Cannabis: Medical Use and Abuse in the Pediatric Population

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Disclaimer

- I am a member of the faculty at the University of Vermont, my expertise in this area comes from:
  - Teaching medical students CNS pharmacology including treatments for pain and drugs of abuse
  - Co-director of Medical Cannabis course
- Materials presented here represent my own findings, views and opinions and do not necessarily reflect the legal views or opinions of the University of Vermont

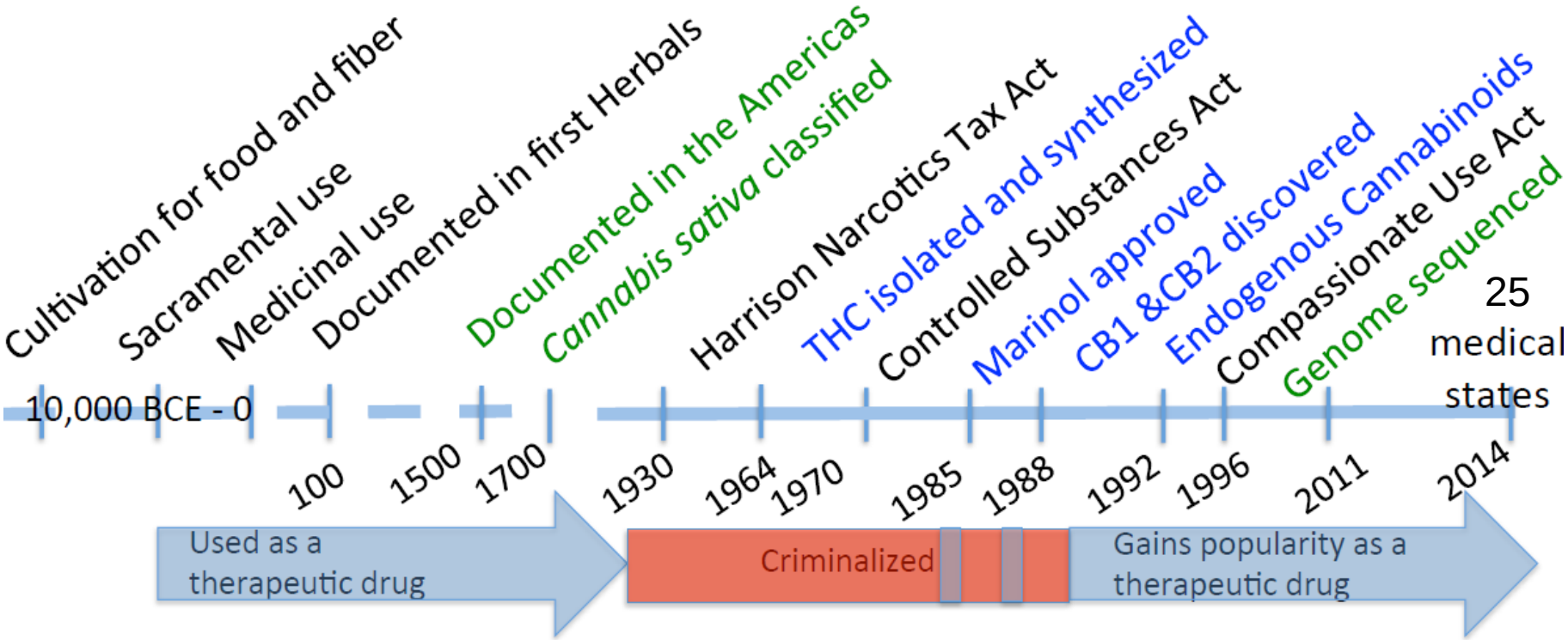
- Conflict of Interest: Pharmaceuticals will be presented according to their FDA approvals and clinical trials. I have no financial interests to disclose.

Objectives

- Outline the biologically active components in cannabis
- Describe the components of the endocannabinoid system that confers the biological effects of cannabinoids
- Outline the cannabinoids with FDA approval and in clinical trials
- Describe the current clinical data supporting use of cannabinoids and cannabis in pain, nausea and seizures.
- Outline the evidence for use of cannabinoids in pediatric patients
- Discuss the abuse potential and vulnerability of adolescent children to cannabis-dependence disorders

Cannabis: Medicine or Drug of Abuse?

A Brief History of Cannabis



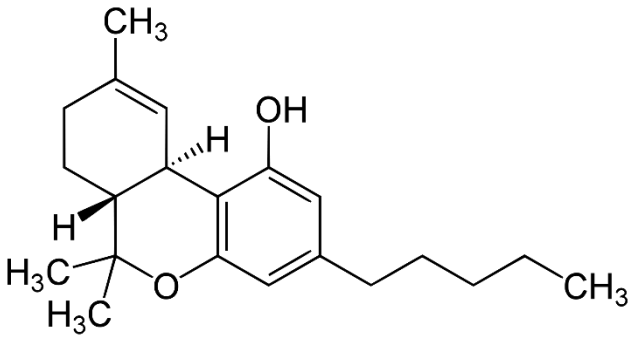
Cannabis and Phytocannabinoids

- *Cannabis* sativa produces many compounds that are secreted by trichromes in the flowers and leaves
- Different strains of *Cannabis* can produce different levels of biologically active components
  - Hemp
  - Charlotte's Web
  - Sativa/Indica

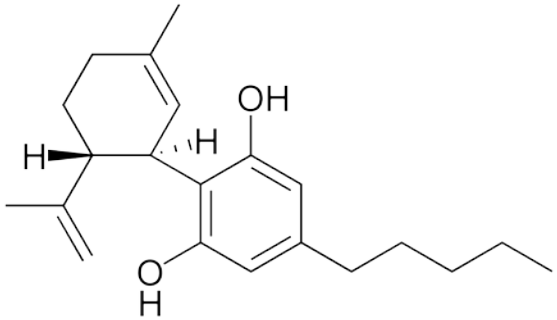
Biologically Active Cannabinoids

Cannabis produces over 100 cannabinoids

- Delta-9-tetrahydrocannabinol (THC)
  - Partial Agonist CB1/CB2 receptors
  - Psychoactive
  - Anti-pain, anti-nausea
  - Anti-spasm, anti-immune



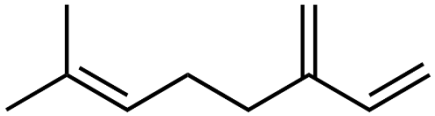
- Cannabidiol (CBD)
  - Antagonist CB1/CB2 receptors
  - Not psychoactive
  - Anti-seizure activity, anti-pain
  - Possible non-receptor activities



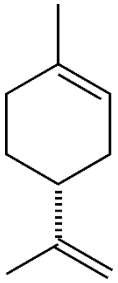
- Activated by heating the plant (smoking, vaping, baking, heat extraction)

Other Cannabis Compounds with Biological Activity

- Terpenes/terpenoids (over 500 compounds)
  - Myrcene, limonene (also produced by many fruits)
  - Entourage Effect: affect uptake or metabolism of THC



Myrcene

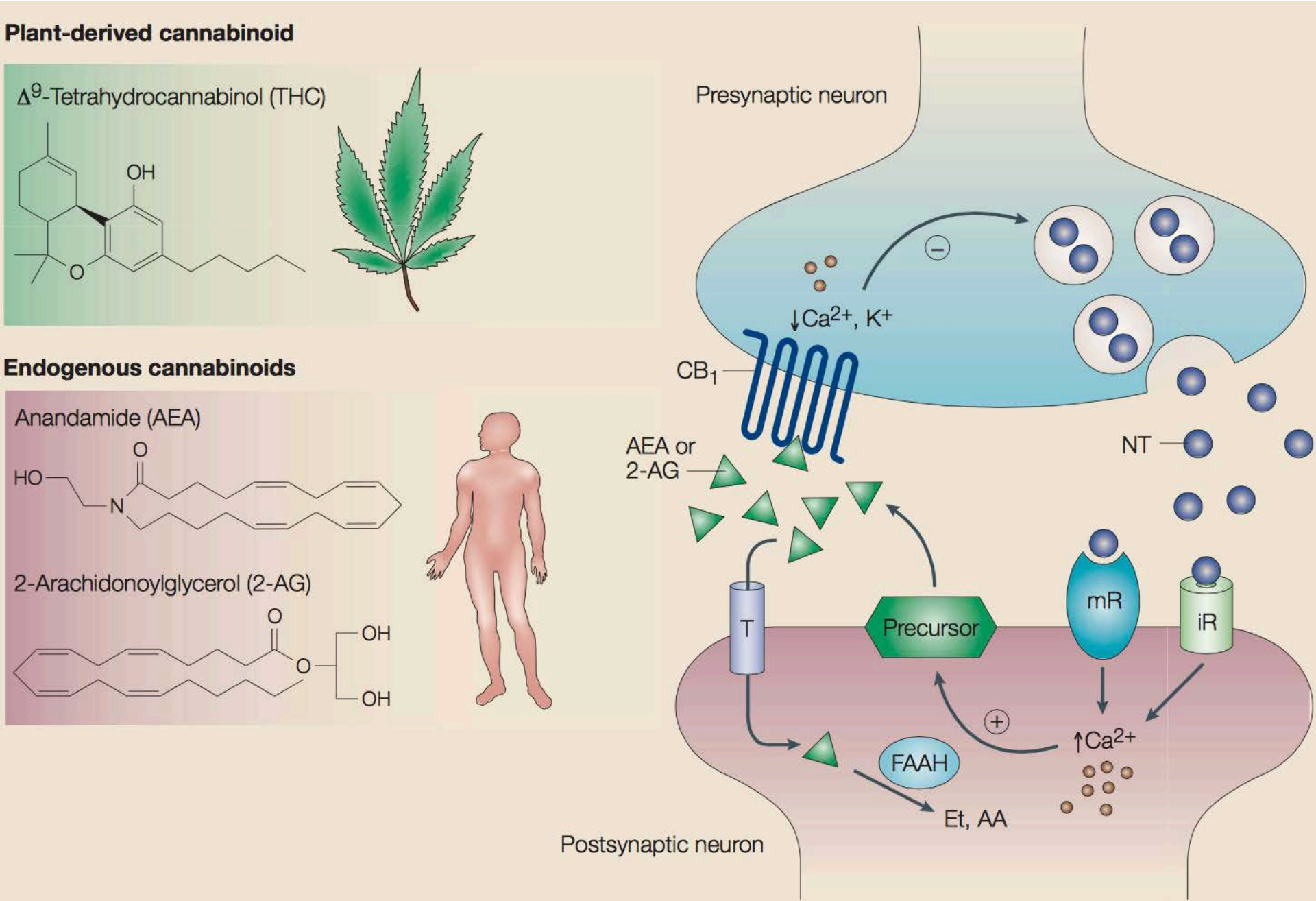


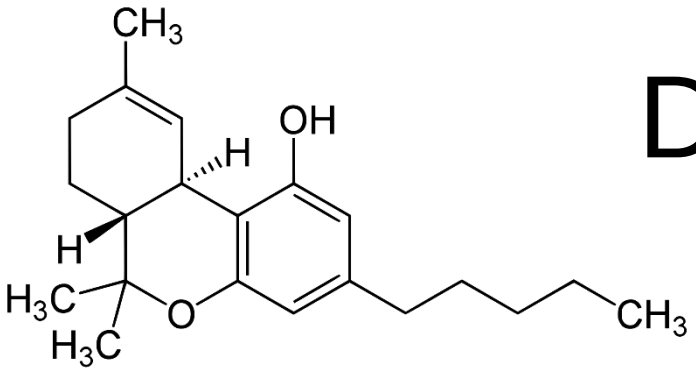
Limonene

The Endocannabinoid System

- Cannabinoid Receptors
  - CB1: Expressed in many tissues, highest in neurons
  - CB2: Expressed highly in immune cells, some in neurons
  - Both are G protein (Gi)-coupled receptors that inhibit neuronal signaling
- Endocannabinoids (anandamide, 2-AG) are expressed in many tissue types
  - Expression in neurons is induced by excess Glutamate receptor signaling
  - Thought to be a feedback mechanism to limit neuronal activity (similar to opioid activity)

Cannabinoid Signaling





Dronabinol (Marinol™)

- Synthetic delta-9-THC
- US FDA approved for nausea due to cancer chemotherapy in 1986
- Approved for HIV-AIDS associated weight loss
- Marinol is an FDA approved Schedule III drug, although dronabinol (THC) is Schedule I
- **Side effects: primarily CNS-related dysphoria**

Cannabis Extracts in Development

- In Phase III Clinical Trials: Plant-derived cannabinoids
  - 1:1 THC/CBD (Sativex™) sublingual spray
  - CBD (Epidiolex™) oral solution
    - FDA approved 2018 for childhood seizure disorders

Cannabinoids in US clinical development

- Epidiolex (CBD)
- Sativex (THC:CBD)

Location of Cannabinoid Receptors in Pain Pathways

- CB1 Receptors
  - High Density in the CNS
  - Sensory Neurons (afferents going to the brain)
  - Autonomic Nervous System (efferents that communicate with organs)

- CB2 Receptors
  - Highly expressed in immune-related organs
  - Spinal Sensory Neurons (afferents going to the brain)
  - Role of CB2 in pain is thought to be mostly immune cell-mediated

Cannabis as a Medicine

- Proven effectiveness (THC):
  - Chronic Pain
  - Chemotherapy-induced Nausea
  - Seizures
  - Spasticity (MS and Cerebral Palsy)
  - Cachexia (wasting disorder)
- Likely effective and in clinical trials (THC):
  - Eating Disorders
  - Glaucoma
  - Anxiety Disorders (OCD, PTSD)
- Possibly effective, needs more research (THC)
  - Addiction
  - Parkinson's/Alzheimer's
  - Inflammatory Diseases
  - Cancer

*Proven effectiveness is through randomized clinical trials using **THC**. Whole plant cannabis has been found effective for Pain, Nausea and Seizures, but these trials are sparse and nonexistent for other conditions.*

***CBD** has only been found effective against seizures, other trials have not shown significant effectiveness, but more are needed*

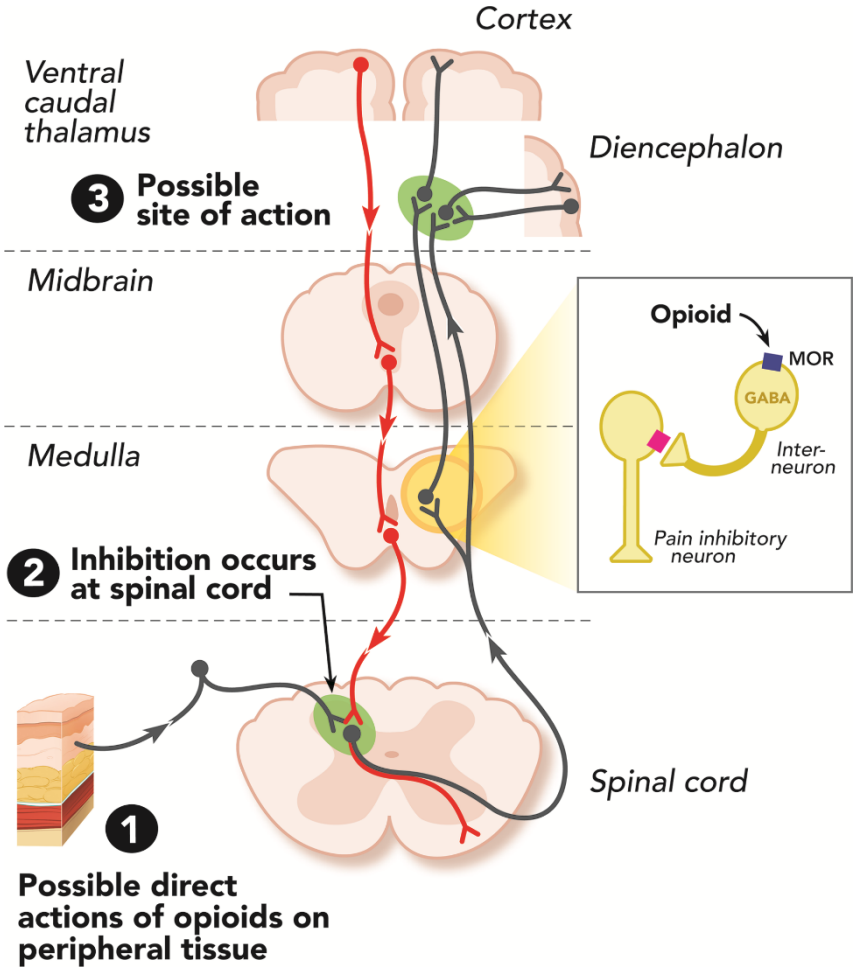
Lynch and Ware. Cannabinoids for the treatment of chronic non-cancer pain: An updated systematic review of randomized controlled trials. Journal of Neuroimmune Pharmacology 10: 293-301, 2015

Wilsey et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain. 2008

Cannabinoids in Treatment of Pain

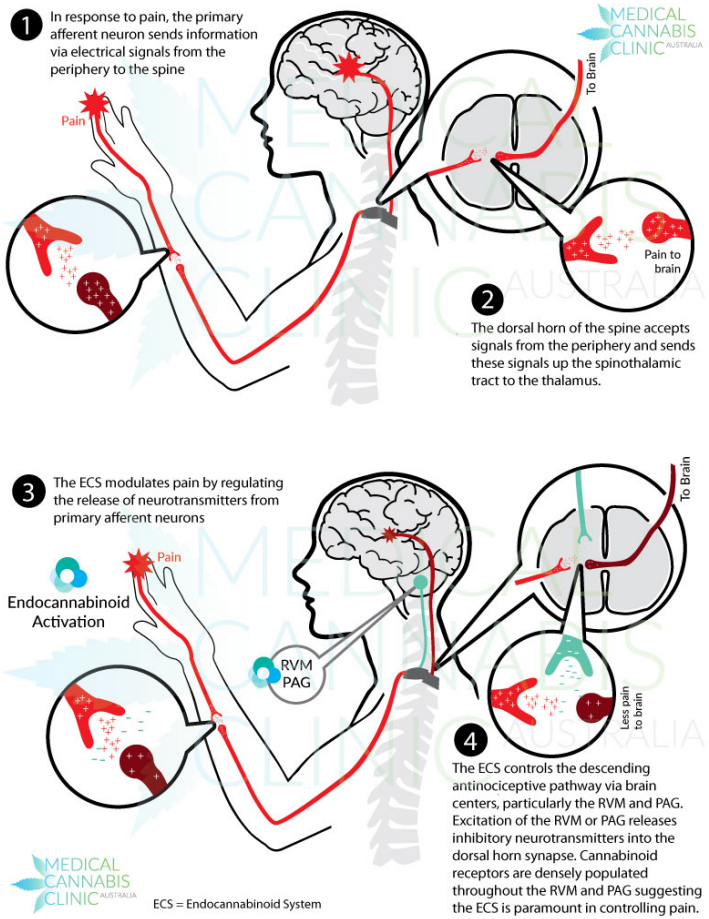
Pain Control with Opioids

- Examples: morphine, hydrocodone (Vicodin), oxycontin, Percocet, fentanyl
- Agonist for the mu opioid receptor
  - Inhibits neuron activity
  - Coupled to Gi
    - Inhibits Ca2+ entry
  - Exhibit tolerance



Cannabinoid Receptors reduce neuronal activity in response to pain

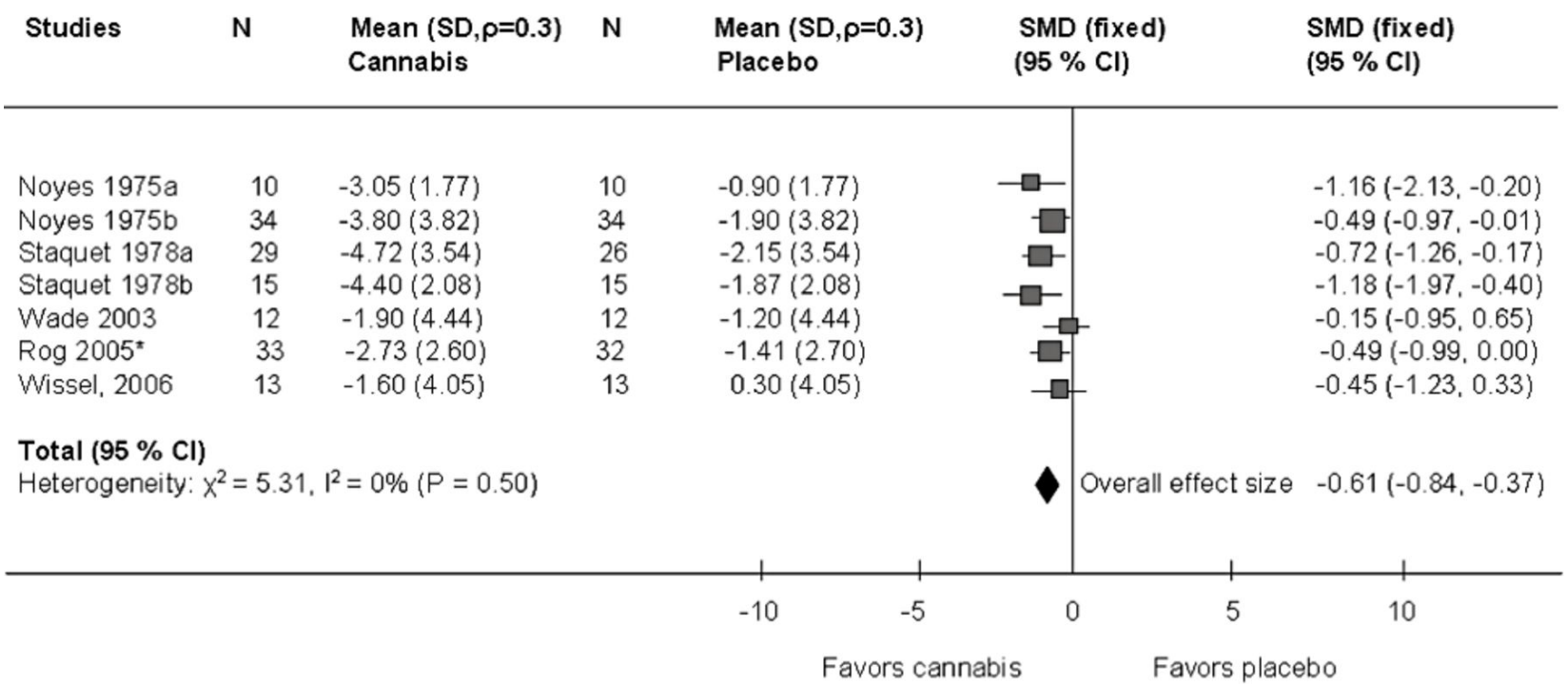
- Both endocannabinoids and cannabis reduce both pain signal and interpretation of pain
- Similar to the action of opioids
  - Not as effective
  - Produce less tolerance
  - Less risk of addiction
  - Low risk of overdose



Inhibiting the breakdown of endogenous opioids and cannabinoids to alleviate pain, 2012
http://www.nature.com/nrd/journal/v11/n4/full/nrd3673.html

Meta-analysis of efficacy: intensity of pain by visual analog scale (VAS). * Parallel design

Studies included cannabis, purified or synthetic THC



Efficacy analysis (visual analog scales) displayed a difference in standardized means in favor of the cannabis arm of -0.61 (-0.84 to -0.37)

Eva Martín-Sánchez et al. Pain Med 2009;10:1353-1368

PAIN MEDICINE

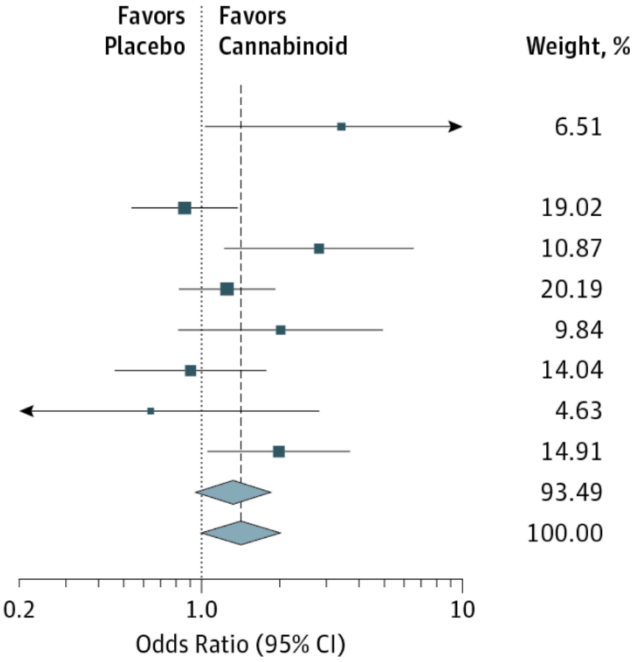
From: **Cannabinoids for Medical UseA Systematic Review and Meta-analysis**

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358

THC

CBD

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)
Tetrahydrocannabinol (smoked)					
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)
Nabiximols					
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)
Subtotal $I^2 = 44.5\%$, ($P = .0.94$)	241	660	209	660	1.32 (0.94-1.86)
Overall $I^2 = 47.6\%$, ($P = .0.64$)	254	685	215	685	1.41 (0.99-2.00)



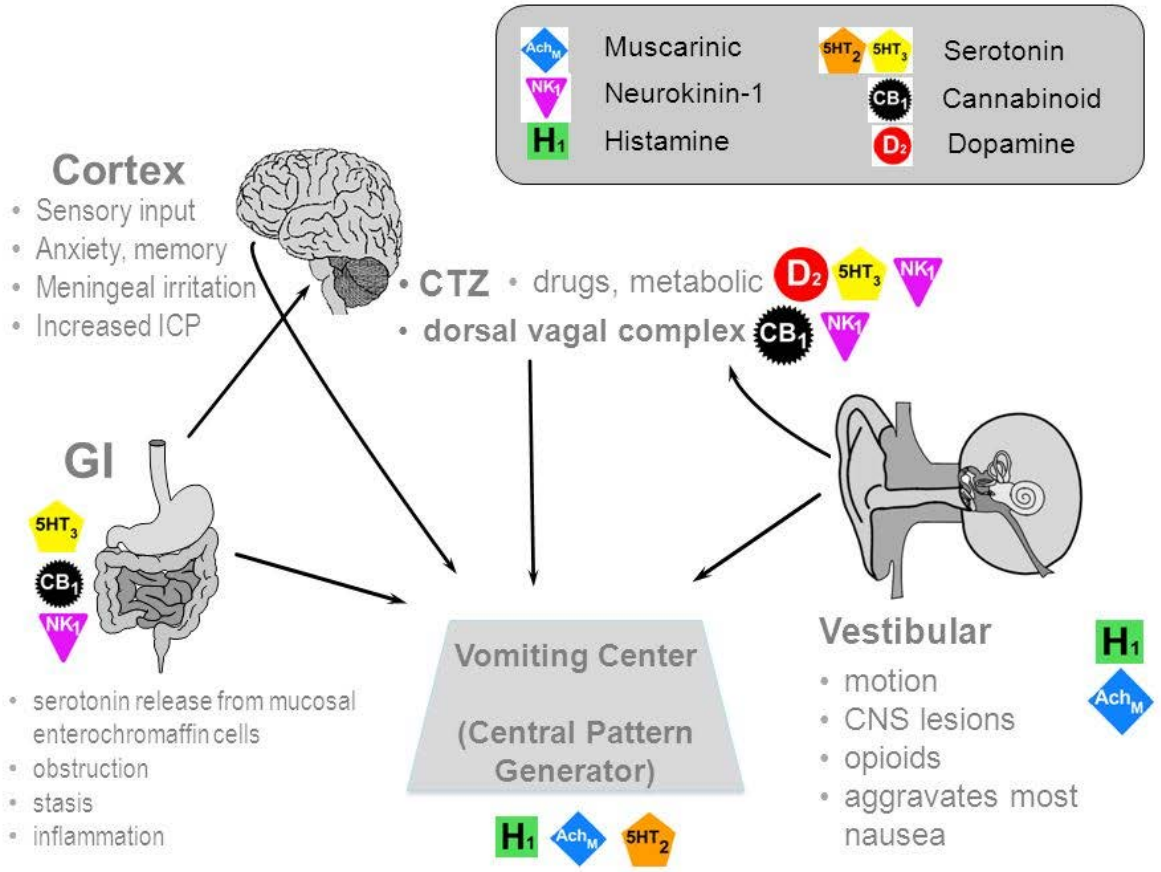
Improvement in PainOdds indicate 30% or greater improvement in pain with cannabinoid compared with placebo, stratified according to cannabinoid. The square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal lines indicate 95% CIs. The blue diamond data markers represent the subtotal and overall OR and 95% CI. The vertical dashed line shows the summary effect estimate, the dotted shows the line of no effect (OR = 1).

Advantage of adding cannabinoid to opioid regimen for pain

- Enhances pain control
  - Different receptor mechanism
- Reduced opioid side effects
  - Nausea and constipation
- Reduced dose of opioid needed
  - Additive pain relief
- Reduced risk of dependence
  - Can reduce withdrawal pain

Cannabinoids in the Treatment of Chemotherapy-induced Nausea

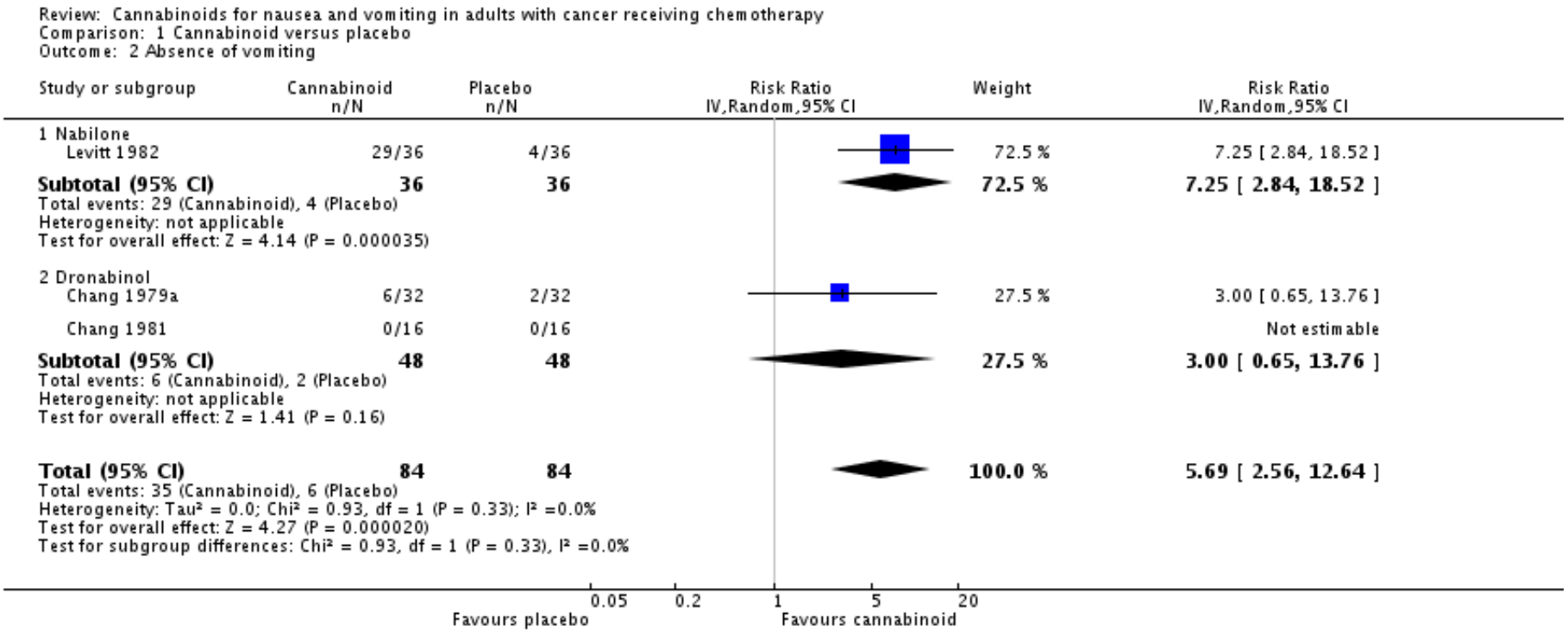
CB1 Receptor Activation Inhibits the Vomiting Center: Physiological antagonist to 5-HT3 receptor action



CTZ=chemoreceptor trigger zone

Courtesy Mike Harlos, University of Manitoba

Effectiveness of Dronabinol and Nabilone



Cochrane Database Syst Rev. 2015 Nov 12;11:CD009464

Only 3 Clinical Trials for whole plant Cannabis as anti-emetic following chemotherapy

- Two trials were in patients that had failed dronabinol, 25% effective
- Only 1 randomized, double-blind, placebo-controlled comparison trial for smoked cannabis with older anti-emetics
  - Canadian study
  - 35% preferred dronabinol
  - 20% preferred smoked cannabis
  - 45% no preference

Reviewed in: Cannabis in Cancer Care
Abrams and Guzman, Clin Pharm. Therap. 97:575. 2015

Cannabis vs. Synthetic THC in Cancer Care

- Advantages of Cannabis
  - "Entourage Effect"
    - Other cannabinoids and terpenes contribute to effects and may reduce side effects (especially CNS side effects)
  - Delivery
    - Inhalation gives faster relief
    - Metabolism profile is different
- Disadvantages of Cannabis
  - Illegal in many states (patients hesitant to use)
  - Few clinical trials to determine effectiveness or drug interactions
  - Difficult to standardize dose
    - Different strains, processing, etc.

Pediatric Clinical Trials: Few studies

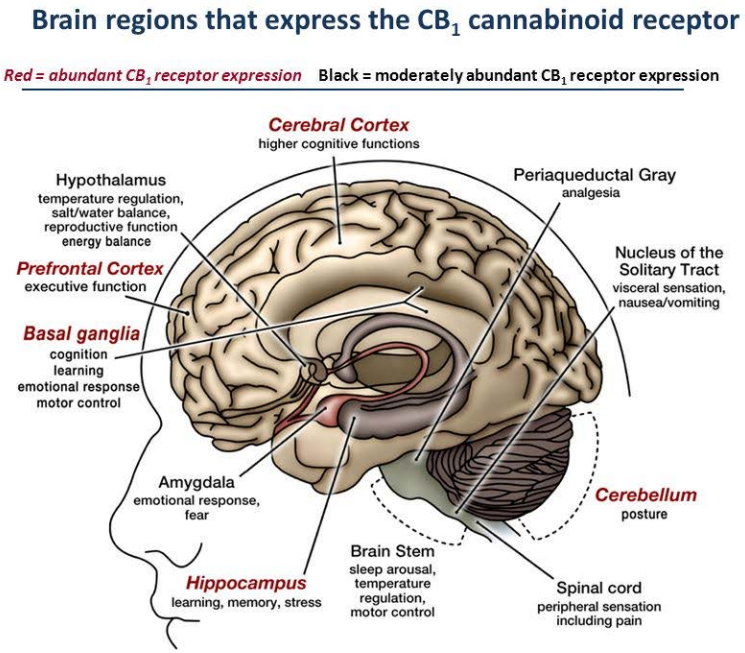
- Most parallel adult results
  - Effective in Pain, nausea, seizure (THC or CBD)
  - Encouraging data in autism
  - Encouraging data for spasticity
    - cerebral palsy
- Adult Cannabinoid trials: >400 current trials, 100 related to abuse
- Pediatric Cannabinoid trials: 125 current trials, 120 related to abuse, 5 related to epilepsy

Cannabis Legalization: What's the Harm?

- Increased accidental ingestion (no deaths)
  - Particular problem with Edibles
- Cannabis intoxication
  - Impaired driving
- Cannabis Dependence
  - Adolescent vulnerability

Cannabis Intoxication:

- *Attributed to THC action in the brain*
- Head rush and euphoria (Reward Pathway)
- Appetite increase (Hypothalamus)
- Decreased attention, sedation (Hippocampus-Prefrontal cortex)
- Altered Perceptions (Pre-frontal corte: inhibition)
  - Awareness of the senses and of music may be increased
  - Distorted sense of time
  - Preoccupation with distractions
  - Giggles



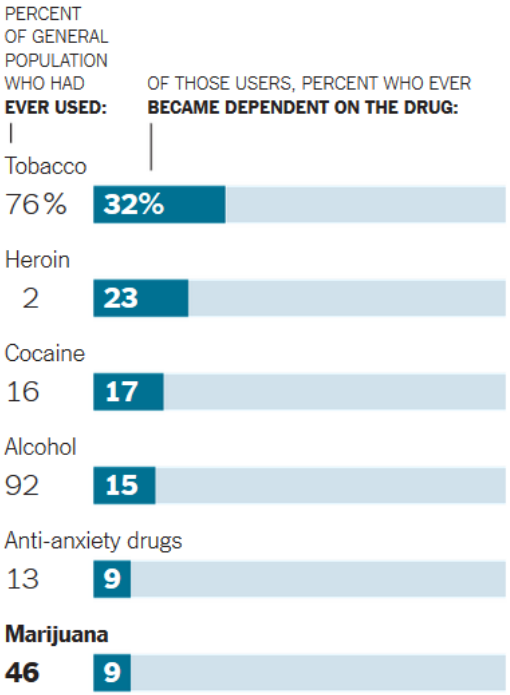
Cannabis Effects on Attention:

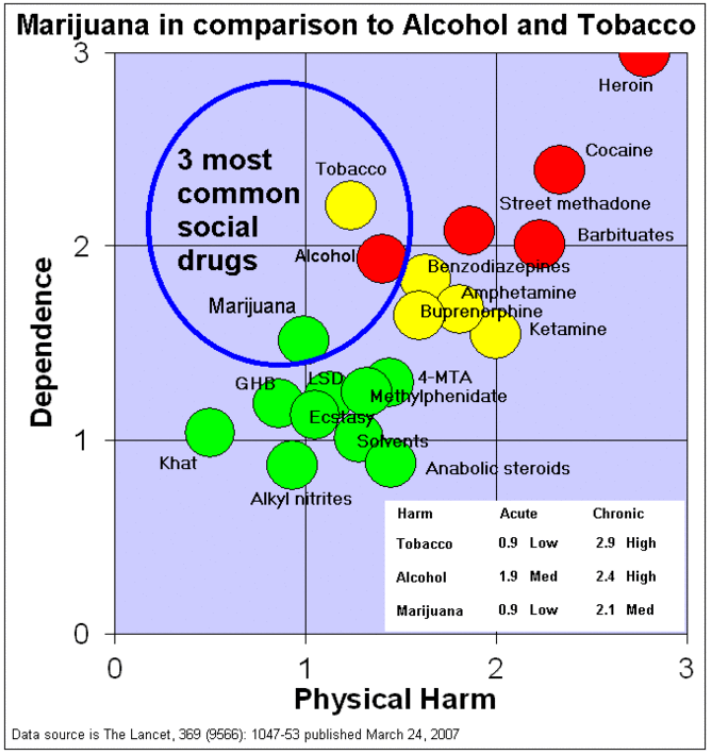
Impaired ability to drive

- Peripheral attention reduced
  - A person who is high may become absorbed in an object, event, or process to the exclusion of everything else
- Memory
  - Both short-term and long-term memory impairment
- Color/Image Perception
  - Hallucinogenic effects
- Motor Coordination
  - Impaired, but much less than alcohol or opioids

States with legalized recreational use have seen increased car accidents in the population that has combined alcohol and cannabis, but there is no significant difference in fatal car accidents in states with legalized cannabis

Cannabis Addiction Potential

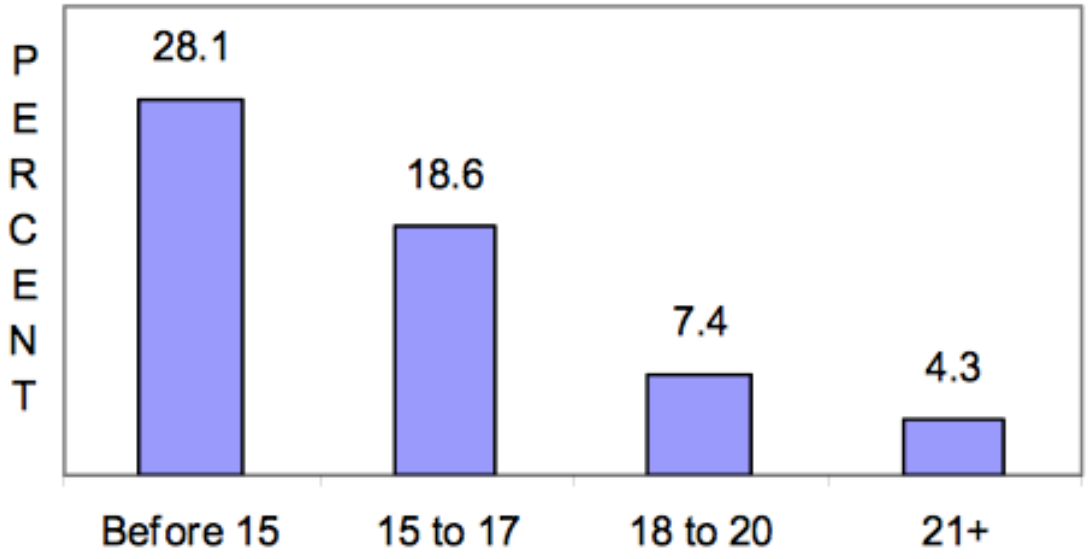




Young People are Particularly Vulnerable

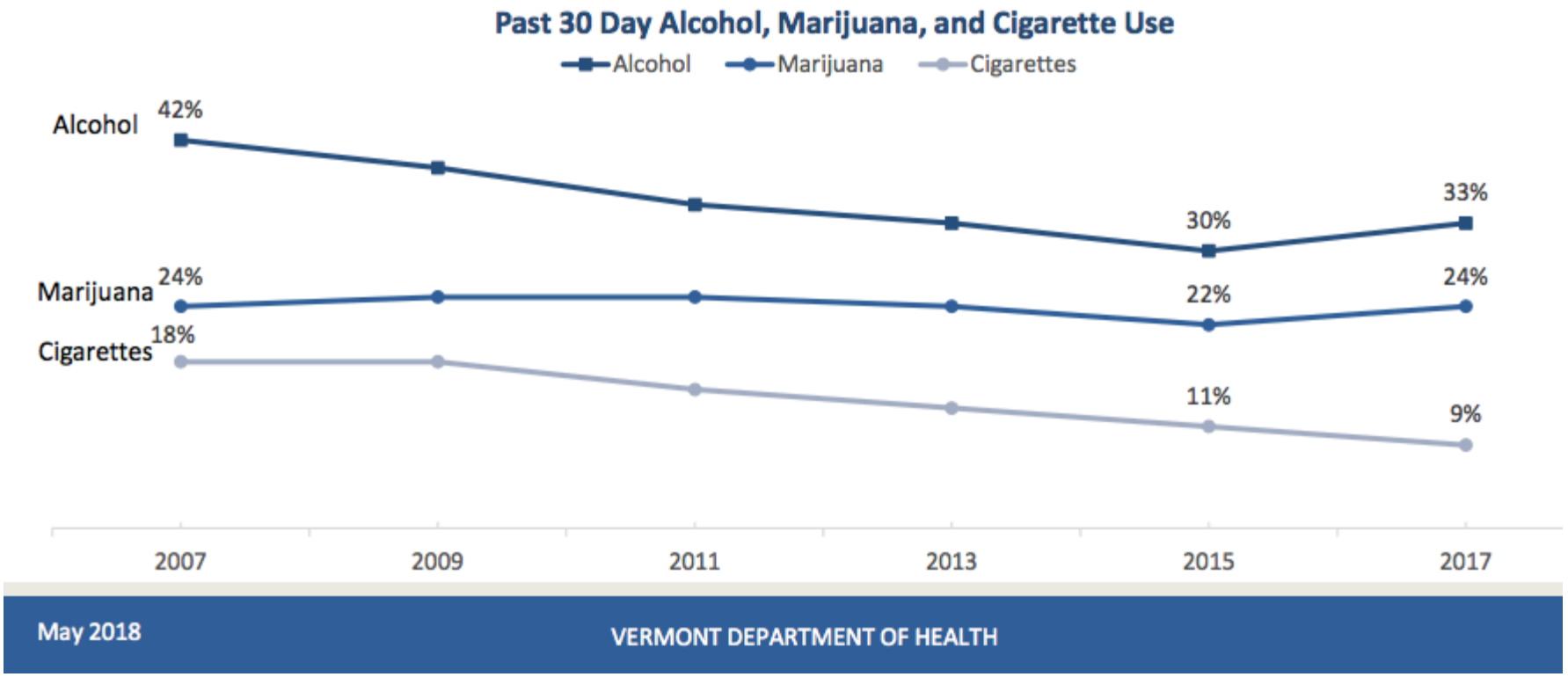
- Substantially higher risk for Substance use disorder when an addicting drug is started before the age of 18, even higher risk with younger patients
- Chronic adverse effects of cannabis are more likely to develop in younger patients
- Amotivation disorder with chronic use

Substance Use Disorders Among Persons 12 and Older, by Age of First Use



Source: CASA analysis of the *National Household Survey on Drug Use and Health* (NSDUH), 2009.

Drug use in Vermont



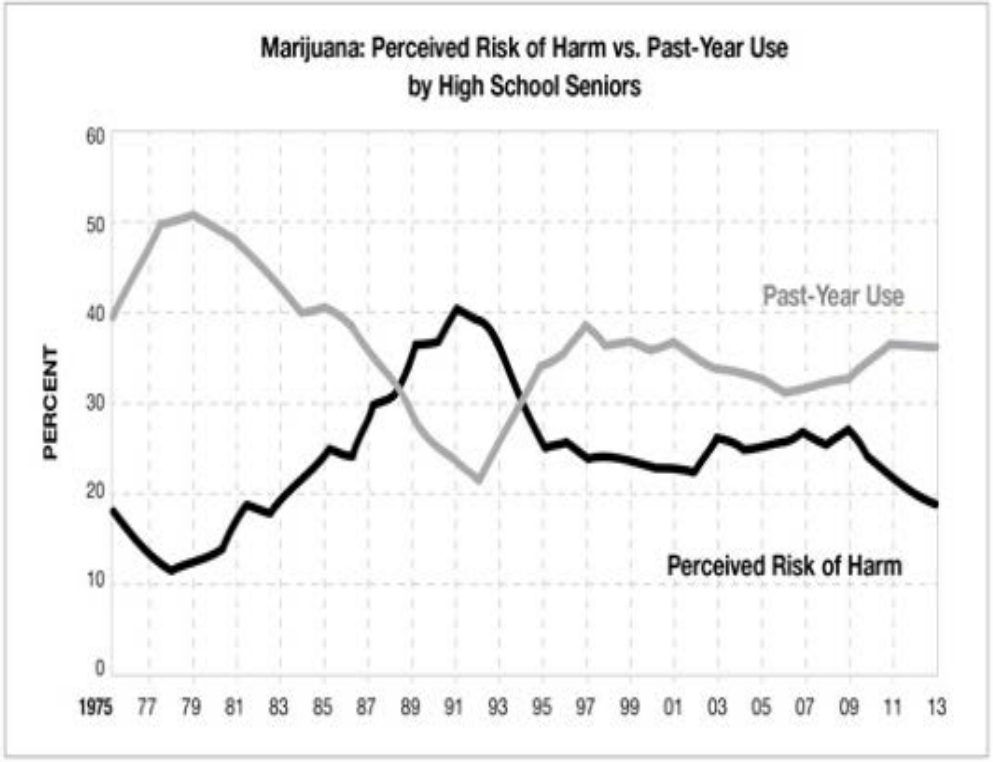
Vermont Trends: Perception of Harm

High School students believing there is a great risk of harm from:

- Binge drinking regularly: 36%
- Smoking a pack or more of cigarettes: 68%
- Using marijuana regularly: 24%

Youth Risk Behavior Survey 2017

Perception of harm is inversely correlated with use



Marketing


Rastafarers
Reefer
Rasta Reeses
KeefKat
OEO
Buddahfinger

American Academy of Pediatrics

- Opposes medical marijuana outside FDA process
- Opposes legalization for recreational use
- Supports research (move from schedule I to schedule II)
- Strict enforcement of rules against marketing and sale to children (age 21 minimum)
- Supports decriminalization for both adults and youth
- Opposes smoking in any form
- Strongly Discourages any use in the presence of children

Navigating the Vermont Medical Marijuana Laws

Eligibility: Debilitating Medical Conditions

- Patients diagnosed with a specific disease or condition where reasonable medical efforts have been made over a reasonable amount of time to relieve the symptoms of:
    - Cancer
    - Multiple sclerosis
    - HIV
    - AIDS
    - glaucoma
    - **or**
    - The treatment of these conditions, if the disease or the treatment results in severe, persistent, and intractable symptoms;
    - **or**
    - A disease, medical condition, or its treatment that is chronic, debilitating, and produces one or more of the following intractable symptoms: cachexia or wasting syndrome; chronic pain; severe nausea; or seizures

Defined: Health Care Professional

- an individual licensed as:
    - an MD or DO
    - a naturopathic physician
    - an Advanced Practice Registered Nurse
    - an individual certified as a physician assistant,

- this includes individuals who are professionally licensed in New Hampshire, Massachusetts, or New York, except for naturopaths

Bona fide health care professional–patient relationship

- A treating or consulting relationship of not less than three months:

  – in the course of which a full assessment of the registered patient's medical history and current medical condition, including a personal physical exam

  – **the three month requirement shall not apply if a patient has been diagnosed with**:
    - (A) a terminal illness,
    - (B) cancer, or
    - (C) acquired immune deficiency syndrome
    - (D) or is currently under hospice care

The VT Registry Process

- The patient who is a VT resident, over 18 years of age, visits the Marijuana Registry website, downloads and completes the Registered Patient Application form
- Patient gives their Health Care Professional a Verification Form to complete
- Patient returns both forms, notarized with $50 fee and digital ID photograph to the state
- Upon approval, patient receives a registration card (valid for 1 year) within 30 days

For more information: Cannabis Science and Medicine Continuing Medical Education (CME)

- Five, two-hour online modules focused on *Cannabis* for therapeutics
- http://learn.uvm.edu/com/program/cannabis-science-and-medicine-continuing-medical-education-cme/
- Developed at UVM by: Monique McHenry, Karen Lounsbury, Kalev Freeman, and Wolfgang Dostmann