



Credit: Atomazul/Shutterstock

Impact of Marijuana on Pregnancy, the Fetus and Neonate

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Disclosures

- I have nothing to disclose



Learning Objectives

At the end of this lecture, participants will be able to:

- Describe the types of cannabinoids and how they work
- Discuss the prevalence and trends of cannabis use in the U.S.
- Describe what is known about the short- and long-term health effects and social consequences of cannabis use
- Discuss the prevalence and impact of cannabis use during pregnancy

Cannabinoids



- Three forms of cannabinoids: phyto (plant), endo (within) and synthetic (manufactured)
- There are >100 unique phytocannabinoids in the *Cannabis sativa* plant along with terpenes (entourage/ensemble effects) and more than 500 other chemicals when combusted
- The most common is the intoxicating THC and the most medically promising for conditions such as epilepsy is cannabidiol (CBD) which is not intoxicating but is psychoactive.

How Cannabis Works



Endocannabinoids
(Brain Derived)



Phytocannabinoids
(Plant Derived)



Synthetic Cannabinoids
(Made in Lab)

Endocannabinoid Receptors: CB1 & CB2

The endocannabinoid system (ECS) is involved in regulating a variety of physiological processes including appetite, pain and pleasure sensation, immune system, mood and memory

Cannabinoid Receptors Are Located Throughout the Brain

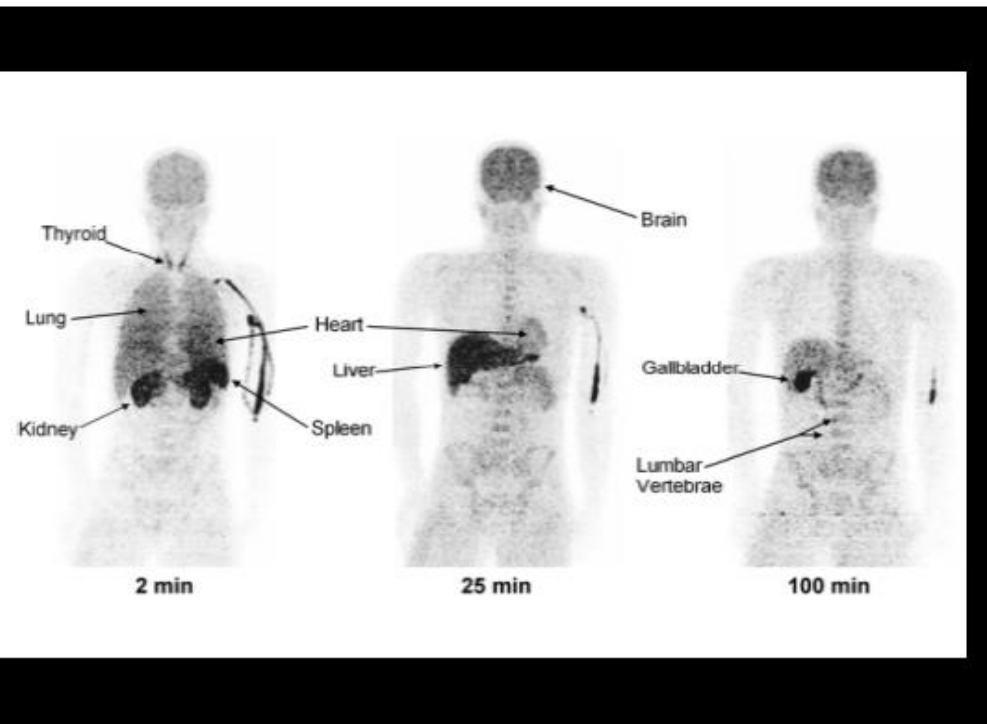
Regulation of:

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

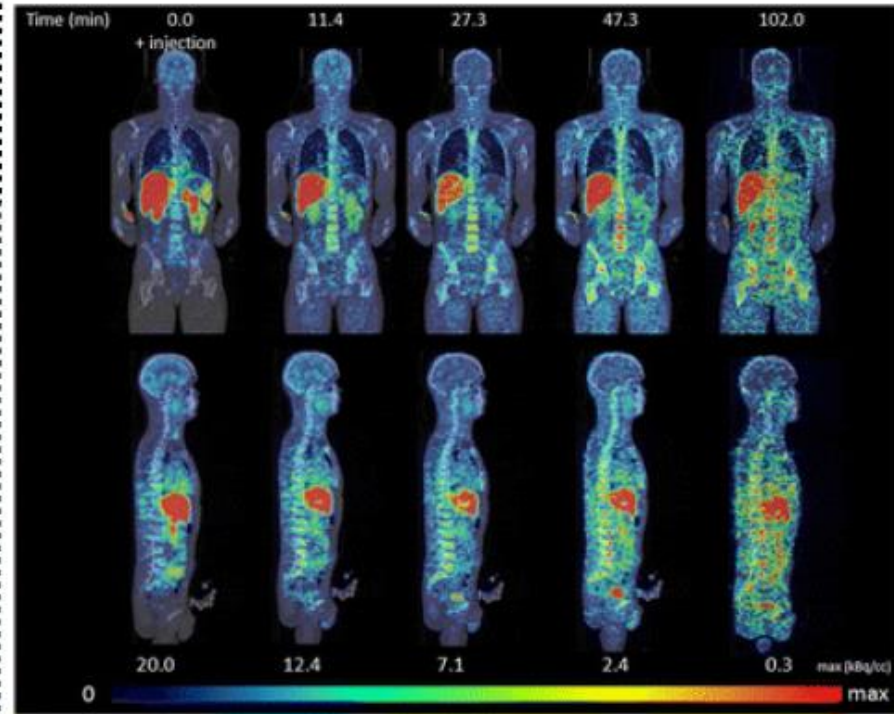


Cannabinoid Receptors Are Also Located Throughout the Body

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



PET images of ^{11}C -NE40 (CB2R radioligand)



The Endocannabinoid System

Brain cells (neurons) communicate with each other by sending chemical messages. The chemicals (neurotransmitters) cross a gap between neighboring neurons before attaching to their specific receptors.

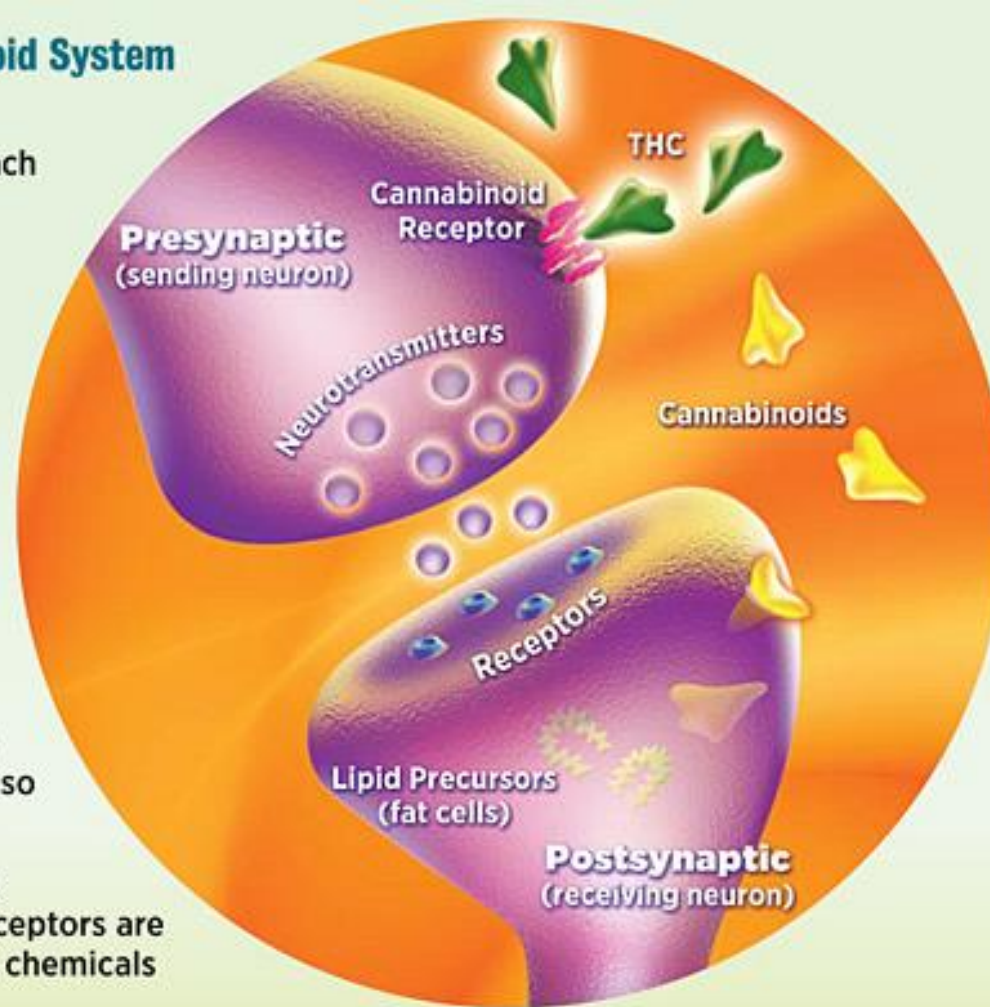
Presynaptic:

The neuron sending a message by releasing a chemical when signaled to do so

Postsynaptic: The neuron receiving the message when its receptors are activated by specific chemicals (neurotransmitters)

Neurotransmitters: The chemical messengers that travel from one brain cell to another

Receptors: Activated by neurotransmitters, receptors trigger a set of events that allows a message to be passed along to other neurons



Cannabinoids: Natural chemicals (anandamide and 2-AG) that bind to cannabinoid receptors in the brain and the body

THC: The main active ingredient in marijuana; THC, also a cannabinoid, interferes with the normal functioning of the endocannabinoid system

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

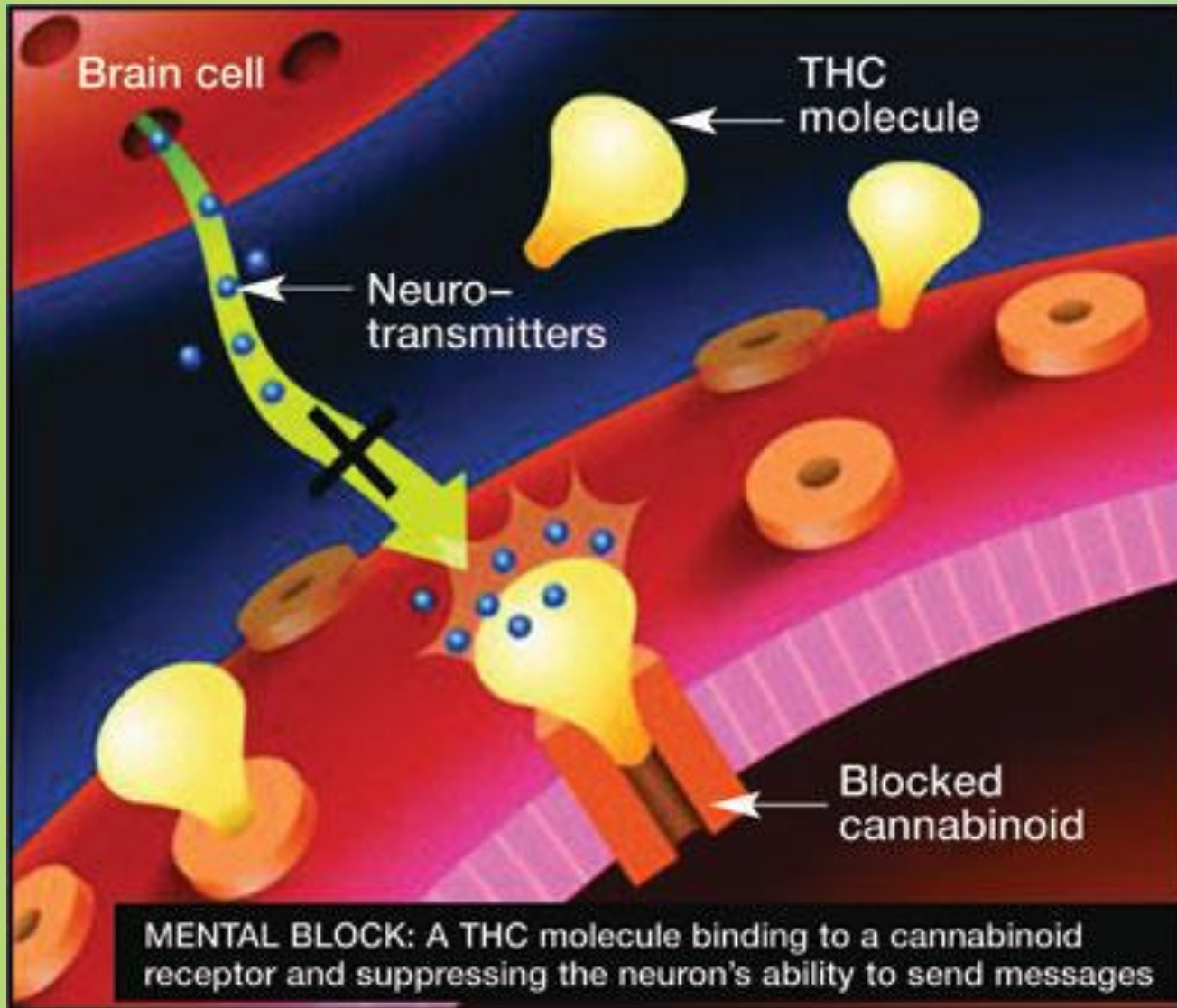
Endocannabinoids

Anandamide is a partial agonist of CB1. **2-AG** is a full agonist of both CB1 and CB2 receptors.

Plant-derived cannabinoid

THC is a partial agonist of CB1 receptors

How Cannabis Works



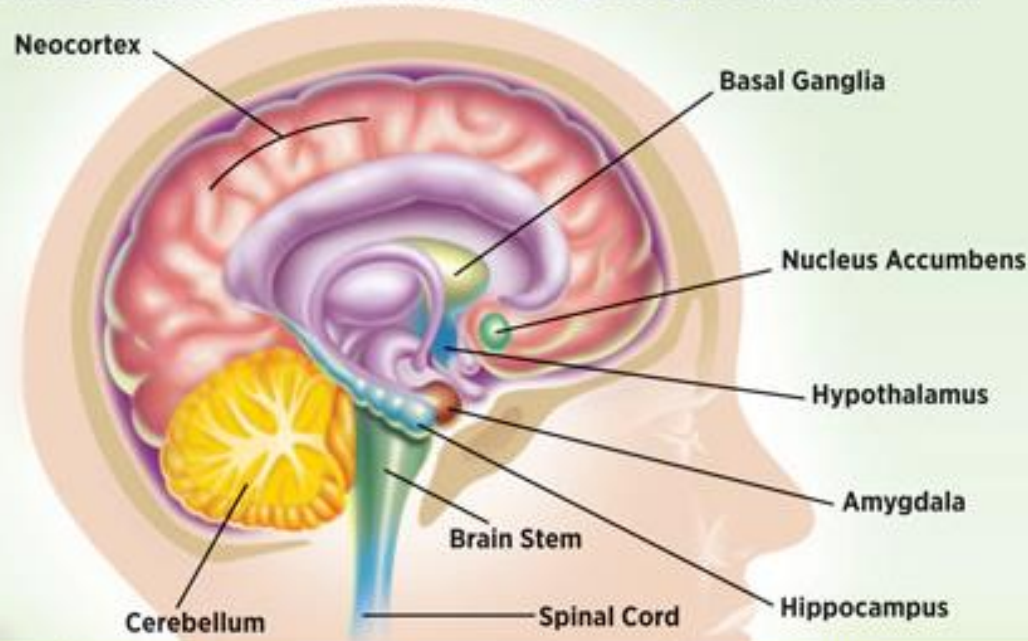
What is marijuana/cannabis?



- Dried flowering heads of the *Cannabis sativa* or *indica* plant cross breeds
- Known as: marijuana (in US legislation), cannabis, pot, weed, ganja, dank, 420, grass, dope, bhang, hashish
- Potency of principal psychoactive cannabinoid delta 9 tetrahydrocannabinol (THC) is generally higher than ever before (15-25%) and greatly differs by preparation technique with levels of cannabidiol (CBD) almost bred out of most strains

Cannabinoid Receptors Are Located Throughout the Brain: THC Effects on the Brain

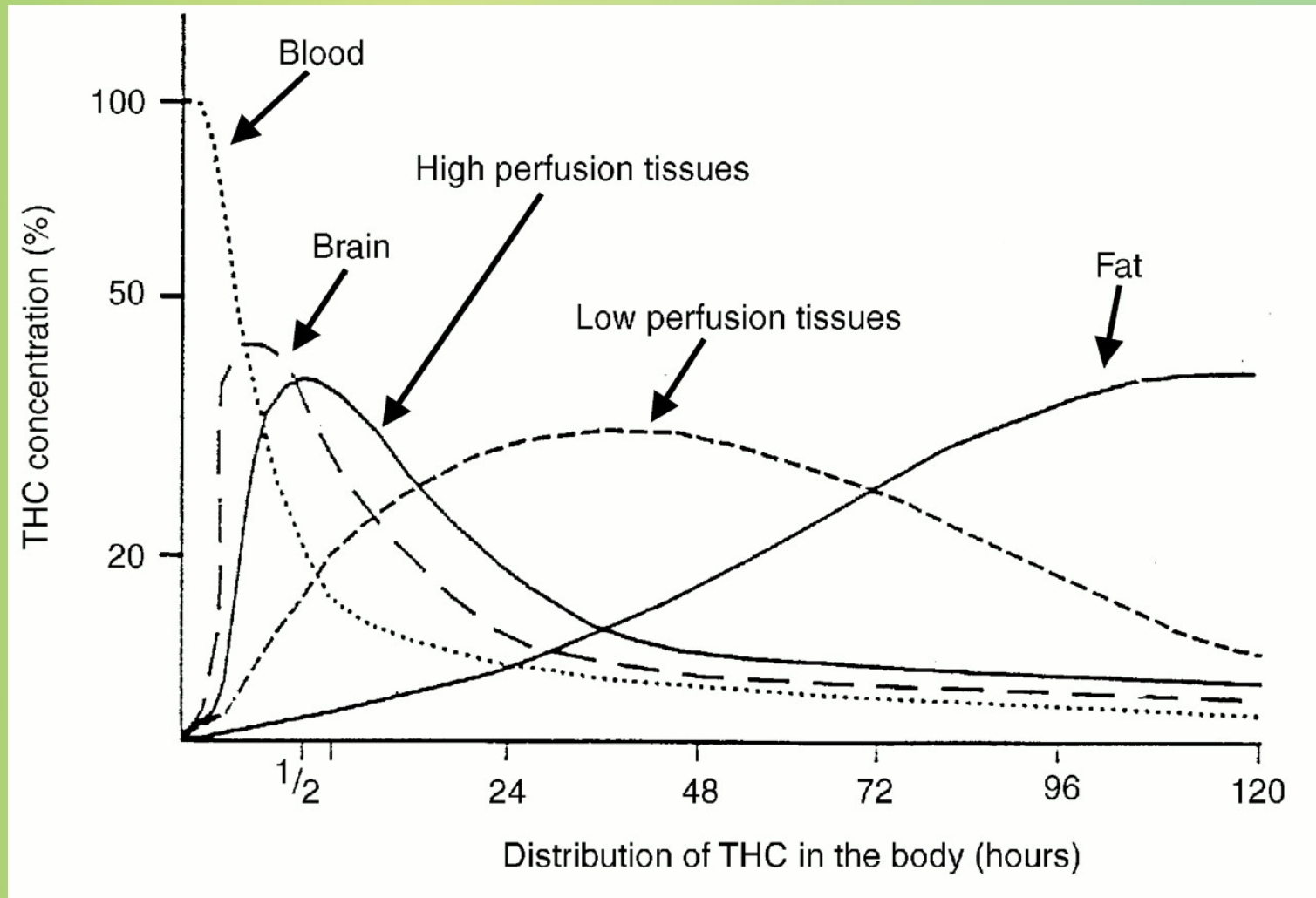
How does THC affect behavior? *It depends on where the CB receptors are in the brain.*



Brain Structure	Regulates	THC Effect on User
Amygdala	emotions, fear, anxiety	panic/paranoia
Basal Ganglia	planning/starting a movement	slowed reaction time
Brain Stem	information between brain and spinal column	antinausea effects
Cerebellum	motor coordination, balance	impaired coordination
Hippocampus	learning new information	impaired memory
Hypothalamus	eating, sexual behavior	increased appetite
Neocortex	complex thinking, feeling, and movement	altered thinking, judgment, and sensation
Nucleus Accumbens	motivation and reward	euphoria (feeling good)
Spinal Cord	transmission of information between body and brain	altered pain sensitivity

The brain structures illustrated above all contain high numbers of CB receptors

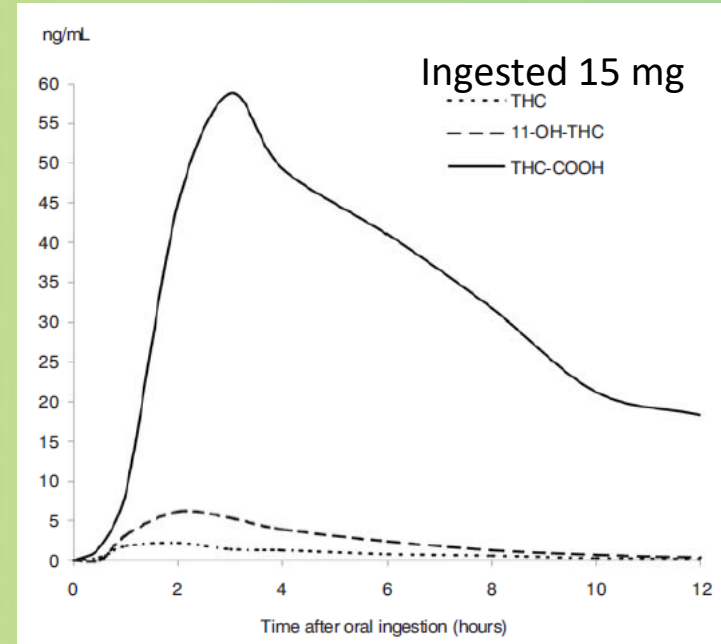
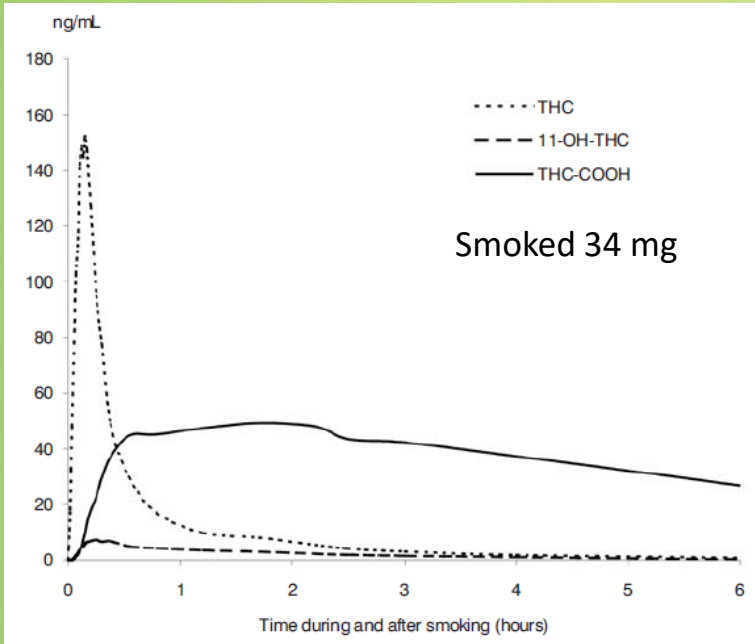
Distribution of THC in the body.



C. HEATHER ASHTON BJP 2001;178:101-106

THE BRITISH JOURNAL
OF PSYCHIATRY

Clinical Pharmacokinetics of Cannabis



	Inhaled	Ingested
Absorption	10-20%	1-10%
Onset of action	6-12 min	30-120 min
Peak effect	20-30 min	2-3 hr
Duration of effect	1-3.5 hr	5-8 hr or more
Toxic dose (THC)	15 mg/kg	
Lethal dose (THC)	30 mg/kg	
Half-life	28 hr (56 hr chronic use)	

Synthetic Cannabinoids

- First developed in 1980s by chemistry professor John Huffman to enhance understanding of the cannabinoid system (JWH-018)
- Known as: spice, K2, fake weed, Yucatan fire, skunk, moon rocks, Black Mamba, crazy clown, Kronik, Kush, Joker
- The synthetic cannabinoids are either sprayed on dried, shredded plant material so they can be smoked (herbal incense) or sold as liquids (liquid incense) to be vaporized and inhaled in e-cigarettes or other devices.
 - Plant matter itself can potentially be poisonous or hallucinogenic
 - Laced with flavors, rat poison, embalming fluids



Synthetic Cannabinoids

- How used: 80% inhalation by smoking, 20% ingestion by eating or drinking as tea
- 7 main structural groups of synthetic cannabinoids:
 - Naphthoylindoles (e.g. JWH-018, JWH-073 and JWH-398).
 - Naphthylmethyloindoles.
 - Naphthoylpyrroles.
 - Naphthylmethyloindenes.
 - Phenylacetylindoles (i.e. benzoylindoles, e.g. JWH-250).
 - Cyclohexylphenols (e.g. CP 47,497 and homologues of CP 47,497).
 - Classical cannabinoids (e.g. HU-210).
- Many synthetic cannabinoids, e.g., JWH-018, are full and potent CB1 agonists and have a **4-fold higher affinity for CB1R and 10-fold higher affinity for CB2R**, accounting for the higher prevalence of adverse reactions and toxicity

Synthetic Cannabinoids

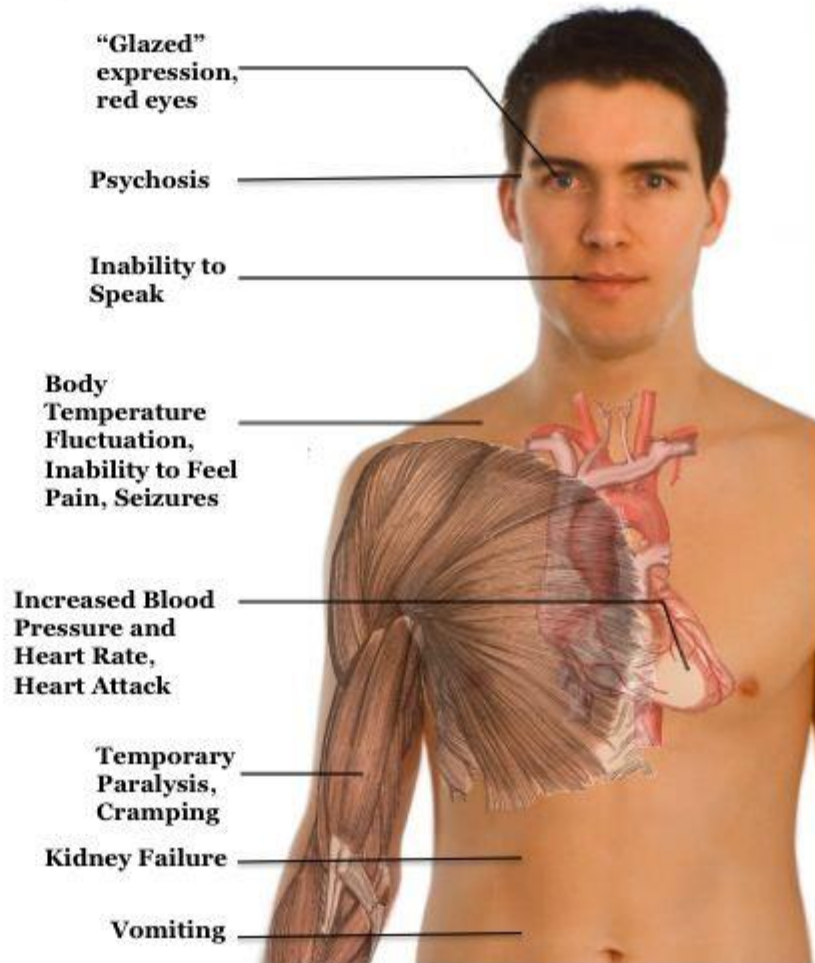
SYMPTOMS OF SYNTHETIC MARIJUANA USE

OVERALL SYMPTOMS

- Increased Agitation
- Paranoid Delusions
- Depression
- Hallucinations
- Exaggerated Thoughts of Suicide
- Feeling of Impending Doom
- Panic Attacks
- Heart Attacks

Please Call 911 IMMEDIATELY if you suspect someone has used Synthetic Marijuana!

Many of these symptoms may be life threatening and may change suddenly.



Major Adverse Rxns:

- Heart attack
- Ischemic stroke
- Acute kidney injury
- Generalized tonic-clonic seizures
- Rhabdomyolysis
- Cannabinoid-induced hyperemesis synd.
- Death
 - Prolonged QTc interval

Not detected on standard blood or urine tox screens

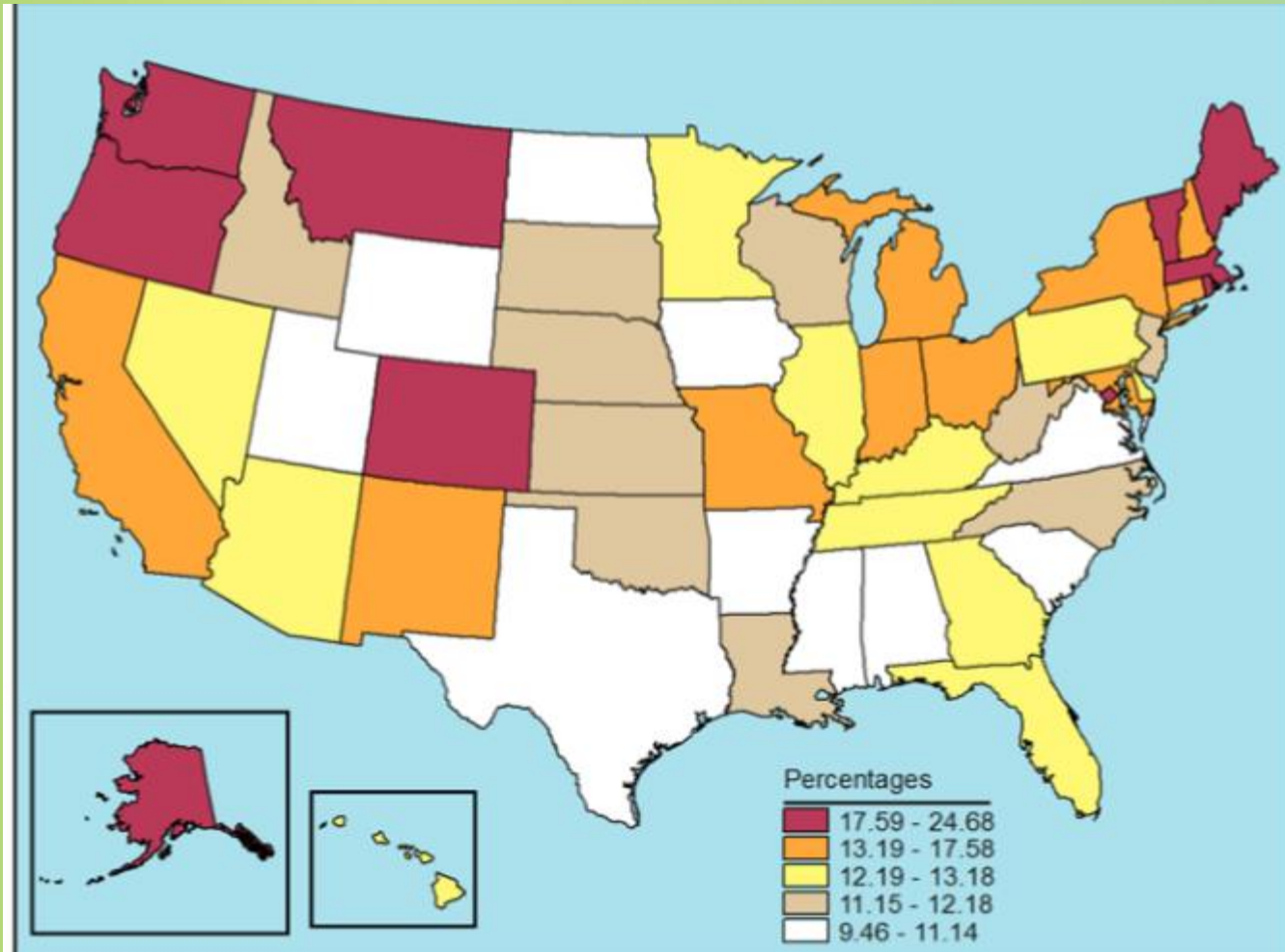
“Cannabis Eyes”



Cannabis: Most Commonly Used “Illicit” Drug in the U.S.

- Over **22 million** Americans 12 and older were past month marijuana users
- Approximately **4.0 million** Americans met criteria for cannabis use disorders in 2015
- An estimated **2.6 million** Americans used it for the first time; **1.2 million** were between the ages of 12 and 17

Marijuana Use in Past Month Among People 12 and Older, by Substate Region



Source: SAMHSA, Center for Behavioral Health Statistics and Quality, NSDUH, 2015 and 2016.

Demographic	Past-Month Use Rate (%)
Ethnicity	
White, non-Hispanic	8.4
African-American	10.7
Hispanic	7.2
Asian, non-Hispanic	3.0
Gender	
Male	10.6
Female	6.2
Education	
< HS	8.2
HS graduate	9.1
Some college	10.5
College graduate	5.9
Family income	
< \$10 k	13.6
\$20 k - \$29.9 k	9.7
\$50 k - \$74.9 k	7.8
\$75 k +	6.6
Age	
12-17	7.1
18-25	20.1
26-34	13.0
35-49	7.1
50+	3.9

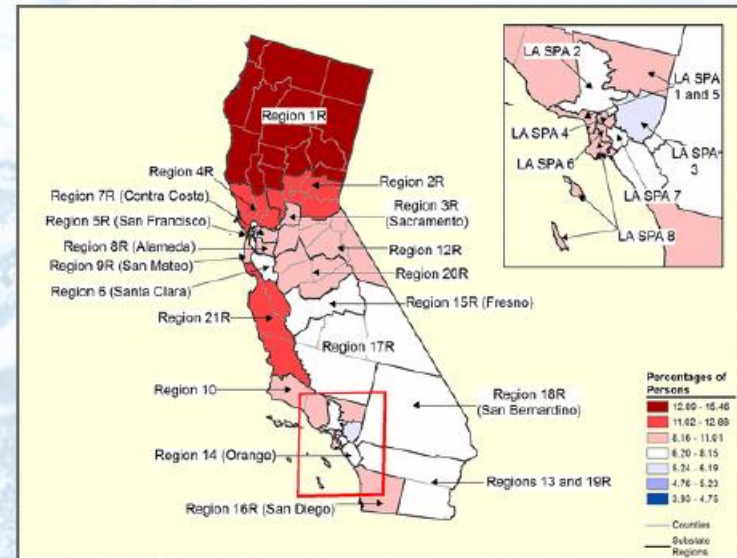
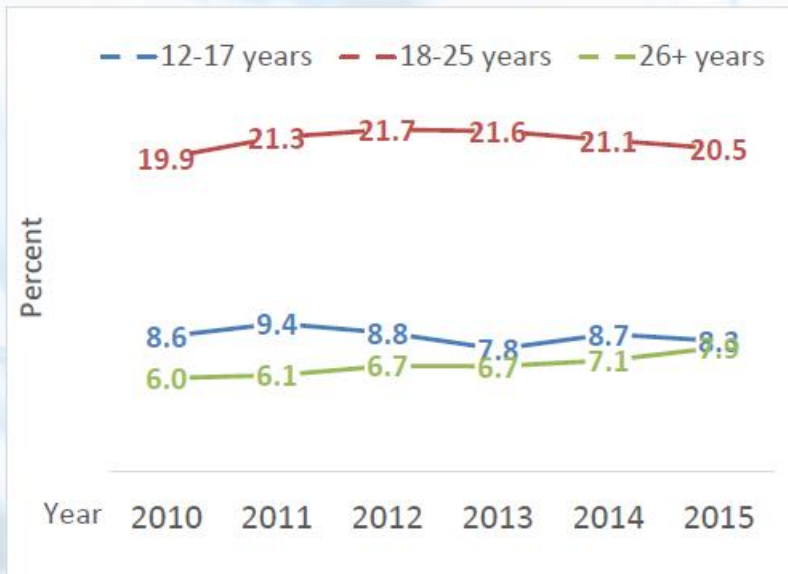
Past Month Use Rates by Demographic, U.S., 2016



Current Usage

Self-Reported Cannabis use in the Past Month Among Californians Aged 12 and Older

National Survey on Drug Use and Health, Substance Abuse and Mental Health Services Administration

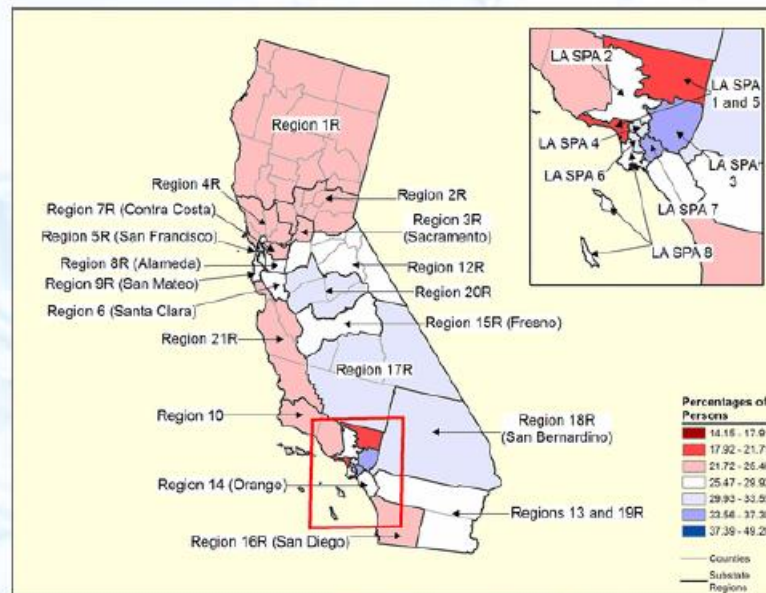


Source: Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2009-2015. <https://www.samhsa.gov/data/population-data-nsduh>

Perceptions of Great Risk

Perceptions of Great Risk from Smoking Cannabis Once a Month among Californians Aged 12 and Older

2012-2014 National Survey on Drug Use and Health, Substance Abuse and Mental Health Services Administration

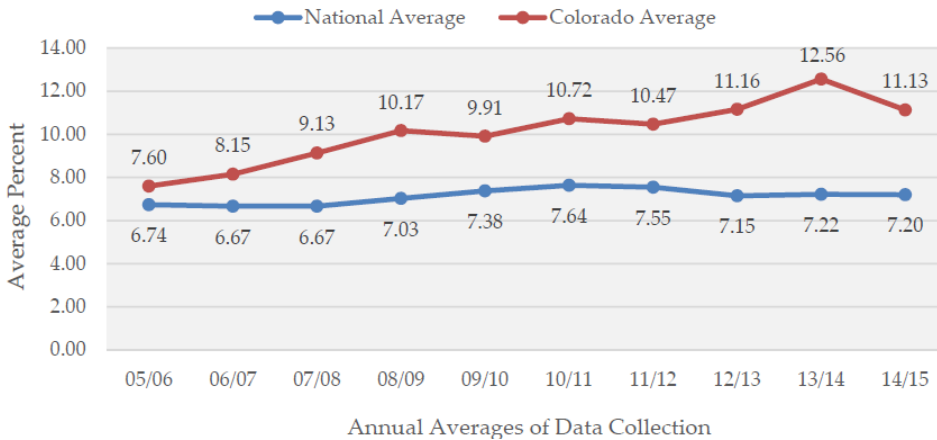


Source: Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2012, 2013, and 2014.

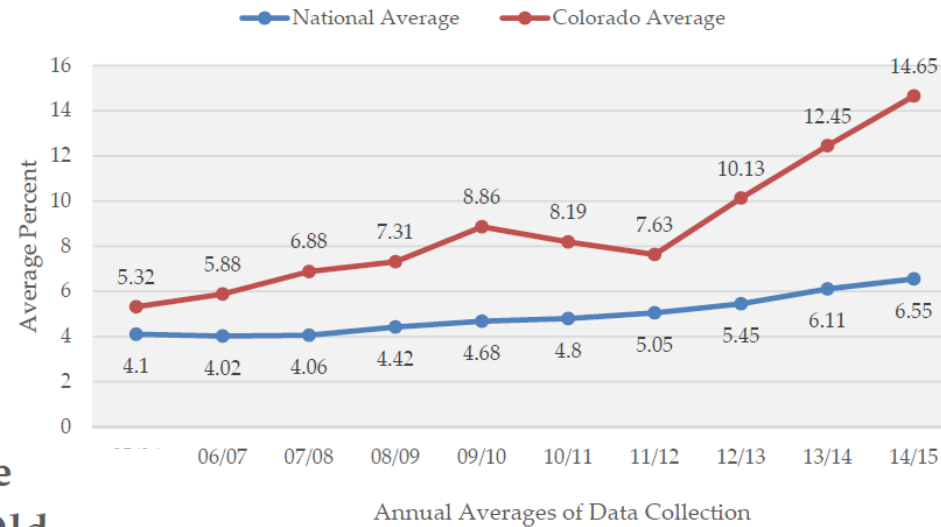


Rising Marijuana Use in Colorado Post Legalization (2013)

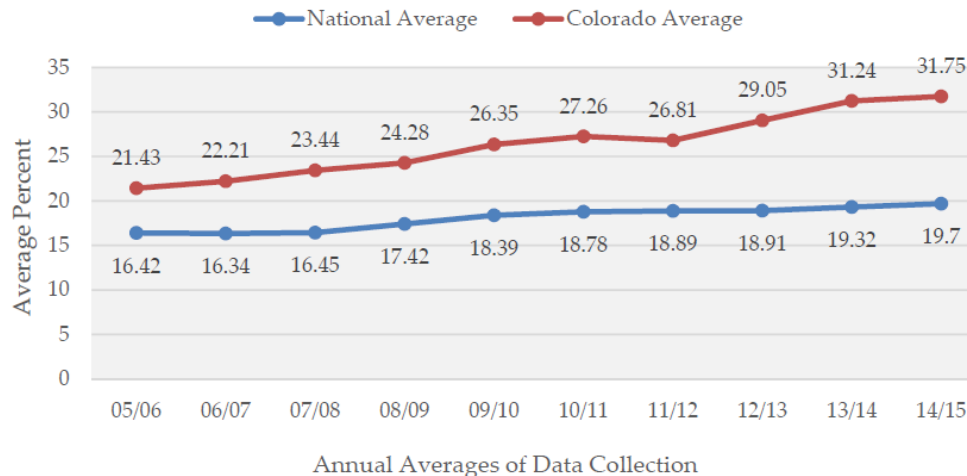
Past Month Marijuana Use Youth Ages 12 to 17 Years Old



Past Month Marijuana Use Adults Age 26+ Years Old

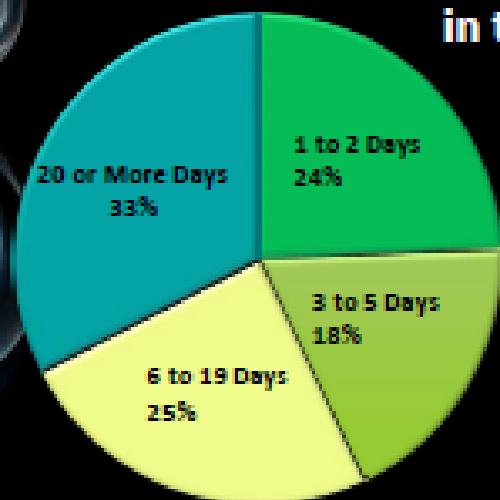


Past Month Marijuana Use College Age 18 to 25 Years Old



Use and Heavy Use Rising: 42% of Current Users are Daily or Almost Daily Users

Number of Days Used Marijuana
in the Past Month



2002



2015

22.2 Million Past Month Users of Cannabis in 2015

14.6 Million Past Month Users of Cannabis in 2002

Source: SAMHSA, 2015 National Survey on Drug Use and Health (September 2016).



Getting It Right

• Promoting Effective Treatment

• Reducing the Burden of Substance Abuse

Trends in Washington State Post-Legalization

- Falling Prices – median price per gram fell from \$25 to \$10 between 2014 and 2016
- % Market share of high potency flower with more than 20% THC increased by 48.4% since 2014, now 56.5% of retail expenditures on flower



State Medical Marijuana Laws

Status of State Medical Marijuana Laws

Operational

States that have passed laws to remove state-level criminal penalties on the use of medical marijuana by patients who are diagnosed with a debilitating illness. The programs in these states are up and running.

Not Yet Operational

States that have passed medical marijuana laws, but programs are not yet up and running.

CBD-Specific

States that have passed laws allowing for the use of cannabis extracts that are high in the non-psychoactive cannabinoid CBD, and low in THC, the psychoactive component of marijuana, to treat severe, debilitating epileptic conditions.

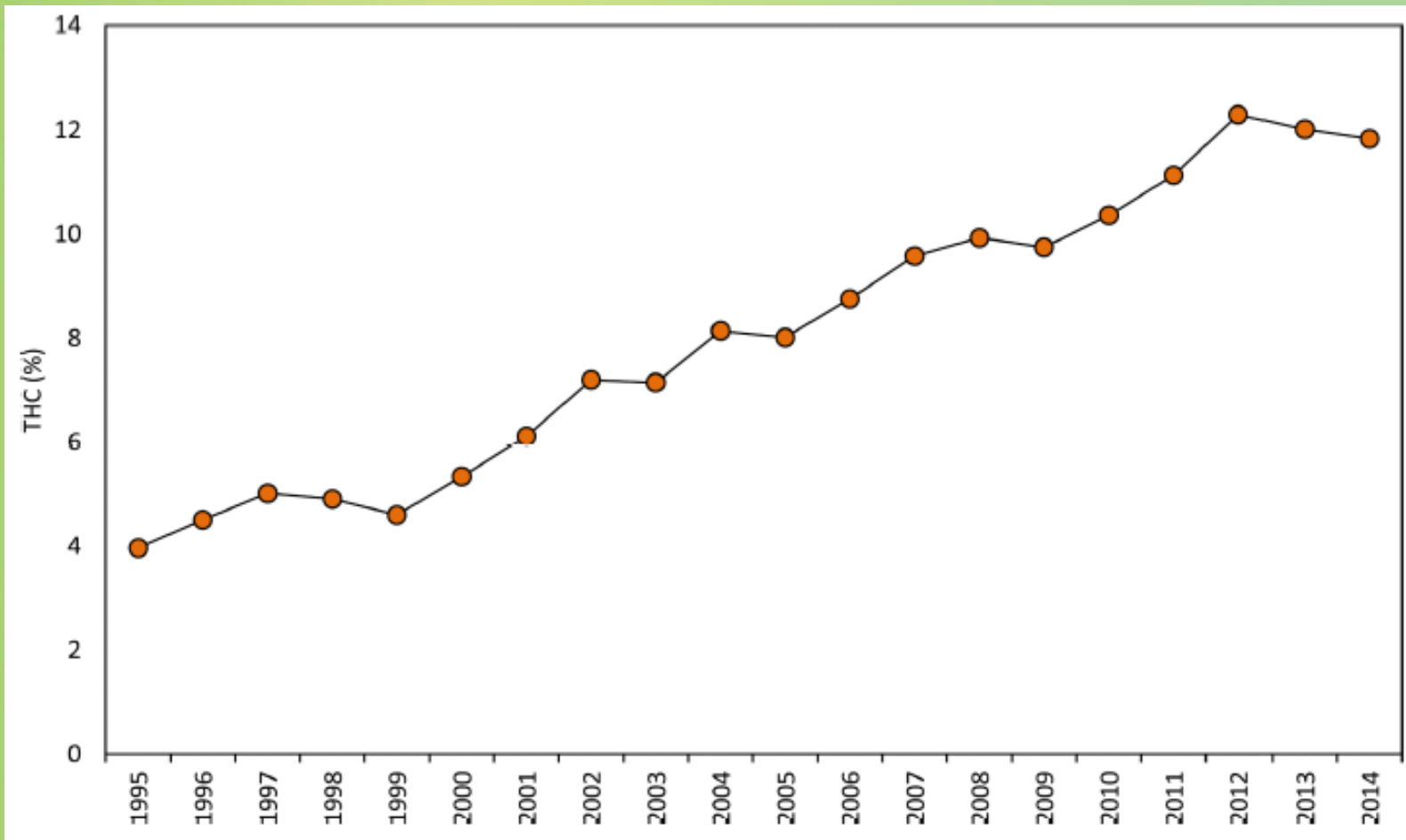
Non-Functional

The language of this law calls for a physician's 'prescription', which is illegal under federal law. Consequently, it remains to be seen whether any licensed physicians will agree to participate in the state's program.

States That Have Legalized Medical Marijuana



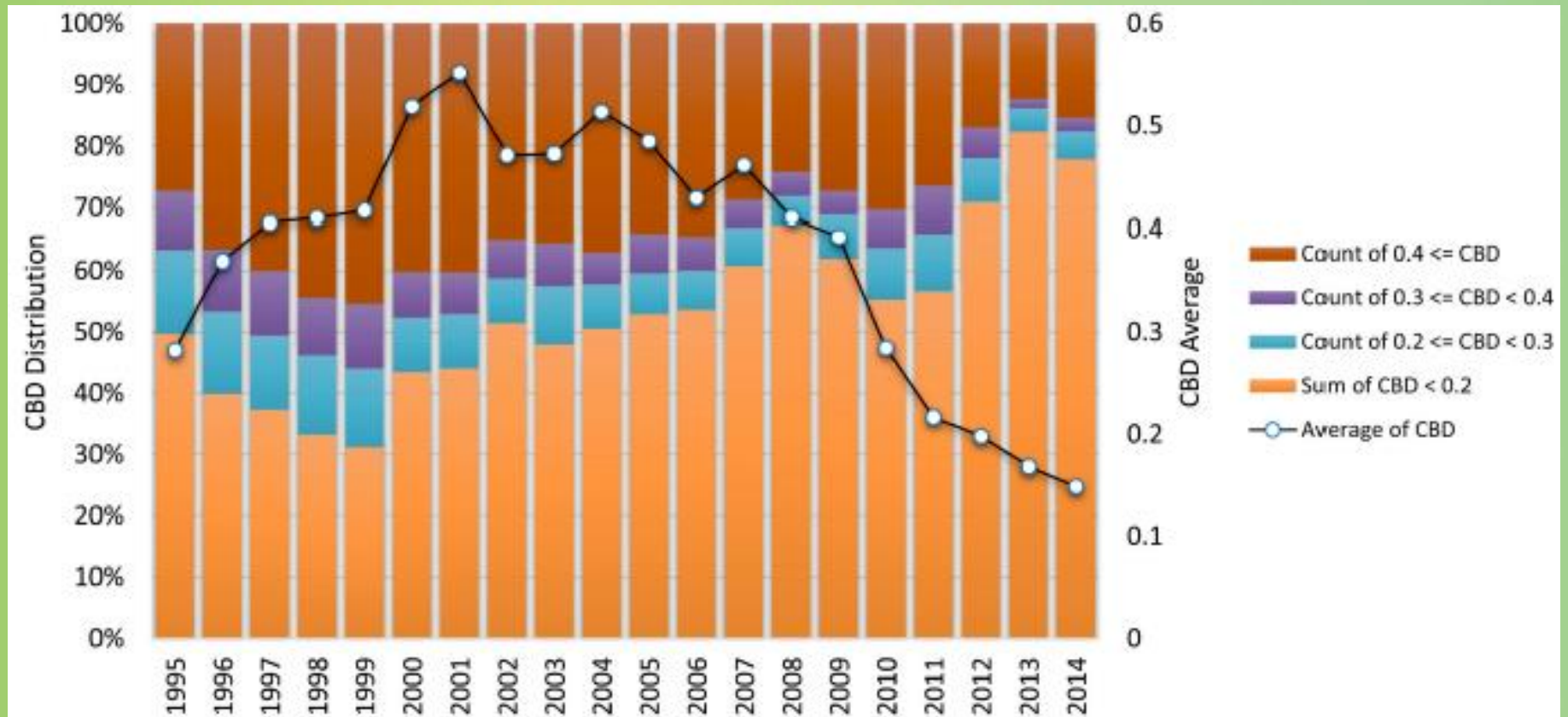
Average Δ^9 -THC Concentration of DEA Specimens by Year



Potency of cannabis judged based on THC content of preparation
Potency > 15% considered to represent “hard drug” in Holland

Biol Psychiatry 2016; 79:613-619

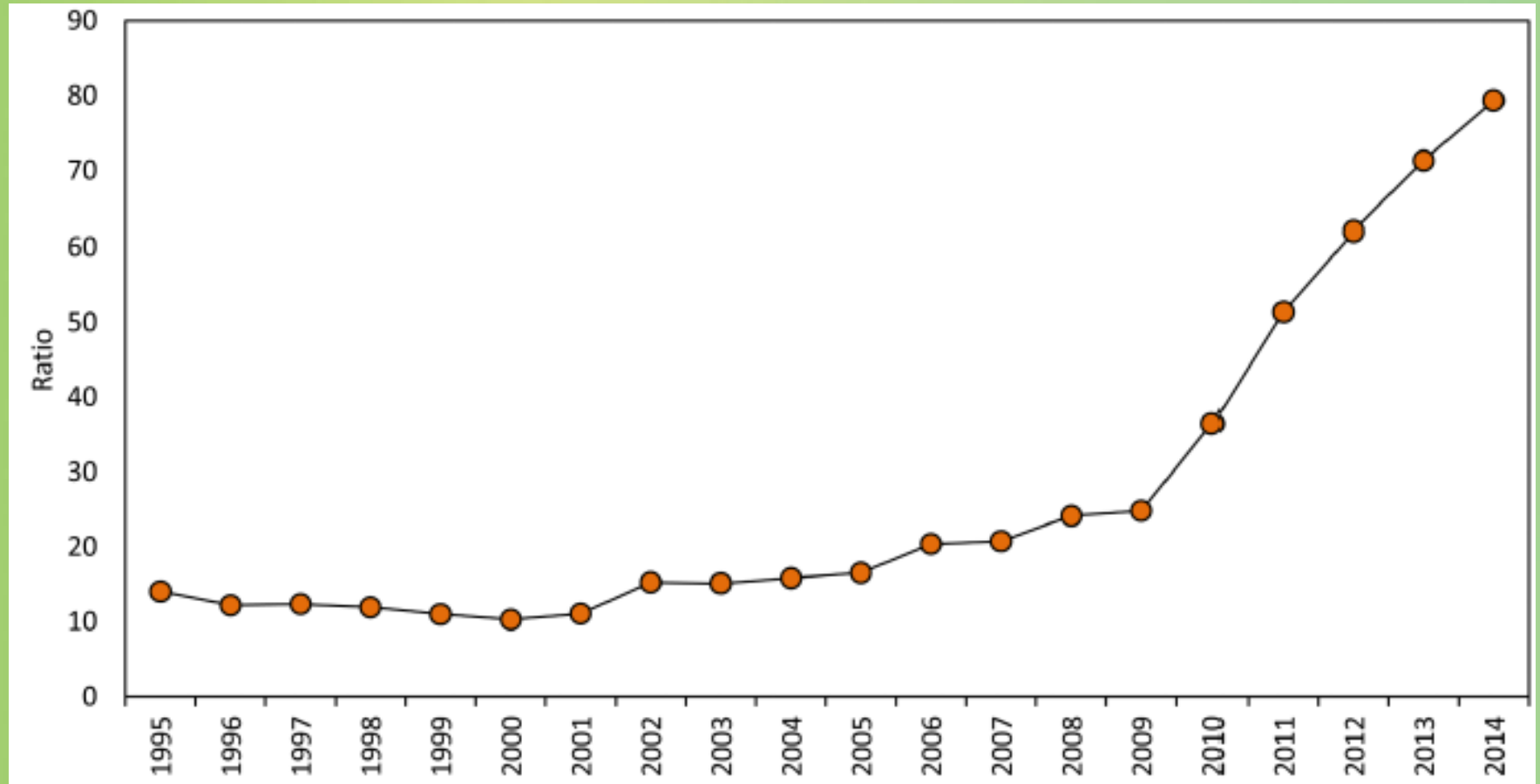
CBD Concentration Distribution in Cannabis Samples Confiscated by DEA and Average CBD



Cannabidiols lessen the psychoactive effects of THC. This means that a plant with a greater percentage of CBD has a lower potency.

Biol Psychiatry 2016; 79:613-619

Ratio of the Average Concentration of THC to CBD in DEA Specimens by Year, 1995-2014



CBD has been almost bred out of cannabis strains

How is marijuana consumed?

■ Smoked

- cigarette (joint/spliff with or without tobacco)
- pipe, a water pipe (bong/cone), or a hookah
- hollowed-out cigar (blunt)



■ Vaporized

- heated plant material
- heated oil or wax (dab)



■ Consumed orally

- baked goods or other food products (brownies, cookies, etc.)
- beverages: tea, milk based products, soda, coffee etc
- capsules (typically synthetic for pharmaceuticals e.g. dronabinol)



■ Other

- Topical
- Pessaries



Dabbing

- Dabs are concentrated, wax-like doses of cannabis made using a solvent like butane or carbon dioxide
- Popular because they can contain up to 90% THC
- Dabs are sometimes called butane honey oil, budder, shatter or wax. Dabs are usually smoked using a water pipe (bong)
- Dabs are often placed onto a glass surface heated with blowtorch. The resulting smoke is inhaled.



Marijuana Edibles

An Introduction



Trends in Routes of Administration

- 40% of 12th grade past-year users reported using cannabis in edible form in MML states vs. 26% in states without MML.
- In WA, an online survey of daily/near-daily users found that 27.5% used edibles, 22.8% used hash resin, and 20.4% “dabbed” in past week.
- In CO’s recreational market, herbal cannabis accounts for 56% of sales and sales of solid concentrates (24%) and edibles(13%) are on the rise.
- In WA, CO, and CA, a “**standard dose**” of THC is defined as 10 mg; in OR, it’s 5 mg.

“Pick Your Poison”



75 mg



120 mg THC



20 mg THC



90 mg THC



151 mg THC

Cannabis' Acute Effects (Intoxication Phase)

- Euphoria
- Calmness
- Appetite stimulation
- Altered perception of time
- Heightened sensation
- Impaired coordination and balance
- Red eyes, dry mouth
- Increased heart rate: 20-100%

Some evidence of increased risk of heart attack, may be exacerbated in vulnerable individuals (e.g., baby boomers?)

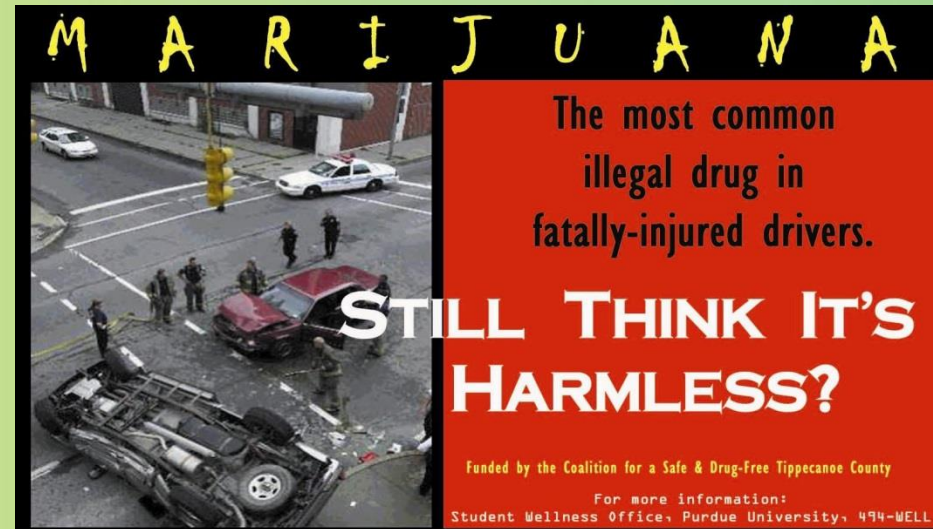
- Orthostatic hypotension initially; then increased BP
 - Risk for ischemic stroke
- **Increased risk of accidents (~2 fold), higher when combined with alcohol**



Credit: Stanimir G.Stoev | Shutterstock.com

Driving Related Impairments

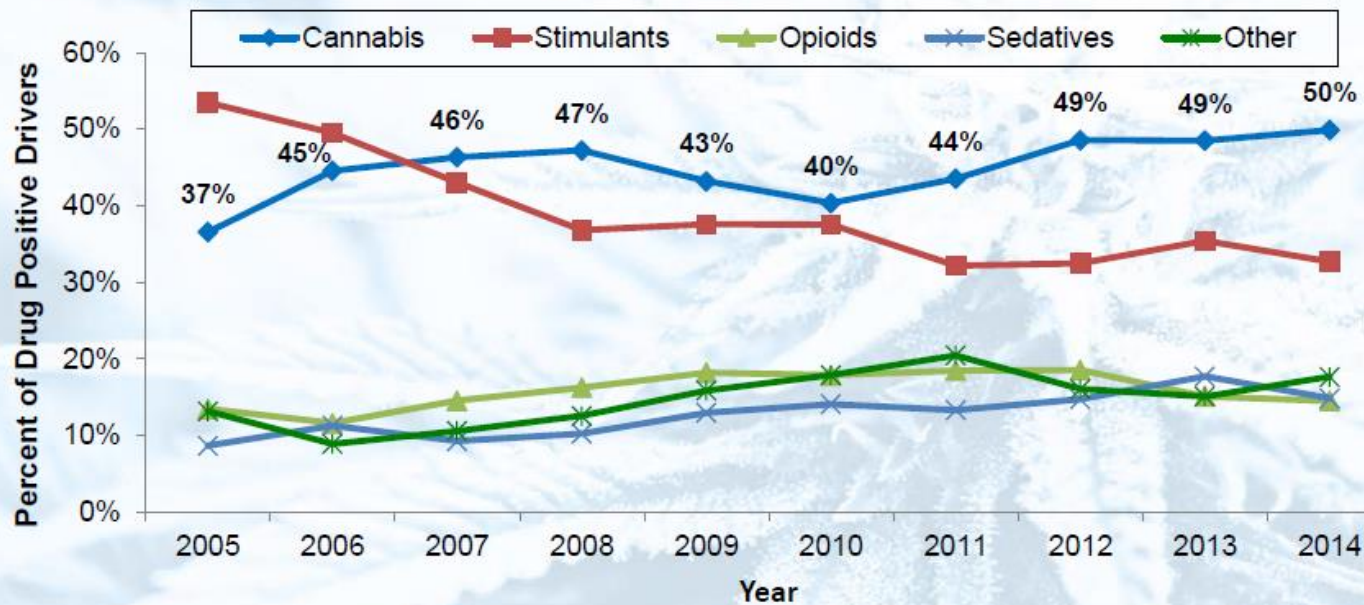
- Cannabis-related impairments detected in a range of skills used in driving:
 - Tracking
 - Reaction time
 - Short-term memory
 - Hand-eye coordination
 - Time and distance perception
 - Decision making
 - Concentration
 - Selective and divided attention
 - Time estimation
 - Executive function
- Size of impairment dose-related
- Impairments for 4+ hours
 - Wait 6 hr after inhaling and 8 hr after ingesting



Fatal Motor Vehicle Crashes

Drugs Detected among Drivers Testing Positive for Drugs in Fatal Motor Vehicle Crashes in California

2005-2014 Fatal Analysis Reporting System, National Highway Traffic Safety Administration



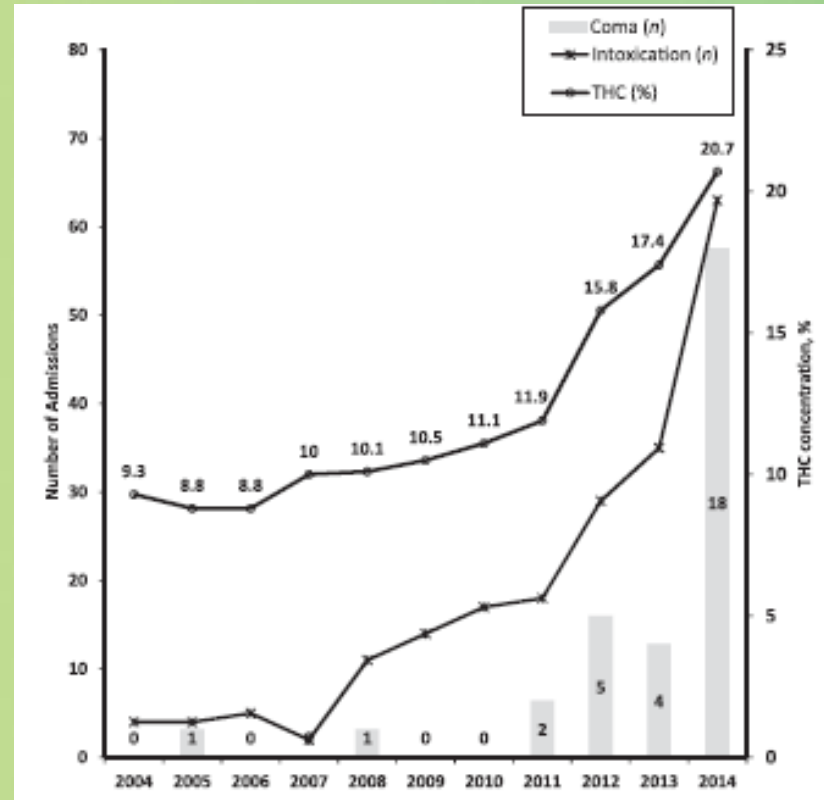
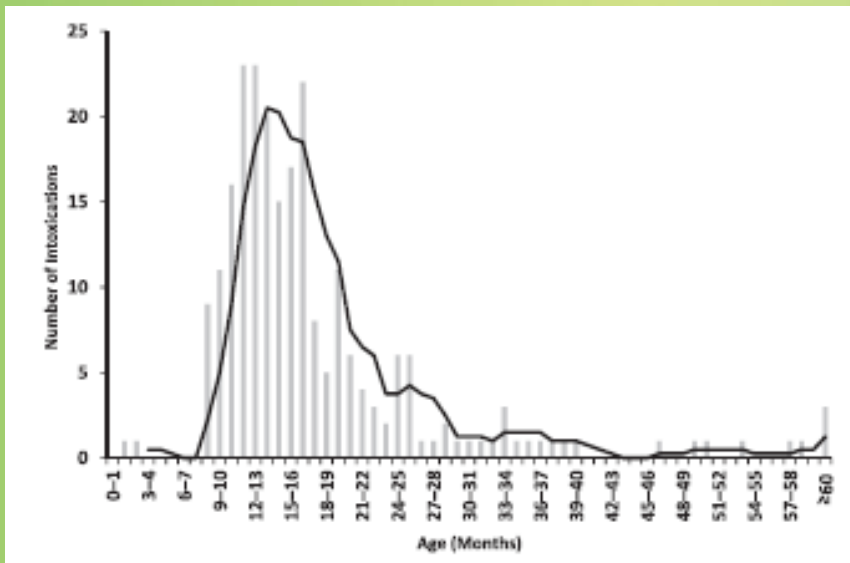
Source: 2005-2014 Fatal Analysis Reporting System data, National Highway Traffic Safety Administration



Cannabis Use and Overdose Injuries or Deaths

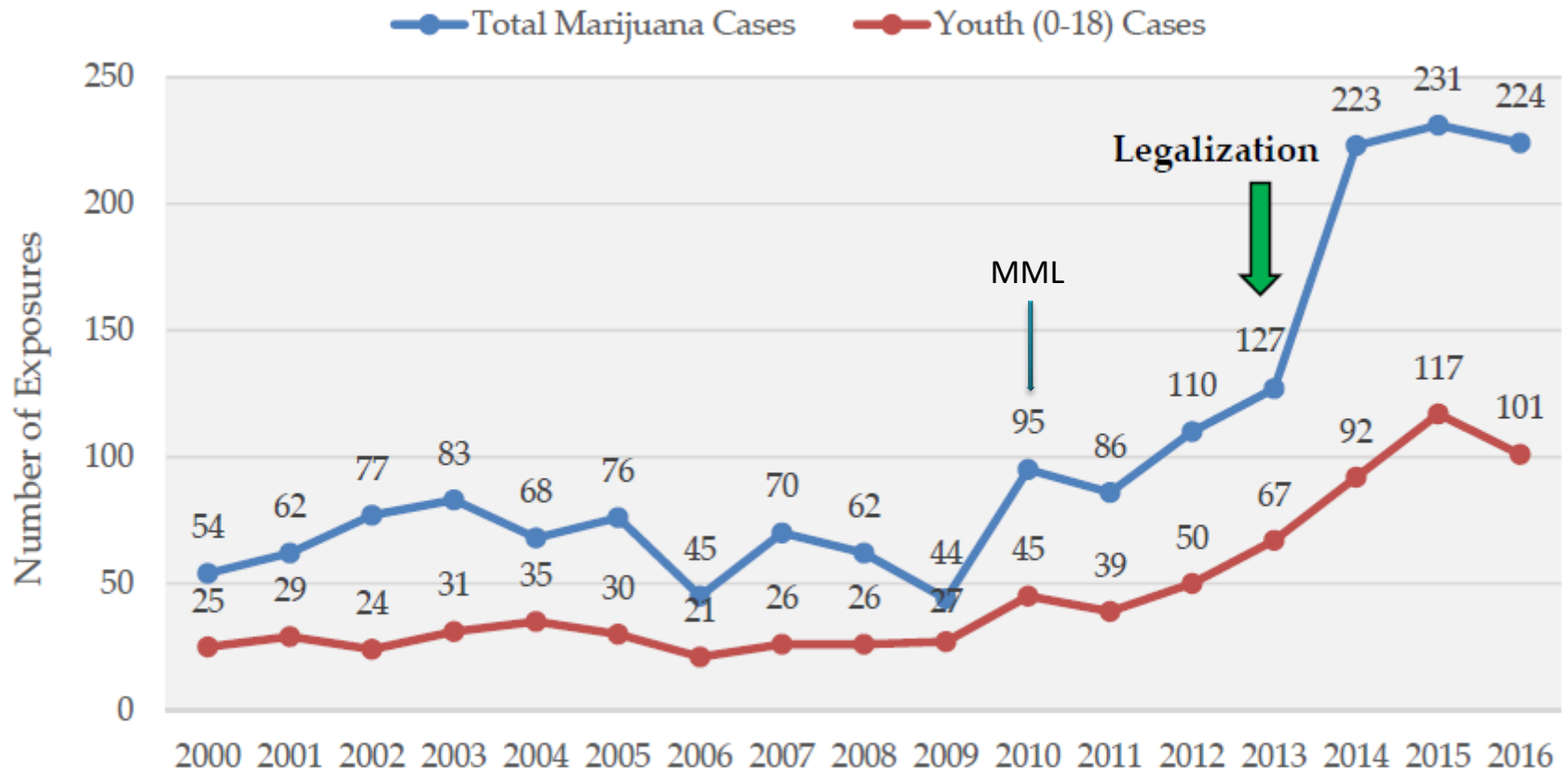
- Moderate evidence of a statistical association between **unintentional cannabis ingestion** and increased risk of overdose injuries including respiratory distress/failure and temporary coma, among **pediatric** populations in U.S. states where cannabis is legal. (edibles)
- Insufficient evidence to support or refute a statistical association between cannabis use and death due to cannabis overdose.
 - CO law states that a single-serving edible cannabis product should contain no more than 10 mg of THC; however, currently available edible products, such as cookies or brownies, may contain as much as 100 mg of THC.
 - Case report of teenager who died after jumping from fourth floor balcony after ingesting a cookie containing 65 mg of THC.

Unintentional Cannabis Intoxication in Toddlers, France, 2004-2014



In France, cannabis consumption is illegal. A retrospective, national, multicenter, observational study of all children <6 yr (N=235) admitted to tertiary-level pediatric ED for proven cannabis intoxication. 71% were ≤ 18 mo old. Hashish resin was the main form ingested (72%).

Exposures Involving* Marijuana



*Other substances may also be reported in the call

SOURCE: Rocky Mountain Poison and Drug Center

Cannabis' Acute Effects (Intoxication Phase)

● Cognition

- Impaired short-term memory
 - Difficulty with complex tasks
 - Difficulty learning

● Executive function

- Impaired decision-making
- Increased risky behavior – STDs, HIV?

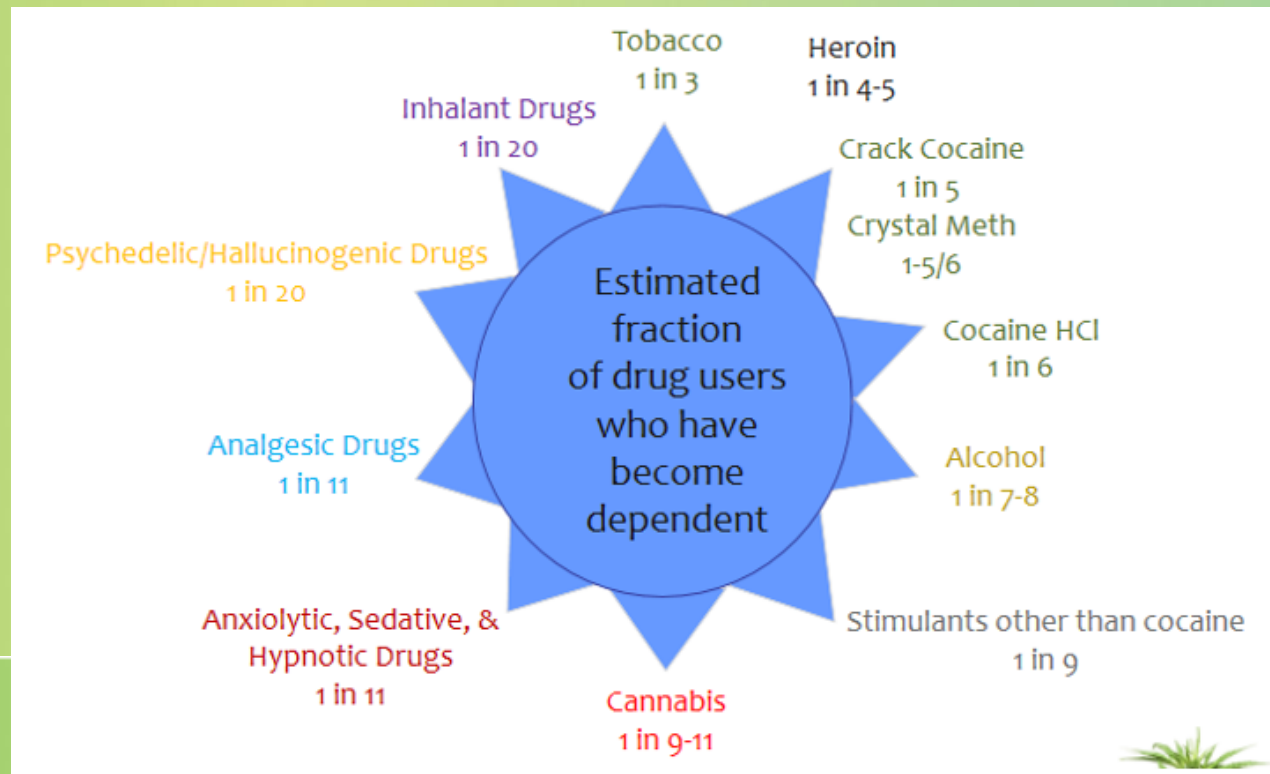
● Mood (especially after high doses or edibles)

- **Anxiety – panic attacks**
- **Psychosis - paranoia**



Myth: You can't become addicted to cannabis

- ~9% of cannabis users become dependent
 - 1 in 6 (17%) who start in adolescence
 - 25-50% of daily users



Cannabis Use Disorder

- A pattern of cannabis use leading to clinically significant impairment or distress that typically includes (DSM-5):
 - Difficulty controlling or cutting down
 - Craving
 - Using more than intended
 - Spending a lot of time on cannabis related activities
 - Giving up or reducing activities in favor of cannabis
 - Continuing to use despite physical/psychological problems
 - Using in high risk situations
 - Problems at work, school, and home related to use
 - Tolerance
 - Withdrawal syndrome upon cessation

Cannabis Use Disorder

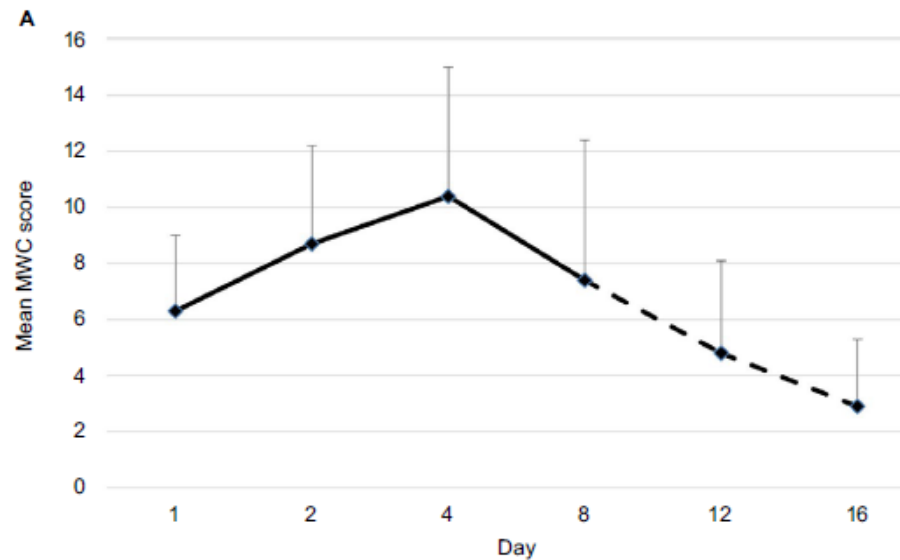
Men	Women
Similarities	
At least one other mental health disorder Low rate of seeking treatment	
Differences	
Other substance use disorders	Panic attacks
Antisocial personality disorder	Anxiety disorders
Severity of disorder	Disorder develops more quickly after first marijuana use

Cannabis Withdrawal Syndrome

Symptoms	None	Mild	Moderate	Severe
Cannabis craving				
Irritability*				
Nervousness/anxiety*				
Increased aggression*				
Restlessness*				
Increased anger*				
Sleep difficulty*				
Strange/wild dreams*				
Depressed mood*				
Decreased appetite*				
Sweating*				
Shakiness/tremulousness*				
Headaches*				
Stomach pains*				
Nausea				
Other				

Notes: A total MWC score is obtained by summing the severity ratings, mild = 1, moderate = 2, severe = 3 points; *symptoms listed in DSM-5. There is no valid definition available for assigning a cannabis withdrawal syndrome to be mild, moderate, or severe. An MWC score of 10 points was found to be comparable with 5 points on the Clinical Global Impression – Severity scale (CGI-S), which is a 7-point scale. Four or more withdrawal symptoms were shown to predict the severity of cannabis-related problems at 1-year follow-up among treated adolescents (N=214, 92% retention). Data from previous studies.^{19,24,26,31,26,27,80}

Abbreviation: DSM-5, *Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition.*



Effects of Long-Term or Heavy Use

- Addiction
- Altered brain development*, teenage girls > boys
- Poor educational outcome, with increased likelihood of dropping out of school*
- Cognitive impairment, with lower IQ among those who were frequent users during adolescence*
- Diminished life satisfaction and achievement
- Symptoms of chronic bronchitis
- Increased risk of chronic psychosis disorders (including schizophrenia) in persons with a predisposition to such disorders

* The effect is strongly associated with initial marijuana use early in adolescence

Role of Cannabinoids in Neuroanatomic Alterations in Cannabis Users

Regular exposure to cannabis associated with neuroanatomic alterations in regions high in cannabinoid receptors: hippocampus (reduced volumes and gray matter density, altered shape), followed by amygdala & striatum, prefrontal cortex, and cerebellum

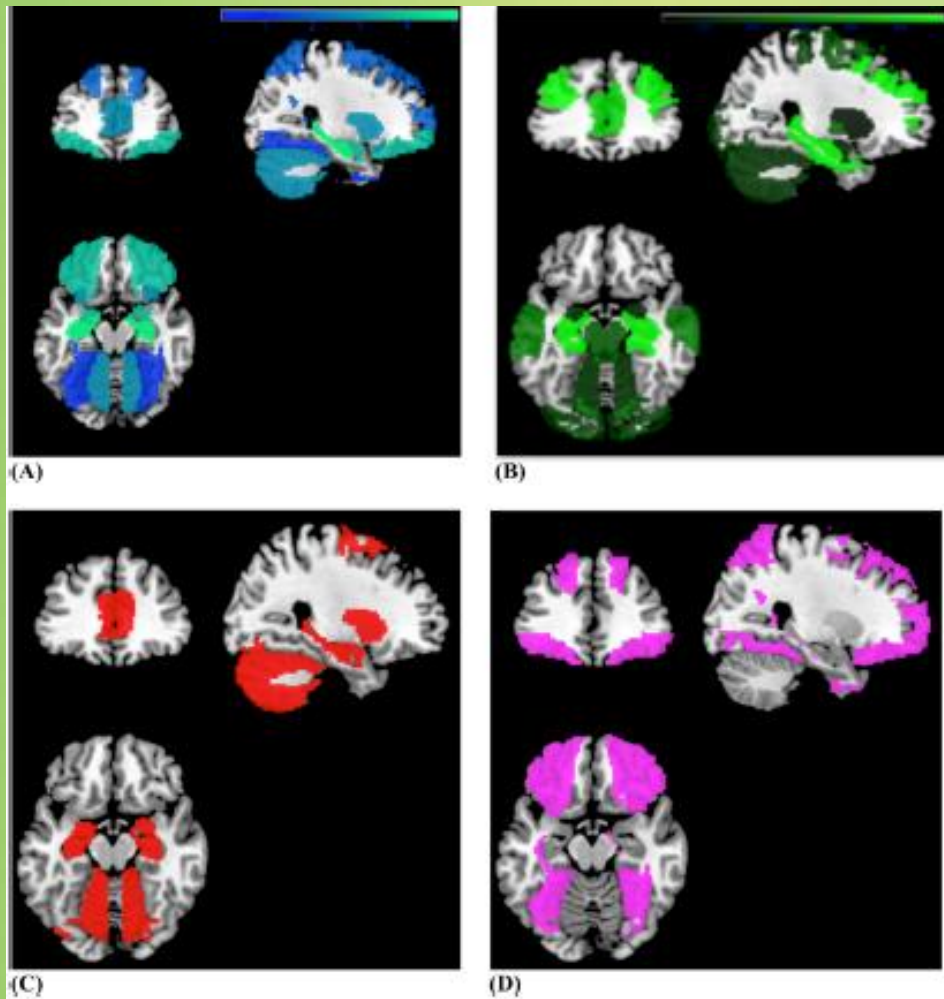


Figure 3. Weighted color maps. **(A)** Neuroanatomical alterations in cannabis users (blue-green), relative to control subjects (two to six studies). **(B)** Brain map with regional distribution of cannabinoid receptor density [dark-light green; range, 40–1680 density of receptor binding sites, measured via autoradiographic techniques (3)]. Lighter colors indicate evidence from more studies and greater density of receptors. **(C)** Binary map (red) illustrates overlap between **(A)** and **(B)**, including regions high in cannabinoid receptors that also show neuroanatomical alterations. **(D)** Binary map (violet) illustrates nonoverlap between **(A)** and **(B)**, including areas that showed neuroanatomic alterations and are low in cannabinoid receptors.

Cannabis Use and Mental Health

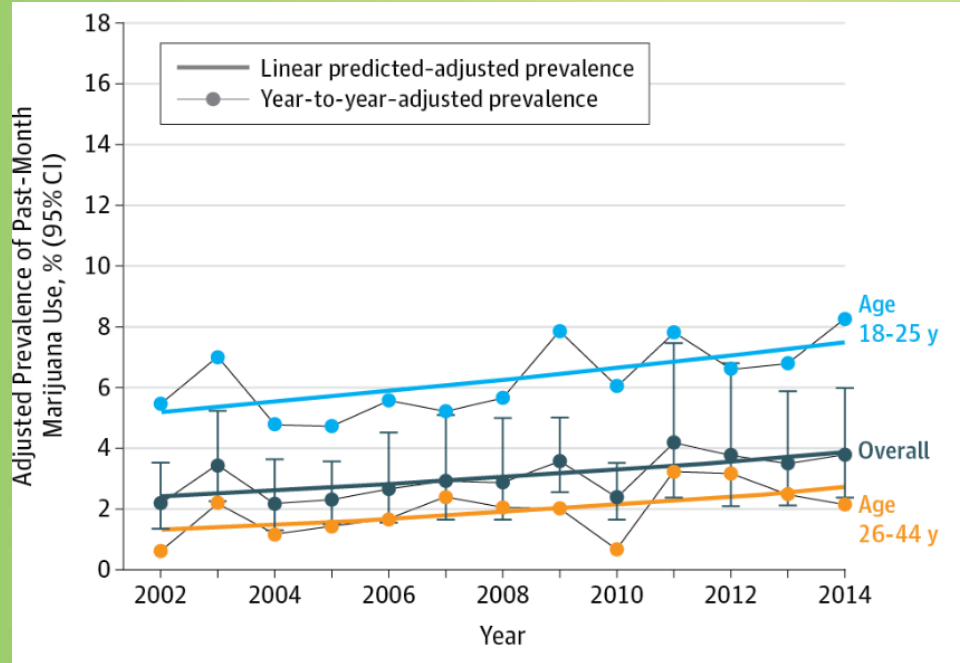
- Substantial evidence of a statistical association between cannabis use and:
 - Development of schizophrenia or other psychoses, with the highest risk among the most frequent users
- Moderate evidence of a statistical association between cannabis use and:
 - Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use)
 - Small increased risk for development of depressive disorders
 - Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users
 - Increased incidence of suicide completion
 - Increased incidence of social anxiety disorder (regular use)

Stoner Things

MARIJUANA AND PREGNANCY: WHAT'S THE RISK?

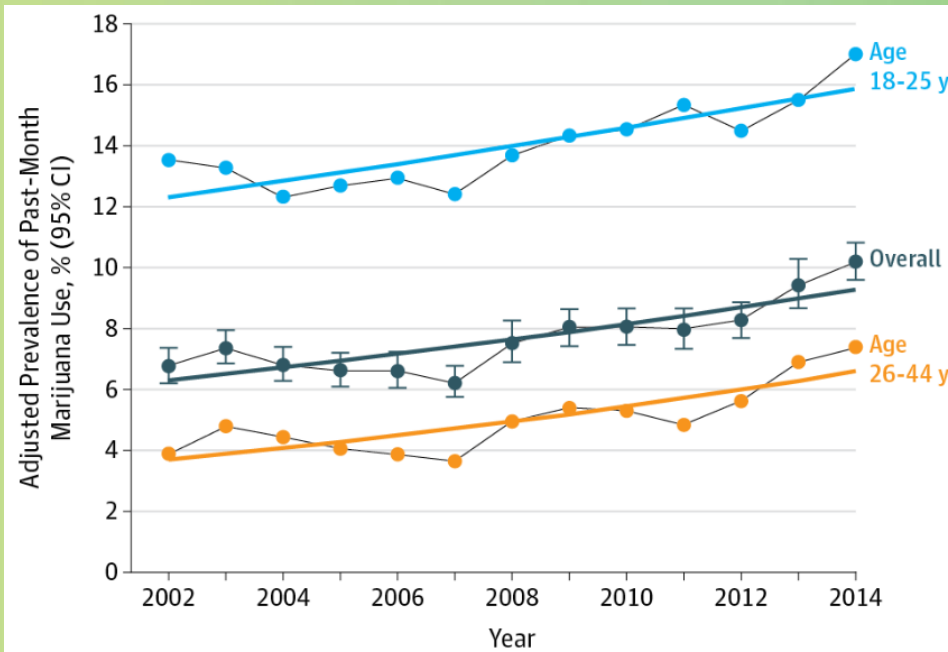


Year-to-Year Prevalence of Past-Month Marijuana Use Among Pregnant and Nonpregnant Women Aged 18-44, 2002--2014

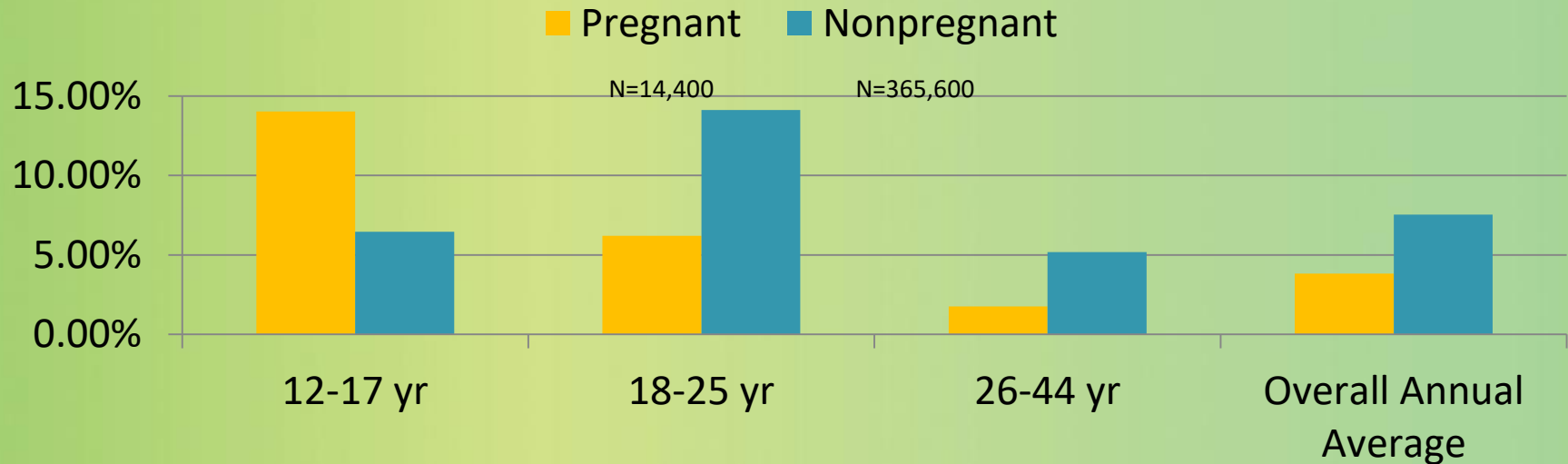


Pregnant Women

Nonpregnant Women



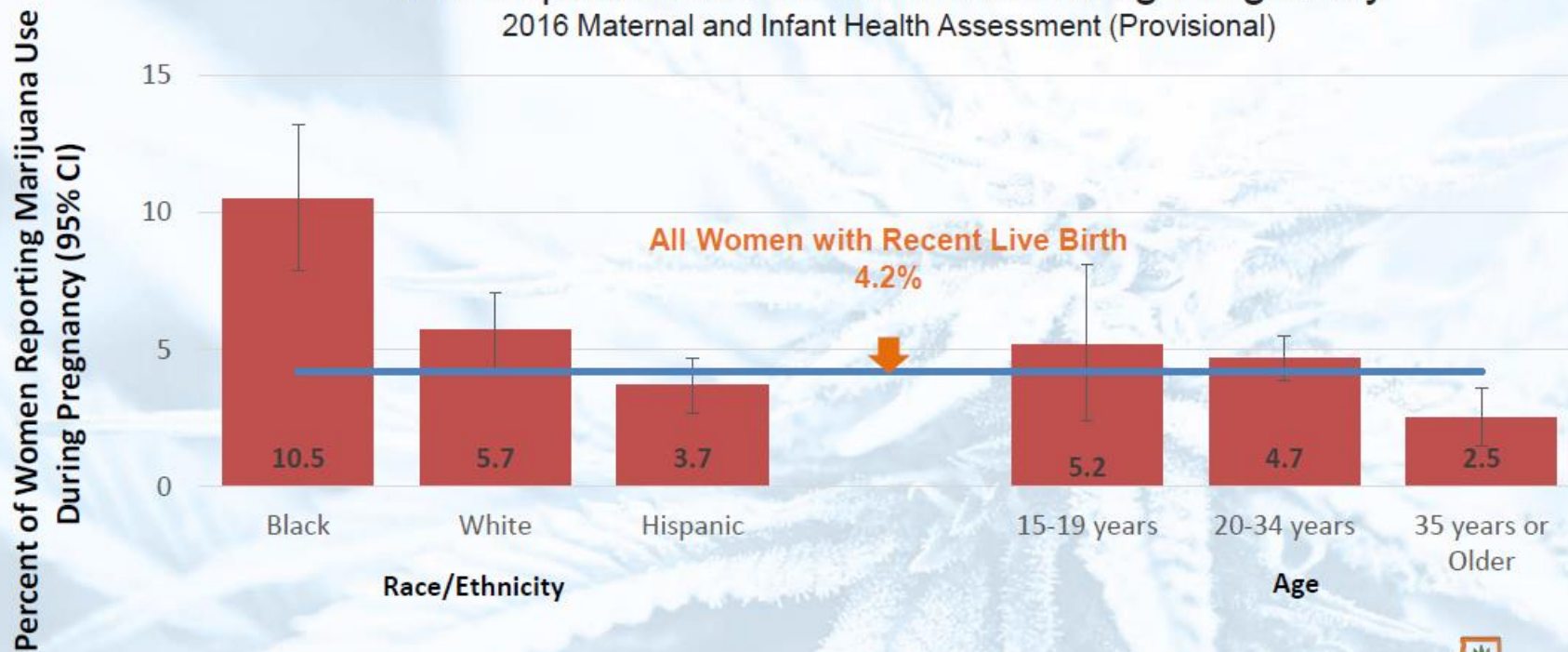
Marijuana Use During Pregnancy in U.S., 2002-2015



- ❖ Marijuana use was higher in first trimester (6.4%) than in the second (3.3%) or third (1.8%) trimesters
- ❖ Among pregnant women, non-Hispanic blacks had a higher prevalence (6.45%) than non-Hispanic whites (3.82%), Hispanics (2.92%), or non-Hispanic others (1.39%)
- ❖ Among pregnant women, those with family income <\$20,000 had a higher prevalence (6.57%) than those with family incomes of \$20,000-49,000 (3.90%), \$50,000-74,999 (2.80%), or \geq \$75,000 (1.86%)
- ❖ Among pregnant women, those who were uninsured or on Medicaid had a higher prevalence (7.87% & 5.55%, respectively) compared to those with private insurance (1.82%)

Usage During Pregnancy

Self-Reported Use of Cannabis During Pregnancy 2016 Maternal and Infant Health Assessment (Provisional)



Source: Provisional 2016 Maternal and Infant Health Assessment (MIHA) Data. Provisional MIHA estimates are weighted to preliminary California birth certificate data and will differ slightly from MIHA estimates weighted to the final 2016 Birth Statistical Master File. Prepared by: Center for Family Health / Maternal, Child and Adolescent Health Division / Epidemiology, Surveillance and Federal Reporting, 2017.



Adjusted Prevalence of Marijuana Use Among 279,457 Pregnant Women in KPNC, 2009-2016

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

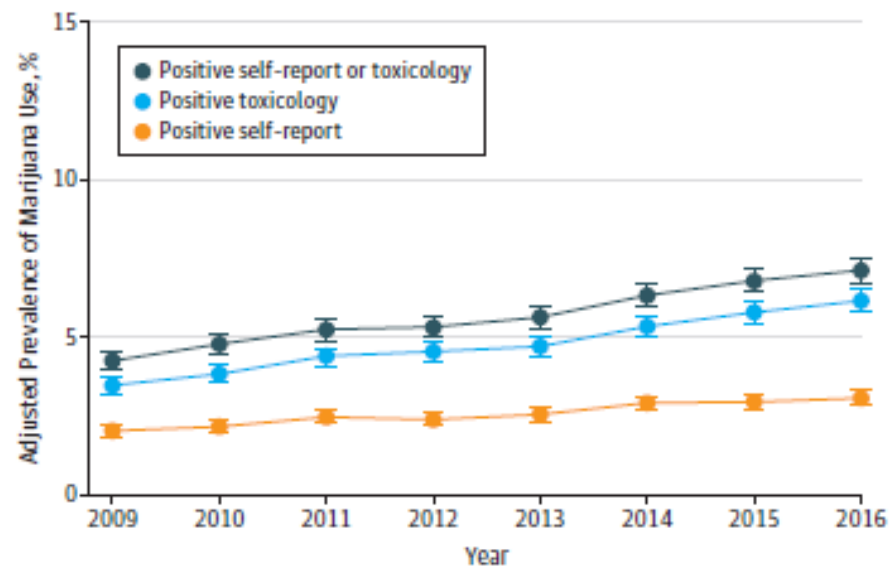
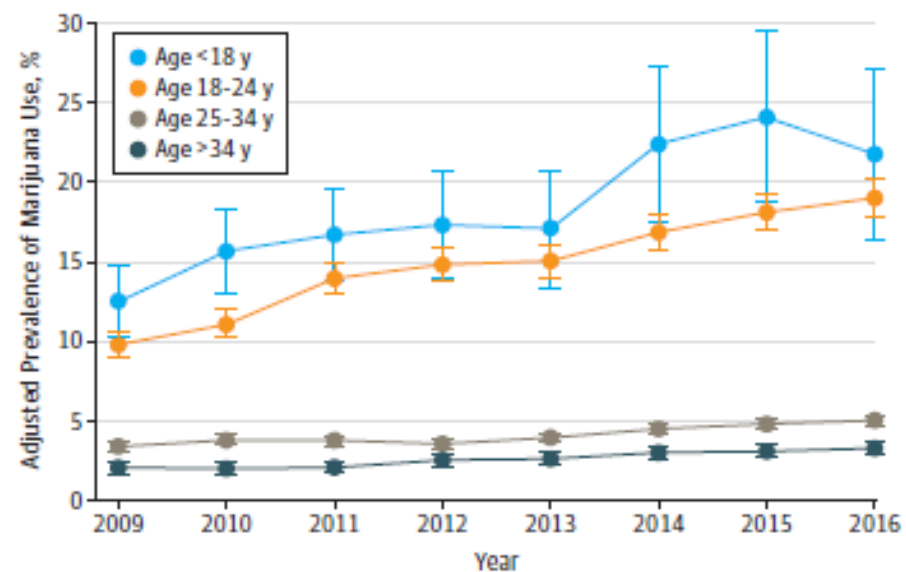


Figure 2. Adjusted Prevalence of Marijuana Use Among 279 457 Pregnant Females in KPNC by Age, 2009-2016



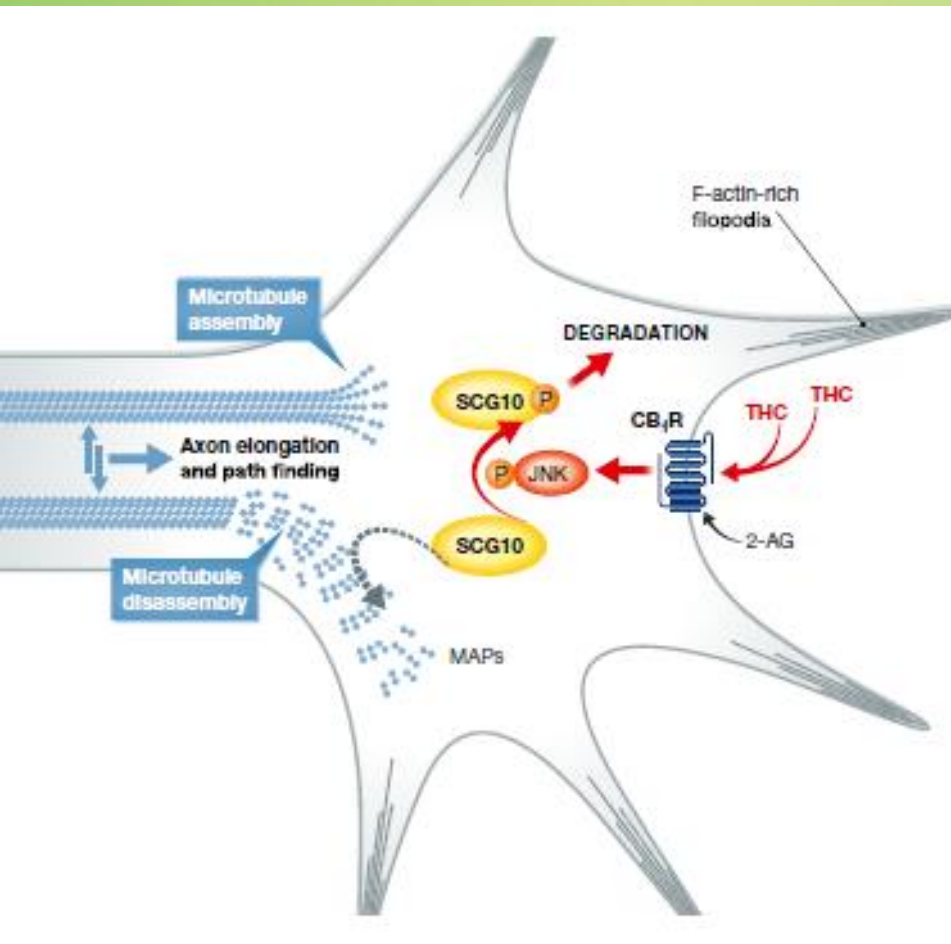
Universal screening for marijuana use done at ~8 wk GA

Why the Concern about Cannabis Use and Pregnancy?



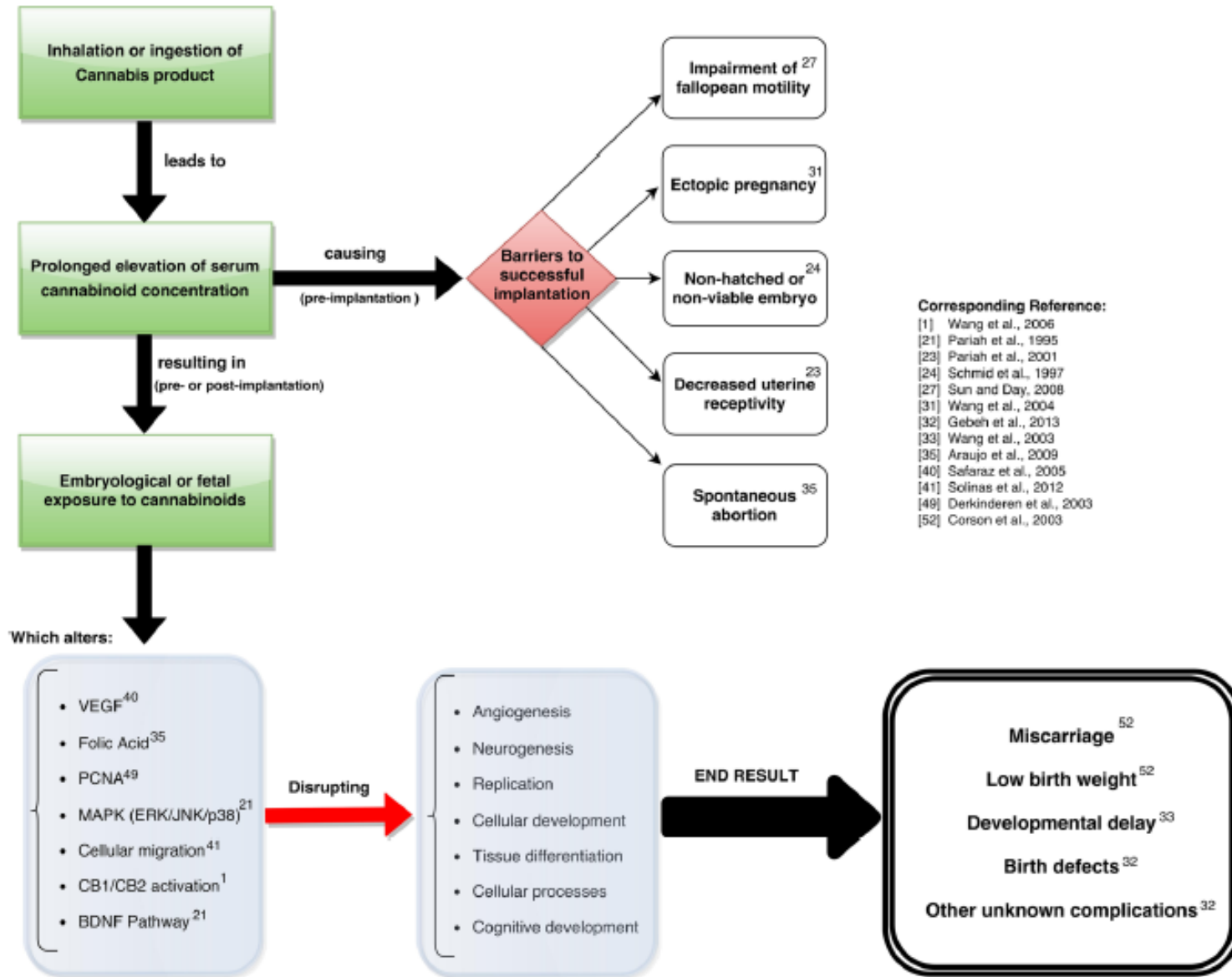
- THC crosses the placenta and BBB
- Highly lipophilic, slow elimination → prolonged fetal exposure
- CB1 receptors are present at 14 wk GA & increase in density during gestation
- Endocannabinoids play roles in a broad array of critical neurodevelopmental processes, from early neural stem cell survival and proliferation to the migration and differentiation of both glial and neuronal lineages as well as neuronal connectivity and synaptic function
 - Cannabis use could modify neurotransmitters (serotonin, dopamine, GABA), alter neuronal growth, maturation, and differentiation, and cause structural or functional abnormalities
- THC is secreted in breast milk and can accumulate to high concentrations (8x)

Fetal Cannabinoid Receptors and the “dis-joint-ed” brain



- Microtubule turnover in the growing axon is required for directional axonal growth and synapse formation in the developing brain
- The microtubule-binding protein SCG10/stathmin-2 is a specific molecular target for a CB₁ receptor-mediated effect of THC in the fetal brain.
- Considering the role of CB₁ in modulating the specification and long distance migration of neurons in the perinatal brain, this study reveals an interesting mechanism potentially accounting for **connectivity deficits** during cortical development following exposure to THC during pregnancy

Cannabinoids Endanger Fetal Development by Multiple Mechanisms



Corresponding Reference:

- [1] Wang et al., 2006
- [21] Pariah et al., 1995
- [23] Pariah et al., 2001
- [24] Schmid et al., 1997
- [27] Sun and Day, 2008
- [31] Wang et al., 2004
- [32] Gebeh et al., 2013
- [33] Wang et al., 2003
- [35] Araujo et al., 2009
- [40] Safaraz et al., 2005
- [41] Solinas et al., 2012
- [49] Derkinderen et al., 2003
- [52] Corson et al., 2003

Cannabis and Congenital Anomalies

- Two prospective studies of cannabis use and congenital anomalies
 - Linn et al (1983) 12,424 women, 10% used cannabis; no association with major congenital anomalies (OR 1.36; 95% CI 0.97-1.91)
 - Gibson et al (1983) 7301 women, 5% used cannabis; no association with congenital anomalies
- Retrospective studies based on birth defects registries, incomplete ascertainment of confounding variable, possible recall bias
- No current evidence of association between cannabis and specific birth defect

Prenatal Cannabis Exposure and Birth Outcomes

- Systematic review and meta-analysis
 - 31 studies included; published between 1982 & 2015
 - 7,851 patients used cannabis during pregnancy (exposed)
 - 124,867 patients did not use cannabis during pregnancy
 - Majority of studies used self-report to define cannabis use during pregnancy
- Based on pooled unadjusted analysis, women using cannabis in pregnancy were at increased risk for:
 - LBW (12 studies: 15.4% vs 10.4%, RR 1.43, 95% CI 1.27-1.62)
 - PTB (14 studies: 15.3% vs 9.6%, RR 1.32, 95% CI 1.14-1.54)

Prenatal Cannabis Exposure and Birth Outcomes (continued)

- Pooled adjusted estimates (after adjusting for smoking, other substance use, demographic and socioeconomic factors) found that women who used cannabis in pregnancy were not at increased risk for:
 - LBW (4 studies: aOR 1.16, 95% CI 0.98-1.37)
 - PTB (4 studies: aOR 1.08, 95% CI 0.82-1.43)

Prenatal Cannabis Exposure and Maternal and Perinatal Outcomes

- Retrospective cohort study (N=12,069)
- Since 2011, patients asked about use of cannabis, tobacco/nicotine products
- Examined maternal and perinatal outcomes of:
 - Cannabis smokers 58 (0.48%)
 - Cannabis & tobacco smokers 48 (0.4%)
 - Tobacco smokers 148 (1.6%)
 - Nonsmokers 11,769 (97.6%)

Prenatal Cannabis Exposure and Maternal and Perinatal Outcomes (continued)

- Cannabis associated with increased risk of:
 - Maternal asthma
 - Cannabis alone (aOR 3.3; 95% CI 1.52-7.17, p=0.003)
 - With tobacco (aOR 2.44; 95% CI 1.10-5.91, p=0.049)
- Cannabis with tobacco associated with:
 - Preeclampsia (aOR 2.6; 95% CI 1.38-4.96, p=0.004)
 - PTB (aOR 2.6; 95% CI 1.3-4.9, p=0.005)
 - ↓(<25%ile) HC (aOR 2.3; 95% CI 1.3-4.3, p=0.006)
 - ↓(<25%ile) BW (aOR 2.8; 95% CI 1.6-5.0, p=0.001)

Prenatal Cannabis Exposure and Maternal and Perinatal Outcomes (continued)

	Overall aOR	Hispanic	Afr-American	Caucasian
Mental Health Comorbidities = depression & anxiety				
Marijuana	5.97 (3.0-20.8)*	7.24 (2.9-18.0)*	5.52 (2.1-14.3)*	1.00 (0.21-19.1)
Cigarettes	4.17 (2.9-6.05)*	5.43 (2.9-10.1)*	4.78 (2.6-8.94)*	2.92 (1.5-5.8)*
Both	7.34 (3.8-13.97)*	7.48 (2.1-27.1)*	11.48 (4.7-28.)*	3.58 (0.85-15.1)

*significant results

Impact of Cannabis Use During Pregnancy on Child Development and Behavior

- **3 prospective longitudinal cohort studies**
 - Ottawa Prenatal Prospective Study (OPPS)
 - Initiated in 1978 & involved a group of Caucasian, predominantly middle-class families (N=698)
 - Fried, 2002
 - The Maternal Health Practices & Child Development (MHPCD) study
 - Started in Pittsburgh in 1982, based on a cohort of children of mostly African-American women from low SES (N=564)
 - Day, Sambaoorthi, Taylor, et al, 1991)
 - The Generation R study
 - Started in 2001, consisted of a multi-ethnic cohort of mothers (N=9778) & children (N=9749) with a predominantly higher SES from Rotterdam with delivery dates from April 2002 until January 2006
 - El Marroun, Tiemeier, Steegers, et al, 2009
- All 3 studies began when women were pregnant and plan to follow their children into early adulthood

Between 1993 and 2008, potency of THC increased from 3.4% to 8.8%

Ottawa Prenatal Prospective Study (OPPS)

- Low risk, Caucasian, middle-class sample of pregnant women (N=698)
- Interviewed every trimester of pregnancy remaining
 - 14% in 1st trimester; 64% in 2nd; 94% in 3rd
 - Reached term between 1980 and 1983
- Interviewed about quantity & pattern of tobacco, cannabis & alcohol use while pregnant
 - Nicotine score = # of cigarettes smoked on daily average by nicotine content of brand specified
 - Alcohol use = absolute alcohol per day based on quantity and pattern of alcohol
 - Marijuana use = # of joints smoked per week

OPPS Results

- Week 1 of life – increased startle & tremor, poorer habituation to visual stimuli as per Neonatal Behavior Assessment Scale (Fried & Makin, 1987)
- Days 9 & 30 – increased fine tremor, tremor associated with Moro reflex, and startle reflex, signs similar to infants with NAS from opioids (Fried et al, 1987)
- 12 & 24 mo. – mental & motor development as measured by Bayley Scales of Infant Development (BSID) and language comprehension & expression (Reynell Scale) at 24 mo (Fried & Watkinson, 1988)
 - No association between prenatal cannabis exposure (N=54) & scores on BSID or language development at 12 & 24 mo

OPPS Results

- Ages 9-12 – children with prenatal cannabis exposure scored lower on WISC-III subtests requiring visual analysis/hypothesis testing and other executive function tests requiring impulse control (Fried et al 1998)
 - Prenatal exposure not related to global intelligence
 - Scored lower on Block Design and Picture Completion subtests
 - Block Design – must assemble blocks to form a design identical to one presented in picture. Requires perceptual organization, spatial visualization, and abstract conceptualization
 - Picture Completion – requires identification of missing portion of an incompletely drawn picture and tests ability to differentiate essential from nonessential details

Maternal Health Practices and Child Development Study (MHPCD)

- Studies long-term effects of alcohol and marijuana during pregnancy, n=564
- High-risk pregnant women 18 yr or older
 - Low SES
 - Mixed ethnicity (57% African American)
 - Single (71%)
- Selected if used > 2 jt/wk
- Women not using cannabis selected randomly
- Cohort of women using alcohol also selected
- Interviewed at 4th & 7th mo GA and at: delivery, 8 mo, 18 mo, 3 yr, 6 yr, 10 yr, 14 yr, 16 yr, 22 yr

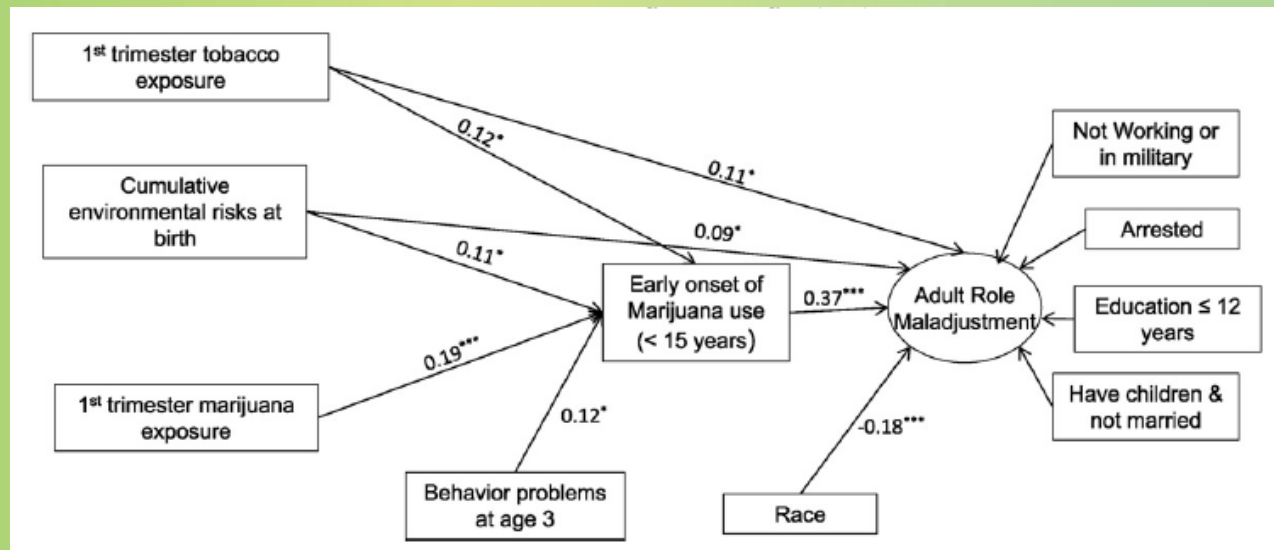
Maternal Health Practices and Child Development Study (MHPCD)

- No effects of prenatal exposure on Neonatal Behavior Assessment Scale when performed on day 2 of life
- 1st trimester prenatal cannabis exposure associated with decreased birth length at birth
- Cannabis exposure during 3rd trimester had positive effect on BW
- At age 6, increased impulsivity on task of vigilance
- At age 10, displayed impulsivity, hyperactivity & inattentiveness per mother's report

Maternal Health Practices and Child Development Study (MHPCD)

- Assessment at age 10
- Exposure to 1+ jt/d of cannabis during 1st trimester predicted:
 - Lower reading and spelling scores
 - Poorer evaluations by teachers
 - These effects persisted when home environment, race/ethnicity, SES, and other prenatal substance use were controlled
 - However, when depression and anxiety were included in regression analysis, first trimester cannabis exposure no longer predicted academic performance
- Prenatal cannabis use in 2nd trimester related to deficits in reading comprehension but not related to performance on WRAT-R subscales
 - 2nd trimester cannabis use also significantly associated with underachievement

Early Marijuana Initiation: The Link Between Prenatal Marijuana Exposure, Early Childhood Behavior & Negative Adult Roles



- Participants from MHPCD Project
 - 43% Caucasian; 57% African American; 48% males
 - 38% reported onset of marijuana use before age 15 (EAOM) and 67.5% of those continued to report marijuana use at 22 yr assessment
- 1st trimester marijuana exposure associated with behavioral problems at age 3 yr and EAOM
- EAOM associated with negative adult roles, including increased risk of being arrested, lower educational attainment, having a child without being married, and unemployment at age 22

Generation R Study: Demographic, Emotional, and Social Determinants of Cannabis Use in Early Pregnancy

- 246 (3.2%) women used cannabis before pregnancy and 220 (2.9%) women used cannabis both before and during pregnancy.
- The strongest determinant for maternal cannabis use during pregnancy was cannabis use by the biological father of the child (OR 38.56; 95% CI 26.1-58.9)
- Maternal cannabis use during pregnancy was also independently associated with:
 - Being single (OR 4.25; 95% CI 2.33-7.75)
 - Having a partner without being married (OR 2.75; 95% 1.56-4.85)
 - Childhood trauma (OR 1.39; 95% CI 1.22-1.57)
 - Delinquency (OR 3.37; 95% 1.90-5.98)

Impact on Pregnancy, Fetal Development and Birth Outcomes

- In Gen R study maternal cannabis use during pregnancy associated with reduced fetal growth reduction of -14.44 g/wk (95% CI -22.94 to -5.94, $p=.001$) and head circumference -0.21 mm/wk (95%CI -0.42 to 0.02, $p=.07$), compared with nonexposed fetuses
 - **Maternal cannabis use during pregnancy resulted in more pronounced growth restriction than maternal tobacco use**
- In a study of a large cohort (n=24,874) of Australian women presenting for public prenatal care at a large hospital between 2000-2006, cannabis use during pregnancy was associated with LBW (OR 1.7; 95% CI 1.3-2.20); PTL (OR 1.5; 95% CI 1.1-1.9); SGA (OR 2.2; 95% CI 1.8-2.7); and admission to NICU (OR 2.0; 95% CI 1.7-2.4)

Impact on Pregnancy, Fetal Development and Birth Outcomes (cont'd)

- In a prospective cohort of 5588 nulliparous women from international Screening for Pregnancy Endpoints (SCOPE) study, continued maternal marijuana use at 20 wk GA was associated with sPTB [aOR 5.44 (95%CI 2.44-12.11)] when adjusted for maternal age, cigarette smoking, alcohol, and SES.

- ~90% Caucasians in this cohort

- Of the women who continued to use marijuana at 20 wk and delivered preterm, nearly 64% delivered at <32 wk GA and 36.4% at <28wk.

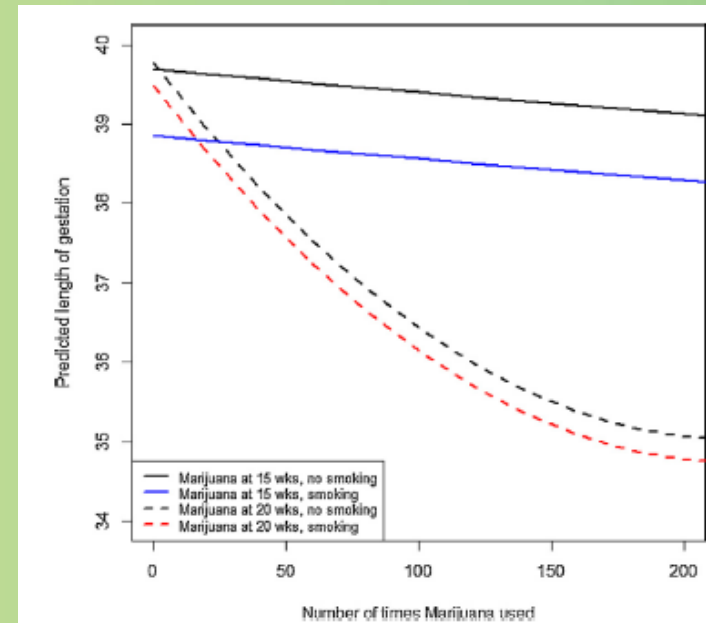



Fig. 2. Predicted length of gestation and number of episodes of marijuana use in women who did or did not also smoke cigarettes in the previous 3 months (adjusted for age, BMI, SEI, cigarette smoking, and alcohol consumption). Note: actual range of marijuana use 0–450 episodes in 3 months.

Effects on Neurocognitive Functioning

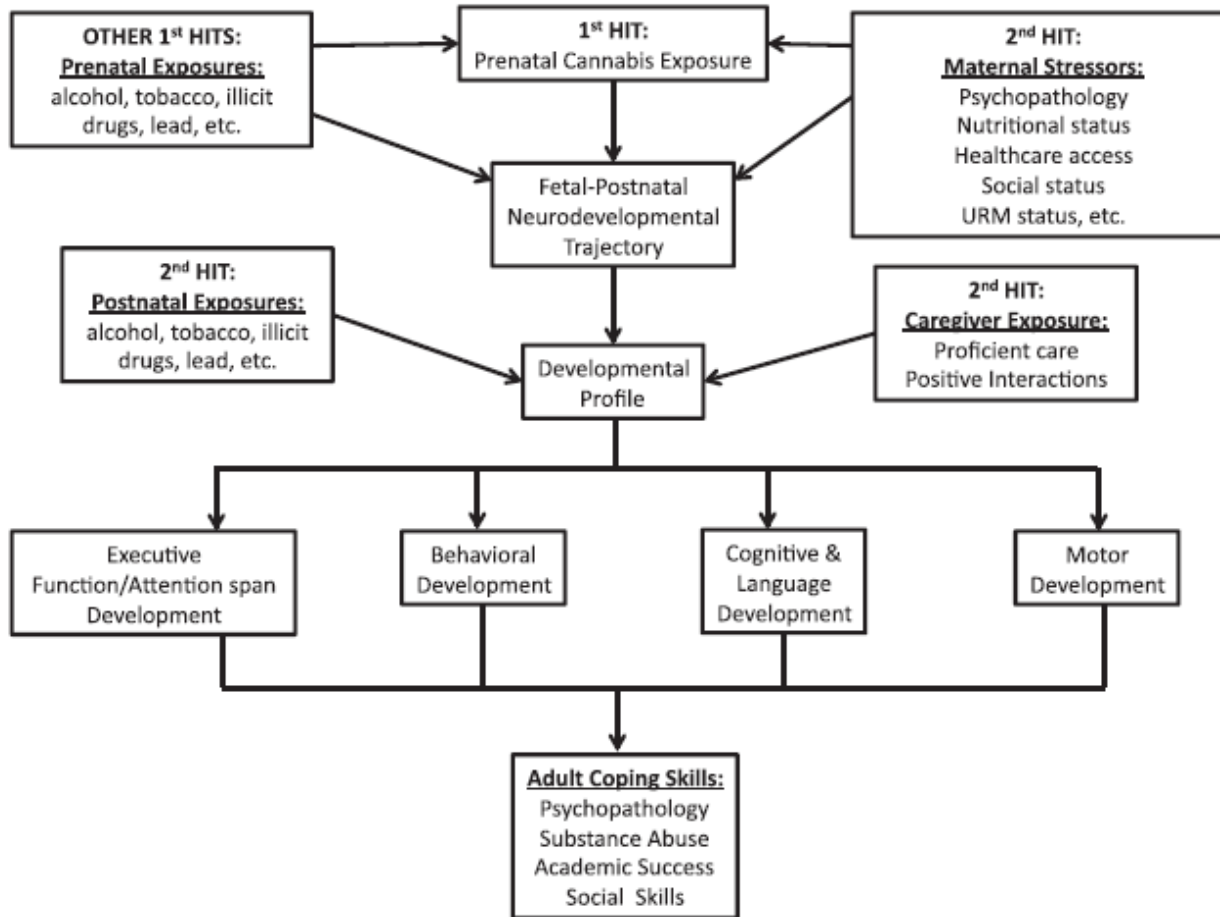
Neurocognitive and Behavioural Effects



18 months	3–6 years	9–10 years	14–16 years	17–22 years
<p>Increased aggressive behaviour^c</p> <p>Attention deficits (females)^c</p>	<p>Deficits in:</p> <ul style="list-style-type: none"> • Verbal and perceptual skills^{ab} • Verbal reasoning^{ab} • Visual reasoning^{ab} • Verbal and quantitative reasoning^b • Short-term memory^{ab} <p>Hyperactivity^{ab}</p> <p>Attention deficits^{ab}</p> <p>Impulsivity^{ab}</p> <p>Impaired vigilance^b</p>	<p>Deficits in:</p> <ul style="list-style-type: none"> • Abstract and visual reasoning^{ab} • Executive functioning^{ab} • Reading^{ab} • Spelling^{ab} <p>Hyperactivity^{ab}</p> <p>Attention deficits^b</p> <p>Impulsivity^b</p> <p>Depressive and anxious symptoms^b</p>	<p>Deficits in:</p> <ul style="list-style-type: none"> • Visual-cognitive functioning^a • Academic achievement^b • Information processing speed^b • Visual motor coordination^b <p>Delinquency^b</p>	<p>Deficits in:</p> <ul style="list-style-type: none"> • Executive functioning^a • Response inhibition^a • Visuospatial working memory^a <p>Smoking^{ab}</p> <p>Substance use^{ab}</p> <p>Early initiation of substance use^{ab}</p>

^aOPPS ^bMHPCD ^cGeneration R

Cannabis as a Neurodevelopmental Teratogen



There is compelling circumstantial evidence based on the principles of teratology and fetal malprogramming suggesting that pregnant women should refrain from marijuana use. The use of marijuana during pregnancy perturbs the fetal endogenous cannabinoid signaling system (ECSS) which is present and active from the early embryonic stage modulating neurodevelopment & continuing this role into adulthood.

The 1st hit is landed by prenatal cannabis exposure (PCE) which leads to asymptomatic changes in the trajectory of fetal-postnatal neurodevelopment (ECSS alterations). The 2nd hit is landed in the form of: maternal stressors which also will impact the trajectory of fetal-postnatal neurodevelopment; postnatal exposure to other substances; or exposure to an incompetent or abusive caregiver which will impact the developmental profile. The **2nd hit is the power punch** that cripples the developing nervous system & manifests in deficits in executive function/attention & behavioral, cognitive, language & motor development. In adulthood, these neurodevelopmental deficits may manifest as psychopathology, substance abuse and/or poor academic or social skills.



The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 637 • July 2015

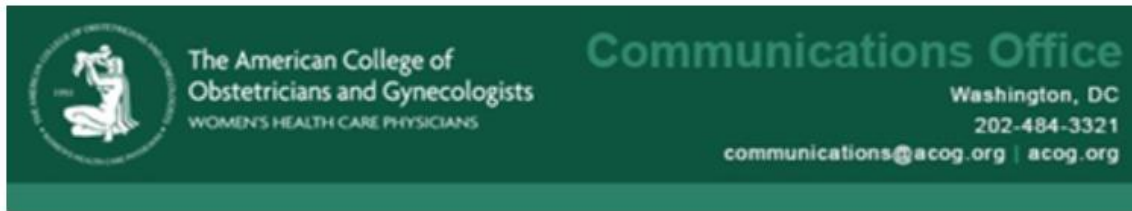
Committee on Obstetric Practice

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Marijuana Use During Pregnancy and Lactation

ABSTRACT: *Cannabis sativa* (marijuana) is the illicit drug most commonly used during pregnancy. The self-reported prevalence of marijuana use during pregnancy ranges from 2% to 5% in most studies. A growing number of states are legalizing marijuana for medicinal or recreational purposes, and its use by pregnant women could increase even further as a result. Because of concerns regarding impaired neurodevelopment, as well as maternal and fetal exposure to the adverse effects of smoking, women who are pregnant or contemplating pregnancy should be encouraged to discontinue marijuana use. Obstetrician–gynecologists should be discouraged from prescribing or suggesting the use of marijuana for medicinal purposes during preconception, pregnancy, and lactation. Pregnant women or women contemplating pregnancy should be encouraged to discontinue use of marijuana for medicinal purposes in favor of an alternative therapy for which there are better pregnancy-specific safety data. There are insufficient data to evaluate the effects of marijuana use on infants during lactation and breastfeeding, and in the absence of such data, marijuana use is discouraged.

Synthetic Cannabis Use During Pregnancy



Synthetic Marijuana Mimics Preeclampsia and Eclampsia in Pregnancy

May 7, 2013

New Orleans, LA -- Use of the synthetic marijuana "Spice Gold" can mimic the symptoms of eclampsia and preeclampsia in pregnancy, according to a retrospective case study presented today at the Annual Clinical Meeting of The American College of Obstetricians and Gynecologists.

Dose-dependent teratogenicity of synthetic cannabinoid CP-55,940 in mice

Neurotoxicology and Teratology 2016; 58:15-22

ABM Clinical Protocol #21: Guidelines for Breastfeeding and Substance Use or Substance Use Disorder, Revised 2015

Sarah Reece-Stremtan,^{1,2} Kathleen A. Marinelli,^{3,4} and The Academy of Breastfeeding Medicine

A central goal of The Academy of Breastfeeding Medicine is the development of clinical protocols for managing common medical problems that may impact breastfeeding success. These protocols serve only as guidelines for the care of breastfeeding mothers and infants and do not delineate an exclusive course of treatment or serve as standards of medical care. Variations in treatment may be appropriate according to the needs of an individual patient.

Breastfeeding and Cannabis

- Cannabinoids are secreted in breastmilk
 - THC is in higher concentrations in breastmilk than in mother's plasma (Perez-Reyes & Wall, 1982)
 - Mother 1: Breastmilk THC 340 ng; Plasma THC 105 ng, 3X difference
 - Mother 2: Breastmilk THC 60.3 ng; Plasma THC 7.2 ng, an 8X difference
 - Concentrations of metabolites 11-OH-THC, 9-carboxy-THC in fetal fecal sample were higher than in mother's milk
 - This indicates that THC is absorbed and metabolized by infant

Breastfeeding and Cannabis

- THC is rapidly distributed to brain and adipose tissue and stored in fat for weeks to months
 - T_{1/2} 25-57 hrs and stays positive in urine for 2-3 wk
- No data evaluating neurodevelopmental outcomes beyond age 1 yr in infants only exposed after birth
 - Potency of cannabis has been steadily increasing from ~3% in the 1980s to over 20% today
- Current concern about cannabis use during lactation stems from possible infant sedation and maternal inability to safely care for her infant while under its influence

Breastfeeding and Cannabis: Recommendations

- Counsel mothers who admit to occasional use to avoid further use or reduce as much as possible while breastfeeding, advise them re its possible long-term neurobehavioral effects, and instruct them to avoid direct exposure of infant to cannabis or its smoke
- Strongly advise mothers with positive urine screen for THC to discontinue exposure while breastfeeding and counsel them as to its possible long-term neurobehavioral effects
- The lack of long-term f/u data on infants exposed to varying amounts of cannabis vis human milk, coupled with concerns over negative neurodevelopmental outcomes in children with in utero exposure, should prompt extremely careful considerations of risks vs benefits of breastfeeding in setting of moderate or chronic cannabis use. A recommendation of abstaining from any cannabis is warranted.

Where Do Pregnant Women Get Info About Cannabis and Pregnancy?

- Most common sources of info reported for perinatal cannabis use:
 - Internet search
 - Anecdotal experiences (family, friends, own prior pregnancies)
 - Most reported not receiving info from HCP or SW
 - Perceived this to mean use is not serious risk; providers are not concerned
 - Some were told not to use cannabis, but not educated why
 - Women were told to stop due to potential involvement with CPS, not given resources to stop, viewed this as punitive

What Type of Info Did Pregnant Women Want About Cannabis Use?

- Improved communication from HCPs about the specific effects of cannabis on the fetus/infant
- They weren't interested in receiving information about cannabis' effect on their own health
- They did not believe receiving a pamphlet at the first prenatal visit would be helpful

Healthcare Providers Responses to Disclosures of Cannabis Use During Pregnancy

- In multivariate analyses with patient race, HCP type, and timing of cannabis use, the only factor significantly associated with whether patients received counseling re cannabis was timing of last use
 - Those who disclosed past use had 6X the odds of receiving no counseling (OR 5.9; CI 1.7-20.5)
 - Those whose last use was undetermined had 12X the odds of receiving no counseling (OR 12.0; CI 2.4-60.9)
- Patients who described their race as African American were 10X more likely to have counseling that was punitive (OR 9.7; CI 1.6-59.0) than patients who described their race as Caucasian

Laws re Women Using Substances During Pregnancy

- Child Abuse Prevention and Treatment Act (CAPTA) requires states to have policies and procedures in place to
 - Notice Child Protective Services (CPS) agencies of substance-exposed newborns (SENs)
 - Establish a plan of safe care for newborns identified as being affected by illegal substance abuse or having withdrawal symptoms resulting from prenatal drug exposure
- 24 states and District of Columbia consider substance abuse during pregnancy to be child abuse under civil child-welfare statutes, and 3 consider it grounds for civil commitment

Pregnant, Drug-Using Women & State Child Welfare Policies

A child may be removed from the home upon consideration by the court of several factors, including the fact that "the mother has given birth to three or more drug-affected infants."

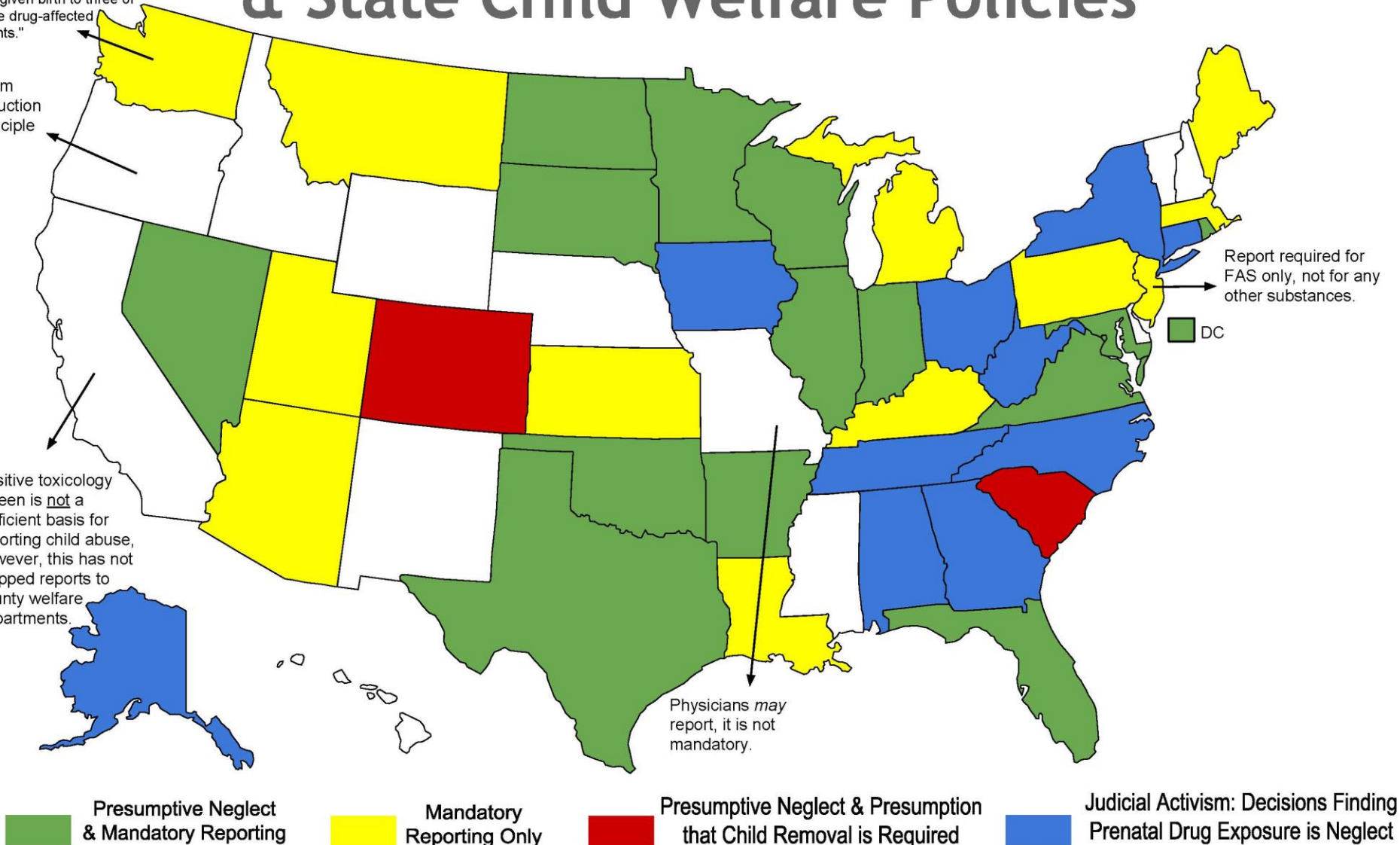
Harm reduction principle

Positive toxicology screen is not a sufficient basis for reporting child abuse, however, this has not stopped reports to county welfare departments.

Report required for FAS only, not for any other substances.

DC

Physicians *may* report, it is not mandatory.



Need More Contemporary Data!

- Most studies done when potency of THC was much lower
 - Now the average potency of THC in CO is 20% and rising
 - Cannabis is stored in fat; we have an obesity epidemic
- Impact of edibles?
- Impact of synthetic cannabinoids on pregnancy unknown
 - Longer half-life, higher affinity for receptors
 - Could result in much higher levels in fetus
- Impact of breastfeeding?





The California Department of Public Health (CDPH) is committed to providing you with the facts you need to make safe and informed choices.

By sharing science-based information, CDPH is working to increase awareness about cannabis and how it affects our bodies, minds and health.

Let's Talk Cannabis

What's Legal?

Pregnant and Breastfeeding Women

Youth

Parents and Mentors

Responsible Use



What's Legal?



Pregnancy and Breastfeeding



QUESTIONS?



