Medical Cannabis

Cannabis constituents, dosage forms and patient information

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Financial Interest Disclaimer

The speaker has an indirect financial interest (ownership of stock) in G. W. Pharmaceuticals
a British biopharmaceutical company known for its multiple sclerosis treatment product Sativex, nabiximols.

Objectives

1. Explain the receptor-based effects of endogenous and exogenous cannabinoids
2. List the principal phytocannabinoids and assess data regarding their therapeutic uses
3. Describe the entourage effect and its importance in cannabis dosing
4. Review cannabis dosage forms and differentiate among their pharmacokinetics
5. Employ patient teaching strategies for safe and effective cannabis use.

Endocannabinoid System

- A homeostatic system found in all vertebrates
- Discovered within the last three decades
  - A PubMed search for "endocannabinoid"
    - 1993: 10 citations
    - 2014: 6141 citations
    - 2016: 7848 citations
- Referred to as the **endocannabinoid** system
  - **endo**genous system whose components interact with or resemble
  - compounds derived from the **cannabis** plant called **cannabinoids**.

McPartland, J. M. (2004). Phylogenomic and chemotaxonomic analysis of the endocannabinoid system. *Brain Res Brain Res Rev, 45*(1), 18-29. doi:10.1016/j.brainresrev.2003.11.005

Pacher, P., Bátkai, S., & Kunos, G. (2006). The endocannabinoid system as an emerging target of pharmacotherapy. *Diabetes, 55*(3), 389-462.

Russo, E. B. (2008). Cannabinoids in the management of difficult to treat pain. *Ther Clin Risk Manag, 4*(1), 245-259.

The Endocannabinoid System

- Three main components:
  - **Receptors**
  - **Endocannabinoids**
  - **Regulatory Enzymes**
- Also interacts with;
  - phytocannabinoids (plant derived cannabinoids)
  - synthetic cannabinoids
  - indirect agonists
  - antagonists

The Endocannabinoid System

- an internal homeostatic regulatory system
- influences multiple physiological processes
  - modulation of pain
  - seizure threshold
  - appetite
  - digestion
  - mood and other processes.
- may also play a role in regulation of the immune system, tumor surveillance, fertility, bone physiology, the hypothalamic-pituitary-adrenal axis and intraocular pressure

Receptors

- Cannabinoid receptor-1 (CB_1)
  - brain, nervous system, connective tissues and gonadal tissues
- Cannabinoid receptor-2 (CB_2)
  - mostly found in the periphery

Di Marzo, V. (2009). The endocannabinoid system: its general strategy of action, tools for its pharmacological manipulation and potential therapeutic exploitation. *Pharmacol Res, 60*(2), 77-84. doi:10.1016/j.phrs.2009.02.010

Location of Cannabinoid Receptors

Location	Structure	Function
CB_1 receptors		
CNS	Hippocampus	Memory storage
	Cerebellum	Coordination of motor function, posture, balance
	Basal ganglia	Movement control
	Hypothalamus	Thermal regulation, neuroendocrine release, appetite
	Spinal cord	Nociception
	Cerebral cortex	Emesis
Periphery	Lymphoid organs	Cell-mediated and innate immunity
	Vascular smooth muscle cells	Control of blood pressure
	Duodenum, ileum, myenteric plexus	Control of emesis
	Lung smooth muscle cells	Bronchodilation
	Eye ciliary body	Intraocular pressure
CB_2 receptors		
Periphery	Lymphoid tissue	Cell-mediated and innate immunity
	Peripheral nerve terminals	Peripheral nervous system
	Retina	Intraocular pressure
CNS	Cerebellar granule cells mRNA	Coordination of motor function

Croxford, JL. CNS Drugs 2003; 17(3)

Endocannabinoids

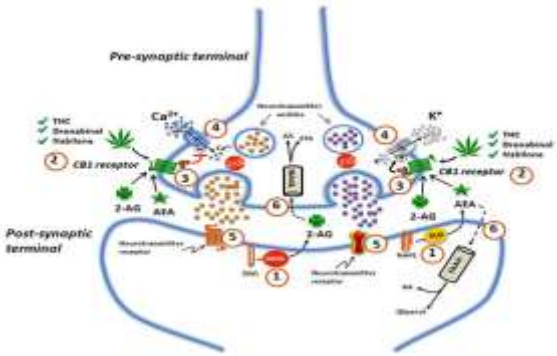
- **N-arachidonoylethanolamine** (also called anandamide or AEA)
  - **Anandamide** (AEA) is a partial agonist of CB_1 receptors; its affinity and efficacy at CB_2 receptors are low. It is a partial agonist at TRPV1 receptors
- **2-arachidonoylglycerol** (2-AG).
  - **2-AG** is a fully efficacious agonist of both CB_1 and CB_2 receptors.

McPartland, J. M. (2004). Phylogenomic and chemotaxonomic analysis of the endocannabinoid system. *Brain Res Brain Res Rev, 45*(1), 18-29. doi:10.1016/j.brainresrev.2003.11.005

Regulatory enzymes

- The enzymes that modulate the levels of endocannabinoids are considered to be part of the endocannabinoid system.
- Some synthesize, some catabolize
  - Fatty acid amidohydrolase (FAAH)
    - Breaks down AEA
  - Monoacetylglycerol lipase (MAGL)
    - Breaks down 2-AG
  - N-arachidonoylphosphatidylethanolamine (NAPE)
    - Synthesizes AEA
  - Diacylglycerol (DAG)
    - Synthesizes 2-AG

Hazekamp A, Fischedick JT. (2012) Cannabis–from cultivar to chemovar. *Drug Testing and Analysis; 4* (special issue): 660-7



The Endocannabinoid System in the Nervous system

Health Canada (2013) *Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids*. Retrieved from http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/med/infoprof-eng.pdf

Endocannabinoid System

- Receptors
  - CB_1
  - CB_2
  - TRPV1 and some other "orphan" receptors
- Endocannabinoids
  - AEA
  - 2-AG
- Enzymes: synthesis
  - AEA – NAPE
  - 2-AG - - DAG
- Enzymes: degradation
  - AEA -- FAAH
  - 2-AG -- MAGL

ECS Imbalance

- **ECS hyperactive:** inflammation, insulin resistance, overweight/obesity, obesity-related cardiometabolic disorders
- CB1 receptor **inverse agonists** might be effective for weight gain but have the potential for serious side effects.

Janero, DR & Makriyannis, A. (2009) Cannabinoid receptor antagonists: pharmacological opportunities, clinical experience, and translational prognosis. *Expert Opinion On Emerging Drugs, 14* (1)

ECS Imbalance

- **ECS hypoactive:** migraine, fibromyalgia and idiopathic bowel syndromes
- Blockers of anandamide hydrolysis (allowing CB1 to accumulate) reduce anxiety, pain, cancer growth, and colitis in animal tests.

Price MR, Baillie GL, Thomas A, Stevenson LA, Easson M, Goodwin R, McLean A, McIntosh L, Goodwin G, Walker G, Westwood P, Marrs J, Thomson F, Cowley P, Christopoulos A, Pertwee RG, Ross RA. Allosteric modulation of the can- nabinoid CB1 receptor. Mol Pharmacol 2005;68(5):1484-95.

Russo, E.B. 2004. "Clinical endocannabinoid deficiency (CECD): Can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment- resistant conditions?" Neuroendocrinol Lett 25 (1-2):31-39.

Cannabinoids: Types

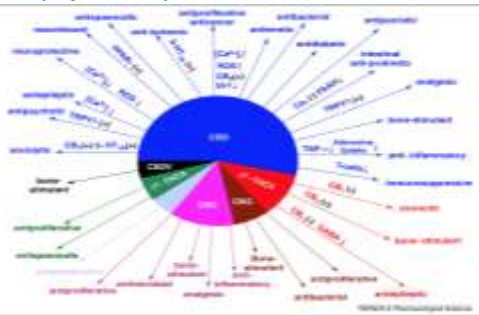
- If naturally occurring in the body, called endocannabinoids
- If naturally occurring in plants, called phytocannabinoids
  - Examples of phytocannabinoids
    - **delta -9- tetrahydrocannabinol (THC)**
    - **cannabidiol (CBD)**
    - cannabichromene (CBC)
    - cannabigerol (CBG)
    - tetrahydrocannabivarin (THCV)
    - cannabinol (CBN)
- Examples of synthetic cannabinoids
  - dronabinol (Marinol)
  - nabilone (Cesamet)

The Entourage Effect

- THC can be co-administered with cannabidiol (CBD)
  - some strains of herbal cannabinoid medicines
  - certain cannabis-based extractions
- Cannabidiol (CBD) antagonizes some undesirable effects of THC:
  - intoxication, sedation and tachycardia
  - contributes analgesic, anti-emetic, and anti-carcinogenic properties in its own right.
- Anxiogenic, dysphoric, and possibly short-term memory-interrupting effects of THC are mitigated

Russo, E., & Guy, G. W. (2006). A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses, 66*(2), 234-246. doi:10.1016/j.mehy.2005.08.026

Pharmacological actions of non-psychotropic cannabinoids



Izzo, A. A., Borrelli, F., Capasso, R., Di Marzo, V., & Mechoulam, R. (2009). Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci, 30*(10), 515-527. doi:10.1016/j.tips.2009.07.006

Therapeutic Activity

- **THC** (delta-9-tetrahydrocannabinol) psychoactive cannabinoid
  - plant strains have been selectively bred to increase its percentage content for recreational use
- **CBD** (cannabidiol) no psychoactive properties
  - may positively influence the side-effect profile of cannabis by influencing receptor-binding and metabolism of THC
- **Other phytocannabinoids** widely varying activity
  - cannabinol, cannabigerol, cannabichromene, and tetrahydrocannabivarin.
- **Terpenes** (also called terpenoids) compounds which give cannabis its distinct smell
  - content may differ highly among cannabis varieties
  - may have synergic effects with phytocannabinoids

Fischedick J, Hazekamp A, Erkelens T, Choi YH, Verpoorte R. (2010) Metabolic fingerprinting of Cannabis sativa L., cannabinoids and terpenoids for chemotaxonomic and drug standardization *purposes Phytochemistry 71*(17-18): 2058-73.

Cannabinoids -- THC

- **THC -** The primary psychoactive cannabinoid
- Most cannabis varieties currently available contain high concentrations - up to 25% by weight - of **THC (delta-9-tetrahydrocannabinol).**
- Responsible for many therapeutic effects
- May also cause dizziness, somnolence and disorientation.

Abrams DI, Couey P, Shade SB, . (2011) Cannabinoid-opioid interaction in chronic pain. *Clin Pharmacol Ther 90*: 844–851.

Bachhuber MA, Saloner B, Cunningham CO, . (2014) Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999–2010. *JAMA Intern Med 174*: 1668–1673.

Cannabinoids -- CBD

- Cannabidiol (**CBD**)
- Possibly the single most important cannabinoid
  - the greatest therapeutic potential
- May positively influence the side-effect profile of cannabis
  - influences receptor-binding and metabolism of THC.

Karniol IG, Carlini EA.(1973) Pharmacological interaction between cannabidiol and delta 9-tetrahydrocannabinol. *Psychopharmacologia 33*(1):53-70

- Appears safe for human consumption.
- Small clinical trial
  - oral administration of 600 mg of CBD
  - 16 subjects
  - no acute behavioral and physiological effects

Martin-Santos R, Crippa JA, Batalla A, Bhattacharyya S, Atakan Z, et al (2012) Acute effects of a single, oral dose of d9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers. *Curr Pharm Des.18* (32):4966-79

Cannabinoids -- CBD

- Limited safety data exist for long-term use of CBD in humans
- There are no known absolute contraindications to cannabidiol (CBD).
- Chronic use and high doses up to 1,450 mg/day of CBD are reportedly well tolerated in humans.

Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. (2011) Safety and side effects of cannabidiol, a Cannabis sativa constituent. *Current Drug Safety* 6(4): 237-49.

Cannabichromene (CBC)

Cannabichromene (**CBC**) is a potent anadamide uptake inhibitor and thus may modulate the endocannabinoid system similarly to CBD.

De Petrocellis L, Ligresti A, Moriello AS, et al. (2011) Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes *Br J Pharmacol 163*(7):1479-94. doi: 10.1111/j.1476-5381.2010.01166.x.

In mice studies, it has been shown that CBC:

- is active in producing **hypothermia** and **hypomotility** (but only at high doses)
- has **anti-inflammatory** properties
- has **analgesic** activity

Wirth PW, Watson ES, ElSohly M, Turner CE, Murphy JC. (1980) Anti-inflammatory properties of cannabichromene. *Life Sci 26*:1991-5.

- has **antidepressant** activity

Izzo AA, Borrelli IAA, Capasso R, Di Marzo, V, et al. (20090 Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci* (10):515-27.

Davis WM, Hatoum NS. (1983) Neurobehavioral actions of cannabichromene and interactions with delta 9-tetrahydrocannabinol. *Gen Pharmacol 14*:247-52.

In in vitro studies, it has been shown that CBC:

- has **antibiotic** and **antifungal** effects

ElSohly HN, Turner CE, Clark AM, Eisohly MA.1(982) Synthesis and antimicrobial activities of certain cannabichromene and cannabigerol related compounds. *J Pharm Sci 71*:1319-23.

has **cytotoxic** activity in certain cancer cell lines

Ligresti A, Moriello AS, Starowicz K, et al. (2006) Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast

Cannabigerol (CBG)

- Cannabigerol (**CBG**) is the phytocannabinoid precursor molecule, and demonstrates weak partial agonism at CB_1 and CB_2
- In rodent models, CBG:
  - displays **antidepressant** properties

Appendino G, Gibbons S, Giana A, et al.(2008) Antibacterial cannabinoids from Cannabis sativa: a structure-activity study. *J Nat Prod 71*:1427-30.

- In in vitro studies, CBG:
  - is a potent GABA uptake inhibitor, suggesting **application in spasticity**
  - displays **analgesic** and **anti-erythemic** effects
  - has **antifungal** properties
  - has **cytotoxic** activity against **human epithelioid carcinoma** and human breast cancer cells

Ligresti A, Moriello AS, Starowicz K, et al.(2006) Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *J Pharmacol Exp Ther 318*:1375-87

Baek SH, Kim YO, Kwag JS, Choi KE, Jung WY, Han DS. (1998) Boron trifluoride etherate on silica-A modified Lewis acid reagent (VII). Antitumor activity of cannabigerol against human oral epitheloid carcinoma cells. *Arch Pharm Res 21*:353-6.

Cannabigerol (CBG)

- In in vitro studies, CBG:
  - displays **anti-hypertensive activity**

Maor Y, Galiliy R, Mechoulam R.(2006) The relevance of the steric factor in the biological activity of CBD derivaties-a tool in identifying novel molecular target for cannabinoids. . *Symposium on the Cannabinoids.* Tihany, Hungary: International Cannabinoid Research Society; 2006:1.

  - inhibits keratinocyte proliferation and this suggests that CBG has application in **psoriasis therapy**)
  - has been shown to exert **anti- proliferative/pro-apoptotic effects** in a panel of tumor cell lines

Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R.(2009) Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci 30*:515-27.

  - has **antibiotic effects against Methicillin-resistant Staphylococcus aureus** (MRSA)

Appendino G, Gibbons S, Giana A, et al. (2008) Antibacterial cannabinoids from Cannabis sativa: a structure-activity study. *J Nat Prod 71*:1427-30.

  - is a α-2 adrenoreceptor agonist, and 5-HT_{1A} antagonist

Tetrahydrocannabivarin (THCV)

- Tetrahydrocannabivarin (THCV) is a CB_1 antagonist at low doses, but displays weak agonistic effects at high doses
- In obese mice models THCV:
  - **reduced appetite**
  - **produced weight loss**
  - **decreased body fat and leptin concentrations**

Cawthorne MA, Wargent E, Zaibi M, Stott C, Wright S. (2007) The CB1 antagonist, delta-9-tetrahydrocannabivarin (THCV) has anti-oebesity activity in dietary-induced obese (DIO) mice. *17th Annual Symposium on the Cannabinoids*. Saint-Sauveur, Quebec, Canada: International Cannabinoid Research Society:141.

Riedel G, Fadda P, McKillop-Smith S, Pertwee RG, Platt B, Robinson L. (2009) Synthetic and plant-derived cannabinoid receptor antagonists show hypophagic properties in fasted and non-fasted mice. *Br J Pharmacol 156*:1154-66.

- In rodent experiments, it has been shown that THCV:
  - has **anticonvulsant properties** in cerebellar and pyriform cortical tissues

Hill AJ, Weston SE, Jones NA, et al. (2010) Delta-Tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rats. *Epilepsia 51*:1522-32.

  - works via CB_2 to **diminish carageenan-induced hyperalgesia** and inflammation, as well as formalin-induced pain behaviour
  - may exert **beneficial effects on bone formation and fracture healing**

Cannabinol (CBN)

- Cannabinol (**CBN**) is the oxidative by-product of THC and appears after long storage. It is a weaker partial agonist at CB_1 and CB_2 as compared to THC .
- In in vitro studies, it has been found that cannabinol is:
  - **anticonvulsant**

Turner CE, Elsohly MA, Boeren EG. (1980) Constituents of Cannabis sativa L. XVII. A review of the natural constituents. *J Nat Prod 43*:169-234.

  - **anti-inflammatory**

Evans FJ.(1991) Cannabinoids: The separation of central from peripheral effects on a structural basis. *Planta Med 57*:S60-7.

  - **potent against MRSA** (MIC 1 $\mu g \cdot ml^{-1}$)

Appendino G, Gibbons S, Giana A, et al. (2008) Antibacterial cannabinoids from Cannabis sativa: a structure-activity study. *J Nat Prod 71*:1427-30.

  - **reduces keratinocyte proliferation**

Wilkinson JD, Williamson EM. (2007) Cannabinoids inhibit human keratinocyte proliferation through a non-CB1/CB2 mechanism and have a potential therapeutic value in the treatment of psoriasis. *Journal of Dermatological Science 45*:87-92.

  - stimulates mesenchymal stem cells in marrow suggesting **stimulation of bone formation**

Scutt A, Williamson EM. Cannabinoids stimulate fibroblastic colony formation by bone marrow cells indirectly via CB2 receptors(2007). *Calcif Tissue Int 80*:50-9.

Metabolism

- Metabolites contribute significantly to cannabis' effects
  - Δ9 THC metabolized to 11-OH-THC by CYP2C and CYP3A4 when absorbed in the small intestine
    - greater activity of metabolite at CB1 receptors in the brain
    - with inhalation (vs. ingestion) Δ9 THC delivered directly to brain
  - CBD metabolized to 7-OH-CBD & 6-OH-CBD
    - little research on their properties
- CBD competitively inhibits THC metabolism resulting in a longer action at a lower intensity
- CBD is a strong CYP450 inhibitor for many drugs when administered in pure form in research settings

Cytochrome-mediated metabolism

- **Inhibitors** of 2C9, 2C19, and 3A4 may **increase** the effect and duration of THC
  - macrolides, OCs, CBD, paroxetine, fluoxetine, some PPIs, Ca^{++} channel blockers, antifungals, HIV antiretrovirals
- **Inducers** of 2C9, 2C19, and 3A4 may **decrease** the effect and duration of THC
  - Carbamazepine, rifanpin, phenytion, ritonavir, St. John's Wort, phenobarbital

Cytochrome-mediated metabolism

- THC is a 1A2 **inducer**
  - May **decrease** the effect of theophilline, clozapine, chlorpromazine
- CBD is a 3A4 and 2D6 **inhibitor**
  - May **increase** the bioavailability and effect of macrolides, CCBs antihistamines, haloperadol, sildenafil
- Clinicians should monitor patients who are concomitantly consuming high doses of cannabis with other medications that are metabolized by the CYP2C9, CYP2C19 CYP1A2 CYP2D6 and CYP3A4 enzymes.

Terpenes

- Volatile aromatic molecules
- Evaporate easily
- Provide evolutionary advantage to cannabis plants
- Buffer THC psychoactivity (along with CBD)
- Amplify effects of cannabinoids

Russo, E. B. (2011). Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol, 163*(7), 1344-1364. doi:10.1111/j.1476-5381.2011.01238.x

Sowndhararajan, K. and Kim S. (2016) Influence of fragrances on human psychophysiological activity: With special reference to human electroencephalographic response. *Scientia Pharmaceutica 84*(4): 724–752. Published online 2016 Nov 29. doi: 10.3390/scipharm84040724

Some Important Terpenes

S. Casano, G. Grassi, V. Martini and M. Michelozzi (2011) Variations in terpene profiles of different strains of Cannabis sativa *L. Acta Horticulturae 925*:115-121

Dispensary Label

Giese MW, Lewis MA, Giese L, Smith KM, (2015) Development and validation of a reliable and robust method for the analysis of cannabinoids and terpenes in cannabis. *J Association of Official Analytical Chemists (AOAC) Int. 98*(6):1503-22. doi: 10.5740/jaoacint.15-116

Effects of cannabis consumption

- Regardless of the specific physiological system, the effects of cannabis are dependent on many factors.
  - Dose of cannabis consumed
  - Route of administration
  - Timing – the effects of cannabis are different right after consumption as compared to hours after consumption
  - Health status of the patient
  - Age of the patient
  - Co-administration of other drugs/medicines
  - Whether or not the patient has been receiving medical cannabis therapy long-term or if the patient is cannabis-naïve

Administration of Cannabis

- (1) **Smoking** and **vaporization** of whole dried plant
- (2) **Liquid, oil or solid** preparations for vaporization
- (3) Liquid or oil preparations for metered **oromucosal** or **sublingual** administration or administration per tube
- (4) **Oral** administration of edibles, teas, beverages, etc.
- (5) **Topical** forms and the cannabis patch

Inhalation of Cannabis

- Cannabis is often inhaled – either through a cigarette (joint), pipe, water pipe (also known colloquially as a 'bong'), or vaporizer.
- Many consumers prefer inhalation to ingestion because cannabis' effects are almost immediately experienced after inhalation.
- This outcome allows one to moderate the dose as needed or in accordance with one's particular preference, as well as to achieve immediate relief from pain, nausea, and other symptoms.

Aggarwal, S. K. (2013). Cannabinergic pain medicine: a concise clinical primer and survey of randomized-controlled trial results. *Clin J Pain*, *29*(2), 162-171. doi:10.1097/AJP.0b013e31824c5e4c

Oral and Oromucosal Cannabis Dosing

- Orally administered cannabis is particularly difficult to titrate. Effects may not be appreciated for 2 hours after consumption
- Cannabis products may not be uniform from purchase to purchase
- A personal "bioassay" of the effects of a cannabis product should be performed each time that a new supply is acquired
- By starting with a low dose, allowing adequate time between doses for the cannabis to take effect, and titrating the dosage slowly, over several days to weeks, a patient should be able to avoid overdosing

Cannabis Dosing: THC in Mg.

- Average adult dose of **THC** for:
  - Cannabis-naïve patient: 2.5-5 mg
  - More experienced patient: 10-20 mg
  - Heavy user: 25 mg or more

Carter GT, Weydt P, Kyashna-Tocha M, Abrams DI. (2004) Medicinal cannabis: Rational guidelines for dosing IDrugs : The Investigational Drugs Journal 7(5):464-70.

- To convert % THC/gram to milligrams, move the decimal one place to the right:
  - e.g., 21.23 % THC + 212.3 mg THC per gram of cannabis
  - The same conversion could be done for other cannabinoids and terpenoids (e.g., 0.39% β-caryophyllene = 3.9 mg per gram of cannabis)

CBD:THC Proportions

- **0:1** Significant "high" (especially if over 30 mg THC ingested)
  - Euphoria, confused thought, uncontrolled laughter.
  - Strong side Effects: tachycardia, anxiety, tension
- **1:2** Noticeable "high" effects
  - Euphoria, laughter and thoughts more calm.
  - Milder side effects: reduced risk of tachycardia, anxiey
- **1:1** Relaxation with very light "high" effects
  - Little euphoria, calmness and tranquility.
  - Few side effects for most users.
- **2:1** Few to no "high" effects.
  - No euphoria, sedation, light-headedness, or dizziness.
  - Practically no psychoactive effects.
- **1:0** No "high" effect, at all.
  - Normal mood.
  - No psychoactive effects

Cannabis Dosage: Smoking

- The active ingredients in cannabis—**Δ^9-tetrahydrocannabinol (THC)**, cannabidiol (CBD) and other phytocannabinoids, as well as terpenoids—are vaporized by the heat of combustion and inhaled.
- Inhaled constituents quickly pass from alveoli into the bloodstream and readily cross the blood-brain barrier.
- This short onset of action makes dose titration possible, by spacing inhalations at intervals.

Geiringer, D. H. (2001). Cannabis "vaporization:" A promising strategy for harm reduction. *Journal of Cannabis Therapeutics, 1*(3/4), 153-170.

Cannabis Dosage: Smoking

- Similar to IV bolus
- Passive diffusion into alveolar capillaries
- Rapid onset (seconds to minutes)
- Peak effect by 15-30 minutes, lasting 2-3 hours
- Elimination $t_{1/2}$ ~20 hours (2-13 days)
- Elimination via feces (65%) and urine (20%)

Grotenherman, F. (2003) Pharmacokinetics and pharmacodynamics of cannabinoids. *Clinical Pharmecokinetics* 42 (4). 327-360.

Cannabis Dosage: Smoking

- Cannabis flowers typically 8 – 25% THC (1 gm contains 80 – 250 mg of THC)
- Average amount of whole plant cannabis in a rolled joint 0.5-1 gm (40 -125 MG THC)
- With reasonably high potency cannabis flowers, 1-3 hits is generally enough, even for experienced users
- Average frequency of use 1-6 x/day
- Average amount used daily may range from 1-12 grams or more

Aggarwal, S. K. (2013). Cannabinergic pain medicine: a concise clinical primer and survey of randomized-controlled trial results. *Clin J Pain*, *29*(2), 162-171. doi:10.1097/AJP.0b013e31824c5e4c

Effects of Smoking

- Some studies have failed to link cannabis inhalation adverse pulmonary effects associated with tobacco smoking
- Other studies suggest an association between smoking cannabis and cancer.
- Still other studies suggest that cannabis does not have negative effects on the respiratory system.

Tashkin DP. 2013. Effects of marijuana smoking on the lung. *Ann Am Thorac Soc. 10*(3):239-47.

Pletcher MJ, Vittinghoff E, Kalhan R, Richman J, Safford M, Sidney S, Lin F, Kertesz S. (2012) Association between marijuana exposure and pulmonary function over 20 years. *JAMA. 307*(2):173-81. doi: 10.1001/jama.2011.1961

Vaporization

- Vaporization: smokeless inhalation delivery system
- Warm air or heat of 180°C to 210°C (356-410° F) rather than a flame is used to convert cannabinoids and other compounds into a fine mist that can be inhaled.
- Cannabinoids and terpenoids boil between 155-250ºC (311-482ºF)
- Herbal cannabis combusts between 500-600ºC (932-1112ºF)
- Vaporizers heat herbal cannabis to the boiling point of cannabinoids and terpenoids but well below the combustion point of herbal cannabis, so no smoke and relatively little tar is generated.
- Ideal temperature is 210°C (410F)

Gieringer D.(2001) Cannabis vaporization: A promising strategy for smoke harm reduction. *J Cannabis Ther* *1*(4):153-170.

Vaporization

- Hazekemp et al. study showed;
  - vaporization is a safe and effective cannabinoid delivery system
  - avoids the respiratory disadvantages of smoking
  - tetrahydrocannabinol (THC) uptake comparable to smoking

Hazekamp et al. (2006) Evaluation of a vaporizing device (Volcano) for the pulmonary administration of tetrahydrocannabinol. *J Pharm Sci* 95(6):1308-17.

- Abrams et al. study showed:
  - carbon monoxide levels lower in patients who consumed marijuana via vaporization as compared to patients who consumed marijuana via smoking.

Abrams et al. (2007) Vaporization as a smokeless cannabis delivery system: a pilot study. *Clin Pharmacol Ther 82*(5):572-8

Types of Vaporizers

- Safety, capabilities and size of the vaporizer
- Vaporizing pens are the smallest and typically have the least power.
- Portable vaporizers pocket-sized.
- Desktop vaporizers largest, require electrical outlet.
- Vapor cannot be stored in the collection balloon
  - condensation of the vaporized cannabinoids occurs.
  - limit the amount of vapor in the balloon to the amount that one plans on inhaling within a ten-minute period.

Convection-based Vaporizer

- **Vaporizer System for the Administration of Marijuana.**
- The cannabis is placed in the chamber and heated to a temperature below that required for combustion. The balloon fills with vapor that contains the active ingredients without the tar or particulates thought to be responsible for most of the drug's adverse effects on the respiratory tract. The patient inhales the vapor from the balloon.

Okie, S. (2005) Medical marijuana and the Supreme Court. *N Engl J Med 353*:648-651. DOI: 10.1056/NEJMp058165

Conduction-based Vaporizer

Hand-held Vaporizers

Vaporization of Whole Plant Cannabis

- Vaporizers may require as much as twice as much plant material to deliver the same dose as smoking (i.e. 2 gm/dose, depending on vaporizer efficiency)
- The Volcano desktop vaporizer was shown in one study to deliver a similar percentage of available THC to smoking (36-61%)
- Absorption may be faster with vaporization, duration of activity is similar to smoking
- Effects last 2-4 hours
- Frequency of use 2-6 x daily

Vaporization of Concentrates

- Concentrates (kief, hash, oil, wax, shatter) are plant extracts
  - may be missing some parts of the entourage
- Much less weight/volume is required
  - 0.1 gm wax might provide 65 mg of cannabinoids
  - some concentrates have higher concentrations of particular terpenes than the whole plant
  - terpenes generally vaporize at a lower temperature than cannabinoids
  - terpenes may have specific therapeutic effects

Traditional Hashish

Refillable Vaporizers

Disposable Vaporizers

Dabbing

Dropping a “dab” to vaporize

Oral-mucosal Route

- Effects begin to develop in less than an hour or up to 2.5 hours after administration
- Duration 2 hours, or 5-6 hours if swallowed.
- Peak effects ~1.5 - 4.25 hours after administration.
- Onset and peak plasma concentrations somewhat sooner than oral
- Oromucosal administration may be more desirable than oral for nausea.
- May be easier to titrate dose than with oral administration

Oral-mucosal Route

- Absorption can be rapid but peak effects may be delayed
  - effects can also be long-lasting
  - some fraction of the dose is usually swallowed rather than sublingually absorbed.
- Effects may be evident within 15-30 min but may not peak immediately.
- Mouth strips, lollipops and lozenges may also provide for sublingual administration.

Oral-mucosal Route

- Tinctures: extracts of cannabis in alcohol or glycerin
  - the primary way in which cannabis medicines were delivered prior to their removal from the USP
  - can be taken sublingually in drops or spray
  - sublingual absorption has the potential to avoid first-pass metabolism.
- Tinctures may also be mixed with a beverage and swallowed with similar effect to other oral forms.

Grotenhermen F. (2003) Clinical pharmacokinetics of cannabinoids. *J Cannabis Ther* 3(1): 3-51.

Oral Consumption

- Available forms: butter, oil, capsules, baked goods, candies, tea, honey
- For cannabis effects to develop, the orally consumed material must be digested.
- Effects may take up to two hours to develop, peak at 2-3 hours, and may last for 4-12 hours.

Grotenherman, F. (2003) Pharmacokinetics and pharmacodynamics of cannabinoids. *Clinical Pharmecokinetics* 42 (4), 327-360.

- Naïve users can easily overdose on edibles
- May require much larger amounts of cannabis (3-5 times) to achieve desired effect.


Cannabis
Brownies


CBD
100 mg
30


wana
CAPS
HIGH CBD CAPSULES
wana
CAPS
wana
CAPS
HIGH THC CAPSULES


CANNI
SOOTHE
Cannabis Lozenges
CANNI
SOOTHE
Cannabis Lozenges


- Medical Cannabis -
Chocolate Chip Cookie Bite
EDICAL USE ONLY
MedicalJane


CBD Cannoil Capsules
Made On:
August 13, 2014


Legal
Legal
Legal


CANNABIS LOLLIPOP


Cannabis Tea


CANNABIS
DARK CHOCOLATE


sweet mary jane
Dazed & Infused Olive Oil
sweet mary jane
Dazed & Infused Olive Oil


Purely Medicinal
THC Honey
THC: 5mg/g
50g per jar
Ingredients:
Unpasteurized Honey,
THC Extract

Prescription Cannabinoids

- Two oral cannabinoid medications available in North America: nabilone (Cesamet) and dronabinol (Marinol)
- Active within 30-90 minutes of dosing, with effects lasting up to 6-8 hours.
- Absorption from the GI tract is variable with generally low bioavailability
- Side effects: principally drowsiness, dizziness and dry mouth.

A Comment on Nabilone and Dronabinol

- Synthetic THC
- Re-scheduled to Schedule III in 1999
- May be problematic even for experienced cannabis users
- Tends to produce dysphoria rather than euphoria
- Dose is often too high
- Effects are erratic
- Very expensive

Hazekamp, A., Ware, M. A., Muller-Vahl, K. R., Abrams, D., & Grotenhermen, F. (2013). The medicinal use of cannabis and cannabinoids--an international cross-sectional survey on administration forms. *J Psychoactive Drugs, 45*(3), 199-210. doi:10.1080/02791072.2013.805976

Topical

- Cannabis products can be applied topically for arthritis, muscle spasm, pain or inflammation
- Also used for psoriasis, dermatitis, dry skin
- Probable to oldest use of cannabis as medicine
- Extracted into alcohol, oil or salve for topical administration.
- Minimal absorption into the bloodstream so minimal psychoactive effects
- Little research exists

Topical

- Dose is determined by area to be covered
- Duration of action has not been studied, but, once absorbed, effects are reported by patients last up to 4 hours or more
- Typically applied 4 times daily
- More plant material may be required to prepare topicals than for other dosage forms

Transdermal

- Transdermal cannabis patch now also available
- Formulated like nicotine patches
- Gradually release 10—20mg of cannabinoids through dermal absorption
- No first-pass effect– effects felt within 15 min
- Sustained effect for 8-12 hours
- Can be cut to adjust dose

High dose oral cannabis

- Capsules containing 25 – 100 mg cannabinoids in oil per capsule (Cannador)
- Oil concentrates containing up to 800 mg/ml of cannabinoids (provided in a syringe)
- "Rick Simpson oil" protocol recommends up to 1 gram of 90% cannabinoid oil per day, containing 900 mg of cannabinoids
- "CBD oil" produced from legally grown industrial hemp

Safety of Cannabis

- With regard to cannabinoid botanicals, the Institute of Medicine concluded after a comprehensive government-commissioned review published in 1999 that "except for the harms associated with smoking, the adverse effects of marijuana [cannabinoid botanicals] use are within the range of effects tolerated for other medications."

Overconsumption

- There have been numerous reports of overconsumption of cannabis-infused products by those not waiting an adequate amount of time for the cannabis to have an effect.
- Re-dosing (particularly of orally administered cannabis) should be based on the fact that individuals who ingest cannabis may not begin to experience psychoactive or physiological effects of oral consumption for 120 minutes after ingestion.
- Overconsumption of cannabis-infused edible products (or oral cannabis medicines) may be associated with hostile behavior, erratic speech and adverse psychological effects.

Murray, R. M., Quigley, H., Quattrone, D., Englund, A., & Di Forti, M. (2016). Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry, 15*(3), 195-204. doi:10.1002/wps.20341

Walsh, Z., Gonzalez, R., Crosby, K., M, S. T., Carroll, C., & Bonn-Miller, M. O. (2017). Medical cannabis and mental health: A guided systematic review. *Clin Psychol Rev, 51*, 15-29. doi:10.1016/j.cpr.2016.10.00

The LESS Method

The L.E.S.S. Method: A Measured Approach to Oral Cannabis **(or How Not to Overdose on Oral Cannabis)**

Start Low

Establish Potency

Go Slow

Supplement as Needed.

https://www.erowid.org/plants/cannabis/cannabis_article1.shtml

The LESS Method

- If one is faced with an edible of unknown potency, and yet is determined to try it, the best way to avoid an overdose is to intentionally underdose.
- Begin with a small piece (less than a quarter of a suggested portion). Measure, photograph or weigh the piece you try and make note of it.
- Then wait a minimum of 90 minutes on an empty stomach, or 120-150 minutes otherwise, before evaluating whether or not to consume another small piece.