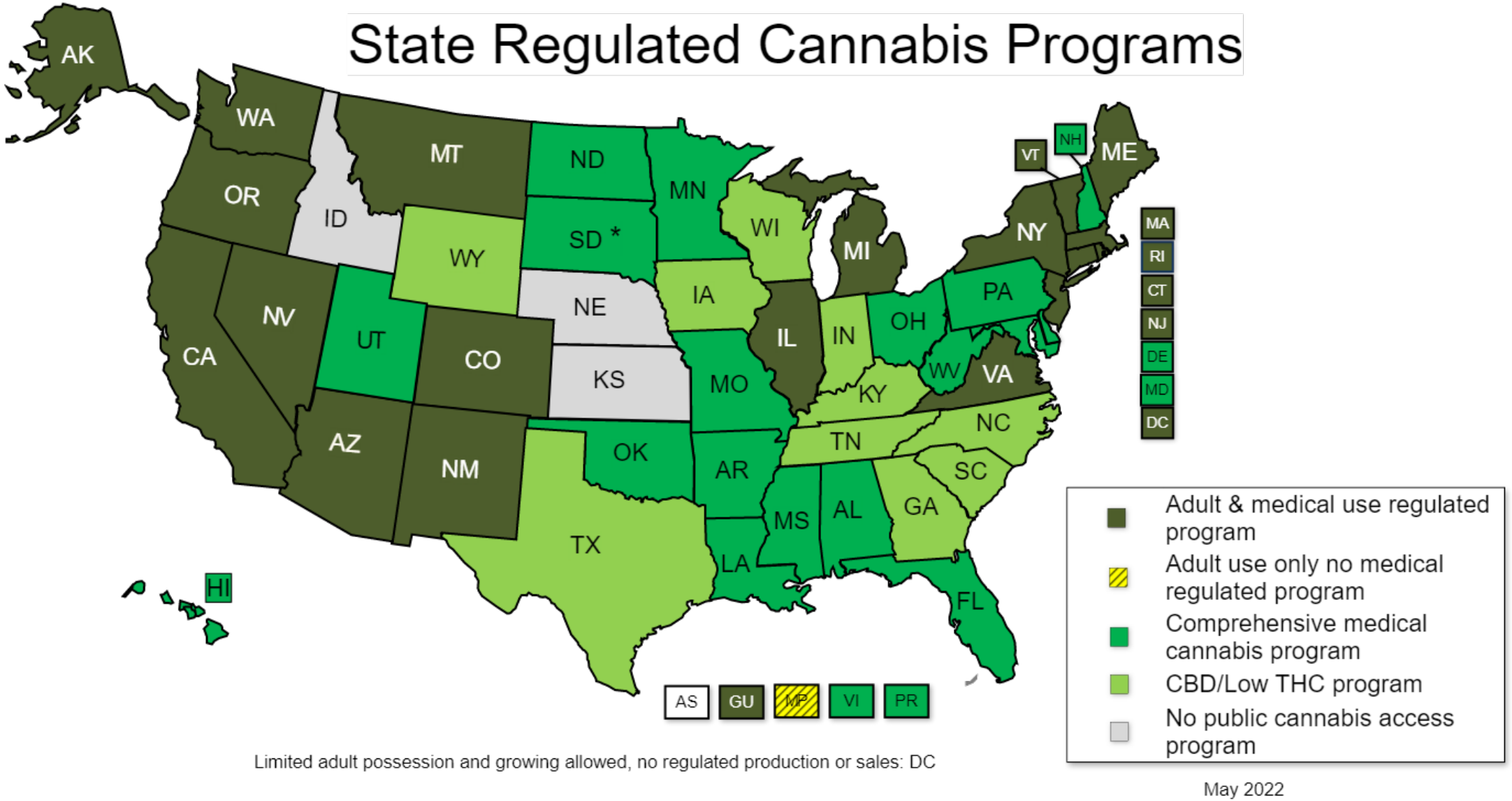
Medical Marijuana

Delving into the Weeds

Kathy Collins PharmD, BCPS
Senior Clinical Pharmacist
Craig Hospital
Englewood Colorado

Disclosure

- Dr. Collins has no financial or non-financial conflicts of interest related to this activity.
- Non-FDA approved products and indications will be discussed during this presentation.


State Regulated Cannabis Programs
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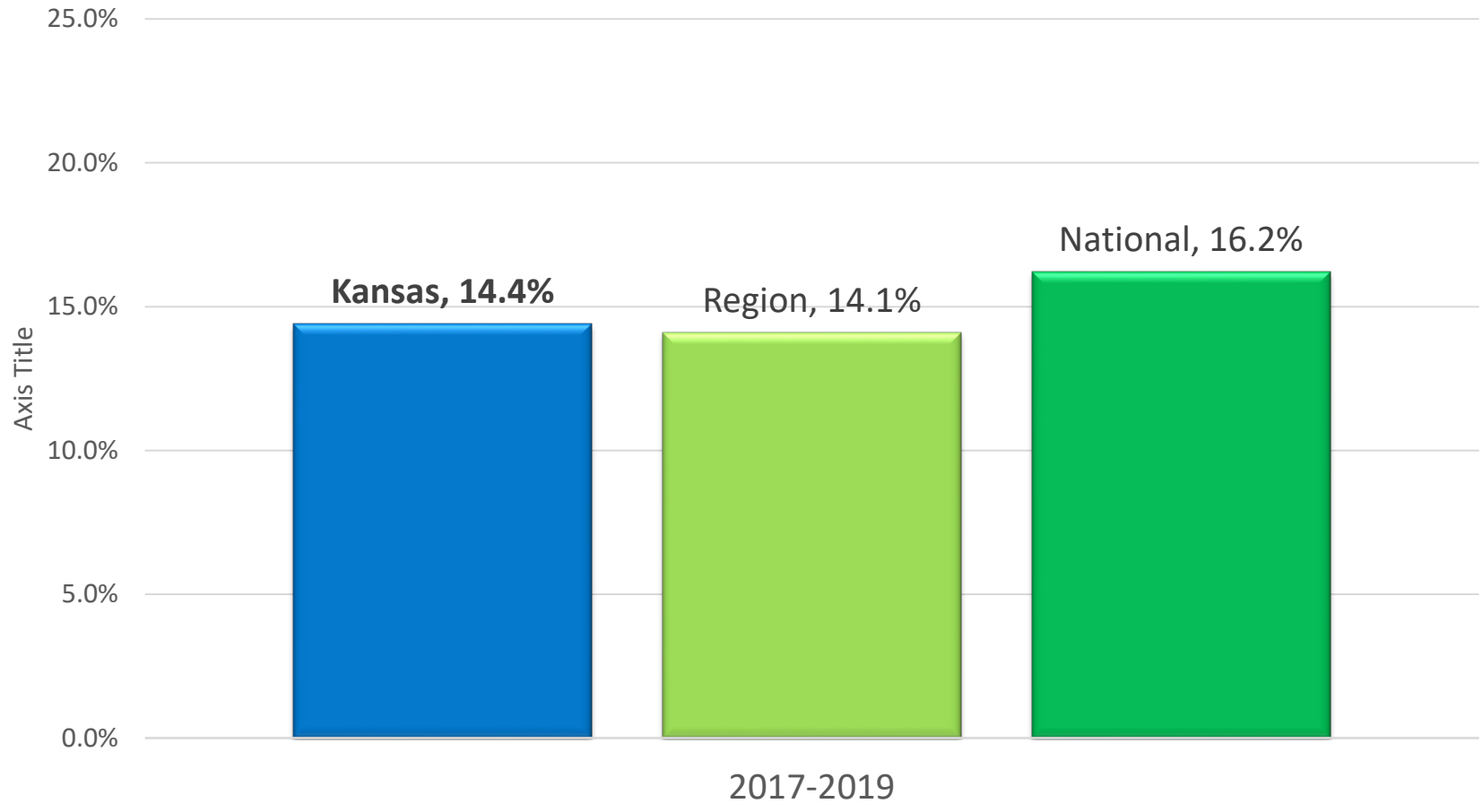
Adult & medical use regulated program
Adult use only no medical regulated program
Comprehensive medical cannabis program
CBD/Low THC program
No public cannabis access program
Limited adult possession and growing allowed, no regulated production or sales: DC
May 2022

NCSL 2022

Past-Year Marijuana Use among People Aged 12 and Older



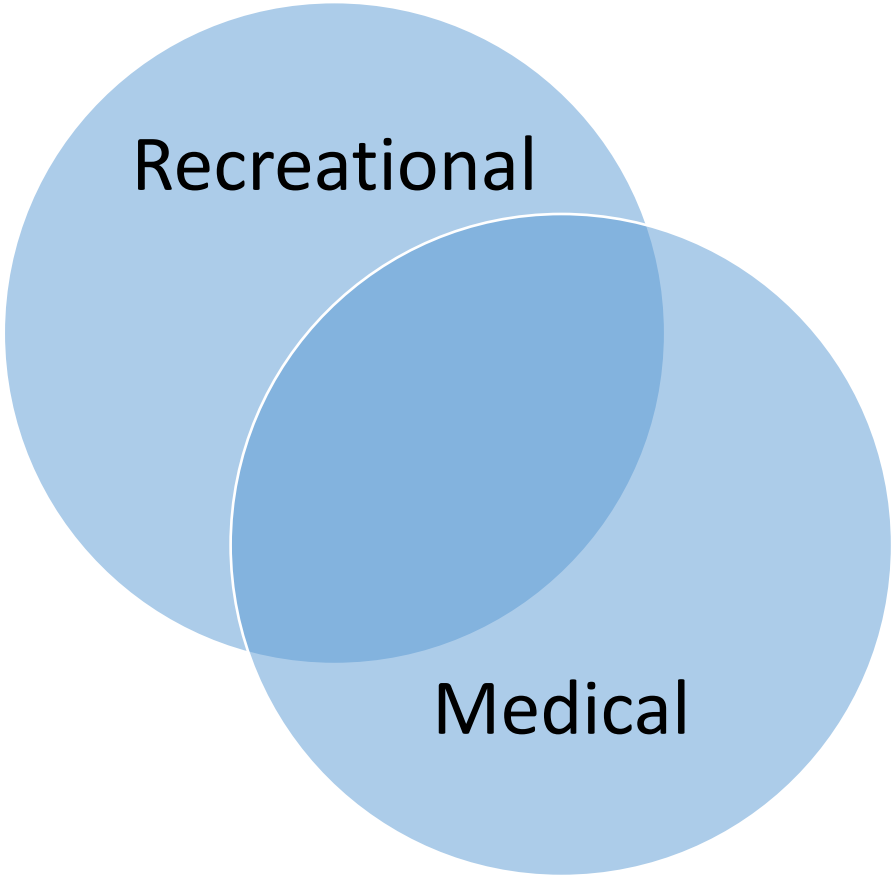
Substance Abuse and Mental Health Services Administration. Behavioral Health Barometer: Kansas, Volume 6: Indicators as measured through the 2019 National Survey on Drug Use and Health and the National Survey of Substance Abuse Treatment Services. HHS Publication No. SMA–20–Baro–19–KS. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2020.

Recreational Versus Medical Use

Risk vs. Risk

=

Risk vs. Benefit



Objectives

- Describe how different types of marijuana products may impact a patient.
- Summarize the available evidence using marijuana for therapeutic purposes.
- List at least three specific safety concerns for the use of marijuana.

Marijuana Basics

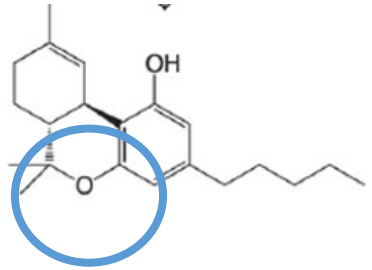
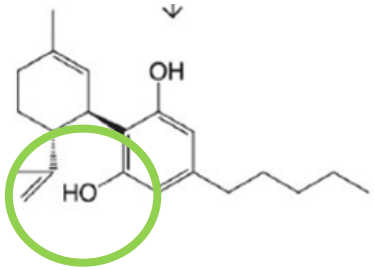
Cannabis

- Contains over 400 compounds
- Over 100 cannabinoids
  - Δ^9 -tetrahydrocannabinol - THC
  - Cannabidiol – CBD
- Over 200 terpenes
- Sterols
- Thiols
- Flavonoids
- Phenols
- Fibrous material

Cannabis Plant

Picture: Creative Commons Blausen 0159 Cannabis Plant.png

Comparing THC and CBD

	THC	CBD
Source	*Cannabis sativa*	*Cannabis sativa*
Molecular Formula	$C_{21}H_{30}O_2$	$C_{21}H_{30}O_2$
Chemical Structure	 Contains **cyclic** ring	 Contains **hydroxyl** group

NASEM 2017. doi: 10.17226/24625.

THC Activity

- Primarily at CB1 receptors in the brain
- Abundant in parts of brain that regulate movement, coordination, learning and memory, higher cognitive functions such as judgement and pleasure

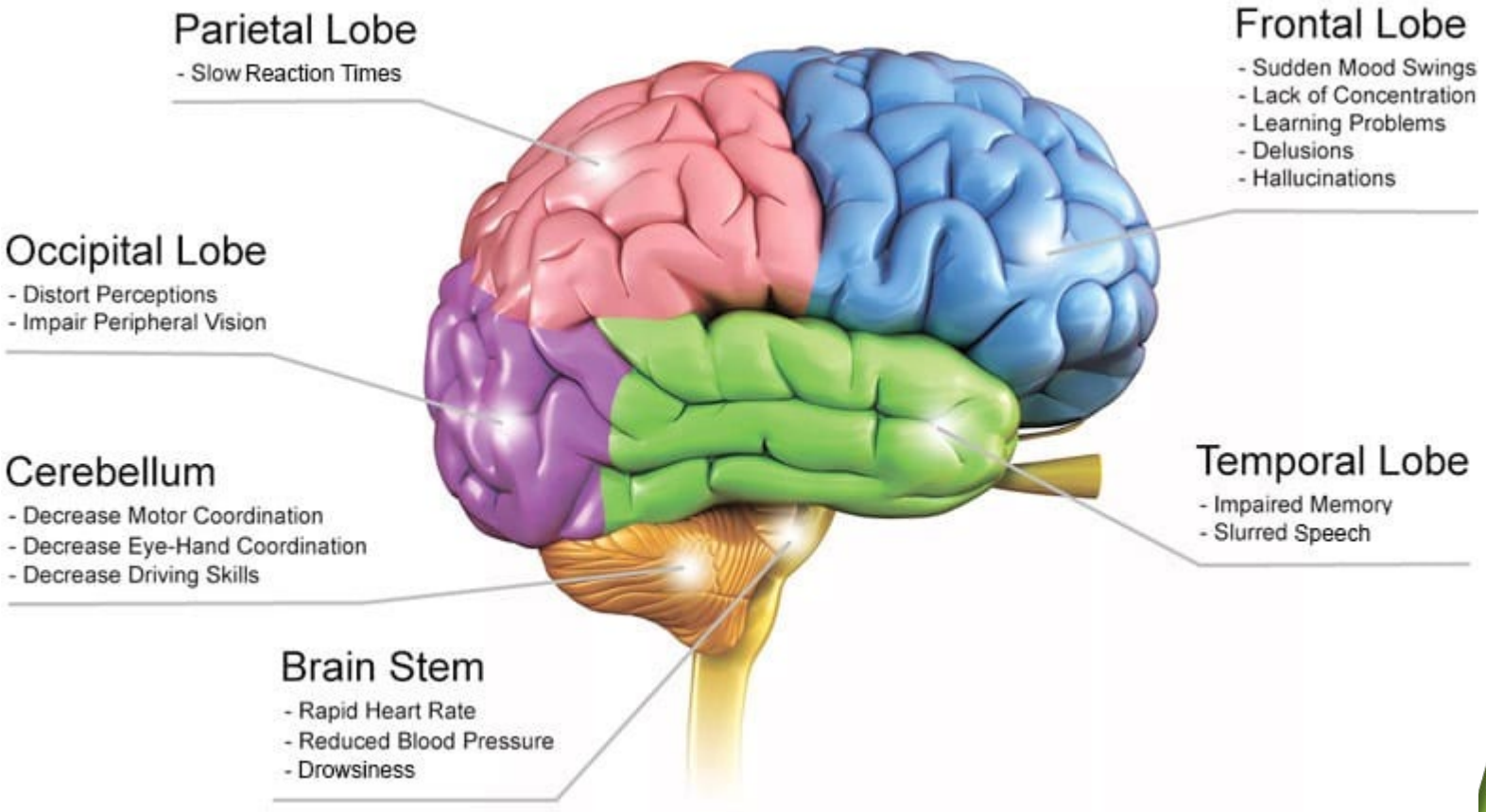
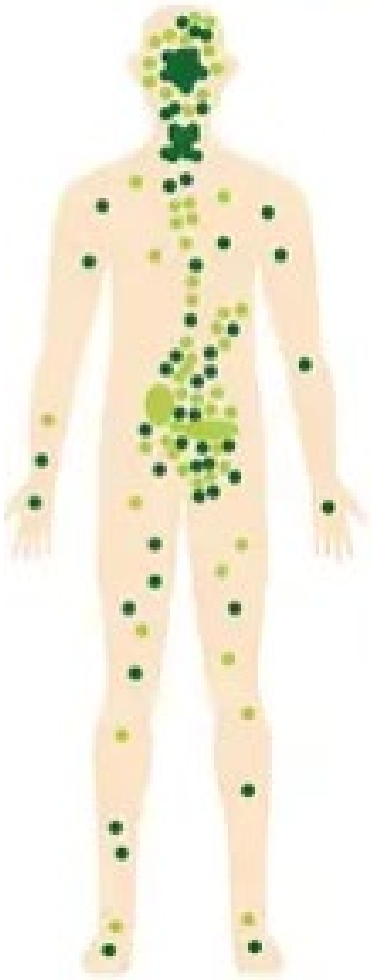


Image: https://www.rtor.org/2019/09/06/worst-side-effects-of-medical-marijuana/

CBD Activity

Receptor	Action	Possible Effect
CB1	Direct antagonist and negative modulator antagonist	Attenuation of impaired learning, memory, and psychosis effects inducted by THC
CB2	Antagonist and inverse agonist	Anti-inflammatory effects
GPR55	Antagonist	Possible vasodilation, anti-inflammatory effects
5HT-1A	Agonist	May have antidepressant and anxiolytic effects
TRPV-1	Agonist	May have a role in pain responses and regulation of body temperatures
Adenosine A2A	Enhanced adenosine concentrations	Pain and anti-inflammatory effects
FAAH enzyme	Inhibition	Decreased breakdown of anandamide and intracellular transport of THC



National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research.* Washington, DC: The National Academies Press. doi: 10.17226/24625.

Hemp

- Federal legal limit of 0.3% THC

Marijuana Effects
Dependent on Formulation

- THC versus CBD
- Concentration of Cannabinoid
- Plant Strain

Marijuana Formulations

Current FDA Approved Cannabis Products

- THC
  - Dronabinol (Marinol®)
    - Capsules (Schedule III)
    - Oral solution (Schedule II)
  - Nabilone (Cesamet®)
    - Capsules (Schedule II)
- CBD
  - Cannabidiol (Epidiolex®)
    - Oral solution (Schedule V)

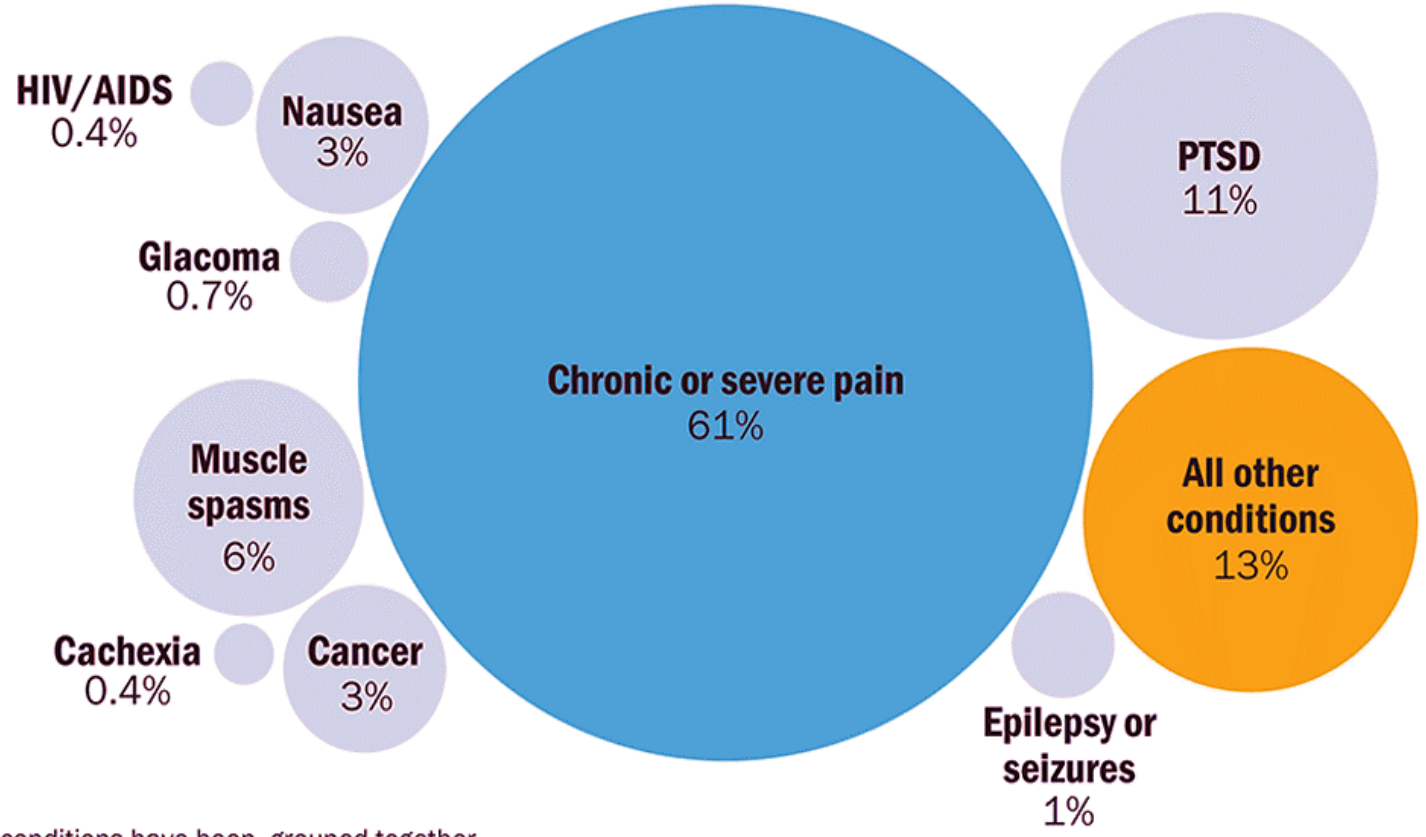
Marijuana Testing

Marijuana Detection Times

Blood & Saliva	A few hours
Urine	
One time use	Up to 13 days
Regular use	Up to 45 days
Heavy use	Up to 90 days
Hair	Up to 90 days

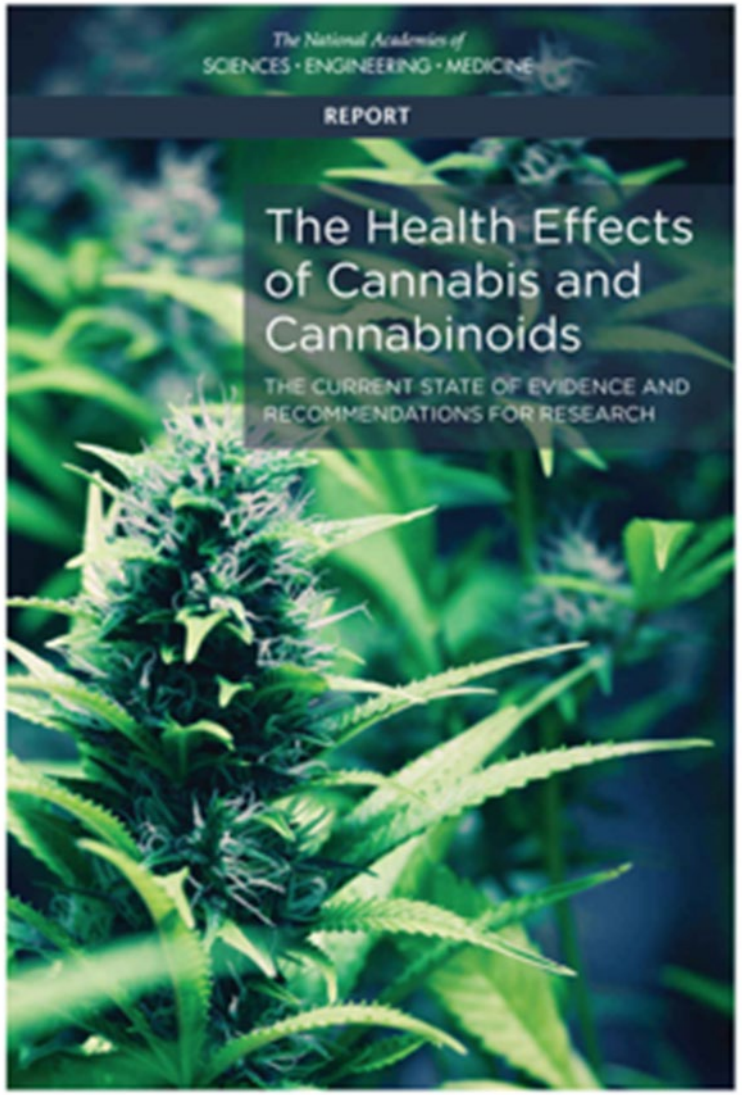
Marijuana Efficacy

Medical Marijuana Patients by Condition



Note: Similar conditions have been grouped together.
Some patients may fall into more than one category.

Source: Arizona, Arkansas, Colorado, Delaware, Illinois, Michigan, Minnesota, Missouri, Montana, Nevada, New Hampshire, New Mexico, Oregon, Rhode Island and Utah state MMJ programs.



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

A Report of

The National Academies of

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National Academies: Health Effects of Cannabis

- **No or insufficient evidence** to support or refute that cannabinoids are effective for…
  - cancer-associated anorexia cachexia syndrome and anorexia nervosa
  - cancers, including glioma
  - irritable bowel syndrome
  - epilepsy
  - spasticity in patients with paralysis due to spinal cord injury
  - chorea and certain neuropsychiatric symptoms - Huntington's disease
  - symptoms associated with amyotrophic lateral sclerosis (ALS)
  - Parkinson's disease or levodopa-induced dyskinesia
  - dystonia
  - treatment for mental health outcomes in individuals with schizophrenia or schizophreniform psychosis
  - achieving abstinence in the use of addictive substances

National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research.* Washington, DC: The National Academies Press. doi: 10.17226/24625.

National Academies: Health Effects of Cannabis

CONCLUSION 4-1

There is substantial evidence that cannabis is an effective treatment for chronic pain in adults.

Cannabinoids for Medical Use
Chronic Pain

- Results
  - Reduction in pain of at least 30%
    - **37% versus 31% placebo** (OR 1.41 95% CI, 0.99-2.00)
  - Reduction in pain on 10 point numerical scale
    - **-0.46** (95% CI, -0.80 to -0.11)
- Limitations
  - Small, short, difficult to blind studies
- Conclusion
  - Cannabis may provide pain relief in the short term

Whiting PF et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015 Jun 23-30;313(24):2456-73

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Medical Cannabis Effects on Opioid Use

- Retrospective study of 77 medical cannabis patients (intractable pain)
  - 45% female; avg 54 years

Primary Outcome: amount of opioid use

- Milligram morphine equivalents

	Baseline (mg)	6 months (mg)	P-value
Morphine equivalents, median (IQR); n=74	105 (43.75 to 155.63)	65.9 (28.13 to 150)	P = 0.001
Morphine equivalents, average ± SD; n=74	140.64 ± 184.64	103.1 ± 115.31	P = 0.009

- Patients using cannabis for intractable pain may have experienced a significant reduction in opioid use.

O'Connell M, Sandgren M, Frantzen L, et al. Medical cannabis: effects on opioid and benzodiazepine requirements for pain control. Ann Pharmacother. 2019;53(11):1081-6.

National Academies: Health Effects of Cannabis

CONCLUSION 4-7

4-7(a) There is **substantial evidence** that oral cannabinoids are an effective treatment for improving patient-reported **multiple sclerosis spasticity** symptoms, but limited evidence for an effect on clinician-measured spasticity.

Cannabis for Spasticity Due to MS

- Systematic review of cloned THC/CBD product used outside the U.S. (Sativex®)
- Results
  - Improved Ashworth scale compared to placebo
    - -12% (95% CI -.24 to 0.01)
  - Improved spasticity using a numerical scale
    - 0.76 (95% CI -1.38 to -0.14)
- Conclusion
  - Cannabis may provide a modest subjective improvement in spasticity due to MS.

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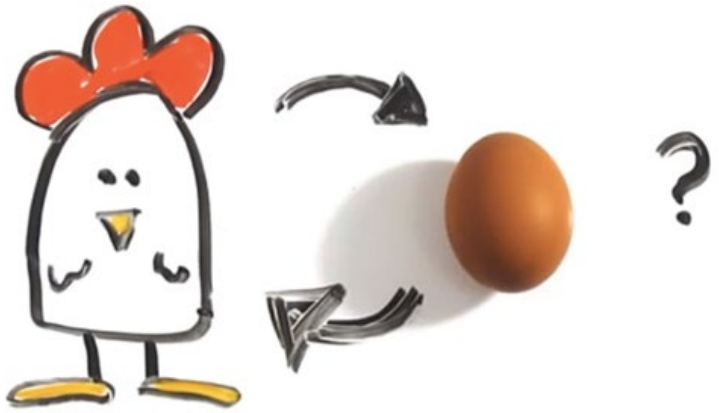
Sleep Abnormalities with Cannabis: A Comprehensive Review

- There is an initial improvement in **subjective** sleep complaints.
- **Objective** measurements have shown both positive and negative effects.
- Tolerance to beneficial effects occurs in chronic users.
- Prominent negative effects on sleep occur during withdrawal.

Angarita GA, et al. Sleep abnormalities associated with alcohol, cannabis, cocaine, and opiate use: a comprehensive review. Addict Sci Clin Pract. 2016 Apr 26;11(1):9.

Cannabinoids and Post-traumatic Stress Disorder (PTSD)

- High prevalence of cannabis use among PTSD patients.
- Higher levels of PTSD symptoms with increased marijuana use.
- Small studies suggest possible benefit



Study	n	cannabinoid	Outcome
Elms (2019	**11**	CBD	“decreased symptoms at 8 weeks”
Roitman (2014)	**10**	THC - nabilone	“improvement in global symptom severity, frequency of nightmares and hyperarousal symptoms”
Fraser (2009)	**47**	THC - nabilone	“lessening in nightmare severity”

Mizrachi Zer-Aviv T, et al. Cannabinoids and post-traumatic stress disorder: clinical and preclinical evidence for treatment and prevention. Behav Pharmacol. 2016 Oct;27(7):561-9.
Orsolini, et al. Use of Medicinal Cannabis and synthetic Cannabinoids in PTSD. Medicina 2019.

Safety Concerns

Cannabis Adverse Effects

Short term	**dizziness** **euphoria** **anxiety** **↓ psychomotor function** **cognitive impairment** **memory impairment** **sedation** **hallucinations** **↑ heart rate,** **wt gain**	**cardiac arrhythmias/MI** **↓ pulmonary function** **vision disturbances** **↓blood sugars** **MS relapse** **↑ risk of bleed** **vomiting** **urinary tract infections** **withdrawal**
Long term	addiction dependence withdrawal depression memory impairment cognition decline ↓ pulmonary function Cannabis Hyperemesis Syndrome	worsening symptoms of schizophrenia MS relapse relationship problems lower life satisfaction less academic success less career success

Wang T, Collet J, Shapiro S, et al. Adverse effects of medical cannabinoids: a systemic review. CMAJ 2008;178:1669-78]

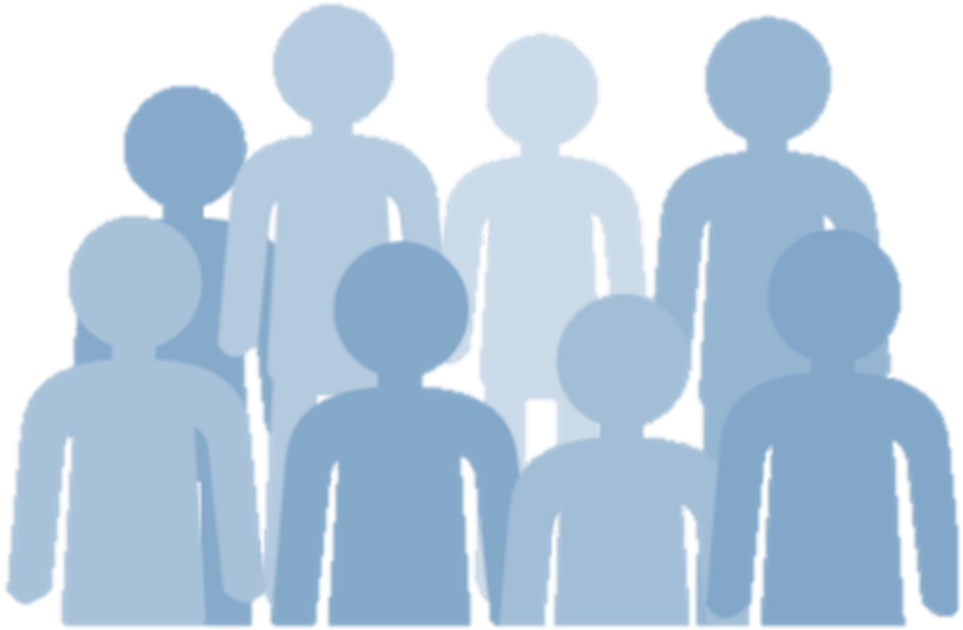
Adverse Effects of Medical Cannabinoids: a Systematic Review

- Review of cannabis studies for adverse drug reactions (ADRs)
  - 23 randomized controlled trials
  - 4779 adverse events reviewed
- Majority of ADRs were non-serious (96.6%)
- Rate of the non-serious events was higher with medical use versus controls (RR 1.86 95% CI 1.57-2.21)

Wang T, Collet J, Shapiro S, et al. Adverse effects of medical cannabinoids: a systemic review. *CMAJ* 2008;178:1669-78]

Patient Safety

- Focus on patient specific factors
  - Drug interactions
  - Comorbid conditions
  - High risk populations



Patient Safety - Drug Interactions

- Many significant interactions including with high risk medications
- Majority of interactions are additive Central Nervous System Depression
  - Systemic >>>Topical
  - Dose dependent
  - Frequency dependent
  - Duration dependent

Image: https://illustoon.com/?dl=4281

Patient Safety - Comorbid conditions Mental Health Conditions

- Acute psychotic symptoms during intoxication
- Decreased memory
  - Worse with increasing years of regular use
- Impaired cognition
  - With regular use impairment lasts up to 2 days after last use

Volkow N et al. *NEJM (2014)*

Patient Safety - Comorbid conditions Mental Health Conditions

- Regular marijuana use is associated with increased risk of anxiety and depression
  - Weekly or more frequent cannabis use in teenagers predicted an approximately twofold increase in risk for later depression and anxiety (OR 1.9, CI 1.1 to 3.3) after adjustment for potential baseline confounders

- Dependence may occur with increased risk with more frequent use
  - Dependence - average 9% lifetime dependence
  - Heavy users - 50%

Patton GC et al. BMJ (2002)
Volkow N et al. NEJM (2014
Wang T et al. CMAJ (2008)

Patient Safety - Comorbid conditions Mental Health Conditions

- Meta-analysis of the association between the level of cannabis use and risk of psychosis. (Marconi 2016)
  - 18 studies
  - 66,816 individuals
- Higher levels of cannabis use were associated with increased risk for psychosis in all the included studies.
- Risk of schizophrenia and other psychosis-related outcomes among the heaviest cannabis users compared to the nonusers OR of 3.90 (95% CI 2.84 to 5.34)

Marconi A Schizophr Bull (2016)
Volkow N et al. NEJM (2014

Patient Safety - High Risk Populations Adolescence

- **38%** of high school students report having used marijuana in their life
- **23%** in the past 30 days
- **71%** of high school seniors do not view regular marijuana smoking as being very harmful

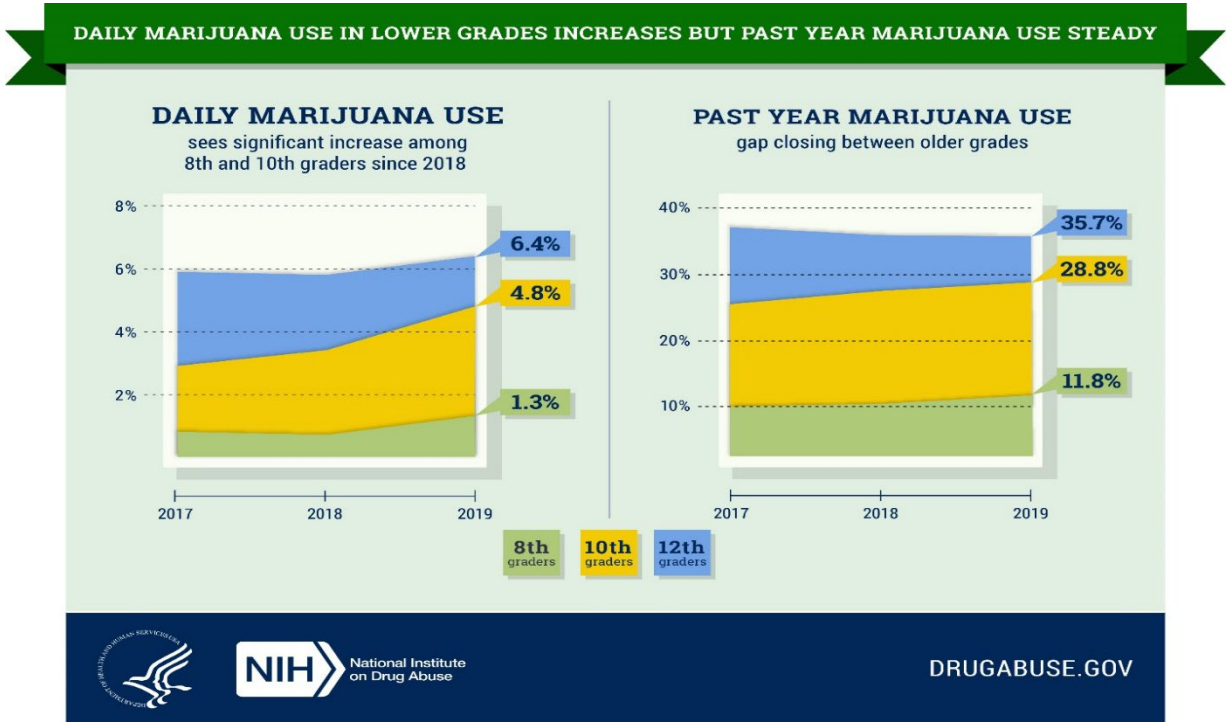


Image: https://www.drugabuse.gov/related-topics/trends-statistics/infographics/monitoring-future-2019-survey-results-overall-findings. nccd.cdc.gov/youthonline/.
NIDA. 2021, June 24.. Retrieved from https://nida.nih.gov/news-events/news-releases/2021/06/adolescent-marijuana-alcohol-use-held-steady-during-covid-19-pandemic on 2022, July 1

Safety - Adolescence

Outcomes with use before age of 17

	Never	Less than monthly	Monthly or more	Weekly or more	Daily	p value	N
Adjusted Odds Ratio							
High School completion	1	**0.78** (0·67–0·90)	**0.61** (0·45–0·81)	**0.47** (0·30–0·73)	**0.37** (0·20–0·66)	0.001	3004
Degree attainment	1	**0.78** (0·69–0·90)	**0.62** (0·47–0·81)	**0.49** (0·32–0·73)	**0.38** (0·22–0·66)	<0.0001	2834
Cannabis dependence	1	**2.06** (1·75–2·42)	**4.24** (3·07–5·84)	**8.72** (5·39–14·12)	**17.95** (9·44–34.12)	<0.0001	2675
Other illicit drug use	1	**1.67** (1·45–1·92)	**2.79** (2·11–3·69)	**4.67** (3·07–7·10)	**7.80** (4·46–13·63)	<0.0001	2832
Suicide	1	**1.62** (1·19–2·19)	**2.61** (1·43–4.79)	**4.23** (1·71–10.47)	**6.83** (2·04–22.90)	0.002	2192

Adapted from Silins E, et al. Lancet Psych (2014)

Safety - Adolescence

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Safety - Adolescence

- Impact of cannabis use during adolescence and subsequent cognitive function

  - Dunedin Study
    - Prospective study following 1,037 individuals followed from birth to age 38
    - Interviews at ages 18,21,26,and 38 years
    - Neuropsychological testing completed at

    age 13 and again at age 38 years

Meier et al. Proc Natl Acad Sci USA (2012)

Safety - Adolescence

IQ before and after cannabis use

Persistence of cannabis use	*n*	% male	Age 7–13 full-scale IQ (SD)	Age 38 full-scale IQ (SD)	Δ IQ effect size
Never used, never diagnosed	242	38.84	99.84 (14.39)	100.64 (15.25)	**0.05**
Used, never diagnosed	479	49.48	102.32 (13.34)	101.25 (14.70)	**–0.07**
1 diagnosis	80	70.00	96.40 (14.31)	94.78 (14.54)	**–0.11**
2 diagnoses	35	62.86	102.14 (17.08)	99.67 (16.11)	**–0.17**
3+ diagnoses	38	81.58	99.68 (13.53)	93.93 (13.32)	**–0.38**

Adapted from: Meier et al. Proc Natl Acad Sci USA (2012)

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Adapted from: Meier et al. Proc Natl Acad Sci USA (2012)

Safety - Adolescence

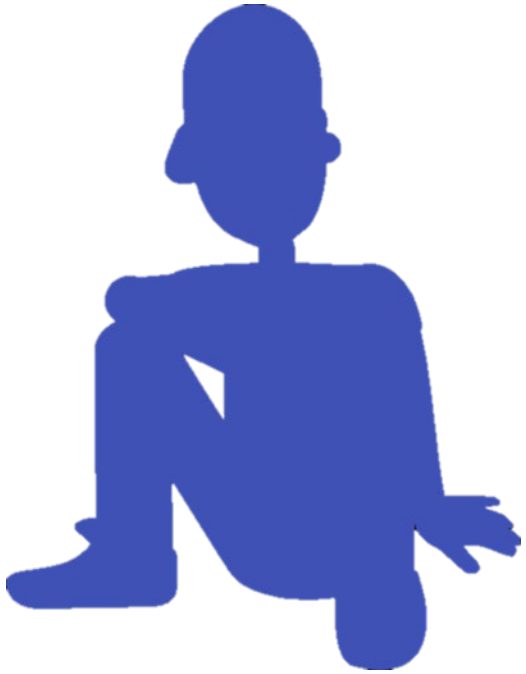
- Or did it?
- Two longitudinal twin studies
  - Risk Factors for Antisocial Behavior (RFAB) study from Southern California (789 children)
  - Minnesota Twin Family Study (MTFS; 2,277 children)

"children's genes and family environments set them on pathways that lead both to the use of marijuana and to IQ decline."

Jackson NJ et al. Proceedings of the National Academy of Sciences (2016)

Patient Safety - High Risk Populations Adolescence

- Perceptions regarding the harm of marijuana may contribute to risky behaviors
- A developing brain may be more vulnerable to marijuana effects
- Higher doses, frequencies, and durations pose greater risk



Volkow ND et al. N Engl J Med (2014)

Other safety considerations

- Labeling
  - May be absent or inaccurate
- Driving
  - Abstain from driving for at least 6 hours after smoking or 8 hours after oral consumption
- Storage
  - Keep in a locked box, away from children and pets

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