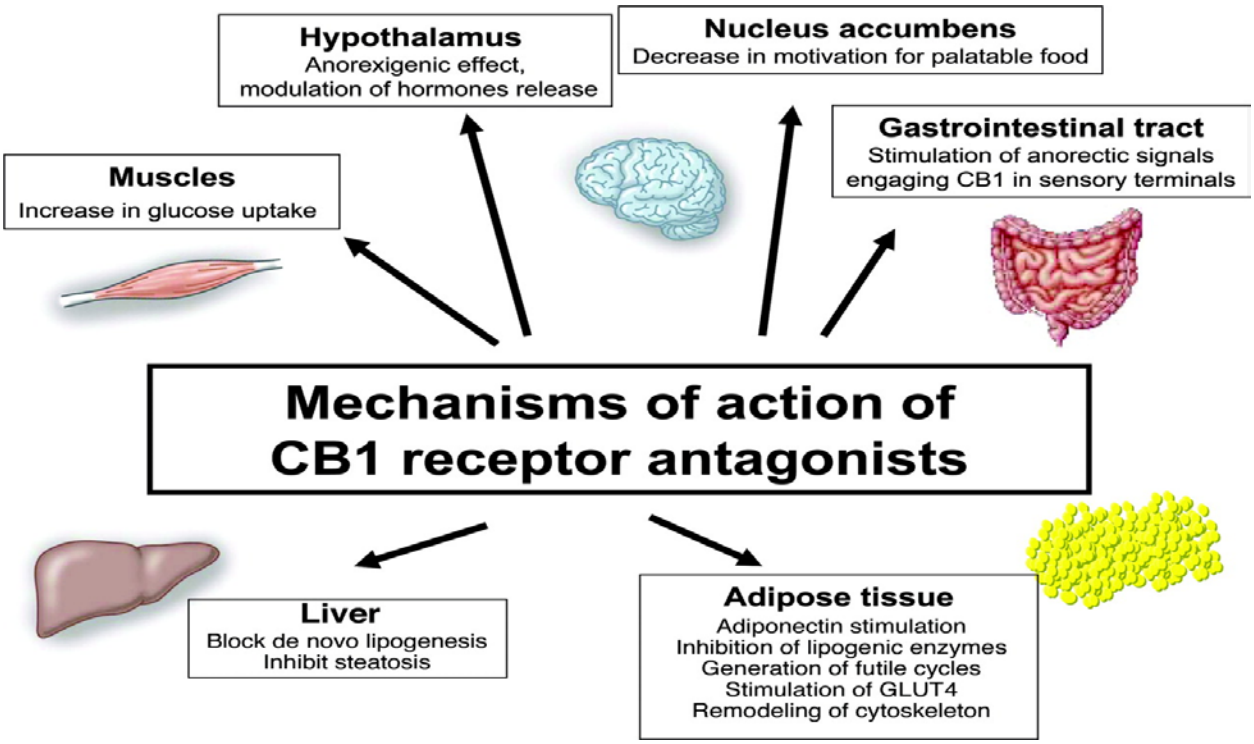


Overview of the localization of endocannabinoid system components at the synapse. Schematic of an inhibitory and excitatory terminal synapsing onto the dendritic shaft of a representative cortical principal neuron. The increased number of CB_1 receptors on the CCK/GABA terminal represents the higher density of CB_1 receptors found on these axon terminals. AA, arachidonic acid; ABHD6, alpha/beta domain-containing hydrolase 6; 2-AG, 2-arachidonoyl glycerol; ATP, adenosine triphosphate; CB_1, CB_1cannabinoid receptor; CCK, cholecystokinin; COX-2, cyclooxygenase-2; DAG, diacylglycerol; DAGLα, diacylglycerol lipase α; GABA, γ-aminobutyric acid; M_1, M_1 muscarinic receptor; MAGL, monoacylglycerol lipase; mGluR5, metabotropic glutamate receptor 5; FAAH, fatty acid aminohydrolase; NAPE-PLD, N-arachidonoyl phosphatidyl ethanolamine-preferring phospholipase D; PGE_2-GE, prostaglandin E_2glycerol ester; PIP_2, phosphatidyl inositol bis-phosphate; PLCβ, phospholipase C β. [19]

Localization studies of CB1 demonstrate that it is highly concentrated in areas of the brain such as the cerebral cortex, basal ganglia, hippocampus and cerebellum, and more moderately abundant in the brain stem, hypothalamus, spinal cord and amygdala[17]. High resolution studies also demonstrated that the receptors are preferentially present on axon terminals and are particularly abundant in GABAergic (inhibitory) interneurons. CB1 receptors are present, but less abundant, on glutamate (activating) terminals as well.

Activation of CB1 results in a number of physiologic consequences, including effects on synaptic function, gene transcription and cell motility[18]. These functions are mediated by the GPCR effects of inhibiting adenylyl cyclase, inhibiting certain voltage-gated calcium channels, activating mitogen-activated protein kinases, and the activation of G protein-linked inwardly rectifying potassium channels[17]. CB1 and endogenous endocannabinoids play a significant role in neurologic development, neuromodulation and neuroprotection. They also play an important role in pain transmission and modulation. Physiologic functions affected include memory, appetite, coordination, judgement, sensation and emotional responses.

Figure 4. The metabolic effects of CB1 receptor antagonists[20].



The psychotropic effects of cannabis garner significant attention. Less well known are the metabolic effects. One of the subtle effects of cannaibs is the so-called “munchies.” This observation, together with the finding that CB1 receptors are ubiquitous in peripheral tissue, including adipose tissue and muscle tissue, led to the discovery that the ECS is involved in every aspect of calorie regulation, including the “search, intake and metabolic handling of calories[14].” The activation of the ECS results in increased hunger, increased motivation to eat, increased food intake and fat storage, insulin resistance and a decrease in adiponectin. All of these actions serve as a major metabolic modulator. These findings, and the discovery of the CB1 reverse agonist, rimonabant, led to the first commercially available weight loss medication directed at the CB1 receptor. The agent was briefly marketed in Europe but was removed from the market due to unacceptable psychiatric side effects.

Even less well understood than the neurologic and metabolic effects of CB receptors is the role of these receptors and endogenous cannabinoids in the inflammatory process. The ECS has been shown to modulate cytokine production, inflammatory-cell migration and T helper cell activity. The ECS system is neuroprotective in brain injury, reduces myocyte and vascular injury and mediates inflammatory processes in inflammatory bowel disease and arthritis[21]. Interestingly, CB2 receptors are highly inducible and may increase up to 100 fold with tissue injury and inflammation[18].

In addition to CB1 and CB2, studies indicate that endocannabinoids activate other receptors, including TRPV1, 5-HT1 and GPR55, PPAR α and PPAR γ[17]. The physiologic effect of these interactions is still under investigation. Another interesting finding is the co-expression of opioid receptors with cannabinoid receptors[22]. The clinical significance of this finding is yet to be defined[23].

Cannabis and the Endocannabinoid System

It is notable that THC is a relatively weak agonist of both CB1 and CB2. It is most similar to anandamide. It has been shown to have a biphasic response, with one effect at low doses and a different effect at high doses. The commonly described subjective effects include relaxation, a pleasant "rush," altered time perception, increased appetite for sweet or fatty foods, tachycardia, dry mouth and increased sensitivity to stimuli such as music and color. Impairment of reaction time, driving and short term memory are also note. At high doses panic attacks, paranoid ideation and hallucinations are seen.

Ironically, CBD does not activate either CB1 or CB2. Yet is has been demonstrated to have a number of effects on the ECS and other clinically important receptors, including the following:

- Anandamide reuptake inhibitor
    - Increases levels of endocannabinoids by competitively binding Fatty Acid Binding Protein (FABP)
- Positive allosteric modulator of GABA-A receptors
    - Increased inhibitory neurotransmitters with sedating effect
- Negative allosteric modulator of CB1,
    - Reduces affinity for THC which mitigates psychoactive effect
- Activates 5-HT1A serotonin receptors
    - Modulates anxiety, addiction, appetite, sleep, pain perception, nausea and vomiting
- Activates TRPV1 (vanilloid) receptors—(also activated by capsaicin, anandamide)
    - Modulates pain perception, inflammation and body temperature
- GPR55 antagonist
    - Reduces cancer cell proliferation and osteoclast activity
- PPARγ agonist—nuclear membrane receptor that regulates genes, energy homeostasis, lipid uptake, insulin sensitivity
    - Anti-proliferative effect and tumor regression in human lung cancer cell lines

Unlike the psychoactive effects of THC, the subjective effects of CBD are less well known. In a study of cannabidiol for the treatment of epilepsy using a dose of 20 mg/kg/day, the most common side effect was somnolence. Others included diarrhea, decreased appetite, lethargy and fatigue[24].

Cannabinoids

In order to understand the medical literature regarding the effectiveness of therapeutic cannabis, it is important to understand how cannabis products are derived, their composition and their pharmacokinetics.

Cannabis producers have exploited cultivation techniques to develop numerous well-defined strains of cannabis that are marketed for their specific qualities, including color, texture, smell and chemical constituents. THC and CBD are derived from the flowering buds of female cannabis plants. These structures have a high content of small, glandular structures, called trichomes, in which THC and CBD are highly concentrated.

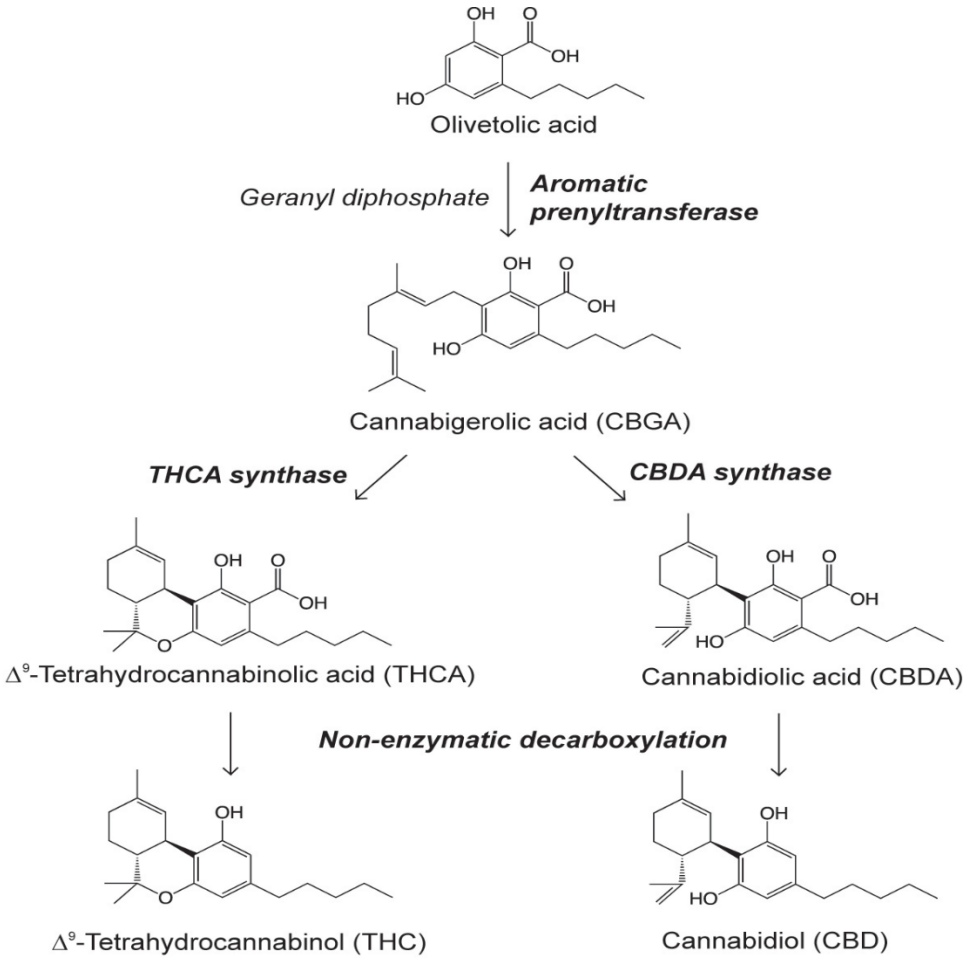
Figure 5. Cannabis trichomes.

While over 100 cannabinoids have been isolated from cannabis, one of the principal phenotypic variants is the relative amount of THC and CBD produced by a plant. Both are derivatives of olivetolic acid and its successor molecule, cannabigerolic acid (CBGA). CBGA is converted to Δ^9-tetrahydrocannabinolic acid (THCA) by THCA synthase, or cannabidiolic acid (CBDA) by CBDA synthase. (Figure 6) Interestingly, THCA is not pharmacologically active. Both THCA and CBDA undergo non-enzymatic decarboxylation under conditions of heat and light. Hence, the common practice of smoking or vaping cannabis products.

Cultivation techniques have resulted in increasingly potent strains of cannabis. In a study of marijuana confiscated by the US DEA, the relative content of THC increase from about 4% in 1995 to about 12% in 2004[19]. Commercially cultivated products are much higher, frequently as high as 25%.

Cannabis products are derived in a variety of ways. Buds of the female plant, rich with trichomes, may be harvested, dried and ground for smoking, commonly known as pot, ganga or weed. Alternatively, the resinous trichomes may be separated from the rest of the plant by mechanical means, producing a source of concentrated THC known as kief or keef. This is a powder that can be sprinkled on edibles or used for smoking. When compressed into a block, it is known as hashish.

Figure 6. Synthetic pathways of Δ^9-tetrahydrocannabinol and cannabidiol[25].



A common technique is to use a solvent such as butane to extract the active ingredient of cannabis. Supercritical CO_2 can also be used. These highly concentrated extracts may yield over 90% THC or CBD. The THC versions and are known as oil, wax, crumble or shatter.

It is important to note that not everything sold as marijuana is actually cannabis. Various plant materials ground to appear like cannabis, then sprayed with synthetic cannabinoids. Examples include K2 and Spice. These agents are very potent activators of endocannabinoid receptors and have a high rate of toxicity.

Pharmaceutical companies have been interested in therapeutic cannabis for decades. Since the introduction of dronabinol on the market in 1985, several other products have been approved and marketed. A number of these are highlighted in Table 1.

Table 1. Commercially available cannabinoids for medical use.

Substance	Form	Description
Epidiolex® Approved in Europe FDA Phase III	Oil (98%)	Concentrated CBD cannabis extract. Dose 5-25 mg/kg/day 200-300 mg/day
Cannador®	Oral capsule	Cannabis extract of THC/CBD in 2:1 ratio Up to 120 mg/day
Nabiximol (Sativex®) Approved in Europe FDA Phase III	Oral mucosal spray	THC/CBD extract from two different plants 2.7 mg THC/2.5 mg CBD per spray—up to 12 sprays per day Up to 120 mg/day
Ajulemic Acid (AjA) FDA Phase II	Oral Capsule	Synthetic non-psychoactive cannabinoid
Dronabinol (Marinol® CIII, Syndros® CII) FDA Approved	Oral Capsule	Synthetic THC Cap: 2.5-10 mg BID Liquid: 2.1-8.4 mg BID
Nabilone (Cesamet® CII) FDA Approved	Oral Capsule	Synthetic THC analogue 1-2 mg BID/TID

The pharmacokinetics of cannabis products are critical to their efficacy and safety. One of the reasons cannabis is smoked is because of its rapid effect. Inhaled cannabis has its psychotropic effect in seconds to minutes. When taken for therapeutic purposes, the agent may be taken in small aliquots every few minutes until a desired effect is achieved. The maximum plasma concentration occurs in 15-30 minutes and has a duration of action of 2-3 hours. In contrast, edible cannabis may not have its full psychotropic effect for 30-90 minutes. The maximal effect occurs in 2-3 hours and the duration of action may last for 4-12 hours. Stacking doses in the first 2 hours may result in significant over-dosage. It is important to note that edible cannabis undergoes extensive first pass metabolism in the liver, resulting in lower bioavailability or just 4-12%, compared to 10-35% for inhaled cannabis. Regardless of the route, cannabis rapidly crosses the placenta and passes into breast milk[26].

While not yet licensed, cannabis products are available as patches, metered dose inhalers, suppositories and topic creams and gels.

Cannabis edibles are hugely popular, allowing primarily recreational users to consume cannabis in an unlimited variety of ways. They are often sold as candies, baked goods and beverages. A concern is that edibles are very attractive to small children and even pets, and account for numerous accidental overdoses[27].

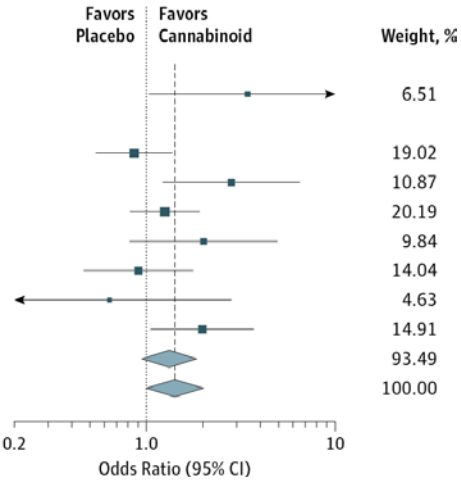
One of the lessons learned following legalization of recreational cannabis was the need for guiding consumers on the effective "dose" of cannabis, whether for recreational or medicinal purposes. Confusion about the amount of THC in certain products resulted in a number of unintended overdoses[27]. In Colorado, a unit "dose" of edible cannabis is now defined as 10 mg of THC. In Oregon, this "dose" is just 5 mg.

Efficacy Studies—Does It Work?

The great question today is, "Does it work?" In 2016, the National Academy of Science set out to answer that question. In the most comprehensive review to date, *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research* was published in January 2017[25]. This work drew upon the systematic reviews, meta-analyses and newer primary studies to establish an extensive list of conclusions about the efficacy of cannabis but also about its side effects. In addition to the National Academies publication, an extensive review was published by Whiting et. al. in JAMA in 2015[28].

Figure 7 The effect of cannabis for pain control[28].

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)	Weight, %
Tetrahydrocannabinol (smoked)						
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)	6.51
Nabiximols						
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)	19.02
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)	10.87
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)	20.19
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)	9.84
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)	14.04
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)	4.63
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)	14.91
Subtotal I^2 = 44.5%, (P = .0.94)	241	660	209	660	1.32 (0.94-1.86)	93.49
Overall I^2 = 47.6%, (P = .0.64)	254	685	215	685	1.41 (0.99-2.00)	100.00



Data from Colorado and Oregon, where therapeutic cannabis has now been legal for nearly 20 years, demonstrate that pain is by far the most common condition treated with therapeutic cannabis[25]. In his 2015 review, Whiting identified 28 randomized trials of pain, 27 of which were placebo controlled. The most common types of pain treated were neuropathy (17 studies), cancer pain, multiple sclerosis-related pain, rheumatoid arthritis, musculoskeletal conditions and chemotherapy-induced pain. An Analysis of 8 of the most robust studies demonstrate about a 40 percent reduction in pain (Figure 7). A similar analysis by Andreae et. al. of inhaled cannabis demonstrated a similar result[29].

But there is another line of evidence that is particularly intriguing and relevant to the current climate of opioid abuse. A study in Michigan suggested that legalizing cannabis resulted in a 64% decrease in opioids use[30]. Another study reported significant reductions in opioid prescriptions in states with legal access to cannabis[31]. Yet another study reported a 23%

reduction in opioid-related hospitalizations and a 13% reduction in opioid-related overdoses[32]. Bachhuber et. al. demonstrated that the reductions in opioid-related mortality in states with legal access to cannabis are not only sustainable but increase in magnitude over time[33].

Data on the effectiveness of cannabis for chemotherapy-induced nausea and vomiting is a bit more elusive. Whiting reviewed 28 trials, most of which were prior to 1984. All of these studies suggested a greater benefit compared to placebo and active agents, but were not statistically significant[28]. In a Cochrane review, Smith reviewed 23 trials and concluded that cannabis was more efficacious than placebo, similar to other active agents, but with more side effects[34]. In a more recent study, Meiri reported a trial of ondansetron vs. dronabinol. The effects were comparable and there was no added benefit to combination therapy[35].

Based on the available data, the National Academy of Sciences concluded that there is conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment of:

Chronic pain in adults (cannabis),
Chemotherapy-induced nausea and vomiting (oral cannabinoids)
Patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids).

They also concluded that there is moderate evidence that cannabis or cannabinoids are effective for improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis (cannabinoids, primarily nabiximols).

Epilepsy is another condition for which cannabis, both THC and CBD, has reached high profile, and currently the only treatable condition under the Texas compassionate use law. Public attention was riveted on this condition following a made-for-television documentary by Dr. Sanjay Gupta, in which he highlighted the case of Charlotte Figi, a young girl with a severe form of epilepsy called Dravet's syndrome. The documentary chronicled the family's battle to save her life and the dramatic response she had with cannabis oil rich in CBD.

There is evidence that THC and CBD can prevent seizures in animal models. It has also been noted the CB1 knock out mice are prone to seizures. However, two reviews in 2014 were unable to identify any high quality studies supporting clinical efficacy[36],[37]. Two non-randomized case series have showed dramatic improvements[38],[39]. Based on the quality of the evidence available, the National Academy of Sciences concluded that there was insufficient evidence to support or refute the conclusion that cannabinoids are effective treatment for epilepsy[25]. Since the time of that publication, two new randomized studies have been published that support the conclusion that CBD oil is at least moderately effective as an add on agent to standard therapy in Dravet Syndrome[24] and Lennox-Gastaut Syndrome[40].

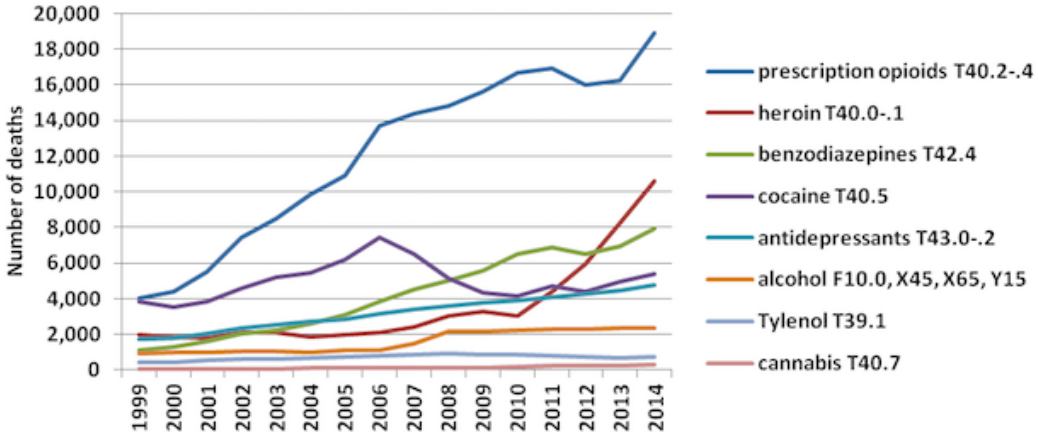
The legalization of cannabis for recreational purpose creates an even greater urgency to get high quality data on effectiveness. In effect, this legalization has created an entire class of over-

the-counter drugs without FDA oversight. While cannabis laws require registration and medical guidance in most states, much, if not most, cannabis therapy is self-treatment. Guidance for this treatment often comes from unreliable internet sources or sales staff at cannabis shops and is done without the knowledge of physicians. Little is known about the potential drug interactions with other prescription medications, potentially increasing the risk of toxic effects or undermining otherwise effective treatment. Further complicating the matter is the enormous variability of products and in some cases the unreliability of their labeling. In a survey by Vandrey et al, only 17% of products evaluated were accurately labeled[41].

Is It Safe?

The other great question about cannabis is, "Is it safe?" A quick scan of the internet shows numerous assertions that cannabis has never killed anyone. While this is not true, it is accurate to say that cannabis has a much better track record than opioids, benzodiazepines and even acetaminophen.

Figure 8. Poisoning deaths from various drugs, US 1999-2014[42].



Cannabis consumption, particularly smoking, has a number of cardiovascular effects, including tachycardia, increase blood pressure, increased cardiac output and increase peripheral blood flow producing a tendency to postural hypotension. Compared to high nicotine cigarettes, cannabis is more likely to increase myocardial oxygen demand and induce ischemia[43]. Numerous case reports describe sudden cardiac death associated with cannabis-induced acute ischemia[44]. There is evidence of cannabis-induced sudden death in setting of cardiomyopathy[45]. Transient asystole has also been reported[46],[47]. As the epidemiology of cannabis use shifts to increasing age, these risks are even more relevant.

Acute ingestion increases the risk of exacerbating psychotic conditions. Following legalization of recreational use of cannabis in Colorado, there were increased calls to poison control centers for children under 9 years of age[48] and an increase in cannabis-related traffic fatalities[49],[27].

The effects of long term use are unclear. Data suggests that 1 in 10 chronic users of cannabis will developed addiction, particularly those who start using it regularly when plasticity of the brain is still active (up to age 26). Brain regions rich in CB receptors experience volume loss with chronic exposure to THC[50]. Smoking cannabis is associated chronic bronchitis. Although smoking cannabis exposes a user to the same carcinogens as regular tobacco products, there is not yet convincing evidence of a causal link to lung cancer or COPD[51]. Pregnant and nursing women are more frequently using cannabis, resulting in perinatal and neonatal exposure at the critical stages of brain development. Perinatal exposure results in lower birth weight[52]. The effects on neurological and cognitive development are still being studied.

Conclusions

The characterization of the Endocannabinoid System was a remarkable discovery. Endogenous cannabinoids and endocannabinoid receptors are ubiquitous in the human body. Research in this area has dramatically increased our understanding of complex neurologic, metabolic and inflammatory pathways and has produced new therapeutic options. Yet there is much that remains unknown. Clinical research has been limited due to the regulatory restrictions on cannabis. With the change in public opinion leading to the legalization of medical cannabis in more than half of US states, it is likely that there will be an expansion of clinical research with cannabis products. Regardless of the outcome of that research, popular interest appears to be growing in crescendo. Consequently, it is more important than ever for clinicians to develop an understanding of the Endocannabinoid System, commercially available therapeutic cannabinoid products and the community practices associated with the self-treatment and recreational use of cannabis products.

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