Cannabis Therapeutics:
Advising Patients on Safe and Effective Use

Maria Mangini, PhD, FNP-BC

Director, Family Nurse Practitioner Program
Holy Names University
Oakland, CA

Faculty Disclosure

- **Dr. Mangini**: Stockholder—GW Pharmaceuticals.

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  - Cannabis is not FDA approved for the treatment of any disease/disorder.

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.

Learning Objectives

- Describe the receptor-based effects of endogenous and exogenous cannabinoids
- List the principal phytocannabinoids
- Describe cannabis dosage forms and differentiate among their pharmacokinetics
- Apply patient teaching strategies for safe and effective cannabis use

Endocannabinoid System

- A homeostatic system found in all vertebrates
- Discovered within the last 3 decades
- A PubMed search for “endocannabinoid”
  - 1993: 10 citations
  - 2014: 6141 citations
  - 2016: 7848 citations
  - 2018: 34,903 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 JM. *Brain Res Brain Res Rev*. 2004;45(1):18-29.
Pacher P, et al. *Pharmacol Rev*. 2006;58(3):389-462.
Russo EB. *Ther Clin Risk Manag*. 2008;4(1):245-259.

Endocannabinoid System

- **3** main components:
  Receptors
  Endocannabinoids
  Regulatory enzymes

- Also interacts with:
  Phytocannabinoids (plant derived cannabinoids)
  Synthetic cannabinoids
  Indirect agonists
  Antagonists

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

1) 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. *Pharmacol Res*. 2009;60(2):77-84.

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
	Cerebellar granule cells mRNA	Coordination of motor function

CNS = central nervous system.

Croxford JL. *CNS Drugs*. 2003;17(3):179-202.

2) Endocannabinoids

- **N-arachidonoylethanolamine** (also called anandamide or AEA)
  - **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

TRPV1 = transient receptor potential vanilloid receptor 1.
McPartland JM. *Brain Res Brain Res Rev*. 2004;45(1):18-29.

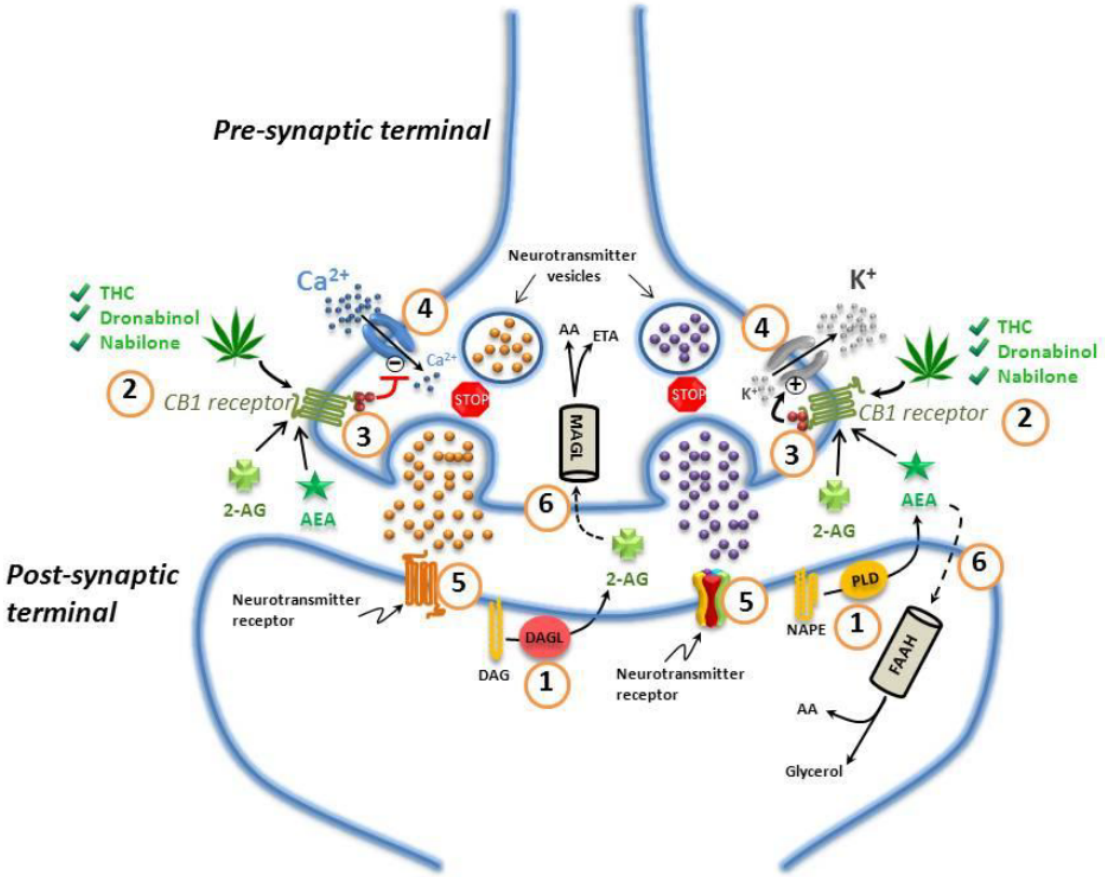
3) Regulatory Enzymes

- 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
- Monoacylglycerol lipase (MAGL)
  - Breaks down 2-AG
- N-arachidonoylphosphatidylethanolamine (NAPE)
  - Synthesizes AEA
- Diacylglycerol (DAG)
  - Synthesizes 2-AG

Hazekamp A, et al. *Drug Test Anal*. 2012;4(7-8):660-667.

The Endocannab
System in th
Nervous Syste



Health Canada. Information for Health Care Professionals: Cannabis (marihuana, marijuana) and the cannabinoids. February 2013. www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/med/infoprof-eng.pdf. Accessed April 9, 2018.

Endocannabinoid System

- **Receptors**
  - CB_1
  - CB_2
  - TRPV1 and some other “orphan” receptors
- **Endocannabinoids**
  - AEA
  - 2-AG
- **Enzymes**
  - **Synthesis**
    - AEA – NAPE
    - 2-AG – DAG
  - **Degradation**
    - AEA – FAAH
    - 2-AG – MAGL

Endocannabinoid System Imbalance

- **ECS hyperactive**: inflammation, insulin resistance, overweight/obesity, obesity-related cardiometabolic disorders
- CB_1 receptor **inverse agonists** might be effective for weight gain but have the potential for serious side effects

ECS = endocannabinoid system.

Janero DR, et al. *Expert Opin Emerg Drugs*. 2009;14(1):43-65.

Endocannabinoid System Imbalance

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

Price MR, et al. *Mol Pharmacol*. 2005;68(5):1484-1495.
Russo EB. *Neuro Endocrinol Lett*. 2004;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
    - Nabilone

The Entourage Effect

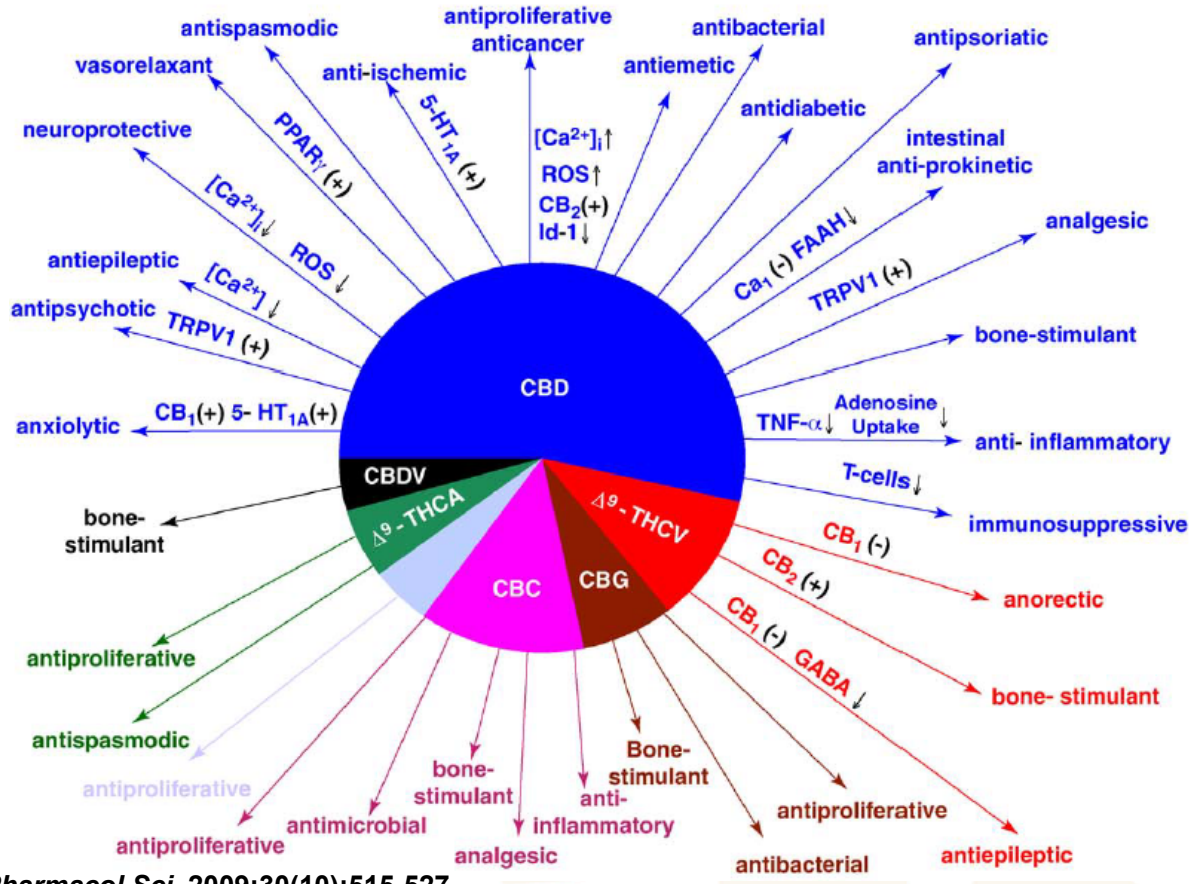
- THC co-administered with CBD
  - Some strains of herbal cannabinoid medicines
  - Certain cannabis-based extractions

- 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, et al. *Med Hypotheses*. 2006;66(2):234-246.

Pharmacological Actions of Non-psychotropic Cannabinoids



Izzo AA, et al. *Trends Pharmacol Sci*. 2009;30(10):515-527.

Therapeutic Activity

- **THC** – psychoactive cannabinoid
  - Plant strains have been selectively bred to increase its percentage content for recreational use
- **CBD** – 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
  - CBN, CBG, CBC, and THCV
- **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 JT, et al. *Phytochemistry*. 2010;71(17-18):2058-2073.

Cannabinoids – 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, et al. *Clin Pharmacol Ther*. 2011;90(6):844-851.
Bachhuber MA, et al. *JAMA Intern Med*. 2014;174(10):1668-1673.

Cannabinoids – 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, et al. *Psychopharmacologia*. 1973;33(1):53-70.

- Appears safe for human consumption

- Small clinical trial
  - Oral administration of 600 mg of CBD, 10 mg of THC, or placebo
  - 16 participants
- No acute behavioral and physiological effects were observed with CBD alone

  Martin-Santos R, et al. *Curr Pharm Des*. 2012;18(32):4966-4979.

Cannabinoids – CBD

- Limited safety data exist for long-term use of CBD in humans
- There are no known absolute contraindications to CBD
- Some studies reported that CBD can induce some side effects, most significantly inhibition of hepatic drug metabolism
- Chronic use and high doses up to 1450 mg/day of CBD are reportedly well tolerated in humans
- Several studies suggest that CBD does not induce changes in food intake, does not induce catalepsy, does not affect physiological parameters (heart rate, blood pressure, and body temperature), and does not affect gastrointestinal transit
- CBD has not been shown to alter psychomotor or psychological functions

Bergamaschi MM, et al. *Curr Drug Saf*. 2011;6(4):237-249.

Cannabichromene (CBC)

- **CBC** is a potent anandamide uptake inhibitor and thus may modulate the endocannabinoid system similarly to CBD
  De Petrocellis L, et al. *Br J Pharmacol*. 2011;163(7):1479-1494.

- In *in vitro* studies, it has been shown that CBC:
  - has **antibiotic** and **antifungal** effects
    Eisohly HN, et al. *J Pharm Sci*. 1982;71(12):1319-1323.

  - has **cytotoxic** activity in certain cancer cell lines
    Ligresti A, et al. *J Pharmacol Exp Ther*. 2006;318(3):1375-1387.

Cannabichromene (CBC)

- 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, et al. *J Pharm Sci*. 1980;69(11):1359-1360.

  - has **antidepressant** activity

Izzo AA, et al. *Trends Pharmacol Sci*. 2009;30(10):515-527.
Davis WM, et al. *Gen Pharmacol*. 1983;14(2):247-252.

Cannabigerol (CBG)

- **CBG** is the phytocannabinoid precursor molecule, and demonstrates weak partial agonism at CB_1 and CB_2

- In rodent models, CBG:
  - displays **appetite stimulant** properties

Brierley DI, et al. *Psychopharmacology*. 2016;233(19-20):3603-3613.

- 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, et al. *J Pharmacol Exp Ther*. 2006;318(3):1375-1387.
Baek SH, et al. *Arch Pharm Res*. 1998;21(3):353-356.

GABA = gamma-aminobutyric acid.

Cannabigerol (CBG)

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

    Maor Y, et al. The relevance of the steric factor in the biological activity of CBD derivatives—a tool in identifying novel molecular target for cannabinoids. Presented at: Symposium on the Cannabinoids. International Cannabinoid Research Society; 2006; Tihany, Hungary.

  - 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, et al. *Trends Pharmacol Sci*. 2009;30(10):515-527.

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

    Appendino G, et al. *J Nat Prod*. 2008;71(8):1427-1430.

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

Tetrahydrocannabivarin (THCV)

- **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, et al. The CB1 antagonist, delta-9- tetrahydrocannabivarin (THCV) has anti-oebesity activity in dietary-induced obese (DIO) mice. Presented at: 17th Annual Symposium on the Cannabinoids. International Cannabinoid Research Society; 2007; Saint-Sauveur, Quebec, Canada.

Riedel G, et al. *Br J Pharmacol*. 2009;156(7):1154-1166.

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

Hill AJ, et al. *Epilepsia*. 2010;51(8):1522-1532.

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

Cannabinol (CBN)

- **CBN** is the oxidative byproduct 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 CBN is:
  - **anticonvulsant**
    Turner CE, et al. *J Nat Prod*. 1980;43(2):169-234.
  - **anti-inflammatory**
    Evans FJ. *Planta Med*. 1991;57(7):S60-S67.
  - **potent against MRSA** (MIC 1 µg-ml-1)
    Appendino G, et al. *J Nat Prod*. 2008;71(8):1427-1430.
  - **reduces keratinocyte proliferation**
    Wilkinson JD, et al. *J Dermatol Sci*. 2007;45(2):87-92.
  - stimulates mesenchymal stem cells in marrow suggesting **stimulation of bone formation**
    Scutt A, et al. *Calcif Tissue Int*. 2007;80(1):50-59.

Metabolism

- Metabolites contribute significantly to cannabis' effects
  - Δ9 THC metabolized to 11-OH-THC by CYP2C9 and CYP3A4 when absorbed in the small intestine

Stout SM, et al. *Drug Metab Rev*. 2014;46(1):86-95.

    - with inhalation (vs ingestion) Δ9 THC delivered directly to brain
    - greater activity of metabolite at CB_1 receptors in the brain

Manwell LA, et al. *Psychopharmacology*. 2015;232(9):1655-1665.

  - CBD metabolized to 7-OH-CBD and 6-OH-CBD, mainly by CYP3A and CYP2C19
    - little research on their properties

Jiang R, et al. *Life Sci*. 2011;89(5-6):165-170.

- CBD competitively inhibits THC metabolism resulting in a longer action at a lower intensity

Klein C, et al. *Psychopharmacology*. 2011;218(2):443-457.

- When administered in pure form in research settings, CBD is a strong CYP450 inhibitor for enzymes that metabolize many drugs

Cytochrome-Mediated Metabolism

- **Inhibitors** of 2C9 and 3A4 may **increase** the effect and duration of THC
  - macrolides, paroxetine, fluoxetine, Ca++ channel blockers, antifungals, HIV antiretrovirals, metronidazole, sulfamethoxazole, suboxone, H_2 blockers

- **Inducers** of 2C9 and 3A4 may **decrease** the effect and duration of THC
  - Carbamazepine, rifampin, phenytoin, ritonavir, St. John's Wort, phenobarbital, modafinil, glucocorticoids

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. 2007. http://medicine.iupui.edu/clinpharm/ddis/main-table. Accessed July 18, 2018.

Cytochrome-Mediated Metabolism

- THC is a 1A2 **inducer**
  - May **decrease** the effect of theophylline, clozapine, chlorpromazine
- CBD is a 3A4 and 2D6 **inhibitor**
  - May **increase** the bioavailability and effect of macrolides, Ca++ channel blockers, antihistamines, haloperidol, 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

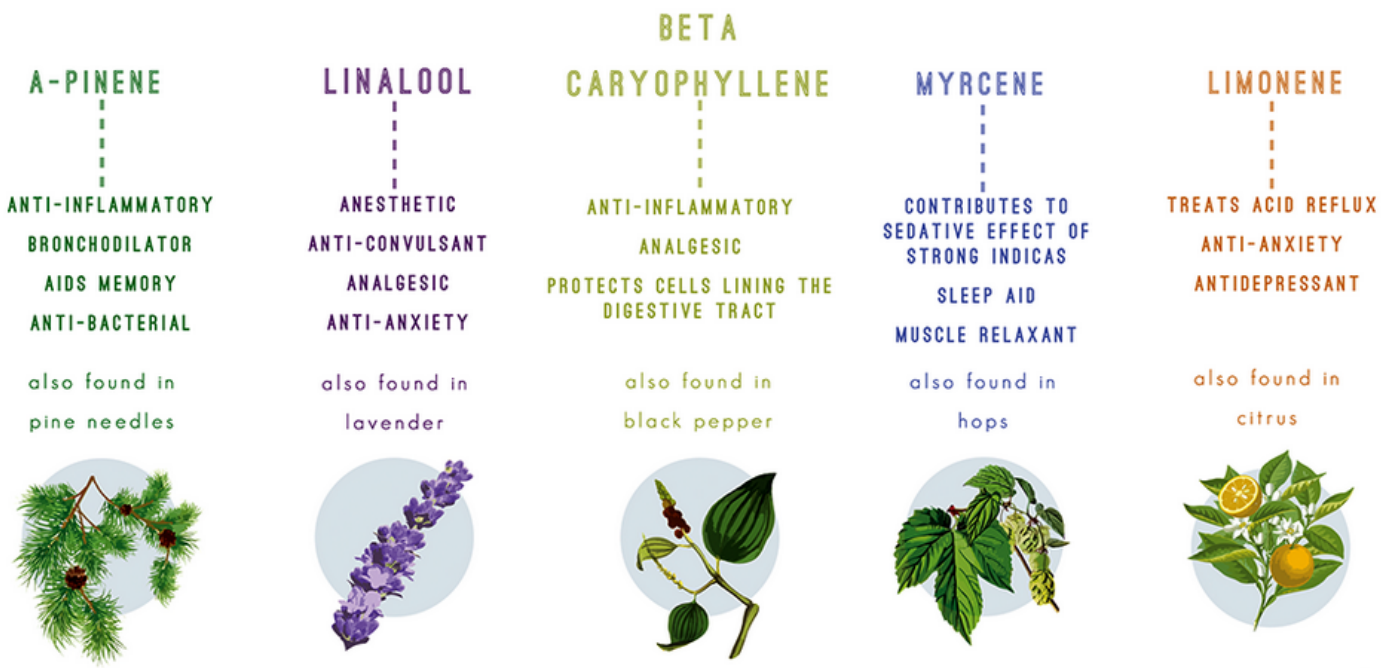
Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. 2007. http://medicine.iupui.edu/clinpharm/ddis/main-table. Accessed July 18, 2018.

Terpenes

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

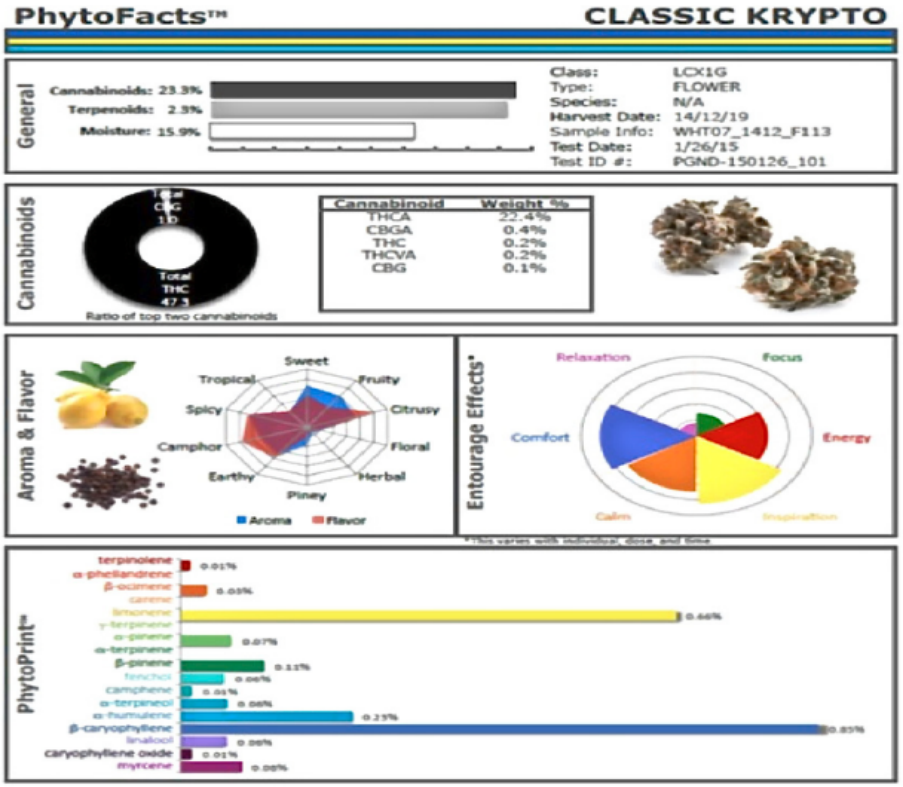
Russo EB. *Br J Pharmacol*. 2011;163(7):1344-1364.
Sowndhararajan K, et al. *Sci Pharm*. 2016;84(4):724-751.

Some Important Terpenes



Casano S, et al. *Acta Horticulturae*. 2011;925:115-121.

Dispensary Label



Giese MW, et al. *J AOAC Int*. 2015;98(6):1503-1522.

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

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 SK. *Clin J Pain*. 2013;29(2):162-171.

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

  Carter GT, et al. *IDrugs*. 2004;7(5):464-470.

- To convert % THC/g to mg, move the decimal 1 place to the right:
  - eg, 21.23% THC + 212.3 mg THC per g of cannabis

- The same conversion could be done for other cannabinoids and terpenoids (eg, 0.39% β-caryophyllene = 3.9 mg per g of cannabis)

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.”

Institute of Medicine. Marijuana and Medicine: Assessing the Science Base. 1999. https://medicalmarijuana.procon.org/sourcefiles/IOM_Report.pdf. Accessed April 9, 2018.

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 RM, et al. *World Psychiatry*. 2016;15(3):195-204.
Walsh Z, et al. *Clin Psychol Rev*. 2017;51:15-29.

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

www.erowid.org/plants/cannabis/cannabis_article1.shtml. Accessed April 9, 2018.

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 to 150 minutes otherwise, before evaluating whether or not to consume another small piece

Cannabis and Psychosis

- Use of cannabis has been associated with an increased risk of developing schizophrenia
- May precipitate the illness in vulnerable populations

Zammit S, et al. *BMJ*. 2002;325(7374):1199.

- Explanations for this association include:
  - Confounding by psychotic predisposition
  - Confounding by use of other drugs such as amphetamines
  - Use of cannabis as a form of self-medication secondary to the disorder

Bostwick JM. *Mayo Clin Proc*. 2012;87(2):172-186.

- There has been a significant increase in cannabis use over past 50 years without a corresponding increase in schizophrenia prevalence

Russo E, Guy GW (2006) A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses 66*(2):234-46.

Cannabis Use Disorder

- Motives for dependent use differ from those for occasional use
  - Reduce tension
  - Reduce negative affect
  - Manage symptoms
  - Stress coping

Matali P, et al. 3.18 Why Adolescents with Dual Diagnosis Consume Cannabis. *J Am Acad Child Adolesc Psychiatry*. 2016;55(10):S147-S148.

Cannabis Use Disorder

- Consistent predictive factors:
  - Early onset of use
  - Frequent use
  - Psychotropic effects
  - Use independent of social contexts
  - Prior drug involvement
  - Male gender
- Comorbid disorders
  - Anxiety, affective disorders, alcohol-related
  - Poly-drug use

Schlossarek S, et al. *Eur Addict Res*. 2016;22(3):131-144. Alcover K, et al. Is risk of cannabis dependence lower for 'cannabis only' users? *Drug Alcohol Depend*. 2017;171:e5.

- Less frequent in "cannabis only" users

Nocon A, et al. *J Psychiatr Res*. 2006;40(5):394-403.

Cannabis Use Disorder

- According to *DSM-5* cannabis intoxication, withdrawal, and use disorder are categorized by meeting specific diagnostic criteria

- Diagnostic Criteria: A problematic pattern of cannabis use leading to clinically significant impairment or distress as manifested by at least 2 of the following occurring in a 12 month period:

Cannabis Use Disorder: *Criteria for Diagnosis*

- Cannabis is often taken in larger amounts over a longer period than was intended
- There is a persistent desire or insignificant effort to cut down or control cannabis use
- A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects
- Craving or a strong desire or urge to use cannabis
- Recurrent cannabis use resulting in failure to fulfill major role obligations at work, school, or home
- Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis
- Important social, occupational, or recreational activities are given up or reduced because of cannabis use

Cannabis Use Disorder: *Criteria for Diagnosis* (cont'd)

- Recurrent cannabis use in situations which is physically hazardous
- Cannabis use is continued despite knowledge of having persistent or recurrent physical or psychological problems that are unlikely to have been caused or exacerbated by cannabis
- Tolerance, as defined by either:
  1) A need for markedly increased amounts of cannabis to achieve intoxication and desired effect, or
  2) A markedly diminished effect with continued use of the same amount of cannabis
- Withdrawal, as manifested by either:
  1) The characteristic withdrawal symptoms for cannabis, or
  2) A closer related substance is taken to relieve or avoid withdrawal symptoms

Simpson AK, et al. *Child Adolesc Psychiatr Clin N Am*. 2016;25(3):431-443.

Cannabis Withdrawal

- Cessation of cannabis use that has been heavy and prolonged (ie, usually daily or almost daily over a period of at least a few months)
- ≥ 3 specific signs and symptoms develop within approximately 1 week after cessation of heavy, prolonged use
- The signs or symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- The signs and symptoms are not attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance

Gorelick DA. *Curr Pharm Des*. 2016;22(42):6409-6419.

Cannabis Withdrawal (cont'd)

- Characterized by the development of specific **symptoms** within 1 week of cessation:
  - Irritability, anger, aggression
  - Anxiety, nervousness
  - Anorexia and weight loss, or increased appetite
  - Restlessness
  - Disturbed sleep, depressed mood

Copersino ML, et al. *Am J Addict*. 2006;15(1):8-14.

Cannabis Withdrawal (cont'd)

- Also may include the development of specific **signs** within 1 week of cessation:
  - Abdominal pain
  - Shakiness, tremors
  - Fever, chills
  - Sweating, headache

Bonnet U, et al. *Subst Abuse Rehabil*. 2017;8:9-37.

Cannabis Intoxication

- Impaired attention, concentration, short-term memory, and executive functioning
  - In the cannabis-naïve this may occur after ingestion of 2.5–5 mg THC
- Nausea, postural hypotension, delirium, panic attacks, anxiety, and myoclonic jerking
  - May occur at > 7.5 mg THC ingestion
- Acute toxic psychosis has also been associated with use of higher potency/ concentrated marijuana products

Grotenhermen F. *Clin Pharmacokinet*. 2003;42(4):327-360.

Cannabis Intoxication (cont'd)

- The physiologic signs of cannabis intoxication in adolescents and adults include:
  - Tachycardia
  - Increased blood pressure or, especially in the elderly, orthostatic hypotension
  - Increased respiratory rate
  - Conjunctival injection (red eye)
  - Dry mouth
  - Increased appetite
  - Nystagmus
  - Ataxia
  - Slurred speech

Bostwick JM. *Mayo Clin Proc*. 2012;87(2):172-186.

Cannabis Hyperemesis Syndrome

- Typically seen with chronic cannabis, use but can be seen with acute or acute on chronic use
- Patients may complain of abdominal pain, vomiting, or nausea that is typically relieved by hot showers
- Possible relief from capsaicin topical

Sontineni SP, et al. *World J Gastroenterol*. 2009;15(10):1264-1266.

Practical Take-Aways

- While patients have broad access to self-directed use of cannabis products, most clinicians do not have adequate training or information to advise about their use
- Clinical studies that might provide evidence of specific clinical benefit or precise dosage guidelines are still quite limited
- The endocannabinoid system is understudied and suggests many interesting possibilities for research and potential new therapies
- Patients should be advised to exercise appropriate caution when self-experimenting with cannabis as a self-directed therapy