CANNABIS RESEARCH: COMPLEXITIES AND PRIORITIES

CO-OCCURRING COLLABORATIVE SERVING MAINE (CCSME)
NOV 1, 2022

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Presentation Overview

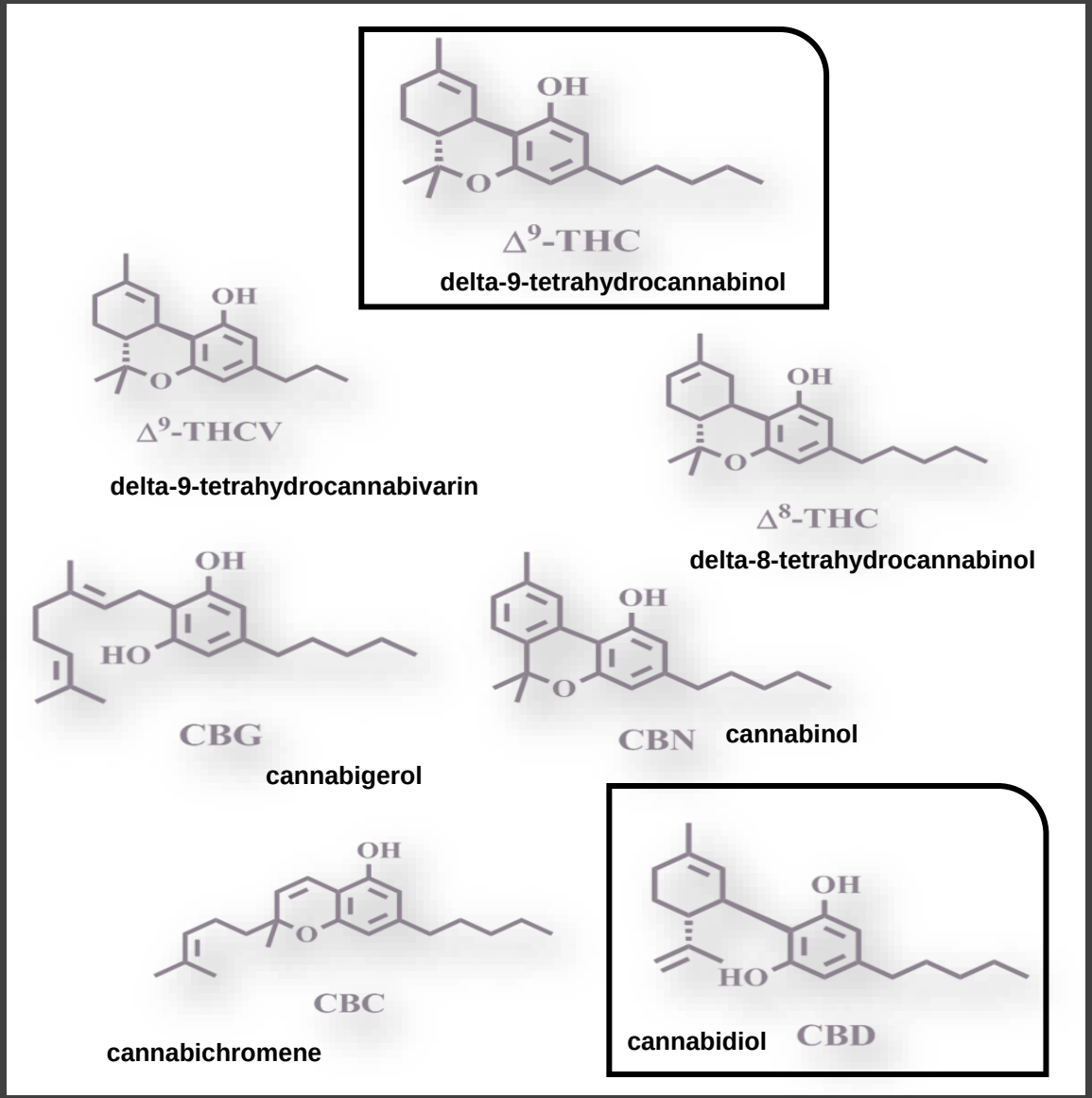
- Cannabis, Cannabinoids and the Endocannabinoid System (ECS)
- Cannabis Use: Complexities of an Evolving Landscape
- Long-Term Health Effects of Cannabis
- Cannabis Policies: Public Health Impact

Disclaimer:

The views and opinions expressed in this presentation are those of the author only and do not necessarily represent the views, official policy, or position of the U.S. Department of Health and Human Services or any of its affiliated institutions or agencies.

CANNABIS CONTAINS >120 CANNABINOIDS

PLUS OTHER CHEMICALS IN VARYING CONCENTRATIONS



- Plant with *long history of use* worldwide
- *Illegal* under US *Federal* law (Schedule I substance)
- *Legal* for *medical use* in 37 *States* + D.C.
- Legal for *adult use* in 19 *States* + D.C.
- Low THC products *legal* for *medical use* in 10 *States*
- *CBD from Hemp* (defined as cannabis sativa <0.3% THC) no longer falls under the Controlled Substances Act (CSA)
- Versions of *active ingredients* approved *(or in clinical trials)* for medical indications in U.S. and other countries
  - Synthetic - Marinol, Syndros, Cesamet
  - Plant Derived- Sativex (THC/CBD)
  - Plant Derived-Epidiolex (CBD: FDA approved; not scheduled)

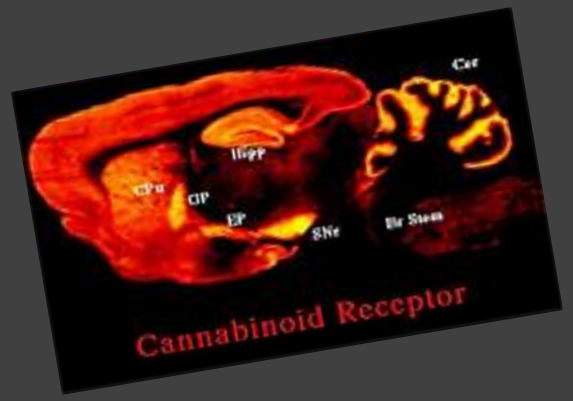
What is Cannabidiol (CBD)?

- Constituent of the cannabis plant (hemp or marijuana)
- Does not have intoxicating effects
- May counteract some adverse effects of THC
  - Bred out of “high potency” cannabis
- Multiple mechanisms of action
- May have a wide range of medical and other health uses
  - Few clinical trials (except epilepsy)
- FDA-approved medication (Epidiolex) for severe childhood epilepsies.
- Widely available in dietary supplement, foods, cosmetics, veterinary products—*not FDA regulated*

CANNABIS *ACUTE* EFFECTS: INTOXICATION PHASE

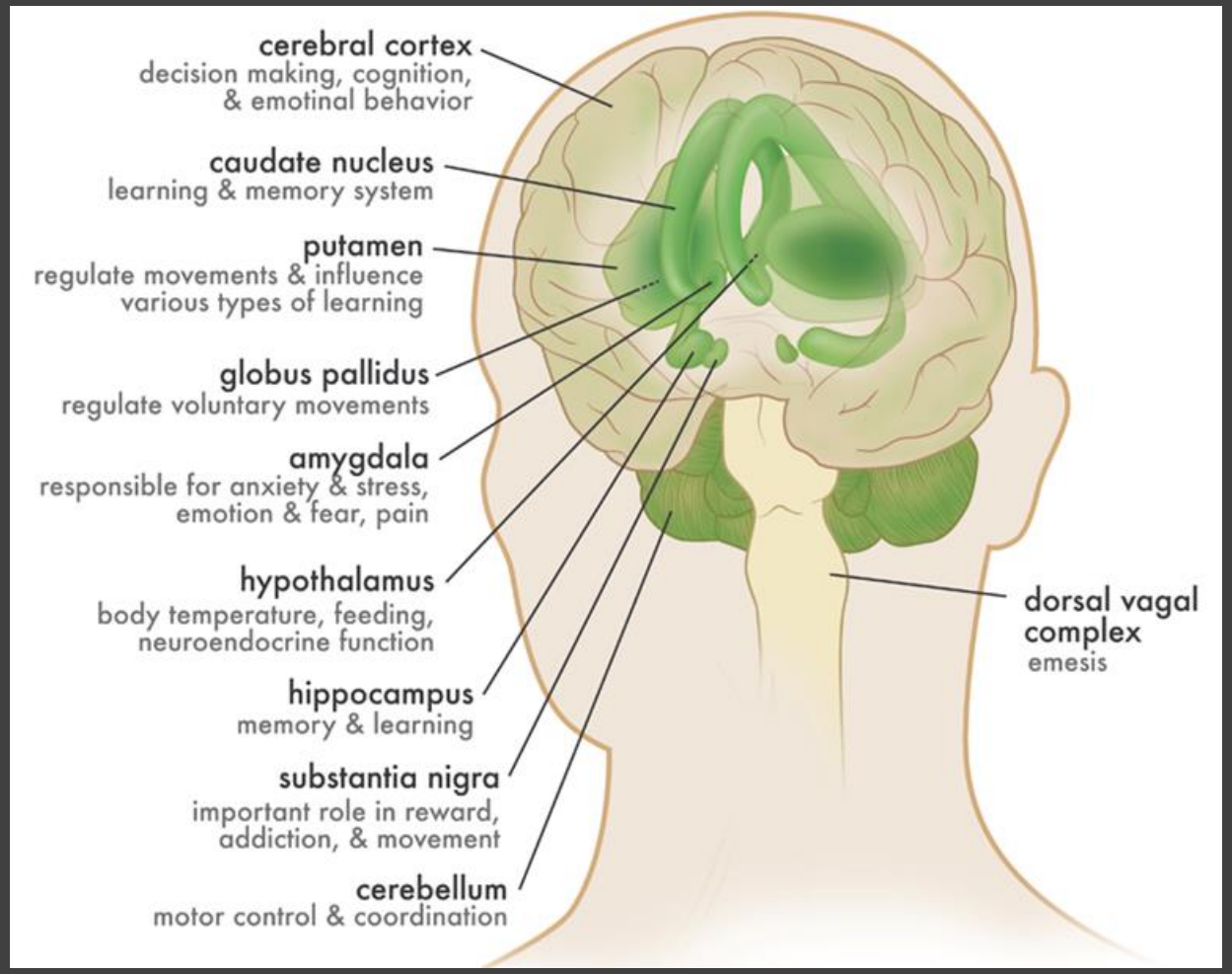
- Euphoria
- Appetite stimulation
- Altered perception of time
- Heightened sensation
- Impaired coordination and balance
- Increased heart rate: 20 - 100%
  - Some evidence for increased risk of heart attack, strokes
- Increased risk of accidents (~2 fold), higher when combined with alcohol
- Cognition
  - Impaired short-term memory
    - Difficulty with complex tasks
    - Difficulty learning
- Executive Function
  - Impaired decision-making
  - Increased risky behavior
- Mood (especially after high doses or edibles)
  - Anxiety – panic attacks
  - Psychosis – paranoia

Cannabinoid Receptors Are Located Throughout the Brain



Regulation of:

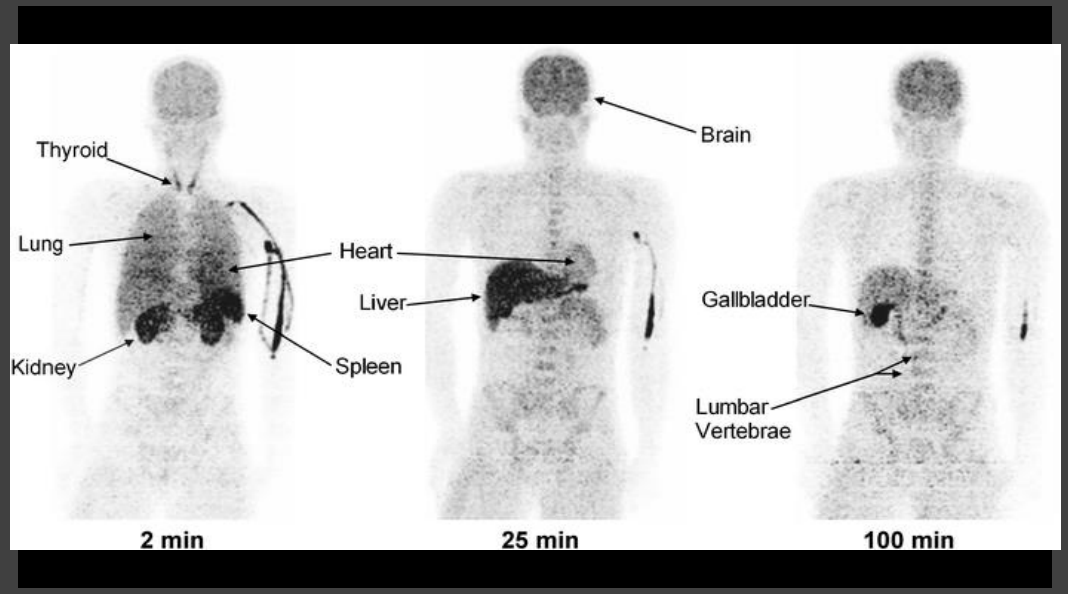
- Brain Development
- Memory & Cognition
- Movement Coordination
- Pain Regulation & Analgesia
- Immune Function
- Appetite
- Motivational Systems & Reward



Source: Canadian Consortium for the Investigation of Cannabinoids, http://www.ccic.net/

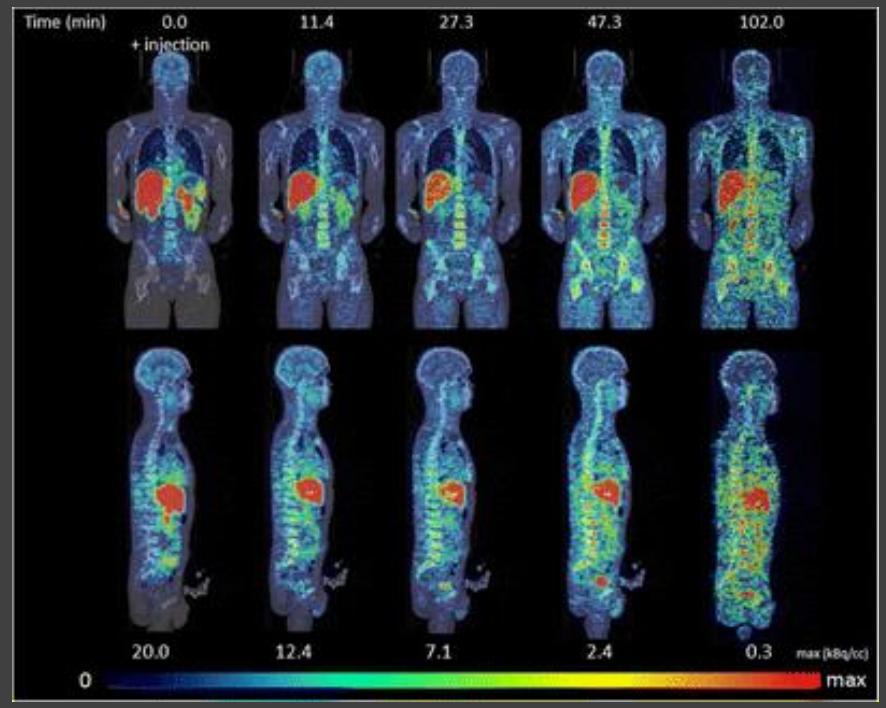
Cannabinoid Receptors Are Also Located Throughout the Body

Whole Body Distribution of CB1 Receptors (2, 25, and 100 min after injection of 11C-MePPEP)

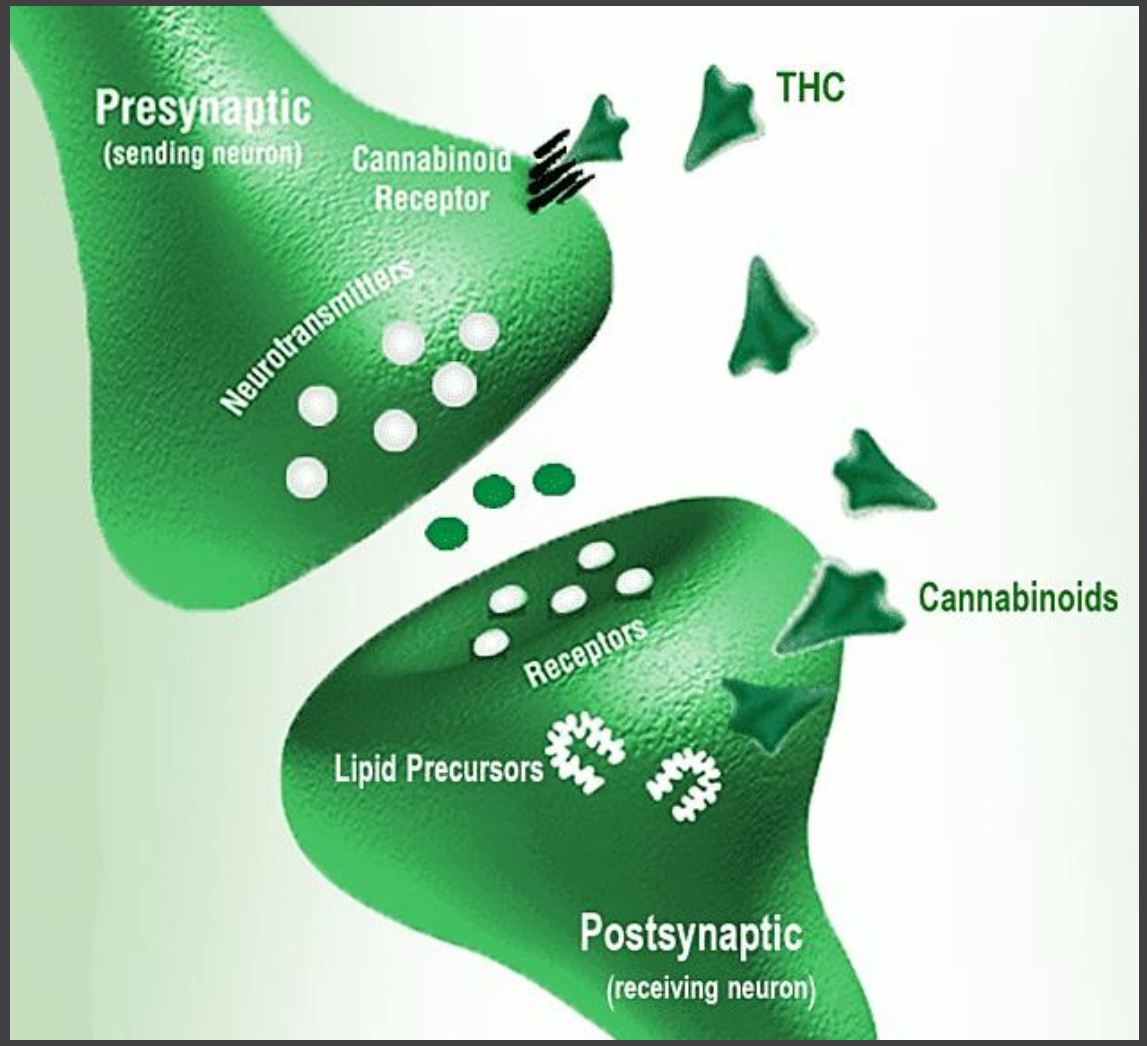


Source: Terry et al., Eur J Nucl Med Mol Imaging. 2010

PET images of [11C]-NE40 (CB2R radioligand)



Source: Ahmad et al., Mol Imaging Biol. 2013 A

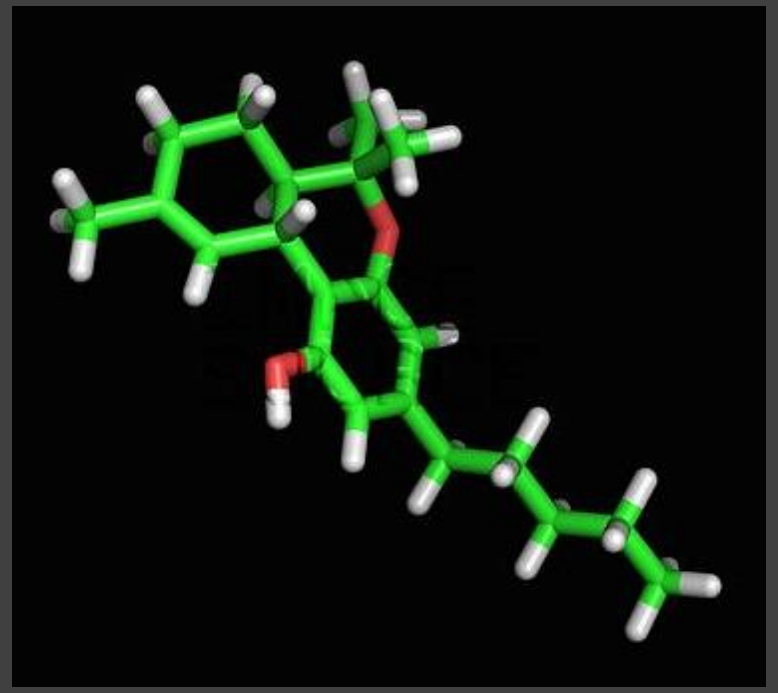


ENDOCANNABINOID SYSTEM

Endocannabinoids are produced *on demand*. They travel back to the transmitting neuron to dampen further activity.

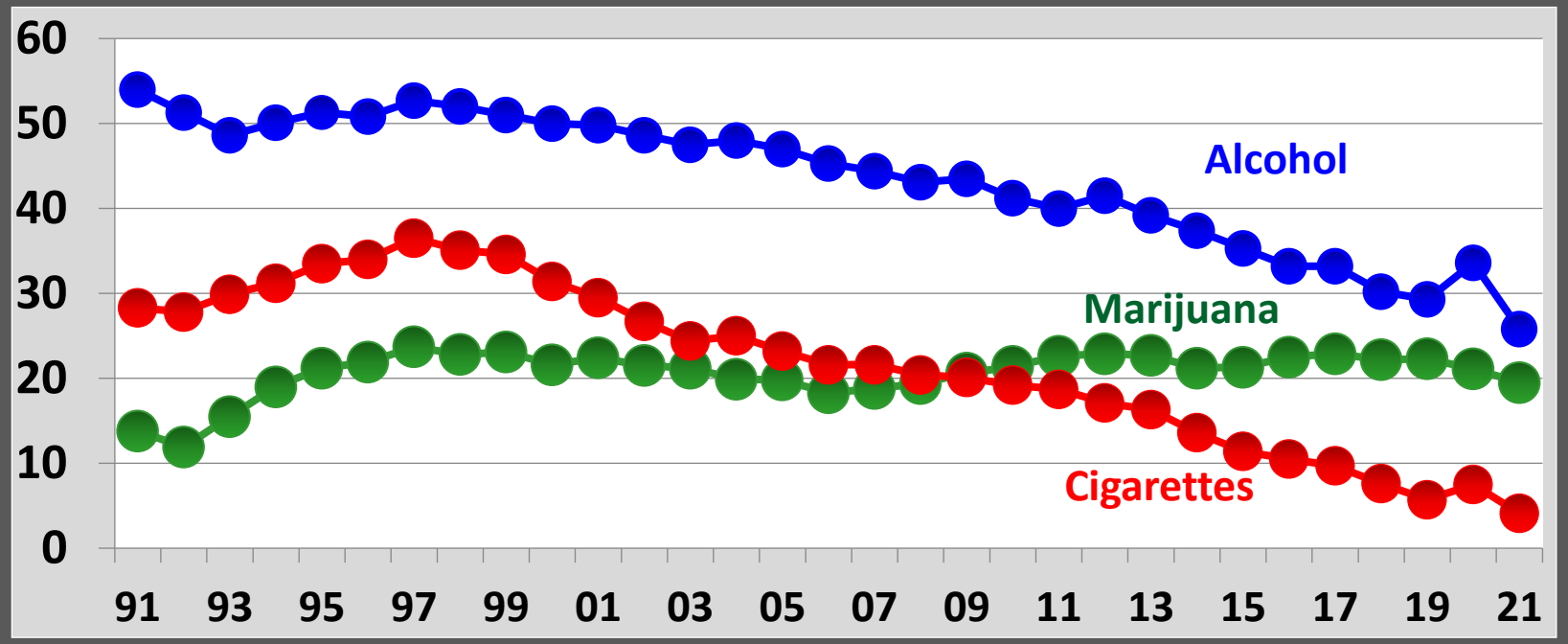
Cannabis: Most Commonly Used "Federally" Illicit Drug In the U.S.

- More than **32 million** Americans 12 and older report past month cannabis use.
- Approximately **14.2 million*** Americans met criteria for cannabis use disorders in 2020.
- An estimated **2.8 million** Americans used cannabis for the first time; **~ 1 million** were between the ages of 12 and 17.



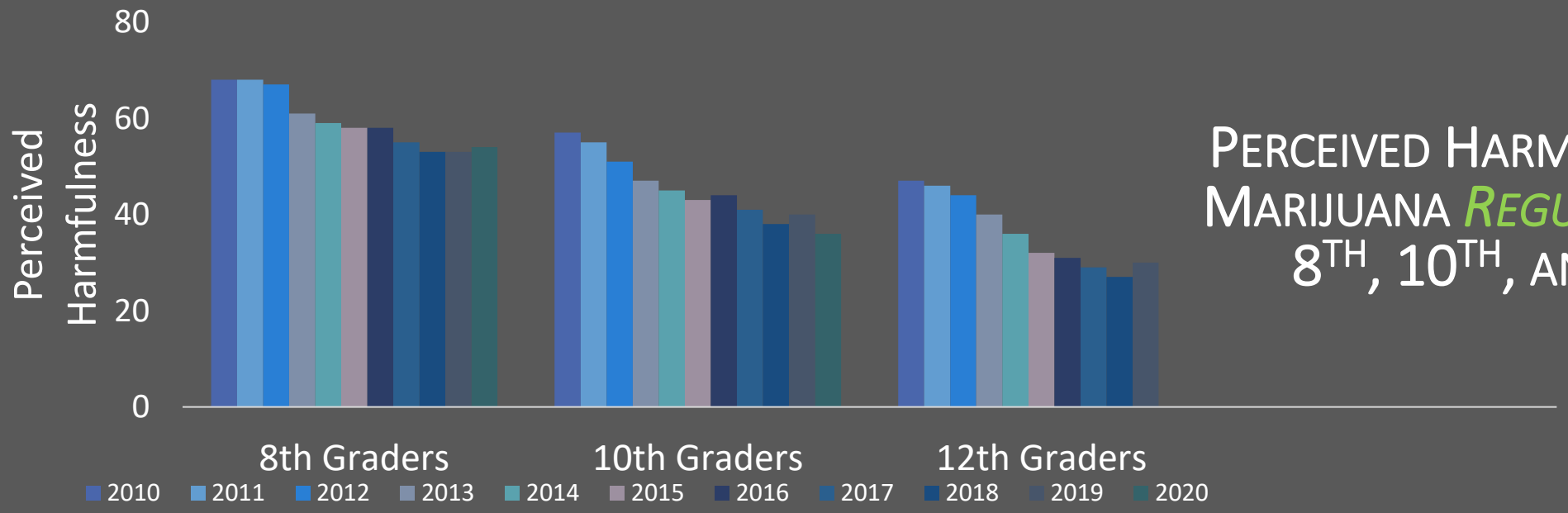
Tetrahydrocannabinol (THC)
Psychoactive Ingredient in Marijuana

*Change in measure from DSM IV to DSM V; not comparable to prior years
Source: 2020 National Survey on Drug Use and Health, SAMHSA



Past Month Drug Use in 12th Graders

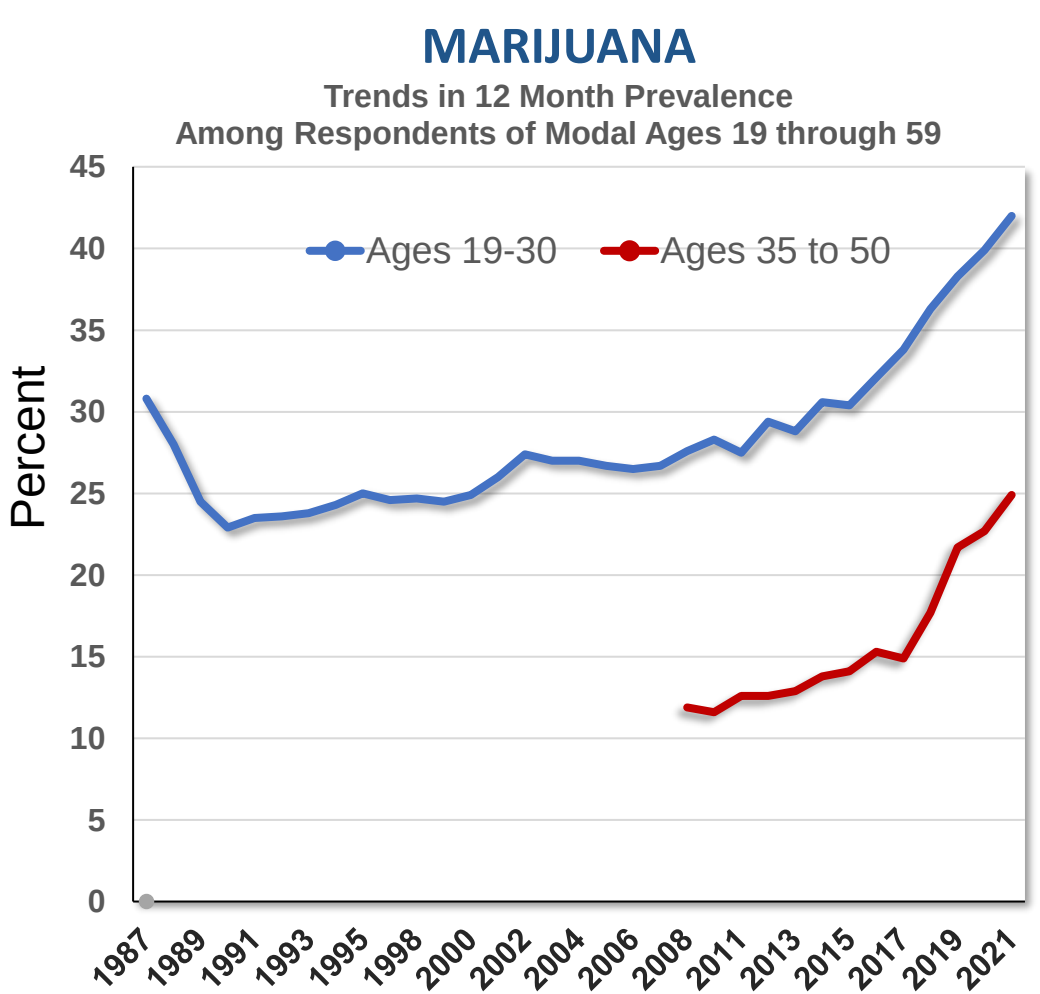
5.8 % report daily or near daily use of marijuana in 2021

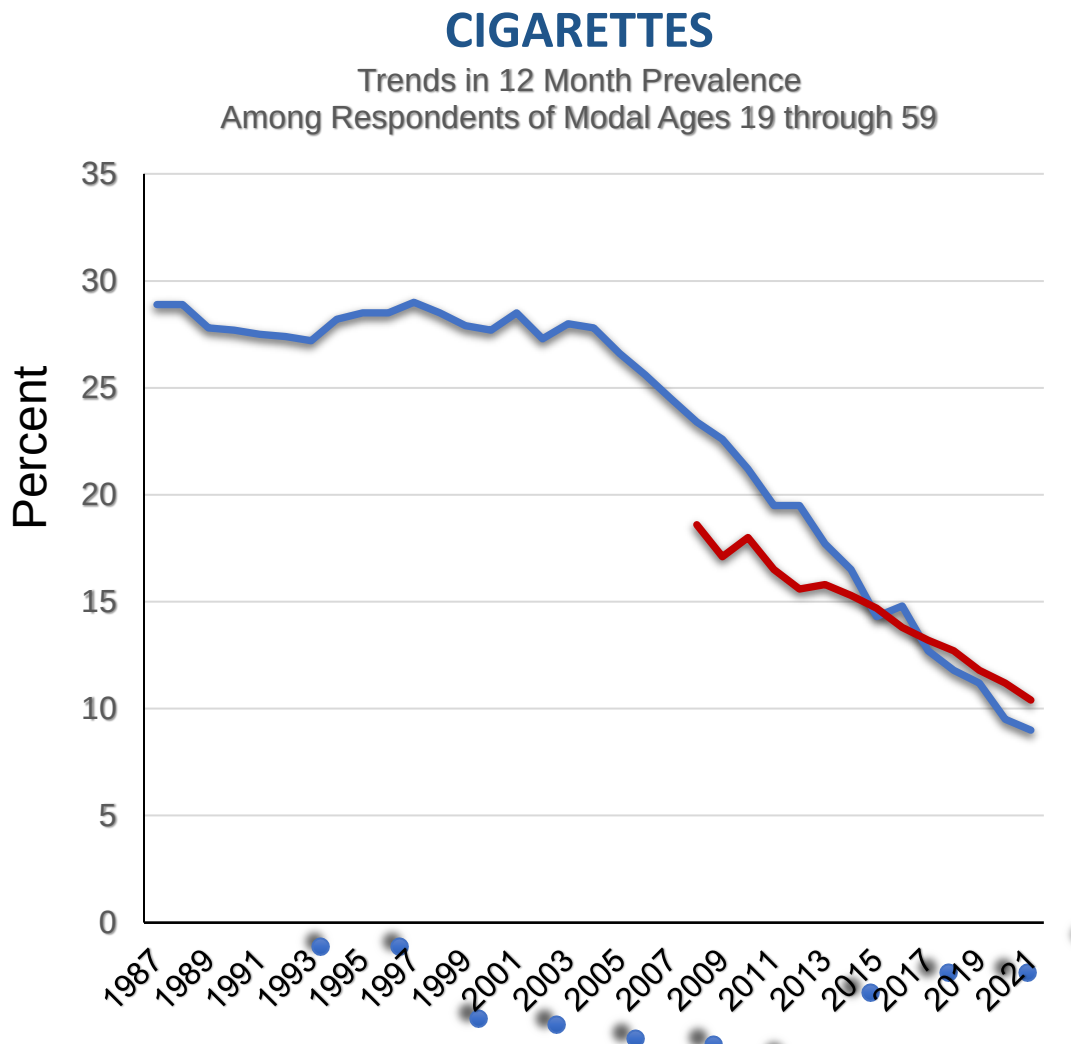


Perceived Harmfulness of Smoking Marijuana *Regularly* is Declining in 8th, 10th, and 12th Graders

Source: University of Michigan, 2021 Monitoring the Future Study

National Data on Substance Use Among Adults Ages 19-59, 1976-2021

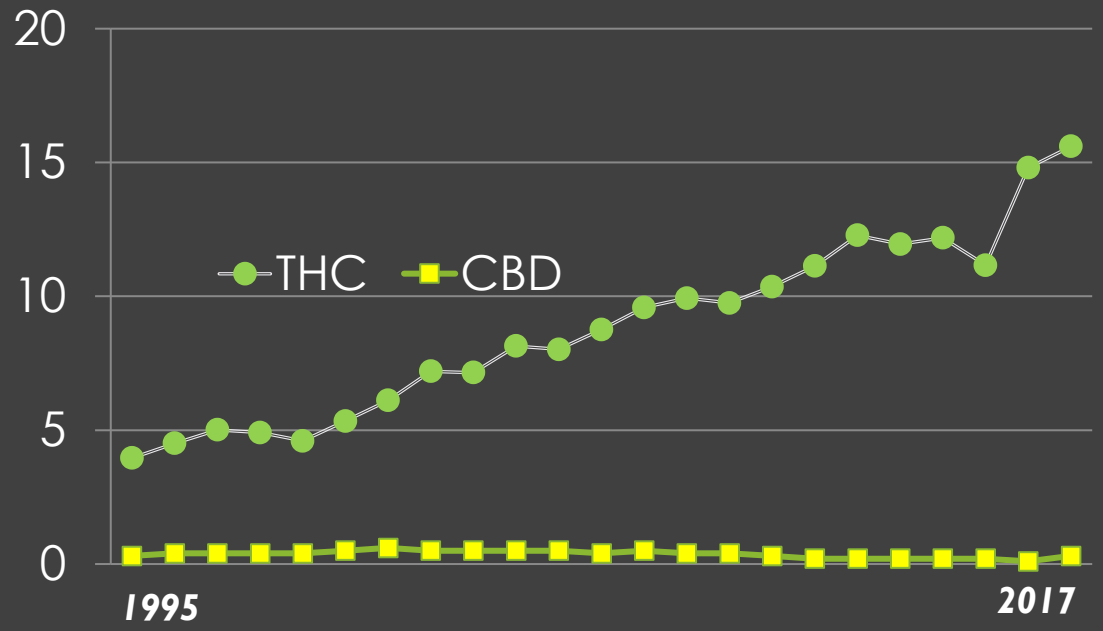




Patrick ME et al (2022). Monitoring the Future Monograph Series. : doi:10.7826/ISR-UM.06.585140.002.07.0001.2022

Changing Landscape: Increasing Potency (%THC), New Routes of Administration, CBD products

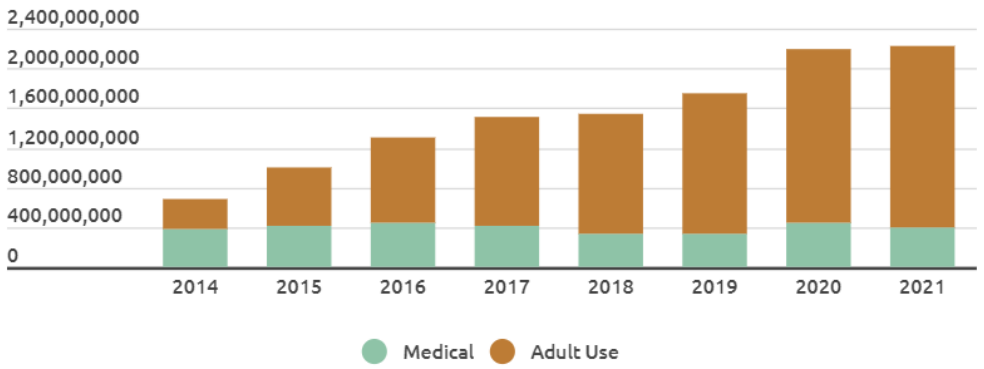
Cannabis Potency Increasing



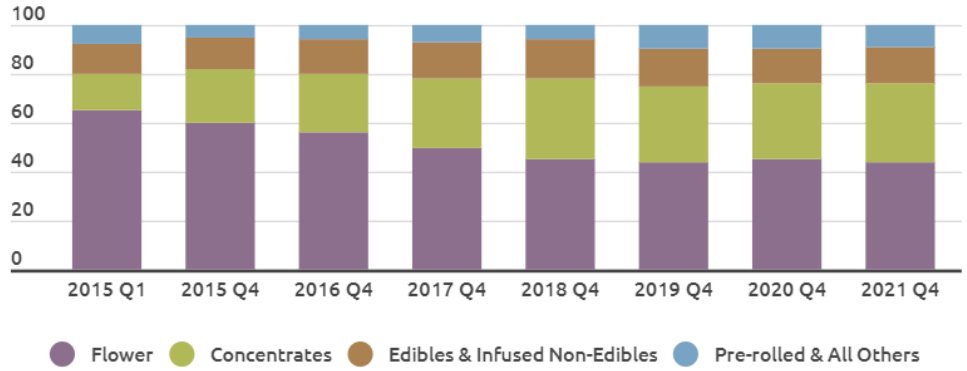
Source: U Miss, Potency Monitoring Project

COLORADO: MARKET SHARE IS SHIFTING AWAY FROM FLOWER TOWARDS CONCENTRATES

Medical and Recreational Sales



Cannabis Products Sales



Colorado cannabis market has been legal for medical use since 2000 and for recreational use since late 2012.

Colorado's retail sales in adult-use and medical dispensaries combined grew from $675 million in 2014, to about $2.19 billion in 2020, including $442 million medical and $1,749 million recreational cannabis sales.

Cannabis consumers spent $2,229 million in 2021, including $404 million medical and $1,825 million recreational cannabis sales, according to data from the Department of Revenue's Marijuana Enforcement Division. Cannabis sales averaged $2.79 million ($2.45 million in 2020) per retail location in Colorado's adult-use market and $0.96 million ($0.77 million in 2020) per location in the medical channel.

Eight months of 2022 brought in $1,210 million, including $163 million medical and $1,048 million recreational cannabis sales.

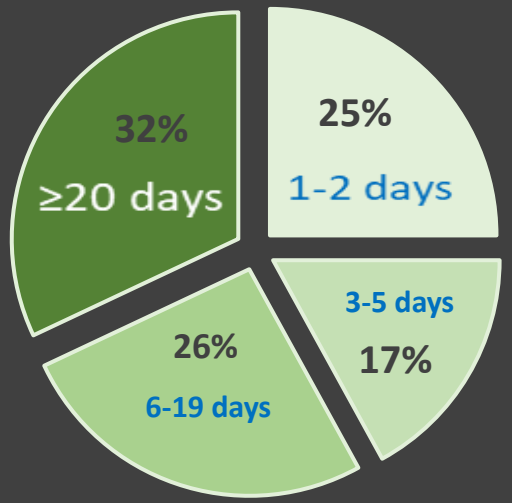
	Number of dispensaries and cultivation sites	Number of registered patients/in-state customers	Actual 2021 marijuana sales via dispensaries/ stores
Medical:	Dispensaries - 420 Cultivators – 484 Manufactures – 226 Testing – 10 Transporters – 13 Delivery – 16	84,179 (down from 85,814 in 2020)	$404 million (versus $442M in 2020)
Recreational:	Retail Stores - 653 Cultivators – 805 Manufactures – 300 Testing – 10 Transporters – 35 Delivery – 48 Hospitality – 6	550,000 - 650,000	$1,825 million (up from $1,749M in 2020)

https://cannabusinessplans.com/colorado-cannabis-market/

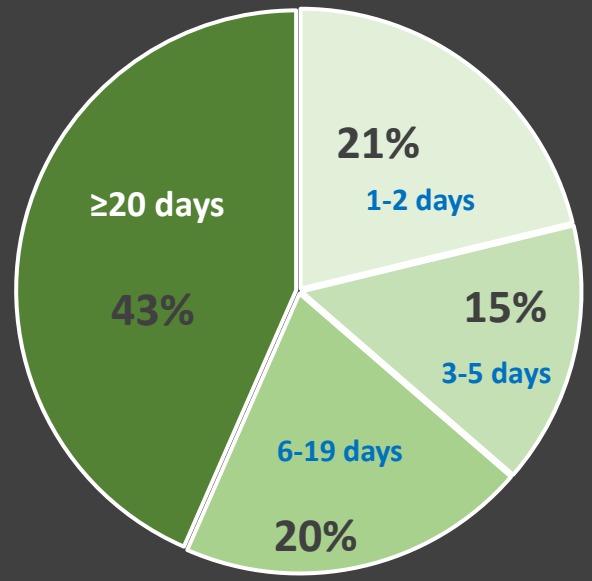
Among Past-Month Cannabis Users Aged ≥12, More than Two in Five were Daily or Almost Daily Users in 2019

Frequency of use	2002	2019	*P* value for the difference between 2002 and 2019
1-2 days	24.55%	20.99%	.015
3-5 days	17.46%	15.09%	.041
6-19 days	25.70%	20.44%	<.001
20+ days	32.29%	43.48%	<.001
Estimated no. past-month users	14.6 Million	31.6 Million	<.001

among 14.6 M people in 2002 reporting past-month use



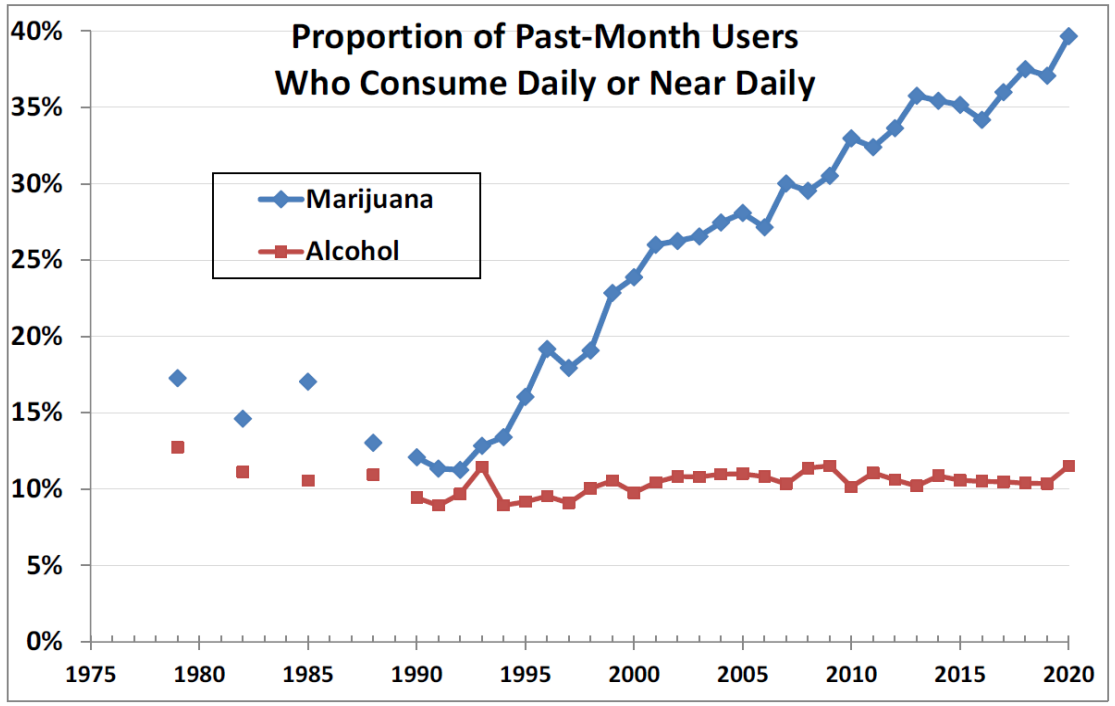
among 31.6 M people in *2019* reporting past-month use



Source: 2002 and 2019 National Surveys on Drug Use and Health (NSDUH) Public Use Files

Patterns of Cannabis Use are Changing

DND Cannabis Use is Relatively New



Contrast THC Consumption of Two Types of Users

- 1 joint each weekend night, pre-2000
  - Assuming 0.4 gms/joint, 4% THC
  - (2/7) * 0.4 * 4% = **4.6 milligrams/day**
- Average daily user in today
  - Assuming 1.6 gms/day, 20% THC
  - 1.6 * 20% = **320 milligrams/day**
- **That's ~70 times as much THC**

Slides Courtesy of Jonathan Caulkins

Adverse Health Consequences: Who Is At Greatest Risk?

Mothers/Newborns

Children and Adolescents

Older Adults?

Persons With Mental Illness

Tobacco Smokers

Marijuana Use Increased in Pregnant Females in California (2009-2016)

Figure 1. Adjusted Prevalence of Marijuana Use Among 279 457 Pregnant Females in KPNC by Screening Type, 2009-2016

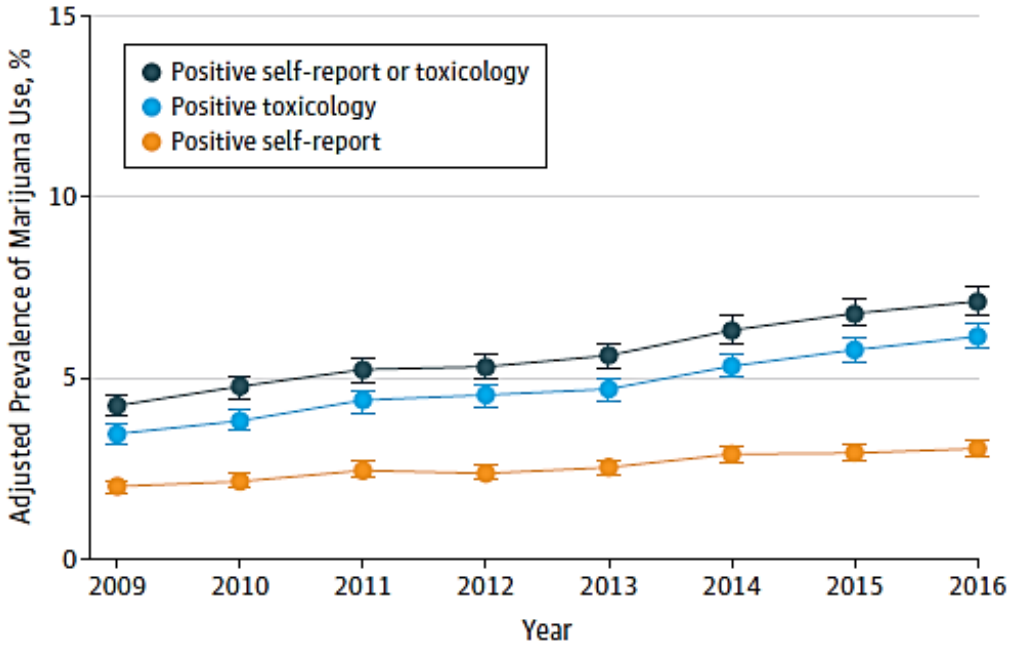
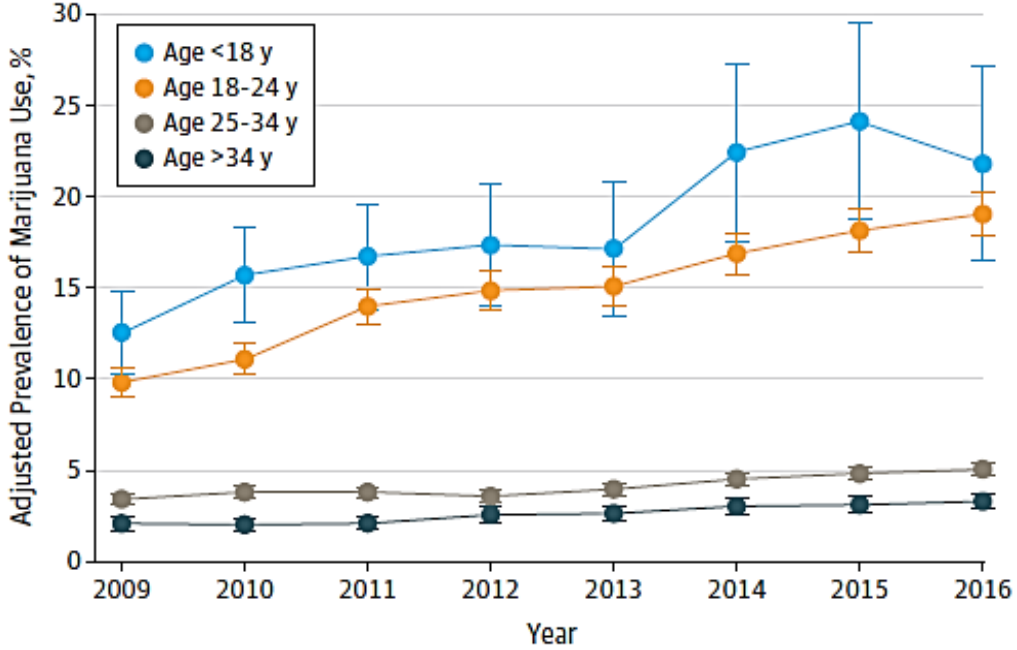
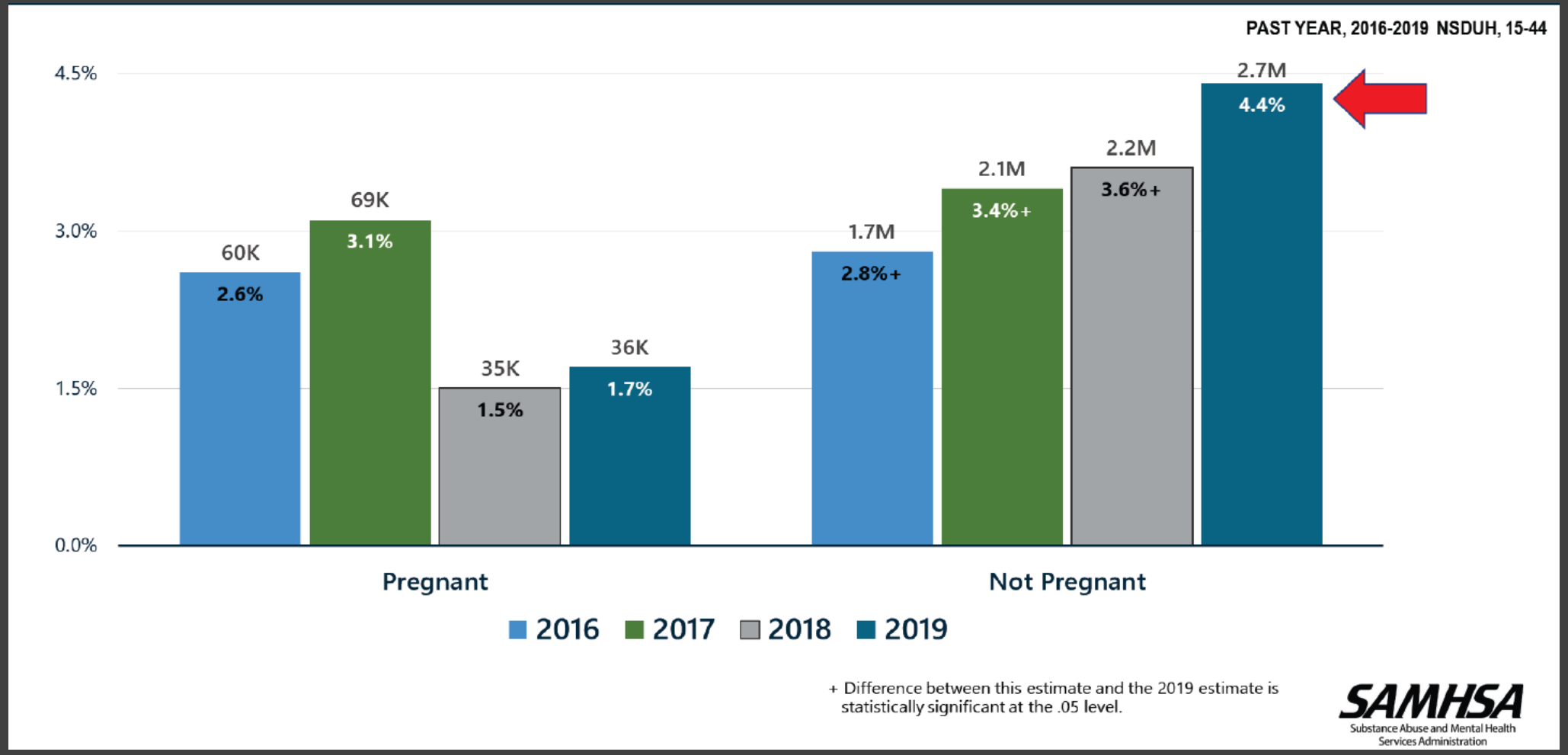


Figure 2. Adjusted Prevalence of Marijuana Use Among 279 457 Pregnant Females in KPNC by Age, 2009-2016

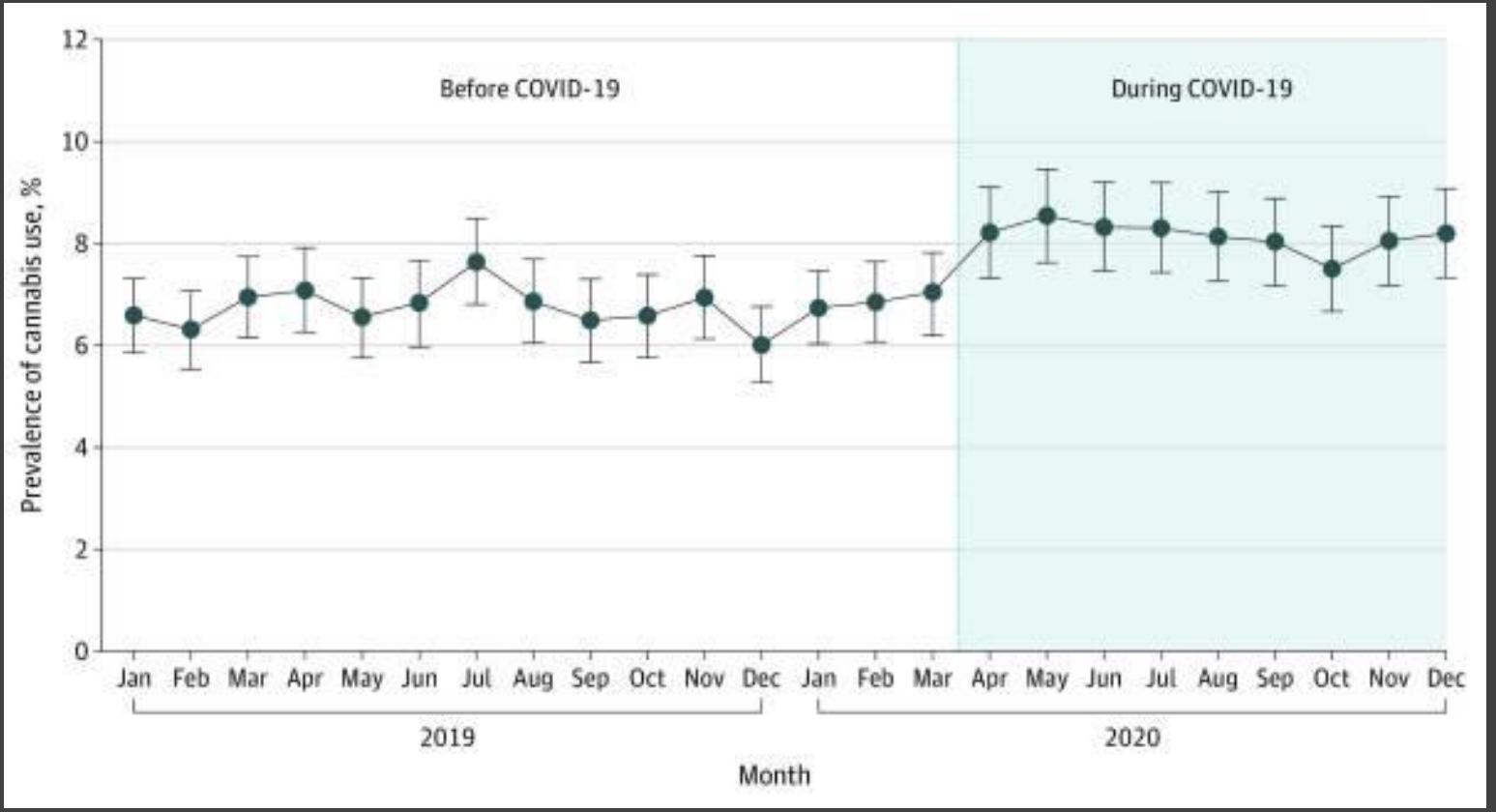


Source: Young-Wolff et al. JAMA. 2017 Dec 26;318(24):2490-2491

Daily or Almost Daily Cannabis Use among Women by Pregnancy Status



Cannabis Use Increased During the COVID-19 Pandemic in Pregnant Women

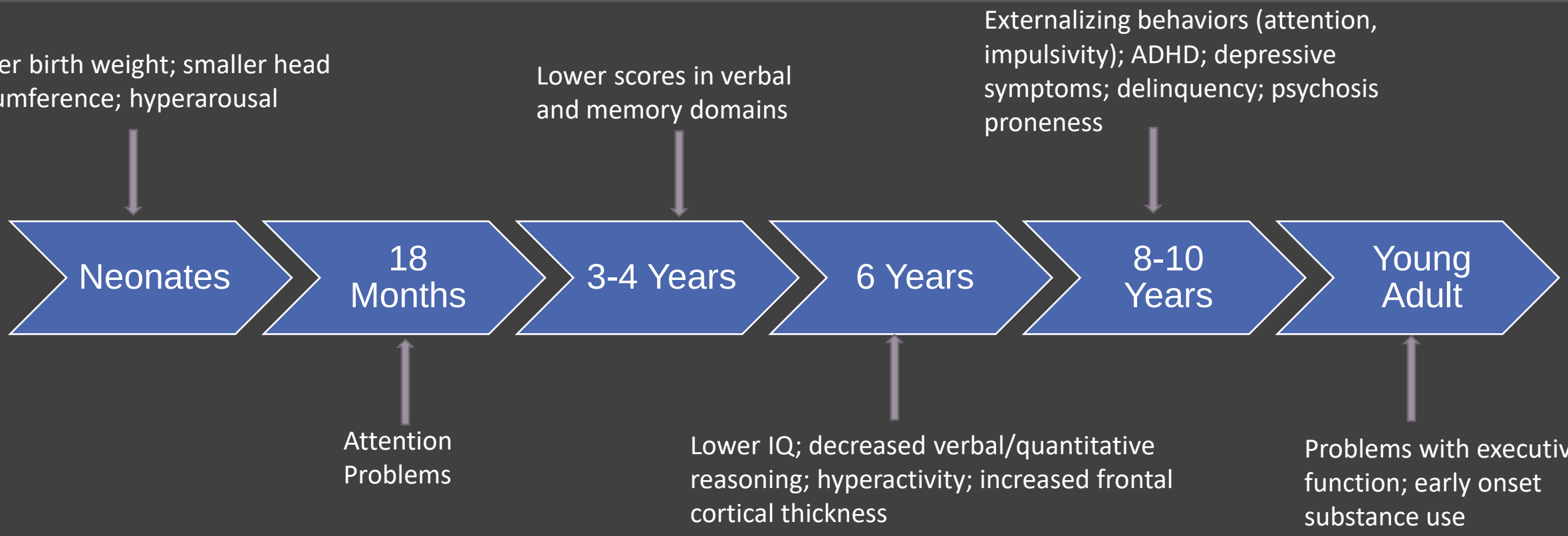


Analysis of patients at 8 weeks of gestation, using urine toxicology

Kaiser Permanente Northern California (N=100,105)

Source: Young-Wolff et al., 2021

Prenatal Cannabis Exposure: Overview of Effects*



Adapted from W. Eric Kuhn, Intersection of Law, Policy, and Prevention, 2014; El Marroun, 2016, 2017 Fried PA et al, 1980, 1988, 1998, Day NL et al, 1991

** Multiple Caveats*

Prenatal Cannabis Exposure (PCE)

- Endocannabinoid system (ECS) is involved in implantation; placentation; fetal organ development; and neural development, including cell differentiation, axon migration, myelination.
- Exogenous cannabinoids cross the placenta and accumulate in fetal tissues, especially brain. Also found in breast milk.
- Human fetal imaging studies find alterations in dopamine D2 receptors; may be sex-dependent.
- PCE is linked to fetal growth restriction and low birth weight.
- Longitudinal studies report subtle to modest impact on cognition and neuropsychiatric outcomes in children, adolescents, and young adults (with multiple caveats).
- Preclinical studies show lasting effects of THC exposure on adult drug seeking, stress responses, and brain reward systems.

Prenatal Cannabis: Research Gaps

Findings are often modest, results are inconsistent, and may be confounded by other variables

- Better measures of cannabis exposure (biological vs. self report)
  - Frequency of use
  - Timing of exposure (1st, 2nd, 3rd trimester; post natal; pre-conception)
  - Quantification of exposure (THC or other components)
- Data from recent cohorts: high potency products; varying THC/CBD ratios; CBD alone
- Consideration of sex dependent outcomes
- Measures of polysubstance use/other adverse or protective factors (prenatal care, food/housing insecurity, stress, support)
- Paternal exposure
- Post-natal parenting behaviors
- Pre-clinical and clinical research, including longitudinal studies

Source: Nashed, Hardy, Laviolette, Frontiers in Psychiatry, 2021

HEALTHY BRAIN AND CHILD DEVELOPMENT (HBCD) STUDY

Multi-site longitudinal study (n=7500) examining individual brain development trajectories and behavior from birth through childhood (ages 9-10) including *in utero* substance exposure and effects of adverse social environments.

EEG, NIRS

Pregnancy History

Biospecimens

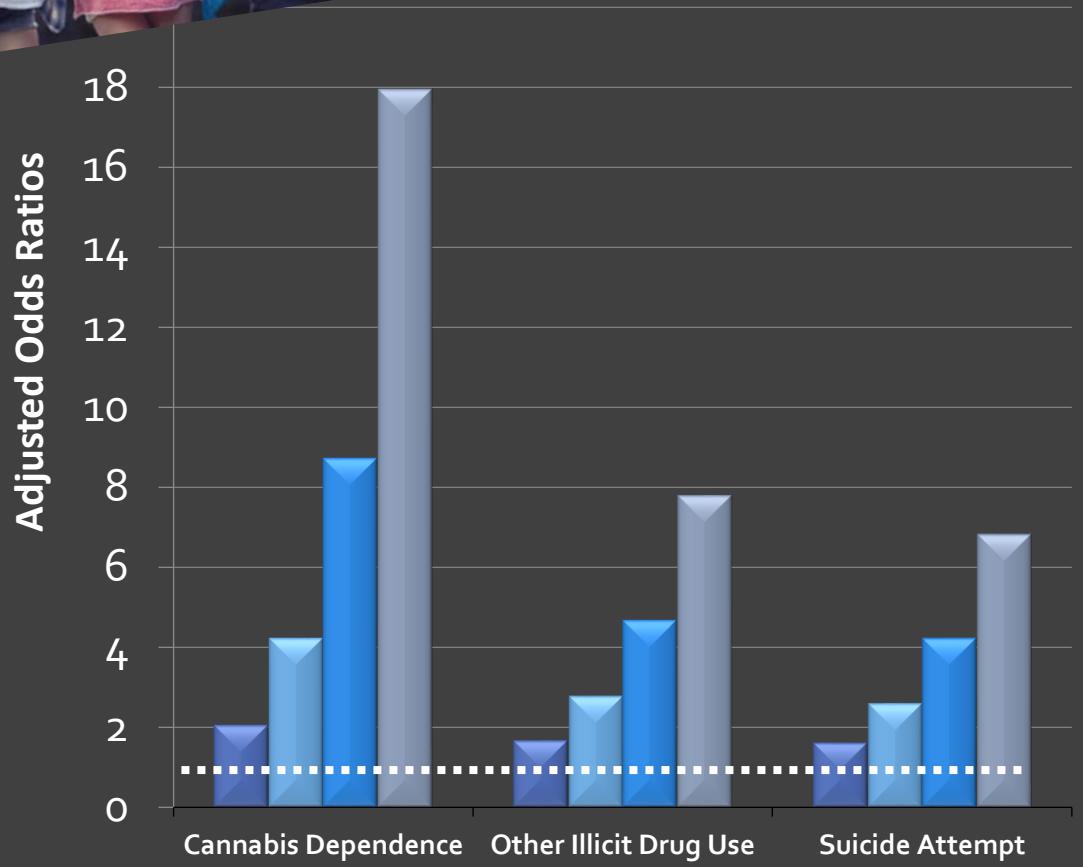
Risk and Protective Factors

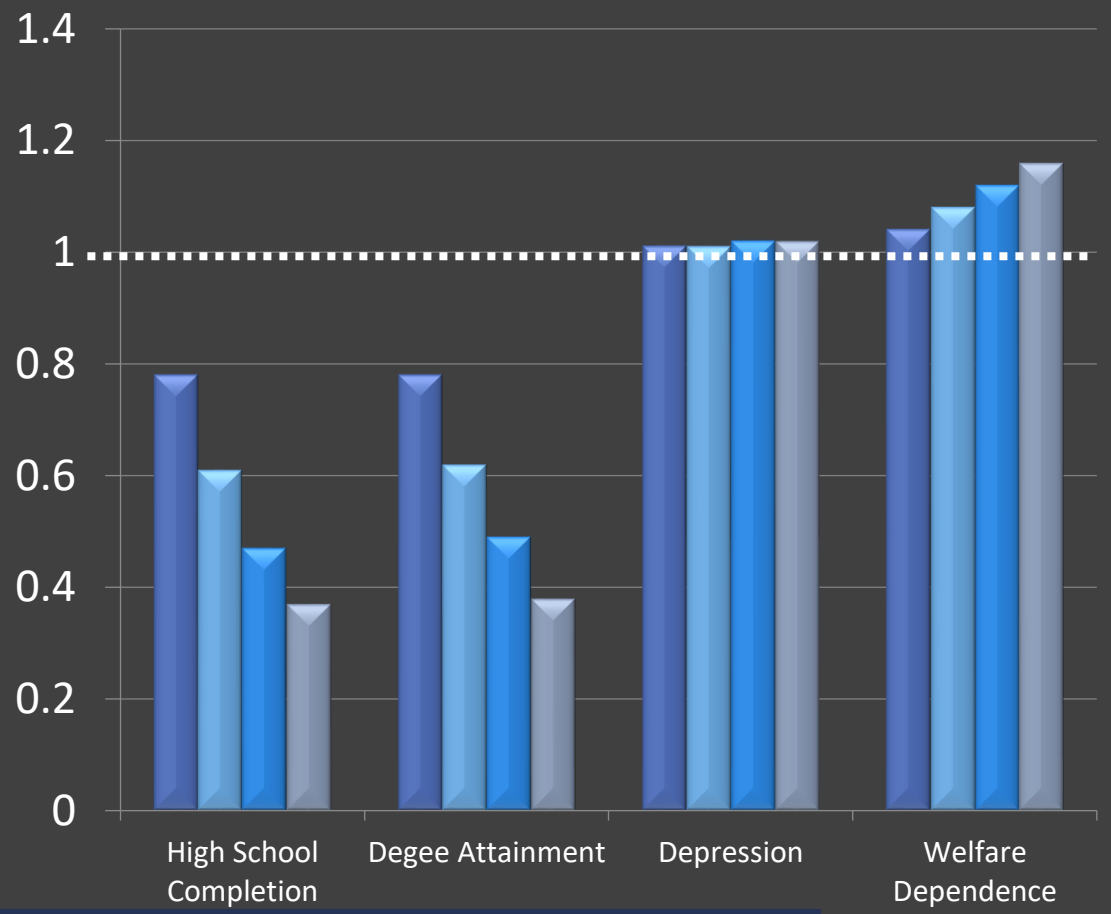
MRI

Behavioral, neurocognitive assessments

Wearables

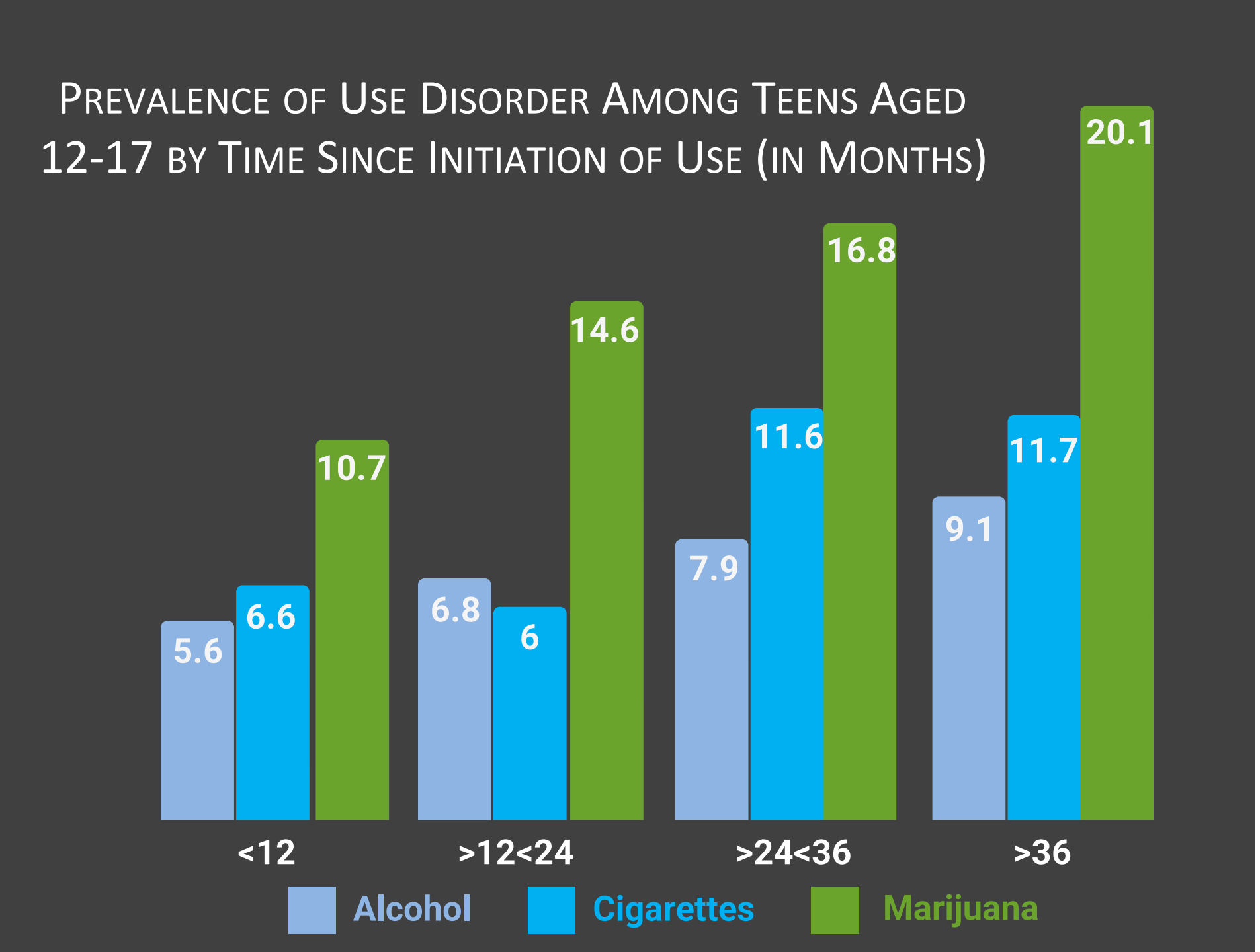
Frequency of Cannabis Use Before Age 17 and *Adverse Outcomes* at Age 30 (N=2500-3700)





Less than Monthly | Monthly or More | Weekly or More | Daily

Source: Silins E et al., The Lancet September 2014

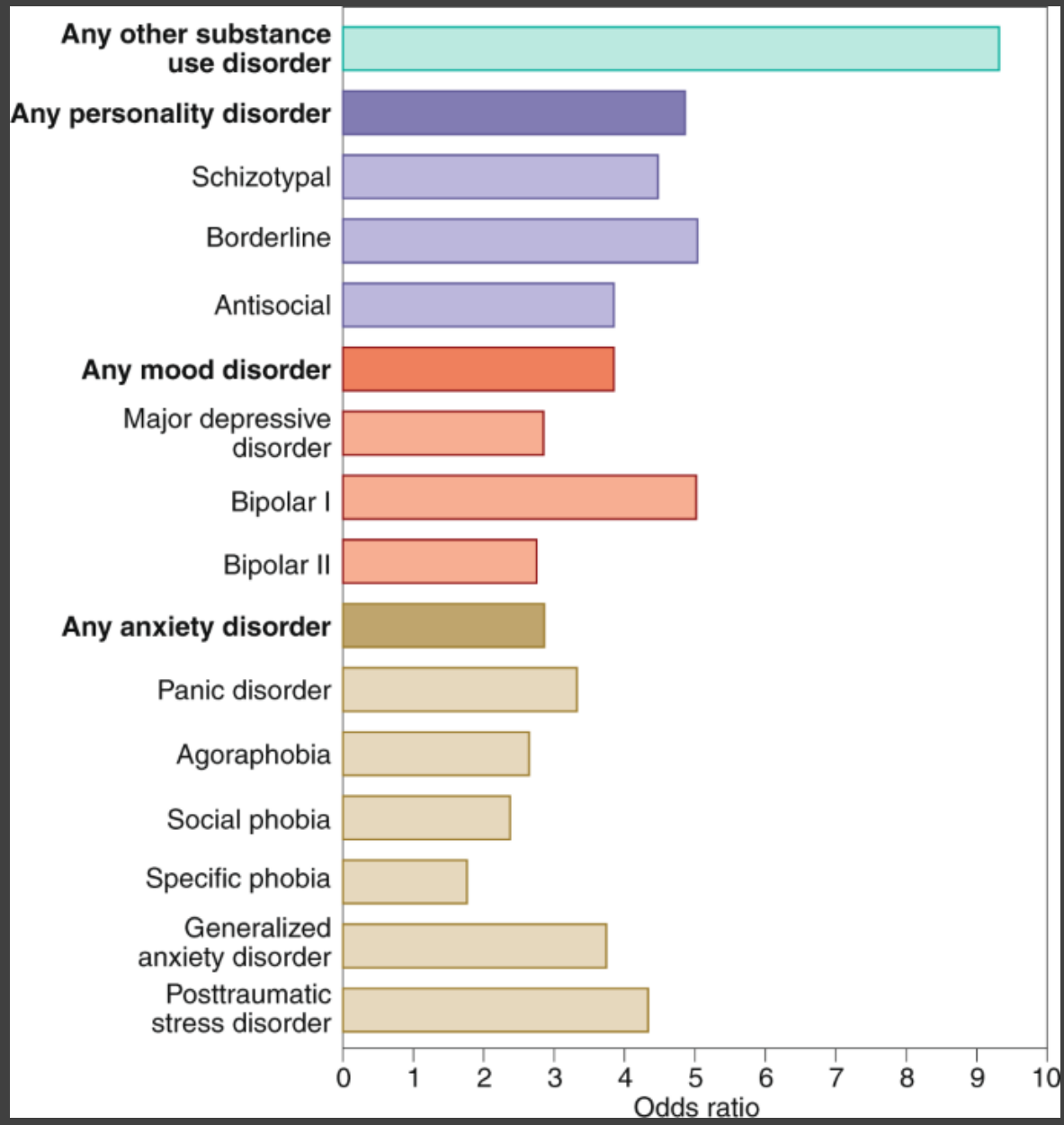


Youth Cannabis Use Disorder: Prevalence Double That of Alcohol & Other Substance Use Disorders

Courtesy of Kevin Sabet, SAM

Volkow et al, JAMA Pediatrics, 2021

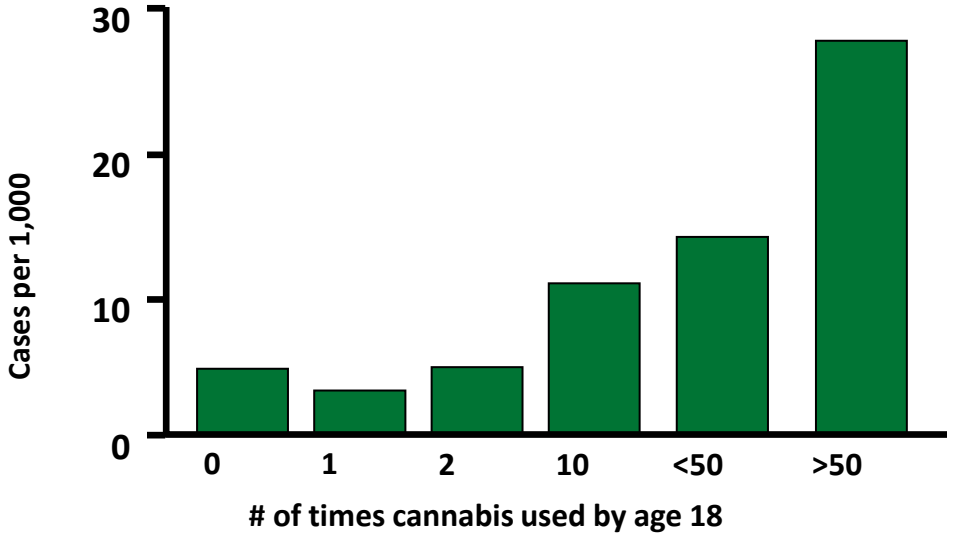
Comorbid Psychiatric Conditions commonly Associated with CUD



Ferland and Hurd Nature Neuroscience, 2020

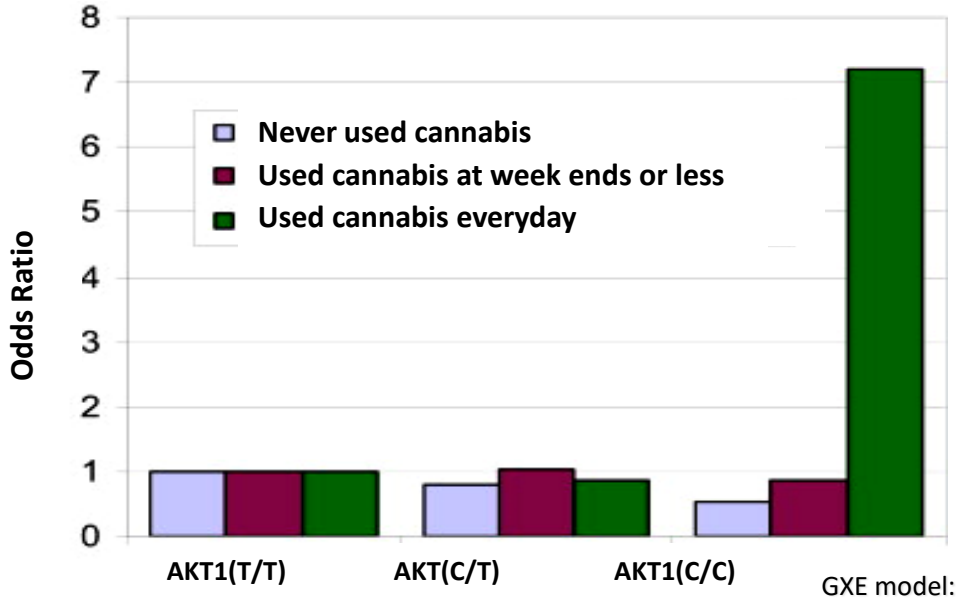
Cannabis-Associated Psychosis

Study of Swedish Conscripts (n=45570)



Source: Andréasson et al Lancet, 1987

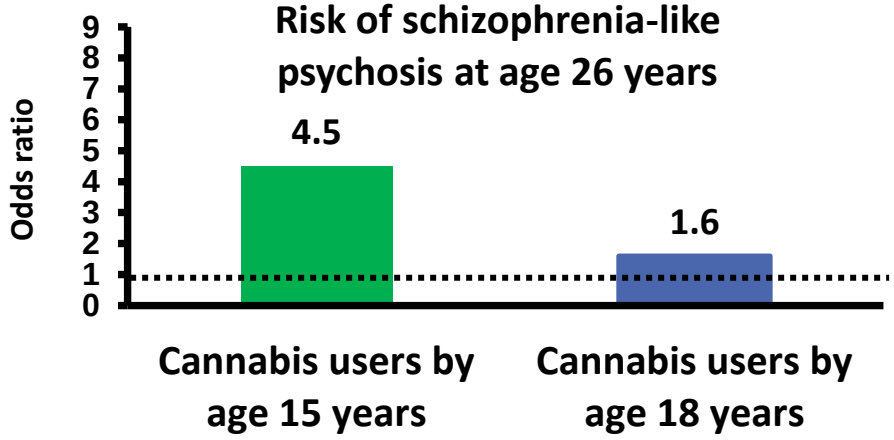
Regular Cannabis Use Increases Schizophrenia Risk in those with AKT1 rs2494732 genotype



GXE model: p*=0.014

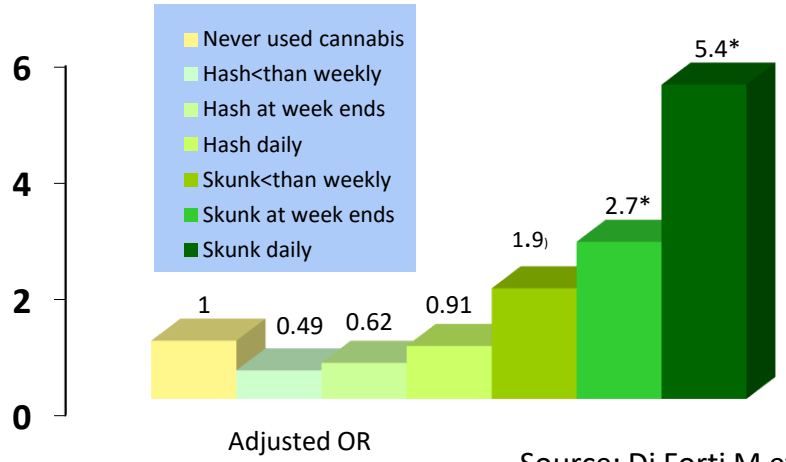
Source: Di Forti et al., Biological Psychiatry, 2012

Prospective Dunedin Study (n=1037)



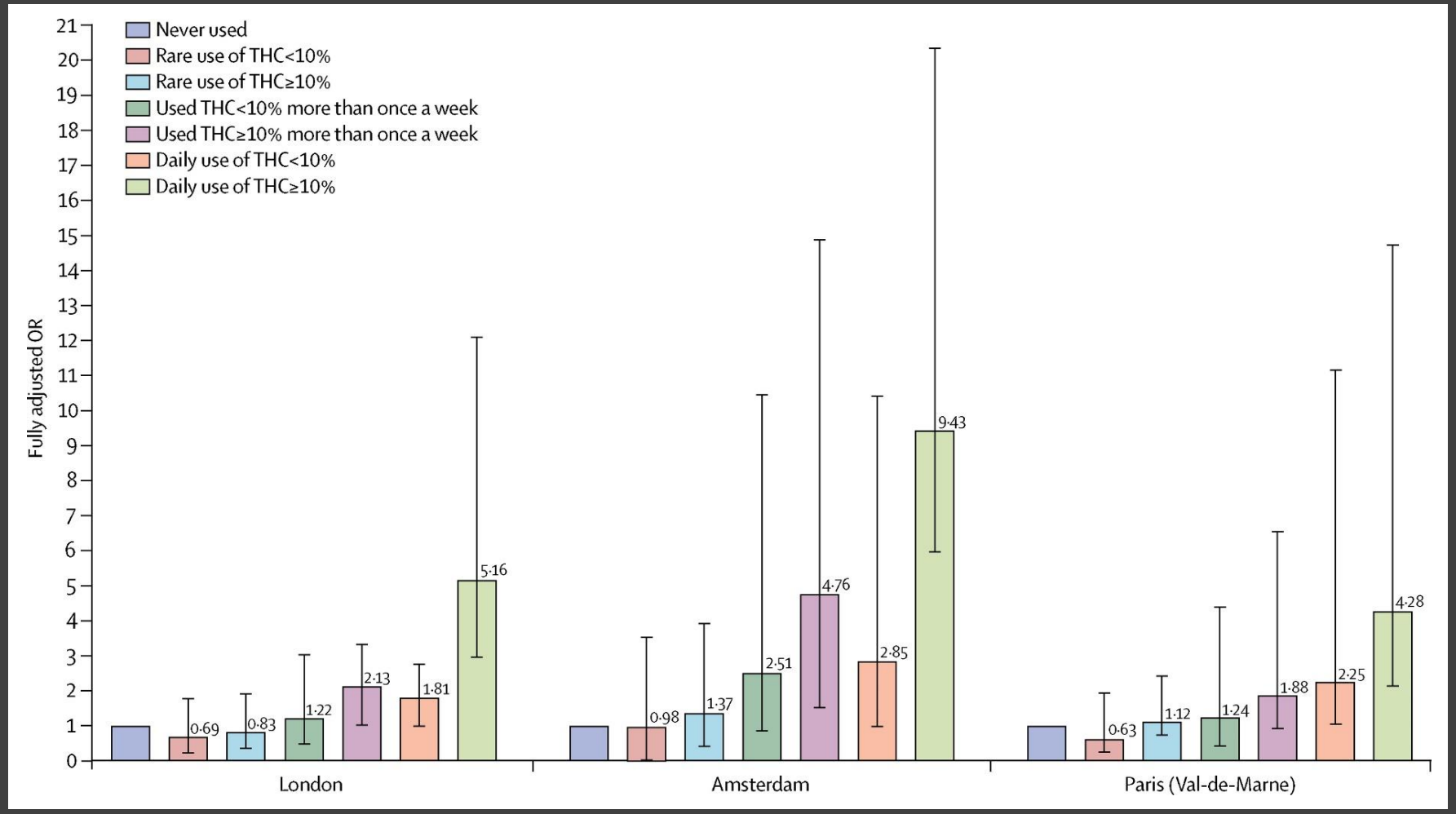
Source: Arseneault et al BMJ 2002

Effect of High Potency Cannabis on Risk of Psychosis



Source: Di Forti M et al., The Lancet, 2015

Odds Ratios of psychotic disorders for the combined measure of frequency plus type of CANNABIS used in three cities: London, Amsterdam, Paris

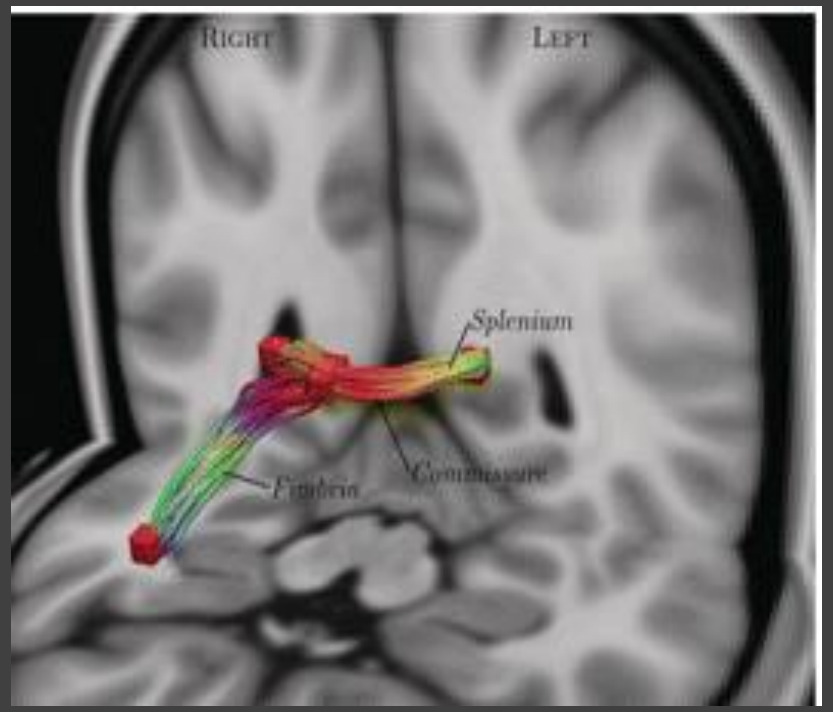


London (201 cases, 230 controls), Amsterdam (96 cases, 101 controls), and Paris (54 cases, 100 controls).
Error bars represent 95% CIs. OR=odds ratio.

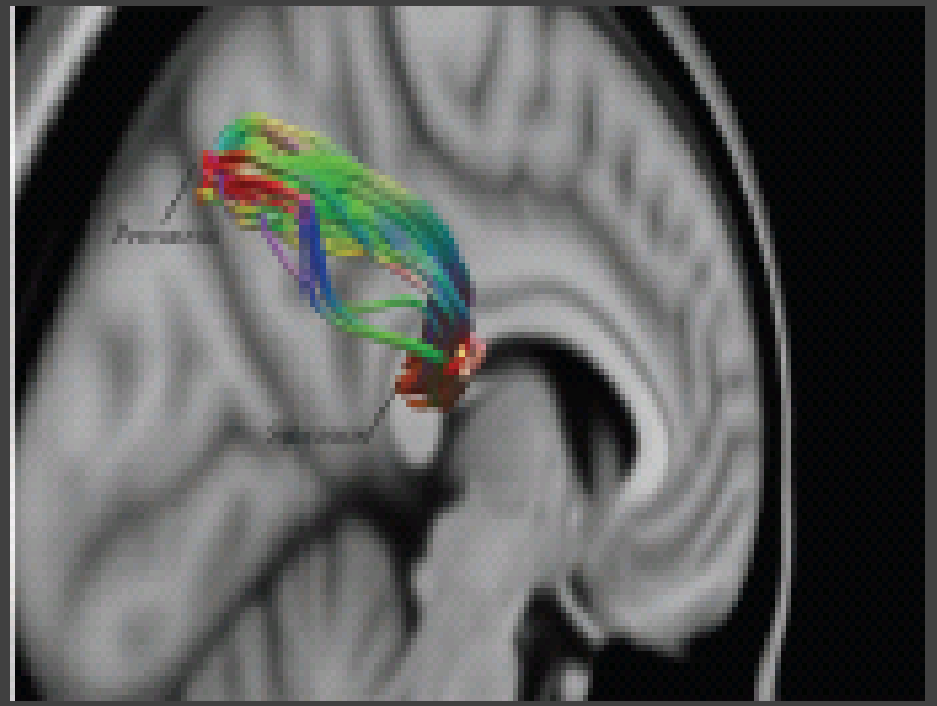
Multiple, but not all, studies show altered Brain Structure and Function in Youth Who Regularly Use Cannabis

Early (<18y) Cannabis Use Decreases Axonal Fiber Connectivity

Precuneus to splenium



Fimbria of hippocampus, hippocampal Commissure, and splenium



Axonal paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33).

Source: Zalesky et al Brain 2012

Adolescent Brain Cognitive Development (ABCD) Study

A Federal Collaboration: NIDA, NIAAA, NCI, NIMH, NIMHD, NICHD, NINDS, NHLBI, OBSSR, ORWH,CDC-DASH, CDC-DVP, DOJ, NEA

Ten year longitudinal study of ~12,000 children starting at ages 9-10 to assess effects of childhood experiences, including use of *cannabis* and other substances, on individual brain development trajectories through adolescence into early adulthood

Adolescent Brain Cognitive Development®
Teen Brains. Today's Science. Brighter Future.

Neuroimaging

Geocoded Data

Neurocognition

Physical Health

Biospecimens

Mental Health

Culture and Environment

Substance Use

Novel technology

Cannabis Use in Adolescents: Risks for Adverse Neurodevelopmental Outcomes

- Endocannabinoid system (ECS) is involved in brain development, e.g., myelination
- Human imaging studies report alterations in CB1 receptor-rich brain areas following cannabis exposure
- Multiple studies indicate effects on learning, IQ, motivation, long term academic and career outcomes, mental health
- Preclinical studies of adolescent exposure show lasting effects of THC on adult drug seeking, stress responses, brain reward systems

Caveats:

- Users who start young and use frequently may have other risk factors for adverse outcomes
- Adolescents who use cannabis regularly often use multiple substances
- And….we don’t know whether effects persist if cannabis use is stopped

What Do We Know Now?

- Risks during intoxication:
  - Psychosis/paranoia
  - Cardiovascular events/Postural hypotension
  - Driving Accidents: slowed reaction time/attention deficits (worse combined with alcohol)
- High Potency Products:
  - Risk of adverse reactions, especially in naïve users; or those exposed accidentally
  - Contribute to psychosis risk
- Risks of Chronic Use (especially in those exposed prenatally or in adolescence)
  - Cannabis Use Disorder
  - Other Substance Use Disorders
  - Mental Illness, especially psychotic disorders; suicidal ideation
  - Poorer academic achievement, financial success, and life satisfaction
  - Hyperemesis syndrome
  - Prenatal exposure: low birthweight, greater risk of NICU involvement, modest effects on brain development and behavioral outcomes through early adulthood

U.S. Federal Policy

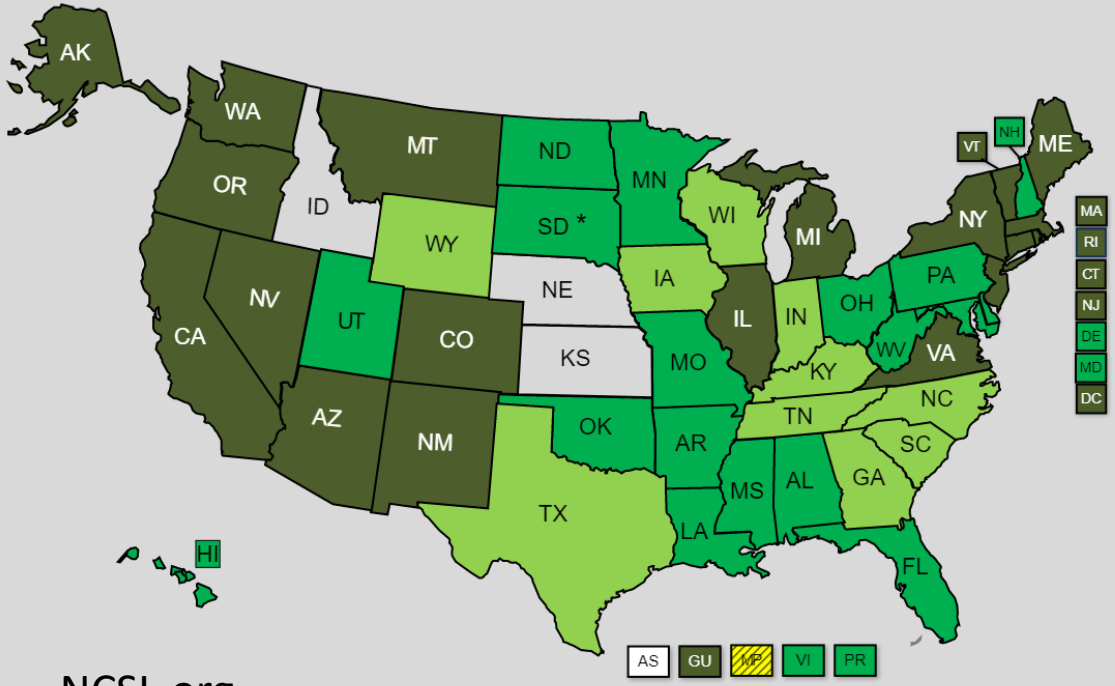
Marijuana (cannabis >0.3% delta-9 THC) is Schedule I under Controlled Substances Act: high risk for abuse; no accepted medical use.

- Illegal to grow, possess, or distribute
- Each nation can designate a single source of marijuana for research purposes
- Until recently, DEA only licensed a single grower (University of Mississippi, since 1968), under a NIDA – supported contract.
- *Several additional growers have just been approved.*

Hemp (not more than 0.3% delta-9 THC dry weight) is not controlled.

- Regulation of growing: Dept. of Agriculture
- Regulation of product quality and labeling: FDA

State Policies (May 2022)



NCSL.org

State Laws vary on:

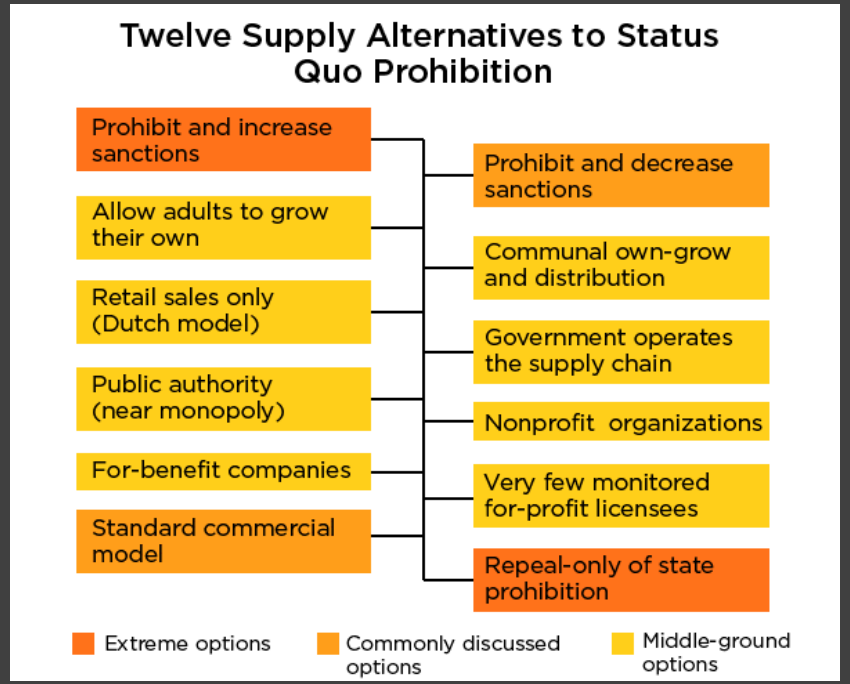
- Marketing, product labeling, distribution
- Product testing
- Public consumption
- Taxation
- Licensing
- Expungement and Equity

Decriminalization, Legalization, and Commercialization:
Different Levels of Risk

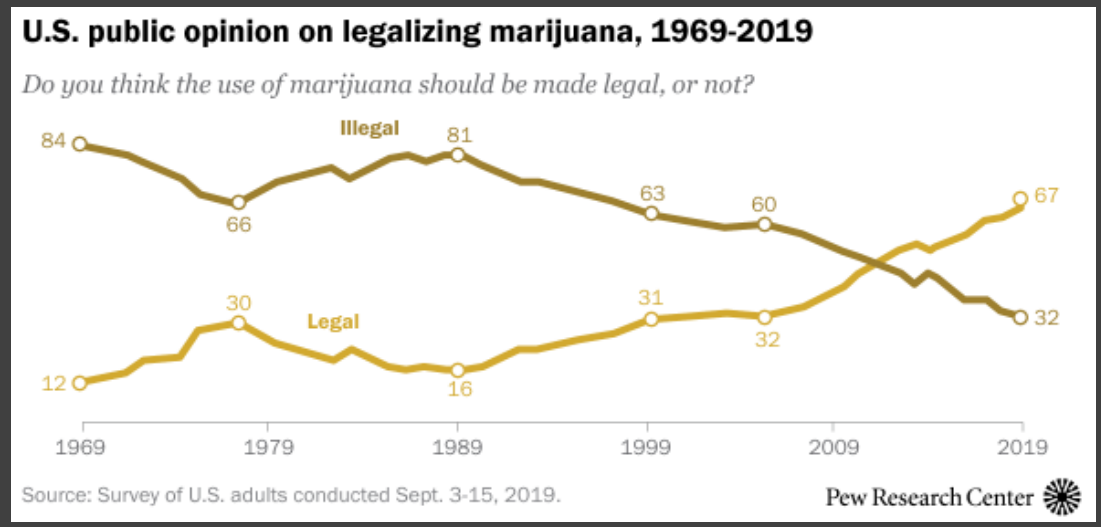
- Commercialization
  - An emerging industry with vested interests in policy and regulation
  - Competitive → product innovation, more effective, lower prices
- Challenging the Regulations
  - Industry and consumer interests vs health and social issues
  - Political influence and impact on other states
- Cultural Acceptance/Public Opinion
  - What is «Acceptable use»
  - Balancing prevention/health messages and stigma
  - Addressing criminal justice disparities
  - Presence in public space, culture, communities

Policy Influencers

- Economic considerations
- Social Justice/Equity
- Media/Messaging
- Federal Agencies
- *Science* (we hope)

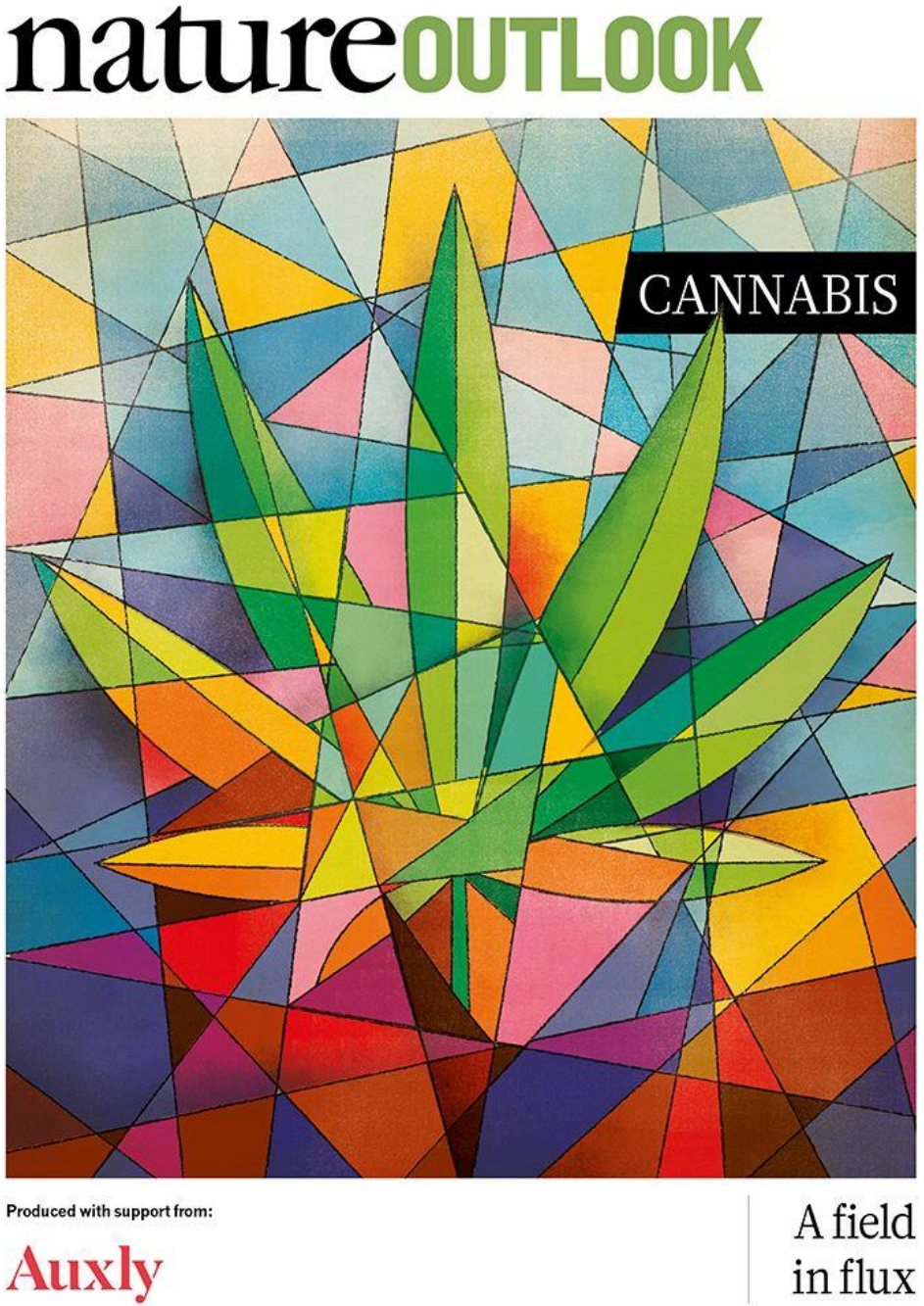


-Caulkins et al, 2015

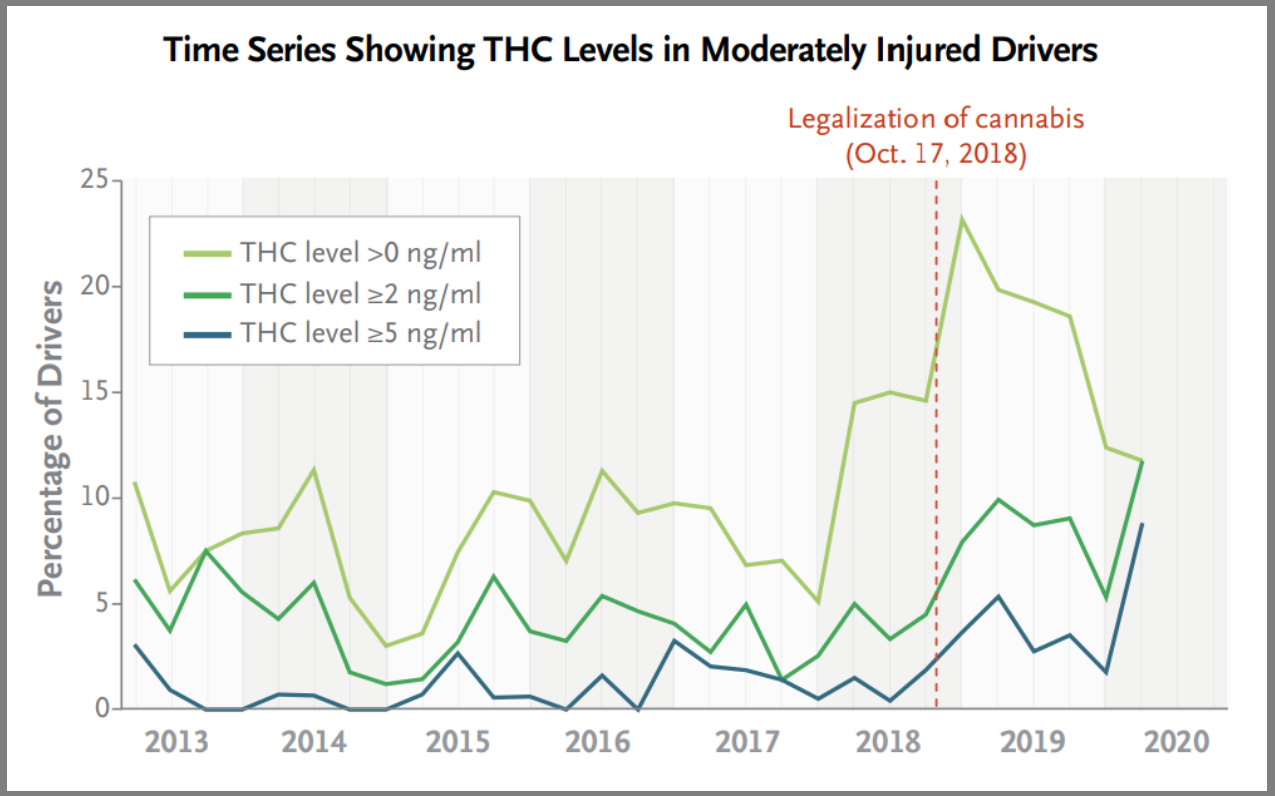


WHAT IS THE IMPACT OF LEGALIZATION?

- Use, Harmful Use, Use Disorders
- Mental Health
- Other Substance Use
- Academic Achievement
- Child/Adolescent Development
- Accidents, ER Visits
- Other Health Effects (e.g., heart, lung)
- Secondhand Smoke
- Pregnancy Outcomes
- Productivity
- Economics (Revenue vs. Costs)
- Criminal Justice Disparities
- Benefits



Cannabis Legalization and Detection of THC in Injured Drivers

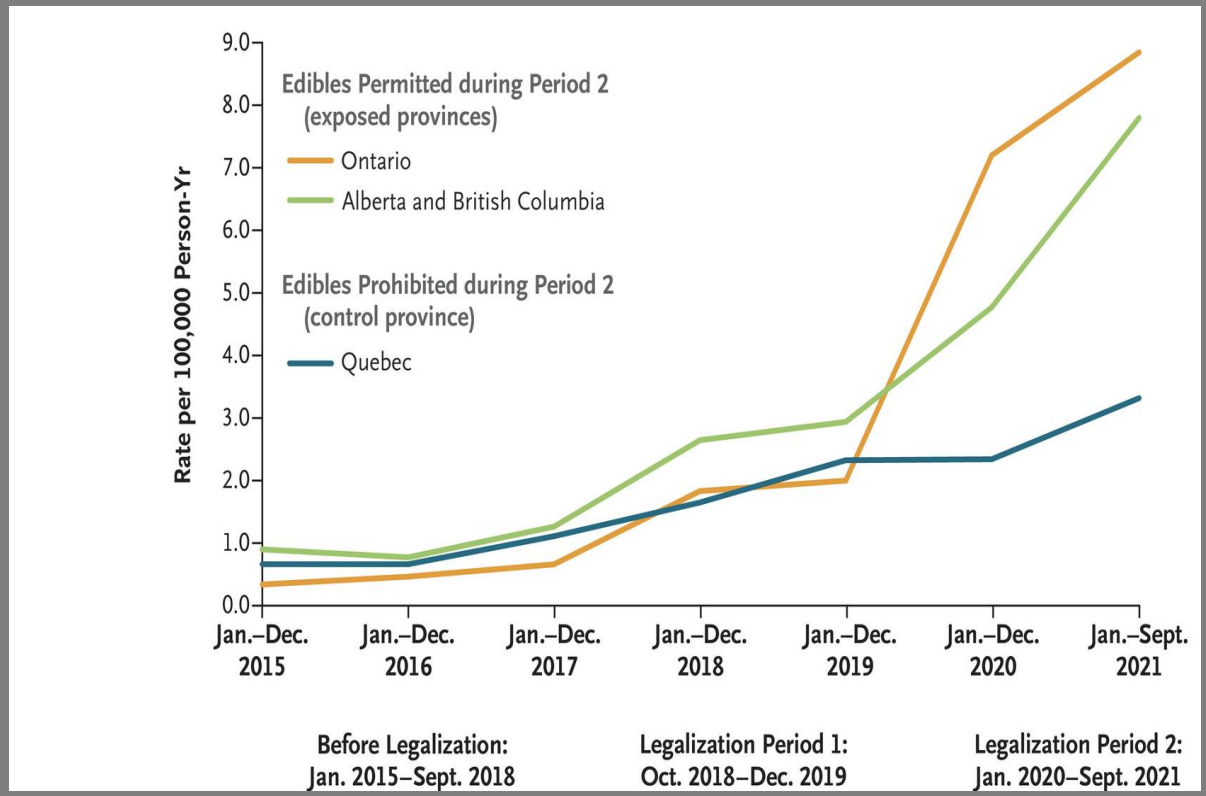


CONCLUSIONS

The percentage of moderately injured drivers who had THC levels above the legal limit more than doubled after cannabis legalization in Canada.

Brubacher JR et al., N Engl J Med 2022; 386:148-156.

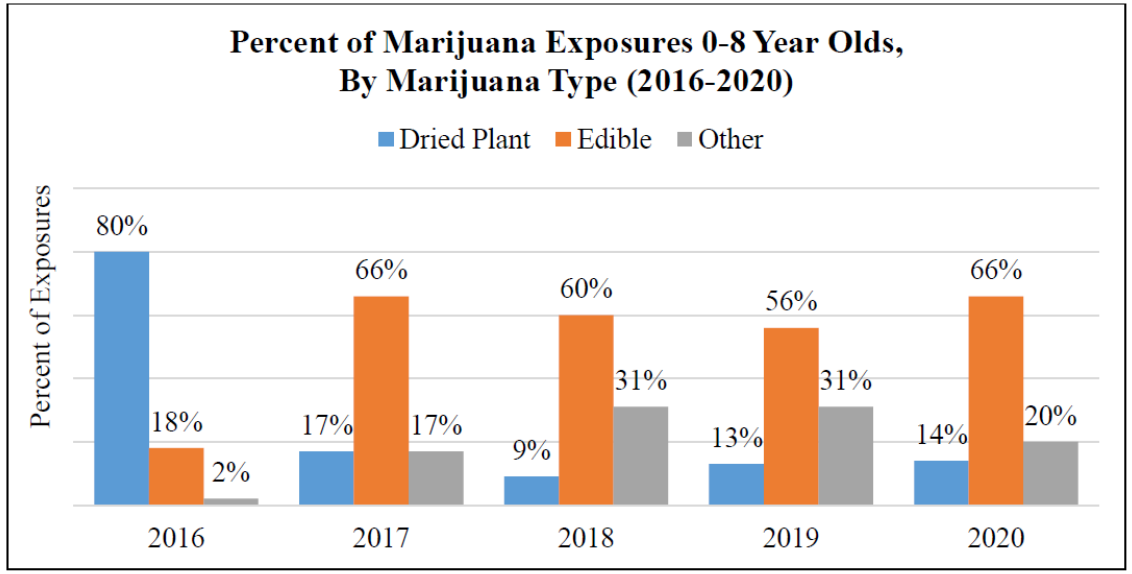
Rates of Hospitalization for Cannabis Poisoning in Children 0 to 9 Years of Age in Four Canadian Provinces, 2015–2021



Significant increases in ED visits due to cannabis exposures among children after legalization of recreational cannabis

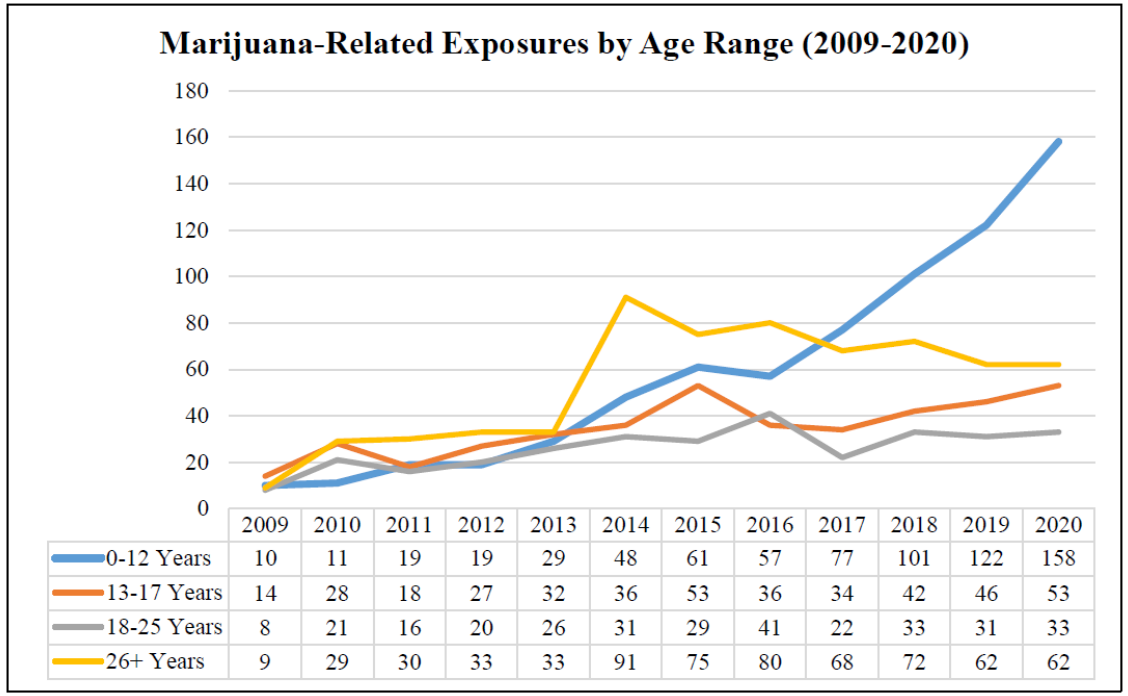
Myran DT et al., JAMA Network Open 2022.

UNINTENTIONAL EXPOSURES



SOURCE: Rocky Mountain Poison and Drug Center

NOTE: The code for marijuana edibles did not go into effect until 2016. Therefore, any cases of edible marijuana exposure which occurred prior to 2016 were coded under "dry plant." Other marijuana includes oral pills/capsules, concentrated extracts (to include oils and tinctures), topical preparations, marijuana devices, and unknown/other forms of mariiuana.

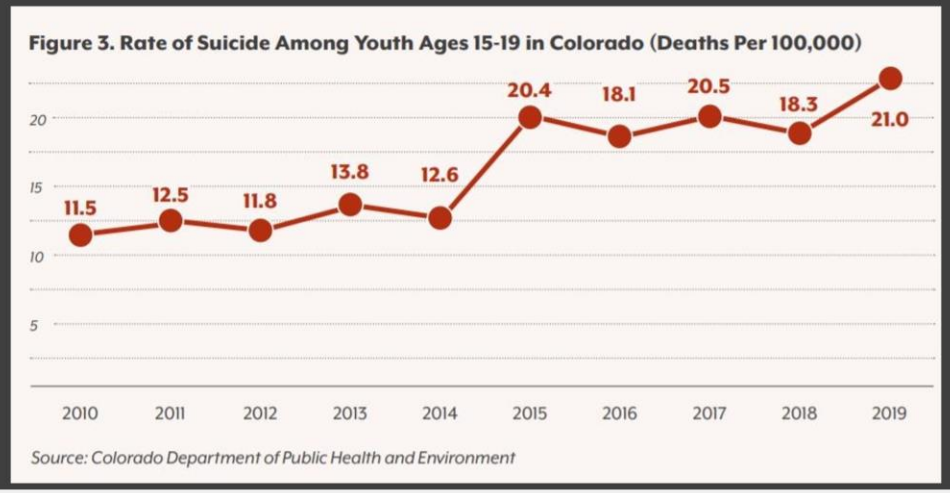


	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
0-12 Years	10	11	19	19	29	48	61	57	77	101	122	158
13-17 Years	14	28	18	27	32	36	53	36	34	42	46	53
18-25 Years	8	21	16	20	26	31	29	41	22	33	31	33
26+ Years	9	29	30	33	33	91	75	80	68	72	62	62

SOURCE: Rocky Mountain Poison and Drug Center

Increase in Teen Suicide Rates Associated with Increased Detection of Marijuana

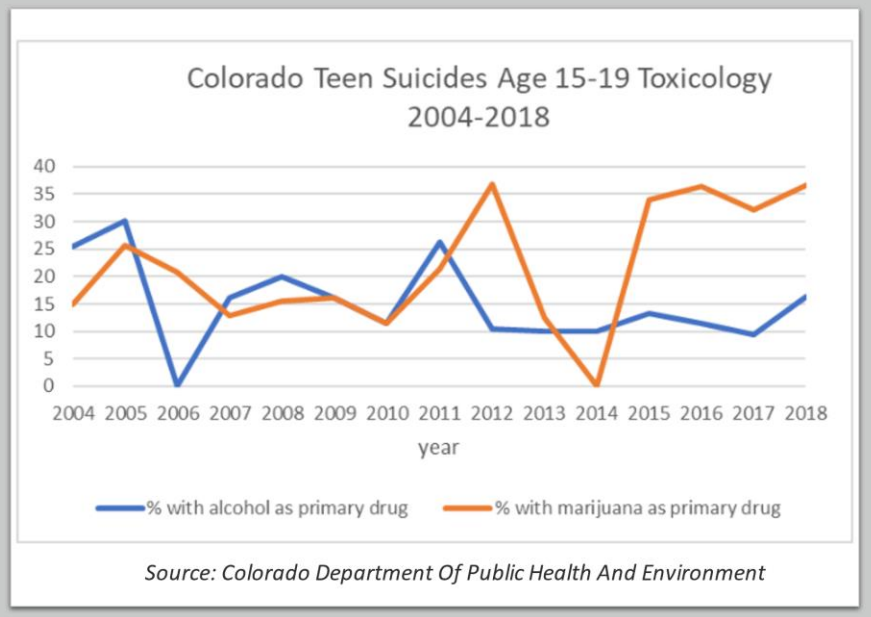
Courtesy of Laura Stack



JOHNNY'S AMBASSADORS

What happened in Colorado in 2014? Coincidence?

In Colorado in 2018, marijuana was present over 36% of the time in suicides ages 15-19.



JOHNNY'S AMBASSADORS

Caveats to HIDTA reports on Colorado

- No baseline data before legalization went into effect (2014) or commercialization (2009)
  - No correction for changes in what is measured following legalization.
- Data on driving accidents or fatalities do not measure impairment (cannabis pharmacokinetics are complex). If use goes up, then increases in positive toxicology would be expected.
- Data not expressed as rates can be misleading since population has increased over time.
- Some serious adverse consequences (e.g., incidence of psychosis) are too rare to measure accurately.
- Uses surveillance measures that are available—not specifically targeted toward cannabis harms; may not have sufficient granularity.

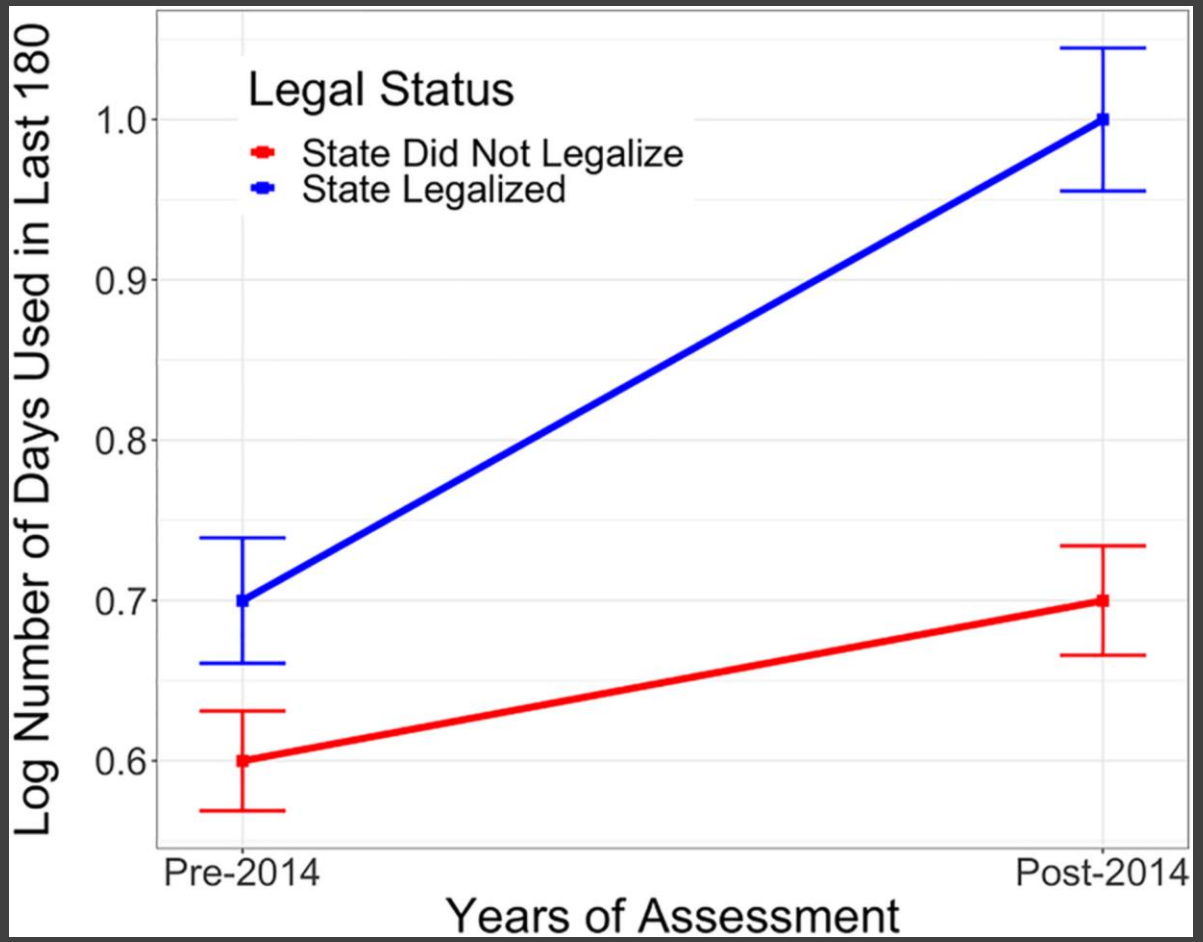
Bottom Line—so far…

- Risks to some can be very serious (youth, pregnant persons, individuals with a propensity for mental illness)
- Perceptions of harm are universally down—even among vulnerable populations
- Patterns of use are changing, likely resulting in consumption of much larger amounts of THC
- Increases in product variety will continue to sustain a market where the costs of manufacturing have plummeted
- Likely that unanticipated harms will emerge with chronic use (especially with high THC exposure)
  - Hyperemesis
  - Suicidal ideation, attempts, completion
  - Increased vulnerability to infections
- While use among adolescents has not increased; use in young and older adults has increased substantially
  - Increases in CUD in adolescents from 2018-2019 (despite lack of overall increases)
  - Adult populations 26 + consistently show changes on many measures (Use, heavy use, treatment admissions)
  - States with more liberal laws have been and continue to be above the National average on most measures (some may show increases in youth cannabis use)
- Regulations matter and can help mitigate potential harms
- Strong public health campaigns need to be in place when laws change
- Baseline data should be collected before changes in the laws go into effect

Public health experiment is still in its early stages—especially related to high potency products, mass media campaigns, commercialization, “Big Cannabis”, etc.

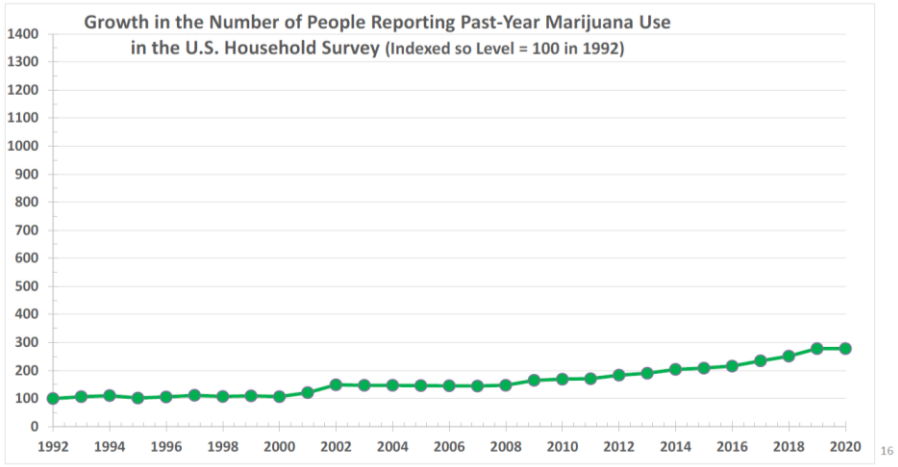
THANK YOU!

Impacts of recreational cannabis legalization on cannabis use: a longitudinal discordant twin study



Zellers et al. Addiction, August 2022, DOI: (10.1111/add.16016)

Since 1992 The Number Reporting Marijuana Use in the Past-Year to NSDUH Has Nearly Tripled



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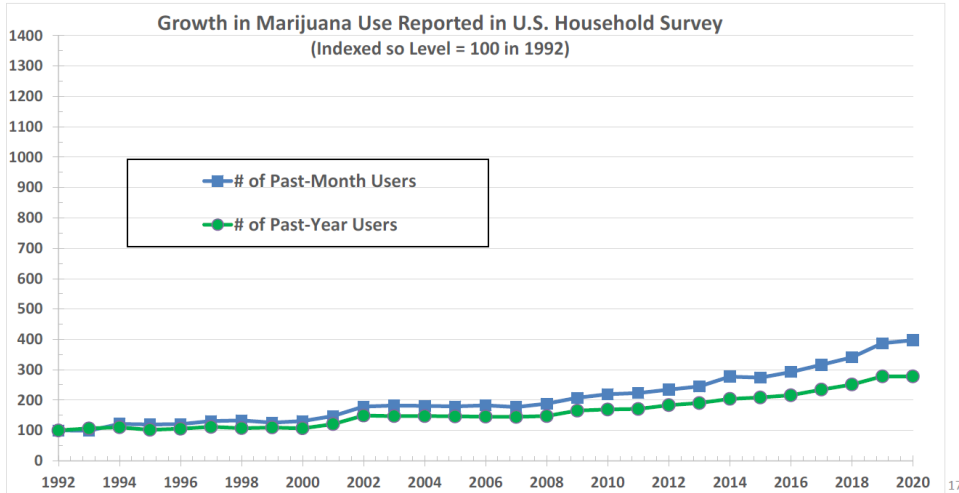
CANNABIS USE IS INCREASING: *USERS ARE USING MORE FREQUENTLY*

The Number of "Current" (Past-Month) Users Has Quadrupled



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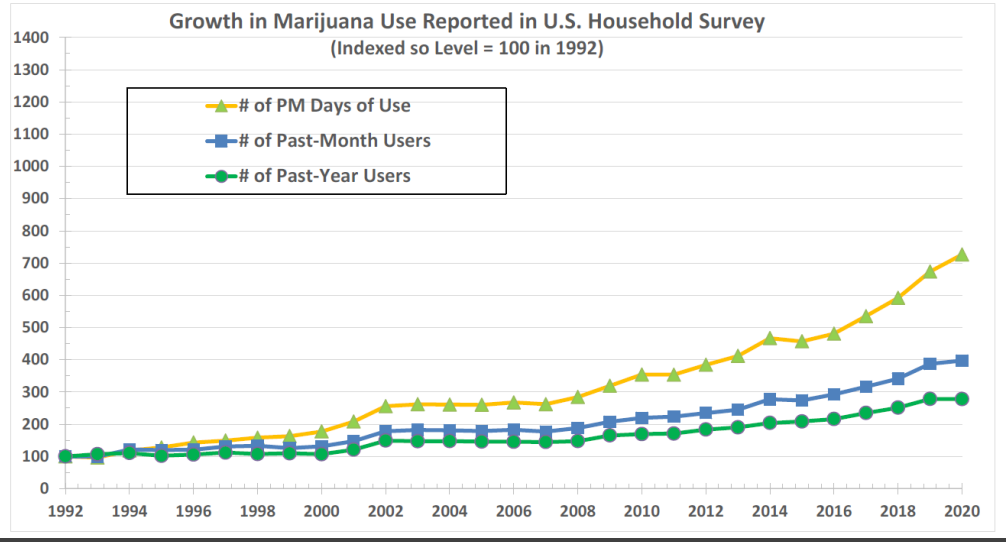
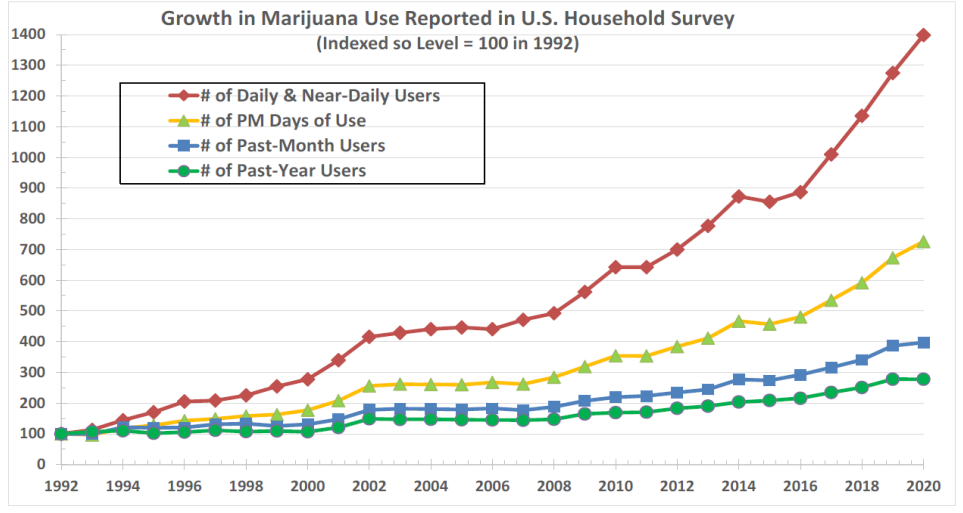
Days of Use Reported Has Increased Sevenfold (to 6 Billion per Year)



NSDUH (AGES 12 AND OLDER)

The Number Using Daily or Near-Daily Has Grown Fourteenfold from 0.9 to 12.4 Million



Slides Courtesy of Jonathan Caulkins