MARIJUANA & ADDICTION

A DISORDER OF THE LEARNING AND MEMORY SYSTEM

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Western States Marijuana Summit
San Diego, California
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("Natural" Marijuana had
< 2% THC in the 1980s)

Disclosures

- I have no relationship with any pharmaceutical company, or any part of the alcohol, tobacco or marijuana industries
- I am on the speaker's bureau for the National Marijuana Initiative and they pay my travel expenses

Why Do People Choose to Try Alcohol, Tobacco, or Marijuana in the First Place?

- Curiosity
- Parents/family members use
- Peer pressure
- Advertising

Why do they Continue to Use?

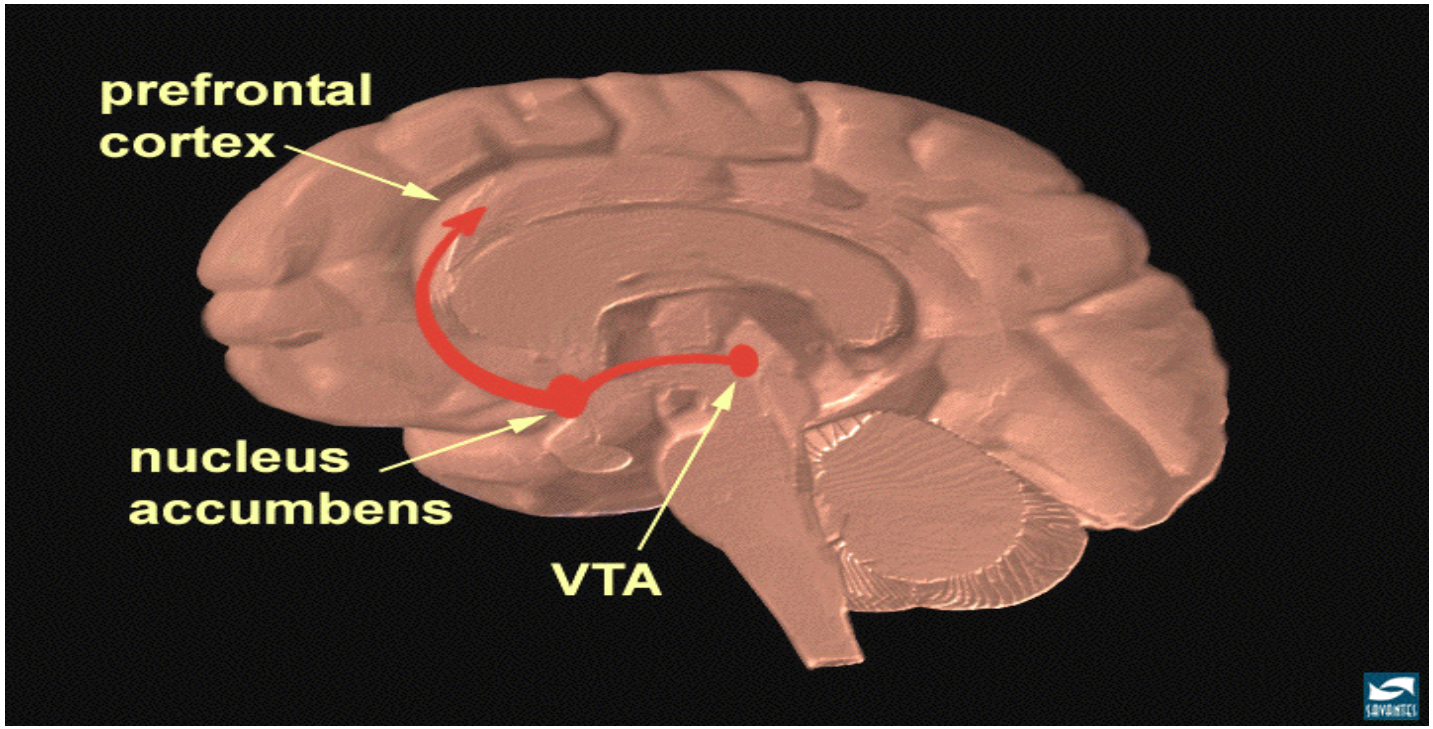
- Numbs pain – physical and emotional
- A way to cope with the effects of trauma/abuse
- Disinhibits – aids social interactions
- Creates energy
- Temporary sense of well being
- Reward pathway – Drugs, alcohol

and tobacco can **hijack the learning and memory part of the brain** and the use becomes - **<u>No Longer a Choice</u>**

Why Do They Become Addicted?

- Rewarding properties of addictive drugs – in the “reward pathway”
- Possible genetic vulnerability factors – decrease in D2 receptors
- Prior sensitization by nicotine or other drugs as a child/adolescent
- Prior sensitization by stress/trauma/abuse

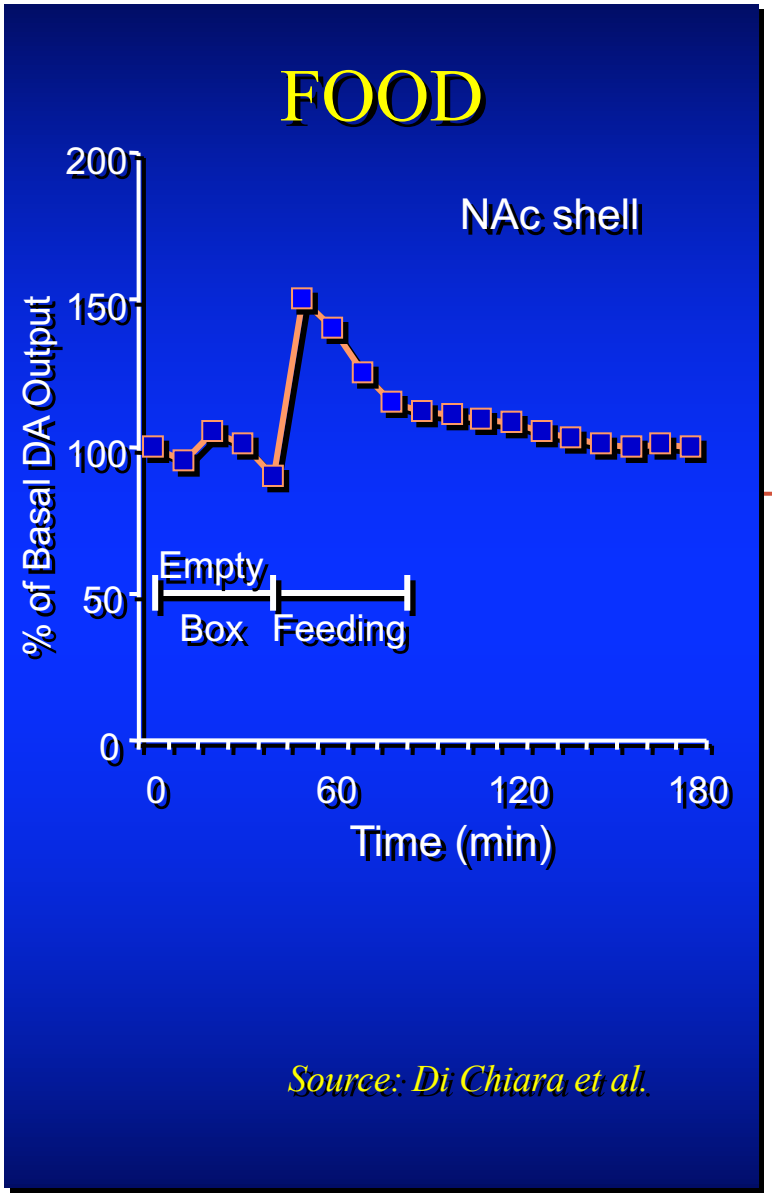
The Reward Pathway – All drugs of abuse release dopamine in this pathway, promoting learning



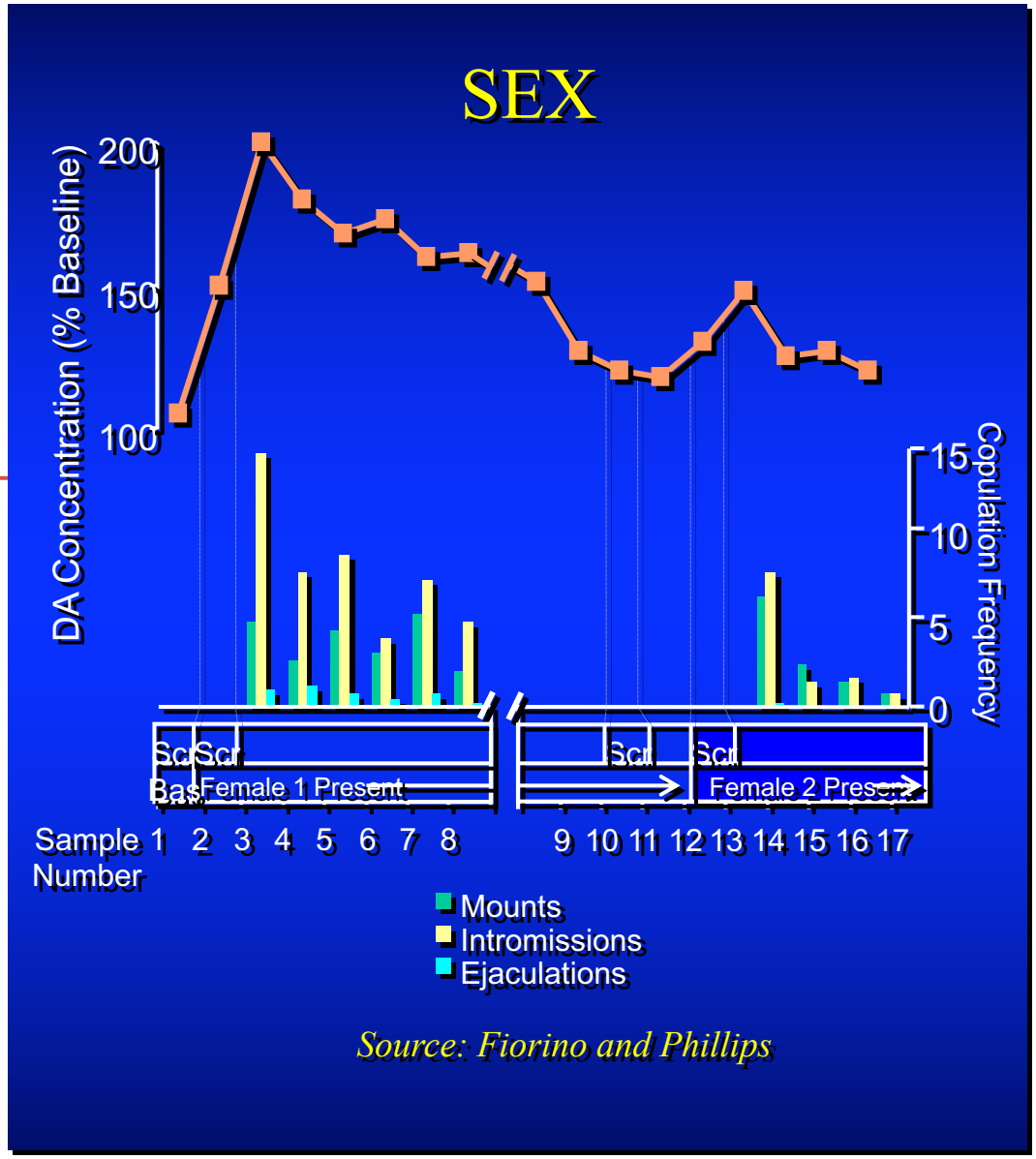
Learning from drug use

- Dopamine is a salience factor that signals the brain that this is a “good” behavior to learn and remember
- Communication between the nucleus acumbens, amygdala, hippocampus and prefrontal motor cortex via glutamate begin to “hard wire” the behavior
- However, not everyone becomes “addicted”

Natural Rewards Elevate Dopamine Levels

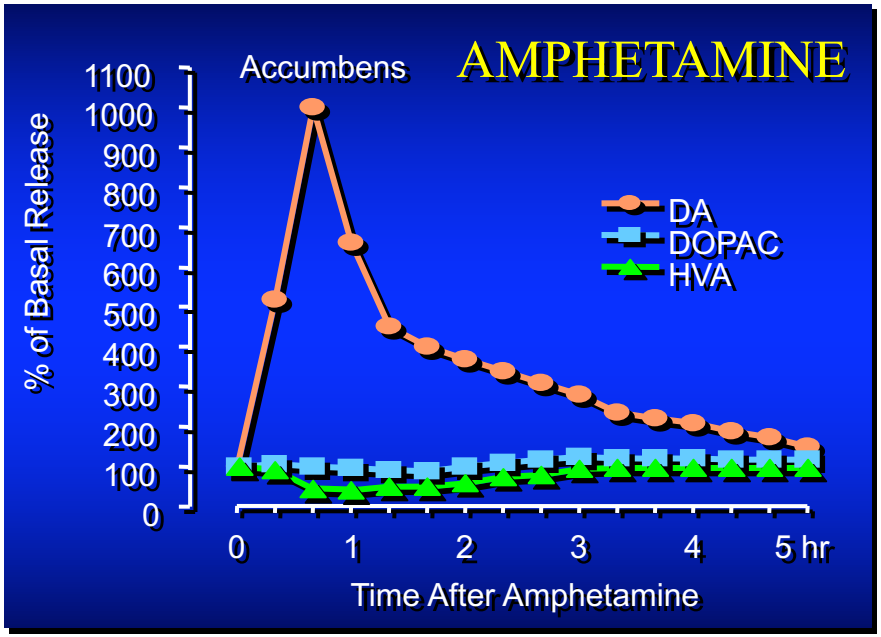


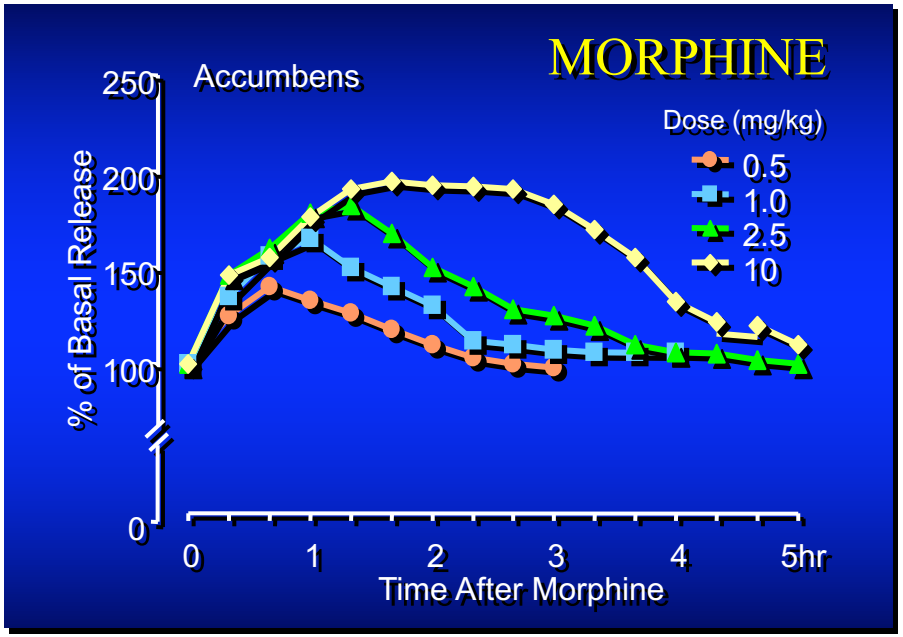
Source: Di Chiara et al.

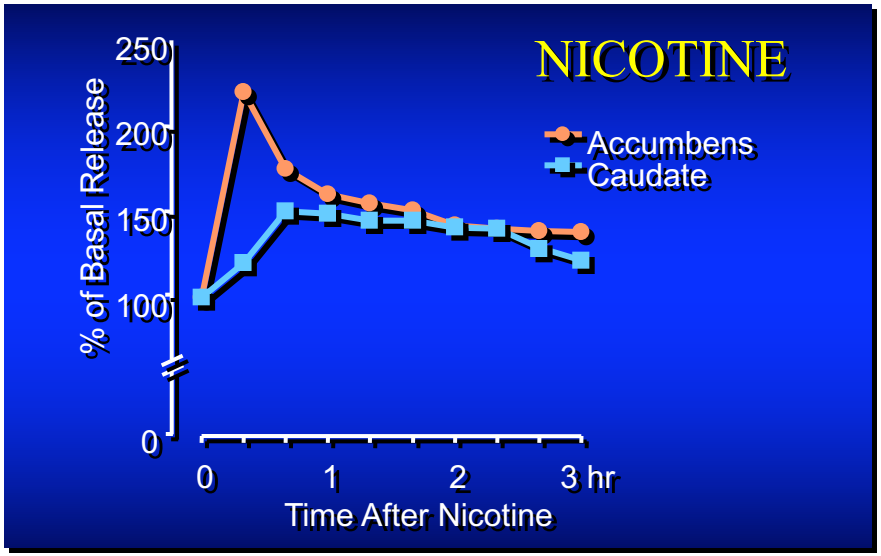


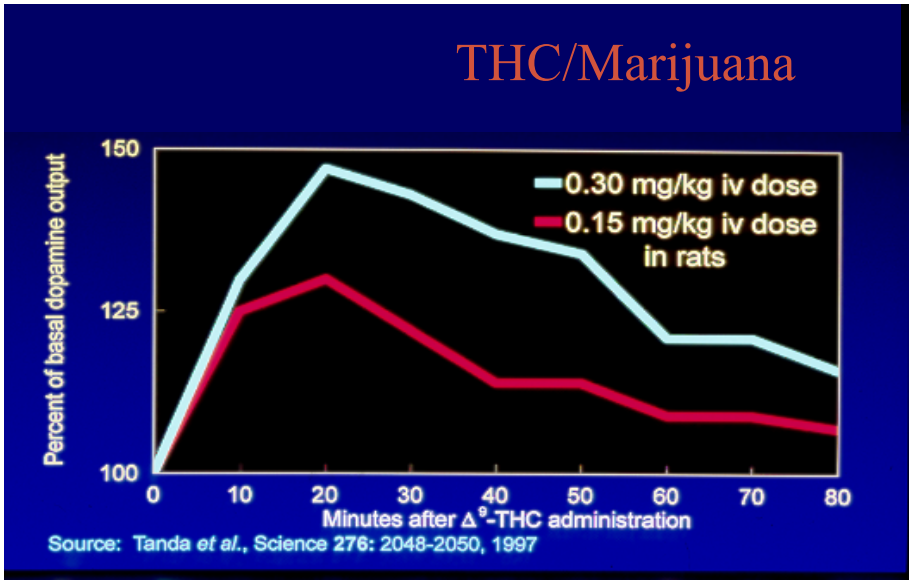
Source: Fiorino and Phillips

Effects of Drugs on Dopamine Levels









Source: Di Chiara and Imperato

A Big Contributing Problem: THC Content is Not Like It Used to Be…

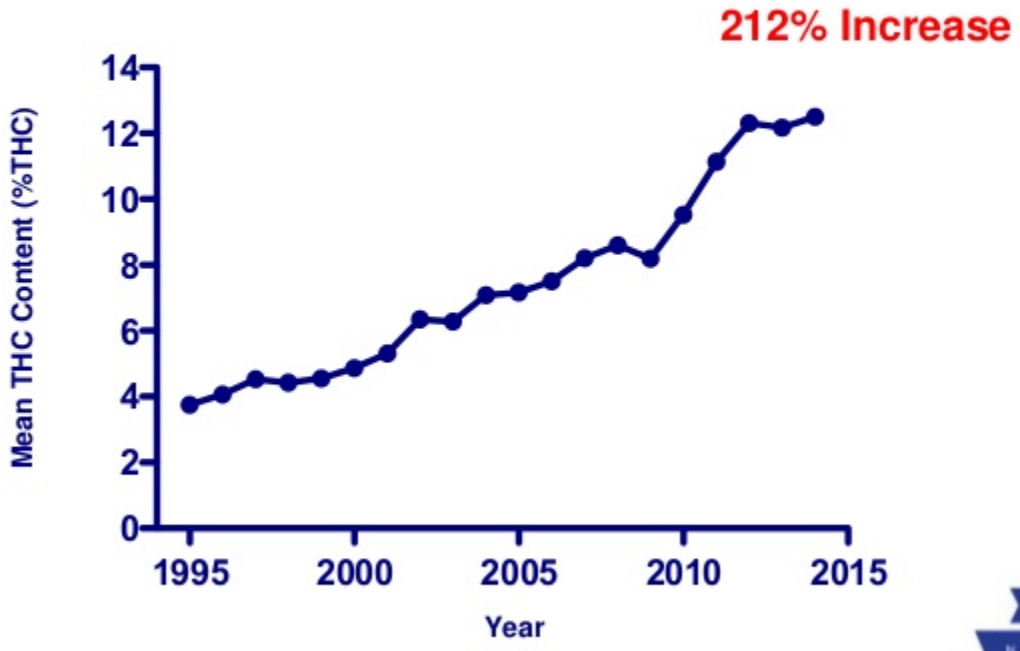
- 1980 THC content was less than 2%
- 1997- 4.5%
- 2006- 8.5%
- 2015- 20% or more
- Average potency of marijuana flowers/buds in Colorado is now 17.1% THC while the average potency for concentrates is 62.1%. Potency rates of up to 95% have been recorded. Smartcolorado.org
- After the Dutch observed negative impacts from rising THC potencies, a team of health experts concluded that THC potencies above 15% should be considered a hard drug.

(Laar, Margriet van, Guus Cruts, Marianne van Ooyen-Houben, Esther Croes, Peggy van der Pol, Ronald Meijer, and Toine Ketelaars. "The Netherlands Drug Situation 2014:" Reitorx National Focal Point, n.d. http://specialtydiagnostix.de/wp-content/uploads/ti/en/trimbos_2014.pdf.)

The higher the potency of the drug the more potential for addiction

- Nicotine – FDA now talking about reducing nicotine concentration in tobacco
- Alcohol – 3.2 beer versus Vodka
- Cocaine – coca leaf versus crack cocaine
- Opioids – codeine versus Oxycontin
- Cannabis – marijuana of the 60s-80s when THC was <2% versus current high potency THC 17-28% in the flower, 85-90% in the concentrates

THC Content Over Last 20 Years



Mahmoud A. Elsohly (2014), Potency Monitoring Program, Supported by NIDA

#RxSummit
NATIONAL RX DRUG ABUSE SUMMIT

The Most Popular Plant Strains

accessed on www.leafly.com – July 15, 2017

Strain	THC content	CBD content
Blue Dream	17-24%	0.1-0.2%
Sour Diesel	19-25%	0.1-0.3%
Girl Scout Cookie	17-28%	0.09-0.2%
Green Crack	13-21%	0-0.1%
OG Kush	19-26%	0-0.3%
Grand Daddy Purple	17-23%	0.1-0.1%

Comparing milligram doses

- A typical joint is 0.5 grams of marijuana
- If the THC % is 12 – 23% THC
- Then there is 60 – 115 mg of THC per joint
- Compare this to a medicinal form of Marijuana Sativex – oral mucosal spray
- It has 2.7 mg THC and 2.5 mg CBD per dose

Formulations

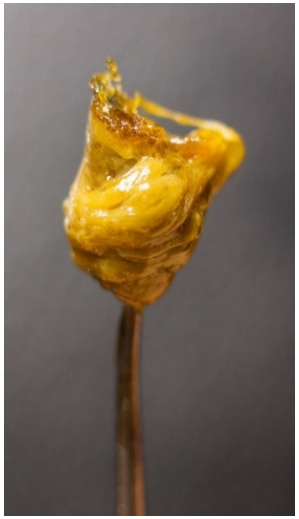
Joint

Bong

Oil

Shatter

Dabbing



Edibles


Ratcheery
Twixed
Munchy Way
Rasta Reeses
KeefKat
Buddahfinger
Tri-Chrome CRUNCH
DEA


KRONDIKE
KEEP OUT OF REACH OF CHILDREN


EdiPure
Raspberry Jellies
Fruit Jellies
Gourmet Tropical fruit
Mixed Nut Clusters
Chocolate Chip Cookies
Cherry Cola Bottles


Beyond
pop tarts
frosted
Cherry
1 TOASTER PASTERIES
3X STRENGTH
Kellogg's
pop tarts
Strawberry
8


Canna Cola
ORANGE KUSH
SOUR DIESEL
12

Dabs, wax and shatter

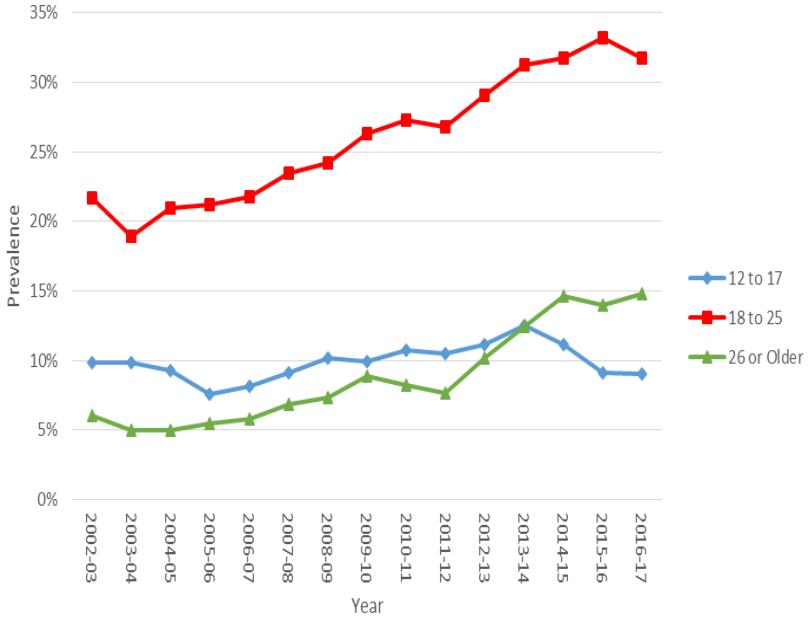
- These are THC concentrates
- Typically made as extracts from the cannabis sativa or indica plant using propane or butane

What's in a dab

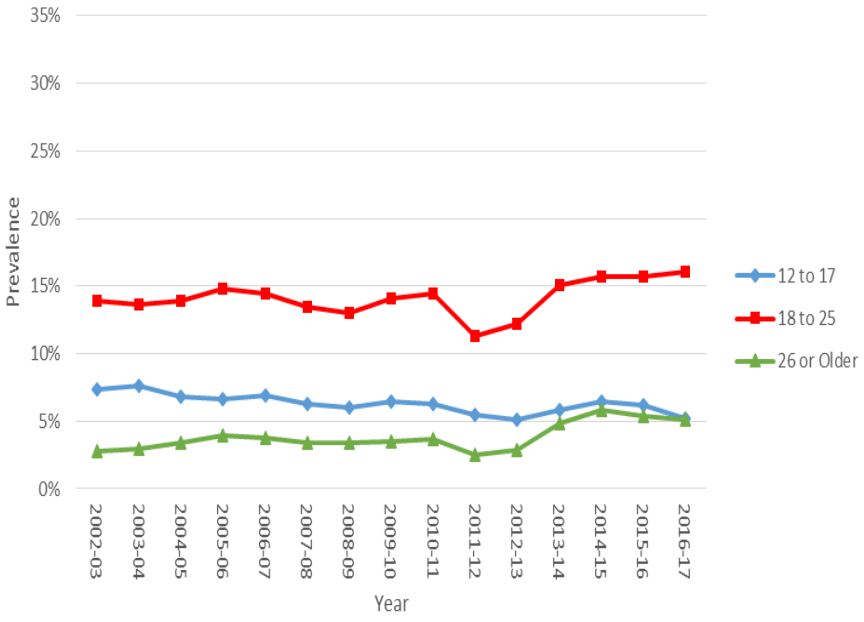
- Dabs can be anywhere from 90 mg to 250 mg typically.
- Internet has videos of people consuming a several GRAM dab
- One 90 mg dab is equivalent to 45 Woodstock joints

Following legalization use rates went up

Marijuana Use in the Past Month in Colorado, by Age Group



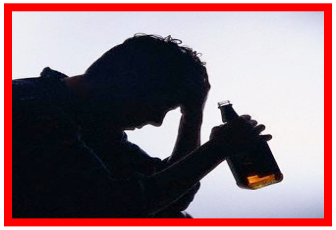
Marijuana Use in the Past Month in Kansas, by Age Group



Source: SAMHSA National Survey on Drug Use and Health: State Estimates

Dopamine D2 Receptors are Lower in Addiction

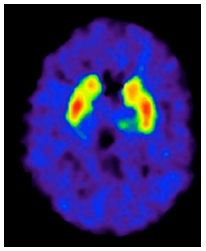
Cocaine

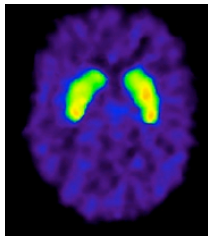


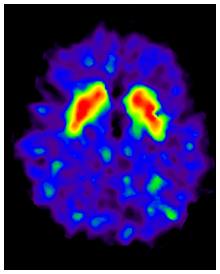
Alcohol

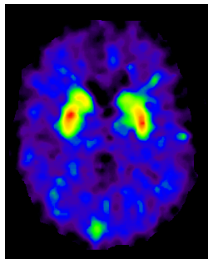
Heroin

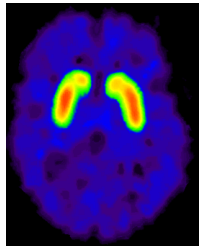
Volkow et al

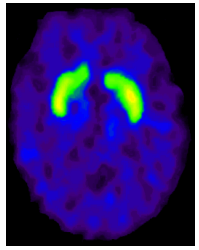






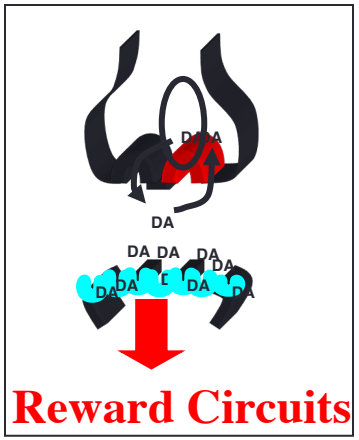




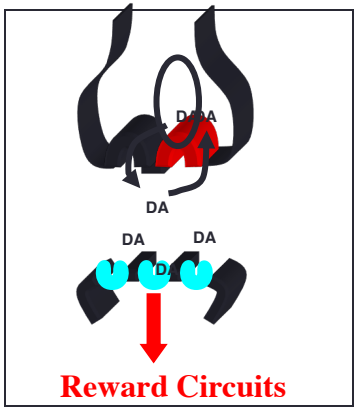


control

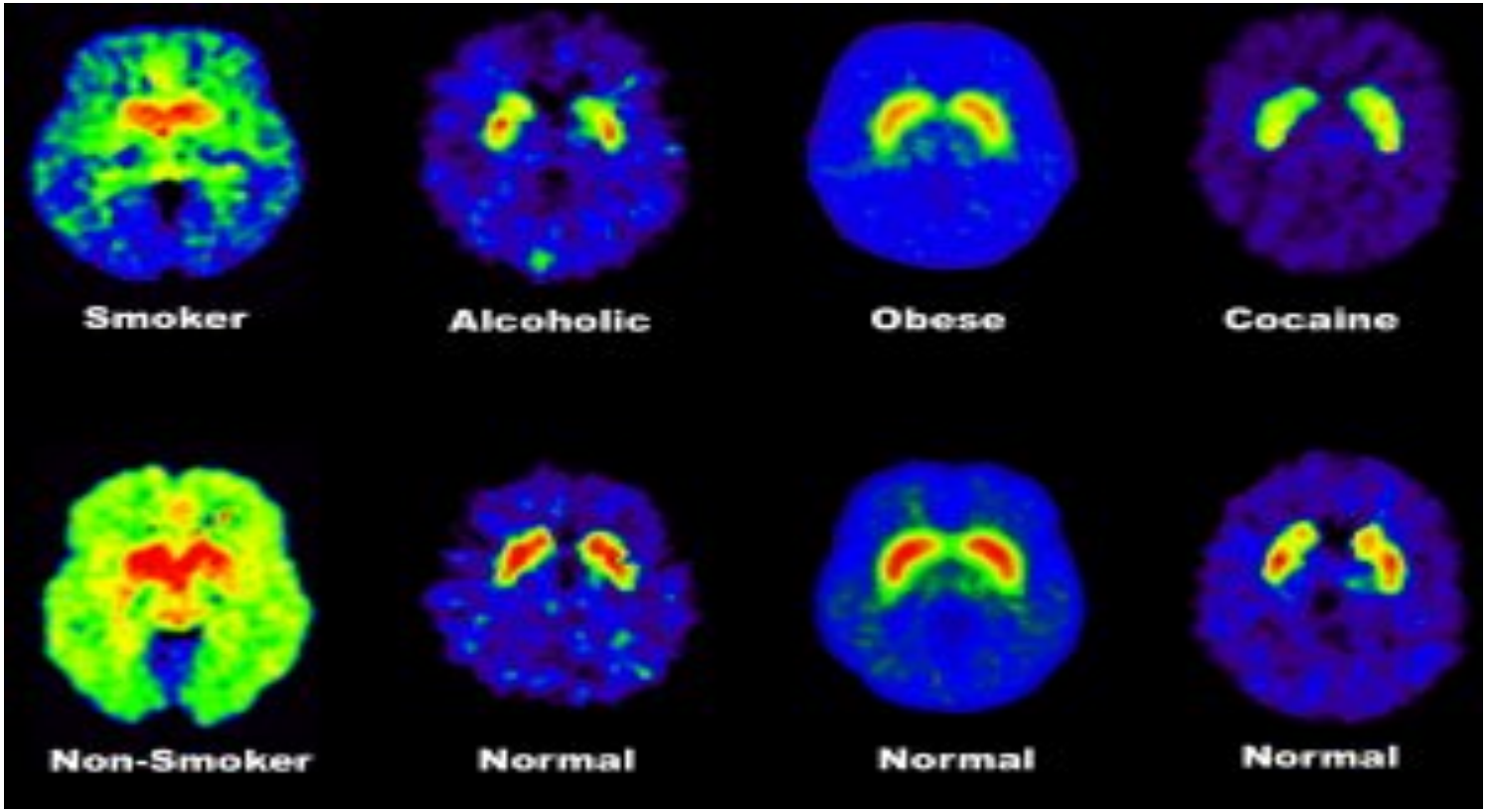
addicted

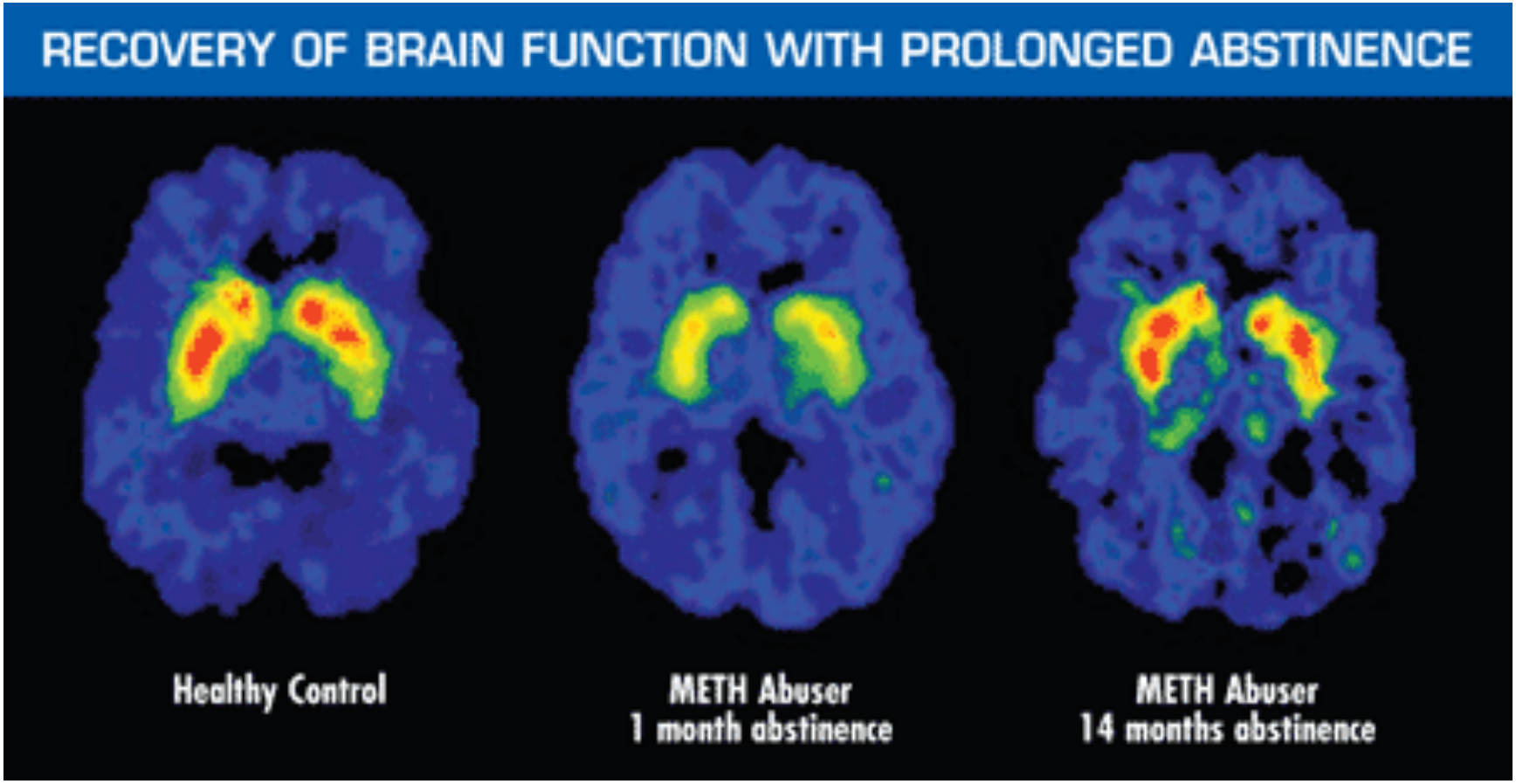


Non-Drug Abuser

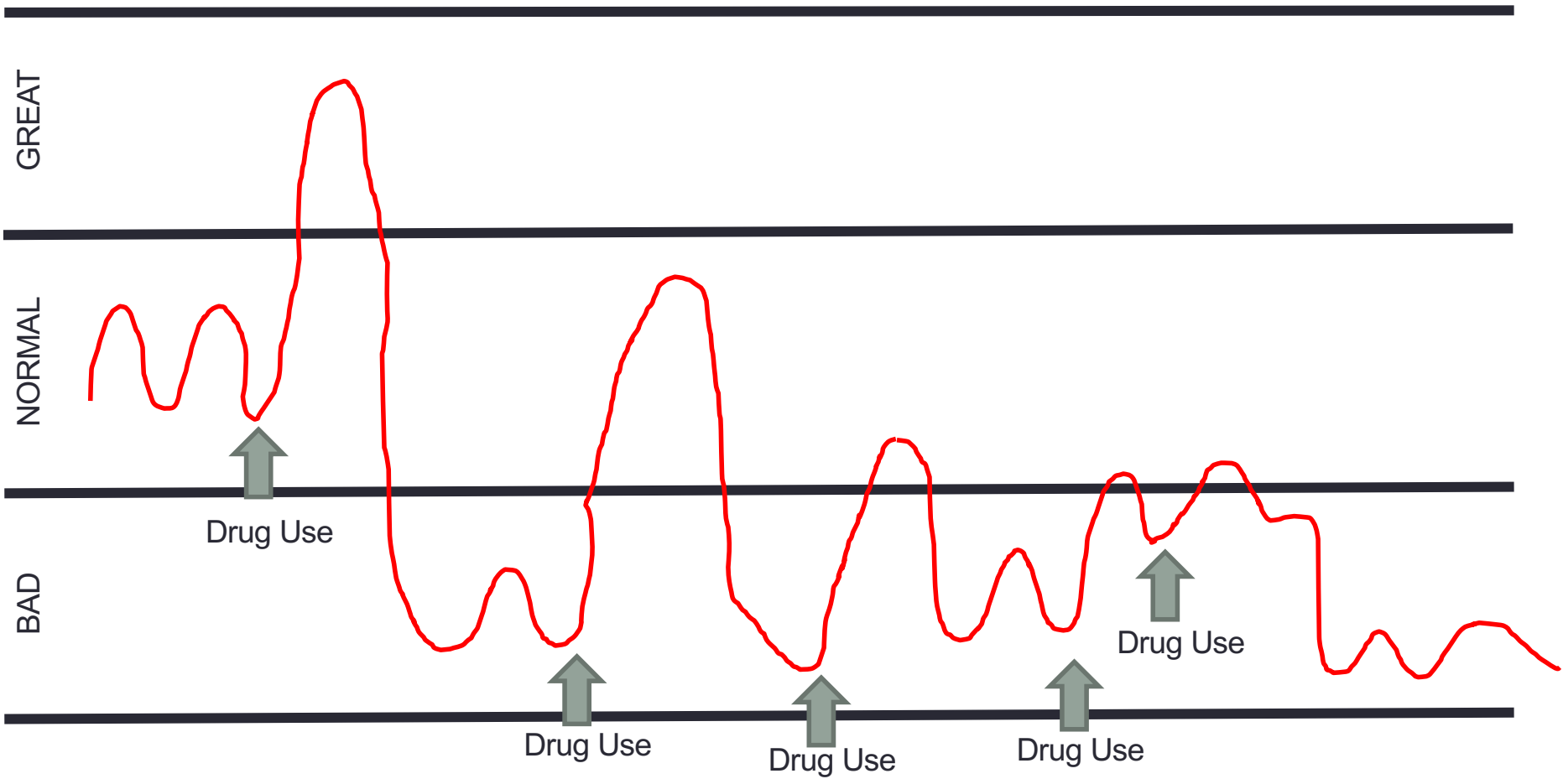


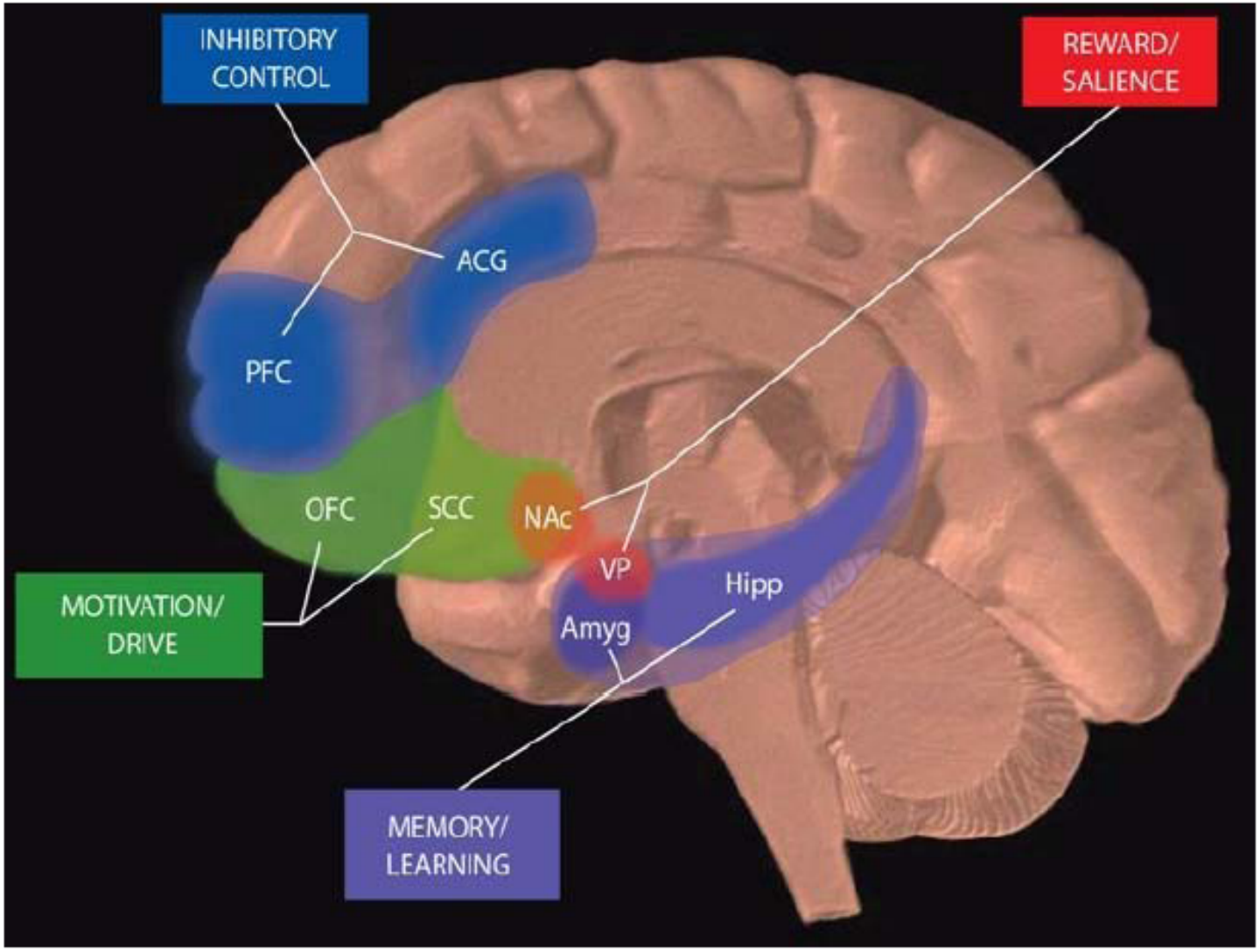
Drug Abuser


Smoker
Alcoholic
Obese
Cocaine
Non-Smoker
Normal
Normal
Normal

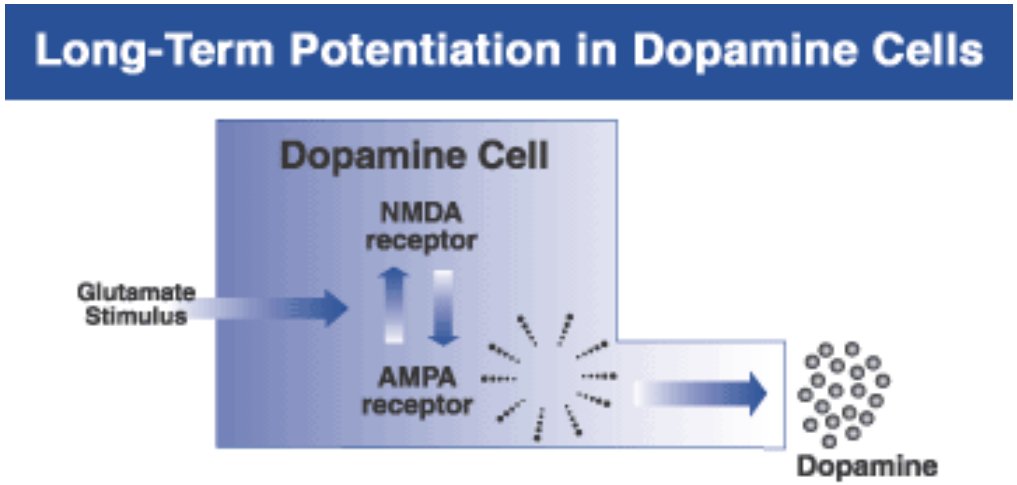

RECOVERY OF BRAIN FUNCTION WITH PROLONGED ABSTINENCE
Healthy Control
METH Abuser
1 month abstinence
METH Abuser
14 months abstinence

"The first time I used it felt great, after that I had to use just to feel normal"




INHIBITORY CONTROL
REWARD/ SALIENCE
ACG
PFC
OFC
SCC
NAc
VP
Hipp
Amyg
MOTIVATION/ DRIVE
MEMORY/ LEARNING

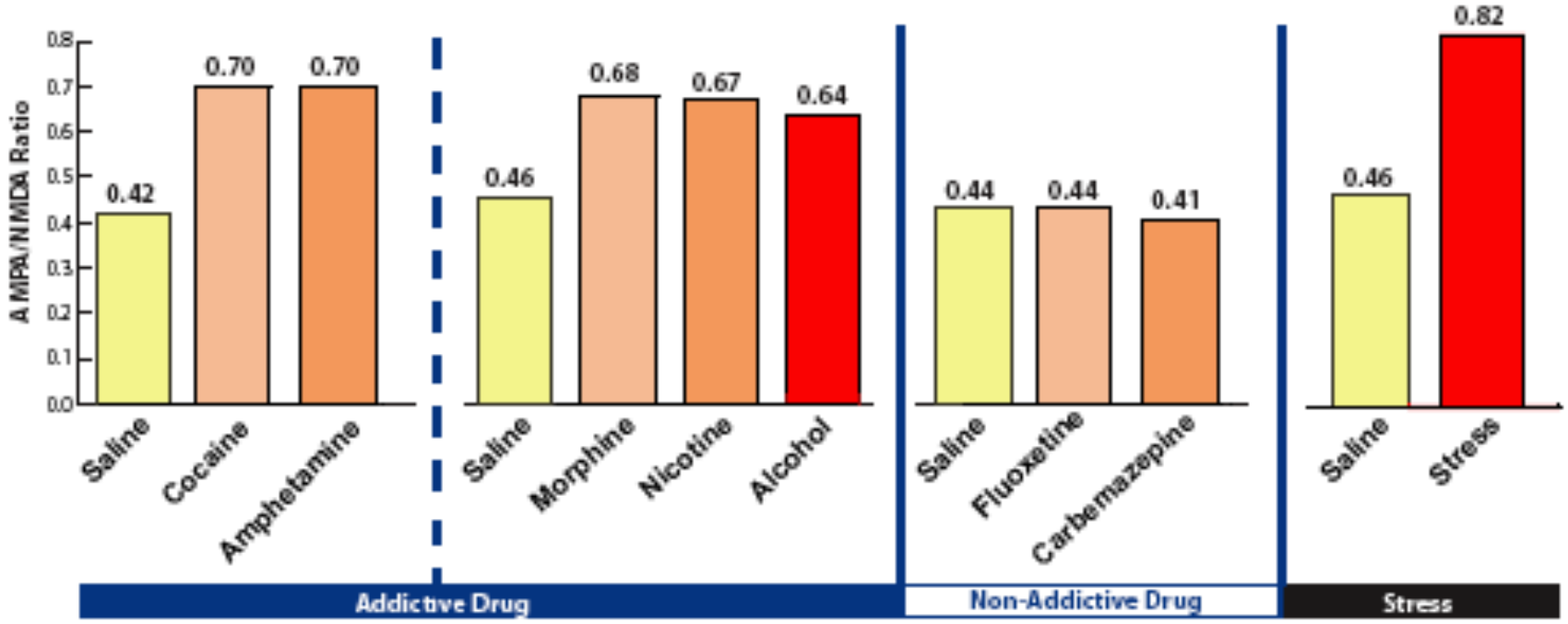
LTP – Increase in AMPA to NMDA ratio



Stress and LTP

- In mice, stress alone can induce increased AMPA:NMDA ratios in VTA cells within 24 hours
- These changes are like those induced by drugs of abuse
- This suggests a priming mechanism – that someone who has experienced stress may be more vulnerable to addiction

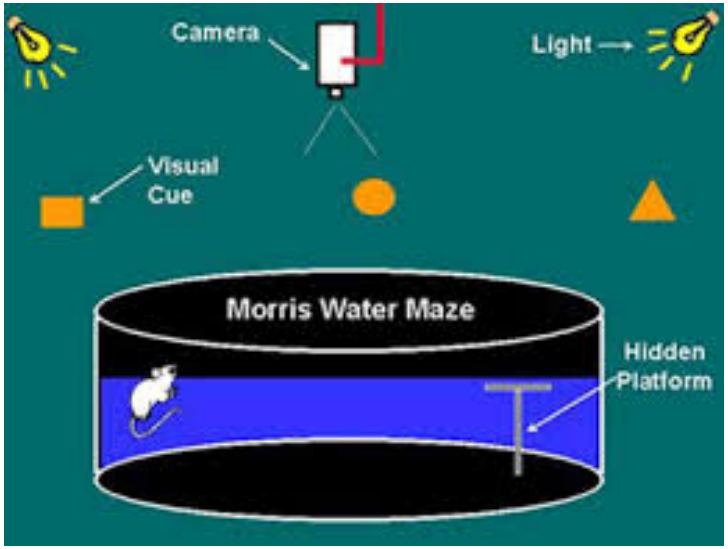
Addictive Drugs and Stress Increase Sensitivity of DA Cells in Mice (Saal et al. Neuron 2003;37:577-582)

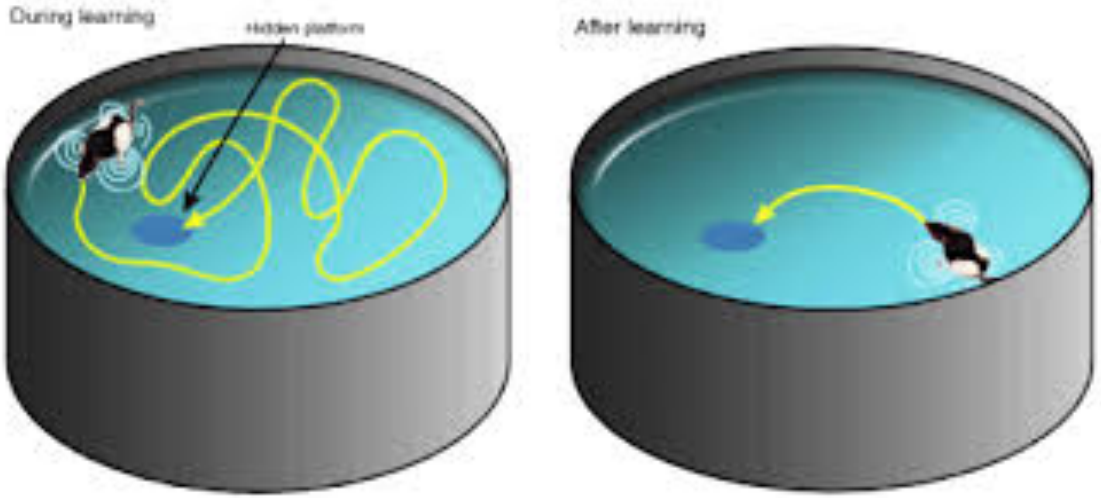


Hippocampus and Neurogenesis

All drugs of abuse negatively effect the Hippocampus, decrease neurogenesis and impair the ability to learn new things - this is true for alcohol, cocaine, methamphetamines, heroin, nicotine, THC

Learning tests





The effects of co-administration of opium and morphine with nicotine during pregnancy on spatial learning and memory of adult male offspring rats

Sepehri G et al. Iran J Basic Med Sci 2014

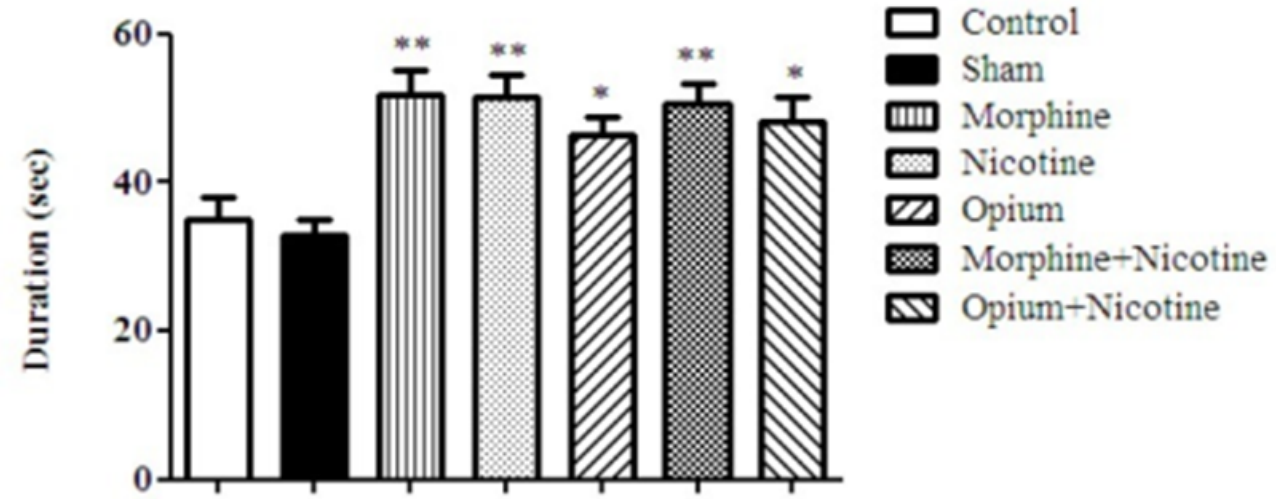
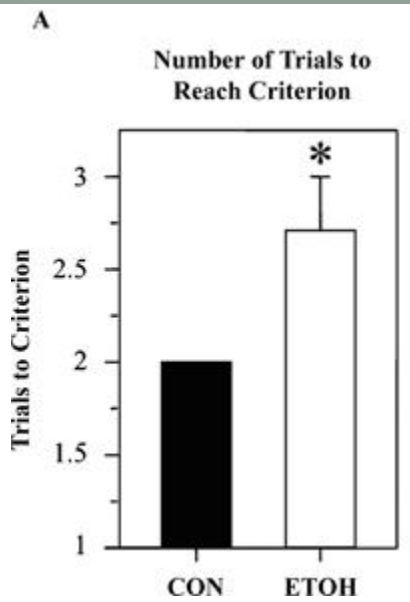
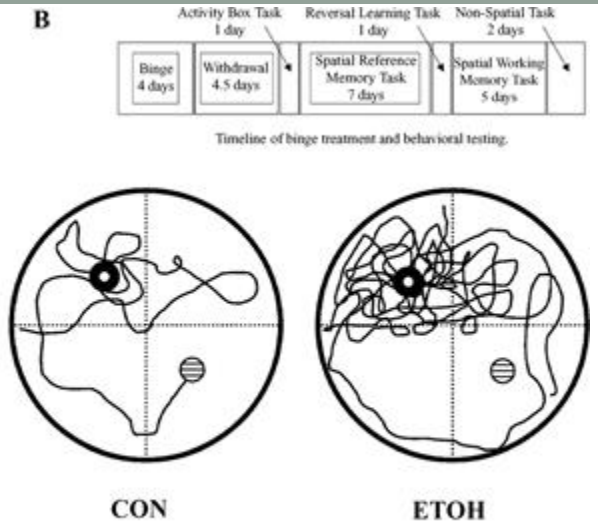


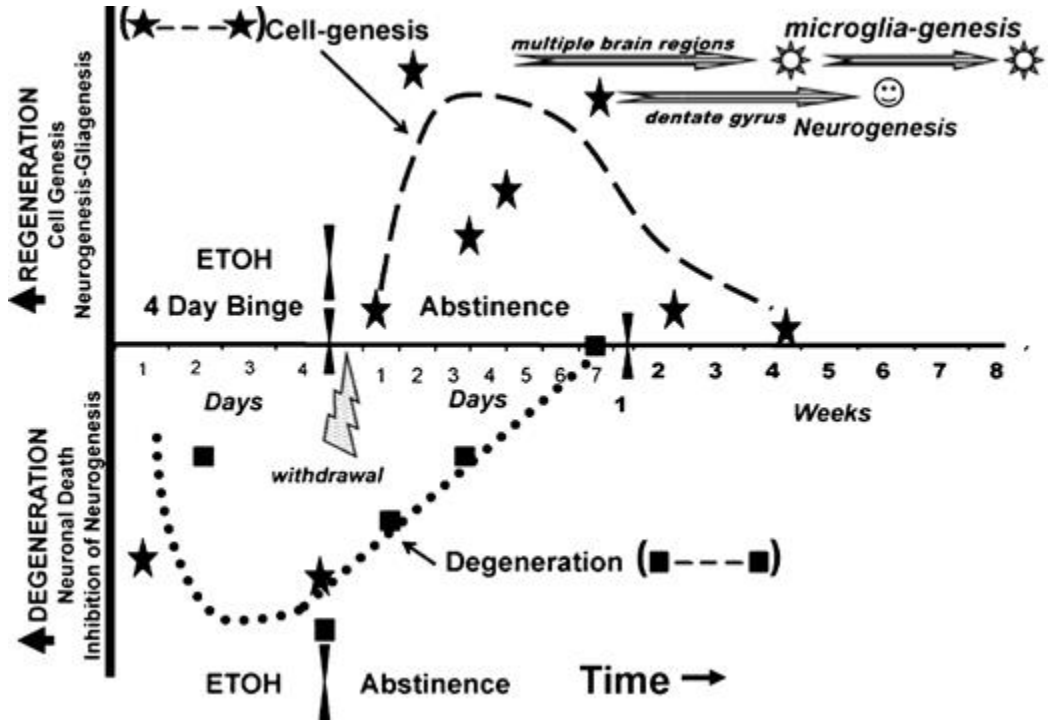
Figure 2: The effect of prenatal administration of opium, nicotine, opium+nicotine and morphine+nicotine on total average duration to find the hidden platform during the four days of training in the Morris water maze of male offspring. Data are expressed as mean± SEM. P-values <0.05 was considered statistically significant (n=7).*=P<0.05, **=P<0.01 prenatal drug exposure group vs. Control group



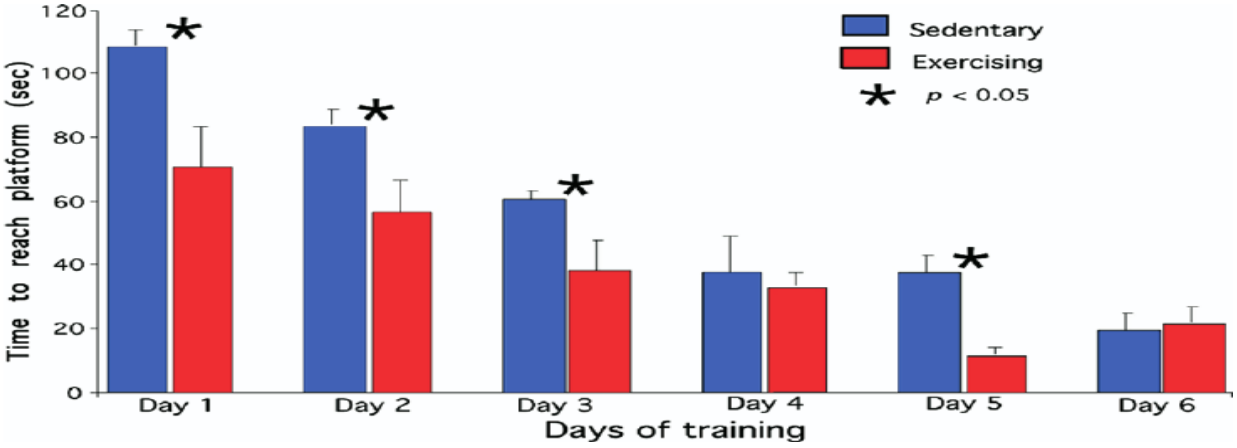


Mechanisms of Neurodegeneration and Regeneration in Alcoholism

Crews FT and Nixon K. Alcohol Alcohol (2009) 44 (2): 115-127

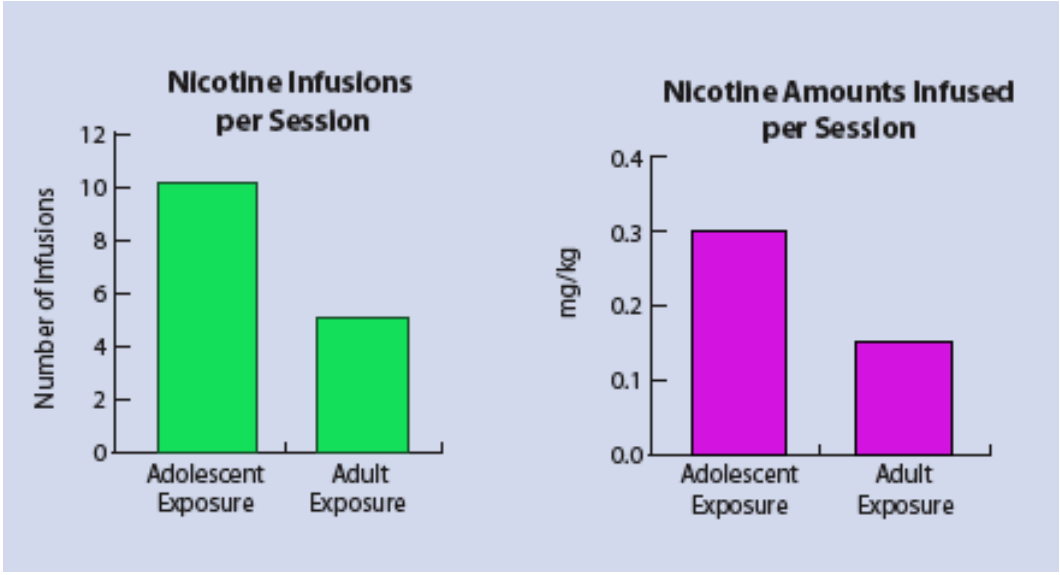


Exercise improves learning

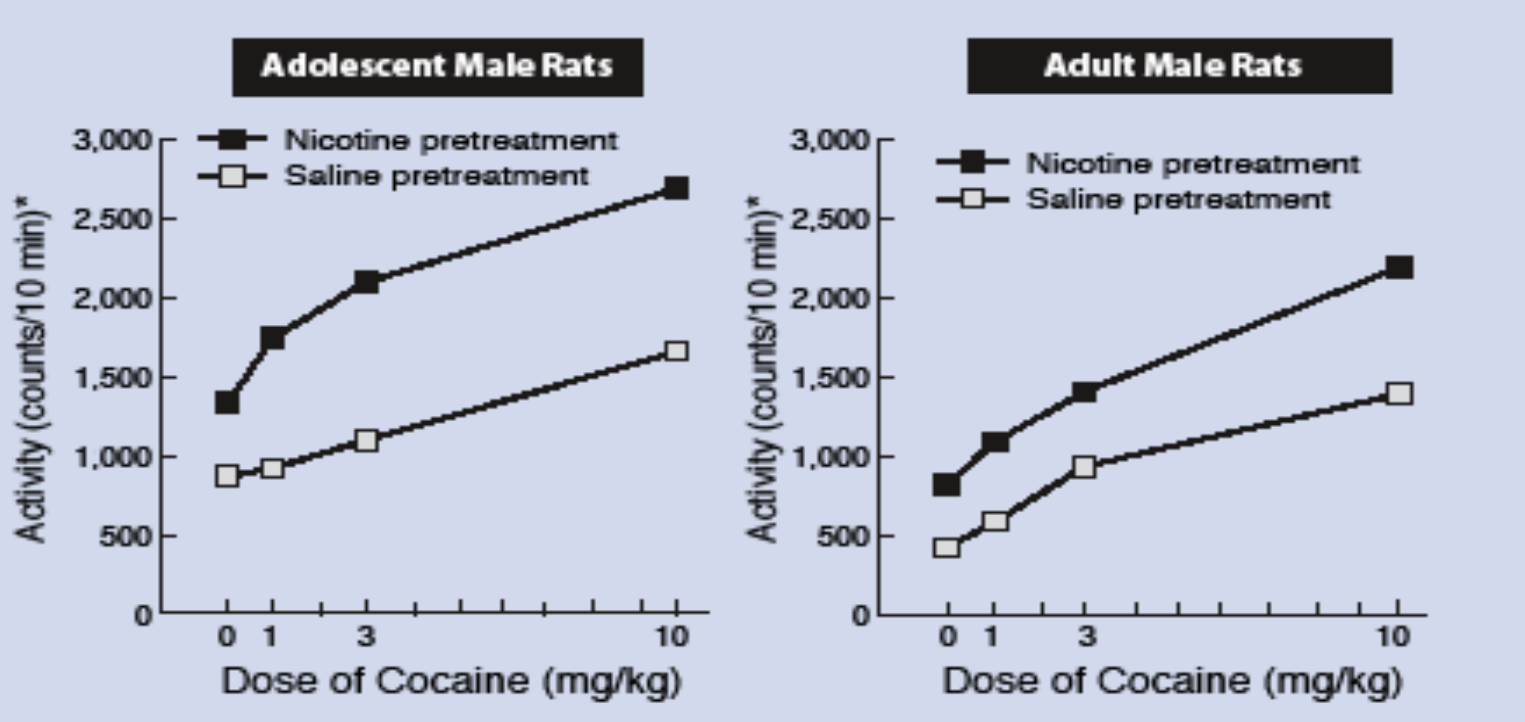


Exposure can start the process – priming the brain

Rats exposed to nicotine as adolescents self-administer more nicotine than rats exposed as adults Levin ED et al. Psychopharm 2000;169:141-149



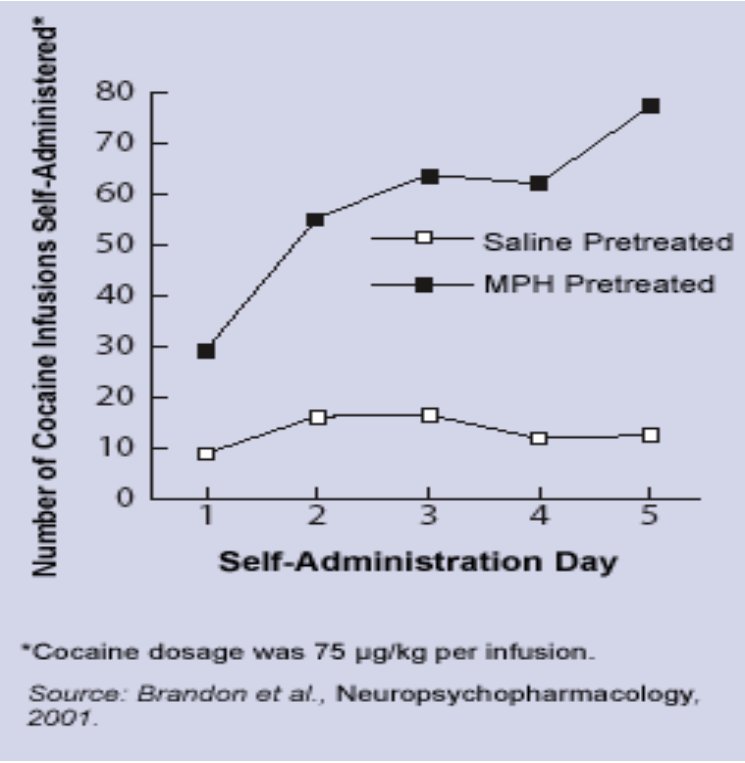
Rats First Exposed to Nicotine in Adolescence Show Greater Sensitization to Cocaine Than Rats First Exposed as Adults



*Activity level after cocaine administration was measured by counting the number of times in 10 minutes each rat crossed light beams projected in a grid across its cage.

Sources: Collins et al, 2004, Levin et al, 2003, NIDA Notes v19.2

Adult rats exposed to Ritalin during adolescence self-administered more cocaine



*Cocaine dosage was 75 µg/kg per infusion.

Source: Brandon et al., Neuropsychopharmacology, *2001.*

Making the Choice to Use

- Exposure as a child can prime the brain and is a risk factor– but this doesn't have to result in addiction
- Addiction occurs when the person makes the **choice** to use – engaging the prefrontal motor cortex
- The person can be addicted from the first use and the behavior is then "hard wired" in the brain

Normal Brain Development during Adolescence - Neurotransmitter Development

- Lots of Dopamine and Glutamate - stimulatory neurotransmitters – "stepping on the gas" – go,go,go – learn, explore, do
- Decreased Serotonin and GABA – suppressive neurotransmitters – "stepping on the brake" located in the prefrontal motor cortex – the last part of the brain to fully develop

Schepis et al. Neurobiological Processes in Adolescent Addictive Disorders. Am J Addictions. 2008;17:6-23

Behavioral Factors Relating to Substance Abuse in Adolescents

- ↑ neurobiological based tendencies for risk-taking with decreased suppressive and regulatory control
- lots of Go, go, go

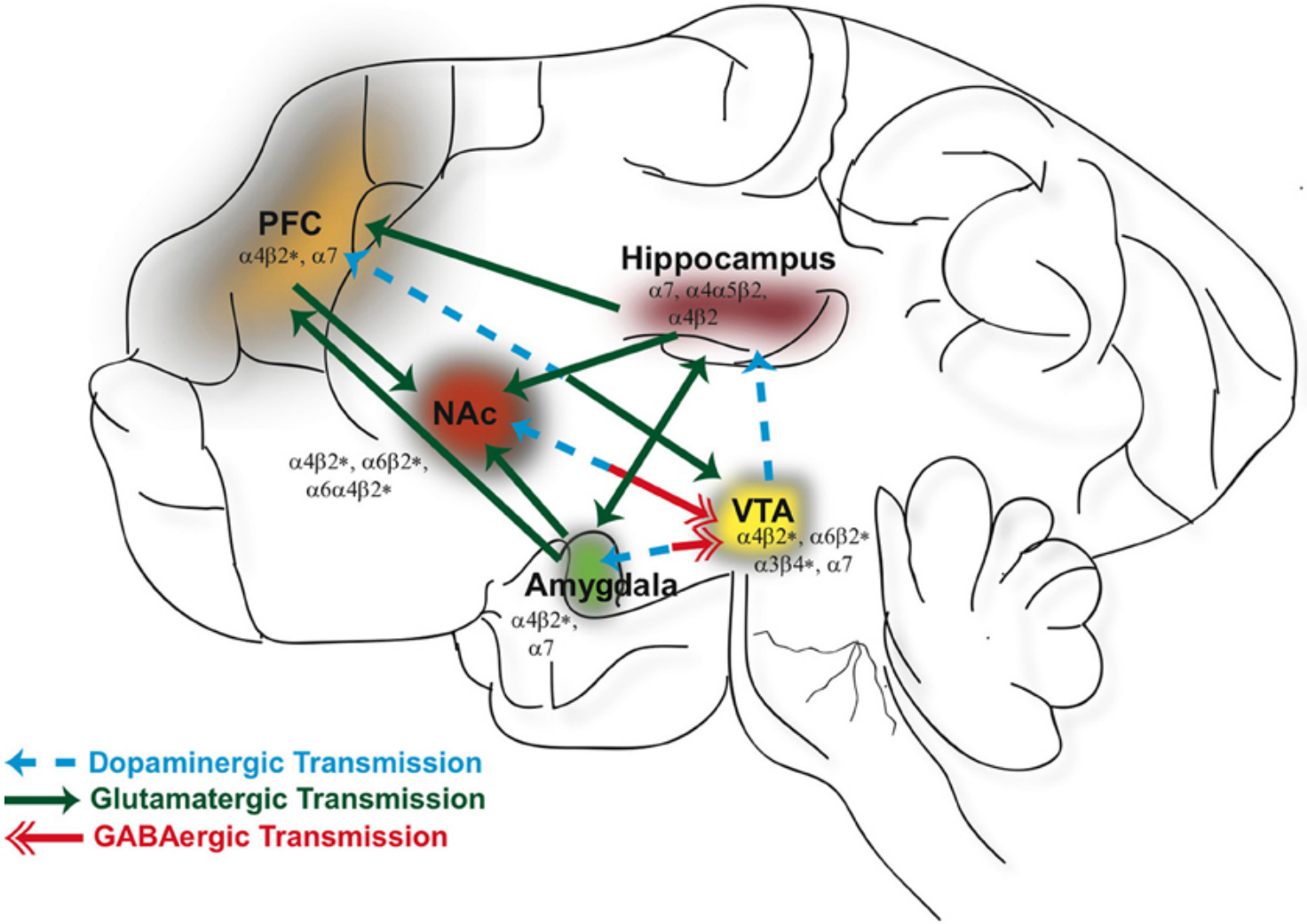
- very little ability to put on the brakes

- ↓ in parental monitoring
- ↑ in peer affiliation

Acetylcholine - ACH

- Another important brain neurotransmitter – helps us focus and concentrate
- ACH innervation of the PFC reaches mature levels during adolescence – receptors = nACHRs
- Involved in promoting or preventing neuronal cell death – depending on developmental stage
- Nicotine works on these receptors and can mess up the fine tuning of the brain during adolescence

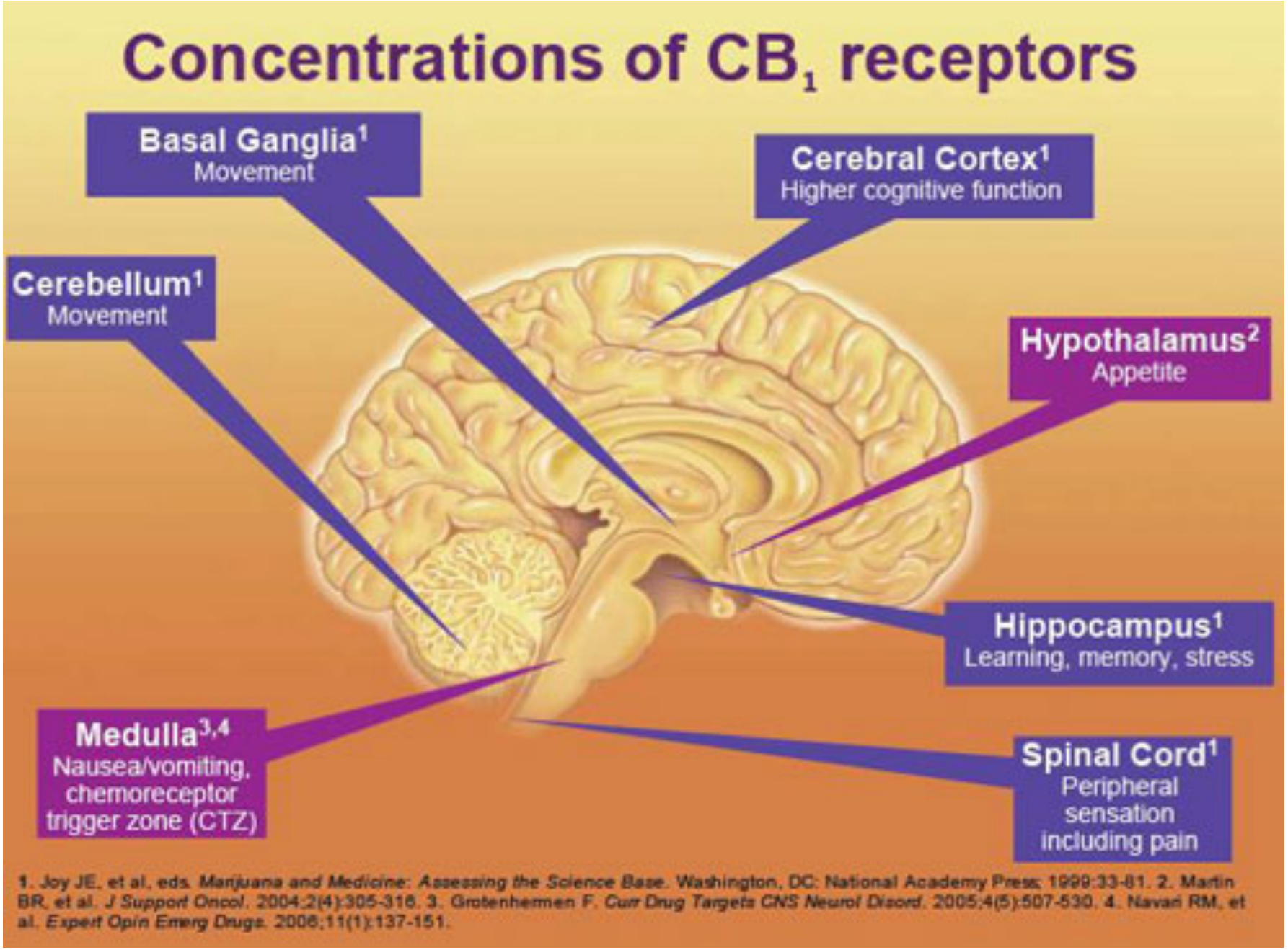
Nicotinic Cholinergic Neurons



Endocannabinoid Receptors

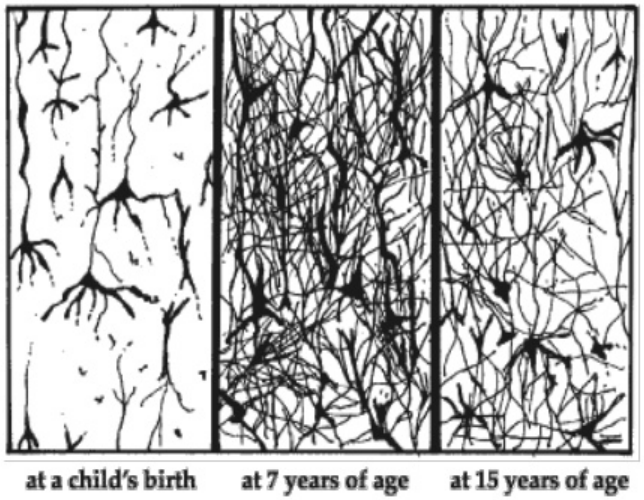
- Are all over the brain – receptors for **anandamides** - “supreme joy”
- CB1 receptors regulate the balance between excitatory and inhibitory neuronal activity – homeostasis
- Exposure to cannabis during adolescence disrupts glutamate which plays an important role in synaptic pruning in PFC – disrupting normal brain development
- Lubman et al. Cannabis and adolescent brain development. Pharmacology and Therapeutics 2015;148:1-16

Concentrations of CB_1 receptors



1. Joy JE, et al, eds. *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: National Academy Press; 1999:33-81. 2. Martin BR, et al. *J Support Oncol*. 2004;2(4):305-316. 3. Grotenhermen F. *Curr Drug Targets CNS Neurol Disord*. 2005;4(5):507-530. 4. Navari RM, et al. *Expert Opin Emerg Drugs*. 2006;11(1):137-151.

Synaptic Pruning

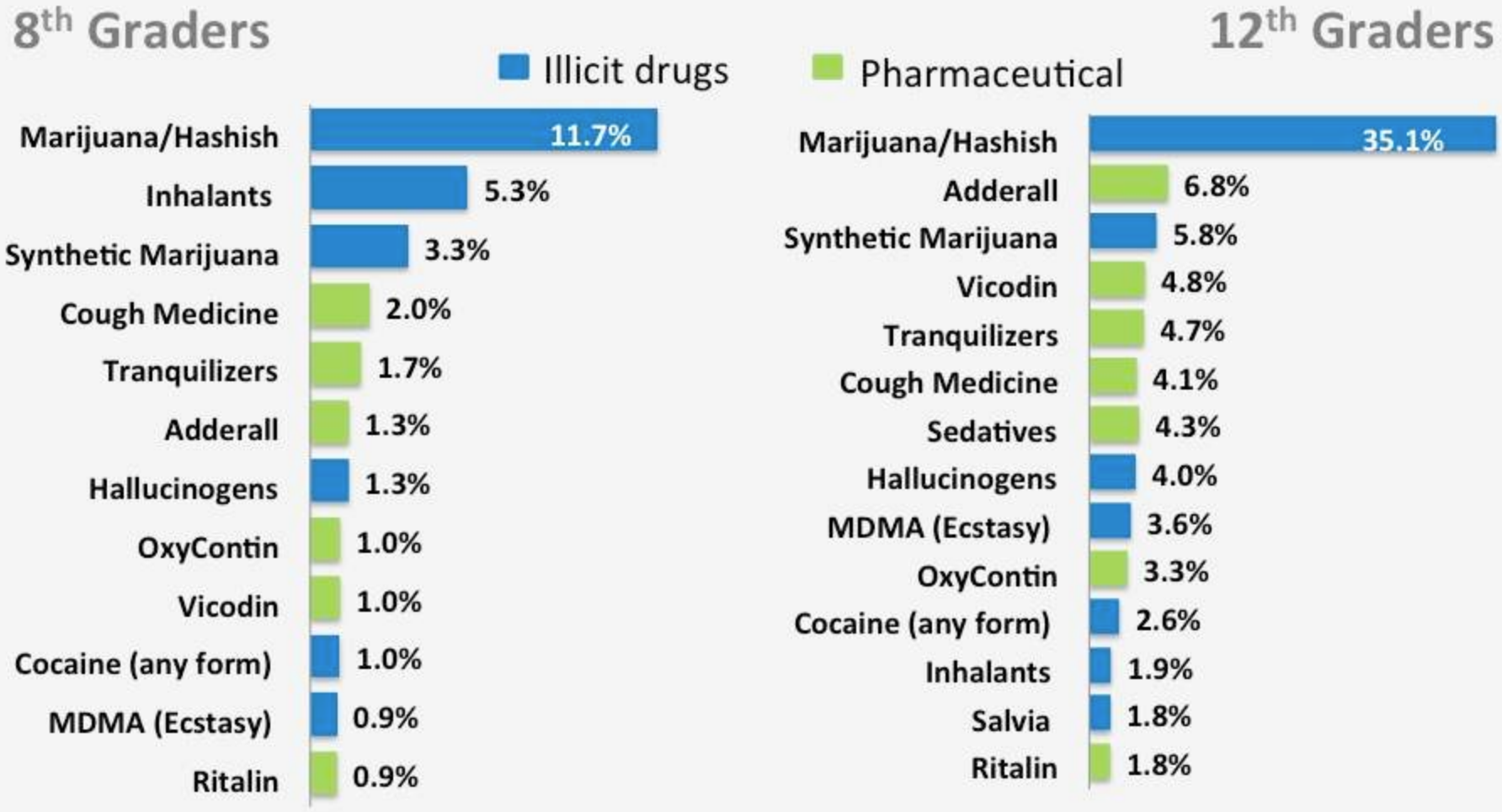


The next change after this synaptic growth spurt is a selective pruning which takes place.

In adolescence, most of this pruning is taking place in the frontal lobes.

The adolescent loses approximately 3 percent of the gray matter in the frontal lobes.

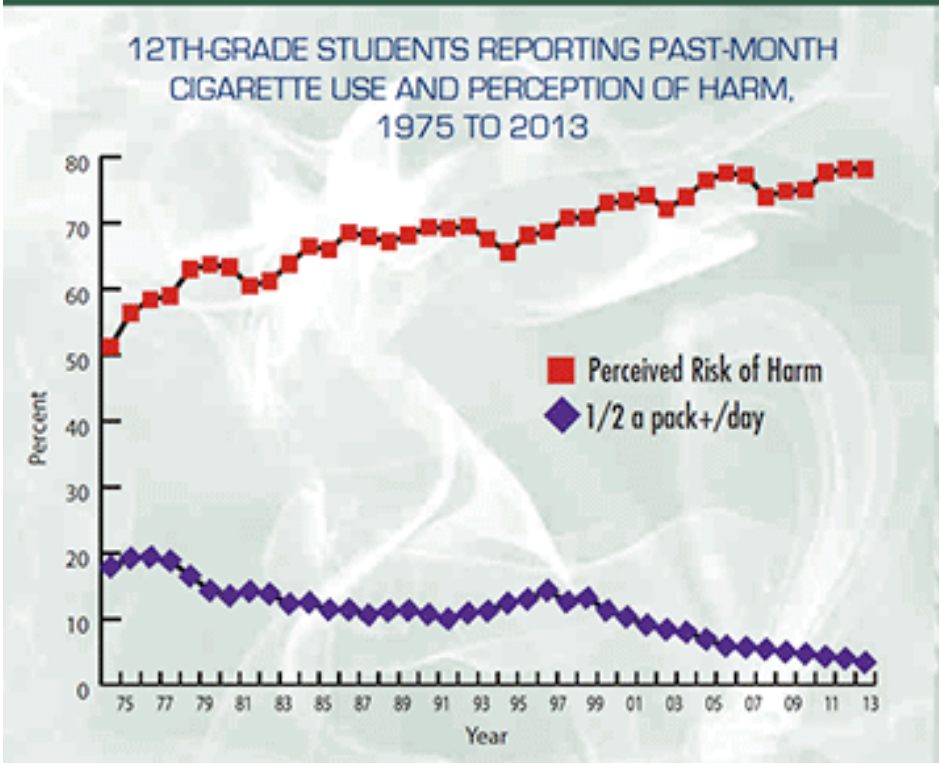
Top Drugs among 8th and 12th Graders, Past Year Use

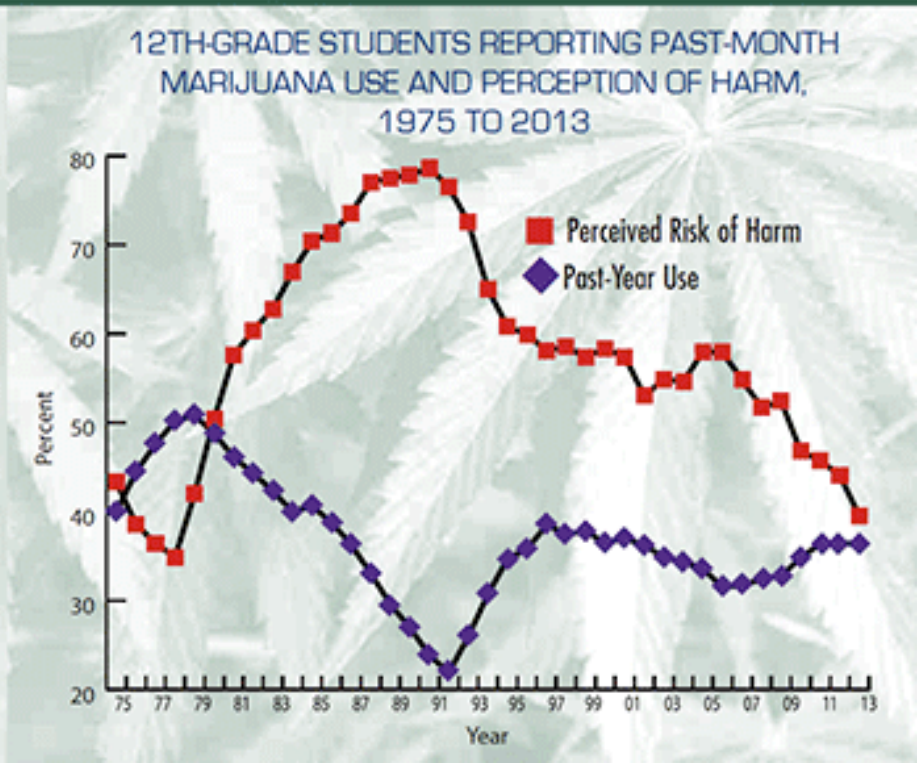


* Only 12th graders surveyed about sedatives use

Source: University of Michigan, 2014 Monitoring the Future Study

DRUG USE DECREASES WHEN DRUGS ARE PERCEIVED AS HARMFUL, AND VICE VERSA





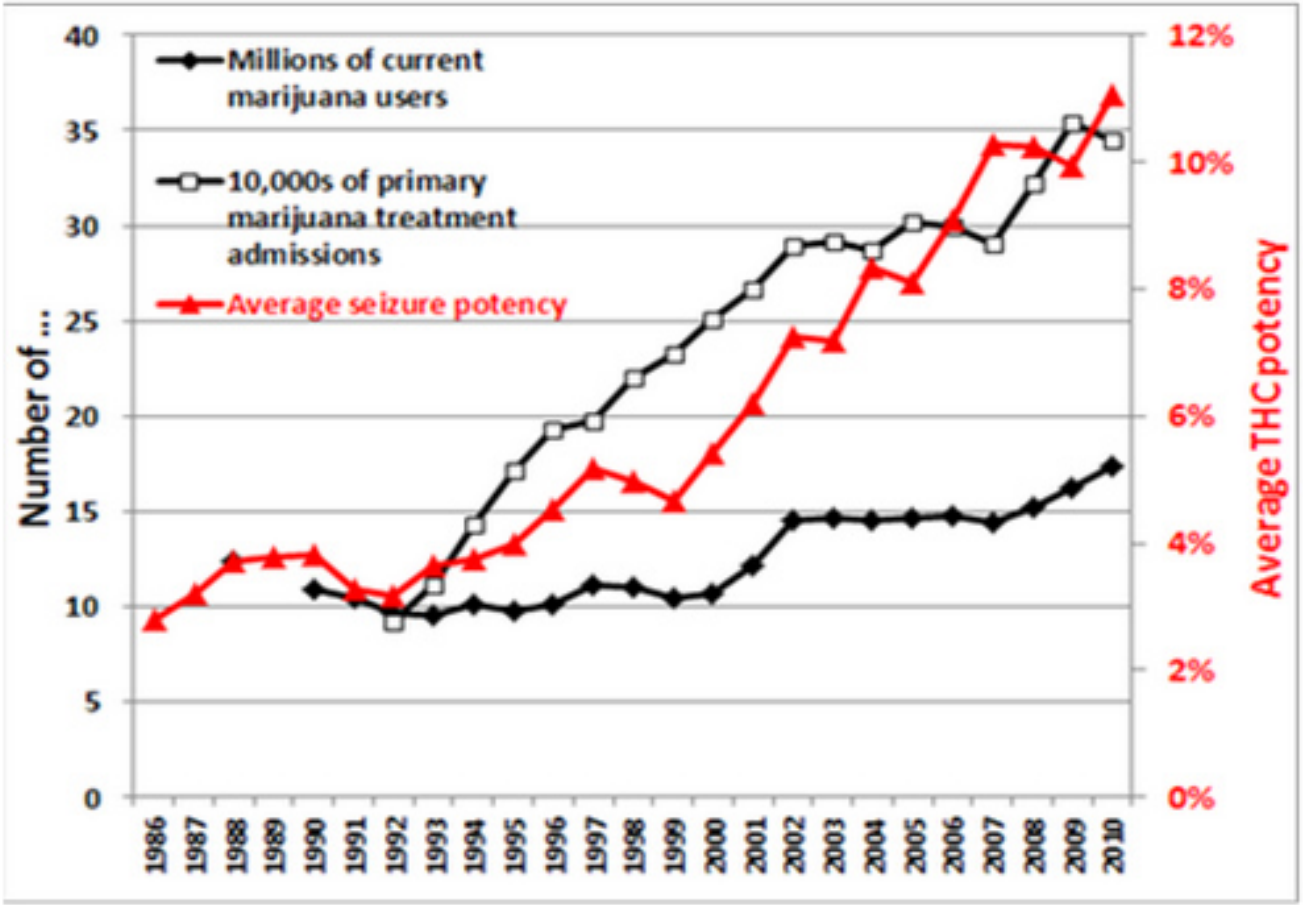
Addiction

Also referred to as Marijuana Use Disorder

- 9% of those who experiment with marijuana will become addicted
- 17% of those who start using as teenagers will become addicted
- 25-50% of those who are daily users will become addicted

Data from NEJM, Adverse Health Effects of Marijuana Use. Nora Volkow. June 5th 2014

MARIJUANA USERS, TREATMENT ADMISSIONS, AND AVERAGE POTENCY: 1986-2010



Sources: NSDUH, TEDS, National Seizure System

Changes in cannabis potency and first-time admissions to drug treatment: a 16-year study in the Netherlands

Freeman TP et al. Psychological Medicine 2018

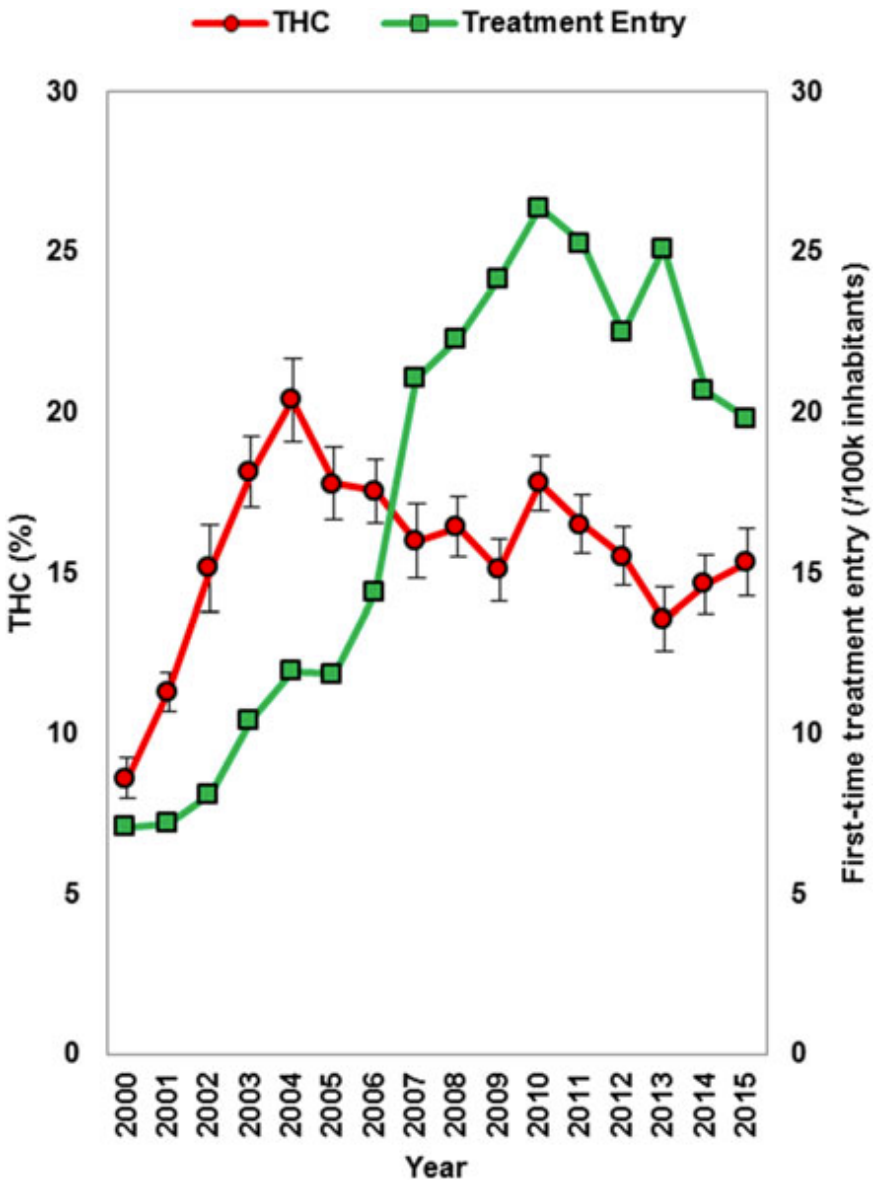


Fig. 1. Mean (95% CI) concentrations of δ-9-tetrahydrocannabinol (THC) in domestic herbal cannabis and first-time cannabis admissions to specialist drug treatment (per 100 000 inhabitants) from 2000 to 2015.

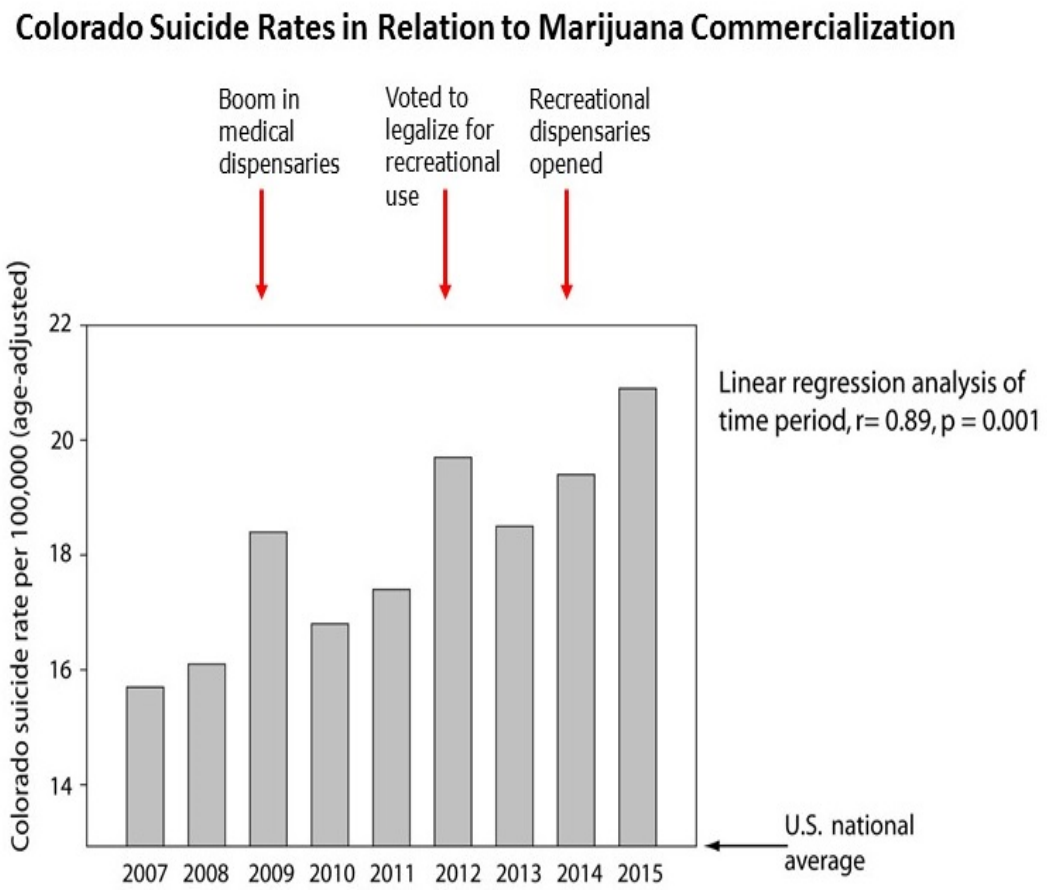
MJ Withdrawal Syndrome

- Increased anger
- Irritability
- Depression
- Restlessness
- Headache
- Loss of appetite
- Insomnia
- Severe cravings for marijuana

Marijuana and Suicide

- Multiple studies have documented a relationship between cannabis use and suicidality – Buckner et al Psych Res 2017;253:256-259 – tested the utility of the interpersonal-psychological theory of suicide
- Large longitudinal study in Australia and New Zealand of over 2000 adolescents and maximum frequency of marijuana use found almost 7X increase in suicide attempts in daily marijuana users compared with non-users – Silins E et al. The Lancet psychiatry Vol 1 September 2014

Correlation of Marijuana and Suicide



In fact veteran suicides have not decreased. Instead, they are up 32% since 2001, compared to a national increase of 23% during the same period – Congressional Hearing 4/27/17

Christine Miller, PhD

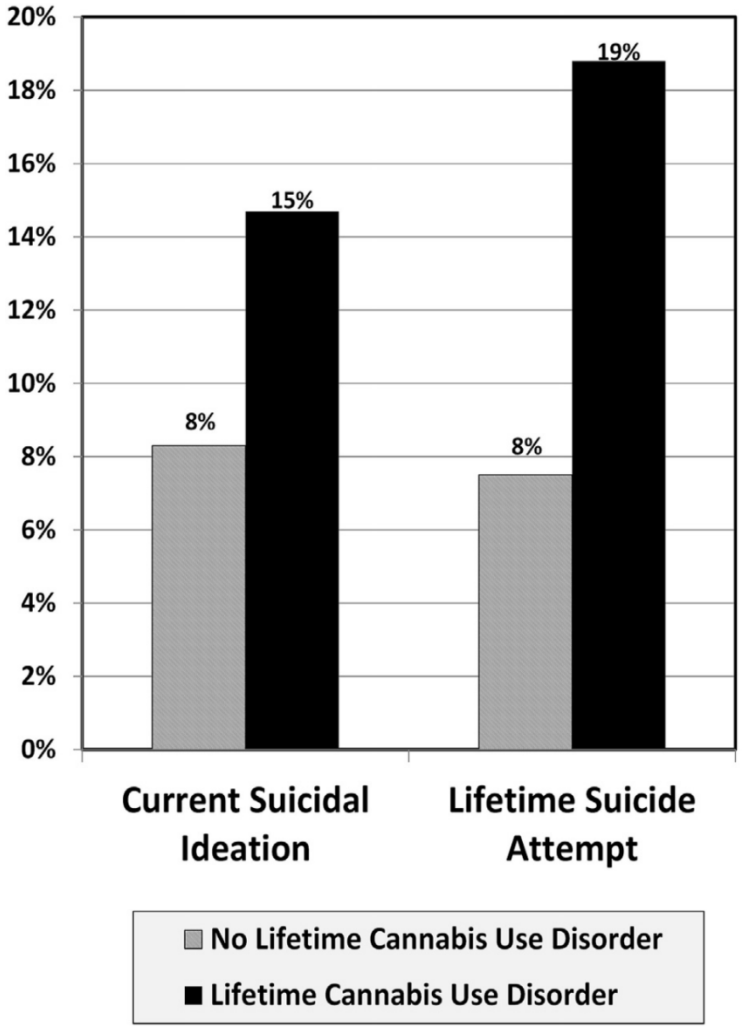
Cannabis use disorder and suicide attempts in Iraq/Afghanistan-era veterans

Kimbrel NA et al. J Psychiatric Research 2017:89;1-5

3233 veterans in cross-sectional, multi-site study by VA

Cannabis use disorder was significantly associated with both current suicidal ideation (p<.0001) and lifetime history of suicide attempts (p<.0001) compared to veterans with no lifetime history of cannabis use disorder

The significance difference continued even after adjusting for sex, PTSD, depression, alcohol use disorder, non-cannabis drug use disorder, history of childhood sexual abuse and combat exposure.



Junior high students walk the hallways of Simla Junior High at Big Sandy School Monday, February 25, 2019. (Mark Reis, Special to The Colorado Sun)

Colorado kids and teens are dying at a rate higher than the U.S. average — and suicide is to blame

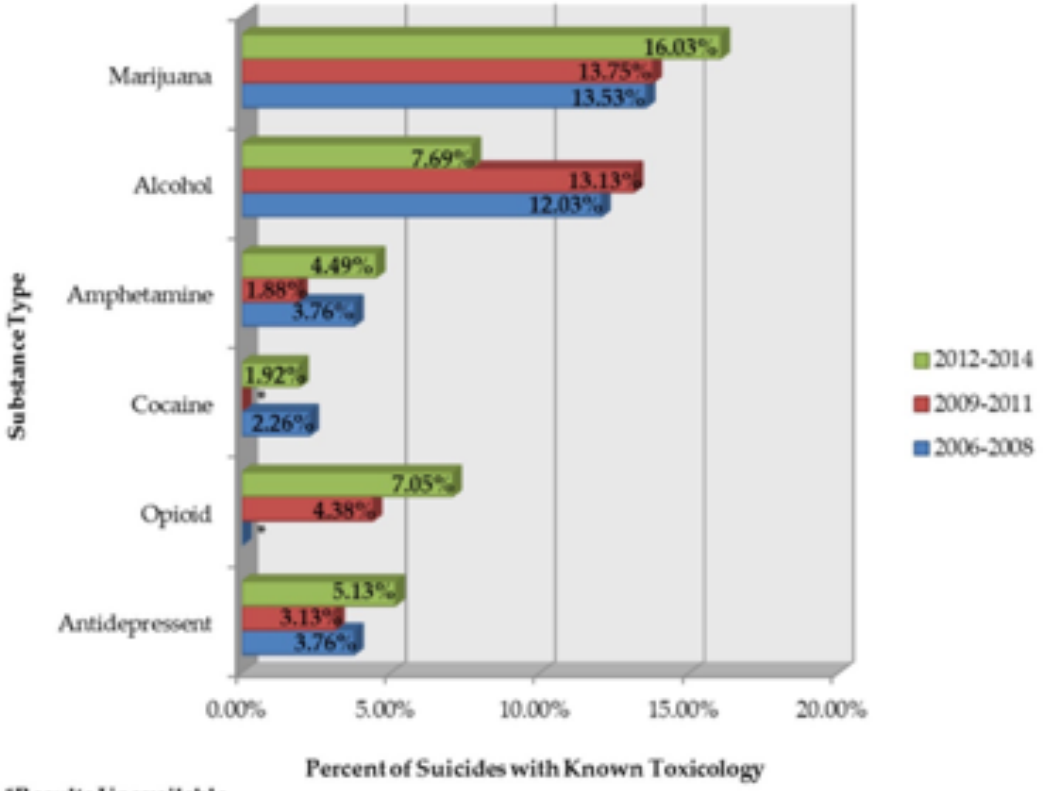
The state ranked poorly in health outcomes and mediocre overall in the latest national report on child well-being by the Annie E. Casey Foundation

JUN 17, 2019 5:05AM MDT | HEALTH

Suicide is the number one cause of death in Colorado for individuals between the ages of 10 and 24

Children's Hospital Colorado has seen the number of patients who have attempted suicide soar 600 percent since 2009.

Average Toxicology of Suicides Among Adolescents Ages 10 to 19 Years Old



*Results Unavailable

SOURCE: Colorado Department of Public Health and Environment (CDPHE), Colorado Violent Death Reporting System

SOURCE: Colorado Violent Death Reporting System, Colorado Department of Public Health and Environment (CDPHE)

The effects of co-administration of opium and morphine with nicotine during pregnancy on spatial learning and memory of adult male offspring rats

Sepehri G et al. Iran J Basic Med Sci 2014

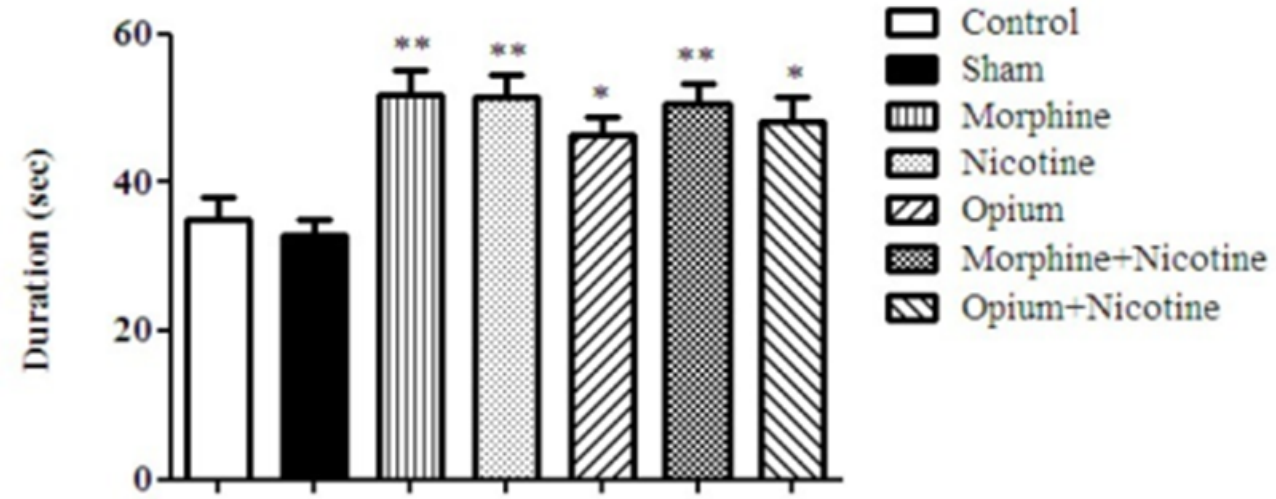
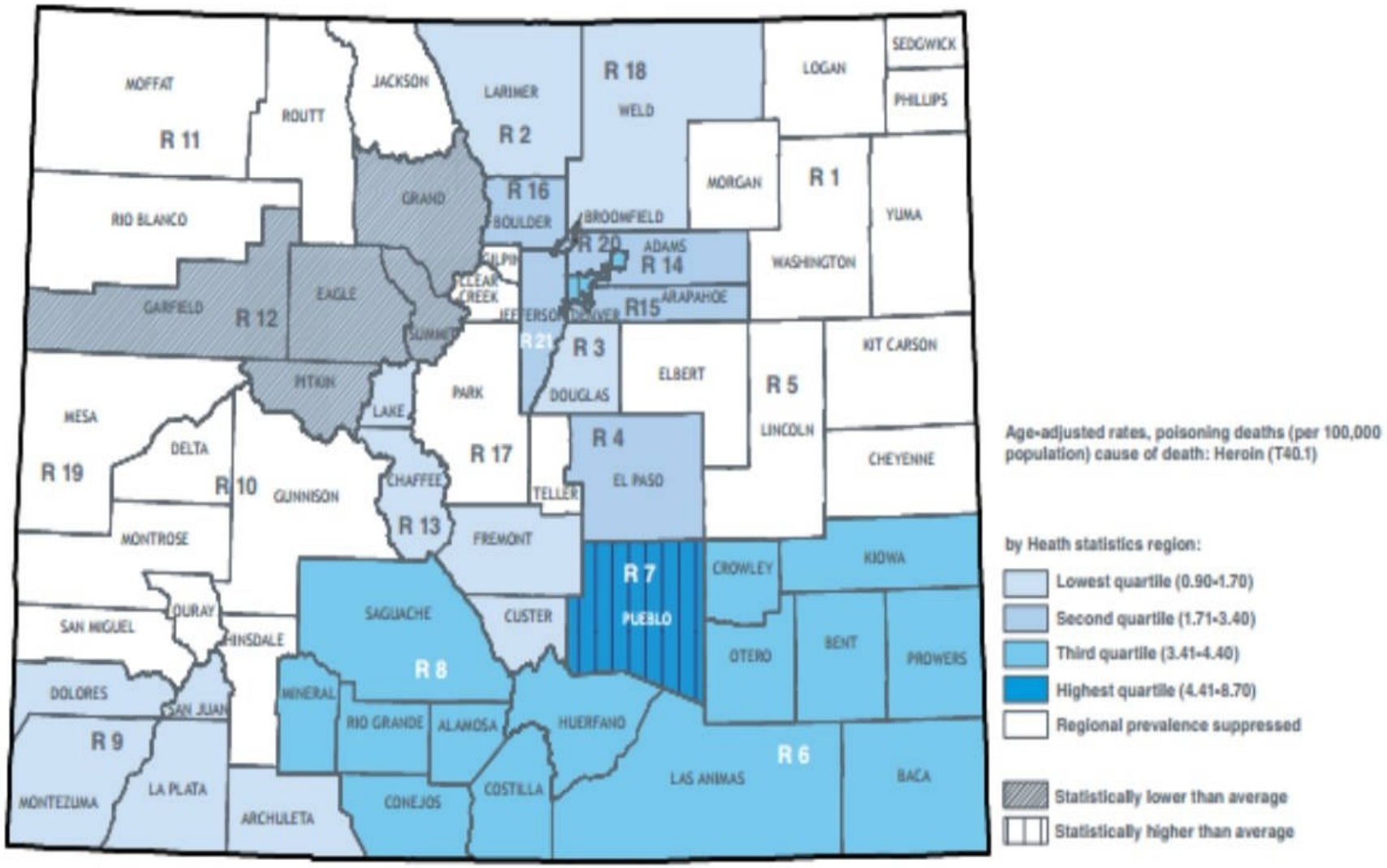


Figure 2: The effect of prenatal administration of opium, nicotine, opium+nicotine and morphine+nicotine on total average duration to find the hidden platform during the four days of training in the Morris water maze of male offspring. Data are expressed as mean± SEM. P-values <0.05 was considered statistically significant (n=7).*=P<0.05, **=P<0.01 prenatal drug exposure group vs. Control group

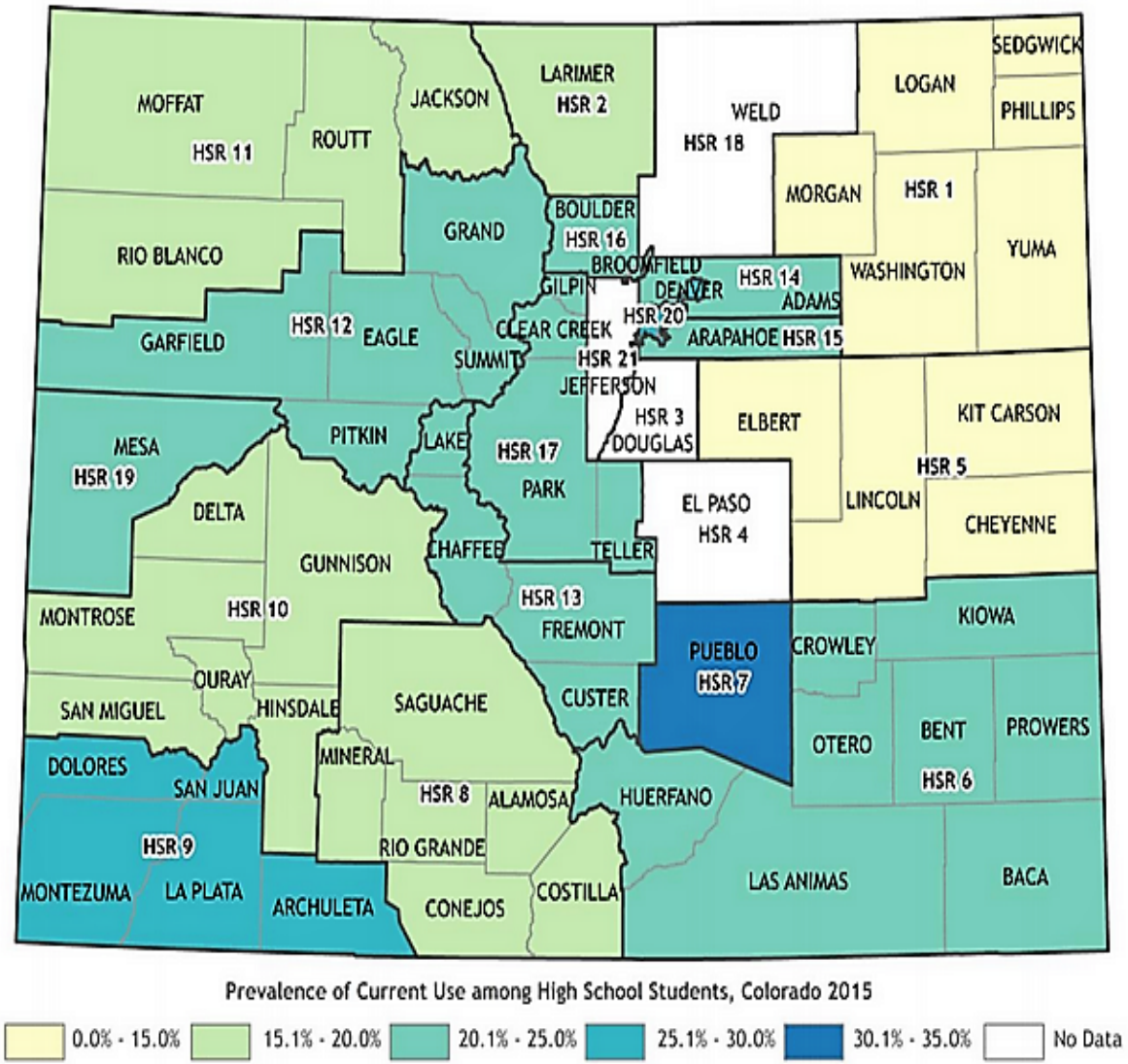
What does MJ have to do with Opiates?

Figure 2.4 Colorado Heroin Use by County



Source: Colorado Department of Public Health and Environment (CDPHE)[4]

Map 2. Prevalence of Current Marijuana Use among High School Students in Colorado, 2015



Major findings

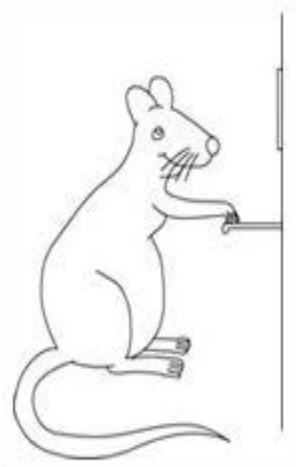
- In 2015, health statistics regions 7 (Pueblo County, 30.1%) and 9 (Dolores, San Juan, Montezuma, La

Prenatal exposure of cannabis alters opioid gene function in humans

- Aborted fetus brains from women using marijuana compared to those from women not using marijuana during pregnancy
- Discovered impaired opioid-related genes in distinct brain circuits that may have long term effects on cognitive and emotional behaviors
- Wang et al. Pharmacogenomics J, 2006;6:255-264

Prenatal cannabis exposure increases heroin seeking in adult rats

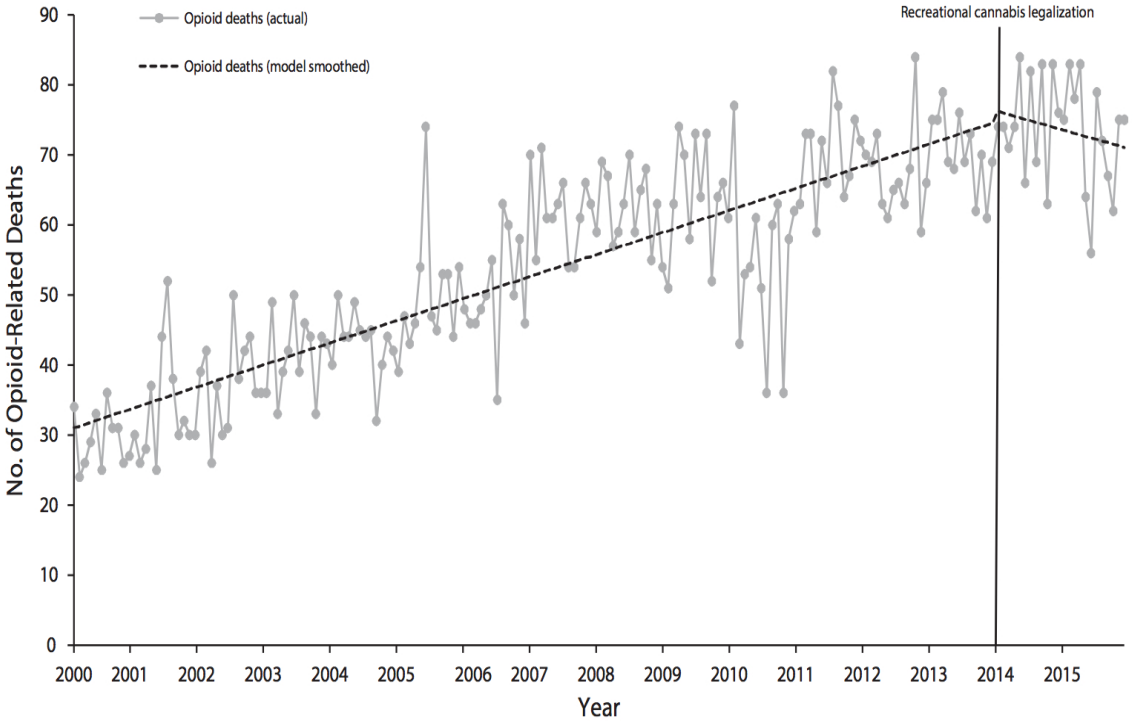
- THC exposed rats exhibited shorter latency to the first active lever press for heroin and had higher heroin-seeking during mild stress and drug extinction than animals not exposed to THC – and exhibited allostatic changes in limbic enkephalin systems in adulthood
- Sapano et al. Biol Psychiatry 2007;61:554-56



Naltrexone maintenance decreases cannabis self-administration and subjective effects of daily cannabis use

- Randomized double-blind, placebo-controlled trial of naltrexone in non-treatment seeking cannabis smokers
- In a laboratory setting those receiving the placebo had 7.6 times the odds of self-administering active cannabis compared with those receiving daily naltrexone
- Haney et al. Neuropsychopharmacology 2015

Example of Premature (and in my opinion irresponsible) Reporting



Note. Change in opioid-related deaths per month following legalization = –0.68 (95% confidence interval = –1.34, –0.03; *P* = .043). Change in model-estimated opioid-related deaths was robust to covariate control of opioid-related deaths in all comparison states. Change in model-estimated opioid-related deaths was robust to whether the prescription drug monitoring program (PDMP) covariate was modeled at the beginning of implementation or at full implementation of the 2014 PDMP change.

FIGURE 1—Changes in Monthly Opioid-Related Deaths Following Recreational Cannabis Legalization in Colorado, 2000–2015

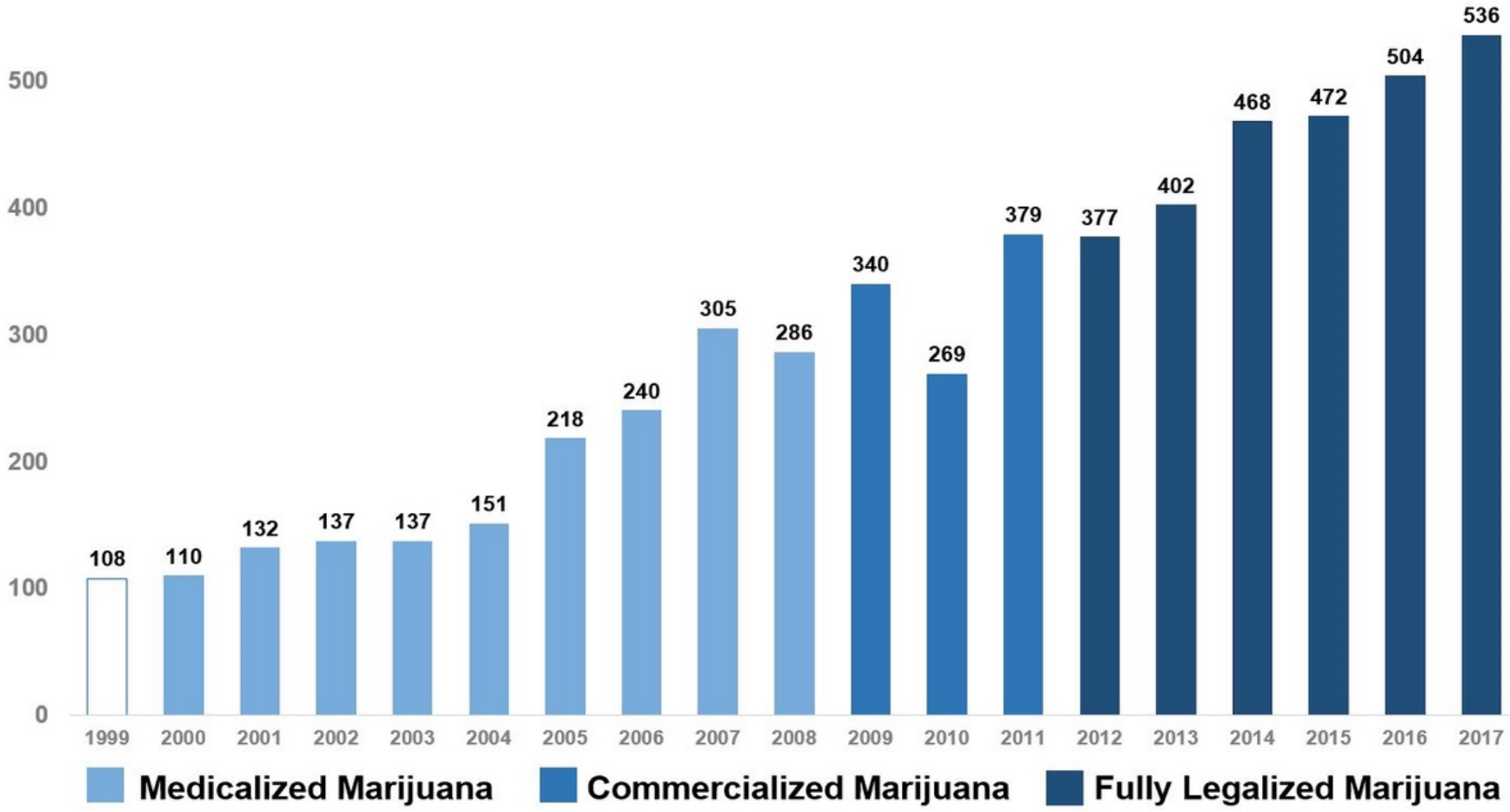
Source: American Journal for Public Health

Livingston et al. Recreational Cannabis Legalization and opioid-related deaths in Colorado, 2000-2015. AJPH 2017;107:1827-1829

2014 was also time when PDMP registration was mandated

"Legal marijuana is saving lives in Colorado, study finds" – report in Washington Post 10/16/17

Opioid Overdose Deaths in Colorado

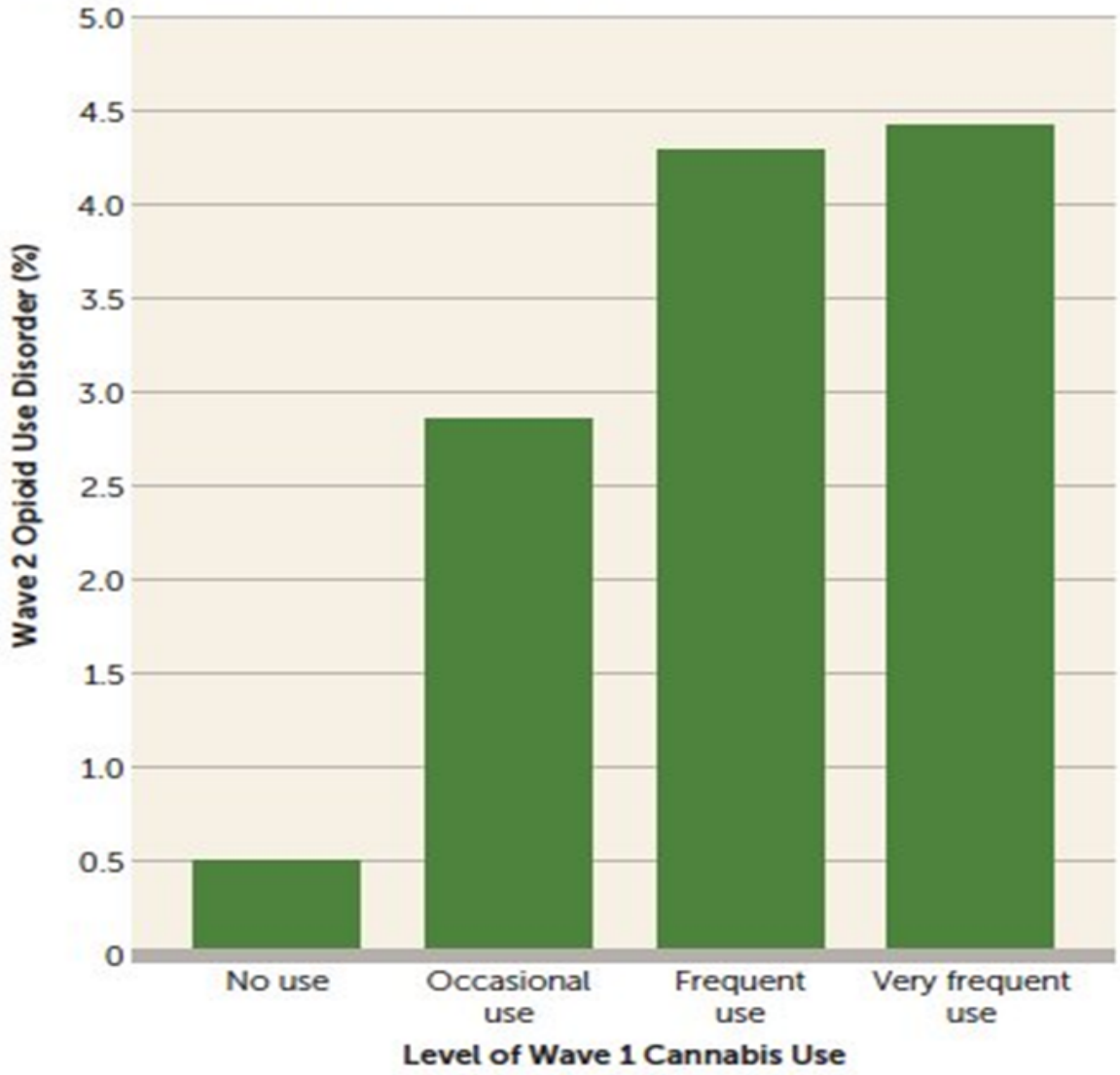


https://www.colorado.gov/pacific/cdphe/vital-statistics-program

Cannabis use and risk of prescription opioid use disorder in the United States

- Olfson M et al. AJP in Advance (doi:10.1176/appi.ajp.2017.17040413)
- 2001-2002 NESARC (wave 1) survey – 81% response
- 2004-2005 (wave 2) survey – 70.2% response rate
- N=34,653
- Compared cannabis use at wave 1 to prescription opioid use disorder at wave 2
- Cannabis use at wave 1 was associated with a significant increase in the odds of having a prescription opioid use disorder at wave 2

FIGURE 1. Level of Wave 1 Cannabis Use and Incident Wave 2 Prescription Opioid Use Disorder in the NESARC[a]



[a] NESARC=National Epidemiological Survey on Alcohol and Related Conditions; wave 1 was conducted in 2001 and 2002, and wave 2 in 2004 and 2005.

Links to other substance abuse

- NASEM, WHO, and CDPHE report all found evidence of a statistical association between cannabis use and the development of substance dependence and/or substance abuse disorder for substances including alcohol, tobacco, and other illicit drugs.
- Four separate discordant twin studies have found that the twin who used marijuana was more likely to use other substances even after controlling for environmental and genetic influences

Solutions/Recommendations

- Educate, educate, educate, increase prevention efforts
- “medical” MJ should come from pharmacies and go through FDA testing as all Rx drugs
- Limit THC concentrations to <10%
- Increase funding and availability of treatment
- Increase research on CBD and lower doses of THC
- Strong ban on any advertising that appears to be directed toward youth – for all drugs including marijuana, tobacco and alcohol