# Cannabis and Pain

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# Disclosures

- I have no relevant relationships with industry
- Discussion represents my interpretation and understanding of the current medical evidence as it applies to the topic and does not necessarily represent the views of my employer
- Medical cannabis is not FDA approved for pain; please be aware of federal/DEA, state, and local statutes concerning the topic
  - *Information taken from this presentation/discussion is for education purposes and should not be used to justify any clinical practice that contradicts local, state, and federal statutes in your practice area

# Learning Objectives

- Understand the current state of knowledge of the endocannabinoid system and potential pharmacologic targets for pain relief
- Identify potential risks associated with the use of cannabinoids for pain
- Be aware of the current state of cannabis regulations

# A brief history of cannabis and medicine

- Earliest account of medicinal cannabis around 2800 BC, Shen Nung (*Pen Ts' ao*) prescribed chu-ma (female hemp) for treatment of RA, nausea, constipation, and anxiety
- Spread to the western world through trade and migration
  - Accounts of use in ancient India, the Middle East, Egypt, and Europe
  - Mesopotamian use for "hand of ghost" (epilepsy), CV, pulmonary, MSK, and skin disorders
  - William O'Shaughnessy: mid-1800's, treatment of tetanus, convulsive disorders
  - Jean-Jacques Moreau de Tours: cannabinoids for mental health disorders
  - North American use of cannabis/hemp peaked in the 1600s, then retracted in the 1900s
  - 1851: cannabis included in the 3rd ed. of the *United States Pharmacopoeia* (revisions describe recipes for extracts and tinctures for analgesic, hypnotic, anticonvulsant use)


Shustorovich, A. Narouze, SN. *History of Cannabis*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 3-7

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Russo, EB. History of cannabis and its preparations in saga, science, and sobriquet. Chem Biodivers. 2007;4(8):1614-48.

National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington DC: National Academies Press; 2017, 2, Cannabis.

# “Reefer Madness”

- Influx of Mexican immigrants into the US after the Mexican Revolution of 1910 introduced recreational marijuana use to the US
- 1930: Harry J. Anslinger, first Commissioner of the Federal Bureau of Narcotics, denounced marijuana
  - Due to increasing use, states were encouraged by the federal government to begin outlawing marijuana
  - National prohibition in the Marijuana Tax Act of 1937
  - With growing national opposition to the plant, the AMA removed Cannabis from the USP in 1942
  - Sentencing laws became more strict during the civil rights movements of the 1960s
  - Countercultural recreational use increased during the 1960s and 1970s
  - Creation of the DEA, and series of significant laws in the 1970s and 1980s severely restricted cultivation, research, and access to marijuana
  - Cannabis rescheduled as Schedule I controlled substance under the Controlled Substances Act of 1970
  - Anti-Drug Abuse Act of 1986 issued mandatory sentences based on amount of drug involved

Shustorovich, A. Narouze, SN. *History of Cannabis*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 3-7

National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington DC: National Academies Press; 2017, 2, Cannabis.

# US History Continued

- CA Proposition 215 in 1996 (medical use)
- 2012: Colorado and Washington State became the first 2 states to legalize recreational use of cannabis
- By Jan 2016, 21 states had legalized medicinal marijuana use, and another 16 had adopted (CBD)-only laws
- 2016 survey revealed that cannabis use remained predominantly recreational (89.5% of adult users) with 10.5% solely for medicinal reasons and 36.1% reporting mixed recreational/medicinal use
- 2018 Farm Bill: legalized low-THC hemp (cannabis plant with 0.3% THC or less) and removed it from the restrictions of the Controlled Substances Act
  - Hemp industry boom (CBD oil, balm, lotion, tinctures) without FDA regulation
- Now at least 15 states and DC have legalized marijuana for adults over age 21
- Medical Cannabis Research Act of 2019; Cannabidiol and Marijuana Research Expansion Act

Shustorovich, A. Narouze, SN. *History of Cannabis*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 3-7

Coffman, K; Neroulias, N. (Nov 6, 2012). Colorado, Washington first states to legalize recreational pot. Reuters.

Shauer GL, King BA, Bunnell RE, Promoff G, McAfee TA. Toking, vaping, and eating for health or fun: marijuana use patterns. Am J Prev Med. 2016;50(1):1-8.

# Cannabis Terminology

- Cannabis sativa L. (C. sativa, C. indica, C. ruderalis)
  - Dioecious species: male and female flowers develop on separate plants (active cannabinoids in female flowers)
  - "cultivars" (more commonly "varieties" or "strains") developed through cross-breeding
  - Most medical cannabis is cultivated via cloning (cuttings from "mother" plants) for consistency of chemotype
  - Chemotype I (THC predominant), II (THC-CBD balanced), III (CBD predominant)
  - Plant can reach 16ft high; grow in various habitats and altitudes

- Endocannabinoid: endogenous cannabinoids produced by the body and active at cannabinoid receptors
- Phytocannabinoid: cannabinoids that are produced by the cannabis plant
- Medical Cannabis: cannabis-based treatment that has not been approved as medical treatment but has been legalized and regulated for patient access
- Pharmaceutical Cannabinoid: cannabinoid-based treatments approved for specific medical applications

Arboleda MF, Prosk E. *Cannabis Terminology*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 31-6

# Cannabis Pharmacology

- The endocannabinoid system (ECS) is present in all animals and developed concurrently with the nervous system
- At least 2 types of cannabinoid receptors: CB1 and CB2, both extracellular binding with G-protein coupling
- CB1: predominantly at nerve terminals and mediate inhibition of transmitter release
- CB2: on immune cells; expression depends on activation state of the cell
- Also action at intracellular binding sites, Transient receptor potential vanilloid (TRPV1, TRPV2, TRPV3, TRPV4, TRPA1, TRMP8)
- Endocannabinoids (eCB) are synthesized on demand, and removed from cites of action by cellular uptake (anandamide membrane transporter, endocannabinoid membrane transporter) and enzymatic hydrolysis (fatty acid amide hydrolase; monoacylglycerol lipase)
- eCB have a short period of activity (~15 min)
- Also suggested that G-coupled orphan receptors (GCPRs) 55 and 119 and transcription factors (peroxisome proliferator-activated receptors, PPARs-alpha –delta and –gamma) are part of the ECS

Rech GR, Narouze, SN. *The endocannabinoid system:* Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 39-45

Silver RJ. The endocannabinoid system of animals. Animals. 2019;9:686

# CB1

- Most widely expressed receptor protein from the GPCR family in the brain
  - High levels in the olfactory bulb, hippocampus, lateral striatum, globus pallidus, entopeduncular nucleus, substantia nigra pars reticulata, cerebellar molecular layer
  - Thalamus, other nuclei in brain stem, and spinal ventral horn are low in binding
- CB1 in peripheral nervous system
  - Mostly in sympathetic nerve terminals
  - Agonists to CB1 in the CV system produce pro-inflammatory effects
  - Agonists to CB1 in the GI tract may contribute to obesity
  - CB1 is present in the liver, skin, muscles, and reproductive system
- CB1 is located mainly on the presynaptic nerve terminal
  - Inhibit neurotransmitter release and the electrical activity accompanying depolarization (L-glutamate, GABA, noradrenaline, dopamine, serotonin, acetylcholine)
  - Can induce either suppression of inhibition or suppression of excitation depending on state of presynaptic terminal
- After activation, CB1 receptors are desensitized and then undergo endocytosis
- Widespread distribution and expression of CB1 on various presynaptic neurons complicates antinociception research

Rech GR, Narouze, SN. *Cannabinoid receptor 1 (CB1)*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 47-54

# CB2

- Receptor exists in 2 isoforms
- Spleen, leucocytes, and other peripheral tissues
  - Macrophages, CD4+ T cells, CD8+ T cells, B cells, Natural killer cells, Monocytes, and Polymorphonuclear Neutrophils immune cells with highest levels of CB2 mRNA
- Thought to primarily be the peripheral cannabinoid receptor, but CB2 is also expressed in the brain (expressed at lower level than CB1 in the brain and are inducible)
- Not as much is known about CB2
  - Lack of selective CB2 receptor antibodies
  - Lack of full knockout CB2 receptor mice
  - Under some conditions, CB1 and CB2 form heteromer, which makes identification of CB2 difficult
  - CB2 receptors from different species exhibit different pharmacological responses to the same agents
- Like CB1, CB2 receptors undergo endocytosis after binding but by varying degrees
- CB2 receptors are highly inducible during nerve injury or inflammation
  - Inflammatory animal models showed upregulation of CB2 in the ipsilateral DRG in response to injury under neuropathic pain conditions

Rech GR, Narouze, SN. *Cannabinoid receptor 2 (CB2)*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 55-61

# The Endocannabinoid System

- Anandamide (N-arachidonoylethanolamine, AEA)
  - Derived from arachidonic acid containing phospholipids; Calcium dependent biosynthesis pathway on demand in stimulated cells
  - Main path of breakdown is via fatty acid amide hydrolase into arachidonic acid and ethanolamine
- Partial agonist at both CB1 and CB2 receptors
- Full agonist at TRPV1
  - Pronociceptive at TRPV1
- Selective for CB1 (at higher affinity than 2-AG)
  - antinociceptive at CB1 (inhibitory interneurons and glial cells)
- "Tetrad" effect in mice when injected: inhibition of motor activation, catalepsy, hypothermia, hypoalgesia
- Regulates pain, depression, appetite, memory, and fertility

Pete DD, Narouze, SN. *Endocannabinoids Anandamide and 2-Arachidonoylglycerol (2-AG)*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 63-70

# The Endocannabinoid System

- 2-Arachidonoylglycerol (2-AG)
  - Also derived from AA-containing phospholipids and has calcium dependent on-demand synthesis; Breakdown via membrane-associated enzyme, monoacylclycerol lipase
- Full agonist at CB1 and CB2
- When 2-AG is released, it controls the activity of the presynaptic neuron by binding CB1 where it prevents neurotransmitter release
- 2-AG is present at higher levels than AEA, so might play a greater role in antinociception and analgesia
- Multiple mechanisms for 2-AG pain modulation: CB2 receptors in inflammatory pain models show inhibiting production and release of reactive oxygen species and cytokines, release of peripheral endogenous opioids, CB1 action to attenuate transduction of noxious stimuli in periphery as well as dorsal horn of spinal cord
- Endocannabinoids show high synaptic plasticity (depolarization induced suppression of inhibition) and are mobilized as needed
- When noxious stimuli occur, endocannabinoids are released and modulate pain in the periphery, spinal, and supraspinal pathways
- At the spinal level, AEA appears to exert its actions at the onset of pain (and subsides as noxious stimulus stops), and 2-AG plays a role in the resolution of pain

Pete DD, Narouze, SN. *Endocannabinoids Anandamide and 2-Arachidonoylglycerol (2-AG)*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 63-70

- Comment about supraspinal?
- ECS is highly plastic, with altered expression and function depending on physiologic state
- Acute and chronic nociception is modulated by endocannabinoids at the peripheral, spinal, and supraspinal levels
- Site specific actions of AEA and 2-AG may provide pharmacologic targets for future research

# Phytocannabinoids

- Over 500 distinct compounds in cannabis, with 18 different chemical classifications and more than 100 cannabinoids

- Cannabinoid subclasses
  - THC (delta-9-tetrahydrocannabinol), CBD (cannabidiol), THCV (delta-9-tetrahydrocannabivarin), CBC (cannabichromene), CBDV (cannabidivarin), CBL (cannabicylol), CBN (cannabinol), CBG (cannabigerol)

- Terpenoids (Terpenes)
  - Essential oils (15-20k fully characterized) not unique to cannabis (150 different types in cannabis)
  - Responsible of the aroma of cannabis

- Other (nitrogenous compounds, amino acids, proteins, enzymes, glycoproteins, hydrocarbons, simple alcohols, aldehydes, ketones, fatty acids, simple esters and lactones, steroids, non-cannabinoid phenols, flavonoids, vitamins, pigements)

# THC

- Main psychoactive compound in cannabis
- Produced in the flowers and leaves in varying concentrations
- Range between different cannabis products may be 5% in marijuana to 80% in hashish oil
- THC exists as several different isomers
- Pharmacologic effects include cognitive changes, psychoactive, anti-inflammatory, antipruritic, bronchodilatory, anti-spasmodic, muscle relaxant
- Negative effects: anxiety, impaired memory, immunosuppression
- MOA: stimulates endocannabinoids (AEA, 2-AG) and is partial agonist at CB1 and CB2 (high affinity for CB1)
  - Activation of CB1 and CB2 results in decreased cAMP by inhibiting adenylate cyclase
  - Can activate or inhibit neurotransmitter release

Roychoudhury P, Wang NN, Narouze SM. *Phytocannabinoids: Tetrahydrocannabinol (THC)*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 71-77

# THC

- CB1 mediated increase in acetylcholine, glutamate, and dopamine in rat prefrontal cortices
- CB1 mediated dopamine release in mouse and rat nucleus acumbens
- In-vivo THC can be pro-convulsant or anti-convulsant
- Other targets than CB1/CB2 – GPR-55, TRPV1/V2/A1, 5-HT2
- High plasma protein binding and large volume of distribution
- Metabolized in the liver (CP450: CYP 2C9, 2C19, 3A4) into active forms 11-OH-THC (mimics THC action in brain)
- 55% THC excreted in feces and 20% in urine

Roychoudhury P, Wang NN, Narouze SM. *Phytocannabinoids: Tetrahydrocannabinol (THC)*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 71-77

# CBD

- Non-psychoactive effects including analgesia, anti-inflammatory, anticonvulsant, anxiolytic, antipsychotic
- Low affinity for CB1 and CB2 receptors
  - Partial agonist CB1 with negative allosteric modulation
  - Weak, inverse agonist of CB2 (anti-inflammatory effect?)
- Other non-CB receptors: 5-HT1A, TRPV1, A2A (regulates perception of pain), GPR3, GPR6, GPR12, GPR55
- Enhances antidepressant effects in mice by enhancing 5-HT and glutamate levels in the prefrontal cortex
- Increases serotoninergic and glutamatergic transmission
- Antagonizes alpha-1-andronergic receptors
- Allosteric modulator at mu- and delta- opioid receptors

Roychoudhury P, Wang NN, Narouze SM. *Phytocannabinoids: Cannabidiol(CBD)*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 78-86

# CBD

- Can work synergistically with THC for analgesic effects
  - Can decrease psychologic and cognitive side effects of THC (sedation, memory impairment)
  - Interactions of CBD with THC are still poorly understood
- Pre-treatment with CBD may prevent acute induction of psychotic symptoms from delta-9-THC
- Large volume of distribution
- Extensive first pass metabolism in the liver (CYP 3A4 and 2C19)
- Excreted in urine (more than 30 different metabolites) and feces (large portion unchanged in feces)

Roychoudhury P, Wang NN, Narouze SM. *Phytocannabinoids: Cannabidiol(CBD)*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 78-86

# Minor Cannabinoids

- Cannabinol (CBN)
  - Non-enzymatic oxidation by-product of THC
  - Moderately psychoactive; small concentrations in cultivars
  - Lower affinity for CB1 and CB2 than THC but more sedating
  - Anti-convulsant, anti-inflammatory, anti-bacterial (MRSA)
  - TRPV2 agonist
  - Inhibits keratinocyte proliferation
- Cannabigerol (CBG)
  - Found in small amounts in cannabis; non-psychotropic
  - Weak, partial agonist at CB1 and CB2; anandamide uptake inhibitor
  - Receptors involved in pain, inflammation, heat sensitization (TRPV1/2/3/4, TRPA1, alpha-2-adrenoreceptor, antagonist of TRPV8, GABA uptake inhibition)
  - Antidepressant properties (5-HT); anti-bacterial
  - Anti-cancer/cytotoxic properties (high doses on human epithelioid carcinoma and breast cancer in basic research models)

Clarke H, Roychoudhury P, Narouze SM. *Other Phytocannabinoids*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 87-92

# Minor Cannabinoids

- Cannabichromene (CBC)
  - Usually 0.3% of cannabis but can be increased with cross-breeding
  - Interacts with TRP cation channels, inhibiting deactivation of endocannabinoids
  - Stimulates CB2, no significant activity at CB1
  - Analgesic, can potentiate analgesia of THC
  - Anti-inflammatory
- Tetrahydrocannabivarin (THCV)
  - Low concentration to 16% in dried weight
  - Can have agonist and antagonist properties at CB1 depending on concentration
  - Anti-convulsant
  - Animal model shows interaction at CB2 to suppress hyperalgesia and inflammation
  - Antagonism at CB1 can suppress appetite and reverse intoxicating effects of THC in animal models

Clarke H, Roychoudhury P, Narouze SM. *Other Phytocannabinoids*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 87-92

# Entourage Effect

- Belief that the pharmacological effects of medical cannabis are not secondary to cannabinoids alone, but also because of the presence of terpenoids and other constituents in the plant (synergism)

# Cannabinoid Drugs

- Dronabinol
- Nabilone
- Cannabidiol
- Nabiximols

# Dronabinol

- Synthetic delta-9-THC; available in 2.5 mg, 5 mg, and 10 mg doses
- Indications:
  - Anorexia associated with weight loss in patients with AIDS
  - Nausea and vomiting associated with cancer chemotherapy in patients who have not responded to other antiemetic treatments
- Equal affinity for CB1 and CB2 receptors (but less efficacy at CB2)
  - Antiemetic effect likely mediated by CB1 and appetite stimulating effects
- Onset of action 30-60 min (max 60-120 min after ingestion); 25-36 hr half-life
- 90% absorbed from GI tract, but only 1—20% bioavailable after first-pass metabolism
- Hepatic metabolism; primary fecal elimination but some urine
- No FDA approved indication for pain:
  - Cooper et. al found that compared to smoked MJ, both decreased pain severity with dronabinol having longer lasting relief and less abuse potential
  - Randomized, double blinded, placebo-controlled crossover trial showed modest but clinically relevant analgesic effects on central pain in patients with MS
  - Due to psychotropic effects and abuse potential, use for pain is controversial
- Side effects are dose dependent (headache, dizziness, fatigue, myalgia, muscle weakness)


Gaisey J, Narouze SN. *Dronabinol (Marinol)*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 105-107

Cooper ZD, Comer SD, Haney M. *Comparison of the analgesic effects of dronabinol and smoked marijuana in daily marijuana smokers.* Neuropsychopharmacology. 2013;38(10):1984-92.

Svendsen KB, Jensen TS, Bach FW. *Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomized double blind placebo controlled crossover trial.* BMJ. 2004;329(7460):253

# Nabilone

- Synthetic cannabinoid with structure that mimics delta-9-THC
- Indication:
  - Chemotherapy induced nausea and vomiting
- Superior efficacy to older antiemetics, but less so with serotonin antagonists
- Not FDA approved for pain control nor widely recommended
  - Clinical trials for pain with inconclusive results

Harrison N, Simpson H. *Nabilone (Cesamet)*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 109-112

# Cannabidiol (Epidiolex)

- Liquid CBD (schedule V) approved for use in seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years or older
- Exact mechanism for anticonvulsant effects is not known but seems unrelated to CB1 or CB2 agonism
  - Antagonizes GPR55 and TRPM8; agonist at 5HT-1a, 5HT-2a, TRPV1-4
  - Inhibits anandamide reuptake
- Maximum plasma concentration 2.5-5 hrs; co-administration with a high fat meal may increase maximum serum concentration 5 fold compared to fasted individuals
- 56-61 hr half-life after BID administration for 1 week
- Primary liver metabolism; primary excretion fecal
- Potential for hepatocellular injury (need for monitoring); dose adjustment needed with severe liver impairment
- Other adverse effects: diarrhea, abdominal pain, decreased appetite/weight loss, somnolence; monitor for changes in mood

Harrison NJ. *Cannabidiol (Epidiolex)*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 113-117

# Nabiximols

- Prescription cannabinoid approved in 29 countries outside of the US
- Formulated from extracts of the Cannabis sativa plant; buccal/oromucosal spray
- Consistently approved as an adjunct for MS spasticity
  - Some countries have approved for MS related neuropathic pain and cancer related pain unresponsive to opioids
- Consistency in production ensures 27 mg of THC and 25 mg of CBD in each mL
- Each botanical drug substance also has a proprietary blend of non-cannabinoid ingredients seen in whole plant extracts (terpenoids, sterols, fatty acids, carotenoids, flavonoids)
- Self-titration schedule with most patients eventually using 4-8 sprays per day

- Canadian product monograph list contraindications:
  - Patients with know or suspected allergy to cannabinoids, propylene glycol, ethanol, or peppermint oil
  - Patients with serious cardiovascular disease (ischemic heart disease, arrhythmias, poorly controlled HTN, severe heart failure)
  - Patients with schizophrenia or any other psychotic disorder
  - Children under 18
  - Women of child bearing potential not on reliable contraceptive or men wanting to start a family
  - Pregnant or nursing women

Boivin M. *Nabiximols (Sativex)*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 119-126

# Nabiximols

- One RCT for MS related neuropathic pain found Nabiximols to be associated wit ha significant reduction in pain intensity and sleep disturbances compared to placebo; no evidence of tolerance at 2 years
  - Another large RCT found a non-significant reduction in pain vs placebo (50% of patients in treatment group vs 45% in placebo group received at least 30% reduction in pain), significant difference in pain relief and sleep quality during the withdrawal phase of nabiximol responders
- Studies evaluating cancer related pain have mixed results
- Current studies for chronic pain related to rheumatoid arthritis and neuropathic pain demonstrate some individuals may benefit
- Adverse effects: dizziness, fatigue, nausea, vertigo, dry mouth, asthenia, diarrhea, disorientation/confusion, disturbances in attention
- Adverse effects more likely in titration phase


Boivin M. *Nabiximols (Sativex)*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 119-126

Langford RM, [et. al.] *A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis*. J Neurol. 2013;260:984-97.

Rog DJ, Nurmikko TJ, Friede T, Young CA. *Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis*. Neurology. 2005;65:812-9

# Cannabis and Pain: mechanism of action and current state of evidence

# Cannabis and drug-drug interactions

- Additive when co-administered with other agents that have similar physiologic effects
  - Increased sedation with opioids, other CNS depressants, alcohol, and antihistamines
  - Increased tachycardia may occur with TCAs, stimulants, and sympathomimetics
- Other drugs may inhibit or induce the CYP enzymes responsible for THC and CBD metabolism
- Anti-inflammatory action is different than that of NSAIDs (COX); no direct drug-drug interaction but more research is needed
- Caution with acetaminophen (increased risk of hepatotoxicity?)
- THC administered with gabapentin may increase antiallodynic effects without significantly increasing risk of negative side effects (suggested similar pain systems, so still need to monitor for overlapping effects if used with gabapentinoids)

Poulson G, Chung M, Hirani S, Le-Short C. *Cannabis Drug Interactions*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 93-101

# Cannabis and drug-drug interactions

- Cardiac side effects reported in recreational cannabis use in those on TCAs
- May have synergistic analgesic effects with opioids and reduction in withdrawal symptoms
  - Vaporized cannabis may show increased antinociception of morphine and oxycodone without significant increased risk of adverse events
  - May see increased serum buprenorphine levels with CBD use; CBD does not increase brain levels of morphine and methadone
  - More evidence is needed regarding if co-administration is recommended outside of palliative care
- May have increased serum levels of some anti-epileptics; increased transaminases with valproate; increased risk of sedation and AMS
  - CBD increased antiepileptic effects of phenytoin and phenobarbital, while decreasing effects of chlordiazepoxide, clonazepam, and ethosuximide

Poulson G, Chung M, Hirani S, Le-Short C. *Cannabis Drug Interactions*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 93-101

# Cannabis and drug-drug interactions

- Increased treatment failure and psychotic relapse in those using illicit cannabis and psychotropic medications
- THC may decrease serum concentration and activity of duloxetine, clozapine, olanzapine, haloperidol, chlorpromazine, risperidone
- THC and CBN may have anti-thrombotic activity and inhibit clot formation
  - Multiple reports of supratherapeutic INR with warfarin and cannabis (THC, CBD, CBN competitive inhibition of CYP2C9)
  - CBD could lead to accumulation of DOACs
  - CBD can decrease metabolism of clopidogrel, leading to increased serum levels
  - No know interaction with heparin or fondaparinux

Poulson G, Chung M, Hirani S, Le-Short C. *Cannabis Drug Interactions*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 93-101

# Dosing? Titration? Monitoring

- Smoking:
  - 5-10 min onset; 2-4 hr duration; rapid action may be helpful for acute or episodic symptoms
  - Not recommended because of toxic biproducts (tar, polycyclic aromatic hydrocarbons, carbon monoxide, ammonia)
  - Chronic respiratory conditions (increased cancer risk if also cigarette smoking)
- Vaporization:
  - Similar onset/duration and advantages to smoking
  - Heats to 160-230 degrees C (smoking 600-900 degrees C)
  - Less harmful biproducts than smoking; decreased pulmonary symptoms
- Oral:
  - Oils, capsules
  - 60-180 min onset; 6-8 hr duration (oromucosal spray may have 15-45 min onset and 6-8 hr duration)
  - Convenient, accurate dosing (edibles like cakes, brownies may be less accurate)
  - Tinctures and lozenges have intermediate onset
  - Titration challenge due to delayed onset
- Other:
  - Topicals for localized symptoms (limited research); variable onset and duration
  - Suppositories possibly for certain populations (cancer, GI symptoms, elderly); THC-hemisuccinate may have best absorption

MacCallum CA, Russo EB. *Practical considerations in medical cannabis administration and dosing*. Eur Journ Int Med. 49(2018);12-19.

# Adverse effects and patient safety

- Impairment
- Cardiovascular risk
- Withdrawal

# Cannabinoids and brain development

# Cannabinoids and mental health risks

# Cannabis use disorder

# Quality control and product safety?

# Federal and state regulation

- According to the Controlled Substances Act of 1970, cannabis and all cannabinoids derived from the plant are classified as Schedule I controlled substances and those who possess, dispense, or prescribe are in violation of the DEA and can theoretically face criminal charges
  - Prohibits clinical trials with cannabis unless part of a federally approved research program
    - Must obtain a schedule I substance specific registration/license and cannabis must be obtained through a facility contracted with the NIDA (National Institute on Drug Abuse)
    - Physicians can only "recommend" their patients use medical cannabis but cannot prescribe
    - According to a 2002 federal appeals court decision *Conant v. Walters*, the First Amendment prohibits the federal government from prosecuting physicians "on the basis of the content of doctor-patient communications"; and that doctors should not be held liable for patients' actions after said communications
- Some state laws allow patients to obtain cannabis through dispensaries after a recommendation from their physician, but this contradicts the CSA
- Petitions as of 2016 to reschedule have been denied based on conclusions by the DEA and FDA that marijuana has no currently accepted medical use, lacks accepted safety for use under medical supervision, and has a high potential for abuse

Eshraghi Y, Duracher D. *Cannabis Regulations*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 9-13.

Hoffmann DE, Weber E. Medical marijuana and the law. N Engl J Med. 2010;362(16):1453-7.

Annas GJ. Medical marijuana, physicians, and state law. N Engl J Med. 2014;371(11):983-5.

Mead A. Legal and regulatory issues governing cannabis and cannabis-derived products in the united states. Front Plant Sci. 2019;10:697.

# Federal and state regulation

- DEA criteria for “accepted medical use”
  - Drug’s chemistry must be known and reproducible
  - Must be adequate safety studies
  - Must be adequate and well-controlled studies for efficacy
  - Drug must be accepted by qualified experts
  - Scientific evidence must be widely available
  - (exception) FDA approval of a substance as a prescription medicine

- Petitions as of 2016 to reschedule have been denied based on conclusions by the DEA and FDA that marijuana has no currently accepted medical use, lacks accepted safety for use under medical supervision, and has a high potential for abuse

Eshraghi Y, Duracher D. *Cannabis Regulations*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 9-13.

Mead A. Legal and regulatory issues governing cannabis and cannabis-derived products in the united states. Front Plant Sci. 2019;10:697.

Drug Enforcement Administration. Denial of petition to initiate proceedings to reschedule marijuana. Administration DE, editor. 81 Fed. Reg;2016. p. 53699.

# Federal and state regulation

- CA: Compassionate Use Act of 1996 decriminalized marijuana for medicinal use
  - Allowed qualifying patients and caregivers to cultivate and possess MJ
- 2009: Department of Justice sent a memorandum to US Attorneys stating that federal funds should not be used to prosecute persons acting within their states' own medical laws
- Amendment to the Consolidated Appropriations Act of 2018 restricts the DOJ from using federal funds to interfere with implementation of state medical MJ laws
- Medical marijuana laws vary from state to state
  - Amount or type of cannabis product allowed to possess
  - Qualifying medical conditions vary
  - Lack of uniform quality control standards for the production of cannabis products for medical use

Eshraghi Y, Duracher D. *Cannabis Regulations*: Cannabinoids and Pain (ed. Narouze, SN.). Springer. 2021. pp 9-13.

Mead A. Legal and regulatory issues governing cannabis and cannabis-derived products in the united states. Front Plant Sci. 2019;10:697.

Hoffmann DE, Weber E. Medical marijuana and the law. N Engl J Med. 2010;362(16):1453-7.

# Future research

- Thank you!