Marijuana and Opioids
Risks for the Unborn, the Born

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(the Honorable)
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Harvard Medical School

Nations at a Crossroads in Drug Policy

Contradictory Views on Marijuana

Scientific evidence INCREASING

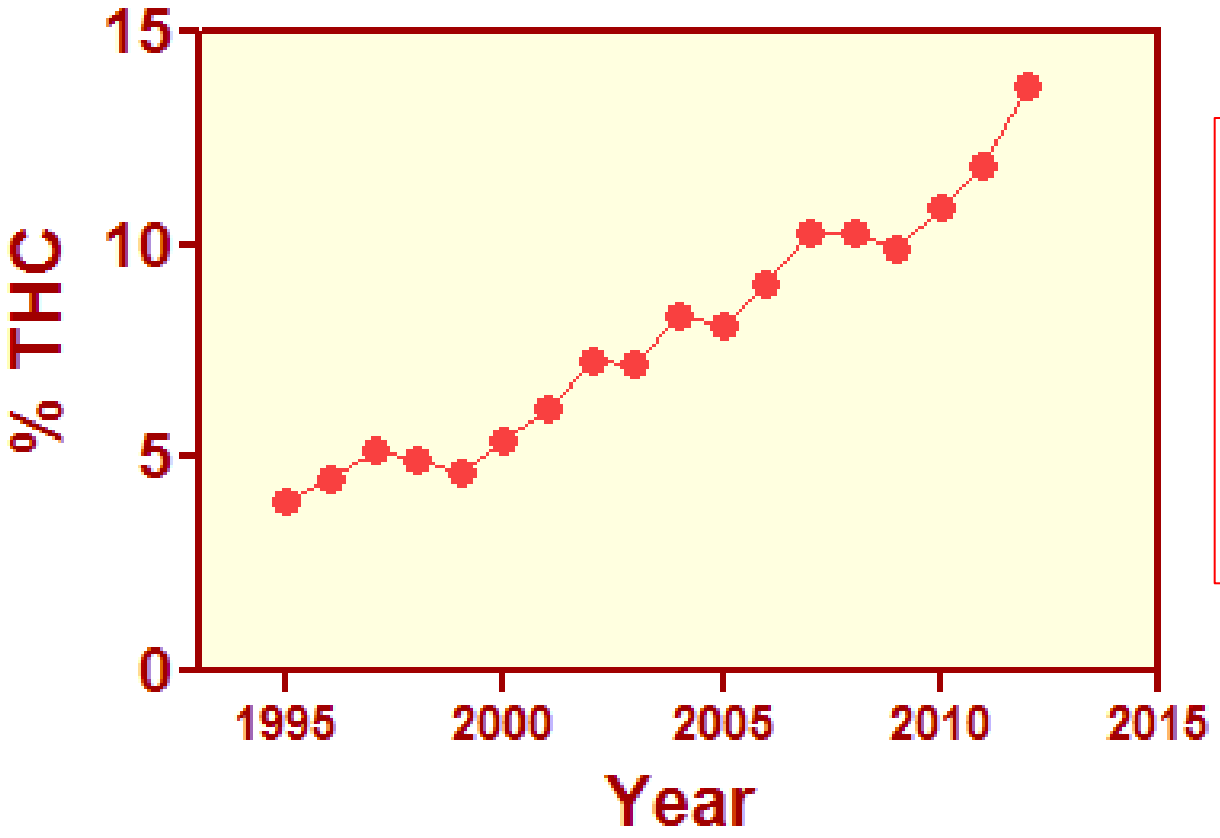
"MARIJUANA IS UNSAFE"!

Marijuana Movement LOUDER:

"SAFE, HARMLESS, BENEFICIAL"

Challenges

THC Potency in Marijuana is Rising Rapidly



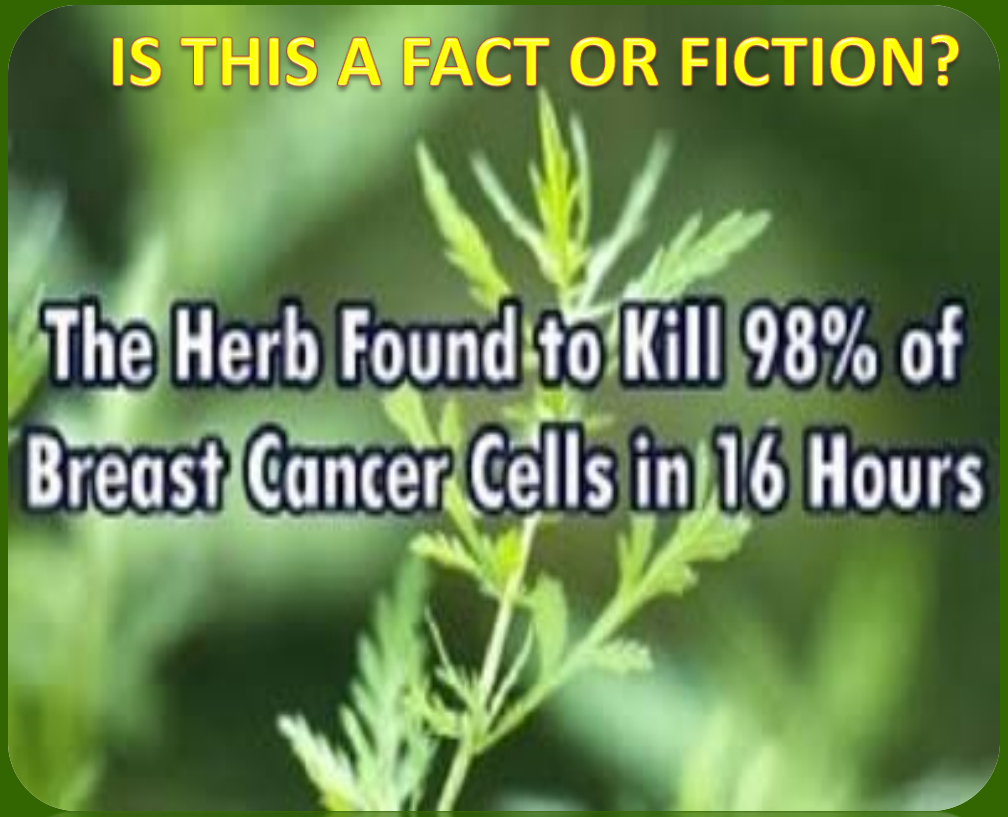
Implications

- **Driving**
- **Addiction**
- **Toxicity**
- **Psychosis**

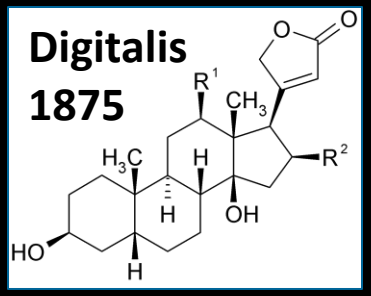
Source: MA ElSohly, NIDA Marijuana Project, **POTENCY MONITORING PROGRAM QUARTERLY REPORT NUMBER 119** REPORTING PERIOD: *09/16/2012 - 12/15/2012*

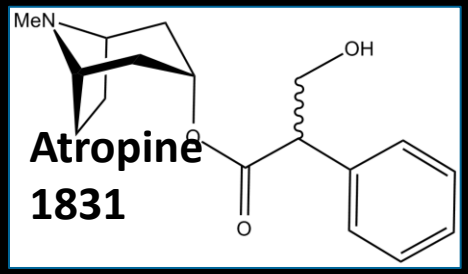
Challenges: Marijuana as a Medicine

Medicinal Plants Sold Today in Markets, Health Food Stores



Medical Progress *Before* the FDA: Pure Products were Isolated





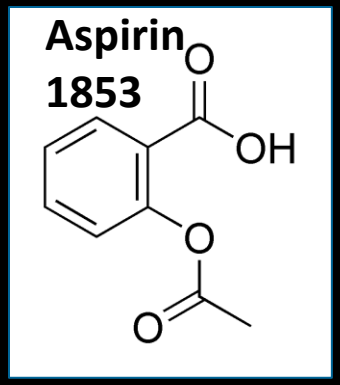
- Highly purified and defined
- Treat specific illness
- Mechanism of action
- Controlled, consistent, regulated doses
- Variations to improve drug possible

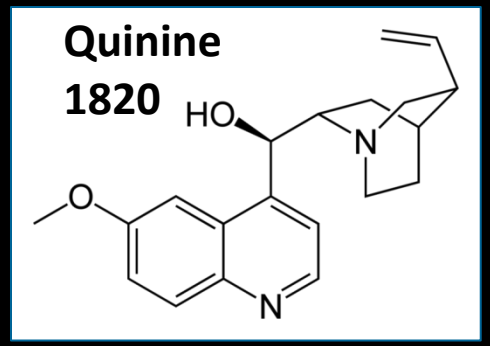
Foxglove (1785)
Dropsy (heart failure)

Belladonna, Jimson weed, Mandrake (400 BC)
Pain, wounds, sleep, love potion

Willow bark (400 BC)
Fever, pain, inflammation

Cinchona tree bark (1620)
Anti-malaria





Horror Stories During 1906-1938

Weight reduction and cosmetics	• **Dinitrophenol:** ***herbicide, insecticide, explosives toxic to humans, animals*** **Lashlure:** ***eye damage***
Diabetes	• **Banbar:** **useless weed concoction; used instead of insulin patients died**
Tuberculosis	• **Liniment useless made of *ammonia, eggs, turpentine* dangerous**
Antibiotic	• **Elixir of Sulfanilamide: disguised bitter flavor of sulfa drugs with sweet-tasting diethylene glycol (*anti-freeze*) One hundred people, mostly children, died from kidney failure**

Consumer Protection, a Critical Role for the Food and Drug Administration (FDA)

1906: Pure Food and Drug Act

Drugs containing alcohol, cocaine, heroin, morphine, and cannabis had to be labeled. Strength and purity known. *No testing*	**Educate public** **Inform**

1938: Food, Drug, and Cosmetic Act

Testing for efficacy and safety	**Protect public**

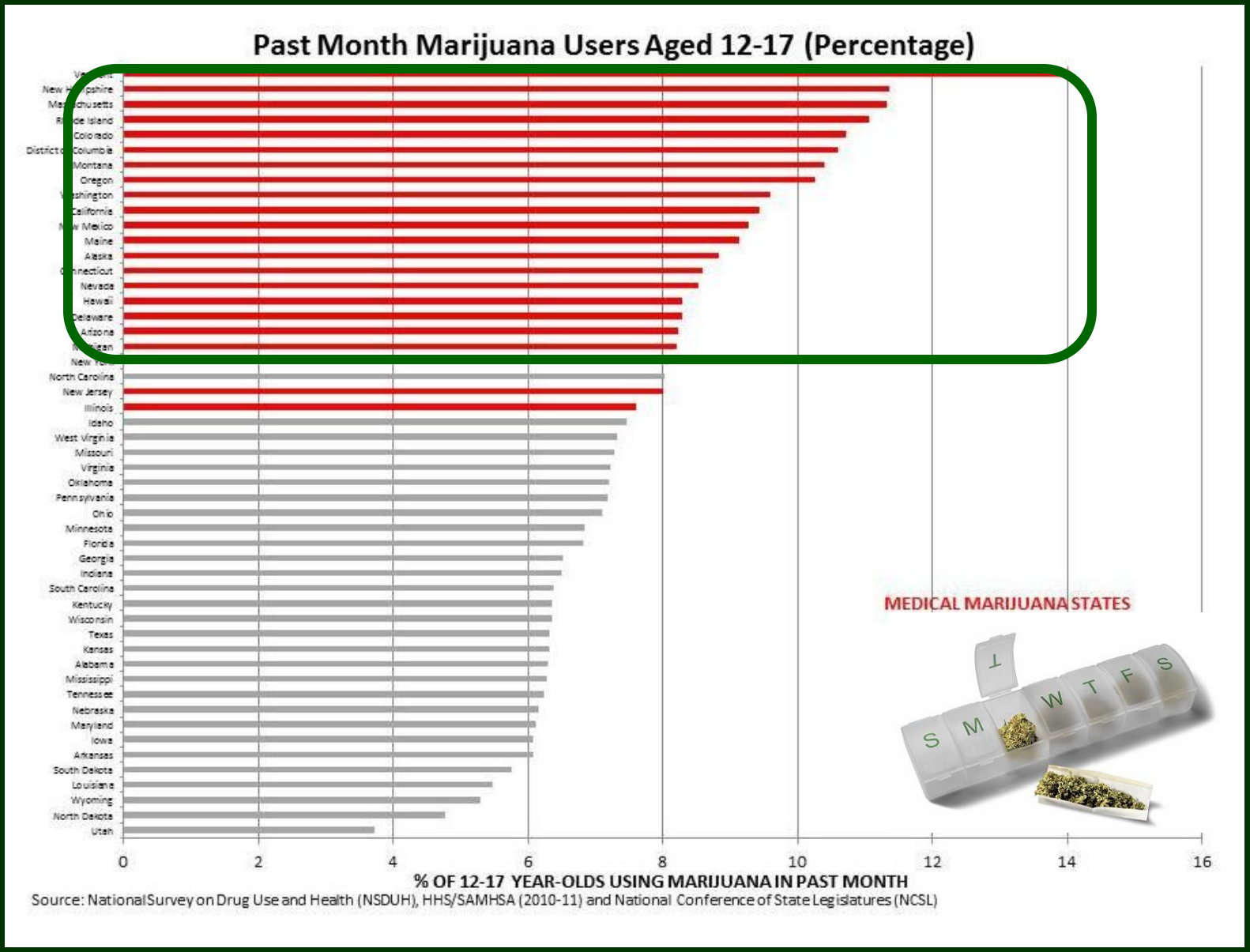
FDA RequireS Clinical Trials to Show that a Drug is Safe and Effective

How Do Drugs Get Approved in the United States? Federal Food and Drug Cosmetic Administration

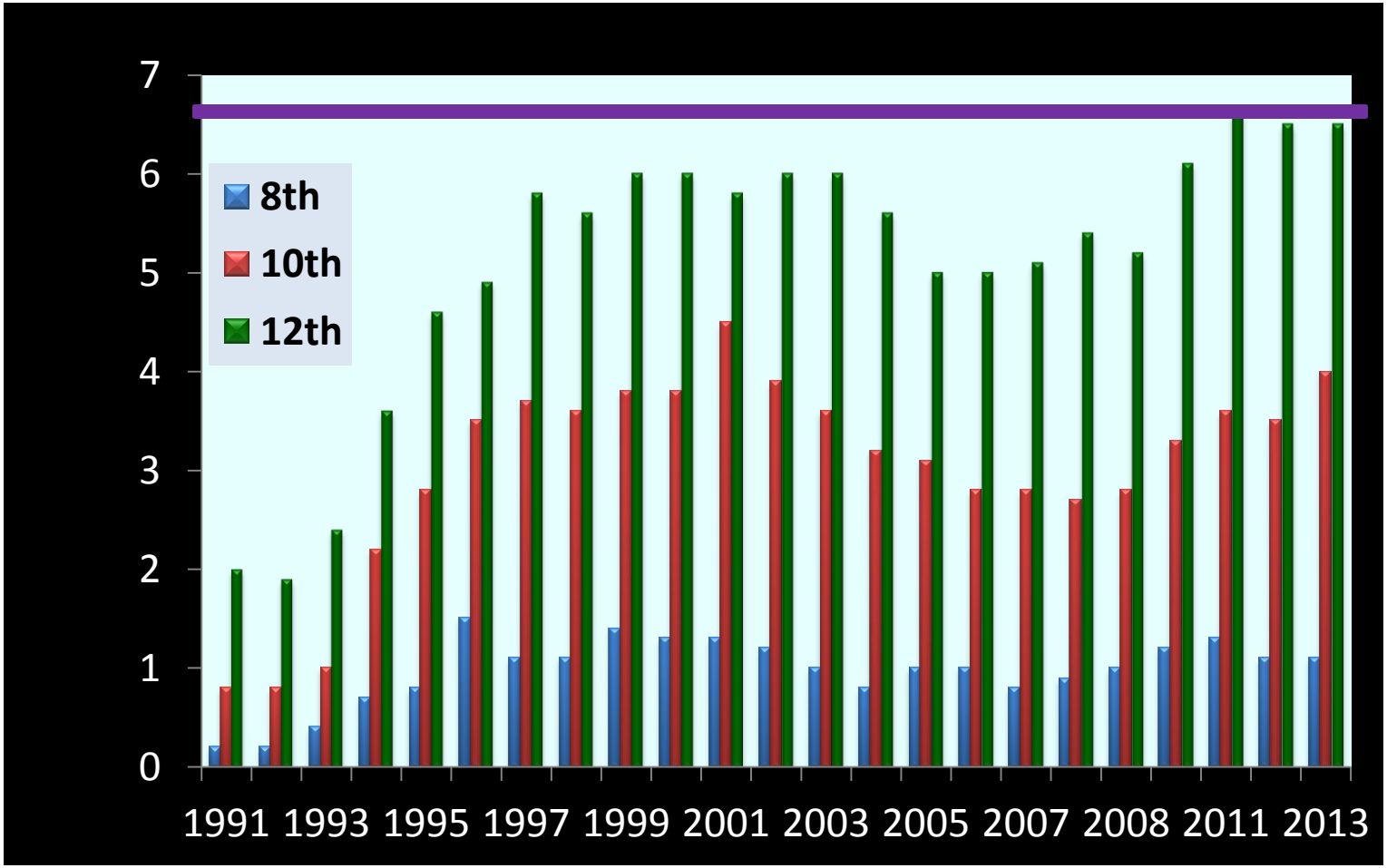
FDA requires new drugs shown to be *safe and effective for intended use* before marketing.

FDA requires research, clinical trials to base approval on safety, efficacy and labeling decisions.

Challenges: 12-17 yr olds Use More Marijuana in States With Marijuana As Medicine



Challenges: Daily Marijuana Use Highest in 22 years (8th, 10th, 12th graders)



Source: Monitoring the Future, 2013

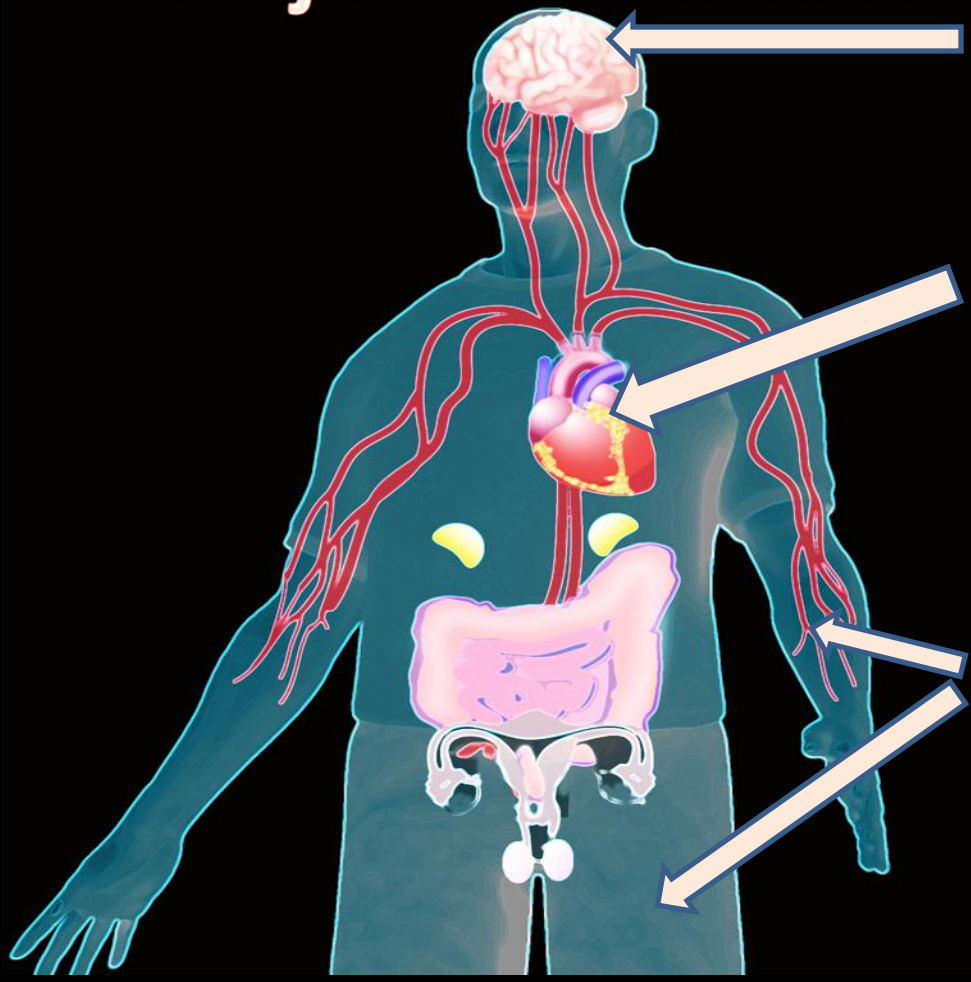
Challenges: Casual Marijuana Use Associated with Brain Abnormalities

Even in young, nondependent marijuana users, shape abnormalities are observable, *which reflect how much as used.*

Marijuana use may be associated with a disruption of neural organization in the nucleus accumbens and amygdala.

Gilman JM, Kuster JK, Lee S, Lee MJ, Kim BW, Makris N, van der Kouwe A, Blood Breiter HC. Cannabis use is quantitatively associated with nucleus accumbens and amygdala abnormalities in young adult recreational users. J Neurosci. 2014Apr 16;34(16):5529-38.

Challenges Beyond the Brain: Marijuana and Cardiovascular System



BRAIN
Transient reduced blood supply
Strokes

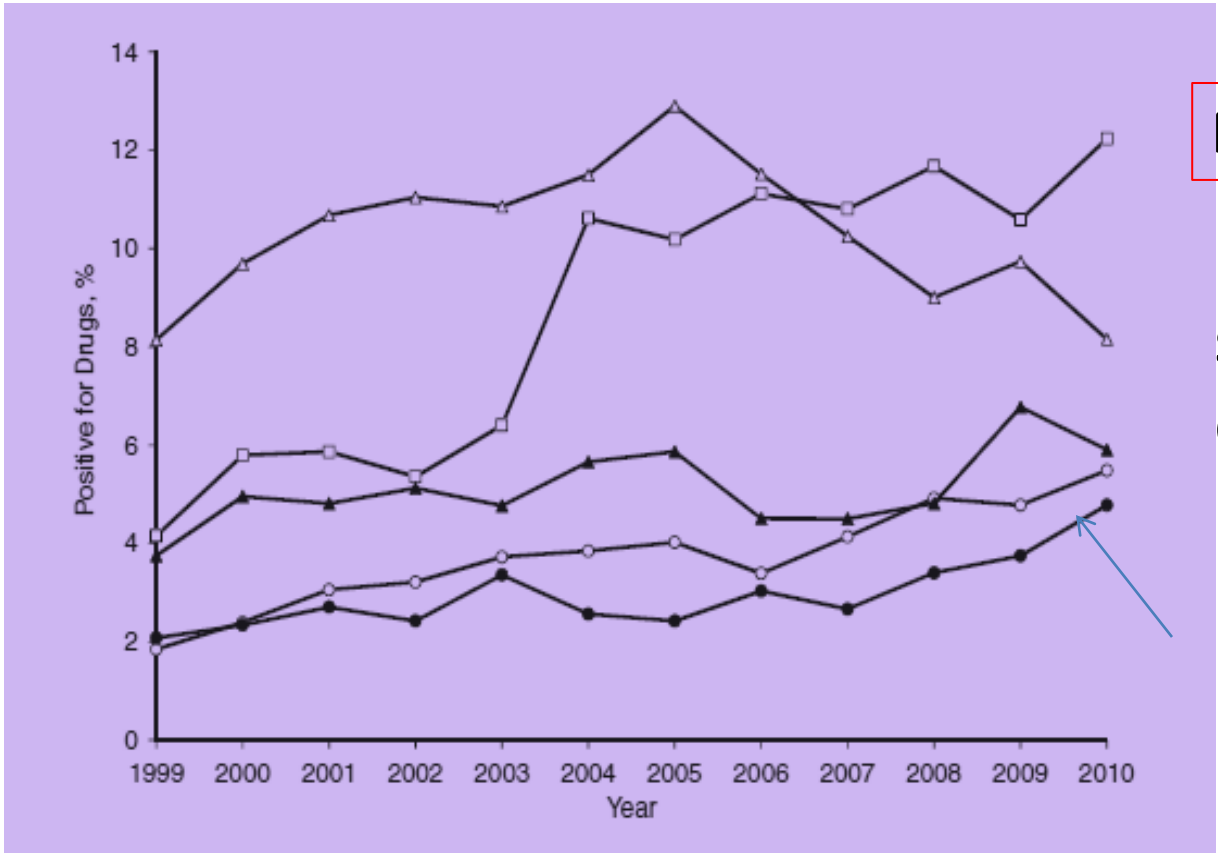
HEART (heart rate, mild blood pressure rise)
Angina
Heart attack
Cardiac death
Enlarged heart
Irregular beats

PERIPHERAL VASCULAR SYSTEM
Inflammation clotting
Raynaud's
Ischemic ulcers
Digital necrosis

Thomas G, Kloner RA, Rezkalla S. Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. Am J Cardiol. 2014 Jan 1;113(1):187-90.

Challenges in US Traffic Safety:

Marijuana Involvement In Drivers Who Died Within 1 Hour of a Crash



Marijuana

Stimulants

Other drugs

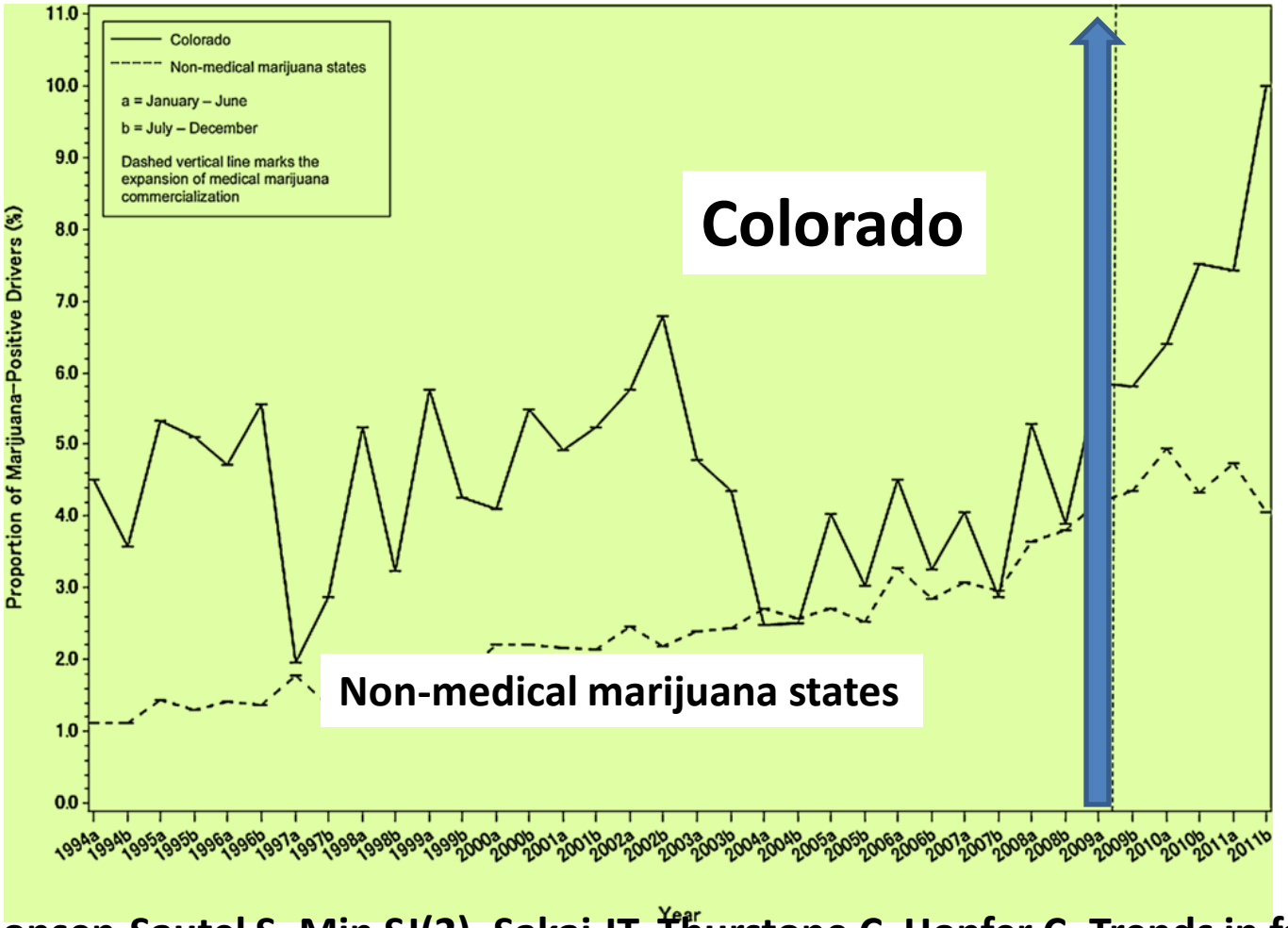
Narcotics

Depressants

Brady JE and Li G, Trends in Alcohol and Other Drugs Detected in Fatally Injured Drivers in the United States, 1999-2010. Am J Epidemiol. 17: 692-699 2014

Challenges in US Traffic Safety:

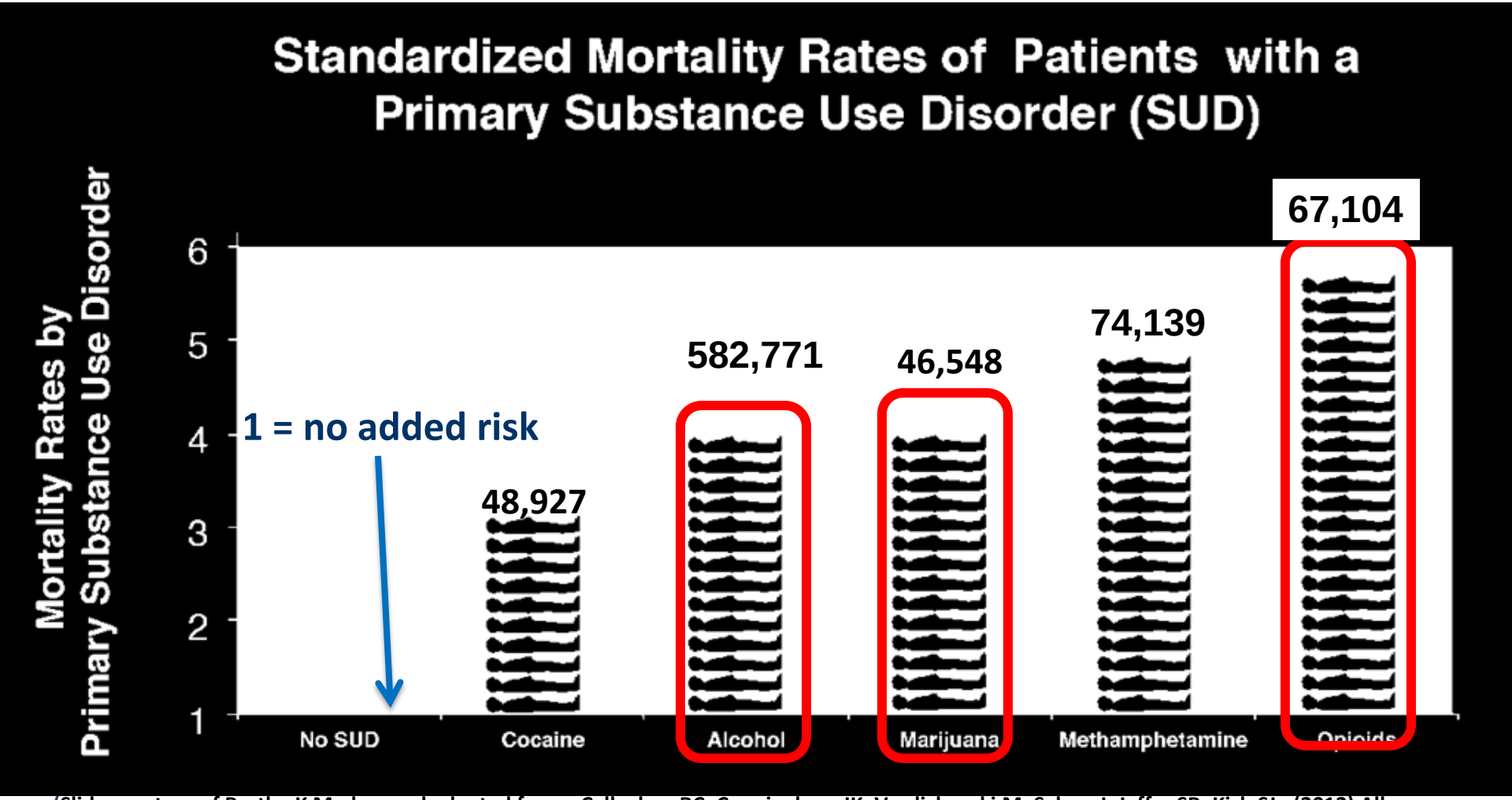
Marijuana Involvement In Drivers Who Died Within 1 Hour of a Crash



Salomonsen-Sautel S, Min SJ(2), Sakai JT, Thurstone C, Hopfer C. Trends in fatal motor vehicle crashes before and after marijuana commercialization in Colorado. Drug Alcohol Depend. 2014 Apr 23.

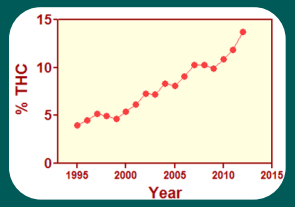
Marijuana Use Disorder: Death Rate 3 Times Higher

Slightly higher than alcohol death rate



(Slide courtesy of Bertha K Madras and adapted from: Callaghan RC, Cunningham JK, Verdichevski M, Sykes, J, Jaffer SR, Kish SJ. (2012) All-cause mortality among individuals with disorders related to the use of methamphetamine: A comparative cohort study. Drug Alcohol Depend. 2012 Oct 1;125(3):290-4.

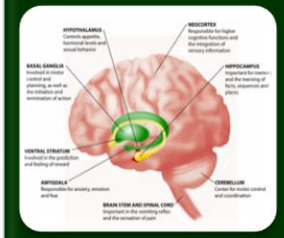
Introduction



Part I

Marijuana: Children at Risk

Part II



Marijuana AND Opioids: Children at Risk

Part III

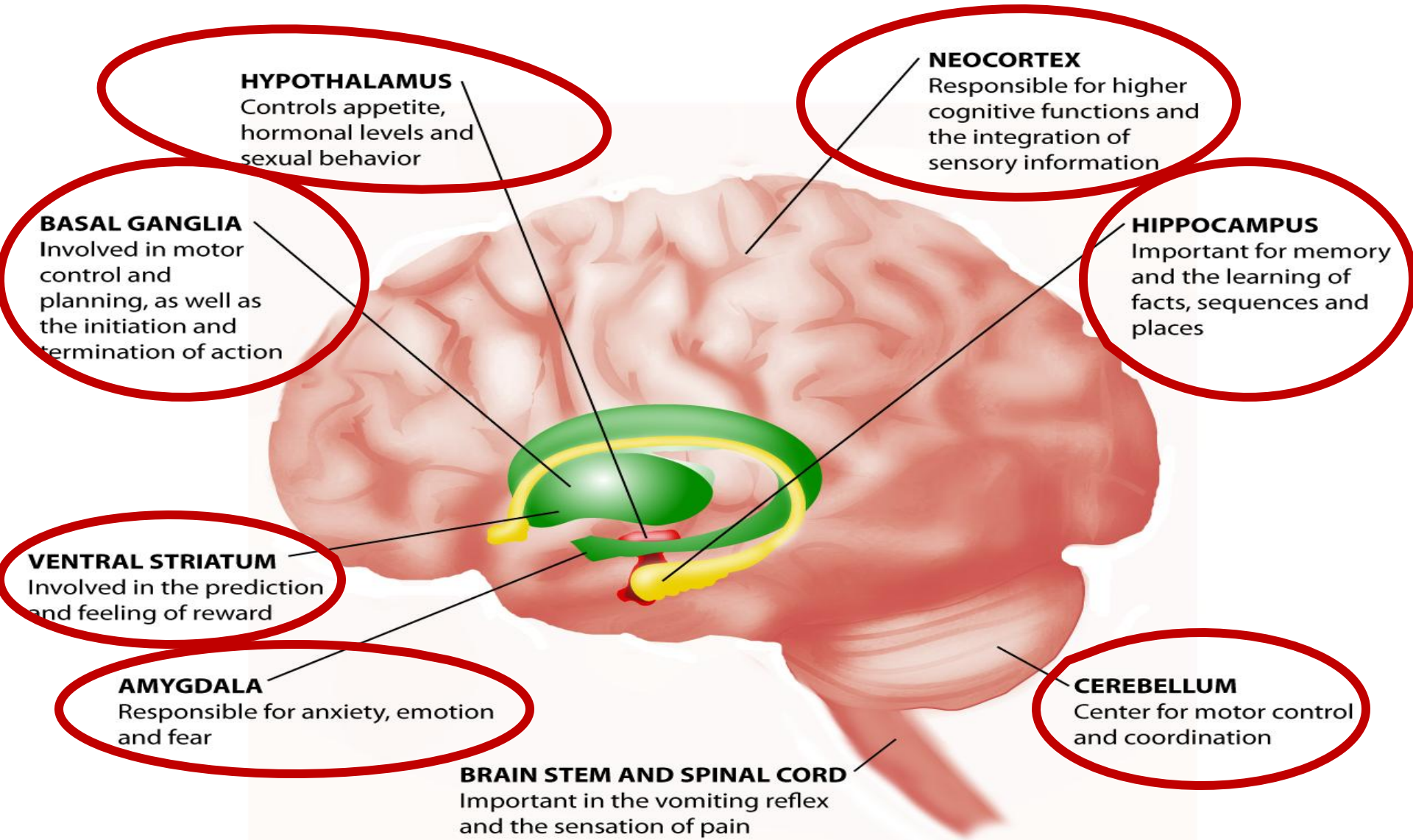
How Can We Respond?

Part I

Marijuana: Children at Risk

- The Developing Adolescent Brain
- Marijuana Can Affect Developing Brain
- Consequences of Early Marijuana Use

Marijuana Affects Many Brain Regions



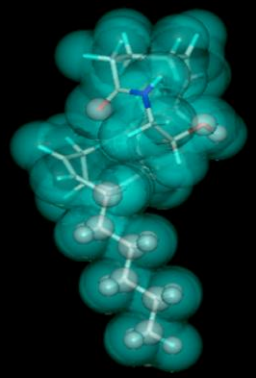
Brain Development

I nerve cell

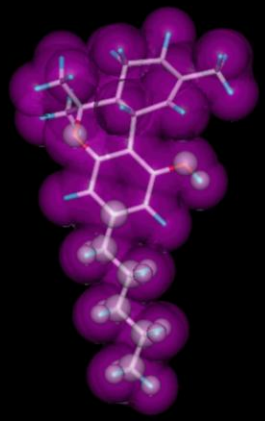
- 100 billion nerve cells
- 1 trillion supporting cells

Livet, et al, 2007, Loulier et al 2014

Brain Cannabinoid Commmunication Helps Regulate Brain Development and Communication



Anandamide



THC

- Modulates communication in brain regions responsible for motivated behavior, learning memory, appetite, motion, pleasure, mood, pain, planning, judgment
- Important for brain development

- THC disrupts and changes anandamide control of brain signals .
- THC effects are prolonged, more powerful, different
- THC affects brain development

Brain Cannabinoids During Prenatal Brain Development

Cannabinoids in brain are implicated in brain development:

- **promote birth of new brain cells**
- **tell cells what type to become**
- **guide them to their targets**
- **help them form connections**

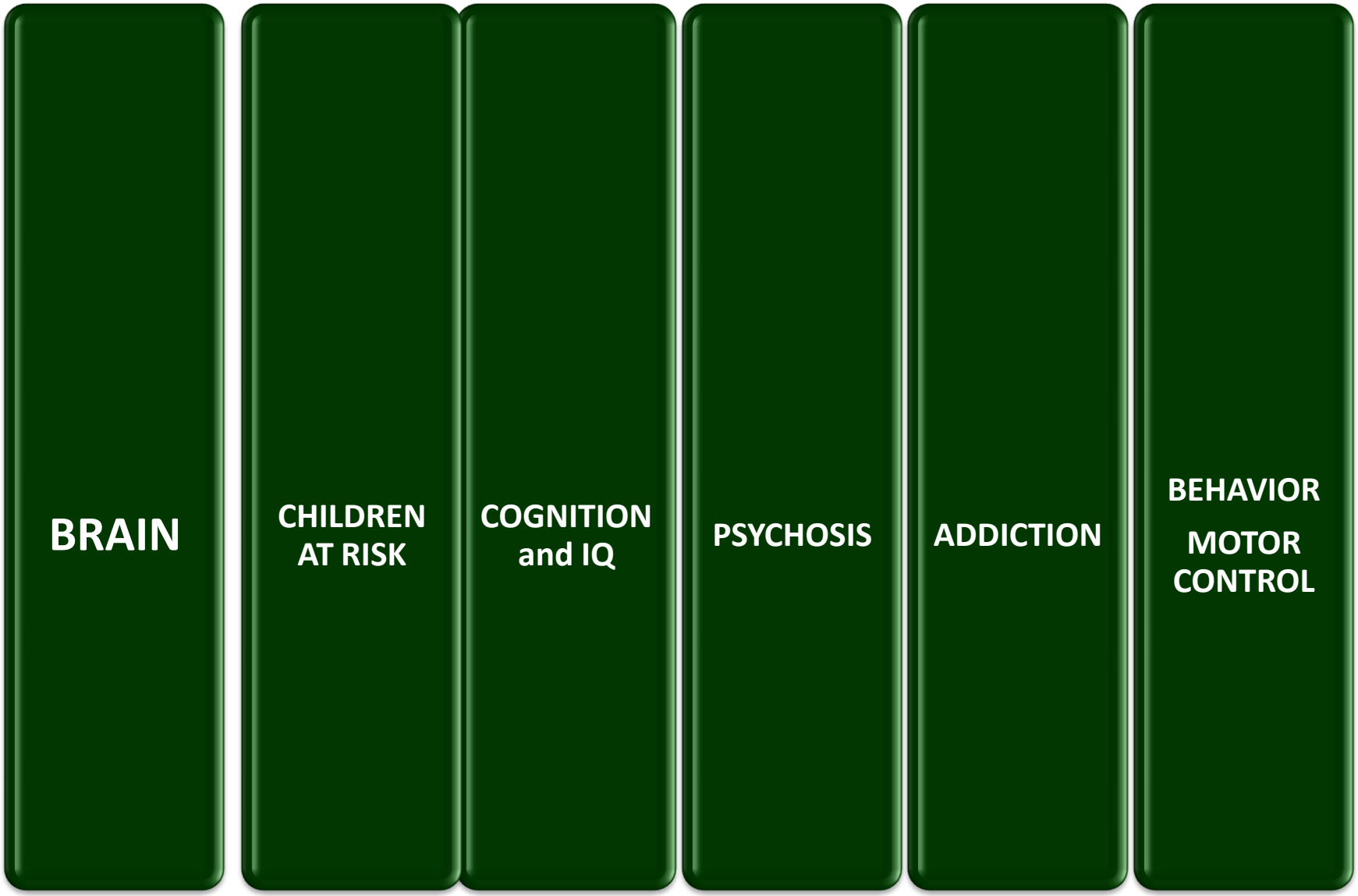
Marijuana in the Developing Brain

The Adolescent: Marijuana Use

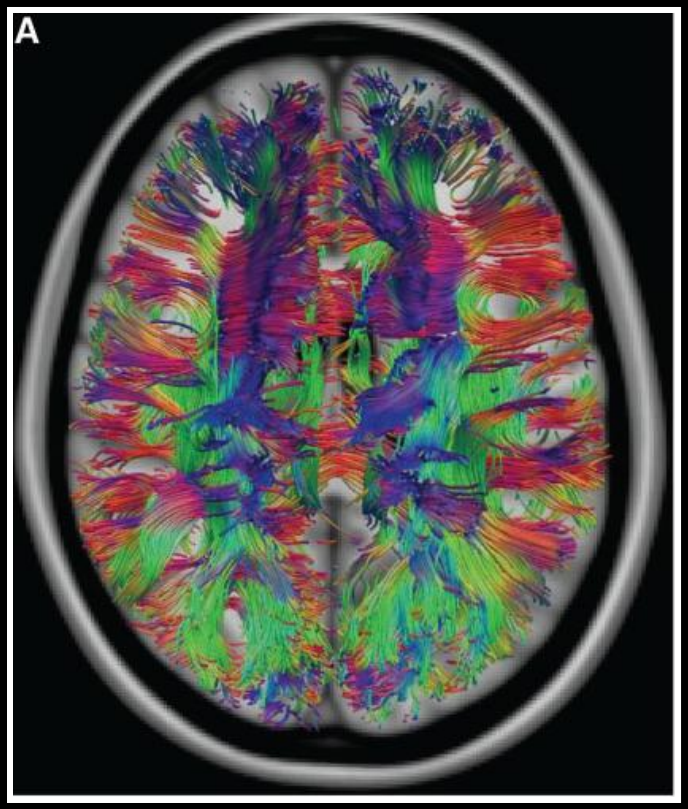
Pregnant Mothers: Marijuana Use

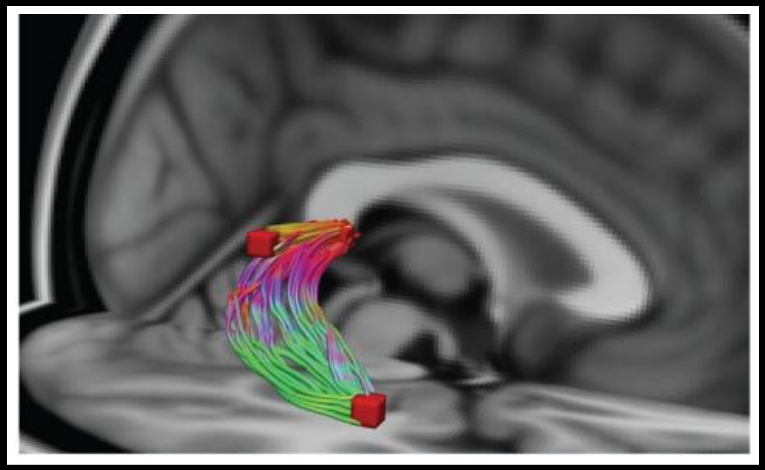
Before pregnancy: Marijuana Use

Children at Risk: Marijuana-Adolescence



Marijuana Damages Brain Connectivity





Zalesky et al Brain, 2012: 135; 2245–2255

Early Onset of Marijuana Use Associated with Learning Deficits

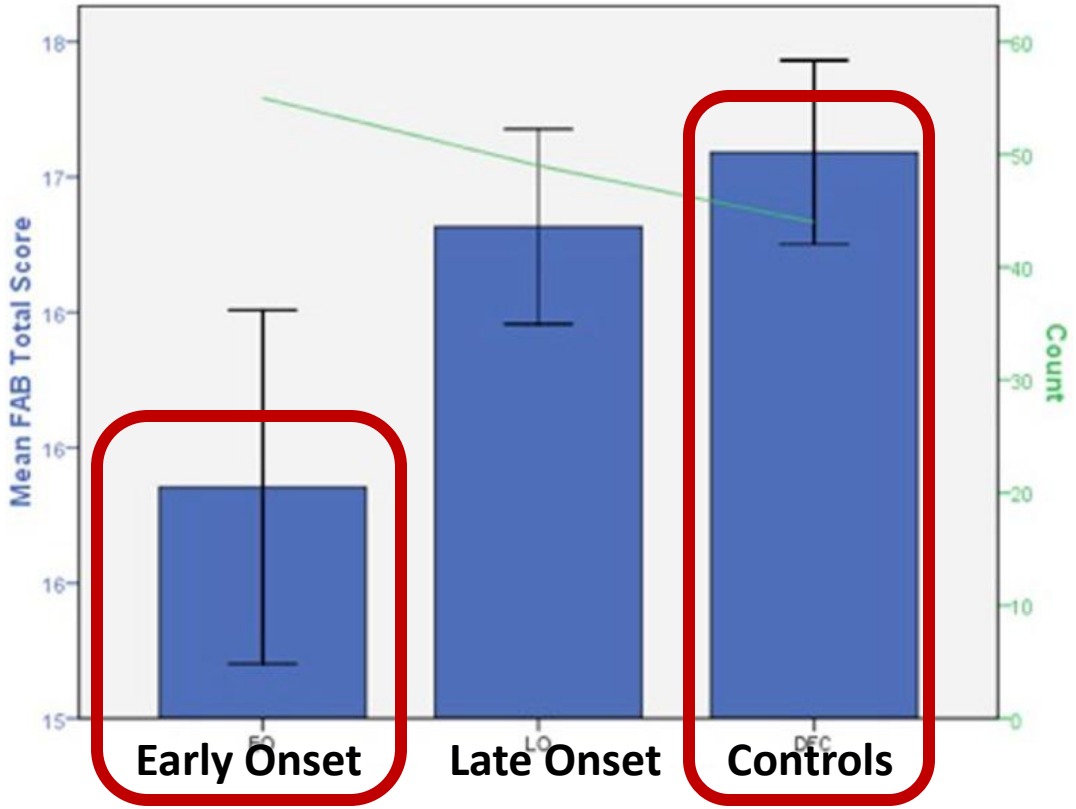
- **Marijuana changes structure and function of adolescent brain – neurotoxic effects**
- **Both changes appear soon after marijuana use**
- **Brain changes associated with learning deficits?**

IMPAIRED BRAIN FUNCTION

Verbal IQ
Memory of word lists
Word associations
Perseveration
Spatial working memory
Executive function

Pope HG Jr, et al. Early-onset cannabis use and cognitive deficits: what is the nature of the association? Drug Alcohol Depend. 2003 ;69(3):303-10. Harvey et al, 2007; Novaes et al 2008; Battisti et al 2010, Ehrenreichet al. 1999.

Deficits in Brain Function Associated with Age of First Use



Deficits in mean total Frontal Assessment Battery (FAB) total score in early adolescent MJ use onset (EO, *n*=49), late adult onset (LO, *n*=55), and control groups (DFC, *n*=44) lower scores indicate impairment; adapted from Fontes et al., 2011) Lisdahl KM(1), Gilbart ER, Wright NE, Shollenbarger S. Front Psychiatry. 2013 Jul 1;4:53. 2013.

Early Adolescent Marijuana Use Associated with Young Adult Psychosis

2 X more likely to develop a non-mood psychosis

4 X more likely to have high psychiatric scores

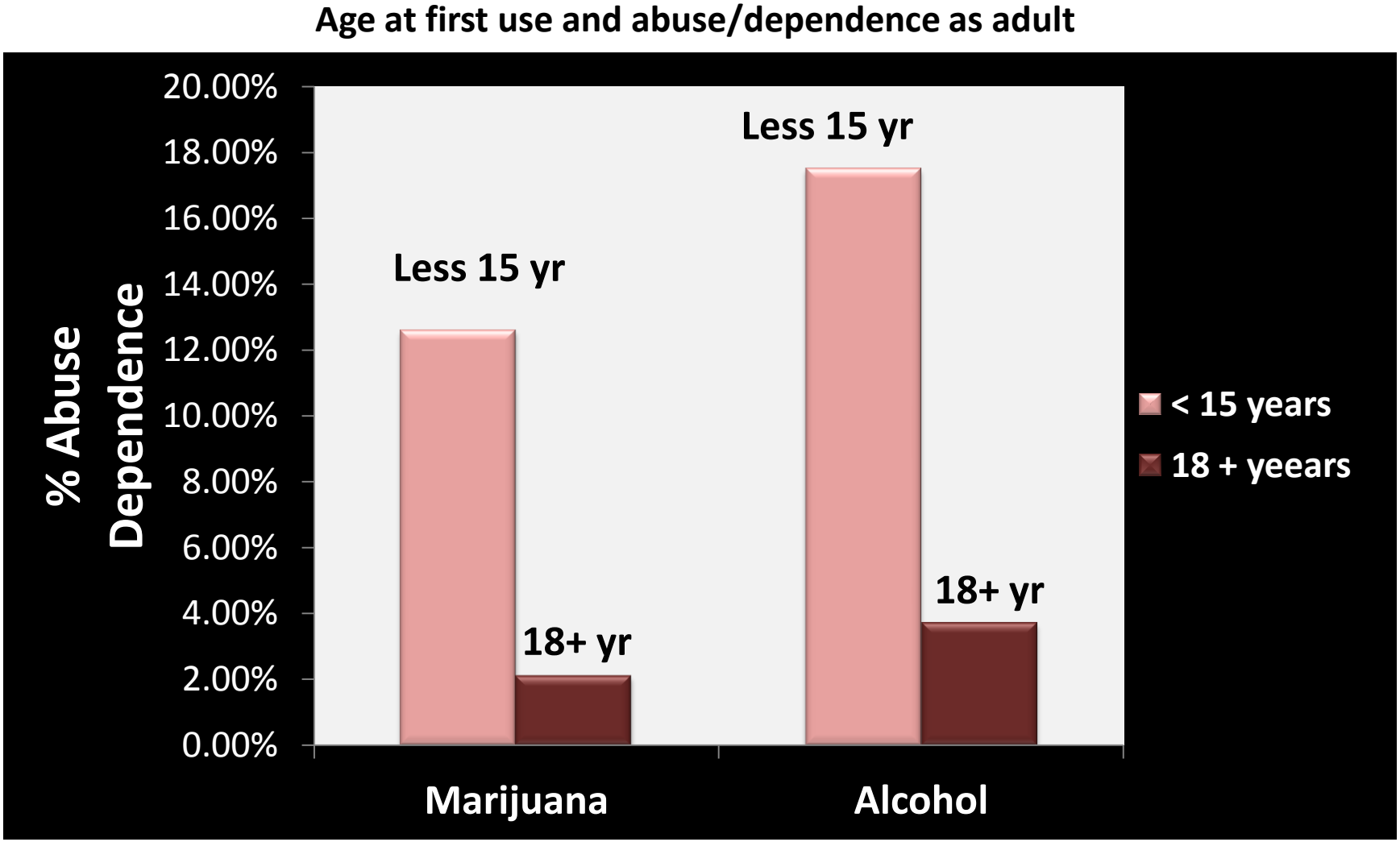
4 X increased risk for schizophrenia

heavy marijuana use during early adolescence

*PDI: Psychiatric Diagnostic Interview McGrath J, et al. Arch Gen Psychiatry. 2010 May;67(5):440-7.
Arseneault et al., 2002; van Os et al, 2002; Zammit et al., 2002; Henquet et al., 2005; Stefanis et al., 2004; Rubino and Parolaro, 2008; Konings et al., 2008; Andreasson et al., 1987; Moore et al, 2007

Addiction to Marijuana or Alcohol

5-6 Times Higher if Teenager Starts Using at Age 14 or Less

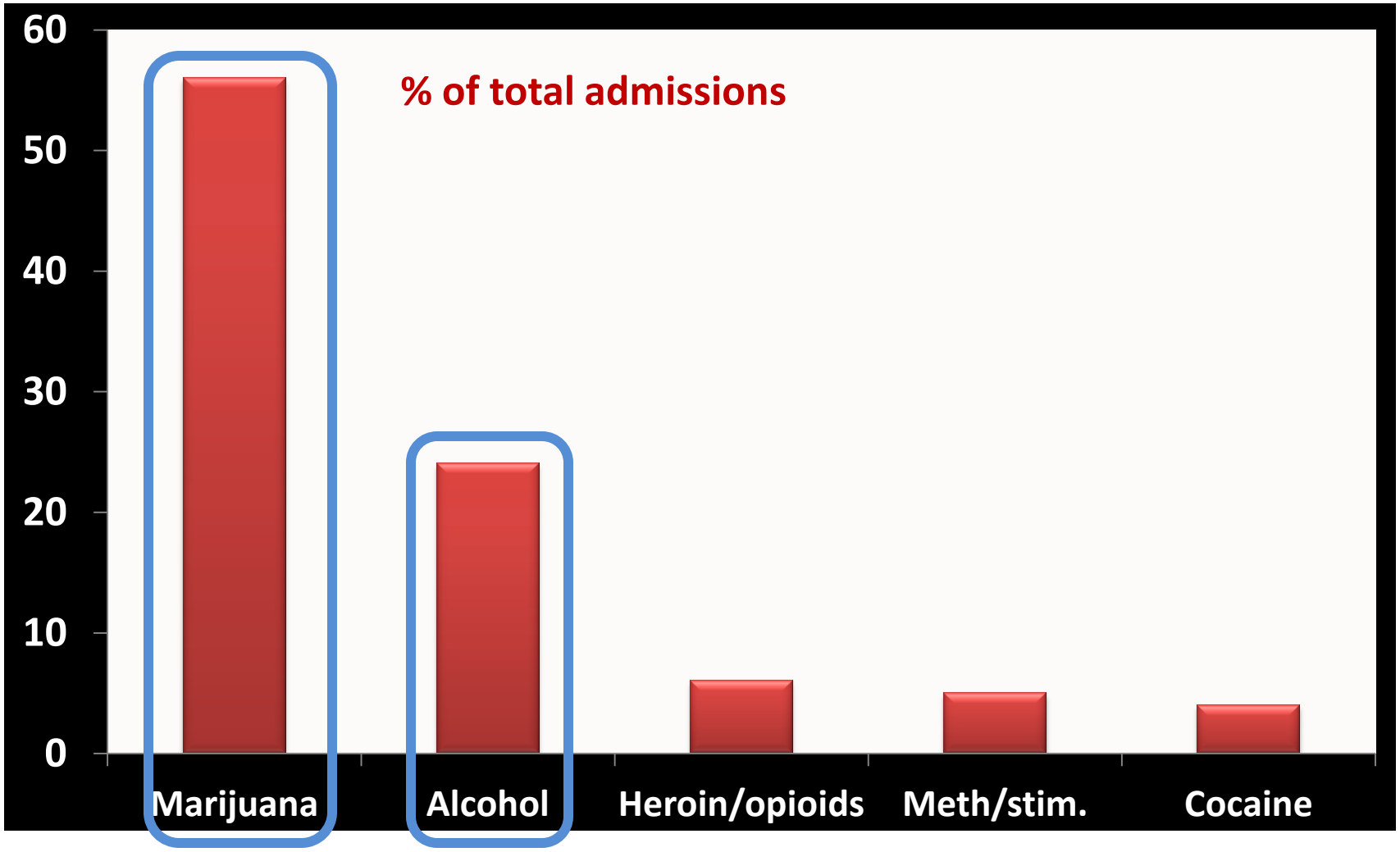


2011 National Survey Drug Use and Health, NSDUH Sept 2012

Marijuana Withdrawal Reflects Brain Adaptation (and addiction)

Psychological	• Anger, Aggression, Anxiety, Irritability, Depression, Nervousness, Restlessness, Sleep disorders
Physical	• Appetite Change, Weight Loss, Chills, Fever, Headache, Shakiness, Stomach Pain, Sweating, Tremors
Addictive	• Craving
Function	• Improved memory (after 12 days for 1 year)

Marijuana Treatment Admissions for 15-19 Year Olds 2x Higher than Alcohol



SAMHSA: Treatment Episode Data Set (TEDS) 2007

Marijuana Use by Pregnant Mothers

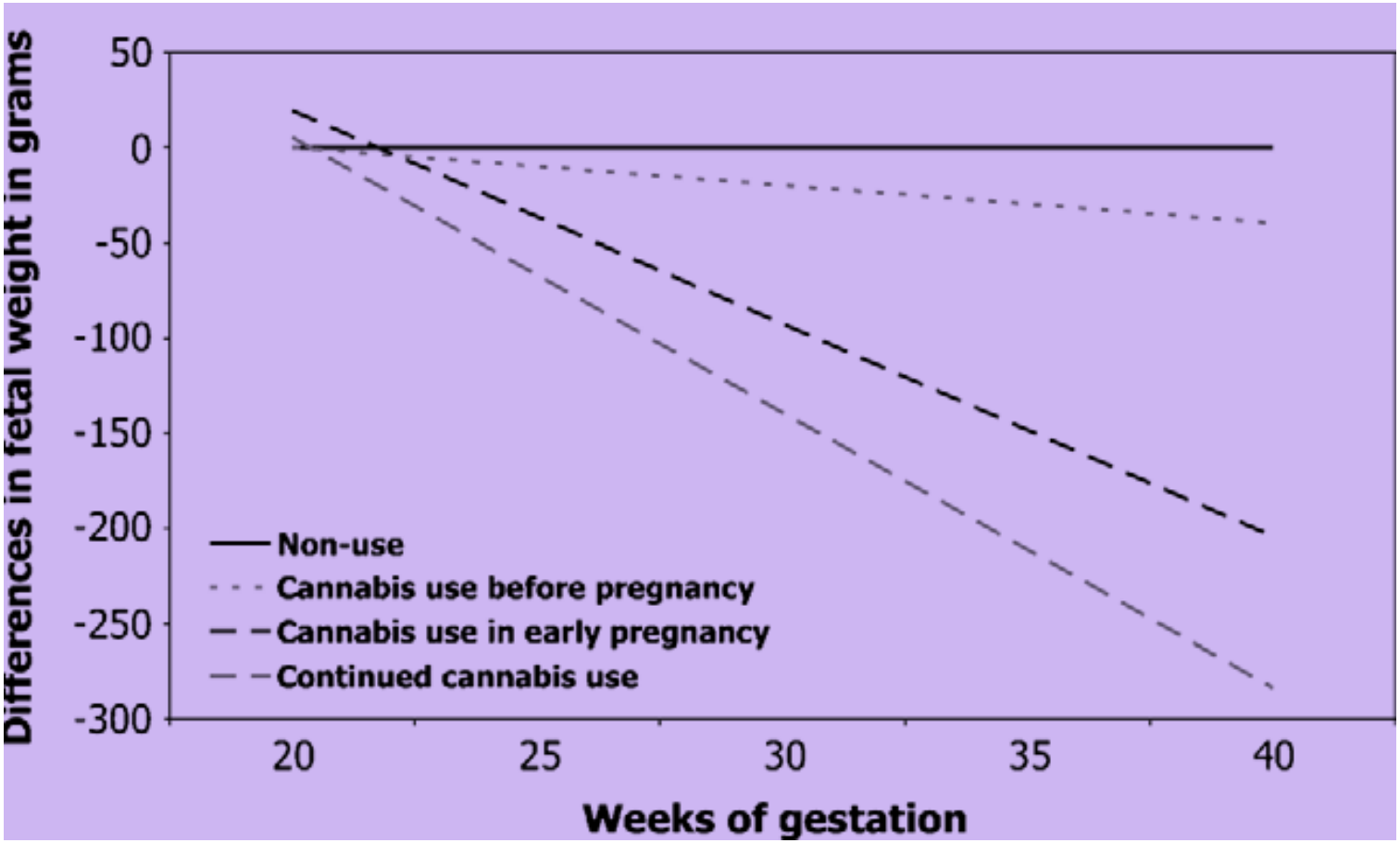
Over 10 % of pregnancies in the US and Europe associated with maternal cannabis exposure.

72.9% of pregnant teen rehab admissions used cannabis

45.7% used alcohol

Eur Child Adolesc Psychiatry DOI 10.1007/s00787-014-0550-y Neuronal substrates and functional consequences of prenatal cannabis exposure Daniela Calvigioni Yasmin L. Hurd Tibor Harkany • Erik Keimpema

Pre and Post-conception Marijuana Affects Fetal Weight



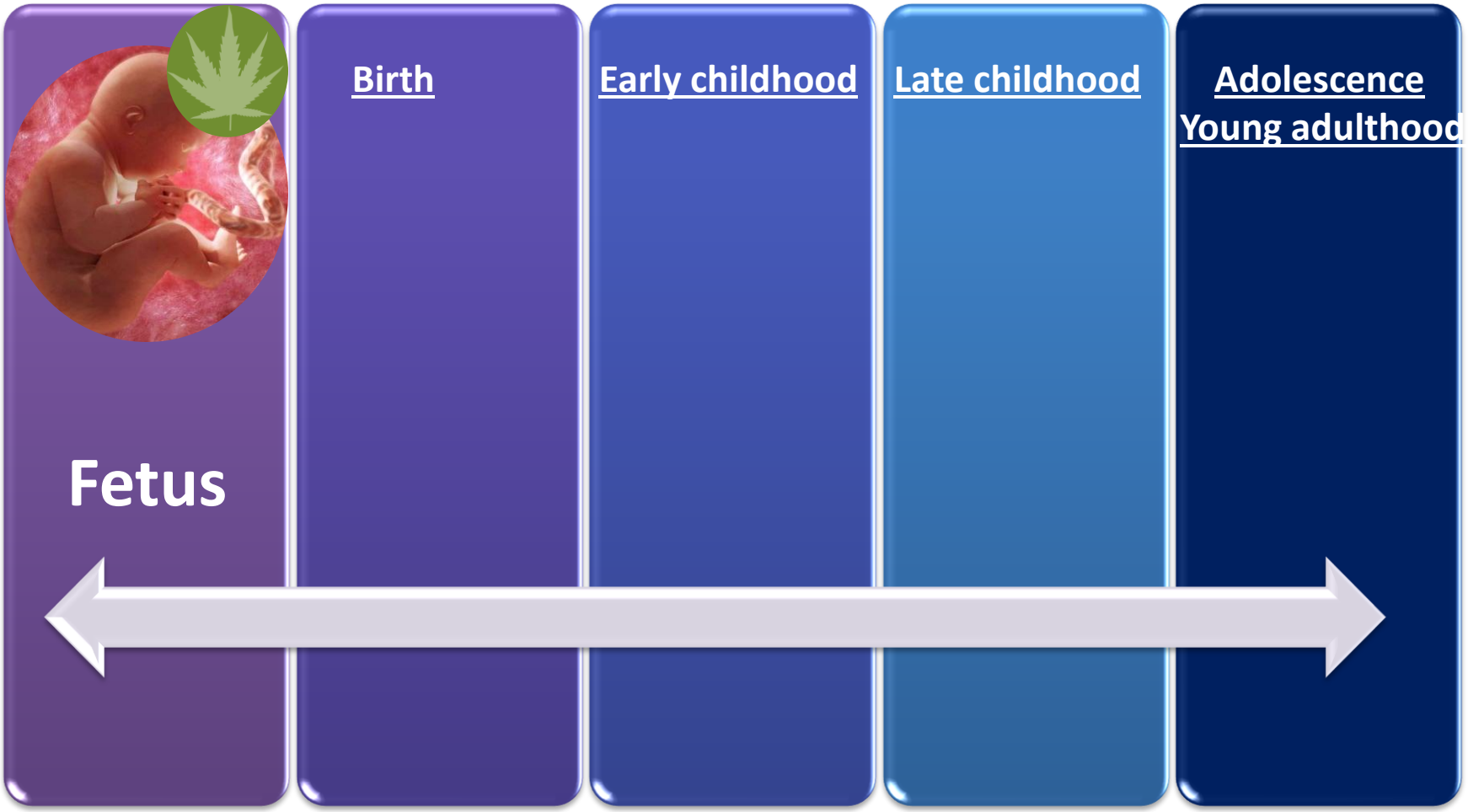
El Marroun H, Tiemeier H, Steegers EA, Jaddoe VW, Hofman A, Verhulst FC, van den Brink W, Huizink AC. Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. J Am Acad Child Adolesc Psychiatry. 2009 Dec;48(12):1173-81.

Miswiring the brain: THC disrupts cortex development in fetus

- **THC reorganizes wires in the developing and adult nervous systems (Kano et al, 2009, Keimpema et al, 2010).**
- **THC impacts cortical wiring in the fetal cerebrum.**
- **THC disrupts development and maintenance of connections critical for executive and cognitive functions (Kittler et al, 2000).**

Tortoriello G(1), Morris CV, Alpar A, Fuzik J, Shirran SL, Calvigioni D, KeimpemaE, Botting CH, Reinecke K, Herdegen T, Courtney M, Hurd YL, Harkany T. Miswiring the brain: Δ9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway. EMBO J. 2014 Apr 1;33(7):668-85.

Marijuana Effects on Developing Fetus



Morris CV, DiNieri JA, Szutorisz H, Hurd YL. Molecular mechanisms of maternal cannabis and cigarette use on human neurodevelopment. Eur J Neurosci. 2011 Nov;34(10):1574-83.

Marijuana Effects on Developing Fetus

Birth

Fetus

< 1 week, 9-30 days:

Increased tremor

Exaggerated startle

9 months: impaired mental development

Morris CV, DiNieri JA, Szutorisz H, Hurd YL. Molecular mechanisms of maternal cannabis and cigarette use on human neurodevelopment. Eur J Neurosci. 2011 Nov;34(10):1574-83.

Marijuana Effects on Developing Fetus

Early childhood

Fetus

- **3 years** impaired verbal, abstract, visual and quantitative reasoning; impaired short term memory
- **4 years**: impaired memory, verbal ability
- **6 years:** impaired sustained attention increased impulsivity and hyperactivity

Morris CV, DiNieri JA, Szutorisz H, Hurd YL. Molecular mechanisms of maternal cannabis and cigarette use on human neurodevelopment. Eur J Neurosci. 2011 Nov;34(10):1574-83.

Marijuana Effects on Developing Fetus

Adolescence Young adulthood

Fetus

- **14-21 years**: increased risk of cigarette smoking, marijuana
- **19-21 years:** altered neuronal function during visuospatial memory task
- **18-22 years**: increased neural activity in PFC during inhibitory control tasks
- ***increased incidence of schizophrenia, depression, addiction***

Morris CV, DiNieri JA, Szutorisz H, Hurd YL. Molecular mechanisms of maternal cannabis and cigarette use on human neurodevelopment. Eur J Neurosci. 2011 Nov;34(10):1574-83; (Substance Abuse & Mental Health Service Administration, 2010; Keimpema et al, 2011).

Part II

Marijuana and Opioids Children at Risk

- Marijuana and Opioid Effects
- Marijuana Use During Adolescence
- Marijuana Use Prior to Pregnancy

Marijuana and Opioid Consequences

Effect	MARIJUANA	OPIOIDS
FATAL OVERDOSE	?	x
ACUTE INTOXICATION		
Accidental injury	X	X
Car accident	X	?
Drug-induced psychotic symptoms	X	-
Myocardial infarction	?	
LONG TERM		
Addiction	X	X
Cardiovascular pathology	X	X
Liver disease	-	X
Lung disease	X	X
Cancers	X	
Cognitive impairment	X	?
Psychotic disorders	X	-

Marijuana and Opioids: parallel effects

MARIJUANA

Sedates
Lowers body temperature
Reduces pain

OPIOIDS

Sedate
Lower body temperature
Reduces pain

Lowers blood pressure

Lowers blood pressure

Inhibits intestinal motility

Inhibit intestinal motility

What does this mean?

Why is this important?

Cannabinoid and Opioid Targets (Receptors) Exist On Same Cells

Lötsch J, Schneider G, Reker D, Parnham MJ, Schneider P, Geisslinger G, Doehring A. Common non-epigenetic drugs as epigenetic modulators. Trends Mol Med.2013 Dec;19(12):742-53.

Cannabinoids and Opioids

CANNABINOIDS AFFECT OPIOID RESPONSE

- Cannabinoids increase opioids in pain regions of brain, spinal cord, rewards regions
- Cannabinoid blockers block opioid reward, precipitate withdrawal
- THC produces tolerance to opioid pain-reducing effects
- THC long-term produces opioid-like withdrawal

OPIOIDS AFFECT CANNABINOID RESPONSE

- Opioid blockers block THC reward
- Opiod blockers block cannabinoid pain-reducing effects
- Opioids produce tolerance to THC pain-reducing effects

Cannabinoid-Opioid Connection
Children at Risk

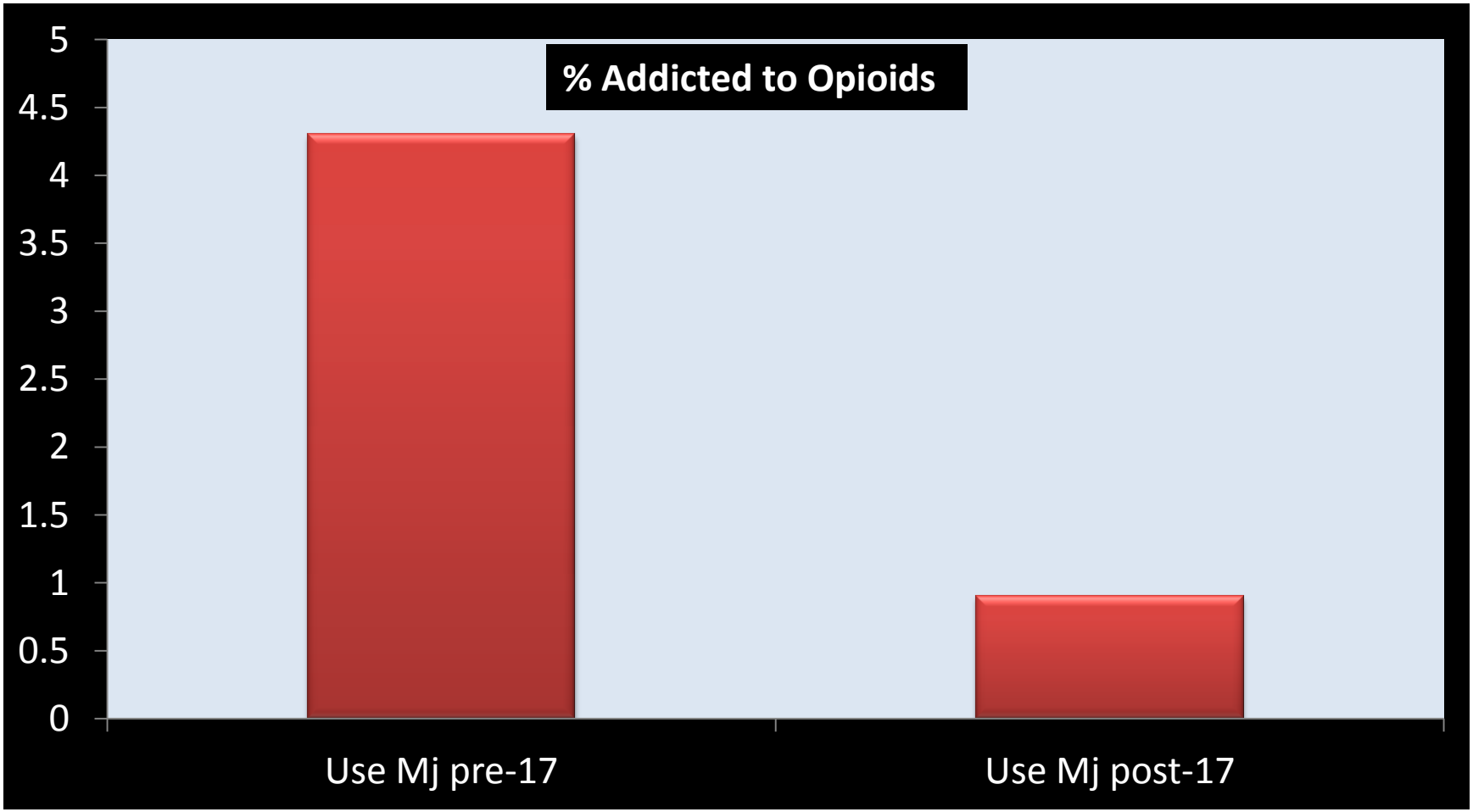
Adolescent

Developing Fetus

Children of parents who used before conception

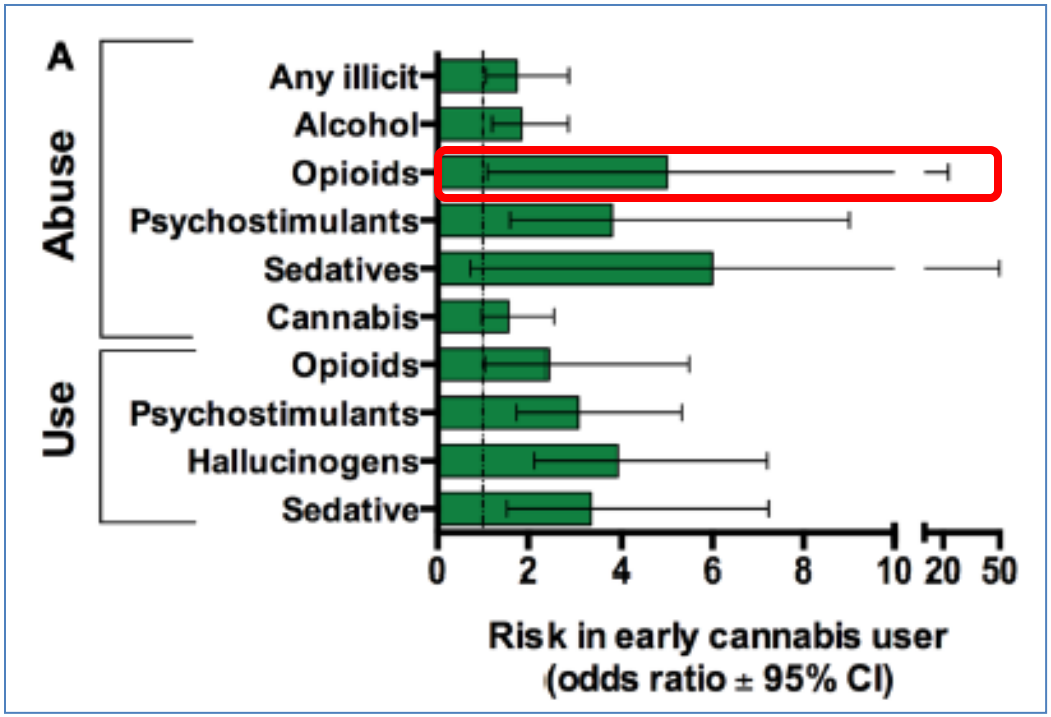
From Marijuana to Opioid Addiction

Twins initiating marijuana pre- or post- age 17



Michael T. Lynskey; Andrew C. Heath; Kathleen K. Bucholz JAMA, January 22/29, 2003—Vol 289, 427-433

Marijuana Use Increases Risk of Using Other Illicit Drugs

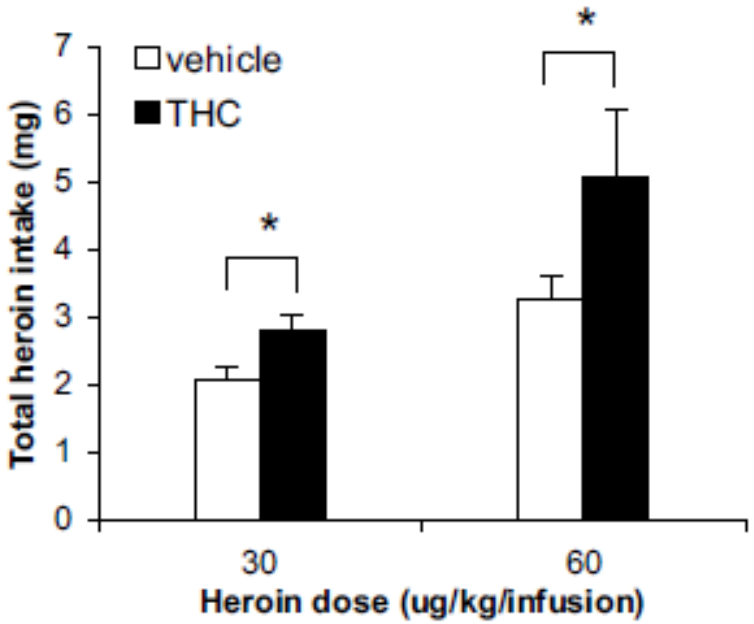


- Twin-studies
- Marijuana users increased risk of developing substance abuse disorder, compared to their discordant twin

Source: Chadwick B, Miller ML, Hurd YL. Frontiers Psychiatry. 2013 Oct 14;4:129. Cannabis Use during Adolescent Development: Susceptibility to Psychiatric Illness. Cannabis use is associated with progression to use other illicit substances in humans. Graph based on data adapted from Lynskey MT, Heath AC, Bucholz KK, Slutske WS, Madden PA, Nelson EC, et al. Escalation of drug use in early-onset cannabis users vs co-twin controls. *JAMA* (2003) 289(4):427–33

Adolescent

Adolescent Exposure to THC Primes Brain to Seek More Heroin During Adulthood



Ellgren M, Spano SM, Hurd YL. Adolescent cannabis exposure alters opiate intake and opioid limbic neuronal populations in adult rats. Neuropsychopharmacology. 2007 Mar;32(3):607-15.

Prenatal Exposure to THC Primes Brain to Respond More to Heroin During Adulthood

Adult rats exposed prenatally to THC show lasting behavioral and neural impairment related to the opioid reward/stress system.

Long-term vulnerability in motivation to self-administer heroin

1. shorter time to the first heroin seeking session.

2. Respond more to lower doses of heroin

3. Increase heroin seeking following a mild stress

4. Higher levels of heroin-seeking if access to heroin removed

Spano MS, Ellgren M, Wang X, Hurd YL. Prenatal cannabis exposure increases heroin seeking with allostatic changes in limbic enkephalin systems in adulthood. Biol Psychiatry. 2007 Feb 15;61(4):554-63.

Developing Fetus

Parental THC Exposure Prior to Conception Primes Brain of Offspring (rodents) to Respond More to Heroin During Adulthood

- **Environmental toxins or drugs of abuse such as alcohol, opiates inherited through the germline from parent to child in rodents.**

Offspring of parents exposed to THC before conception

THC Given to future rodent parents during adolescence

Behavioral, brain abnormalities in the next generation

Increased effort to self-administer heroin

Changes in cannabinoid, dopamine, glutamatergic R genes, key components of the circuitry mediating reward

Parental history of THC exposure may impact offspring behavior, and possibly confer enhanced risk for psychiatric disorders in the next generation.

Szutorisz H, Dinieri JA, Sweet E, Egervari G, Michaelides M,Carter JM, Ren Y, Miller ML, Blitzer RD, Hurd YL. Parental THC Exposure Leads to Compulsive Heroin-Seeking and Altered Striatal Synaptic Plasticity in the Subsequent Generation. Neuropsychopharmacology. 2014 May;39(6):1315-23.

Drug Consumption By *Future* Parents (Rodents) Can Affect Offspring

Opiates given to future parents during adolescence:
Brain reward system changed in offspring for 2 generations.

Cannabinoid agonist given to future parents during adolescence:
adolescent, adult offspring exhibit greater sensitivity to morphine reward.

Evidence of transgenerational effects of adolescent drug use.

1. **Byrnes JJ, Johnson NL, Schenk ME, Byrnes EM. Cannabinoid exposure in adolescent female rats induces transgenerational effects on morphine conditioned place preference in male offspring. J Psychopharmacol. 2012 Oct;26(10):1348-54.**

2. Byrnes JJ, Johnson NL, Carini LM, Byrnes EM. Multigenerational effects of adolescent morphine exposure on dopamine D2 receptor function. Psychopharmacology (Berl). 2013 May;227(2):263-72.

3. Vassoler FM, Johnson-Collins NL, Carini LM, Byrnes EM. Next generation effects of female adolescent morphine exposure: sex-specificalterations in response to acute morphine emerge before puberty. Behav Pharmacol. 2014 Apr;25(2):173-81

How Do Youth Perceive Marijuana?

Part III

How Can We Respond

Preventing adolescent use is an imperative

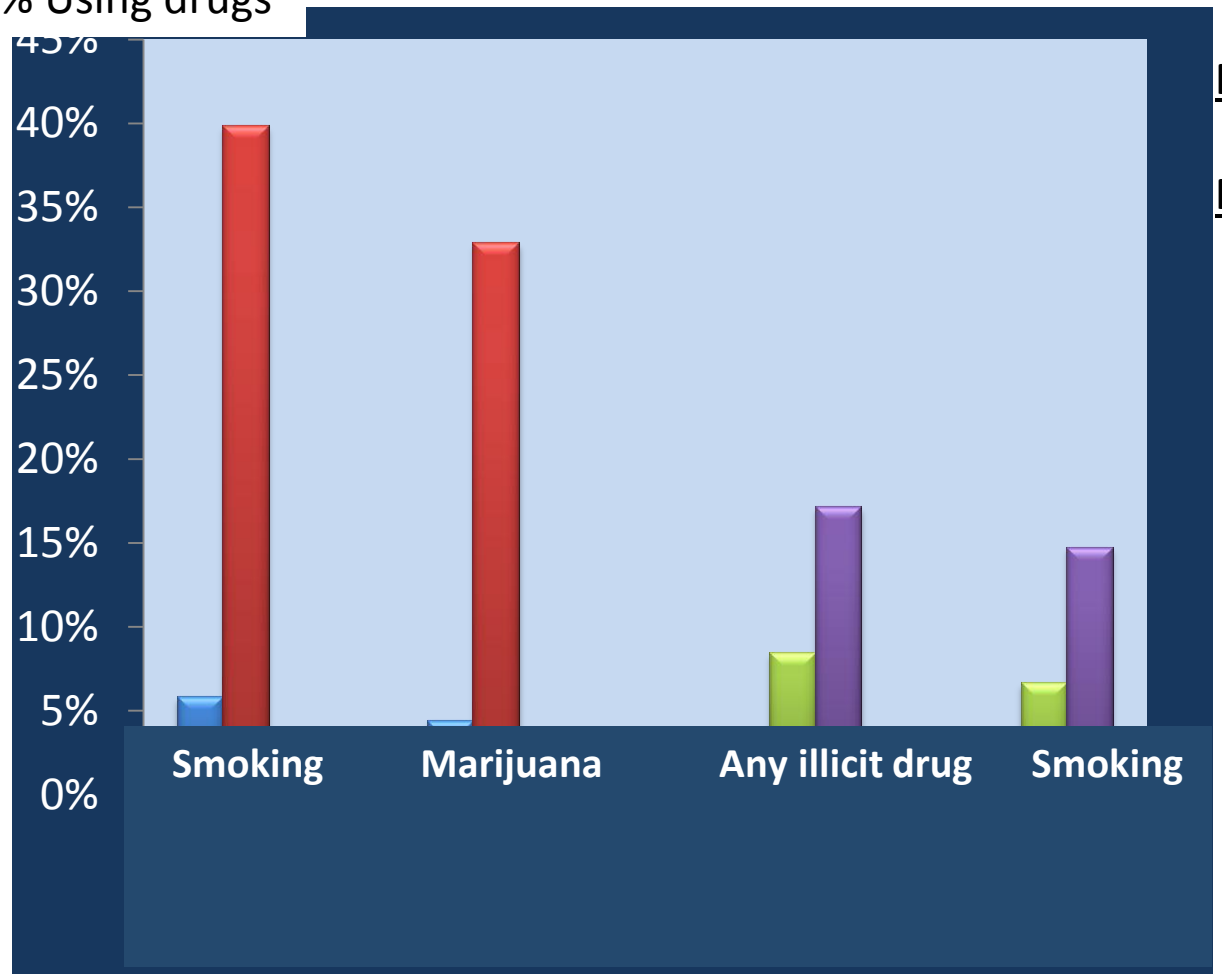
Go Forth and Educate

Recruit Parents into Prevention

Recruit Physicians into SBIRT

Never Surrender Science

Parents, Their Views, Their Help Have Enormous Impact on Drug Use



Source: NSDUH, 2010 published Sept 2011; http://www.samhsa.gov/data/NSDUH/2k10NSDUH/2k10Results.htm

Screening, Brief Intervention, Referral to Treatment (SBIRT) for Adolescents

Prevent, delay, or reduce drug use in children and adolescents

Intervene with problematic users: use in high-risk situations, e.g. driving a car, school suspension.

Patnode CD, O'Connor E, Rowland M, Burda BU, Perdue LA, Whitlock EP. Primary Care Behavioral Interventions to Prevent or Reduce Illicit Drug and Nonmedical Pharmaceutical Use in Children and Adolescents: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 106. AHRQ Publication No. 13-05177-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2014.

SBIRT Adolescents: Marijuana Results

4/6 studies found reduced marijuana use

12 - 24 months in intervention group

Primary care: marijuana-related consequences decreased in recipients of computer-based or therapist-led. No decease in control group.

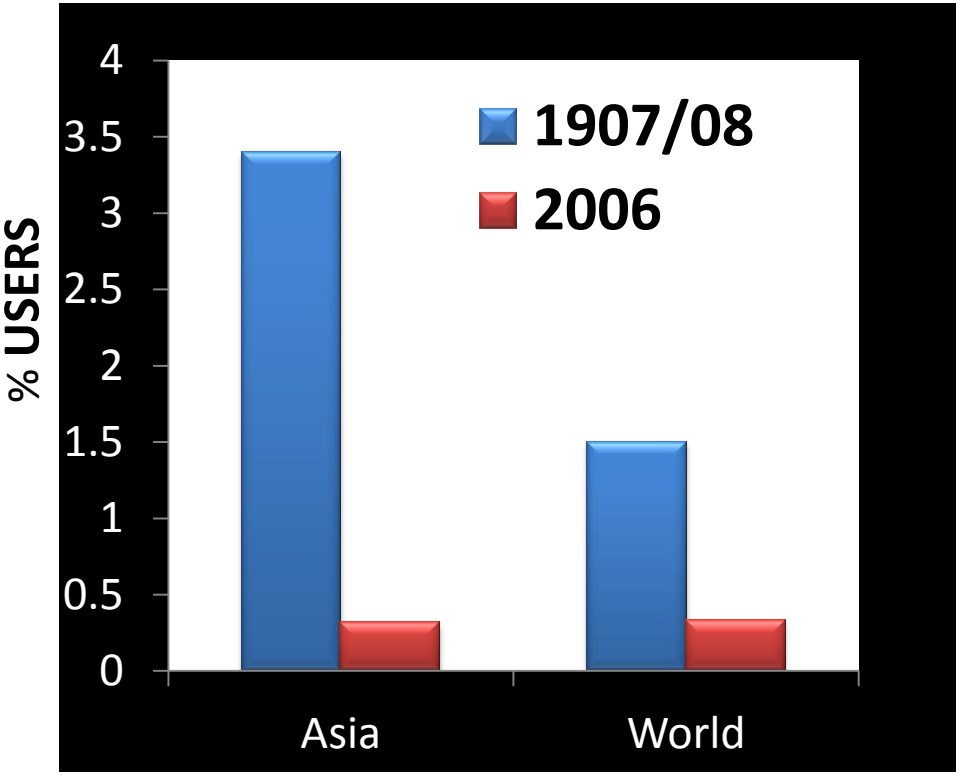
Pediatric ED: reduced marijuana to abstinence in 45 % of those intervention group compared with 22 % of controls (Bernstein et al).

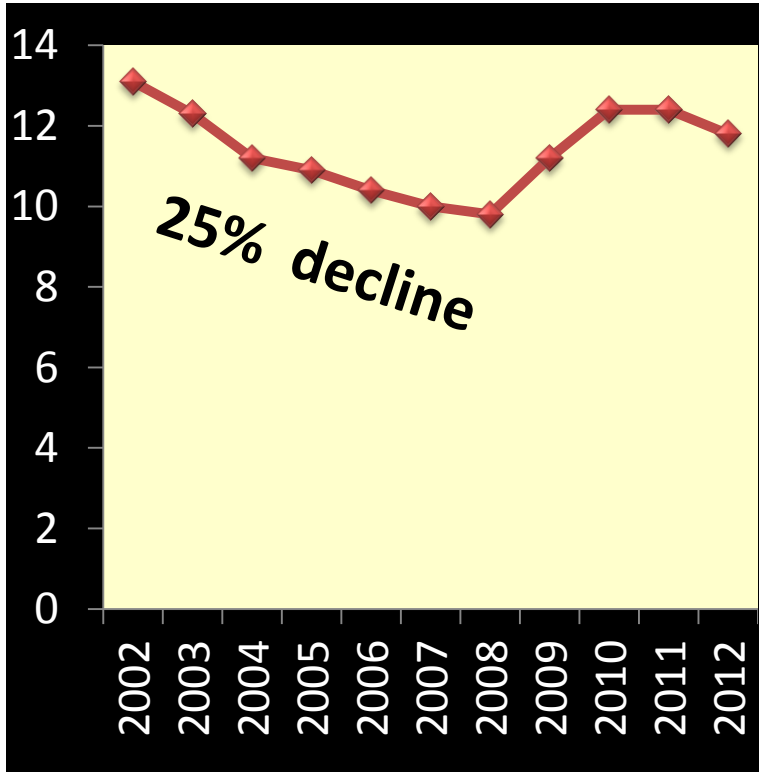
Nonmedical prescription drug use: 3 computer-based trials reported decreases

Drug Use Can Be Reduced with Public Education and Resolve

Opioid Use fell dramatically from 1907/08 to 2006

Marijuana Use Fell Dramatically Among 12-17 yr olds 2002-2008





Source: UN Office on Drugs and Crime, 2008 Report; Source: MTF, 2007

The Present and Future

Scientific data will trump passion

FULL ACCESS

- SAFE
- Pleasure
- Victimless
- Civil right
- Only a plant
- Beneficial
- Alcohol worse
- No addiction
- Patients suffering
- FDA cumbersome
- Difficult to patent
- Cheap alternative
- Easy access

RESTRICT

- UNSAFE
- Inadequate science
- No accountability
- Circumvents FDA
- Cognition impaired
- Adolescents at risk
- Cognitive effects
- Addiction
- Medical, psychiatric
- Behavioral
- Social
- Public Safety

DEFEND OUR BRAINS!

"The brain is the repository of our humanity. It is where our wisdom, our ability to love, learn, create, compute, compose, contemplate, think, to remember, to feel empathy for others, to engage in justice and compassion arises.

We recognize how precious, unique and fortunate we are to be the bearer of functional minds. We are united in a passionate desire to protect the minds of our most vulnerable – the children…" Bertha Madras