Endocannabinoid System and Cannabinoid Therapies

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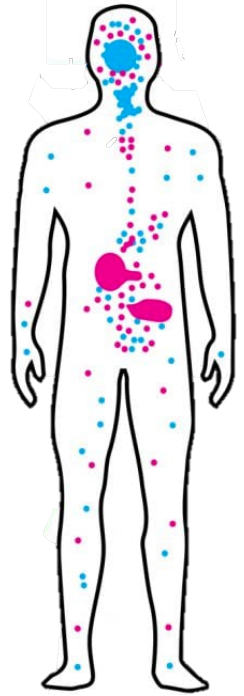
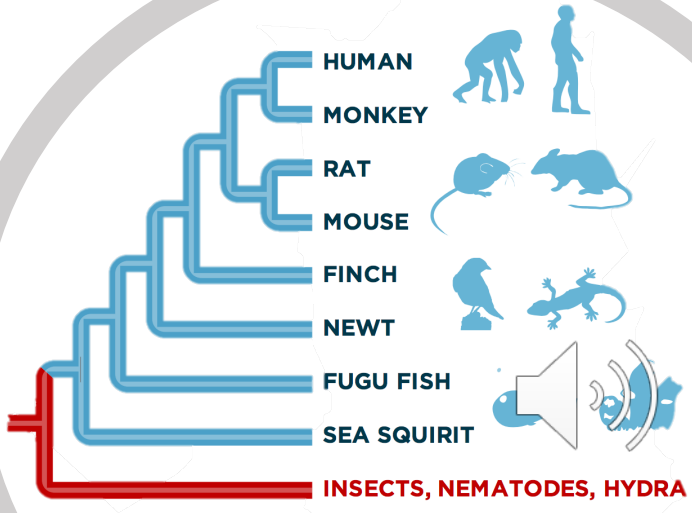
Learning Objectives

- Describe the endocannabinoid system
- Review cannabis botany and US policy
- Discuss therapeutic applications and risks of THC and CBD use
- Identify important considerations for cannabis product selection

Endocannabinoid (eCB) System

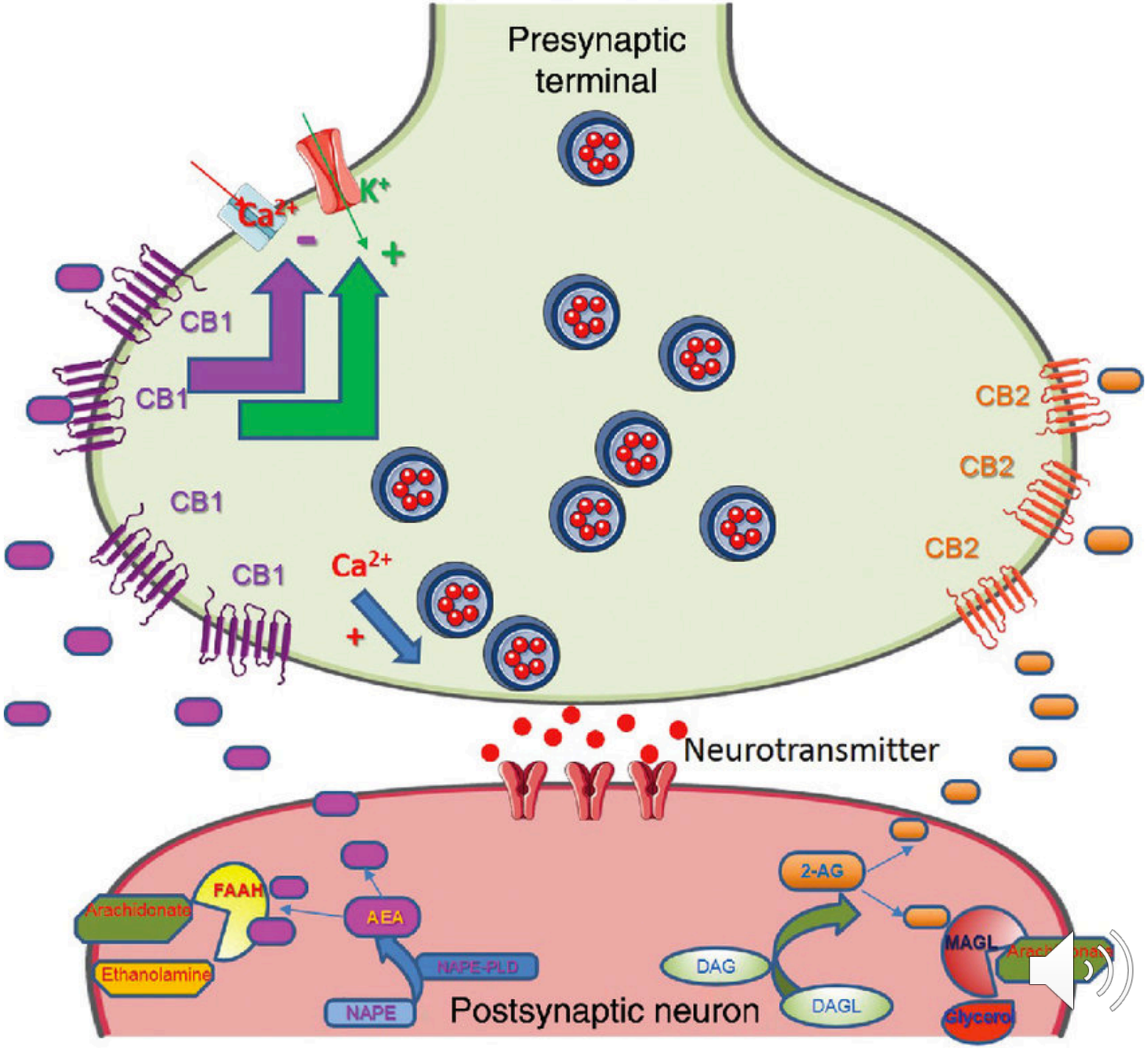
- All vertebrate animals
- Functions: ‘relax, eat, sleep, forget and protect’
- eCB has homeostatic roles in:
  - Hunger, feeding, and energy
  - Neural plasticity
  - Neuroprotection
  - Nociception, pain
  - Autonomic tone
  - Immune response
  - Connective tissue repair
  - Human behavior





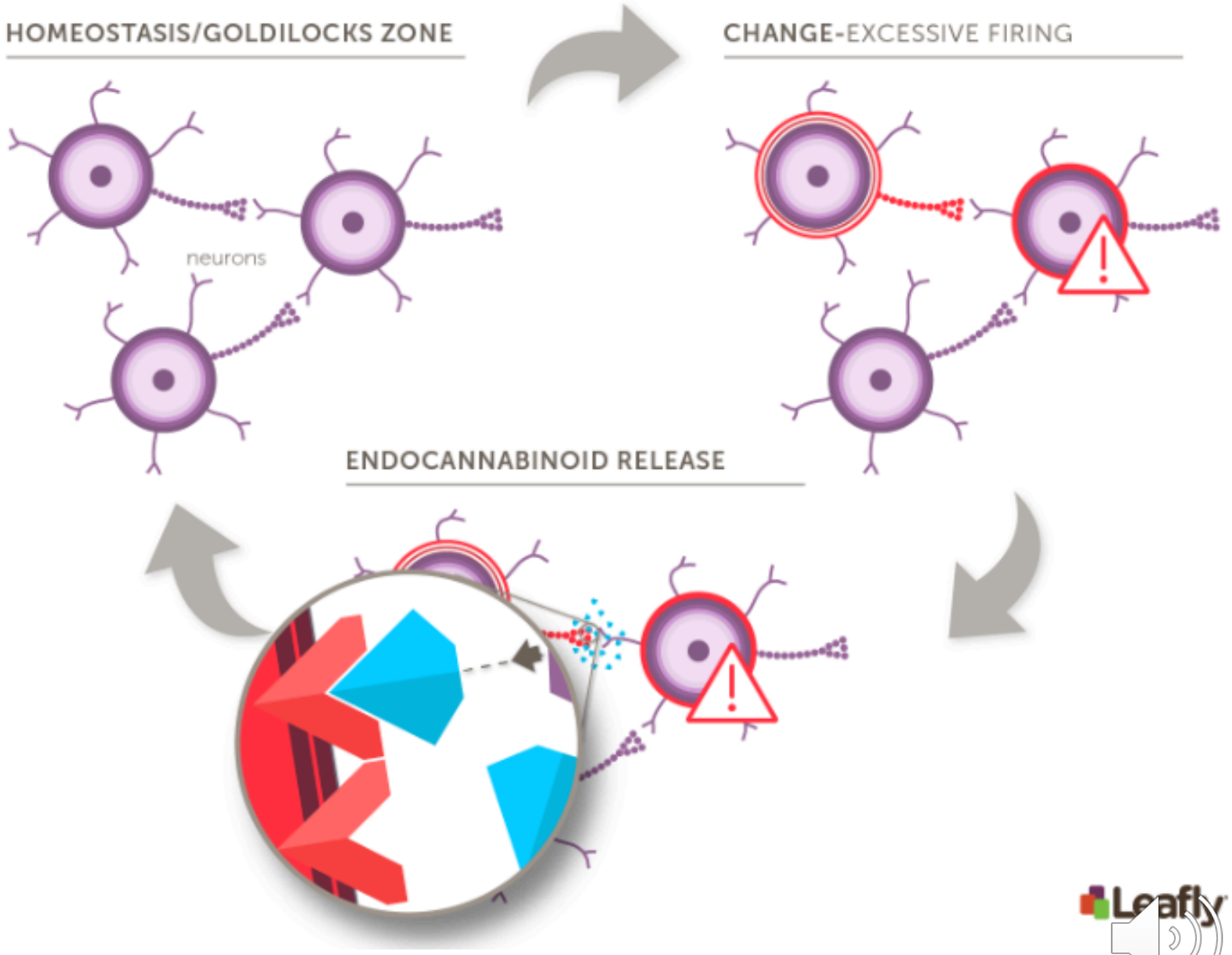
Endocannabinoid System

- 3 key components:
  - Cannabinoid Receptors
    - CB1 and CB2
    - Orphan receptors (GPR 19, 55, 119)
  - Cannabinoids
    - Endogenous
      - Anandamide (AEA)
      - 2-arachidonoylglycerol (2-AG)
    - Exogenous
      - Synthetic
      - Phytocannabinoids
  - Enzymes that synthesize and degrade cannabinoids
    - Fatty acid amide hydrolase (FAAH)
    - Monoacylglycerol lipase (MAGL)



Mastinu et al. 2018

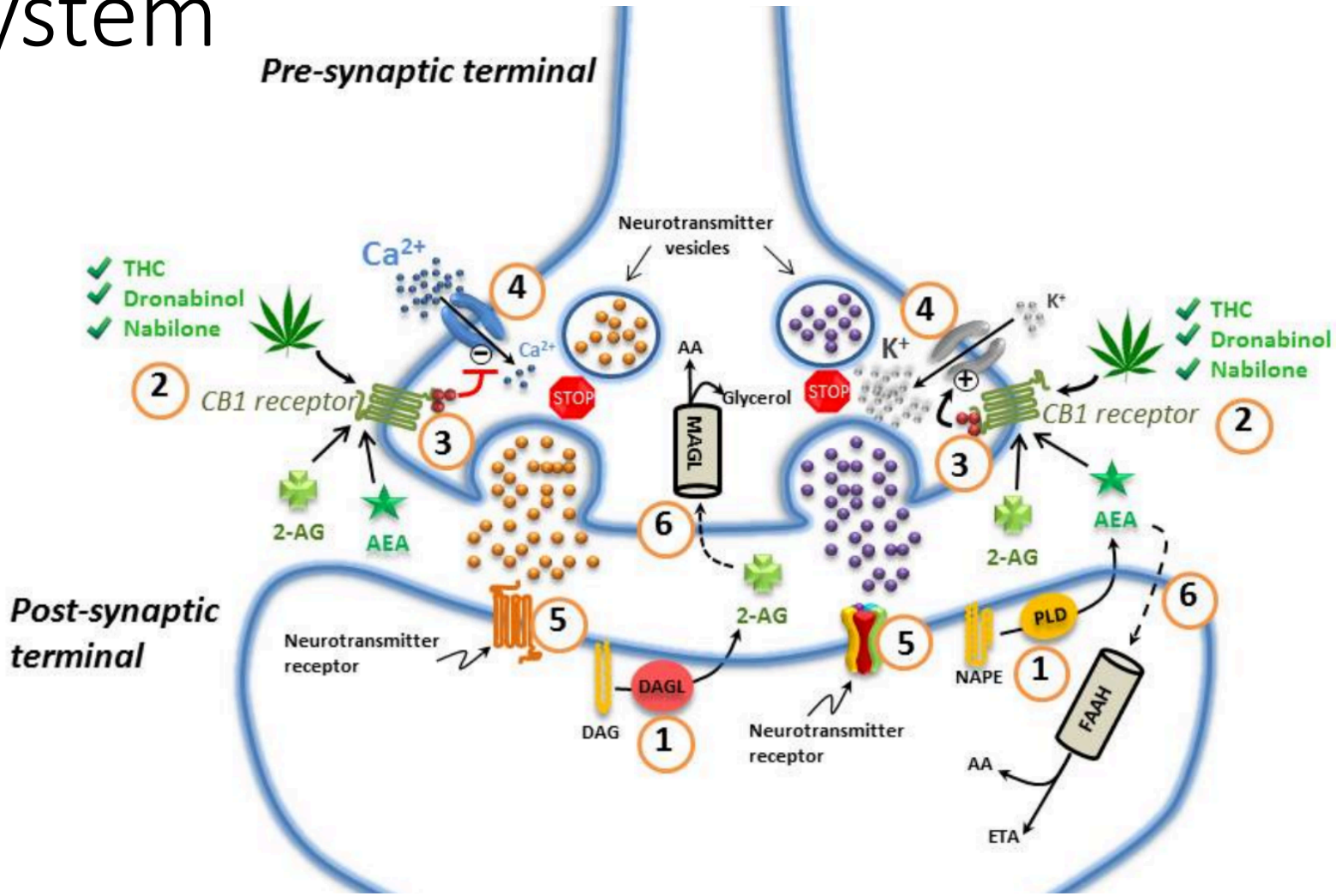
Regulation of Cell Firing



https://www.leafly.com/news/science-tech/what-is-the-endocannabinoid-system

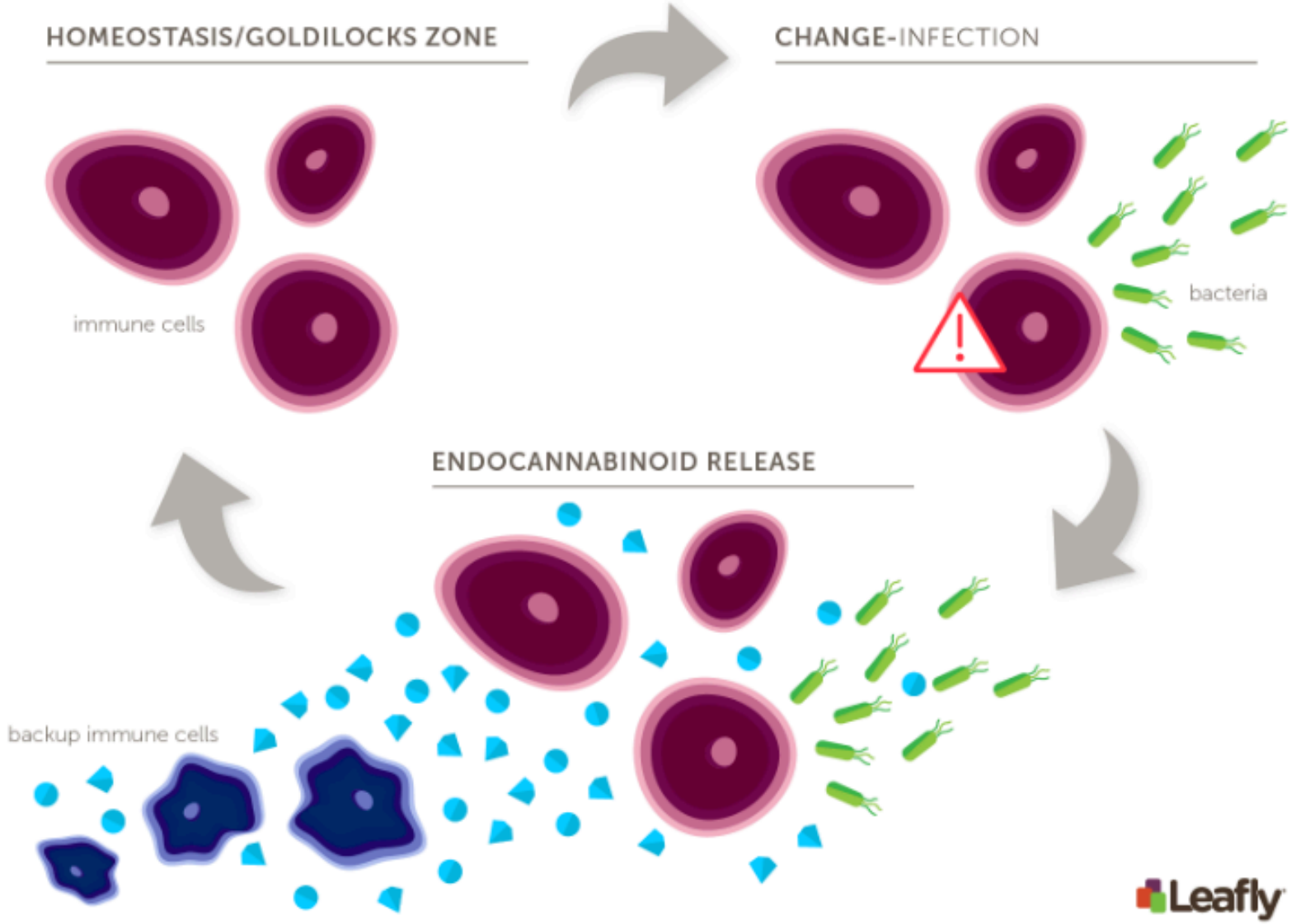
Endocannabinoid System

1. Endocannabinoids synthesis
2. Endocannabinoids diffused retrogradely towards pre-synaptic terminals and bind to G-protein coupled CB1 receptors
3. CB1 receptor binding triggers signaling cascades
4. CB1 receptor binding results in G-protein dependent opening of K^+ channels and closing of Ca^{2+} channels causing release of neurotransmitters
5. Neurotransmitters bind to post-synaptic receptors
6. AEA and 2-AG re-enter post- or pre-synaptic nerve terminals where they are degraded



Abramovici et al. 2018

Regulation of Inflammation



https://www.leafly.com/news/science-tech/what-is-the-endocannabinoid-system

Endogenous vs Exogenous Cannabinoids

Endocannabinoids

- Anandamide (AEA) and 2-arachidonoylglycerol (2-AG)
- Synthesized at or near the site of action
- Rapidly broken down at the site of action
- Signals are quick and localized

Synthetic or Phytocannabinoids

- THC and CBD
- Marinol, Nabilone, Sativex, Epidiolex
- Large volume of distribution
- Metabolized by the liver
- Sustained and global effect

Terminology

- Cannabis – plant family that includes many species
- Cannabinoid – chemical compounds found in the cannabis plant
- Cannabidiol – CBD
- Hemp – variety of the cannabis plant, traditionally used for making ropes and other fibrous materials (< 0.3% THC)
- Marijuana - variety of the cannabis plant
- Isolate – one pure cannabinoid
- Full spectrum – full range of cannabinoids, terpenes, and flavonoids
- Broad spectrum - range of cannabinoids, terpenes, and flavonoids but not THC

What's in the plant?

Cannabinoids

- > 100 cannabinoids
- THC
- CBD

Terpenoids: aromatic, organic compounds found in many plants

- Therapeutic potential
- Myrcene
- Caryophyllene
- Linalool
- Pinene
- Humulene
- Limonene

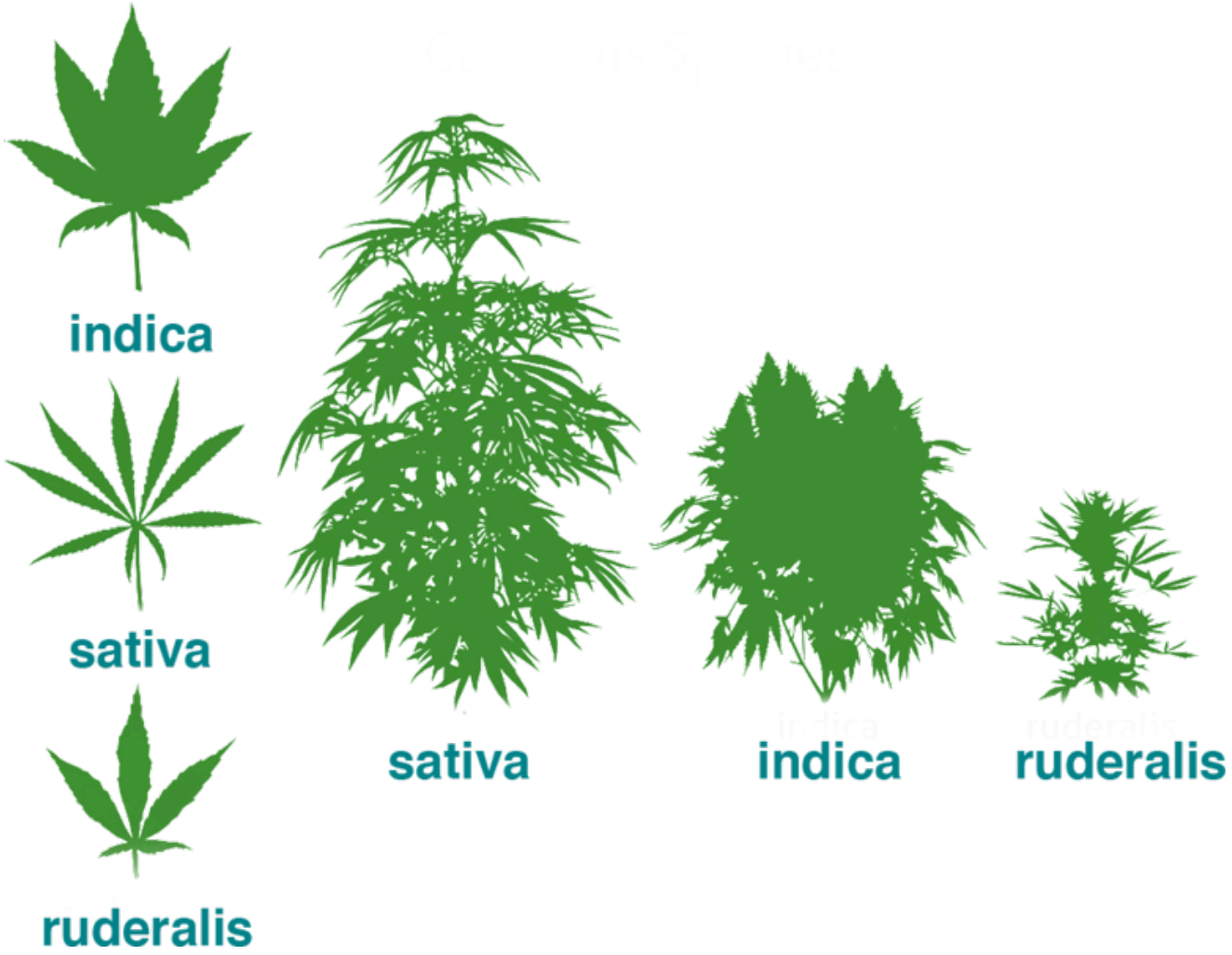
Plant Anatomy

https://nationalholistic.com/understanding-the-cannabis-plant-physiology

Botany

- *Cannabis Sativa*
  - Cannabis, Marijuana, Hemp

- Var.
  - C. sativa
  - C. indica
  - C. ruderalis



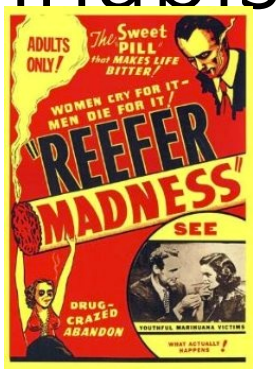
https://craftsense.co/cannabis/cannabis-levelup/cannabis-ruderalis-having

Chemistry vs Cultivars

- Cultivar names are applied to domestic plants that have undergone years of breading to express desired traits
  - ‘Haze’, ’G-13’, ’White Widow’, ‘Hindu Kush’
  - ‘Harlequin’, ‘Cannatonic’, ‘AC/DC’
- Many are not being properly stabilized leading to batch-to-batch variations
- Cross breeding and bleeding of strains make these names meaningless
- A product’s chemical profile is more important that the strain name

Hazekamp and Fishedick 2012

Brief History of Cannabis



1500 BC — Earliest written description of cannabis

1611-1762 — Cultivation of *C. sativa* for fiber in US

1851 — Cannabis sativa var. indica appeared in the US Pharmacopeia

1911 — Massachusetts outlaws cannabis

1930 — Federal Bureau of Narcotics is established

1936 — "Reefer Madness"

1937 — Marijuana Tax Act

1970 — Controlled Substance Act

1972 — NORML vs DEA to reschedule marijuana to Schedule II

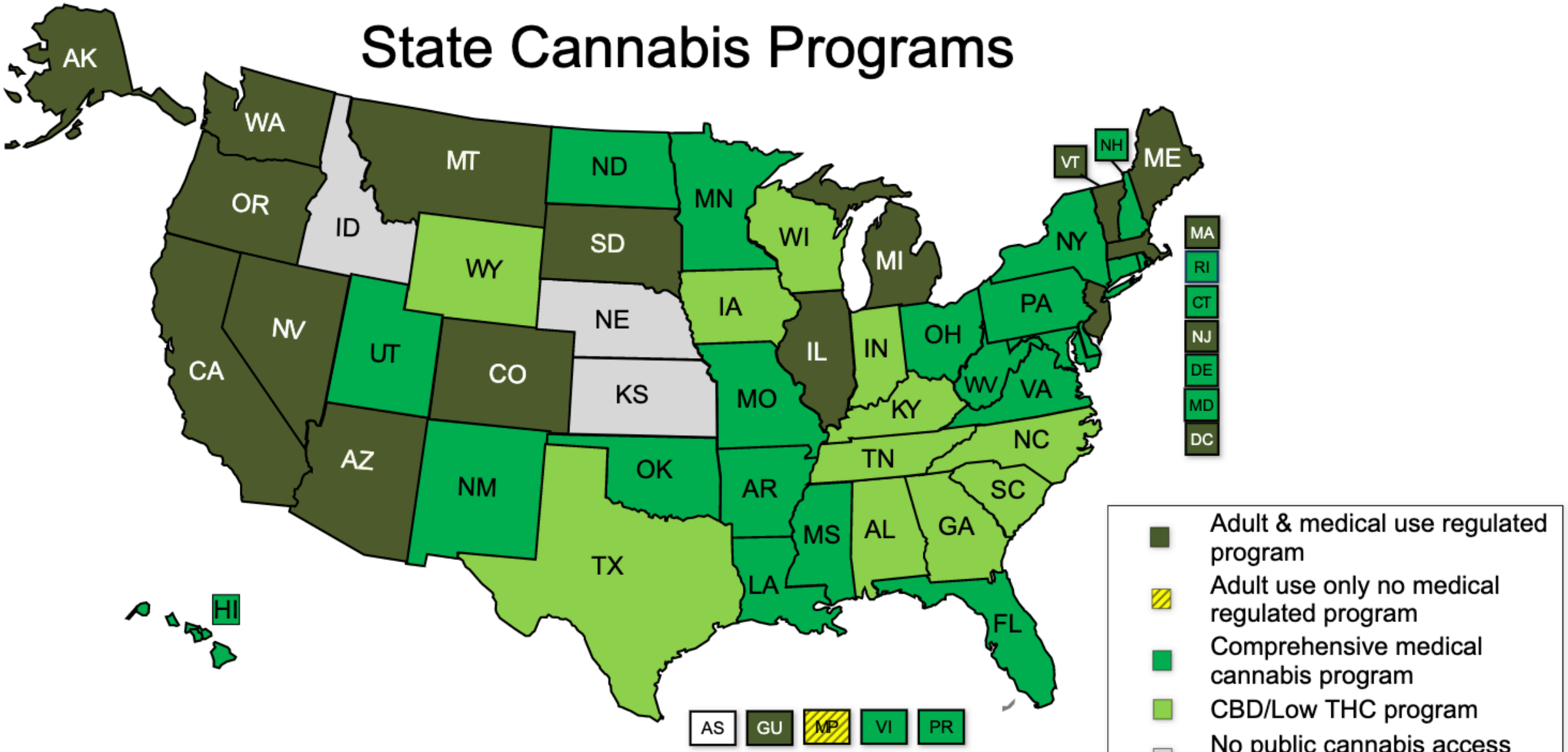
1994 — Appeals continue - Marijuana remains Schedule I controlled substance

1996 — California legalizes cannabis for m[illegible]ical purposes

Conflicting Regulations

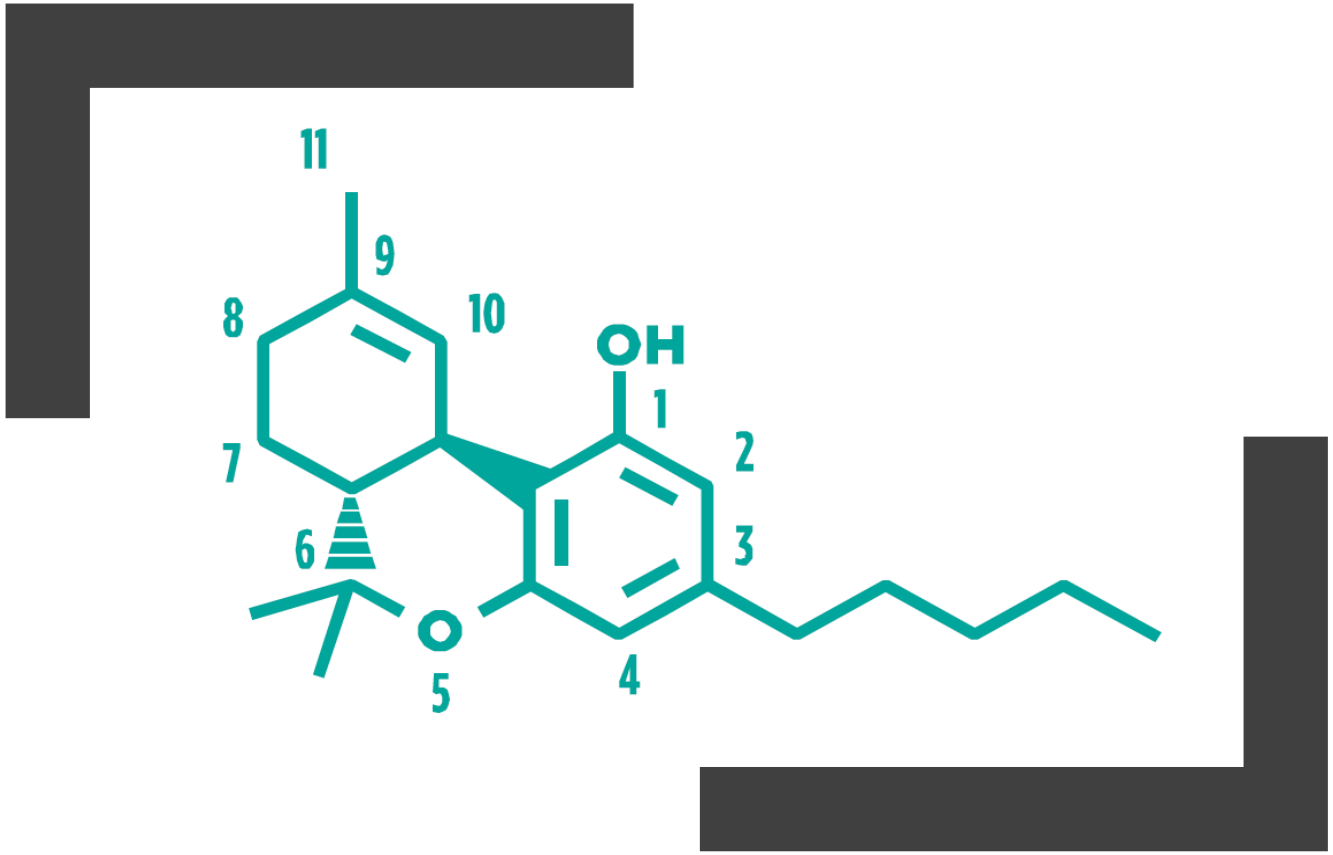
- Cannabis (C-I)
- Epidiolex is FDA approved (C-V)
- By State:
  - Recreational
  - Medicinal
  - CBD only
- 2018 Farm Bill
  - Made CBD from hemp (with < 0.3% THC) legal

State Cannabis Programs



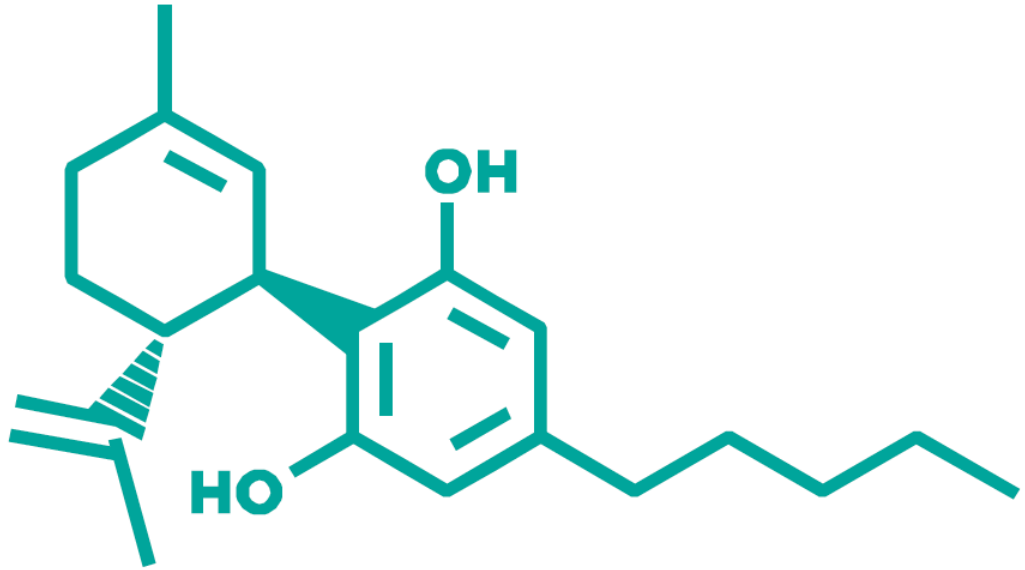
https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx

Δ-9-tetrahydrocannabinol (THC)



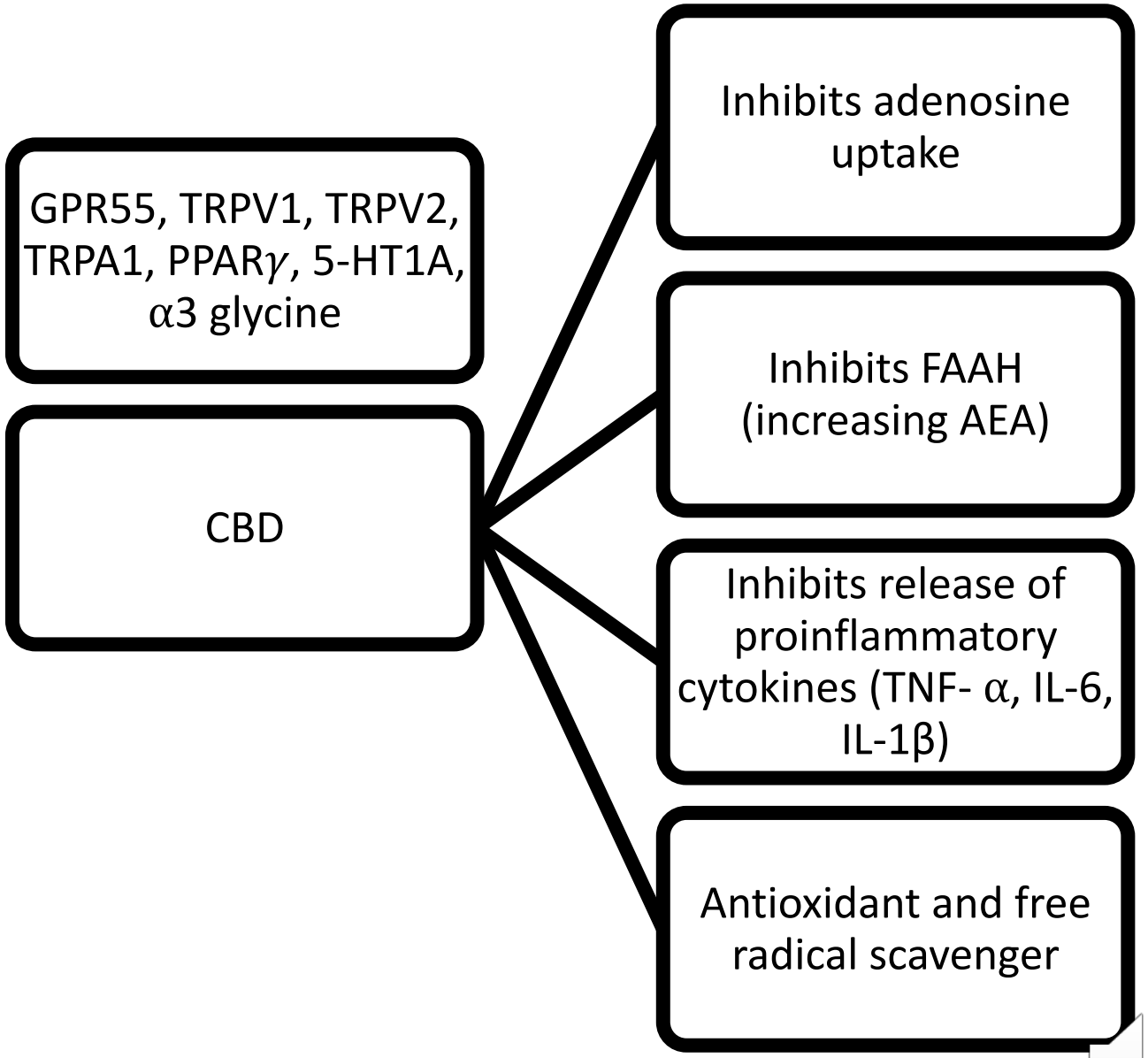
- CB1 and CB2 partial agonist
- Psychoactive
- Anti-inflammatory
- Neuro-protective
- Anti-nausea
- Analgesic (neuropathic, chronic, and cancer pain)
- 11-OH-THC is estimated to be 4x more psychoactive than THC

Cannabidiol (CBD)



- Non-intoxicant
- No significant affinity to CB1 and CB2 receptors
- Blocks the formation of 11-OH-THC
- Mitigates side effects of THC while improving THC's therapeutic activity
- Most common side effect is diarrhea

CBD Targets and Action



Proposed Pharmacologic Effects of Cannabinoids

- Analgesic
- Antispasmodic
- Anti-anorectic
- Antiemetic
- Neuroprotectant
- Anti-cancer
  - Antiproliferative
  - Anti-metastatic
  - Anti-angiogenesis
- Antioxidant
- Antibacterial
- Antifungal
- Antiparasitic
- Anti-inflammatory
- Immunosuppressive
- Anti-host vs graft
- Dermatologic
  - Anti-psoriatic
  - Anti-eczema
  - Anti-keratotic
  - Anti-pruritic
  - UV light reducing
- Bronchodilatory
- Anti-glaucoma
- Anti-diabetic
- Bone-stimulant
- Anxiolytic
- Antipsychotic
- Antidepressant
- Vasorelaxant
- Anti-ischemic
- Anticonvulsant
- ↓ GI motility
- ↓ GI secretions
- ↓ Stomach acid
- ↓ Acid reflux
- ↓ Sleep induction

Evidence of Cannabinoid Efficacy

Target symptom	Tetrahydro-cannabinol	Cannabidiol
Neuropathic pain	+++	+
Chemotherapy-induced		
Peripheral neuropathy	++	?
Nausea or vomiting	+++	Preclinical animal models
Anticipatory nausea	+	Preclinical animal models
Appetite stimulation	++	?
Spasticity or spasms	+++	+
Inflammation	+	++
Seizures	+	+++
Anxiety	+ or –	Simulated situations
Depression	+ (adjuvant)	Preclinical animal models
Malignancy		
Preclinical	++	++
Clinical	+	?

The Health Effects of Cannabis and Cannabinoids. 2017

Conditions in Clinical Practice

- Pain (acute pain, chronic inflammatory, neuropathic)
- Mental disorders
- Cancers
- Gastrointestinal disorders
  - Chron’s
  - Ulcerative colitis
- Insomnia
- Migraine headaches
- Harm reduction, alternative to opioids
- Spastic disorders
- Autoimmune disorders
- Neurodegenerative disorders
  - Alzheimer’s disease
  - Parkinson’s disease
  - ALS
- Glaucoma
- Skin diseases
- Epilepsy
- Autism
- Tourette's
- HIV/AIDS

Bridgeman et al. P&T 2007; Hergenrather 2016

Anti-Inflammatory

- Inflammation has a role in many diseases
  - Autoimmune disorders
    - Rheumatoid arthritis
    - Multiple sclerosis
  - Diabetes (type I and II)
  - Atherosclerosis
  - Neurodegeneration
    - Alzheimer's disease
    - Parkinson’s disease
  - Metabolic syndromes
  - Neuropathic pain
- Preliminary evidence that CBD modulates the immune cascade to reduce inflammation

The Health Effects of Cannabis and Cannabinoids. 2017

Pain

- Most common condition cited for medical use of cannabis
- Some use it to replace conventional pain medications
- 5 reviews with consistent conclusions – modest effect on pain
- Whiting et al 2015
  - 23 RCT in chronic pain (n= 2,454)
  - 22 plant derived THC, 5 synthetic THC
  - 17 neuropathic pain, others included cancer pain, MS, rheumatoid arthritis, musculoskeletal issues, chemotherapy-induced pain
- Suggest that plant-derived cannabinoids increase odds for improvement of pain by ~40%
- Some evidence of dose-dependent effect

The Health Effects of Cannabis and Cannabinoids. 2017

Seizures

- THC and CBD can prevent seizures in animal models
- Epidiolex approved for seizure disorders
- CBD has anti-inflammatory and anticonvulsant properties

The Health Effects of Cannabis and Cannabinoids. 2017

Anorexia and Weight Loss

- CBD has no appetite inducing effects
- Some evidence for oral cannabis in increasing weight in patients with HIV-associated wasting syndrome and anorexia nervosa
- No benefit has been demonstrated on cancer-associated anorexia-cachexia syndrome
  - Small studies
  - Short duration
  - Potentially not the optimal dose

The Health Effects of Cannabis and Cannabinoids. 2017

Sleep

- Affect on Sleep disorders
  - THC
    - Decrease time to sleep
    - Conflicting studies on sleep quality
  - THC/CBD combination – increased wakefulness
  - CBD
    - Biphasic effect (low doses increased total time of waking, high doses increased sleep time and sedation)
    - Positively affected REM sleep behavior disorder
  - May depend on time of administration
  - Definite conclusions are not possible at this point due to differences in study quality and assessment methods

The Health Effects of Cannabis and Cannabinoids. 2017

Anxiety and Depression

- Anxiety
  - Some evidence that CBD improves anxiety symptoms – assessed by public speaking test
  - Daily cannabis use is associated with increased anxiety symptoms
- Depression
  - No clinical trials addressing the effects of cannabinoids for major depressive disorder

The Health Effects of Cannabis and Cannabinoids. 2017

Anti-tumor Effects

- THC slowed the growth of lung and breast cancer, and a virus induced leukemia in mice
- Cannabinoids decrease tumor progression through 2 mechanisms
  - Apoptotic death
  - Inhibition of tumor angiogenesis
- One small clinical trial and serval preclinical studies found anti-tumor effects of cannabinoids on gliomas
- Animal studies demonstrate significant reductions in tumor volume
- US Clinical trials of THC+CBD with temozolomide are under progress
- No efficacy studies or reliable case studies are available

The Health Effects of Cannabis and Cannabinoids. 2017

Cancer Risk

- Likely not associate with lung cancer, or head and neck cancers
- Limited evidence of a statistical association between frequent/chronic cannabis smoking and testicular tumors

The Health Effects of Cannabis and Cannabinoids. 2017

Respiratory Disease Risk

- Long-term cannabis smoking could cause more frequent bronchitis episodes and worsen respiratory symptoms
  - Vaporizing compared to smoking causes fewer respiratory symptoms
- Evidence that cessation of cannabis improves respiratory symptoms
- Cannabis is not associated with COPD
- May improve airway dynamics with acute use (increased forced vital capacity), but not with chronic use

The Health Effects of Cannabis and Cannabinoids. 2017

Cardiometabolic Risk

- Association with heart attack, stroke, and diabetes is unclear
- Acutely THC can cause tachycardia
- Chronic users may develop bradycardia
- Changes in blood pressure
  - High doses can cause orthostatic hypotension
  - Can acutely increase blood pressure
- Increase risk of angina

The Health Effects of Cannabis and Cannabinoids. 2017, Handbook on Cannabis 2015, Frost et al. 2013,

Mental Health Impact

- Association between cannabis use and the development of schizophrenia or other psychoses
- Individuals with schizophrenia and other psychoses, with a history of cannabis use, may be linked to better performance on learning and memory tasks
- Daily cannabis use may increase symptoms in people with bipolar disorder
- Does not increase likelihood of developing depression, anxiety, and PTSD

The Health Effects of Cannabis and Cannabinoids. 2017

Drug Safety

Contraindications

- Acute psychosis or unstable psychiatric condition
- Severe and unstable cardio-pulmonary disease
- Pregnant or breastfeeding
- History of alcohol or substance abuse

Precautions

- Severe cardiovascular, immunological, liver, or kidney disease
- History of arrhythmias
- Personal history of psychiatric disorder
- Family history of schizophrenia
- Association with hyperemesis syndrome
- Pediatric and elderly patients
- Drug interactions

Drug Interactions: CYP540 Enzymes

Metabolism

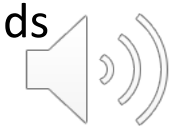
- THC and CBD are metabolized by CYPs 3A4, 2C9, and 2C19

Induction

- THC is a CYP1A2 inducer
  - May reduce serum drug concentrations of clozapine, duloxetine, naproxen, cyclobenzaprine, olanzapine, haloperidol, and chlorpromazine

Inhibition

- THC and CBD - CYP3A4
  - May increase serum drug concentrations of macrolides, calcium channel blockers, benzodiazepines, cyclosporine, PDE5 inhibitors, antihistamines, haloperidol, antiretrovirals, and some statins
- THC and CBD - CYP2D6
  - May increase serum drug concentrations of SSRIs, tricyclic antidepressants, antipsychotics, beta blockers and opioids



Yamaori et al 2012, Watanabe et al 2007, Stout and Cimino 2014. Flockhart 2007

Drug Interaction Studies

Warfarin

- THC and CBD increased warfarin levels
- Frequent cannabis use is associated with increased INR

Alcohol

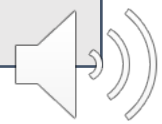
- Alcohol can increase THC levels

Theophylline

- Smoked cannabis can decrease theophylline levels

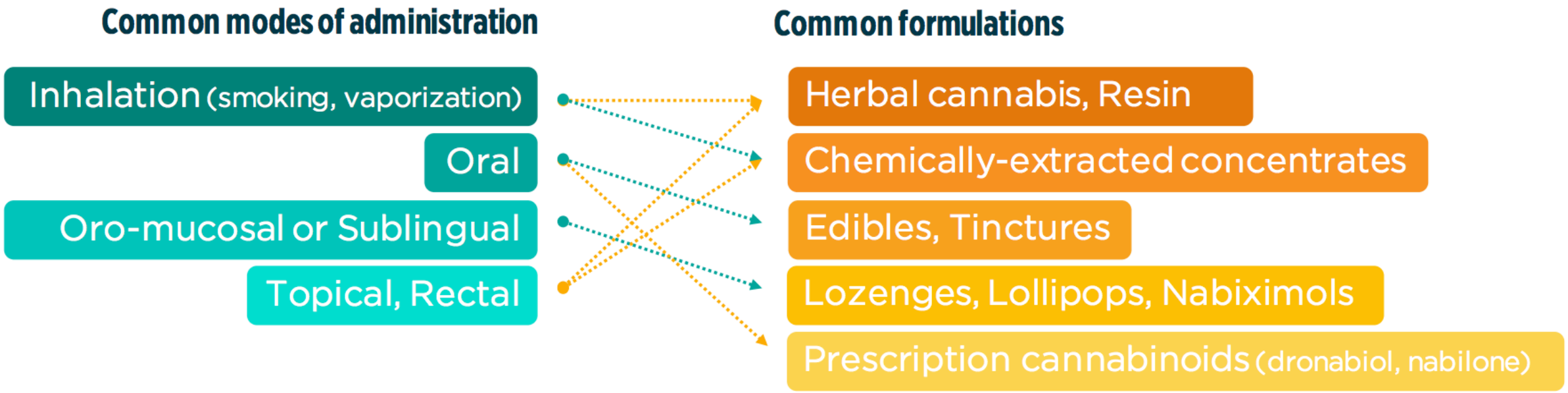
CNS depressants

- Additive CNS depressant effects with alcohol, barbiturates, and benzodiazepines



Yamaori et al 2012, Hartman 2015, Stout and Cimino 2014, Abrams et al 2003, Engels et al 2007, Geffrey et al 2015

Formulations and Routes of Administration



Route of Administration: Inhalation

- Variable absorption due to inhalation technique
- 20-70% of THC reaches the lungs
- ~ 30% enters systemic circulation
- Shortest onset of action making dose titration possible
- Advantages
  - Simple
  - Effective
- Disadvantages
  - Can contain irritants

Route of Administration: Oral

- Types
  - Oral solution
  - Capsules
  - “Edibles”
- Delayed onset of action
- Longer effect
  - Low and erratic gastrointestinal absorption (< 15%)
  - THC is metabolized into the active metabolite

Route of Administration: Sublingual

- Types
  - Spray
  - Tincture
  - Lozenge
  - ODT
- Pharmacology
  - Mixed absorption, some drug passes through oral mucosa but other is ingested

Route of Administration: Topical

- Types
  - Creams
  - Ointments
  - Transdermal patch
- Pharmacology is poorly understood
- There is systemic absorption

Route of Administration: Rectal

- Stable and bioavailable suppositories have been formulated
- Absorption is ~2x oral administration
- Onset of action ~ 10 minutes
- Avoids metabolism to active metabolite

El Sohly et al 1991

Cannabis Onset and Duration of Action

Route of administration	Action		Amenable to self-titration
	Onset (min)	Duration (h)	
Smoked	5	2–4	++++
Vaporized	5	2–4	++++
Oral			
Botanical			
Cooked	30–60	8–12	+
Oil	30–60	8–12	+
Tea	30–60	8–12	+
Nabilone	60–90	8–12	+
Dronabinol	30–60	4–6	+
Oromucosal (nabiximols)	15–40	2–4	++

Cannabinoid Therapies in Oncology – Current Oncology 23: 398 - 406

Product Selection

- Pure cannabis vs crude cannabis
  - Side effects/health risk
  - Cost – crude cannabis may be cheaper
  - Lack of control
    - Cannabis content
    - Contaminants
    - Dosing
  - Fewer available routes of administration
    - Crude – smoking or ingested
    - Pure – inhaled, oral, topical, sublingual, rectal
  - Illegal in some states
- Potential Contamination
  - Fungal and bacterial pathogens
  - Pesticides
  - Heavy metals
- Labeling Accuracy

Questions?