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An Introduction to the **Biochemistry & Pharmacology of Medical Cannabis**

Presented by:

- **Adriane Fugh-Berman**, MD
- **Susan Wood**, PhD
- **Mikhail Kogan**, MD
- **Donald Abrams**, MD
- **Mary Lynn Mathre**, RN, MSN, CARN
- **Andrew Robie**, MD
- **Janani Raveendran**, MEd
- **Kofi Onumah**, PharmD, RPh
- **Rikin S. Mehta**, PharmD, JD, LLM
- **Shauna White**, PharmD, RPh
- **Jawara Kasimu-Graham**, RPh
- **Patricia D'Antonio**, RPh, MS, MBA

Important Information

- The slides will progress at their own pace.
- Do not attempt to speed up the video.
- The Post Test will only unlock after the entire video has been viewed.
- The video can be paused and resumed later.

Learning Objectives

- Define cultivar and chemovar, and describe continuing controversies related to these terms.
- Identify and describe the major cannabinoids in cannabis.
- Identify and describe the components of the endocannabinoid system.
- Identify the most common modes of administration and formulations of medical cannabis.
- Compare and contrast the benefits and drawbacks of modes of administration and formulations of medical cannabis.

HISTORY OF MEDICAL CANNABIS

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600 BCE

The earliest medical description of cannabis appears in *Shénnóng Běn Cǎo Jīng,* compiled *ca.* 100 CE from earlier oral knowledge. Earliest archeological evidence of cannabis drug use dates to *ca.* 600 BCE in Yánghǎi, China.

1850-1942

Cannabis sativa var. *indica* appeared in the United States Pharmacopeia between 1850 and 1942.

1616

The cultivation of *Cannabis sativa* for fiber in the U.S. dates to 1616 in Jamestown.

1937-1999

Social reform movements put constraints on medical cannabis in the 20th century. The 1937 Marihuana Tax Act taxed and criminalized the possession and sale of marihuana in all states. Medical cannabis remained technically legal, but increasing taxation and bureaucratic regulations discouraged its use.

HISTORY OF MEDICAL CANNABIS

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1970

In 1970, The Comprehensive Drug Abuse Prevention and Control Act (also called the Federal Controlled Substance Act) classified substances into five schedules. Cannabis/marijuana became a Schedule I controlled substance – no accepted medical use and high potential for abuse.

1970-1972

President Nixon appointed the Shafer Commission in 1970 to review cannabis. After a two-year review, the commission concluded that cannabis did not belong in Schedule I, and marijuana should be decriminalized (the First Report of the National Commission on Marihuana, 1972). Nixon ignored their findings.

1972

In 1972, the National Organization for the Reform of Marijuana Laws (NORML) petitioned the Drug Enforcement Administration (DEA) to reschedule cannabis. The NORML vs. DEA decision was reached in 1988 by the DEA's Administrative Law Judge Francis Young, who ruled that marijuana should be a Schedule II substance.

1994

Appeals and legal machinations continued until 1994, and another round began in 2002, but marijuana remains a Schedule I controlled substance.

TERMINOLOGY

"Marijuana" or "Marihuana"

- Originates from Mexican Spanish; the exact meaning is not known.
- The term was popularized by Harry Anslinger in the 1930s. Anslinger was the first commissioner of the Federal Bureau of Narcotics (which later became the DEA).

TERMINOLOGY

"Cannabis"

- Genus name originates from κάνναβις, written by Herodotus in 440 BCE.
- Main segregates include *Cannabis sativa* and *Cannabis indica*, best separated at the botanical rank of variety, rather than species.

TERMINOLOGY

"Hemp"

- Cannabis plant with a THC content less than 0.3%, grown for its seed and fiber
- Has been used commercially in thousands of products for more than 12,000 years
- Can describe any industrial or nutritional product from cannabis that is not used as a drug

STRAINS OF CANNABIS

- There are three commonly recognized "strains" of cannabis – ***C. sativa, C. indica,*** *and* ***C. ruderalis*****.** "Strain" names should not be confused with the formal botanical taxa *C. sativa and C. indica* because they do not correlate.
- Cannabis vendors often characterize "Sativa" as a high-THC* plant, "Indica" as a mixed THC-CBD** plant, and "Ruderalis" as a high-CBD plant. However, these concepts are simplistic and often inaccurate (McPartland 2014).

***THC =** tetrahydrocannibinol*

***CBD =** cannabidiol*

SATIVA VS. INDICA

- Some claim that "**Sativa**" is "**more stimulating, uplifting, energizing, and creativity enhancing,**" whereas "**Indica**" is "**relaxing, sedating, and pain reducing.**"
- Some also claim that "Sativa" is better at treating depression, headaches, nausea, and loss of appetite, while "Indica" is better at treating pain, inflammation, muscle spasms, epilepsy, glaucoma, and insomnia (British Columbia Compassion Club 2003).
- **Although there is some truth to these characterizations, Sativa-Indica hybrids dominate the cannabis market, thus blurring distinctions.**
  - Dispensaries often classify products by their percentage "Sativa" or "Indica." This is a ballpark estimate at best.

SOME CULTIVARS OF CANNABIS ARE RELIABLE

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- Cultivar (variety) names are applied to domesticated plants that have undergone years of breeding and genetic stabilization to express desired traits.
- For example, the cultivar **'Skunk #1'** underwent ten years of cross-breeding and inbreeding before it was released.
- Other well-stabilized cultivars were bred in the 1970s-1990s. Cultivars that underpin today's Cannabis genetics include: **'Haze,' 'Northern Lights,' 'G-13,' 'AK-47,' 'White Widow,' 'Hindu Kush,' 'Bubblegum,' 'Chronic,' 'Sour Diesel,' 'Blueberry,'** and others.
- Well-documented high-CBD cultivars include **'Harlequin'** (THC:CBD ratio from 3:2 to 1:1 in various analyses), **'Cannatonic'** (around 1:2.5), and **'AC/DC'** (around 1:20).

Flowering top 'Skunk #1'
(© John McPartland 2015)

PROBLEMS WITH CULTIVAR NAMES

- New names have cachet, and the Cannabis Strain Database (2015) now lists 597 cultivar names. Doyle (2007) refers to this meaningless proliferation of names as **"ganjanyms."**
- Many new cultivars have not been properly stabilized, causing batch-to-batch variation in seeds purchased from seed banks.
- There has been so much cross-breeding and blending of strains that strain names have become meaningless.
- A wide variety of products sold under the same cultivar name have been found, and products have been relabeled based on cultivar prices (Samuels 2008, Lee 2013).

DEPEND ON CHEMISTRY, NOT CULTIVARS

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- Instead of spurious cultivar names, products should be characterized by analytical chemistry – percentages of cannabinoids and terpenoids in dried flowering tops.
- **A product's chemical profile is more important than its strain name.**

  (Hazekamp and Fischedick 2012)

Cannabinoids and Terpenoids

- Cannabinoids include endocannabinoids, synthetic cannabinoids, and phytocannabinoids (derived from cannabis and other plants).
- The most abundant cannabinoid found in cannabis is tetrahydrocannabinolic acid (THCA),which is decarboxylated by smoking, vaporization, or processing to Δ9-tetrahydrocannabinol (THC).
- The cannabis-derived cannabinoids of most therapeutic interest are THC and cannabidiol (CBD). Minor cannabinoids include cannabigerol, cannabichromene, and tetrahydrocannabivarin (a short-chain C19 homolog of THC).
- Terpenoids are common, often aromatic, organic compounds found in many plants. Terpenoids found in cannabis include β-caryophyllene, myrcene, limonene, and pinene.

Cannabinoids
THC

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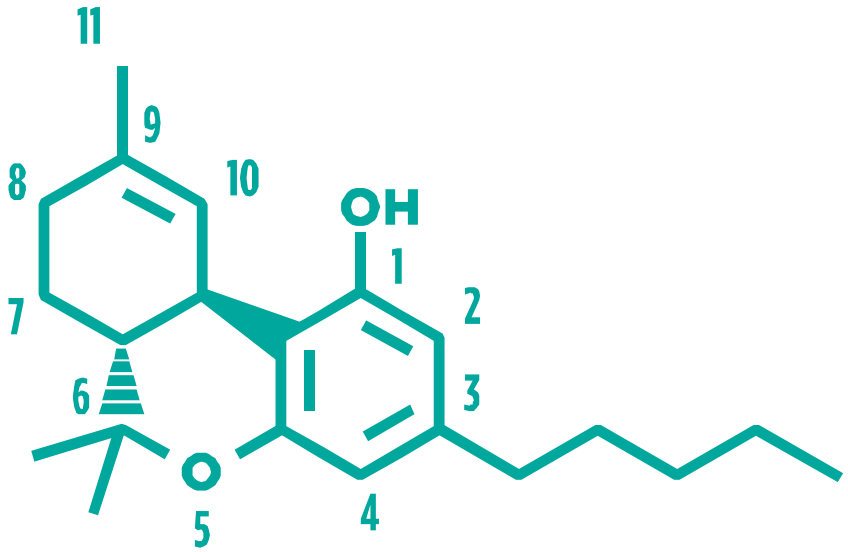
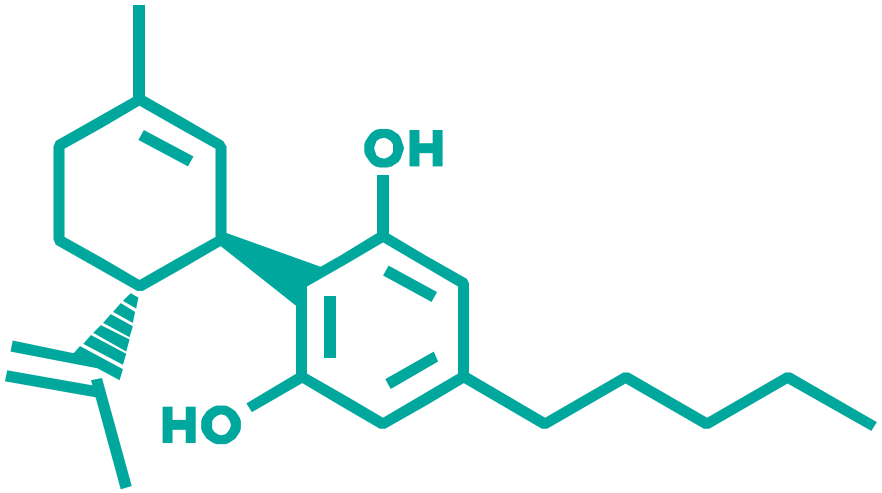
THC
discovered in 1964



- Psychoactive
- Anti-inflammatory
- Neuro-protective
- Anti-nausea
- Analgesic (neuropathic, chronic, and cancer pain)
- 11-OH-THC, the metabolite formed when THC undergoes first-pass metabolism, is estimated to be 4 times more psychoactive than THC.

Cannabinoids
CBD

CBD
discovered in 1940



- Non-psychoactive, with no significant affinity for CB1 and CB2 receptors
- Blocks formation of 11-OH-THC (the most psychoactive metabolite of THC)
- Potent CYP450 3A1 inhibitor
- Mitigates the side effects of THC (anxiety, dysphoria, panic reactions, and paranoia) while improving THC's therapeutic activity (Izzo *et al* 2009, Russo 2011).

Cannabinoids
Manifold Targets of CBD and Minor Cannabinoids

- CBD targets other receptors (GPR55, TRPV1, TRPV2, TRPA1, PPARγ, 5-HT1A, α3 glycine, etc).
- CBD inhibits adenosine uptake (caffeine, in contrast, increases adenosine), inhibits FAAH (increasing AEA), inhibits release of proinflammatory cytokines (TNF-α, IL-6, IL-1β), and acts as an antioxidant and free radical scavenger that is more potent than Vitamin C or Vitamin E.

  (McPartland *et al* 2015)

Chemical Profile

- Percentages of cannabinoids in cannabis determine its potency and effects.
- Many dispensaries provide chemical profiles of their products.
- High Pressure Liquid Chromatography (HPLC) coupled with Diode Array Detection (DAD) is the best method for separation and quantitative determination of major cannabinoids (Hillig and Mahlberg 2004).

Chemical Profile

- Qualitative characterizations can be based on the ratio of THC to CBD.

- Drug-type (Chemotype I) plants
  - **High THC/CBD ratio (>>1.0)**
  - THC percentage is usually 5-10%, but may be up to 25% in dried flowering tops.

- Intermediate-type (Chemotype II) plants
  - **THC/CBD ratio close to 1.0**
  - THC and CBD percentages are variable.

- Fiber-type (Chemotype III) plants ("Hemp")
  - **Low THC/CBD ratio (<<1.0)**
  - THC percentage is less than 0.3% in dried flowering tops.
  - In countries where hemp cultivation is permitted, strains are tested to verify that psychoactive potency is below 0.3% (Small 1999).

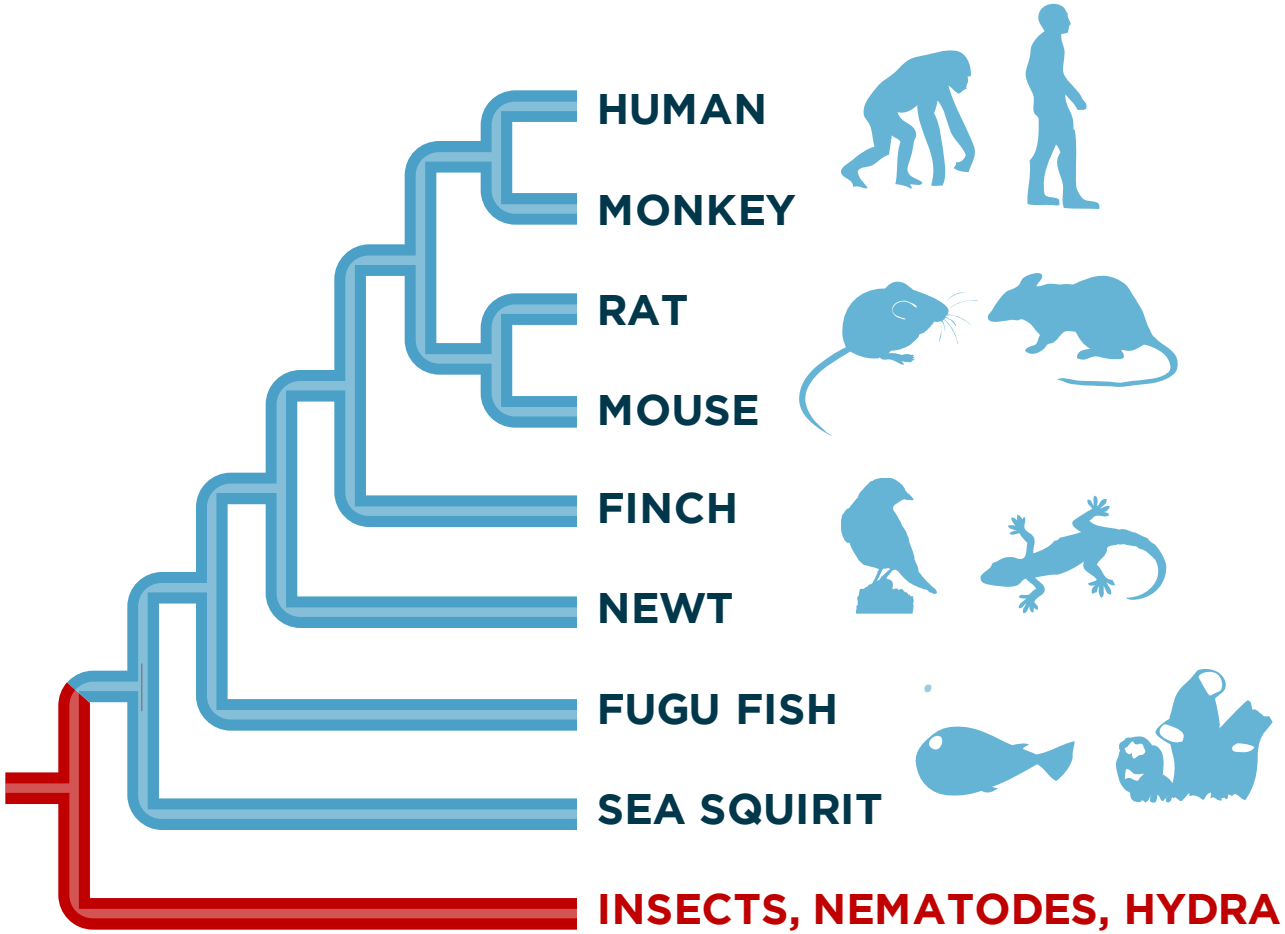
(Hillig and Mahlberg 2004)

The Endocannabinoid **(eCB)** System

- Cannabis primarily impacts all vertebrate animals through the endocannabinoid (eCB) system, which consists of:
  - Cannabinoid receptors: CB1 and CB2
  - Endogenous agonists
  - Agonist-metabolizing enzymes

- The eCB system has homeostatic roles in:
  - Hunger, feeding, and energy metabolism
  - Neural plasticity and neuroprotection
  - Nociception, pain, painful memory, and suffering
  - Autonomic tone
  - Immune response
  - Connective tissue repair
  - Human behavior

Cannabinoid Receptors
Phylogenetically Ancient



- Genomic and phylogenetic studies indicate that CB receptors evolved around 600 million years ago.
- CB receptors are present in every vertebrate investigated to date.
- CB receptors are *absent* in non-chordate invertebrates (insects, nematodes, *Hydra*), fungi, and plants.
- CB receptors existed long before cannabis evolved, *ca.* 25 million years ago.

(McPartland *et al* 2001, Matias *et al* 2005, McPartland *et al* 2007)

CB1 Receptors

- CB1 is primarily expressed in the **central nervous system**, but also in the uterus, testes, gut, adipose tissue, and elsewhere.
- In contrast to opioid receptors, there are no CB1 receptors in cardiorespiratory drive centers.
  - This may explain the lack of lethal overdoses from cannabis.
- Human brains have more CB1 receptors than opioid receptors.

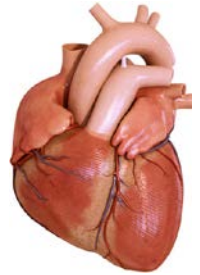
(Piomelli *et al* 2003)

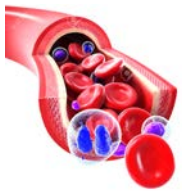
CB1 Receptors Beyond the CNS

CB1
Activation

CNS

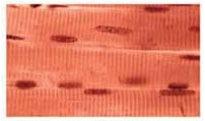
Appetite ↑
Cerebal Dilation ↑
Core body temperature ↓





CARDIOVASCULAR SYSTEM

Heart rate ↓
Blood pressure ↓
Myocardial contractility ↓
Coronary dilation ↑



LIVER

Lipogenesis Cerebal ↑
Adiponectin ↓
Plasma triglyceride ↑
HDL cholesterol ↓

ADIPOSE TISSUE

Insulin and leptin resistance ↑
Glucose tolerance ↓
Thermogenesis ↓

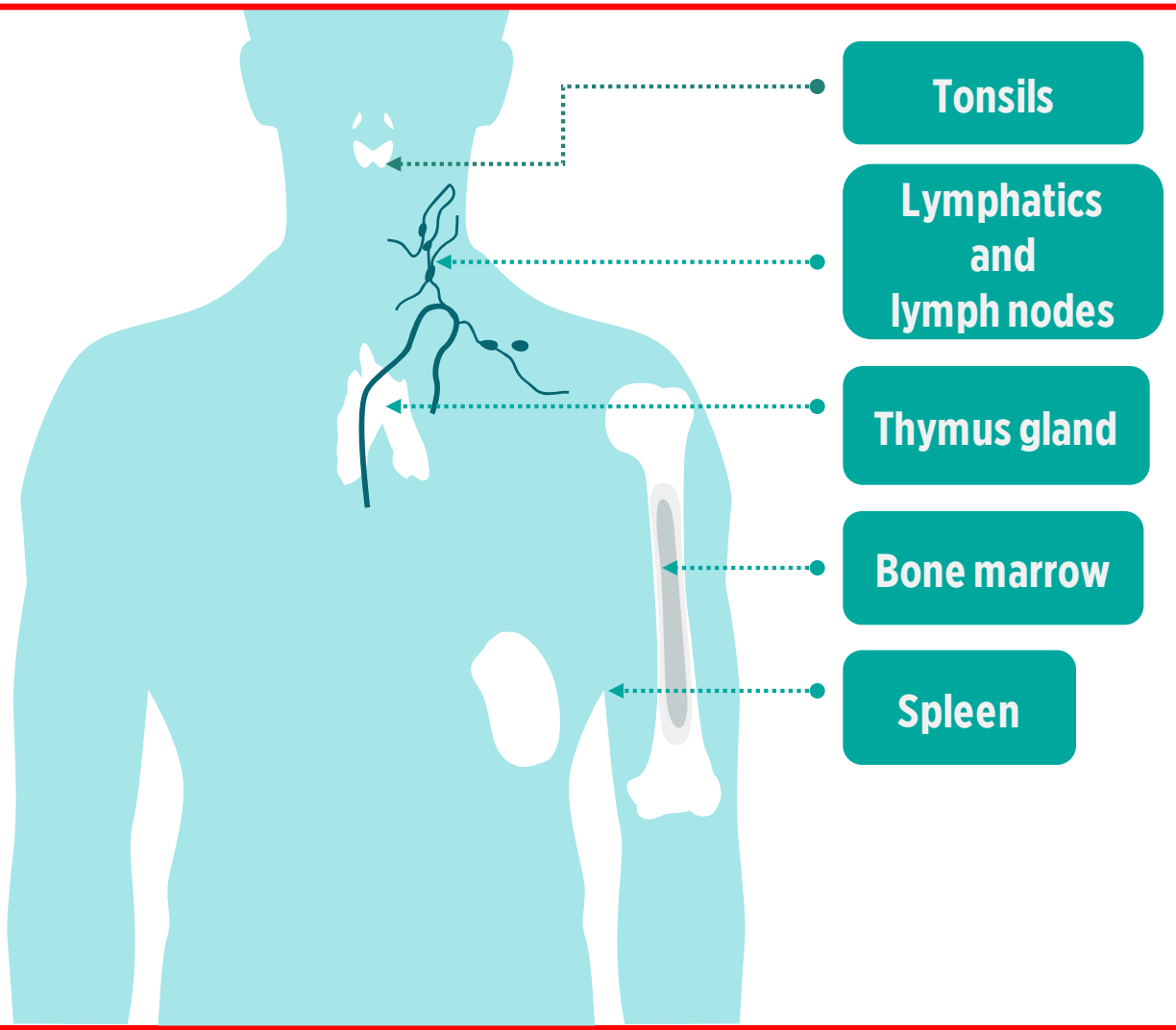
SKELETAL MUSCLE

(Pacher *et al* 2008)

CB2 Receptors

- CB2 is primarily expressed in **peripheral tissues of the immune system** (leukocytes, spleen, tonsils, thymus, bone marrow) and the gastrointestinal system.
- Cannabinoids have immunomodulating effects:
  - ↓ Th1 cytokines
    - IL-2, IFNγ, TNFα
  - ↑ Th2 cytokines
    - IL-5, IL-6, IL-10
  - ↓ Activity of mast cells, possibly neutrophils
  - ↓↑ Activity of macrophages

(Pertwee 2014)

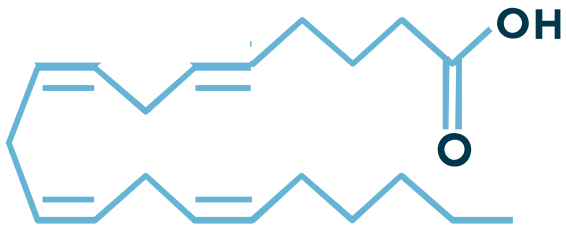


"Classical" Endogenous Cannabinoid Agonists

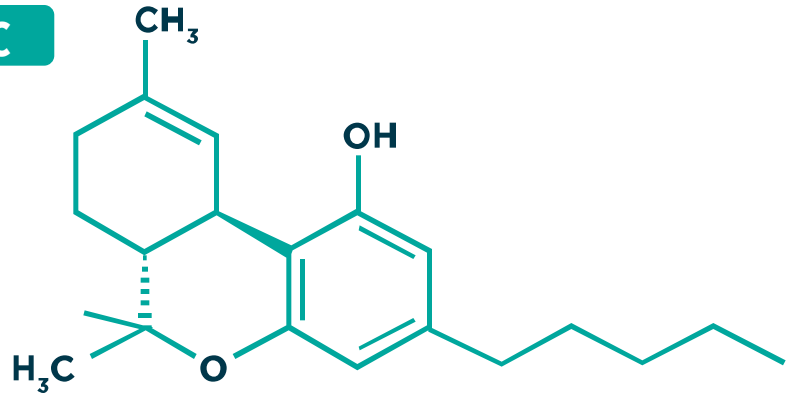
- There are endogenous cannabinoids that the body synthesizes and degrades as needed.
- The two best-characterized endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG), but "minor" endocannabinoids have been identified.
- They bind with and activate CB1 and CB2 receptors.

"Classical" Endogenous Cannabinoid Agonists

arachidonic acid

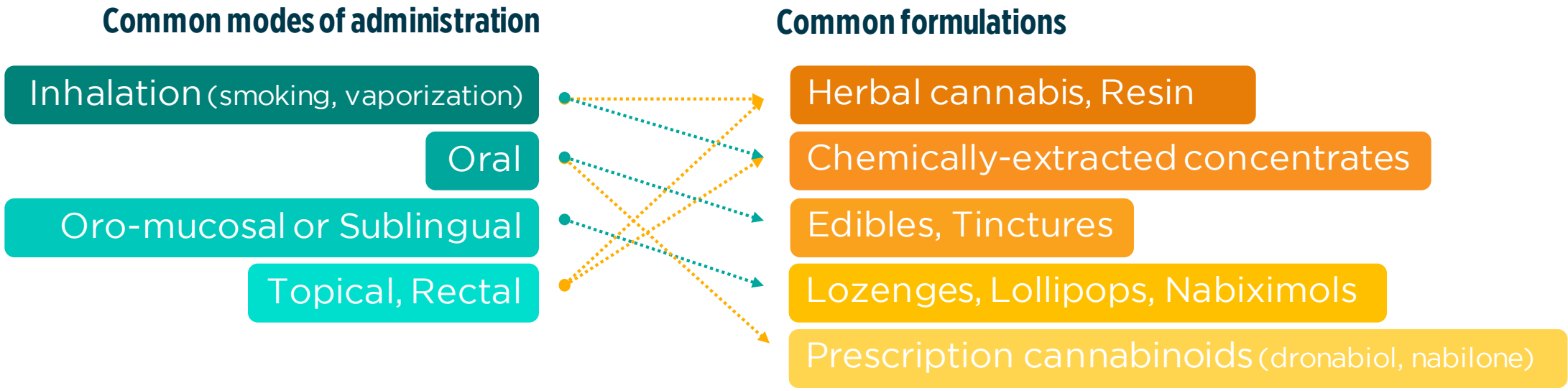


THC



- AEA and 2-AG are metabolites of arachidonic acid, and do not resemble THC.
- The primary biosynthetic enzymes are NAPE (AEA) and DAGL (2-AG). These enzymes cleave AEA and 2-AG from larger precursor phospholipids in cell membranes. They are not stored in synaptic vesicles like most neurotransmitters.
- The primary hydrolytic enzymes are FAAH (AEA) and MAGL (2-AG). These enzymes cleave AEA and 2-AG into arachidonic acid and either ethanolamine (AEA) or glycerol (2-AG).
- Arachidonic acid links the endocannabinoid system with the prostaglandin system, an interplay not yet fully elucidated.

Administration and **Formulations**



The following slides will describe each mode of administration and their associated formulations.

Route of Administration
Inhalation

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Inhaled cannabinoid drugs are available in several formulations

- Herbal cannabis
- Resin
- Chemically-extracted concentrates

Pharmacology

- A typical cannabis "joint" contains 0.5 to 0.8 grams of cannabis with about 8% THC.
  - About 20-70% of THC (~5 mg) reaches the lungs.
  - About 30% of THC enters systemic circulation and becomes bioavailable.
- The short onset of action makes dose titration possible, by spacing inhalations at 90-second intervals.
- THC peaks in plasma in 3 to 10 minutes, and is cleared in about 3 hours.
- Psychoactive effects appear within 90 seconds, and last 1-4 hours (Grotenhermen 2003).
- Smoking heats cannabis to the combustion point (500- 600ºC). Vaporizers, on the other hand, heat cannabis to the boiling point (155-250ºC), but well below the combustion point.

Route of Administration
Smoking

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Benefits of smoking

- Smoking cannabis in a cigarette or a pipe is simple and effective.

Disadvantages of smoking

- Cannabis and tobacco smoke contain similar bronchial irritants and carcinogens (Moir *et al* 2008).

Benefits of water pipes

- Drawing smoke through a water pipe effectively removes gas-phase smoke toxicants, including carbon monoxide, acetaldehyde, ammonia, and nitrosamines.

Disadvantages of water pipes

- Particulate-phase toxicants such as "tar" (polycyclic aromatic hydrocarbons) are not readily removed by water pipes.
- One study found that water pipes actually removed more THC than tar, which makes water pipes counterproductive (Gieringer 1996).

Route of Administration
Vaporization

- Vaporizers specifically made for cannabis go back to the 1970s.
- Vaporizers cause trichomes to burst and vaporize their contents, leaving behind a toasted brown chaff that smells a bit like popcorn.
- There are a wide variety of vaporizers commercially available. Options include The Volcano®, vapor pens, and other hand-held devices.
  - The Volcano® (Storz & Bickel, Germany) has been evaluated, clinically tested, and approved as a medical device. It retails for $380-$480.
  - Other portable vaporizers are shaped like pipes or e-cigarettes. They are less expensive, but their extraction efficiency and reproducibility have not been adequately tested.

The Volcano®
(Storz and Bickel 2009)

Portable vaporizers
(© John McPartland 2015)

Route of Administration
Vaporization

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Benefits of vaporization

- More efficient THC delivery compared to smoking
- No smoke and relatively little tar is generated.
- Vaporizers deliver a 1:10 cannabinoid-to-tar ratio (Gieringer 1996).
  - Cigarettes average 1:13; Pipes average 1:27
- Second-generation vaporizers are far more efficient, and generate up to a 9:1 cannabinoid-to-tar ratio (Hazekamp *et al* 2006, Pomahacova *et al* 2009).
- Lower risk of accidental burn injuries or fires
- In patients with respiratory disease, vaporizers provide cannabinoids with decreased bronchial distress.

Disadvantages of vaporization

- Need special equipment
- More difficult to use
- Higher cost (equipment, batteries, etc.) – equipment ranges from $50-500

Route of Administration
Topical

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Topical cannabinoid drugs are available in several formulations

- Herbal cannabis
- Resin
- Chemically-extracted concentrates

Types

- Creams (oil and water in equal proportions)
- Ointments (oil and water in a 80%:20% ratio)
- Transdermal patches (10 mg THC mixed in a polymer matrix and ethanol carrier)
- Herbal poultices

Pharmacology

- The pharmacokinetics of topically administered THC are poorly understood.

(The Pot Book 2010)

Route of Administration
Rectal

Rectal cannabinoid drugs are available in several formulations.

- Herbal cannabis
- Resin
- Chemically-extracted concentrates

Types

- Stable and bioavailable THC-ester suppositories have been formulated (El Sohly *et al* 1991).

Pharmacology

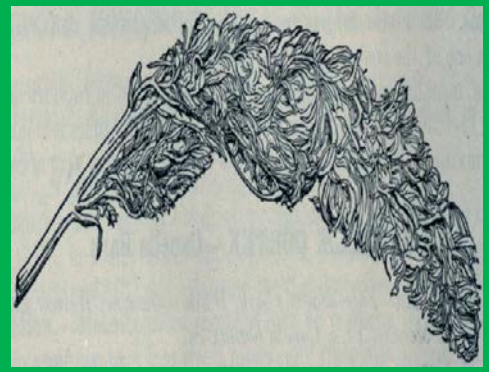
- Rectally administered suppository avoids first-pass metabolism through the liver, making THC more bioavailable than orally administration (El Sohly *et al* 1991).
- Onset of action is about 10 minutes (similar to oro-mucosal).

(The Pot Book 2010)

Formulations
Herbal cannabis

Description

- "Sinsemilla," the dried flowering tops of unseeded female plants, is the most common – and oldest – formulation of medical cannabis.
- In 2015, the average cost of cannabis flowers/buds sold in DC dispensaries was $20 per gram.* Cannabis is not covered by insurance.



sinsemilla
(United States Dispensatory 1905)

Potency

- THC content has increased over the years.
- Between 1979 and 2008, THC increased five-fold, from 1.58% to 8.80% (El Sohly *et al* 2000, Mehmedic *et al* 2010, Potter *et al* 2008).
  - This might be compared to the five-fold difference in caffeine between a typical cup of green tea and filtered coffee (McPartland 2008).

**DC dispensaries include: Metropolitan Wellness Center; Capital City Care; Takoma Wellness Center; National Holistic Healing Center; and Herbal Alternatives.*

Herbal cannabis

Despite legalization, quality control problems persist.

- Sloppy growers may sell herbal cannabis contaminated with fungi and bacteria (McPartland and Pruitt 1997).
- Some growers spray crops with dangerous pesticides, and the residues pass into cannabis smoke (Sullivan *et al* 2013).
- Standards for quality control (cultivation, drying, packaging) and analytical testing have been published (Upton *et al* 2013), and should be enforced.

Formulations
Resin (hashish)

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Description

- Resin (hashish) is composed of glandular trichomes mechanically extracted from flowering tops and upper leaves, formulated as powder or pressed into solids.

Potency

- THC content in hashish is usually 15-20%.

Adulteration

- Hashish from Morocco is reportedly adulterated (Caligani *et al* 2006), but no adulterated products have been found in U.S. medical dispensaries.

Magnified view of glandular trichomes (plant hairs) on a high-yield cultivar (Psychonaught 2009)

Formulations
Chemically-Extracted Concentrates

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Description

- Formulations include yellow waxy chips, dark brown viscous oil, and cartridges similar to electronic cigarettes (e-cigarettes) made from concentrates of dabs, wax, budder, honey oil, shatter and butane hash oil.
  - THC and CBD are lipophilic, so polar solvents, such as butane, hexane, or liquid carbon dioxide, must be used.

Potency

- Varies (up to 70% THC)

Chemically-Extracted Concentrates

Problems associated with chemical extraction

- The extraction processes may leave residual solvents. For example, extraction with lighter fuel may leave mercaptans behind. Amateur attempts at butane extraction using open systems have resulted in explosions and injuries.
- E-cigarette formulations often contain propylene glycol. Vaporizing propylene glycol may create carbonyls such as formaldehyde (Marco 2015).
- Chemical extraction often removes terpenoids, which have medical benefits.

Route of Administration
Oral

Oral cannabinoids are available in several formulations.

- "Edibles"
- Tinctures
- Prescription cannabinoids: dronabinol, nabilone

Pharmacology

- Differs from inhalation route of administration
- Delayed onset of action (about 90 minutes)
- Lasts longer, as peak plasma concentrations achieved in 1-6 hours, with terminal half-life of 20-30 hours (Grotenhermen 2003)
- Low and erratic gastrointestinal bioavailability
- Undergo first-pass metabolism; 50% of THC metabolized to 11-OH-THC before entering systemic circulation

Route of Administration
Oral

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Benefits of oral administration

- Useful for chronic conditions requiring higher dosage and longer half-life
- Lacks the pulmonary side effects associated with smoking

Advise patient to "Start low and go slow."

Disadvantages of oral administration

- Delayed onset of action makes dose titration difficult (some conditions, including muscle spasms, pain, PTSD, and nausea benefit from fast onset of action).
- Erratic gastrointestinal bioavailability also makes dose titration difficult.
- The first-pass metabolite 11-OH-THC may have 4-fold greater psychoactivity than THC (Browne and Weissman 1981).
- Overdosing is far more common with oral administration than inhalation.

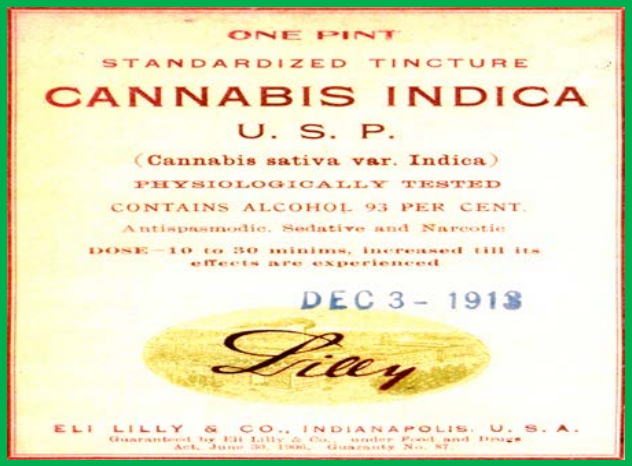
Edibles, Tinctures, Oils

Description

- Edibles (brownies and cookies), tinctures, and oils are formulated from herbal cannabis, resin, or concentrates.
- Brownies and cookies use butter or oil to extract cannabinoids and terpenoids.
- Tinctures and beverages use glycerin or ethanol to extract cannabinoids and terpenoids.

Potency

- The cannabinoid dosage in a commercial product is labeled - THC dosage is usually in the 10-25 mg range.



Cannabis ethanol tincture from 1913. Note small print regarding dosage titration: "10 to 30 minims, increased till its effects are experienced"

(© Mary Lynn Mathre 2015)

Edibles, Tinctures, Oils

Benefits of edibles, tinctures, oils

- Same benefits as oral cannabinoids
- Cost of active ingredients (per mg) is often less expensive.
- Some commercial products are high in CBD, and are therefore minimally psychoactive.
  - Useful for pediatric and geriatric populations

Disadvantages of edibles, tinctures, oils

- Same disadvantages as oral cannabinoids
- No clinical evidence base
- Edibles are attractive to children and must be stored securely.
- THC degrades faster in ethanolic tinctures than in frozen herbal cannabis.
- Preparation of edibles, tinctures, and oils is best left to a professional.
  - Dosage standardization for edibles is complex, prone to batch-to-batch variability.
  - Potency may vary within a single batch of edibles.

Prescription Cannabinoids
Dronabinol (Marinol®)

Description

- Dronabinol is a single-ingredient pharmaceutical of synthetic THC, approved as a DEA Schedule II drug in 1986, and moved to Schedule III in 1999 (Cooper 2013).
- The average cost of one month's supply of 2.5 mg dronabinol (1 capsule BID) is estimated to be $200 (GoodRx.com). Dronabinol is not covered by insurance.

Potency

- Capsules contain 2.5 mg, 5 mg, or 10 mg THC formulated with sesame oil (Cooper 2013).

Nabilone (Cesamet®)

Description

- Nabilone is a synthetic derivative of THC, approved by the FDA in 1985, but not marketed in the U.S. until 2006, as a Schedule II drug.
- The average cost of one month's supply of 1 mg nabilone (1 mg BID) is estimated to be $2000 (GoodRx.com). Nabilone is not covered by insurance.

Potency

- Capsules contain 1 mg nabilone formulated with povidone powder and corn starch.

Prescription Cannabinoids
Dronabinol and Nabilone

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Benefits of dronabinol and nabilone

- Same benefits as oral cannabinoids
- Products are standardized, legal, supported by many clinical trials, and approved by the FDA.
  - FDA-approved clinical indications for dronabinol
    - Chemotherapy-related nausea and vomiting
    - AIDS-associated anorexia/weight loss

    (Cooper 2013)
  - FDA-approved clinical indications for nabilone
    - Chemotherapy-related nausea and vomiting
- Nabilone causes minimal to no euphoria.

Dronabinol and Nabilone

Disadvantages of dronabinol and nabilone

- Same disadvantages as oral cannabinoids
- They lack other constituents in cannabis that mitigate the side effects of THC.
- Harms of either drug may outweigh benefits in elderly and frail populations.
  - Frequent lethargy and dizziness (possibly severe)
  - Anxiety and paranoia may be more pronounced in elderly
  - Dronabinol produces psychoactivity described as "weird"
  - Seizure risk greater than that of CBD-containing cannabis
  - Several deaths, mostly due to seizures, have been reported with dronabinol.
- Dronabinol precipitated dysphoria, depersonalization, anxiety, panic reactions, and paranoia in clinical trials (Cocchetto *et al* 1981). These adverse effects occur less frequently with whole cannabis (Grinspoon and Bakalar 1997).
- Nabilone adverse effects include lethargy, vertigo, xerostomia, depression, and psychosis.

Route of Administration
Oro-mucosal or Sublingual

Oro-mucosal cannabinoid drugs are available in several formulations.

- Lozenges, lollipops, and mouthstrips
- Tinctures dispensed with an atomizer spray
- Standardized whole-plant extract (nabiximols) dispensed in a metered-dose spray pump

Pharmacology

- Mixed absorption spectrum: some of the drug passes through the oral mucosa directly into the bloodstream, but the majority undergoes first-pass metabolism.
- Onset of action and peak plasma concentrations (C_{max}) occur sooner than the oral route (Karschner *et al* 2011).
- C_{max} values from nabiximols are below those reported from inhaled cannabis, imparting less psychoactivity (Stott *et al* 2013).

Oro-mucosal or Sublingual

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Benefits of oro-mucosal administration

- Better than oral route for patients with nausea

Disadvantages of oro-mucosal administration

- Makes it less psychoactive than either smoked or ingested cannabis, but still too psychoactive for some patients

Formulations
Lozenges and Lollipops

Description

- They are based on herbal cannabis, resin, or concentrates, extracted using glycerin, ethanol, or butane.

Potency

- The amount of THC in a product is labeled and is usually in the 10 mg range.

Child-proof container of cannabis lozenges. Label states "not tested for contaminants or potency, consume with caution."
(© John McPartland 2015)

Formulations
Lozenges and Lollipops

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Benefits of lozenges and lollipops

- Same benefits as oro-mucosal cannabinoids

Disadvantages of lozenges and lollipops

- Same disadvantages as oro-mucosal cannabinoids
- No clinical evidence base
- Like edibles, may be attractive to children, and should be stored securely.
- Dosage standardization is complex; these products are difficult to prepare at home.

Formulations Not Available in U.S.

Nabiximols (Sativex®)

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Description

- It is a standardized whole-plant extract delivered through metered spray pump (Guy and Stott 2005).
- It costs £175 ($191) per bottle (Johnson 2013).

Potency

- Delivers 27 mg THC and 25 mg CBD, plus minor cannabinoids and terpenoids (Guy and Stott 2005)

Formulations Not Available in U.S.

Nabiximols (Sativex®)

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Benefits of nabiximols

- Same benefits as oro-mucosal cannabinoids
- THC:CBD in 50:50 ratio decreases THC-associated side effects.
- Product is standardized, legal, supported by many clinical trials, and approved for neuropathic pain and muscle spasticity in Canada and Europe only.
- A related CBD-based whole-plant extract, Epidiolex®, was granted orphan drug designation by the FDA for two rare pediatric seizure disorders (Dravet Syndrome and Lennox-Gastaut syndrome), as well as neonatal hypoxic-ischemic encephalopathy; the drug is currently undergoing trials.

Disadvantages of nabiximols

- Same disadvantages as oro-mucosal cannabinoids

Formulations Not Available in U.S.

Ophthalmic Formulations

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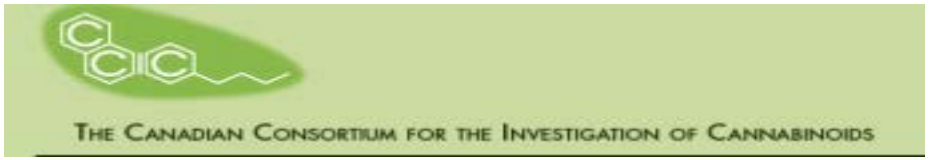
Description

- Ophthalmic drops of an unknown formulation have been licensed since 1987 in Jamaica (Canasol®), but no ophthalmic preparations are licensed in the U.S.
- Formulations with cyclodextrin have improved the aqueous solubility of THC in eye drops (Järvinen *et al* 2002).

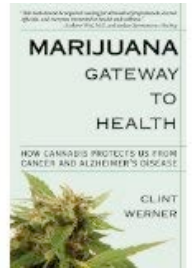
SUMMARY

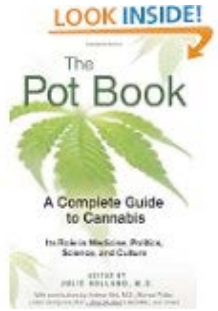
- A product's chemical profile is more important than its strain name.
- THC is the primary psychoactive ingredient of cannabis.
- CBD is non-psychoactive and has little affinity for CB1 and CB2 receptors.
- CB1 receptors are primarily expressed in the central nervous system.
- CB2 receptors are primarily expressed in peripheral tissues of the immune system.
- Common modes of administration of medical cannabis include inhalation (smoking, vaporization), oral, oro-mucosal or sublingual, topical, and rectal.
- Common formulations of medical cannabis include herbal cannabis, resin, chemically-extracted concentrates, tinctures, edibles, lozenges, lollipops, and prescription cannabinoids.
- Each mode of administration and formulation of medical cannabis has its strengths and drawbacks.
- Physicians should make recommendations for medical cannabis based on medical history, current medical condition, and a review of other medications or treatments that might also treat the condition for which the cannabis would be prescribed.

RESOURCES



- ICRS - http://www.icrs.co/index.html
- IACM - http://www.cannabis-med.org
- Patients Out of Time - http://www.medicalcannabis.com
- University of California's Center for Medicinal Cannabis Research - http://www.cmcr.ucsd.edu
- The Canadian Consortium for the Investigation of Cannabinoids - http://www.ccic.net





RESOURCES

For more information on prescribing in the District and to become a recommending physician visit:

doh.dc.gov/mmp

Please visit DCRx for a full list of references and more information on these and other treatment-related subjects.

doh.dc.gov/dcrx

Questions can be sent by email to doh.mmp@dc.gov or by regular mail to:

Medical Marijuana Program
Health Regulation and Licensing Administration
899 N. Capitol Street, NE
2nd Floor
Washington, DC 20002