

Medical THC: Risks and benefits for

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Objectives

- Discuss the history of medical use of marijuana and the current political and psychosocial climate surrounding the use of medical marijuana.
- Discuss and identify various components on the marijuana plant and their known/hypothesized mechanisms of action.
- Discuss the current evidence available for the use of medical marijuana in identified disorders.

DISCLOSURE

No financial conflicts of interest

Views expressed are my own and not representative of those of the University of Florida or The American Society of Addiction Medicine

(....and I DID inhale)

Conundrum

- Cannabis is labeled as schedule 1 drug
- Medical/ recreational marijuana is approved in 29 states
- Inadequate scientific evidence exists for rational of medical marijuana use
- Hotly contested issue – more political/sociocultural than medical?



Nov. 4, 2002

Pro & Con Arguments

Addictiveness of Marijuana

Pro

"For some users, perhaps as many as 10 per cent, cannabis leads to psychological dependence, but there is scant evidence that it carries a risk of true addiction. Unlike cigarette smokers, most users do not take the drug on a daily basis, and usually abandon it in their twenties or thirties.

Unlike for nicotine, alcohol and hard drugs, there is no clearly defined withdrawal syndrome, the hallmark of true addiction, when use is stopped."

Colin Blakemore, PhD
Chair, Dept. of Physiology, University of Oxford (U.K.), and
Leslie Iversen, PhD
Professor of Pharmacology, Oxford University
Editorial, The Times (U.K.)
Aug. 6, 2001

Con

"[T]he evidence clearly indicates that long-term marijuana use can lead to addiction. Indeed, approximately 9% of those who experiment with marijuana will become addicted (according to the criteria for dependence in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition [DSM-IV]. The number goes up to about 1 in 6 among those who start using marijuana as teenagers and to 25 to 50% among those who smoke marijuana daily. According to the 2012 National Survey on Drug Use and Health, an estimated 2.7 million people 12 years of age and older met the DSM-IV criteria for dependence on marijuana... There is also recognition of a bona fide cannabis withdrawal syndrome (with symptoms that include irritability, sleeping difficulties, dysphoria, craving, and anxiety), which makes cessation difficult and contributes to relapse... [E]arly and regular marijuana use predicts an increased risk of marijuana addiction, which in turn predicts an increased risk of the use of other illicit drugs. As compared with persons who begin to use marijuana in adulthood, those who begin in adolescence are approximately 2 to 4 times as likely to have symptoms of cannabis dependence within the 2 years after first use."

Nora D. Volkow, MD
Director of the National Institute on Drug Abuse (NIDA) at the
National Institutes of Health
"Adverse Health Effects of Marijuana Use,"
New England Journal of Medicine
June 5, 2014

Marijuana Has Been Used As Medicine Throughout History

Ancient History

- Used in Chinese medicine dating back 10,000 years, still basic herbal in Traditional Chinese Medicine
- Ancient Egypt- hemorrhoids and other inflammatory conditions
- India- used for insomnia, pain, digestive problems
- Ancient Greece- extensive veterinary uses, also in humans (nosebleeds, tapeworms)
- Middle East- used as antiemetic, diuretic, antiepileptic, anti-inflammatory

Western medicine

- Europe- used for muscle spasms, stomach cramps
- America- widespread use in “patent medicines”

Modern times- Advocates support use for

- Insomnia
- Pain
- Nausea and vomiting
- Appetite with weight loss
- Muscle spasms
- Epilepsy
- Glaucoma

U.S. in 19th and early 20th Centuries



The drug has certain remarkable properties and **if its chemical structure were determined and synthetic variations developed**, some of these might prove to be particularly valuable, both as therapeutic agents and as experimental tools.

-Dr. Robert Walton, 1937

Professor at the University
of South Carolina

Reports from Expert Bodies

The Institute of Medicine (IOM) recommended:

- 1) Increased research into synthetic and plant derived cannabinoids (not just THC)
- 2) Clinical trials of cannabinoids (non-smoked)
- 3) Study health risks of marijuana
- 4) Study psychological effects of cannabinoids in clinical trials
- 5) Trials should be less than 6 months and approved by IRBs
- 6) For patients with debilitating symptoms, the following criteria should be met:
 - Documented failure of all approved meds for that condition
 - Symptoms can be expected to be relieved by rapid onset cannabinoids
 - Medical supervision to assess efficacy and oversight.

The IOM stated:

...the purpose of clinical trials of smoked marijuana would not be to develop as a licensed drug, but such trials could be a first step towards the development of rapid-onset, nonsmoked cannabinoid delivery systems.

There is little future in smoked marijuana.

The American Medical Association,
American College of Physicians, and
American Nurses Association
all have similar opinions....

FDA Determines Medicine

- The FDA has reviewed policy on marijuana multiple times; most recently in 2011. In 2006, they said:
 - “No sound scientific studies supported medical use of marijuana for treatment in the United States, and no animal or human data supported the safety or efficacy of marijuana for general medical use. There are alternative FDA-approved medications in existence for treatment of many of the proposed uses of smoked marijuana.”

Potential non-psychiatric medical benefits of marijuana include

1. Treatment of refractory seizures
2. Improvement of appetite in AIDS patients
3. Relief of neuropathic pain and other chronic pain
4. Relief of spasticity in multiple sclerosis
5. Treatment of nausea and vomiting associated with cancer chemotherapy
6. Colic, GI cramps and spasms associated with Crohn's disease
7. Migraine
8. Rheumatoid arthritis

None is proven and therefore FDA continues to opine that marijuana has no medical benefit

Potential psychiatric medical benefits of cannabis include

1. Post-Traumatic Stress Disorder
2. Tourette syndrome
3. Depression
4. Anxiety disorders
5. Schizophrenia
6. Insomnia

None is proven and the evidence is weaker than for other medical conditions

Groundbreaking Findings about Medical Marijuana

- Has anti-cancer effects
- Can slow the progression of Alzheimer's and Parkinson's diseases
- Reduces the debilitating seizures caused by epilepsy
- Reduces spasms experienced by chemotherapy and traditional AID/HIV treatments so that patients can more comfortably continue medical care.
- Minimizes the neurological damage caused by spinal cord and traumatic brain injuries

Source: Medical Marijuana, Inc.

(First Publically Traded Cannabis Company in the US: MJNA)

Medications

- Are standardized by identity, purity, potency, and quality
- Are accompanied by adequate directions for use in the approved medical indication
- Have risk/benefit profiles that have been defined in well controlled clinical trials

Botanically Derived Medication

- Botanical Raw Material (BRM) – fresh or processed (e.g., cleaned, frozen, dried, etc.) part of a single species of plant, alga, or fungus.
- Botanical Drug Substance (BDS) – prepared from BRM materials by pulverization, aqueous extraction, ethanolic extraction, or other similar process. Can be powder, paste, concentrated liquid, juice, gum, syrup, or oil.
- Botanical Drug Product (BDP) – finished product from BDS. Can be solutions, powders, capsules, elixirs, and topicals.

FDA Approval Process

- It takes, on average, 12 years and over \$350 million to get a new drug from the laboratory onto the pharmacy shelf
- Once a drug is developed, it undergoes around 3 ½ years before an application is made to the FDA for human testing. Only 1 in 1000 compounds that enter laboratory testing ever make it to human testing.

FDA Phases

- Phase 1 uses 20-80 health volunteers to establish a drug's safety and profile. (1 year)
- Phase 2 employs 100-300 patient volunteers to assess the drug's effectiveness (2 years)
- Phase 3 involves 100—3000 patients in clinics and hospitals who are monitored carefully to determine effectiveness and identify adverse reactions (3 years)
- The company then submits an application (usually about 100,000 pages) to the FDA for approval.

Entourage Effect

- Refers to a concept that the compounds present in cannabis interact synergistically in such a way that smoking the whole plant is of greater therapeutic benefit than use of any of the isolated compounds.
- Taken root in cannabis industry without any scientific merit.

Basics- Biology of Cannabis

- Intricate and widespread Endocannabinoid System
- CNS, ANS, immune system, GI system, reproductive system, CVS, Endocrine network
- In CNS, ubiquitous network regulating inhibitory and excitatory neurotransmission- “Homeostasis”
- Endogenous cannabinoid (eg., anandamide, 2-Arachidonoylglycerol 2-AG)
- Two receptors
 - CB1: mainly CNS [cerebellum, basal ganglia, frontal cortex, hippocampus, mesolimbic, spinal cord] and Gut
 - CB2: Mainly in the periphery: spleen, macrophages, other

Endocannabinoid System

- 1) G-protein coupled cannabinoid CB1 and CB2 receptors
- 2) Endogenous endocannabinoids that target these receptors, and possibly other receptors
- 3) Enzymes that catalyze endocannabinoid biosynthesis and metabolism
- 4) Mechanisms involved in cell accumulation of specific endocannabinoids

Endocannabinoid/Cannabinoid Roles

Central Nervous System

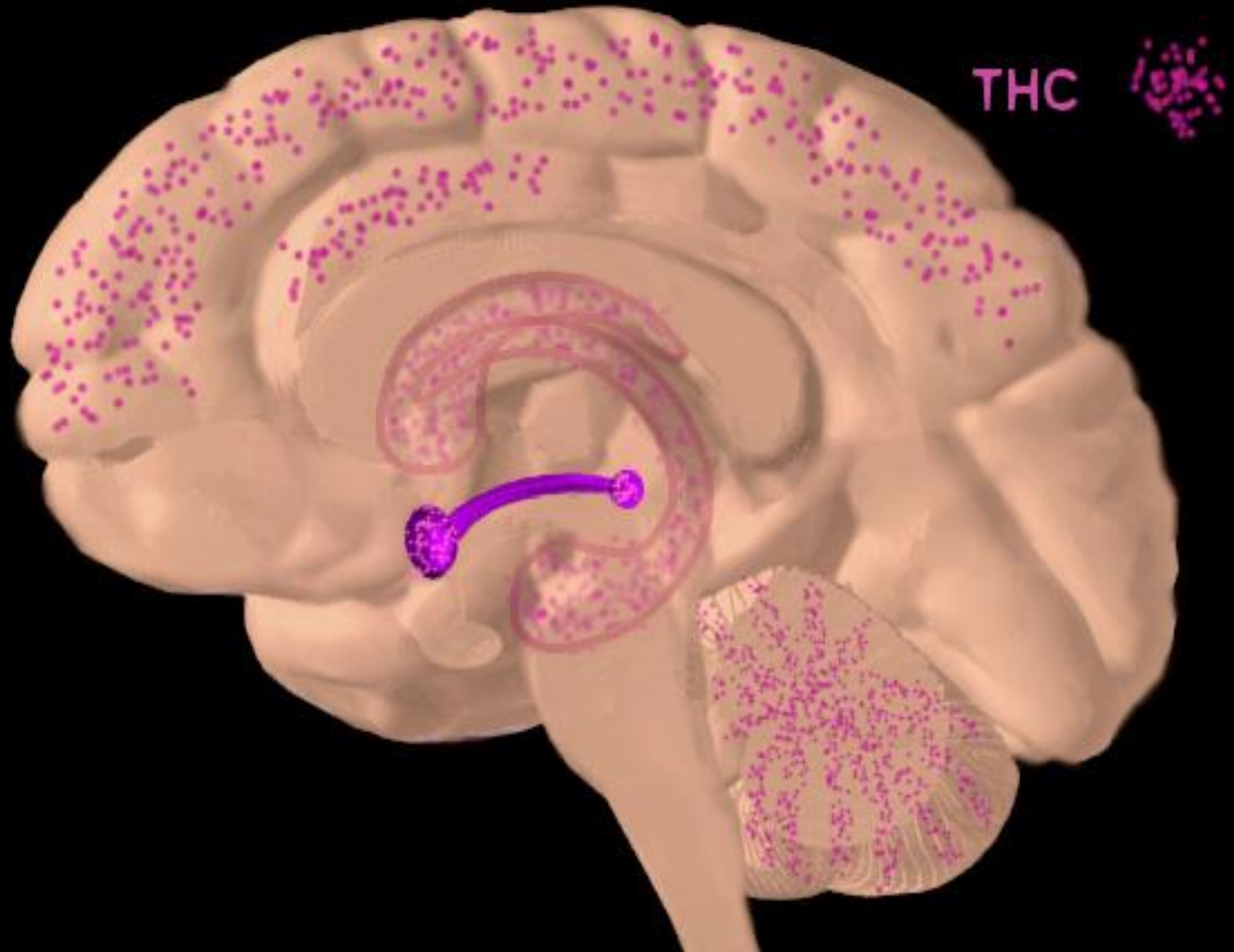
Brain signaling and role regulation of:

- Cognition
- Appetite/Nausea
- Pain
- Motor Function/Movement
- Sensory Function
- Neurogenesis/Brain Development
- Neuroprotection
- Psychiatric Disorders
- Sleep Disorders
- Seizure Activity

In peripheral

- GI Tract
- Cardiovascular Function
- Liver Function
- Immune System
- Musculoskeletal
- Reproductive
- Skin

Cannabinoid (CB1) Receptors in Human Brain



Cannabis sativa



- Annual plant in tropical and temperate zones
- Generally flowering in the late summer months
- Originally native to the Far East, now found worldwide
- Hotter, dryer climates yield higher resin content

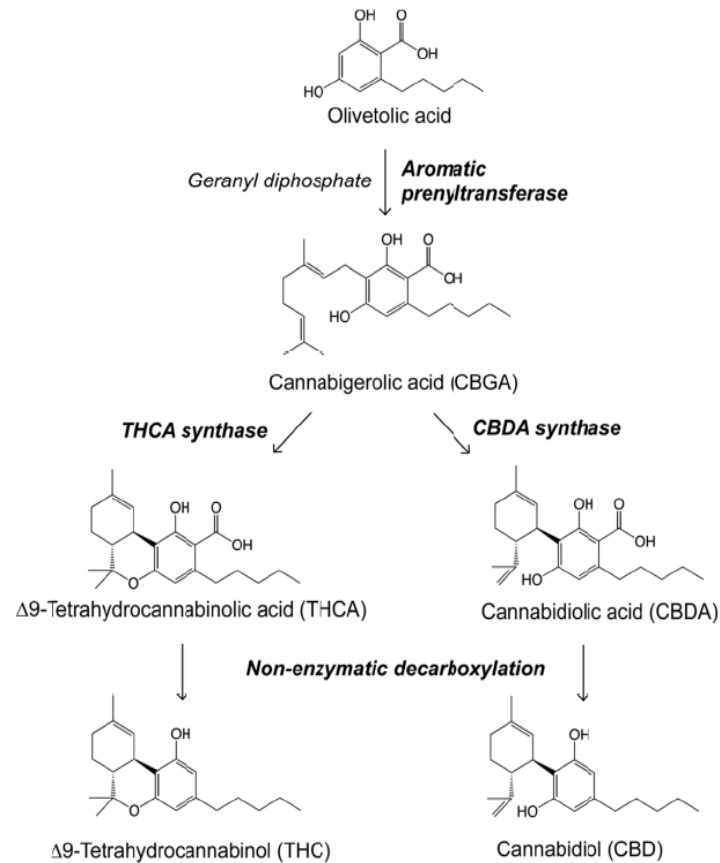


FIGURE 2-1 Synthetic pathway of the main cannabinoids, Δ^9 -THC and CBD, from the common precursor, olivetol.

Cannabis Chemistry

- Ever changing as research increases
- THC, CBD, CBN (cannabinol): now over 100 identified cannabinoids
- Chemical elements have increased from 400 to between 650 and 750
- Potency (THC levels) increasing - some preparations have 80-90% THC
- In unregulated environments, different percentages of microbials (fungi, bacteria, and algae), pesticides, soil, animal waste, heavy metals, etc., can be found

THC Metabolism

- THC is lipophilic and is distributed widely in the body
 - Less acute withdrawal
 - Utility of drug testing
- Oxidized to two active metabolites in liver
 - 11-hydroxy- Δ^9 -THC
 - further oxidized to 11-nor- Δ^9 -THC-9-carboxylic acid (THC-COOH), which is conjugated with glucuronic acid and predominantly excreted in the urine
 - 8- β -hydroxy- Δ^9 -THC
 - These metabolites may be responsible for discrepancy between peak high effect and THC levels
- Other inactive metabolites are also formed

Absorption

- ~60% of THC absorbed when smoked
- 3% of THC absorbed orally
- Ethanol increases THC absorption

Dose and Dose Delivery

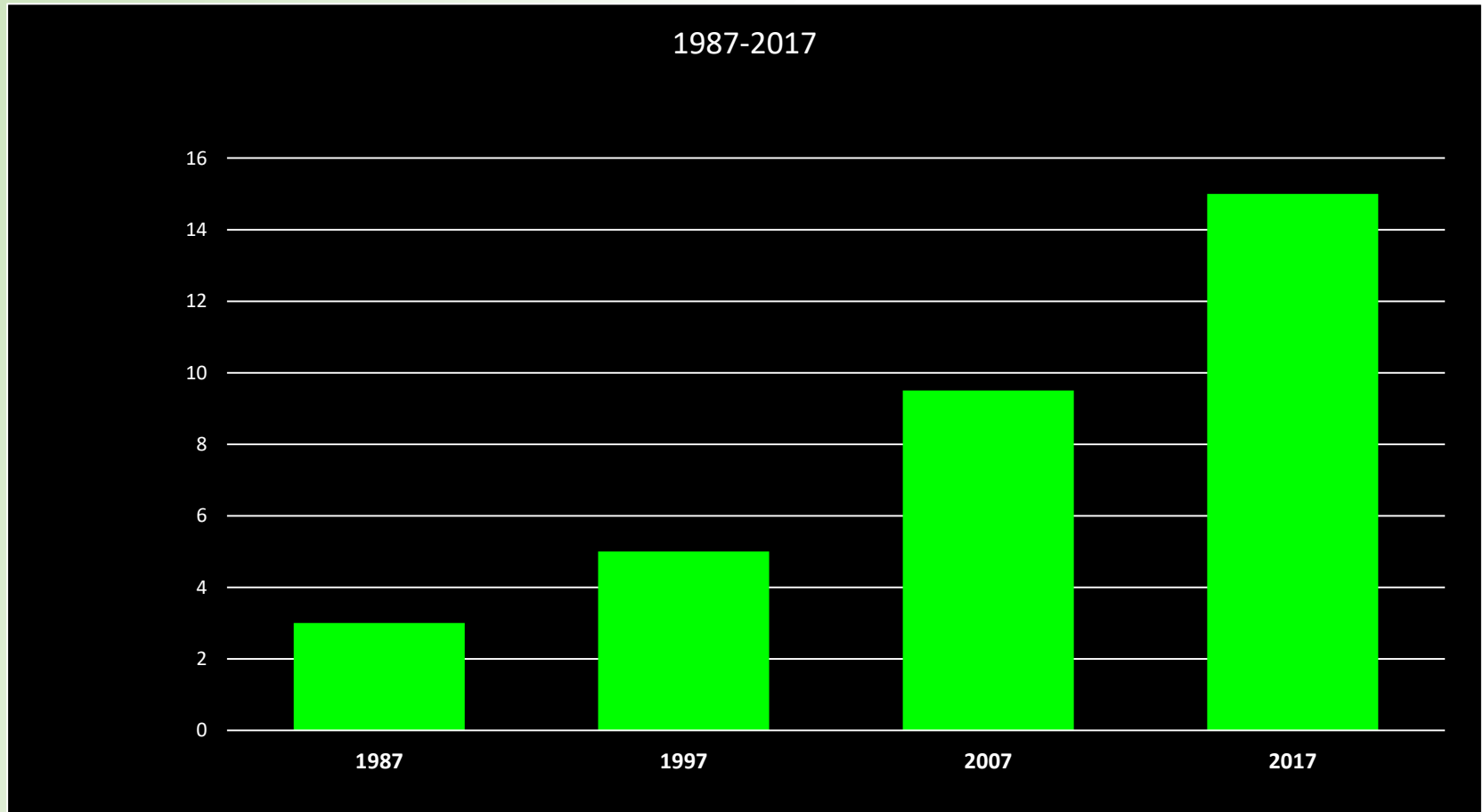
- Smoking, vaping, and oral (“Dabbing”)
- Smoking or vaping peak near 15-30 minutes – amount of THC depends on concentration rate, depth of inhalation, extent of breath holding, vital capacity, etc.
- Smoking MJ exposes one to numerous known carcinogens and 2-4 x amount of tar as cigarettes
- Vaping is not benign – propylene glycol, heavy metals, etc with significant cytotoxic potential
- Oral use has a slower onset, but a later peak and lasts longer

CBD

- Non psychoactive
- Low affinity for CB₁ and CB₂ receptors
- Interferes with deactivation of anandamide (indirectly activated CB₁)
- Agonist of 5-HT_{1A}
- Antioxidant and anti-inflammatory properties

Marijuana - Potency

D.E.A. Seizure Data



“Dabbing”

Vaporizing concentrated marijuana, usually in the form of wax or hash, by placing it on an extremely hot metal object, called a nail, and inhaling the vapors produced. The nail is usually heated via blowtorch.



Trends in Roots of Administration

- Increase use of edible and vaporized forms in states with medical/legal marijuana
- In Washington state, (among daily users in 2013) survey shows that 27.5% used edibles, 22.8% hash resin, and 20.4% had dabbled in the past week.

S. KELLY ©1996 SAN DIEGO UNION-TRIBUNE
CAPLEY NEWS SERVICE
STEVE KELLY '96



The Marijuana High

- Euphoria or “high” within minutes of smoking or about ½ hour if taken orally
 - Sense of well-being
 - Feelings of relaxation
 - Altered perception of time and space
 - Laughter
 - Talkativeness
 - Intensified sensory experiences
- High typically lasts hours depending on dose and other factors

Cannabis Toxicity

- Must differentiate between acute and chronic
- Psychomotor
- Behavioral
- Respiratory
- Immunologic
- Cardiovascular
- Cognitive
- Psychiatric

Long Term Risks of Marijuana Use

- Academic failure and low professional achievement
- Poorer long-term life outcomes
- Mental health problems
 - Increased risk of schizophrenia
 - Increased risk of depressive and anxiety disorders
- Addiction
 - In about 9 % of users (higher in younger users)
 - Gateway drug
- Altered Brain Development
- Frequent use impairs cognitive ability
- Smoked marijuana contains cancer-causing compounds
- Chronic Bronchitis and lung cancer

Addiction Liability

- ~10% who ever use marijuana become daily users
- Conditional dependence – risk of dependence of those who ever use substance
 - Marijuana 9%
 - Ethanol 15%
 - Cocaine 17%
 - Heroin 23%
 - Tobacco 32%

	CANNABINOID-BASED MEDICATIONS		
	Substance	Route of Administration	Description
Natural Product Derived Compounds	Cannabidiol (CBD)	Oral capsule Oromucosal spray	Cannabinoid extracted from <i>Cannabis</i> plant
	Cannabis	Multiple	Multiple active cannabinoids
	Cannador	Oral capsule	THC and CBD from <i>Cannabis</i> extract
	Epidiolex® (FDA Fast Track)	Oil	Concentrated CBD from <i>Cannabis</i> extract
	Nabiximol (Sativex®) (FDA Fast Track)	Oromucosal spray	THC and CBD extract from two <i>Cannabis</i> plant varieties
	Tetrahydrocannabinol (THC)	Oral capsule Smoked Oromucosal spray	Active cannabinoid of <i>Cannabis</i> plant
	THC/CBD	Oral capsule	Combination of cannabinoids
Synthetic Compounds			
	Ajulemic acid (Aja) (FDA PHASE II Active)	Oral capsule	Synthetic nonpsychoactive cannabinoid
	Dronabinol (Marinol®; Syndros®) (FDA approved)	Oral capsule	Synthetic THC
	Nabilone (Cesamet®) (FDA approved)	Oral capsule	Synthetic cannabinoid—THC analogue

Prevalence of Use

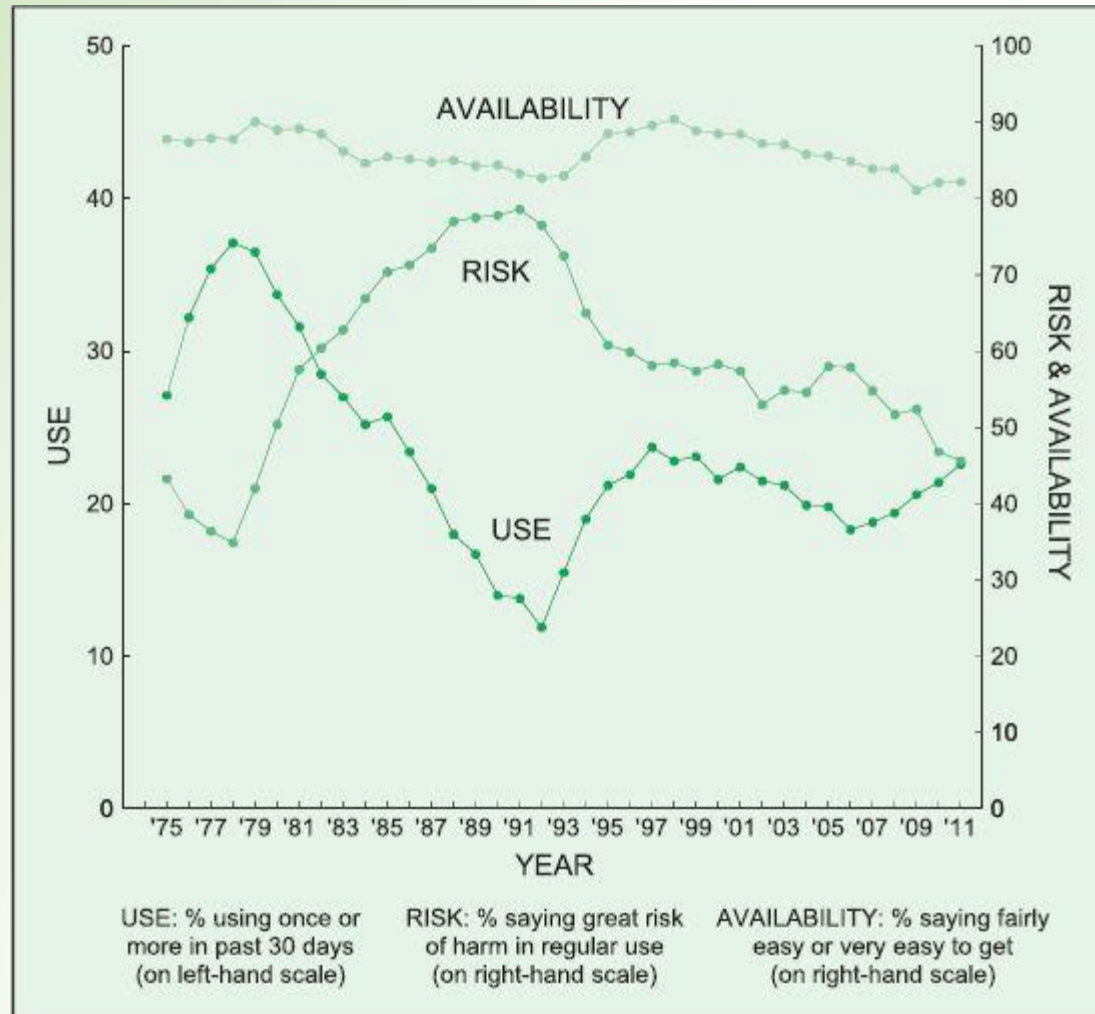
- Most popular illicit drug
- Monitored by MTF (Monitoring the Future) and National Survey on Drug Use and Health (NSDUH)
- Peaked in late 70's (37%) HS seniors and 1 in 8 under age of 12
- Decreased in late 80's and early 90's and rose again by late 90's
- Since 2007, increase of between 5.8-8.4% found in all ages
- Interestingly, since 2002, slight decrease in 12-17 year olds with an increase in 55+ year olds
- All groups have increased since 2002, except ages 12-17, with 18-25 year olds increasing the most

Monitoring the Future Study: Trends in Prevalence of Various Drugs for 8th Graders, 10th Graders, and 12th Graders; 2014 - 2017 (in percent)*

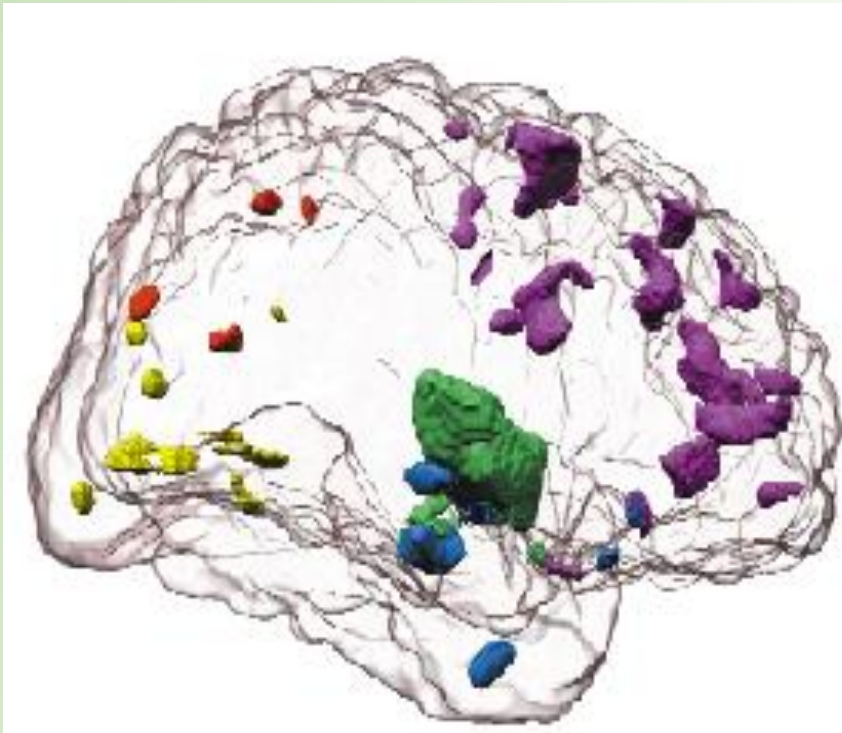
Drug	Time Period	8th Graders				10th Graders				12th Graders			
		2014	2015	2016	2017	2014	2015	2016	2017	2014	2015	2016	2017
Marijuana/ Hashish	Lifetime	15.60	15.50	[12.80]	13.50	33.70	[31.10]	29.70	30.70	44.40	44.70	44.50	45.00
	Past Year	11.70	11.80	[9.40]	10.10	[27.30]	25.40	23.90	25.50	35.10	34.90	35.60	37.10
	Past Month	6.50	6.50	[5.40]	5.50	16.60	14.80	14.00	[15.70]	21.20	21.30	22.50	22.90
	Daily	1.00	1.10	[0.70]	0.80	[3.40]	3.00	2.50	2.90	5.80	6.00	6.00	5.90

<https://www.drugabuse.gov/trends-statistics/monitoring-future/monitoring-future-study-trends-in-prevalence-various-drugs>

Marijuana Perceived Risk vs. Use

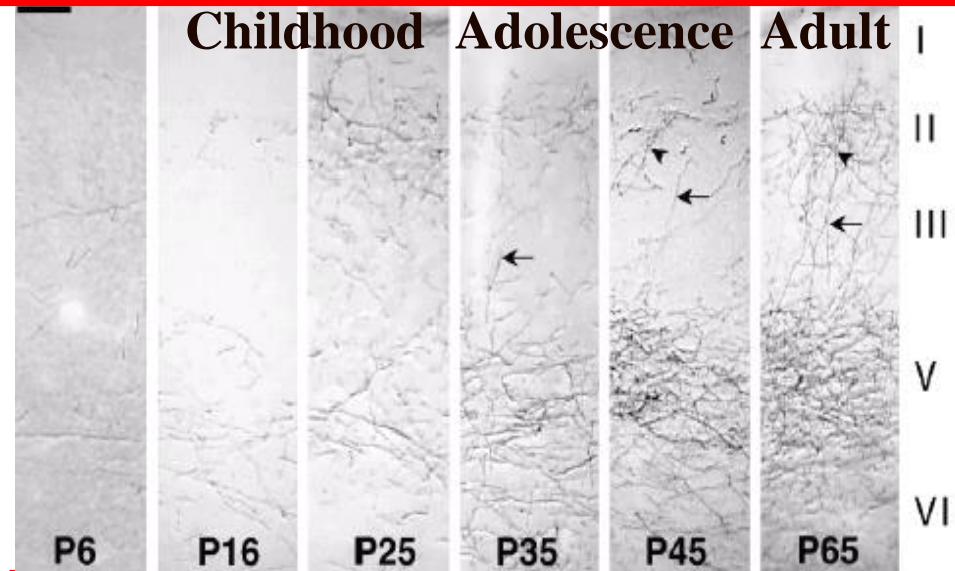


The Adolescent Brain is Still Developing



Brain areas where volumes are smaller in adolescents than young adults

Amygdalo-cortical Sprouting Continues Into Early Adulthood



*During Adolescence the **COGNITION-EMOTION** Connection is Still Forming*

Adolescent Brains

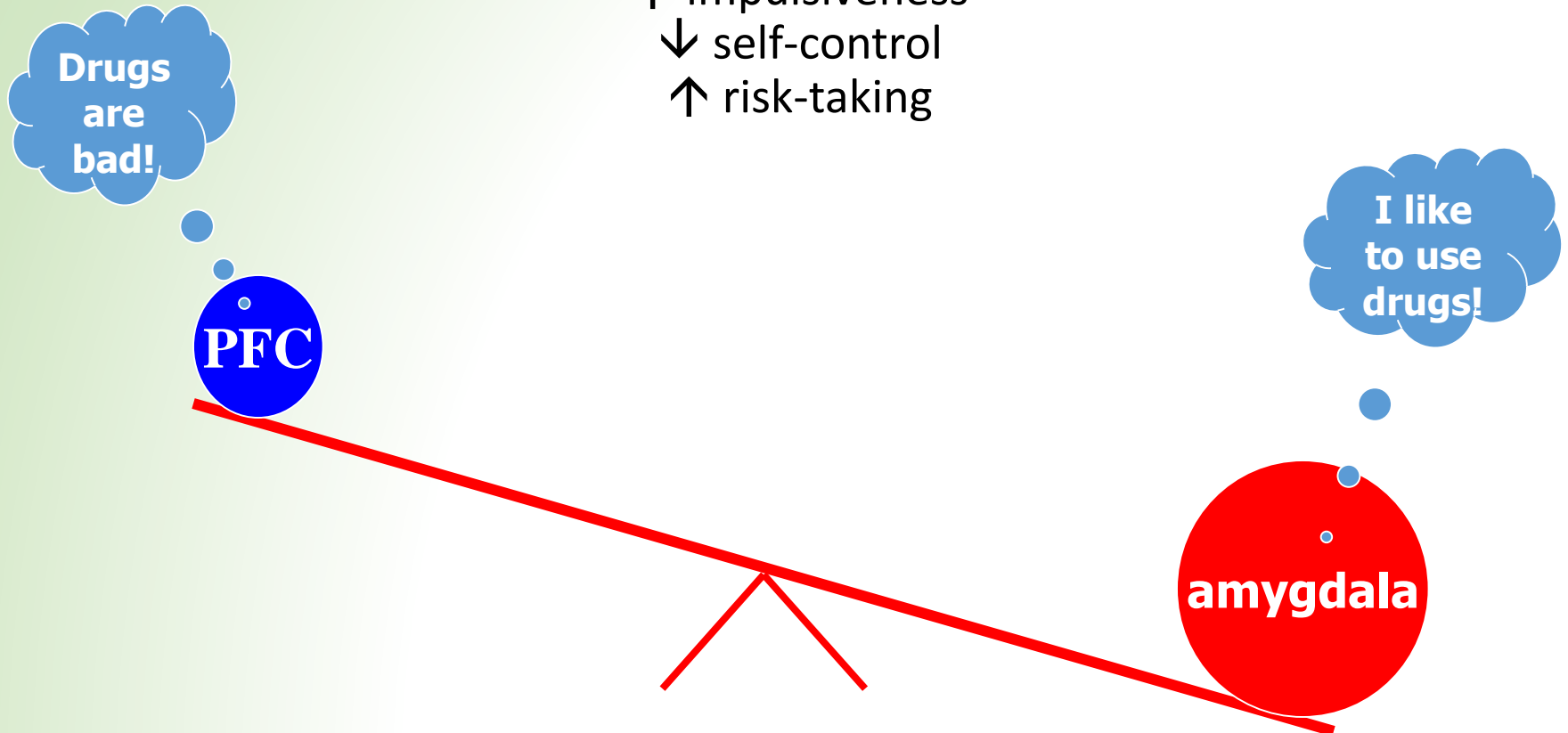
Motivational brain circuitry for pleasurable events develops much faster than the brain mechanism that restrains urges and impulses:



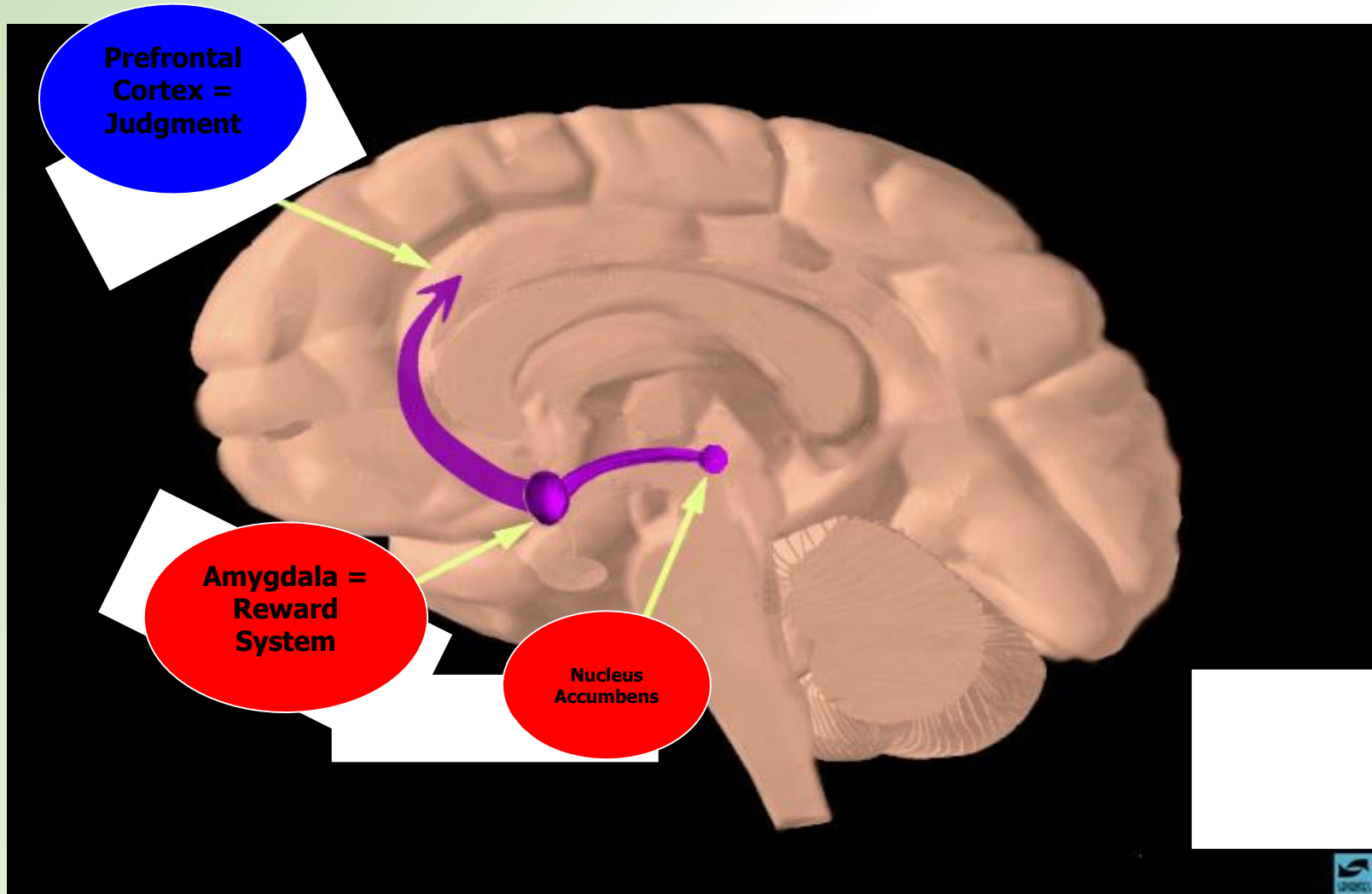
More likely to try drugs!

Adolescent Brain

- This imbalance leads to...
 - ↓ planned thinking
 - ↑ impulsiveness
 - ↓ self-control
 - ↑ risk-taking

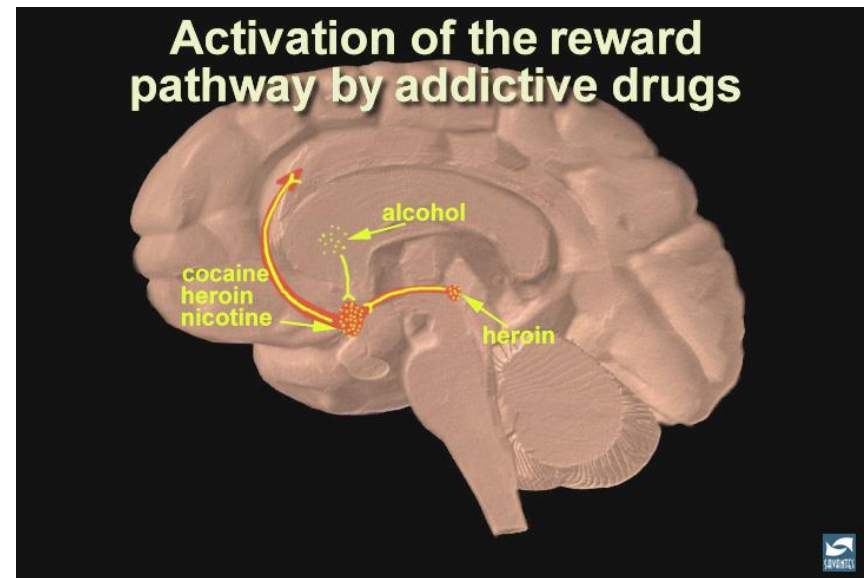


Judgment vs. Reward



“Oops Phenomenon”

- First use to “FEEL GOOD”
- Some continue to compulsively use because of the reinforcing effects (e.g., to “FEEL NORMAL”)
- Changes occur in the “reward system” that promote continued use





Volume and Intensity of Cannabis Use Today

- Different story for heavy users (uses 20 of the past 30 days)
- 22.2% of Americans 12 and over report current use in the past 30 days
- As a proportion of past month users, heavy users increased from 1 in every 9 in 1992 to 1 in every 3 in 2014
- Using population of heavy users has become larger and older
- Bulk of consumption is concentrated among more heavy users



Photo © StevieLea

Cannabis Regulation in the US

- At turn of 20th century, marijuana use was more for medical purposes
- Food and Drug Act of 1906 – required labeling of quantity of THC present
- The Harrison Act did not address marijuana
- As a result of fear of immigration from Mexico, the Marijuana Tax Act of 1937 was introduced to regulate production, distribution, and use of cannabis via Congress's power to tax commerce
- Today ??? CSA has marijuana as a schedule 1, although Marinol is a schedule 3

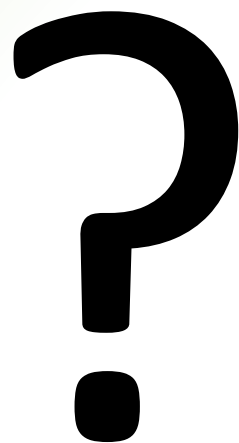
Legal Changes

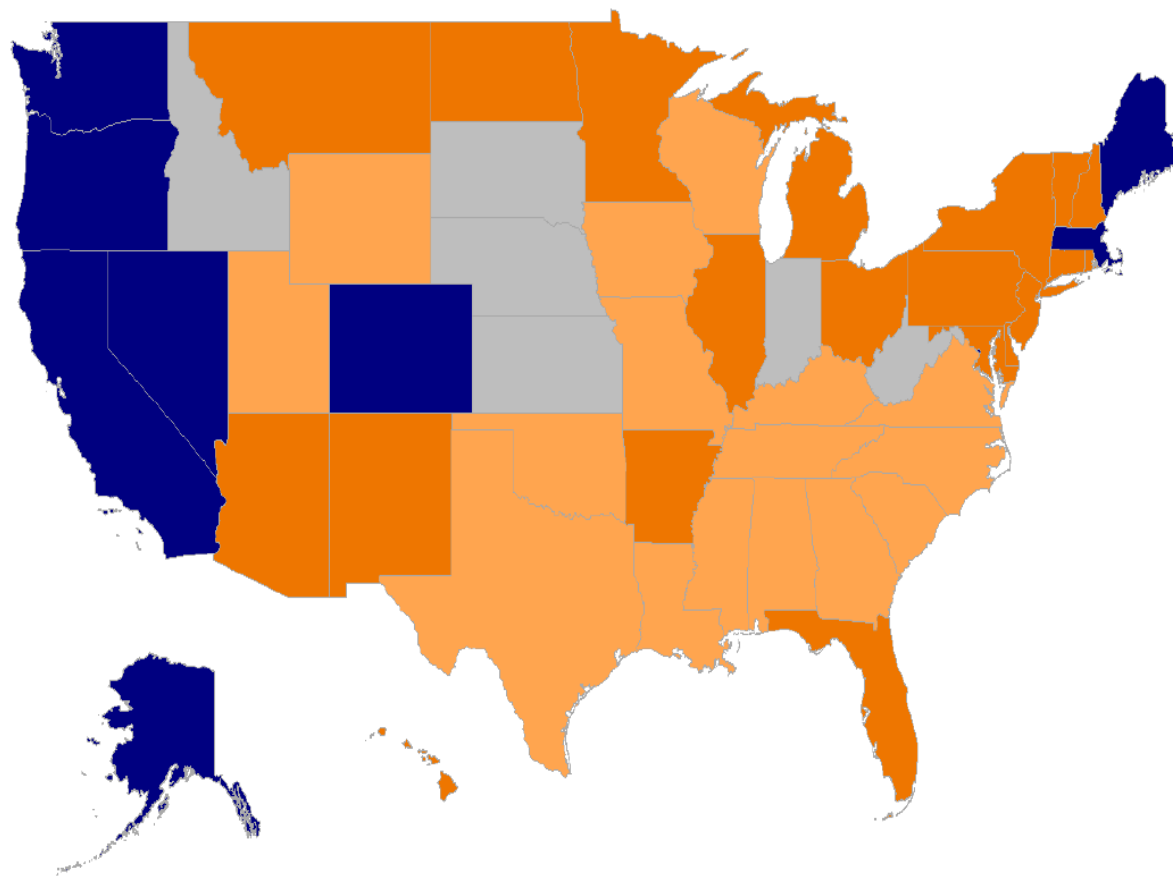
- In past 50 years, legal changes in cannabis policy characterized by
 - 1) Decriminalization laws beginning in 1970's which preceded medical laws and regulated licensed recreational laws
 - 21 states covering 40% of the population have decriminalized possession of small amounts of marijuana
 - Starting in 1996 in California with proposition 15, now 28 states, and D.C. allow limited access to the marijuana flower with 16 states allowing individual access to low THC/high CBD –

State Legal Changes

- Marijuana policy changes occurred secondary to changing public sentiment, not science
- Laws broadly divided into 3 categories
 - 1) loose medical
 - 2) restricted access
 - 3) non-THC
- 28 states categorized as loose or restricted with 16 being categorized as non-THC
- Cancer, HIV/AIDS, MS, glaucoma, and seizures are the most recognized qualifying ailments
- Pain is the most common compliant

Federal Position





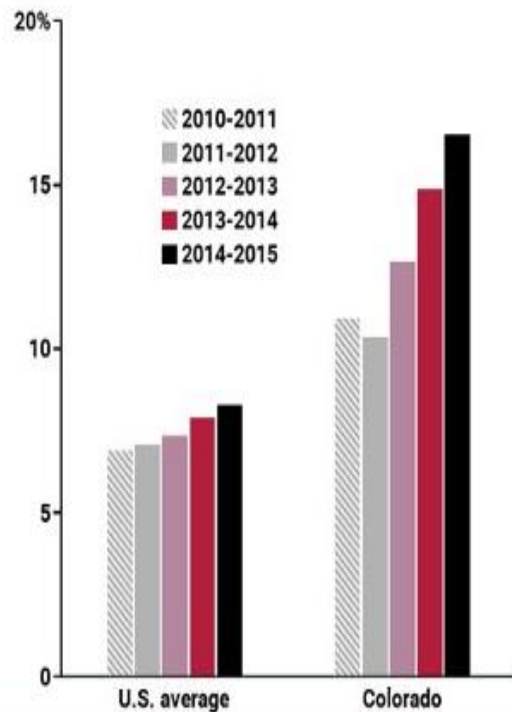
Law

- Limited Medical Access, Low THC/High CBD
- Medical and Recreational Marijuana
- Medical Marijuana
- No Medical Marijuana

FIGURE 3-3 Cannabis laws by state, November 2016.
SOURCE: Adapted from NCSL, 2016.

Since legalization, pot use in Colorado has steadily climbed, well outpacing the national average

Percentage of population ages 12 and up who used marijuana in the past month

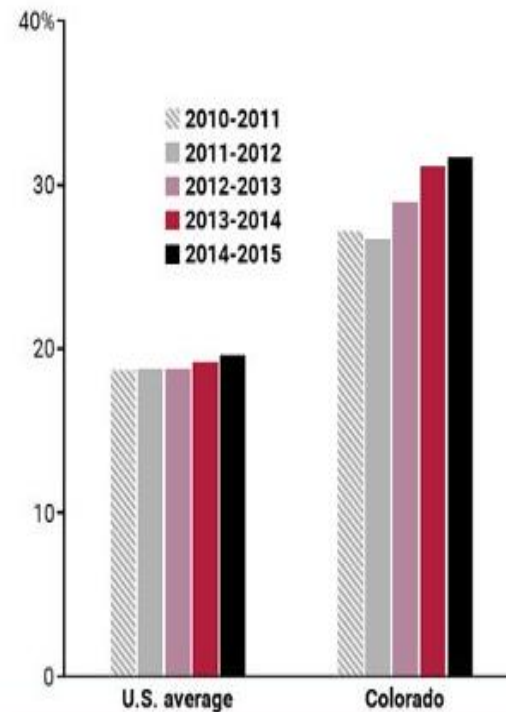


Avg.
change
per period

4.7%

10.8%

Percentage of population ages 18 to 25 who used marijuana in the past month

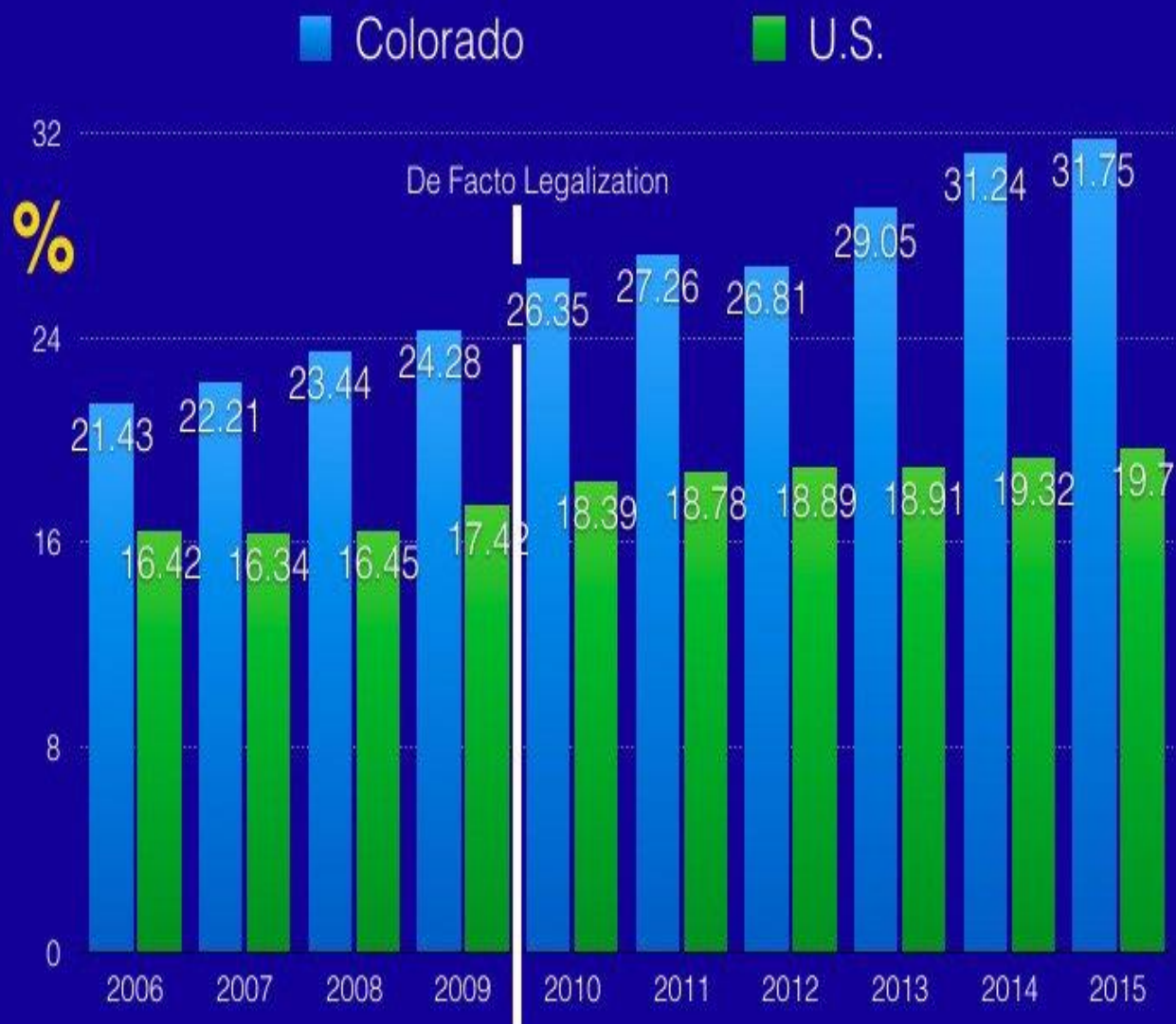


Avg.
change
per period

1.2%

3.9%

% past month mj use 18-24 year olds



National Survey on Drug Use and Health

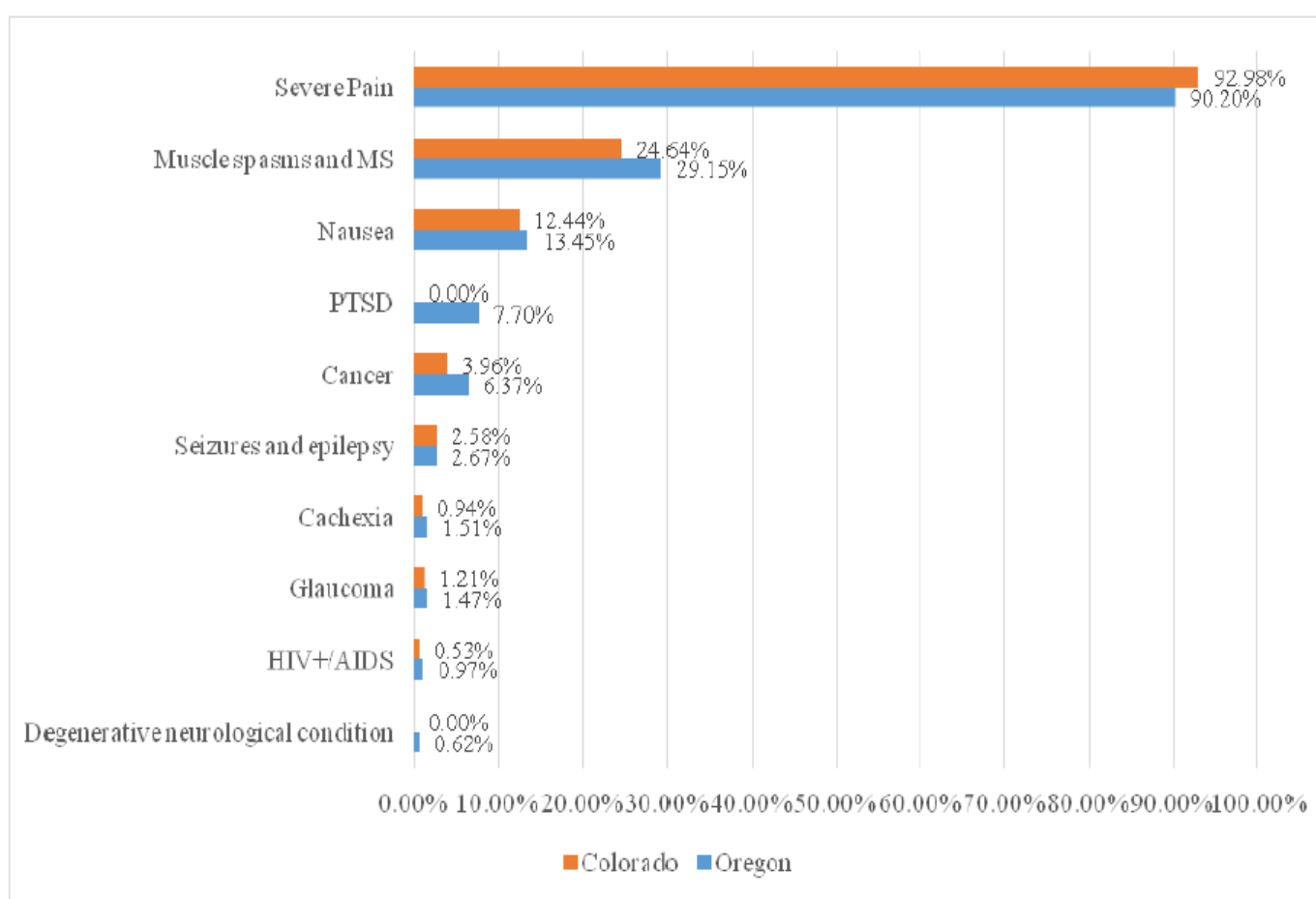


FIGURE 3-4 Number of medical cannabis patients in Colorado and Oregon in July 2016.

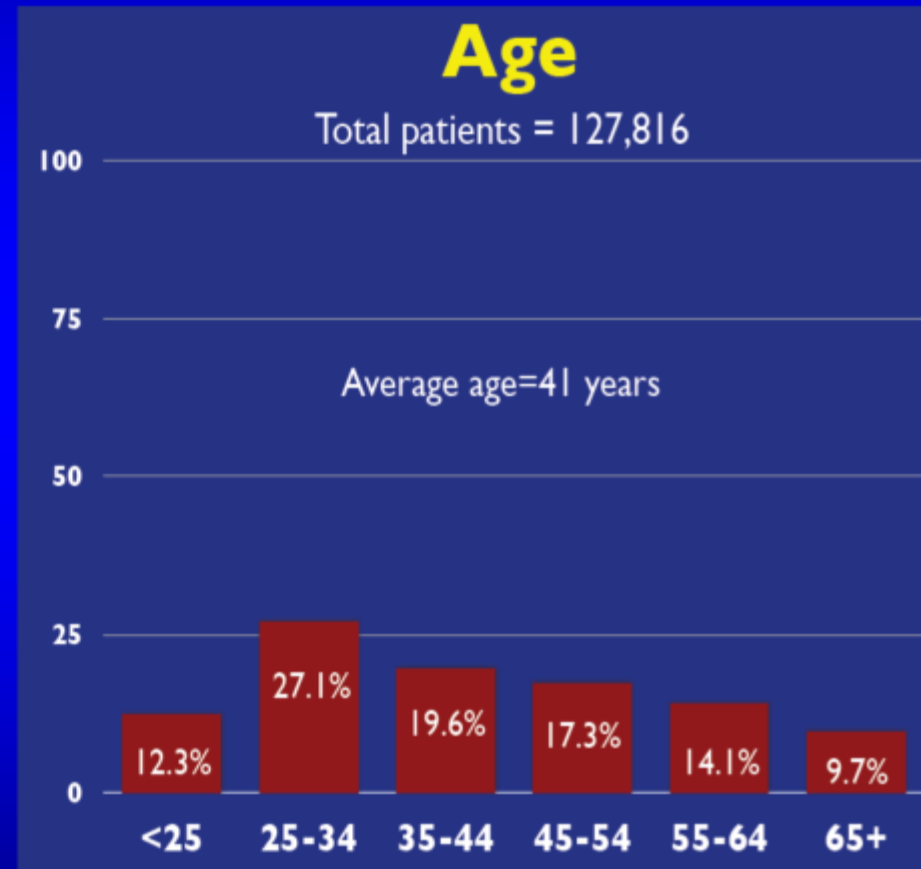
NOTE: Patients may report multiple qualifying ailments

SOURCES: Adapted from CDPHE, 2016; OHA, 2016.

Who uses medical marijuana in Colorado?

Majority of current medical marijuana card holders are...

- Male (68%)
- Under 45 years olds (59%)
- Using for “severe pain” (94%)



Slide and graph courtesy of Sharon Levy MD MPH, and Christian Thurstone MD.

Source: Colorado Department of Public Health and Environment

Public Opinion

- Gallup Poll shows that in 1977, 28% thought “use of cannabis should be made legal”. In 2015, that number grew to 58%!
- Quinnipiac 2016 poll showed 89% of respondents supported medical marijuana – no distinction made

Cannabinoids for Medical Use

- JAMA Systematic Review of Meta-analysis . Whiting et al. 2015.
- 79 trials – nausea and vomiting secondary to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to MS, depression, anxiety and/or sleep disorder, psychosis, glaucoma, or Tourette syndrome.
- Moderate quality evidence for treatment of chronic pain and spasticity. Low evidence for improvement in nausea or vomiting secondary to chemotherapy, weight gain in HIV, sleep disorder, and Tourette syndrome. Increased risk of adverse effects.

Marijuana Study Caveats

- Most of what is known about human pharmacology of smoked MJ comes from experiments with plants containing variable amounts of THC
- Experiments are typically done in laboratory settings with relatively young, medically screened, healthy male volunteers well experienced with effects of MJ
- Studies done with THC cannot necessarily be extrapolated to marijuana smoking because of the over 650 compounds found in *C. sativa*



The National Academies of
SCIENCES • ENGINEERING • MEDICINE

REPORT

The Health Effects of Cannabis and Cannabinoids

THE CURRENT STATE OF EVIDENCE AND
RECOMMENDATIONS FOR RESEARCH

The National Academies Press

Authors

Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda; Board on Population Health and Public Health Practice; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine

PDF Available at:
<http://www.nap.edu/24625>

Cannabis vs Isolated Cannabinoids

- Differences in composition, bioavailability, pharmacokinetics, pharmacodynamics of plant vs isolate cannabinoids.
- Bioavailability cannot be predicted because of differences in smoking or vapor inhalation in individuals and types of delivery systems.
- Must be careful about extrapolating studies of approved cannabinoid formulations to safety or efficacy of smoking cannabis.

Study Approach

- Literature Search: 19,189 articles on health effects of cannabis and cannabinoids between 1999 and 2016
- Systematic Review: Identification, Quality Review
- Primary Literature Review: Identification, Quality Review
- Data Synthesis and Weight of Evidence Assessment

Weight of Evidence Categories

- *Conclusive:*
 - **Strong** evidence from randomized-controlled trials.
 - There are many supportive findings from **good-quality** studies with no credible opposing findings.
 - Firm conclusion can be made.
 - Limitations to the evidence (chance, bias, confounding factors) can be **ruled out** with reasonable confidence.

Weight of Evidence Categories

- *Substantial:*
 - Strong evidence.
 - Several supportive findings from **good-quality** studies with very few or no credible opposing findings.
 - A **firm** conclusion can be made, but minor limitations (chance, bias, confounding factors), **cannot** be ruled out with reasonable confidence.

Weight of Evidence Categories

- *Moderate Evidence:*

- Some evidence.
- Several supportive findings from **good-to-fair quality** studies with very few or no credible opposing findings.
- A **general** conclusion can be made, but limitations (chance, bias, confounding factors), cannot be ruled out with reasonable confidence.

Weight of Evidence Categories

- *Limited Evidence:*

- **Weak** evidence.
- There are supportive finding from **fair-quality** studies or mixed findings with most favoring one conclusion.
- A conclusion can be made but there is **significant uncertainty** due to chance, bias, and confounding factors.

Weight of Evidence Categories

- *No or Insufficient Evidence to Support the Association:*
 - There is no or insufficient evidence.
 - There may be mixed findings or a single poor study or a health endpoint has not been studied.
 - No conclusion can be made because of substantial uncertainty.

Therapeutic Effects of Cannabis: Key Points

- Illnesses studied include:

- Chronic pain
- Chemotherapy-induced nausea & vomiting
- IBS
- Spasticity r/t MS
- ALS
- Parkinson's Disease
- Alzheimer's/ Dementia
- TBI/ Spinal Cord Injury
- Anxiety
- Sleep Disorders
- Schizophrenia
- Cancer
- Appetite and weight loss
- Epilepsy
- Tourette's Syndrome
- Huntington's Disease
- Dystonia
- Glaucoma
- Addiction
- Depression
- PTSD

PREVALENCE OF USE, REGULATION, AND CURRENT POLICY

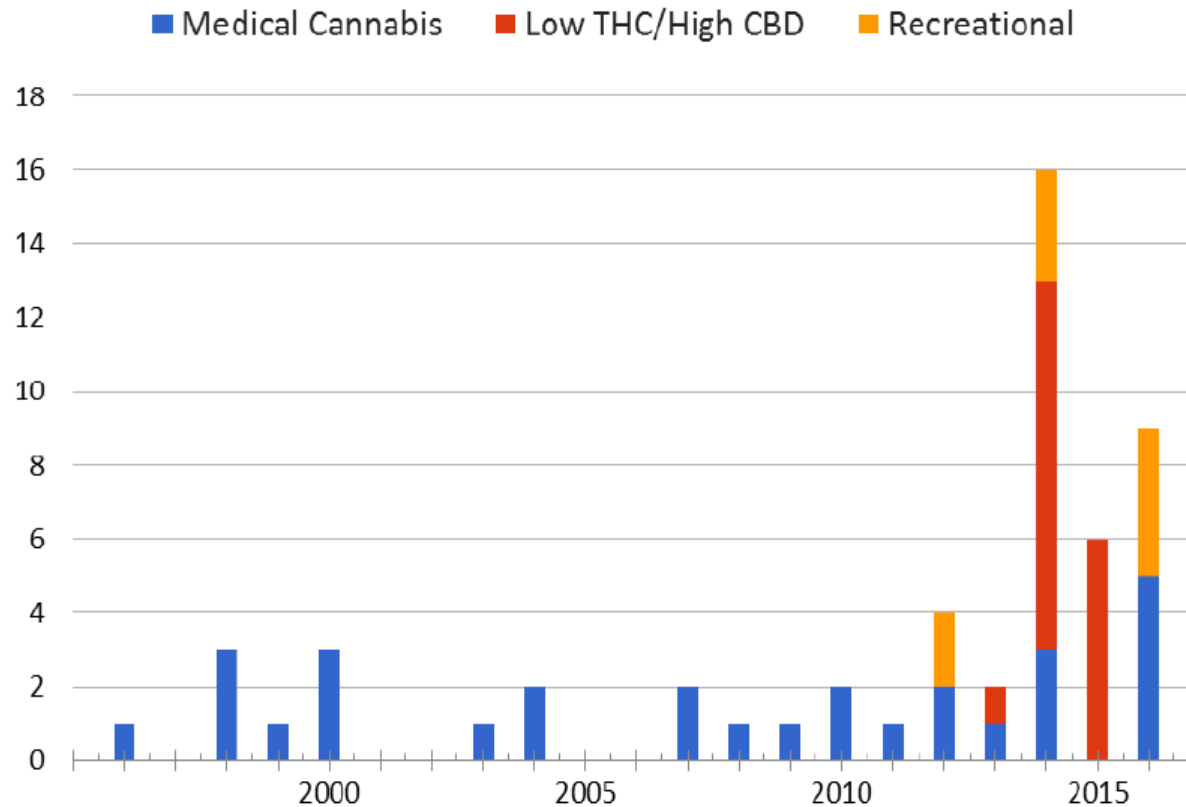


FIGURE 3-2 Passage of state cannabis laws (figure includes Washington DC).
SOURCE: Adapted from NCSL, 2016.

Therapeutic Effects of Cannabis: Key Points

- In adults with chemotherapy-induced nausea & vomiting, oral cannabinoids are effective anti-emetics. Evidence is conclusive
- In adults with chronic pain, cannabis treated patients were more likely to experience a clinically significant reduction in pain symptoms. Better results with neuropathic pain. Evidence is substantial
- In adults with MS-related spasticity, short-term use of oral cannabinoids improves spasticity symptoms. Evidence is substantial
- For these conditions, results were **modest**. For all other conditions, there is inadequate information to assess effects. This includes disorders that cannabinoids have been used extensively

Health Effects on Cardio-metabolic Risk

- The evidence is unclear as to whether and how cannabis use is associated with heart attack, stroke and diabetes.
- There is limited evidence of a statistical association between cannabis use and ischemic stroke or subarachnoid hemorrhage.
- There is limited evidence of a statistical association between cannabis use and increased risk of prediabetes (but not diabetes).

Health Effects of Cannabis and Cannabinoids on Cancer

- The evidence suggests that smoking cannabis does not increase the risk for certain cancers (lung, head and neck) in adults.
- There is modest evidence that cannabis use is associated with one sub-type of testicular cancer (non-seminoma-type testicular germ cell tumors)
- There is minimal evidence that parental cannabis use during pregnancy is associated with greater cancer risk in offspring.

Health Effects on Respiratory Disease

- There is substantial evidence of a statistical association between long-term cannabis smoking and worse respiratory symptoms and more frequent chronic bronchitis episodes.
- Quitting cannabis smoking is likely to reduce chronic cough and phlegm production.
- It is unclear whether cannabis use is associated with COPD, asthma, or worsened lung function.

Health Effects on Immunity

- There exists a paucity of data on the effects of cannabis or cannabinoid-based therapeutics on the human immune system.
- There is insufficient data to draw overarching conclusions concerning the effects of cannabis smoke or cannabinoids on immune competence.
- There is limited evidence to suggest that regular exposure to cannabis smoke may have anti-inflammatory activity.
- There is insufficient evidence to support or refute a statistical association between cannabis or cannabinoid use and adverse effects on immune status in persons with HIV.

Cannabis Use in Immunocompromised Host

Consensus guidelines suggest that immunocompromised patients avoid cannabis use due to its potential for increasing the risk of *Apergillus* infection.

Effects on Injury and Death

- Cannabis use prior to driving increases the risk of being involved in a MVA. The evidence is substantial.
- In states where cannabis use is legal, there is increased risk of unintentional cannabis overdose injuries among children.
- It is unclear whether and how cannabis use is associated with all-cause mortality or with occupational injury.

Prenatal, Perinatal and Neonatal Exposure to Cannabis

- Smoking cannabis during pregnancy is linked to lower birth weight in the offspring. Evidence is substantial.
- The relationship between smoking cannabis during pregnancy and other pregnancy and childhood outcomes is unclear.

The Psychosocial Effects of Cannabis

- Recent cannabis use impairs the performance in cognitive domains of learning, memory and attention. Recent use may be defined as cannabis use within 24 hours of evaluation.
- A limited number of studies suggest that there are impairments in cognitive domains of learning, memory, and attention in individuals who have stopped smoking cannabis.
- Cannabis use during adolescence is related to impairments in subsequent academic achievement and education, employment and income, and social relationships and social roles.

Development Implications Among Adolescents

- Data continues to indicate that early age of initiation tends to be connected to greater deficits in cognitive functioning during adulthood.
- Brain does not complete development until approximately age 25. Exposure to a potential neurotoxic agent during this critical development could have lasting impact on cognition and maturation.
- Increasing potency of Cannabinoid products.

Effects on Mental Health

- Cannabis use is likely to increase the risk of developing schizophrenia and other psychoses; the higher the use the greater the risk.
- In individuals with schizophrenia and other psychoses, a history of cannabis use may be linked to better performance on learning and memory tasks.
- Cannabis use does not appear to increase the likelihood of developing anxiety, and posttraumatic stress disorder (Small increased risk of depressive disorders).
- For individuals diagnosed with bipolar disorders, near daily cannabis use may be linked to greater symptoms of bipolar disorder than non-users.
- Heavy cannabis users are more likely to report thoughts of suicide (and have more attempts) than non-users. Higher rates of suicide completion among users.
- Regular cannabis use is likely to increase the risk for developing social anxiety disorder.

Co-Morbidity in Substance Abuse and Mental Illness

- Substance use may be a potential risk actor for developing mental health disorders.
- Mental illness may be a potential risk factor for developing a substance use disorder.
- An overlap in predisposing risk factors (ex: genetic vulnerability, environment) may contribute to the development of both substance abuse and a mental health disorder.

Problem Cannabis Use

- Substantial evidence to show greater frequency of cannabis use increased the likelihood of developing problem cannabis use,
- Substantial evidence that initiating cannabis use at a younger age increased the likelihood of developing problem cannabis use.

Risk Factors for Problem Cannabis Use

- Anxiety → Limited
- Depression → Moderate
- ADHD → Does not appear to be (stimulant use doesn't increase risk)
- Male gender → Moderate (higher with cigarette use)
- Use with other agents → Moderate

Cannabis and Other SUDs

- Cannabis use is likely to increase the risk for developing substance dependence (other than cannabis use disorder)

Relation between Marijuana & other Drug Use

- Early age of onset is a major predictor both of continued frequent marijuana use & of likelihood of using other drugs (Denenhardt, et al. 2001, Lynsky, et al. 2003)
- The increased potency of marijuana may make the brain less responsive to endogenous cannabinoids. This may be especially marked in the still developing adolescent brain
- Combination of earlier onset & stronger marijuana may increase anxiety & apathy in teens & make other drug use more attractive
- Twin studies found early marijuana users had increased rates of other drug use and problems later on; odds of other drug use ranged from 2.1-5.2 times higher

Challenges and Barriers

There are several challenges and barriers in conduction cannabis and cannabinoid research, including:

- There are specific regulatory barriers, including the classification of cannabis as a Schedule I substance, that impede the advancement of cannabis and cannabinoid research
- It is often difficult for researchers to gain access to the quantity, quality, and type of cannabis product necessary to address specific research questions on the health effects of cannabis use
- A diverse network of funders is needed to support cannabis and cannabinoid research that explores the beneficial and harmful health effects of cannabis use
- To develop conclusive evidence for the effects of cannabis use on short- and long-term health outcomes, improvements and standardization in research methodology (including those used in controlled trials and observations studies) are needed

Cannabis Use and Opioids

Olfson et al. American Journal of Psychiatry. 2018

- Cannabis use increased risk of developing opiate use disorder


National Epidemiological Survey on Alcohol and Related Conditions (NESARC)

- Data showed MJ users greater than 2x more likely to meet criteria for OUD

A number of recent papers have suggested MJ may reduce risk of opiate overdose. However that this may be as much related to other factors such as the use of Narcan rescue in “progressive” states as opposed to MJ use.

NASEM Recommendations to Support and Improve the Cannabis Research Agenda

- Recommendation I: To develop a comprehensive evidence base on the short- and long-term health effects of cannabis use.
- Recommendation II: To promote the development of conclusive evidence on the short- and long-term health effects of cannabis use.
- Recommendation III: To ensure that sufficient data are available to inform research on the short- and long-term health effects of cannabis use.
- Recommendation IV: Funding should be given to create a committee of experts tasked to produce an objective and evidence-based report that fully characterizes the impacts of regulatory barriers to cannabis research and that proposes strategies for supporting development of the resources and infrastructure necessary to conduct a comprehensive cannabis research agenda.



Dude, we totally
forgot our slogan.

American Medical Marijuana Assn.

INFINITY

POST

Conclusions

- There is evidence of efficacy for cannabinoids in treatment of certain medical conditions (such as neuropathic pain, MS, spasticity, nausea/vomiting secondary to chemotherapy). Although these efficacies are not superior to existing approved medication, reversal may squander U.S. opportunity to dominate multibillion-dollar global market.
- There are numerous significant risks associated with smoked marijuana, including addiction, psychiatric disorders, motor vehicle accidents, cognitive deficits, etc.
- Movement to revive cannabis as a medicine is driven by many factors other than science.

Source: Market Watch



**“Ok, I’m going to prescribe marijuana.
But you have to promise not to enjoy it.”**

Thank you

