Medical Cannabis

Kari L. Franson, PharmD, PhD, BCPP
Associate Dean and Associate Professor
Department of Clinical Pharmacy

Objectives

- Identify the main constituents of cannabis
- Review the endocannabinoid system
- Describe the pharmacology of cannabis to explain:
  - Medical uses
  - Effect on the reward pathway
  - Acute toxicity and long term risks
- Review various dosing methods for medical cannabis
- Outline the pharmacokinetic differences between different cannabis dosage forms

Faculty Disclosure

- Dr. Franson has nothing to disclose and no conflicts of interest or funding sources

- Dr. Franson will be discussing unapproved drugs and unapproved uses for drugs

Identify the main constituents of cannabis

Cannabis

- Contains over 400 compounds
  - » Over 100 cannabinoids have been isolated
  - » Terpenes are variable, contribute to aroma (limonene, pinene) and serve as a precursor to cannabinoids
- Cannabinoids & terpenes are found in flowering tops > buds > top leaves > lower leaves > stems stalks
- *indica* and *sativa* have been cross-bred so no generalizable characteristics

Borgelt LM, Franson KL, Nussbaum AM, Wang GS. Pharmacotherapy. 2013

What are the different CBs?

- Δ^9-tetrahydrocannabinol – THC; most psychoactive & has most medical claims
- Cannabidiol – CBD; reduce THC effects & most medical 'promise'
- Cannabichromene – CBC; anti-inflammatory, anti-bacterial/fungal
- Cannabigerol – CBG; decrease GI inflammation
- Tetrahydrocannabivarin – THCV; hypophagia possible diabetes treatment

- Tetrahydrocannabinolic acid – THC-A; THC precursor, anti-spasmodic
- Cannabinol – CBN; THC metabolite & less psychoactive

Pertwee RG. Br J Pharmacology. 2006
Pertwee RG. Br J Pharmacology. 2008

Other common cannabinoids

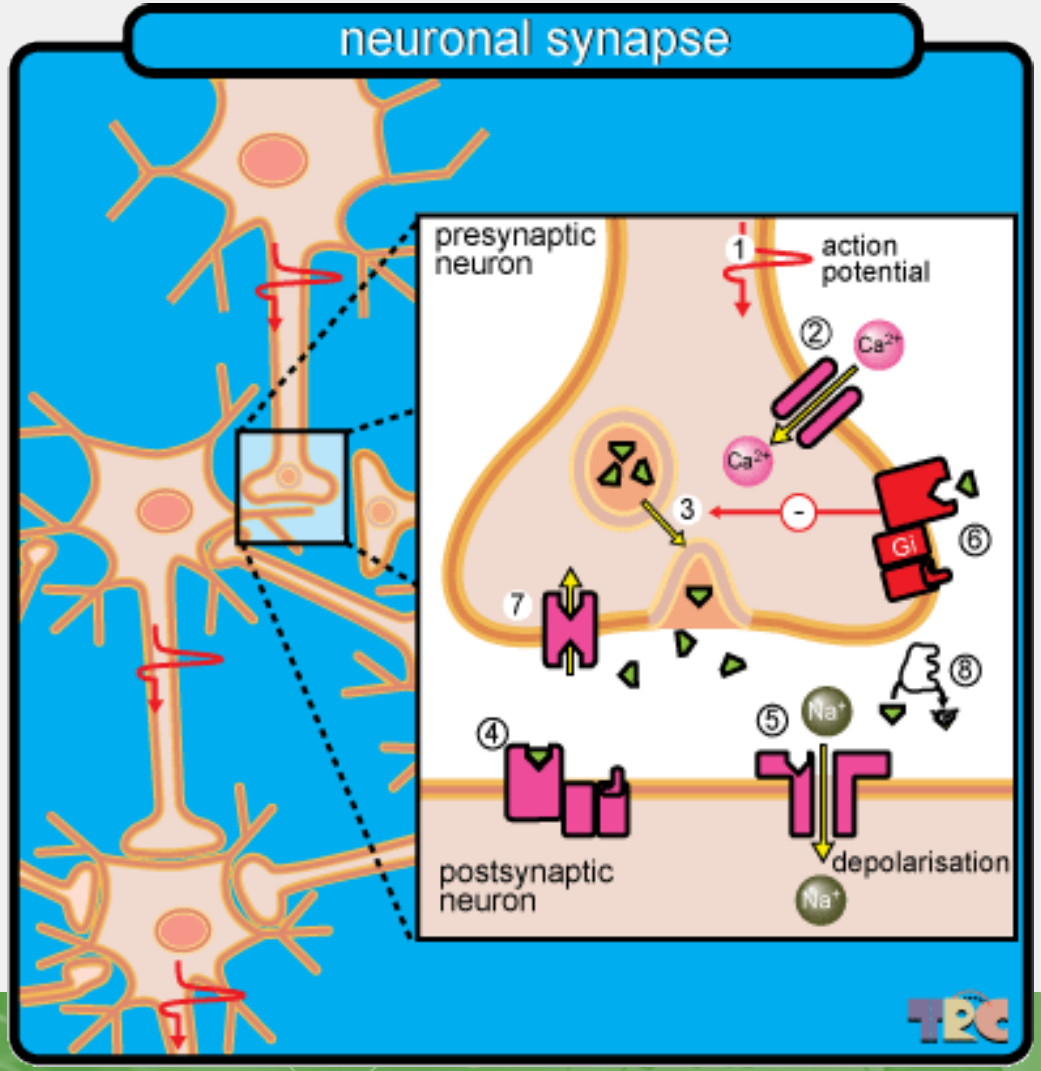
- Anandamide, 2-arachidonoylglycerol (endocannabinoids)
- Dronabinol, nabilone (THC molecule Pharma products)
- Epidiolex® (CBD extract Pharma product)
- Sativex® (THC & CBD extract Pharma product)
- Rimonabant (CB1 receptor inverse agonist Pharma product)
- HU-210 (‘Spice’, synthetic cannabinoid on street)

- Most interact with the endocannabinoid system via G-protein-coupled receptors in the body, but not CBD

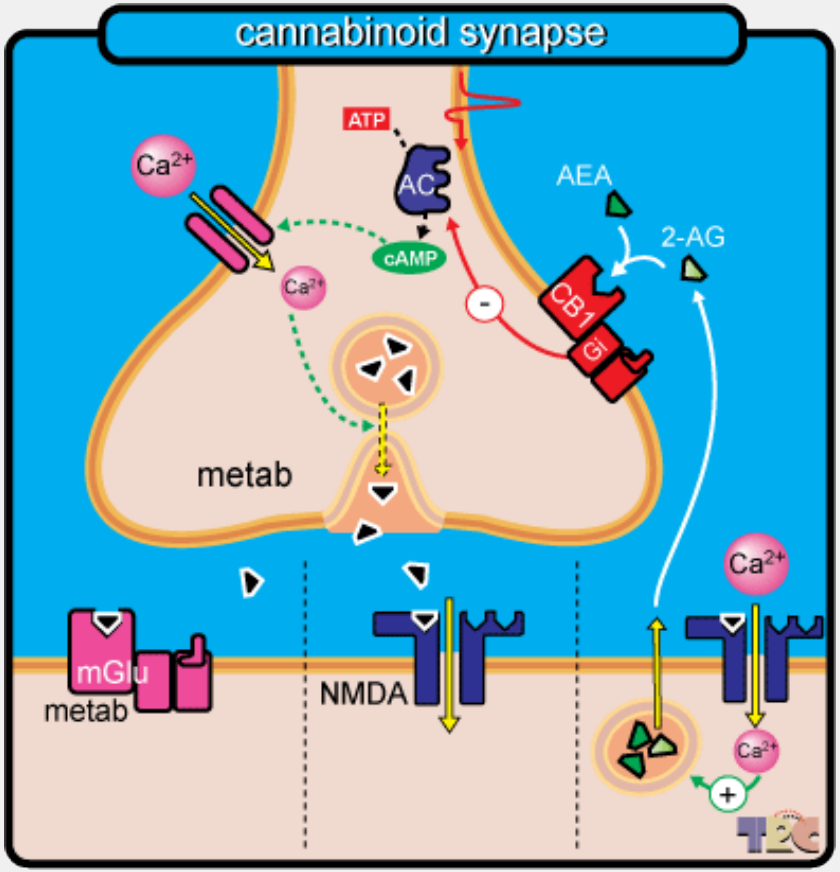
Borgelt LM, Franson KL, Nussbaum AM, Wang GS. Pharmacotherapy. 2013

Review the endocannabinoid system

Normal neuro-transmission



Regulatory effect of cannabinoids at the CB1 receptor



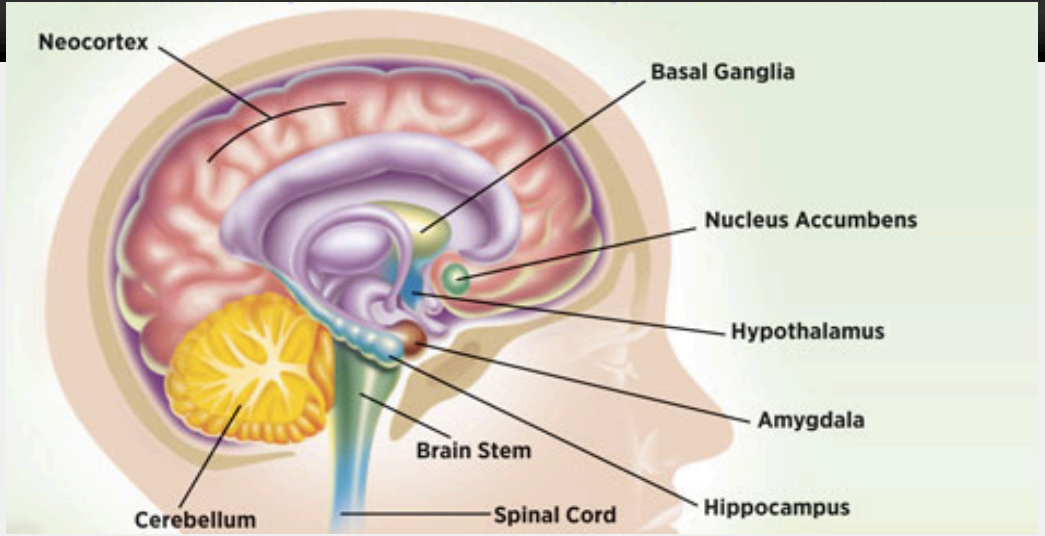
1. Inhibition of adenylyl cyclase activity

2. Alter second messenger systems such that CA++ influx is inhibited

Neuromodulation by anandamide particularly relevant to modulation of GLU (shown), Ach, GABA, DA, NE

Pertwee RG. Br J Pharmacology. 2008

Functional effects of anandamide at CB1 receptors in the CNS



http://headsup.scholastic.com/students/endocannabinoid

Structure	Anandamide Regulates	Resultant effect
Basal ganglia	Modulate DA & GABA, motor activity	Slowed reaction time
Hypothalamus	Appetite (2-AG) Stimulate DA & inhibit NE	↑ Appetite Inhibition of prolactin, enhances ACTH
Amygdala	Emotions, fear, anxiety	Anxiety stimulation, reduction, & sedation
Nucleus accumbens	Motivation (2-AG)	Engages reward pathway
Hippocampus	Inhibit release Ach, short term memory Inhibit release GLU, long term memory	Impaired short term (working) memory Impaired long term memory consolidation
Cerebellum	Inhibit GLU, motor coordination	Impaired coordination, balance
Brain stem	Modulates info transfer between brain & spinal cord	Anti-nausea effects
Hippocampus, TL, forebrain	Inhibit GLU & neuronal excitability	Increased seizure threshold

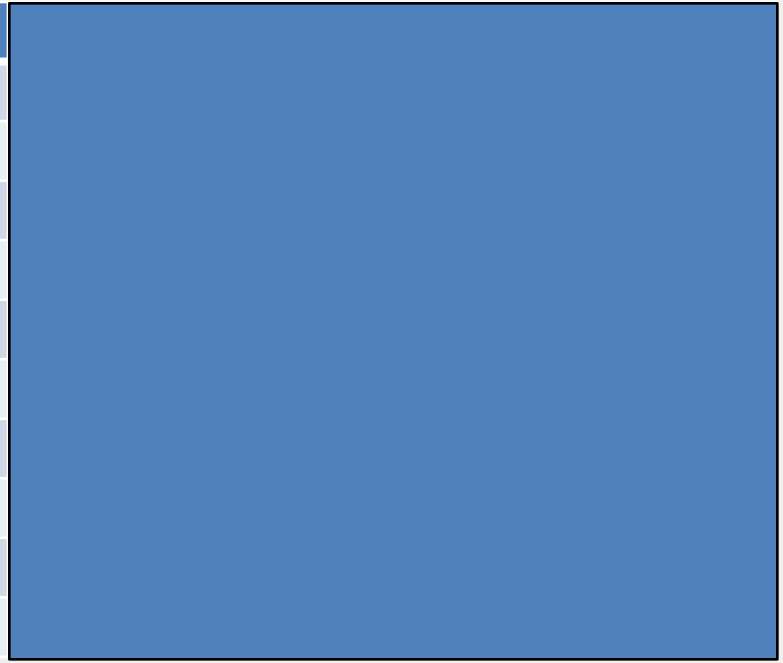
Functional effects of anandamide at CB1 & CB2 receptors

http://headsup.scholastic.com/students/more-facts-about-how-drug-abuse-puts-your-whole-body-at-risk

Structure	Anandamide regulates	Resultant effect
Spinal cord	Inhibit GLU & info transfer between body & brain	Decreased pain sensitivity
Parasympathetic system	Inhibit Ach release, HR regulation, urination regulation	HR stimulation, sometimes inhibits urination
Sympathetic system	Inhibit NE release, HR regulation, blood vessel constriction	Delayed reduction in HR and blood pressure
Neuronal cells	Inhibition GLU-induced excitotoxicity	Neuroprotective effect to prevent cell injury
Adipose tissue	Stimulates lipogenesis	Increased adiposity, insulin resistance
Reproductive tissue	Reduces testosterone, luteinizing hormone	Reduced fertility, altered menstrual cycle
Skin	Reduces histamine	Anti-pruritic effect
General	Role in relaxing, eating, sleeping, forgetting protecting	Provide relief from stress, reduction of injury
General	Inhibits immune B lymphocytes, natural killer cells	Anti-inflammatory activity

Cannabis activity at CB1 receptors

Structure	THC effect	
Neocortex	Altered thinking, judgement	
Basal ganglia	Slowed reaction time	
Hypothalamus	↑ appetite	1992
Amygdala	Panic, paranoia	
Nucleus accumbens	Euphoria	
Hippocampus	Impaired memory	
Cerebellum	Impaired coordination	
Brain stem	Anti-nausea effects	1985
Hippocampus, forebrain	Anti-epileptic effects ?	
Spinal cord	Altered pain sensitivity	1996



Dose-response effects of CBD not established

- low dose < 300 mg → inconsistent effects
- typical response can be seen at 600mg

Medical cannabis is known to interact with cannabinoid receptors in which structure to cause a decrease in pain?

A. Amygdala
B. Cerebellum
C. Neocortex
D. Spinal cord

Describe the pharmacology of cannabis to explain:

- **Medical uses**
- **Effect on the reward pathway**
- **Acute toxicity and long term risks**

I believe that patients gain the most benefit using medical marijuana for:

A. Nausea and vomiting control
B. Appetite stimulation
C. Pain control
D. Seizure control
E. Feeling of euphoria

Number of states with various approved medical conditions

Alzheimer's disease (8)	Epilepsy/seizures (24)	Nausea (22)
ALS (11)	Glaucoma (22)	Pain (22)
Arthritis (4)	Hepatitis C (10)	Parkinson's disease (7)
Cachexia (22)	HIV/AIDS (23)	PTSD (9)
Cancer (25)	Multiple sclerosis (22)	Terminal condition (4)
Crohn's/GI disorders (16)	Muscle spasticity (22)	

http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881 accessed 5/17/2016

Chemotherapy induced nausea and vomiting

- Small studies compared cannabis (nabilone, THC, levonantradol, dronabinol) to dopamine antagonists
- Dronabinol showed anti-emetic efficacy over neuroleptics (but high risk of bias) NNT = 3.4
- Depression (13%), hallucinations (6%), paranoid delusions (5%), occurred, but patients preferred cannabis over control (RR 0.33; 95% CI 0.24-0.44)
- Smoking relief 70-100% vs. capsule relief 76-88%

Tramer MR, Carroll D, Campbell FA, et. al. BMJ 2001
Machado Rocha FC, Stefano SC, De Cassia Haiek R, et. al. Eur J Cancer Care 2008
Musty RE, Rossi R J Cannabis Ther 2001

Cachexia and appetite stimulation

- 8 controlled studies, mostly in patients with cachexia related to AIDS or cancer
- 3 of these are with smoked marijuana (largest with 67 patients) otherwise used dronabinol
- Generally seems to promote weight gain/retard weight loss, although this was not statistically significant
- 5 mg dronabinol < 750 mg oral megestrol acetate
- Results in 5 cancer patient studies were less consistent

Abramovici H. Health Canada 2013
Timpone JG, Wright DJ, Li N, et. al. AIDS Res Hum Retro 1997

Chronic (neuropathic and cancer) pain

- Review of trials with >30% reduction in pain
  - 2 cancer pain trials
  - 6 neuropathic pain trials
- Concluded moderate quality of evidence to support the use of cannabis for chronic pain

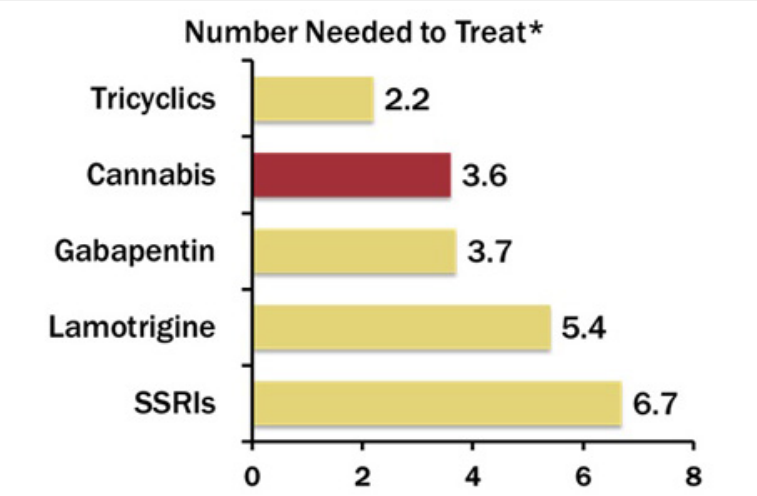


Figure 1. Common analgesics for neuropathic pain.
*to achieve a 30% reduction in pain.
Number needed to treat (NNT) = **1/(E-P)**, where E is the proportion improved in experimental condition and P is the proportion improved on placebo. Example: If 60% "improve" (according to a given definition) in the experimental condition, while 30% "improve" in the placebo condition, then NNT = 1/(.6-.3) = 3.3. Data adapted from Abrams et al. [3] and Ellis et al. [4].

Whiting PF, Wolff RF, Deshpande S, et al. JAMA 2015
Grant I. Report to the State of California 2010

EBM guideline CAM for MS

CAM intervention	Number and class of studies	MS types studied	Outcome	Recommendation level
Cannabinoids				
OCE	2 Class I,[13,14] 1 Class II,[17] 1 Class III[18]	RRMS, SPMS, PPMS, MSU	Symptoms of spasticity, pain	A Effective
	1 Class I[13]	RRMS, SPMS, PPMS	Signs of spasticity (short-term), tremor (short-term)	B Ineffective
	1 Class II[17]	MSU	Signs and symptoms of spasticity (long-term)	C Effective
	2 Class I,[13] 1 Class II[16]	RRMS, SPMS, PPMS, MSU	Bladder symptoms, urge incontinence	U
Synthetic THC	1 Class I,[13] 1 Class II[17]	RRMS, SPMS, PPMS	Symptoms of spasticity, pain	B Effective
	1 Class I[13]	RRMS, SPMS, PPMS	Signs of spasticity (short-term), tremor (short-term)	B Ineffective
	1 Class II[17]	MSU	Signs and symptoms of spasticity (long-term)	C Effective
	1 Class I,[13] 1 Class II,[16] 1 Class III[19]	RRMS, SPMS, PPMS, MSU	Bladder symptoms, urge incontinence, central neuropathic pain	U
Sativex oromucosal spray	3 Class I,[23-25] 2 Class II,[26,27] 3 Class III[28-30]	MSU	Symptoms of spasticity, pain, urinary frequency	B Effective
			Signs of spasticity, incontinence episodes	B Ineffective
			Tremor	C Ineffective
			Anxiety/sleep, cognition, QOL, fatigue	U
Smoked cannabis	2 Class III[31,32]	RRMS, SPMS, MSU	Spasticity, pain, balance and posture, cognition	U

Yadav V, Bever C, Bowen J, Bowling A, et. Al. Neurology 2014

Seizures

- Most data in pediatric refractory epilepsies
  - » CBD 0.5 to 28 mg/kg/day, in 2 or 3 divided doses
  - » THC less than 0.8 mg/kg/day
  - » 84% parents reported reduction in seizure frequency
    - > 50% of these were decreased by 80%
    - Most weaned patient from another AED after starting CBD
- Adults case reports and patient surveys
  - → Seizure exacerbation with discontinuation
  - → German study no effect

Friedman D, Devinsky D, NEJM 2015
Gloss D, Vickery B. Cochrane Database Syst rev 2014

Glaucoma

- Systemic administration of cannabis ↓ IOP by 30%
- Pilot study of 6 patients ↓ IOP for 2 hours
- Uncontrolled study 9 patients with open-angle glaucoma THC qid ↓ IOP
- Patients appeared to develop tolerance, and all discontinued the study

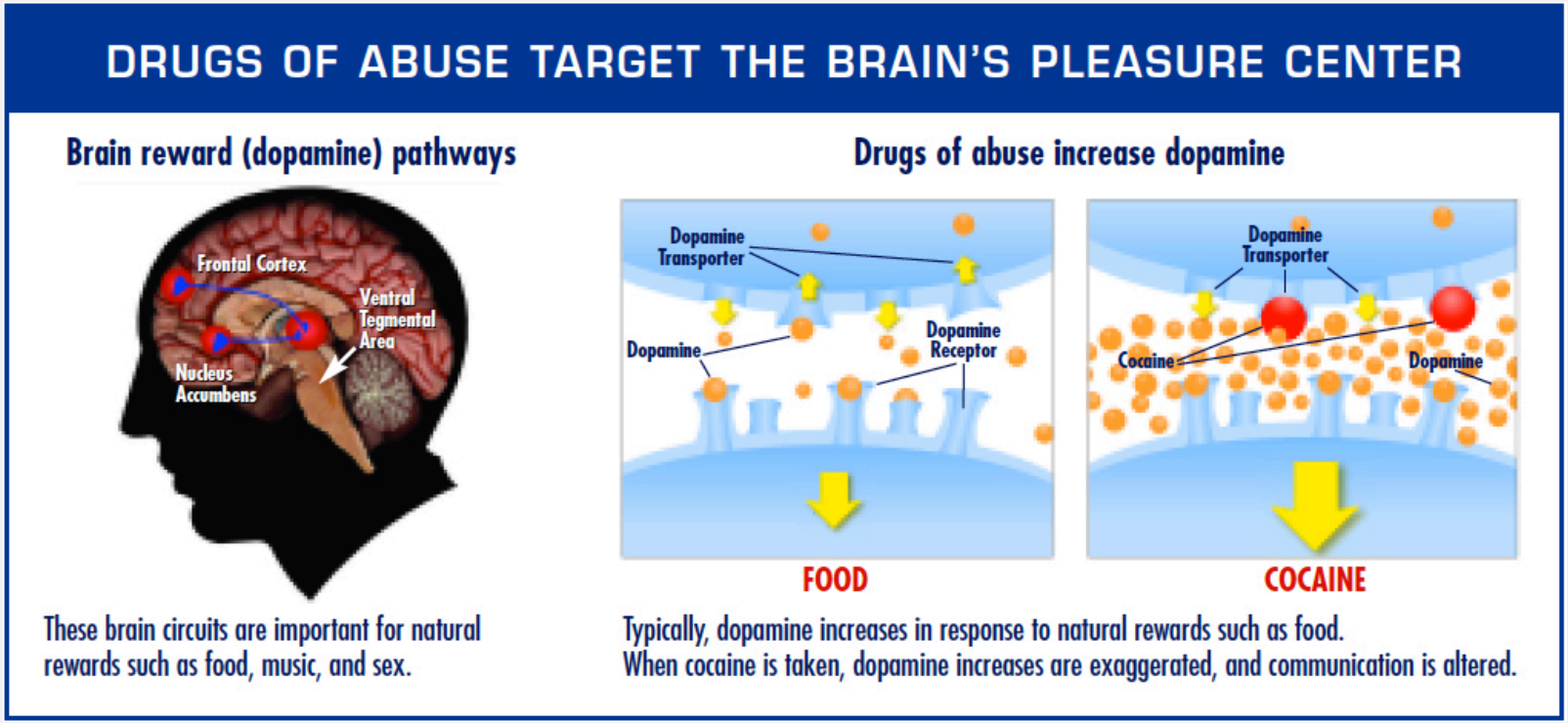
Recommendations from review in JAMA

Recommendations
Treat debilitating medical conditions
Patients have failed trials of 1st & 2nd line agents
Failed trial of FDA approved dronabinol or nabilone
Avoid in patients with active substance abuse or psychotic disorder
Know states MMJ laws and advise patients accordingly

What is the evidence?

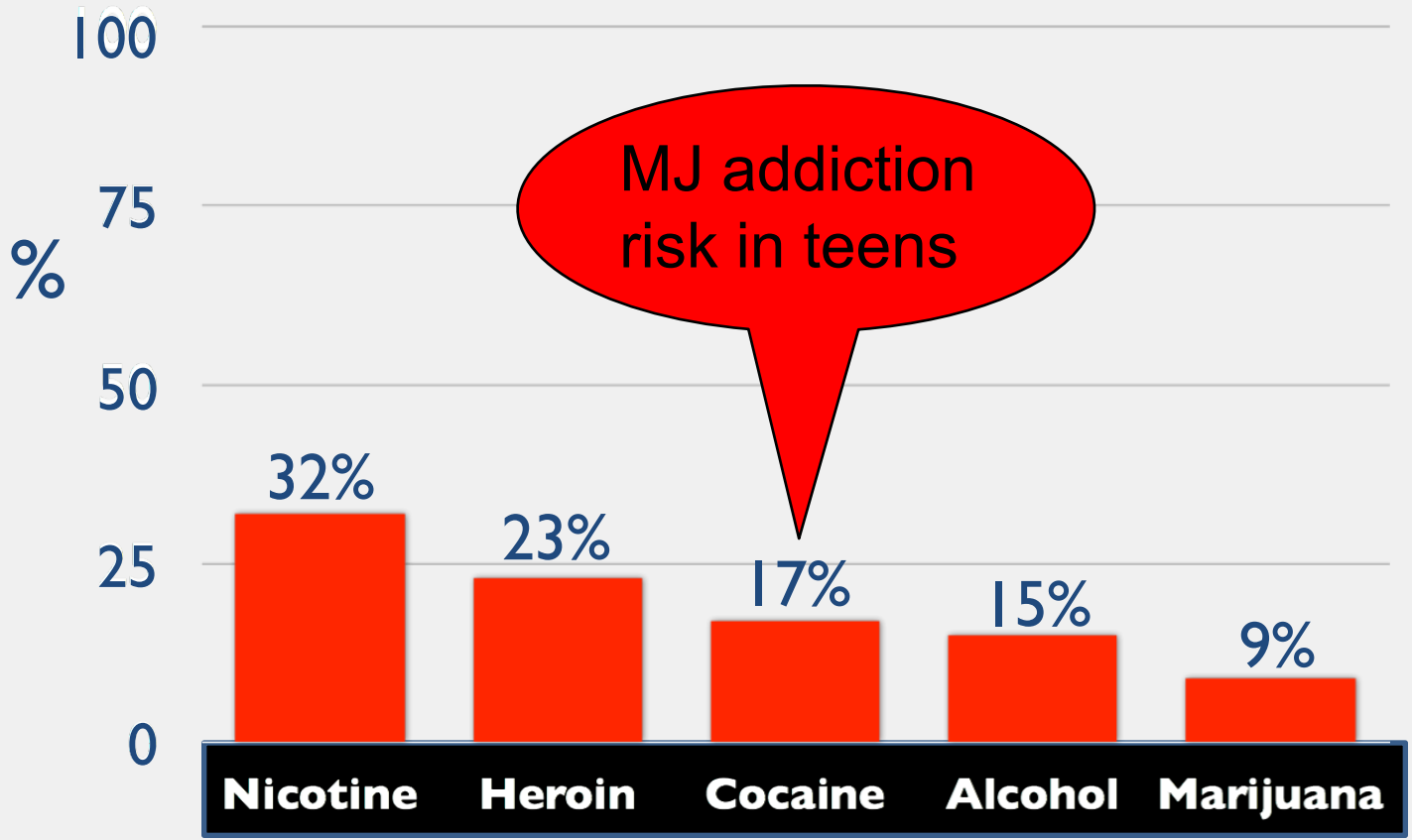
Hill KP. JAMA 2015

The reward pathway



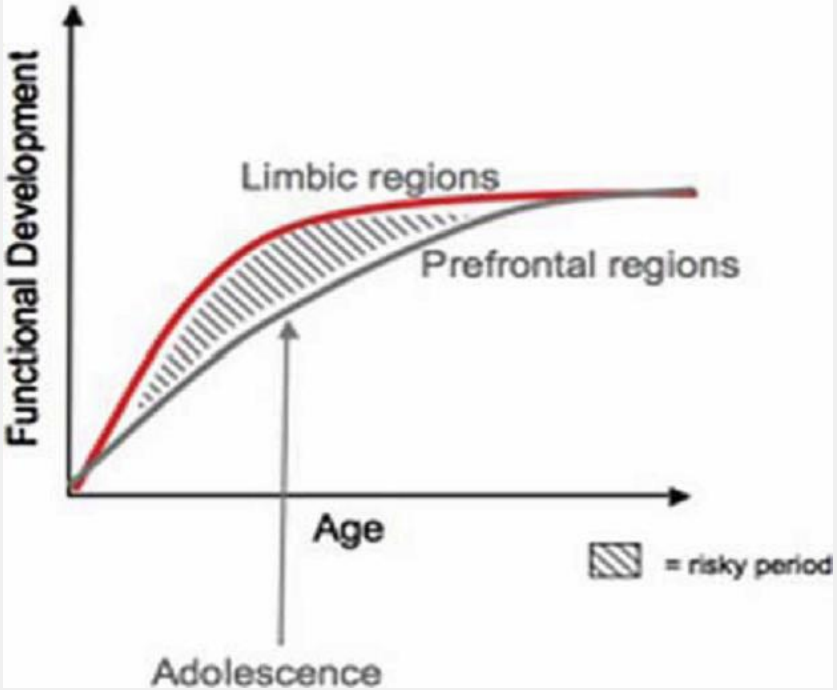
NIDA (http://drugabuse.gov/sciencefair/)

Lifetime dependency risk with use

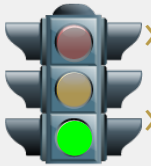


Hall and Degenhardt. Lancet. 2009
Strahny A. CBHSQ Report. 2013

Brain development in adolescence



Limbic region



- Immediate rewards
- Impulsive behavior

Cortex

- Long term gain
- Thoughtful behavior

http://erichengelhardt.net/neuro-facts.html accessed 5/28/2013

Long term exposure causes reduced cerebral blood flow and enhanced dopaminergic neurotransmission

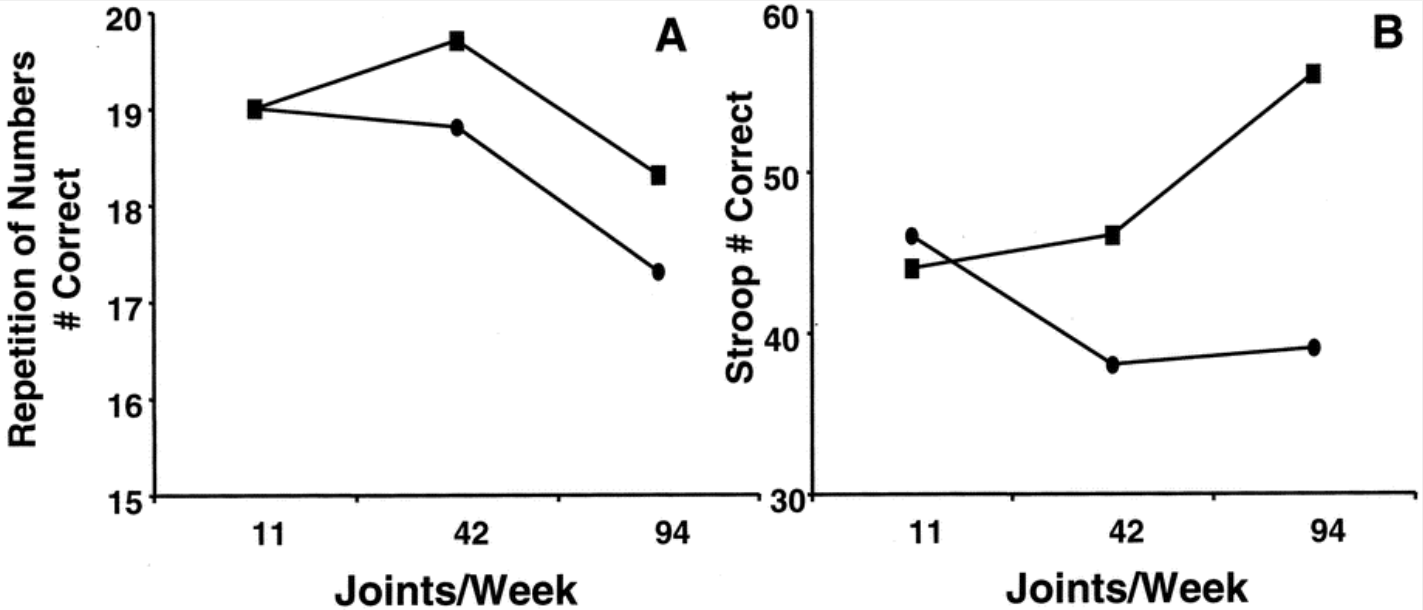
- Implicated in psychosis
- Can disrupt long-term memory
- Can lead to cognitive decline

Persistent cannabis users show neuropsychological decline from childhood to midlife

Madeline H. Meier[a,b,1], Avshalom Caspi[a,b,c,d,e], Antony Ambler[e,f], HonaLee Harrington[b,c,d], Renate Houts[b,c,d], Richard S. E. Keefe[d], Kay McDonald[f], Aimee Ward[f], Richie Poulton[f], and Terrie E. Moffitt[a,b,c,d,e]

Kulhalli V, et al. Indian J Psychiatry. 2007
Meier MH, et al. Proc Natl Acad Sci. 2012

Chronic cognitive effects of cannabis

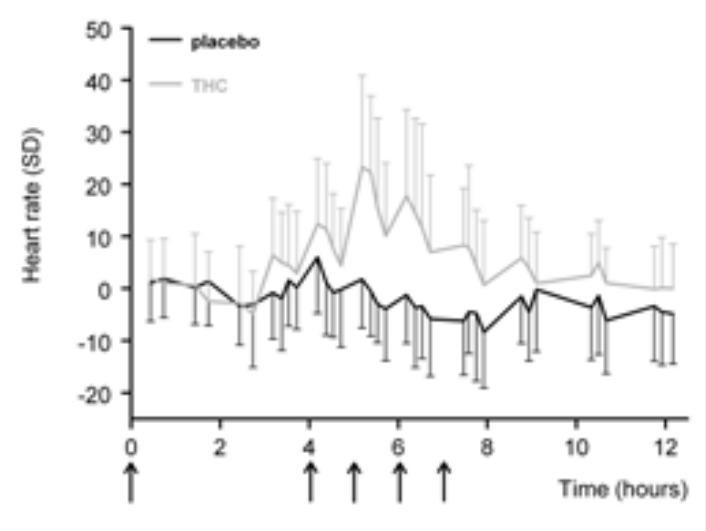


(A) Relation between amount of marijuana smoked[2] and Repetition of Numbers Task, number correct for the high Shipley IQ group (squares) and the low Shipley IQ group (circles). (B) Relation between amount of marijuana smoked[2] and performance on the Stroop task for the high Shipley IQ group (squares) and the low Shipley IQ group (circles)

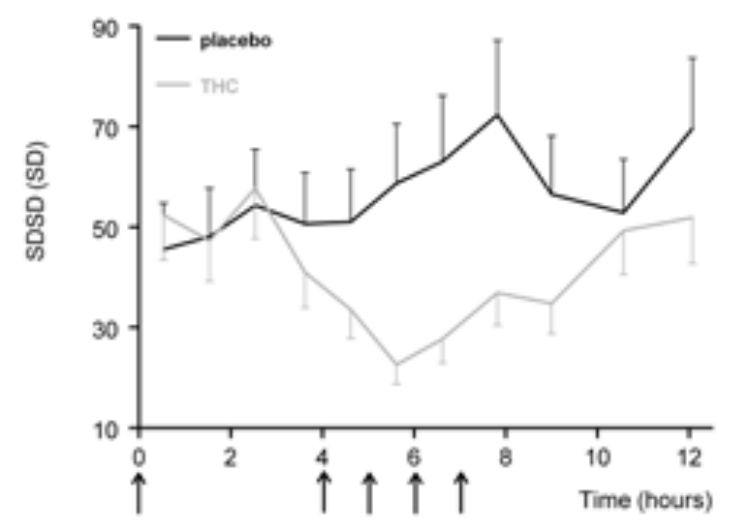
Bolla KI, et al. Neurology, 2002

Acute cardiovascular effects of THC

Heart rate



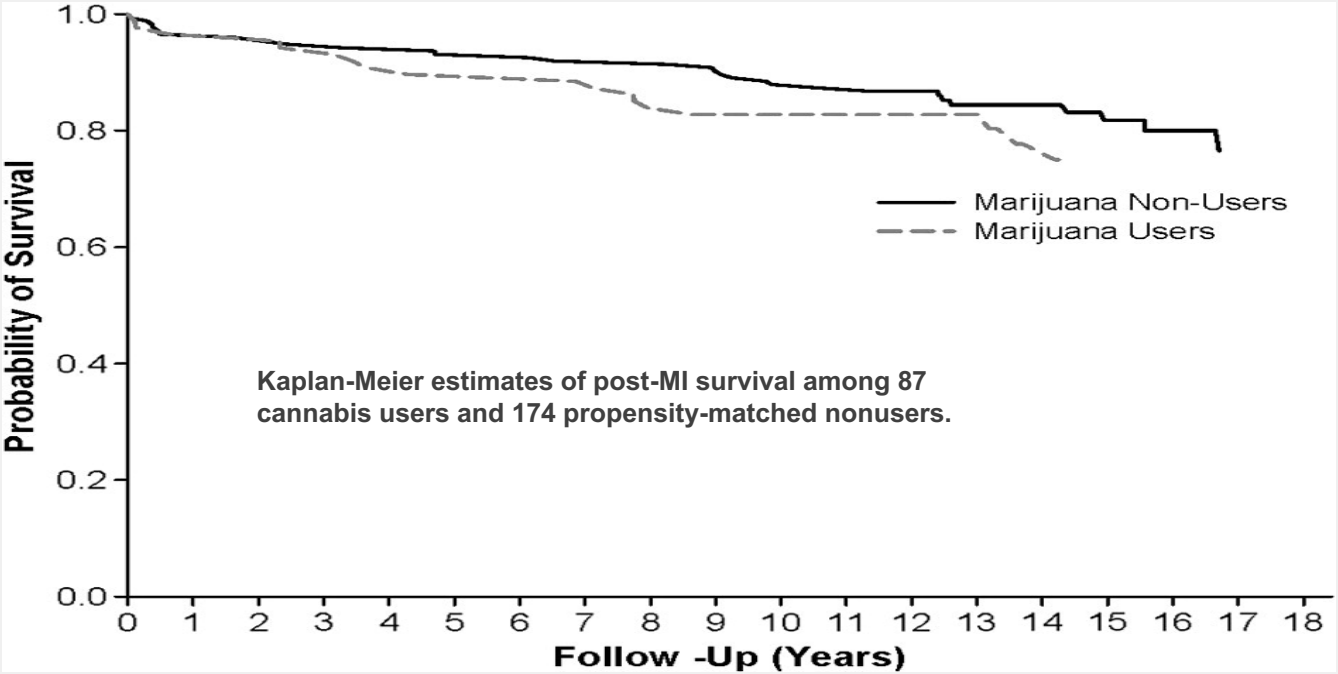
HRV



- The variation in the time interval between heartbeats (RR-interval)
- ↓ HRV is a predictor of mortality after MI

L Zuurman, et al. Br J Clinical Pharmacology. 2008

Cannabis use and long-term mortality among survivors of AMI



Frost L, et al. American Heart Journal. 2013

Review various dosing methods for medical cannabis

THC dosing is known; but not known for other CBs

Typical "effective" dosing of inhaled THC

- Low dose < 7 mg
- Medium dose = 7 – 18 mg
- High dose > 18 mg

There is a known tolerance to THC down regulation of CB1 receptors, and G-protein activation

High probability of tolerance with chronic use, and low with intermittent

Chronic = daily for a week, intermittent = weekly

L Zuurman, et al. Br J Clinical Pharmacology. 2008

Cannabis plant products

- Little active CBs, needs decarboxylation
- Strains vary substantially in CB content and depend on growth conditions and time of harvest
- May be contaminated by pesticides, mold, fungus
- Entourage effect from multiple CB may moderate THC psychoactive effects
- Less expensive

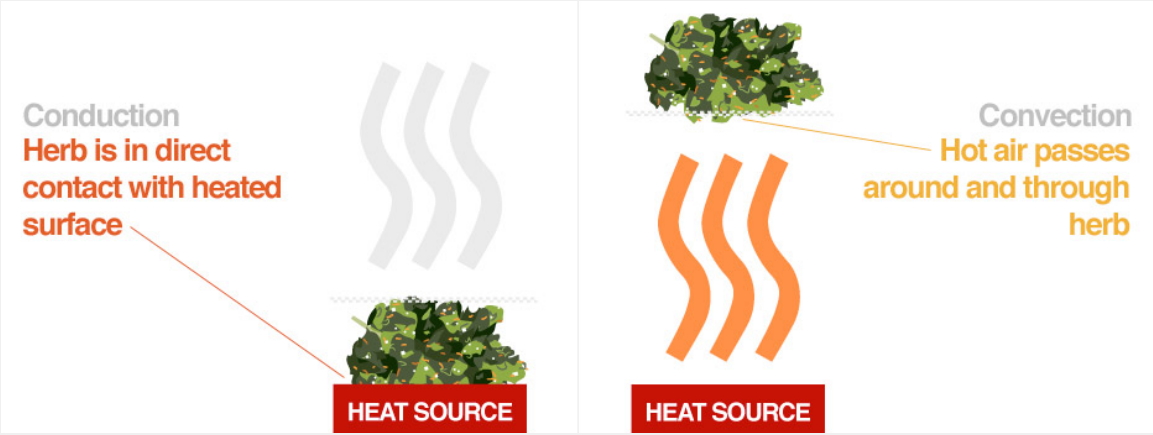
Smoking cannabis plant

- Burns 500-2000°F, cannabis combusts at > 392°F
- Benzo[a]pyrene is formed from partial combustion, binds to DNA guanine causes distortions and leads to mutations, causes drug interactions
- Immediate effects, feedback possibly leads to moderation, less consumption
- Less erratic absorption than FDA medications

Image from: https://www.addict-help.com/cannabis/smoking-weed.asp

Vaporizing cannabis plant

- Heats 285 - 392°F vaporizing CBs
- Conductive vs. convective heating



- Can be up to 95% smoke & carcinogen free
- Same immediate effects and benefits

Images from: www.cannastick.com; https://spendabit.co/go?q=vape&offset=0
www.procon.org

Vaporizing cannabis concentrates

- CBs extracted by solvents (butane, CO2, ethanol)
- Hashish oil 20% CBs, others ~80% CBs
- Conduction can lead to carcinogens

Images from: https://www.leafly.com/news/cannabis-101/the-great-wide-world-of-cannabis-concentrates

Dabbing cannabis concentrates

- CBs are extracted by solvents
- Butane hash oil (BHO), dabs, earwax, butter or shatter
- >90% of CBs
- Superheat nail (with blow torch) and add dab
- Users quickly develop tolerance

Images from: https://www.zamnesia.nl/dabbing/2365-glazen-olie-bong-blaze-swirl.html

Edible baked goods, candies, tinctures

- Edibles have CBs added, or are infused with CB butter, oil or alcohol
- Considered intense high
- Doesn't release toxins
- Discreetly consumed

- Pharmacokinetics are a problem as ingested CBs take time to reach site of action, difficult to predict

Images from: http://www.leafscience.com/2015/10/27/beginners-guide-marijuana-edibles/

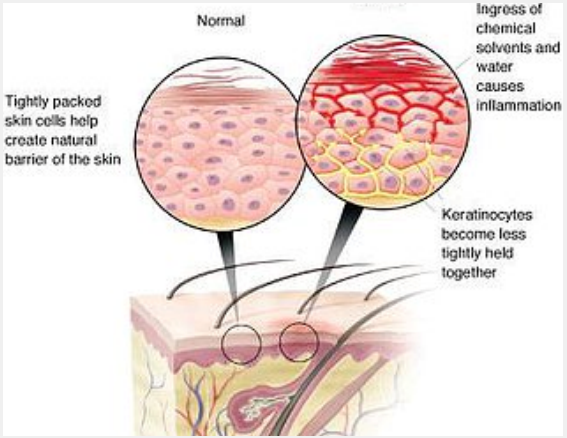
Edible baked goods, candies, tinctures

- In Colorado 10mg serving size and 100mg maximum/package
- Now also prohibit edibles that resemble animals, people or fruit
- Must exit dispensary in child resistant packaging

Images from: http://www.thecannabist.co/2016/04/19/marijuana-edibles-shaped-animals-fruit-targeted-colorado-bill/52324/

Cannabis infused creams, lotions and oils

- THC-A is charged, doesn't cross stratum corneum
- THC not charged, but lipophilic properties limit it getting to site of action
- Most products claim no psychoactive effects, so not getting absorbed

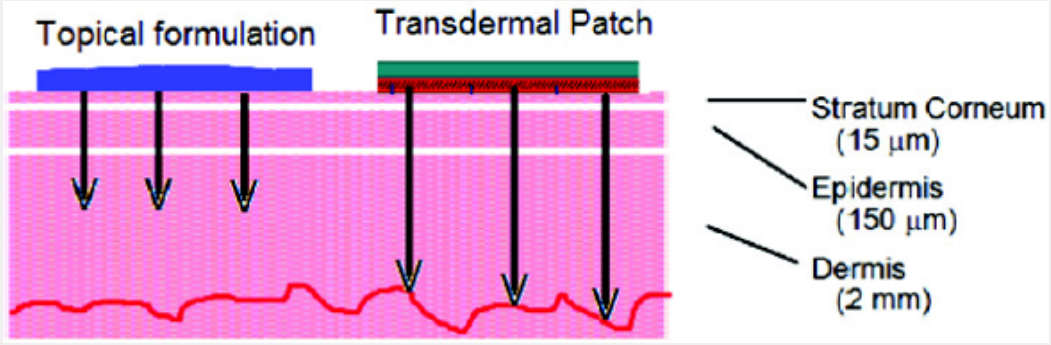


Best products would have an agent to disrupt the layer of dead skin to reach epidermis → solvents, surfactants

Images from: http://www.vaildaily.com/news/14759677-113/soaking-in-the-cannabis-what-topical-thc-products-can-do http://www.defensintherapeutics.com/?

Transdermal patches

- Patch or gel designed to be absorbed through skin to membrane
- Reservoir & occlusion provides constant & complete dosing
- Vehicle enhances absorption to blood stream
- Can reach site of action

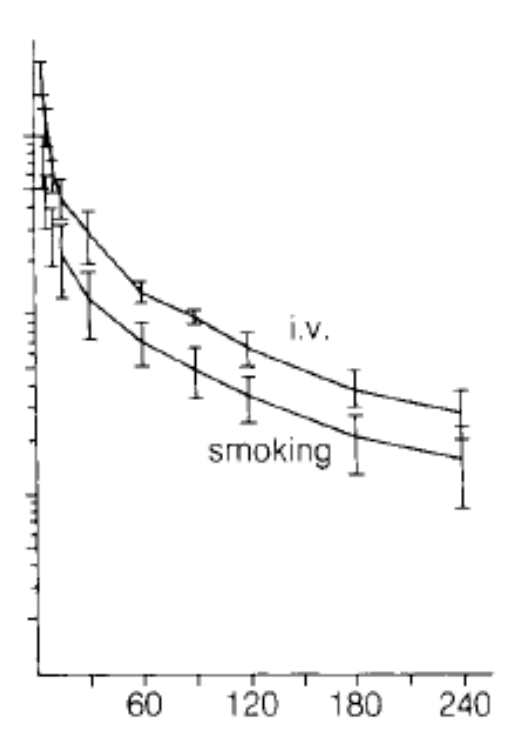


Images from: http://www.americanpharmaceuticalreview.com/Featured-Articles/170872-Lipids-in-Transdermal-and-Topical-Drug-Delivery/
http://grandorganics.org/menu/

Outline the pharmacokinetic differences between different cannabis dosage forms

PK profile of smoked THC

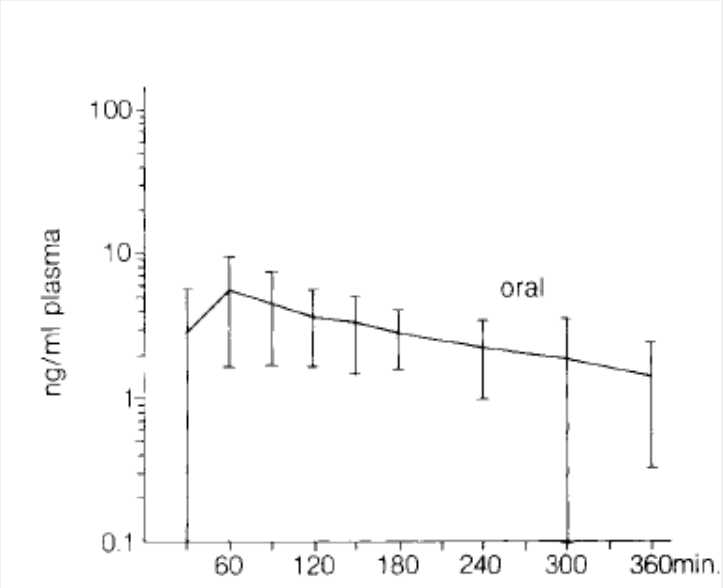
- Smoking cannabis turns ~50% of the THC content into smoke
- Up to 50% of inhaled smoke is exhaled again, and some undergoes localized metabolism in the lung
- Bioavailability of a inhaled dose of THC is between 10-25%
- Effects are perceptible within seconds and fully apparent in a few minutes



Strougo A, et al. J Psychopharmacology. 2008

PK profile of oral THC

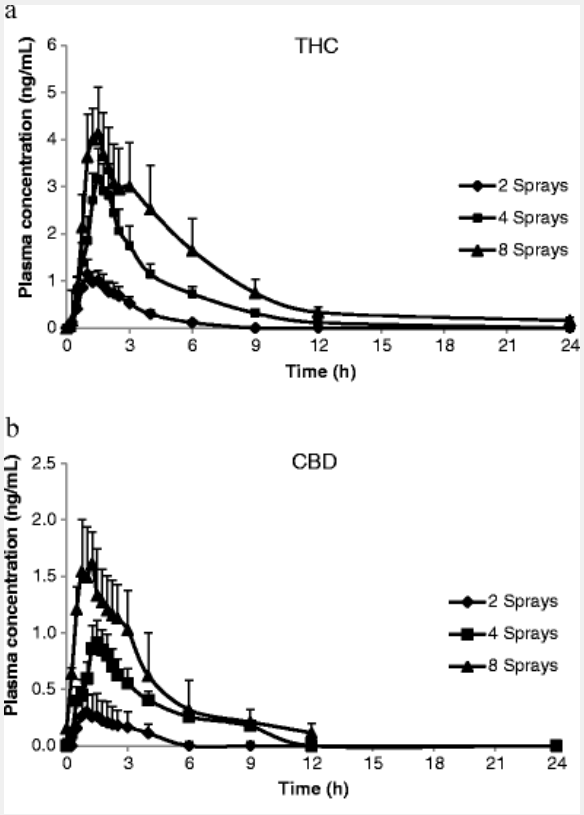
- Bioavailability of THC after oral ingestion ranges from 5-20% in the controlled environment of clinical studies
- Onset of effect is delayed: 1-3 hours
- Duration is prolonged due to continued slow absorption from the gut
- Weight, metabolism, gender and eating habits also play a role



Agurell S, Halldin M, Lindgren JE, et al. Pharmacological reviews. 1986

PK profile of oromucosal THC/CBD - Sativex

- One study did not find difference between oral THC and oromucosal spray PK
- Peak concentration THC 1.5 hours
- Peak concentration CBD 1.3 hours
- 2-fold inter-patient variability in peak THC and CBD levels



Hazenkamp A. J Pharm Sci June 2006

Oral formulations (edibles) increase risk of toxicity

- The slow onset, extended duration & variable absorption lead to toxicity → user's can't wait for effect
- People rely on others' description of potency
- JAMA study: Too much product variability → 23% under-labeled, 60% over-labeled

http://www.thecannabist.co/2014/03/09/tests-show-thc-content-marijuana-edibles-inconsistent/6421/
Vandrey R, et al. JAMA, 2015, Erowid E, Erowid F. Erowid Extracts. 2011

A patient is trying an edible cannabis product to reduce worsening chronic back pain and is worried about the reports that people often overdose using edibles. Which of the following BEST represents the counseling points to address the patient's concerns?

A. It is important to start with no more than 20 mg, and to take no more than once a day

B. First try about ¼ of standard dose, and do not supplement the dose before ½ hour to establish the dose

C. Be aware that there can be 4 fold variability in how much gets in each time, and it may take up to 3 hours to get full effect

Further dosing considerations

- THC substrate of CYP3A4 & 2C9
- CBD substrate of CYP3A4 & 2C19
- Possible drug interactions
  - ↑ sedation, ataxia: CNS depressants, anticholinergics
  - ↑ heart rate: sympathomimetics
  - ↑ effects of: hexobarbital, hydrocortisone, clozapine, phenytoin, warfarin
  - ↓ effects of: propofol, indinavir, theophylline

Horn JR, Pharmacy Times 2014

Review today's session

- Identified the main constituents of cannabis
- Reviewed the endocannabinoid system
- Described the pharmacology of cannabis to explain:
  - Medical uses
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- Reviewed various dosing methods for medical cannabis
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