

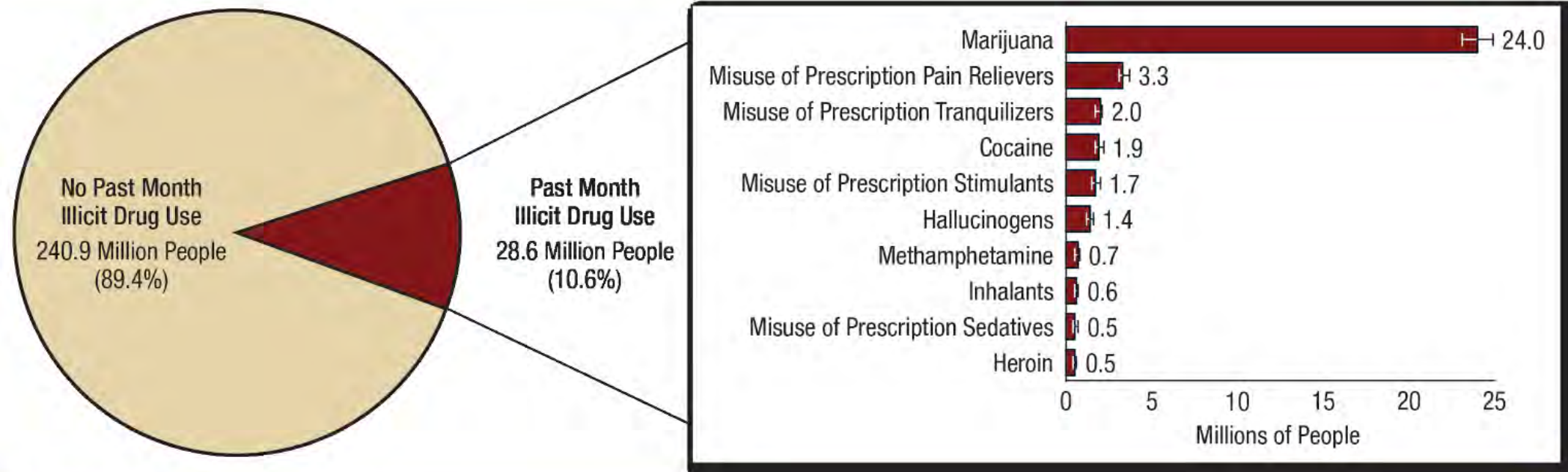


Marijuana Use, Effects, and Public Health Implications

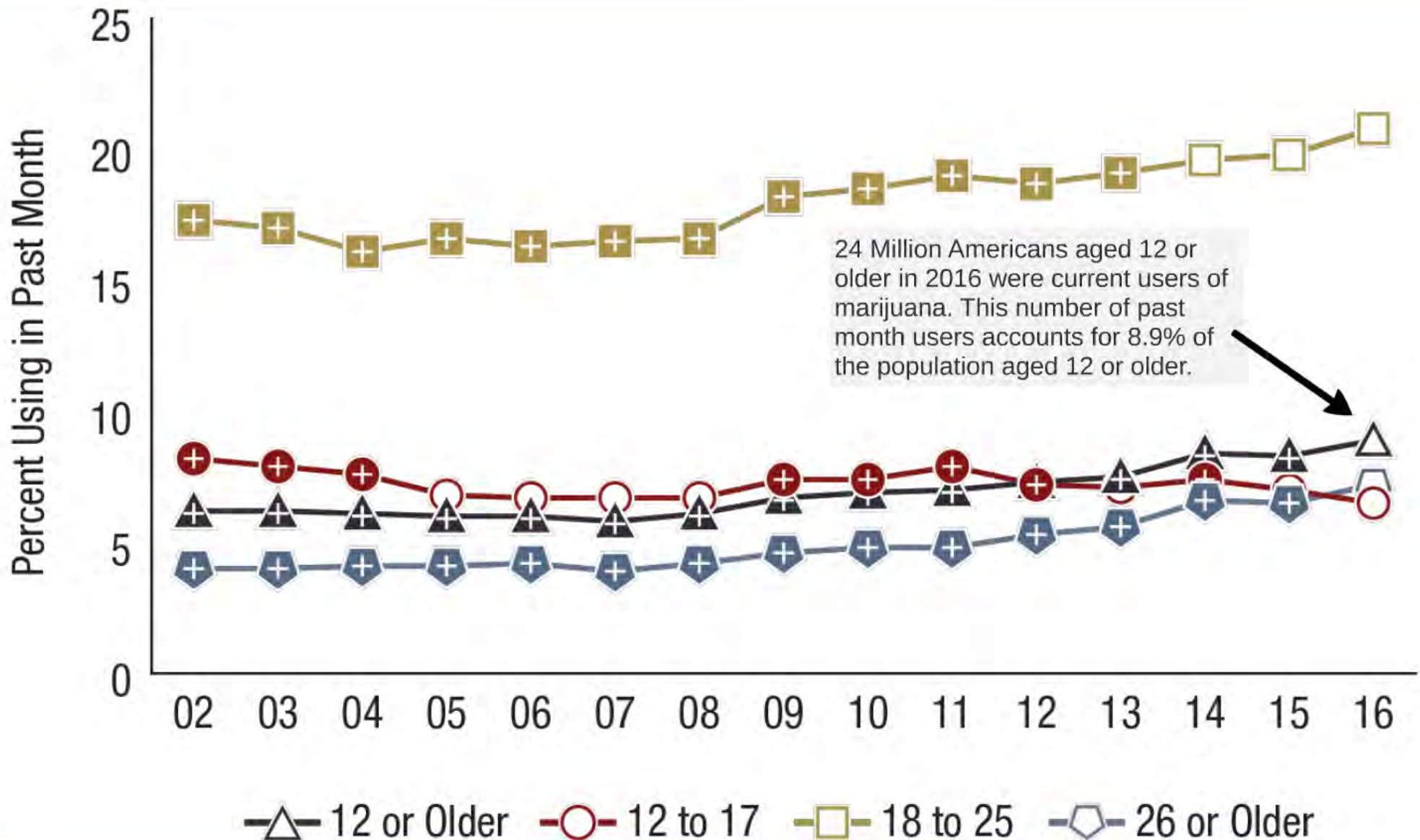
Jane Metrik, Ph.D.
Center for Alcohol and Addiction Studies
Brown University
Providence VA Medical Center

- Dependence
- experimental
- Those who
- Daily use
- Treatment

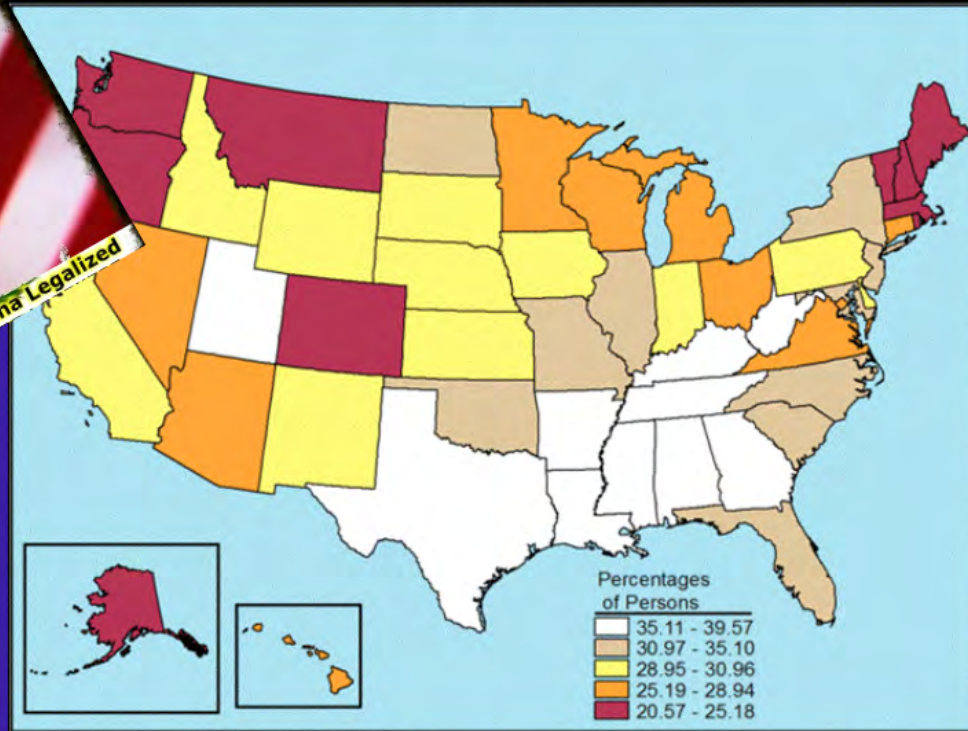
Numbers of Past Month Illicit Drug Users among People Aged 12 or Older: 2016



Aged 12 or Older: 2016



Perceptions of Great Risk of Smoking Marijuana Once a Month (age: 12+) by State



SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 2011-2012



Cities

018



WIKILEAF.COM

FORTUNE

MARIJUANA INC.

Meet the Entrepreneurs and Investors
Firing Up a New Industry

The emerging cannabis industry took in nearly \$9 billion in sales in 2017 (BDS Analytics).

That was before California opened its massive retail market in January 2018. Estimated national marijuana sales will rise to \$11 billion in 2018, and to \$21 billion in 2021.

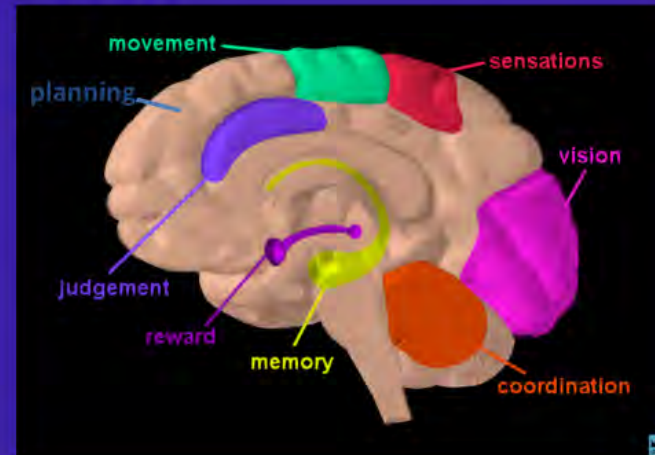
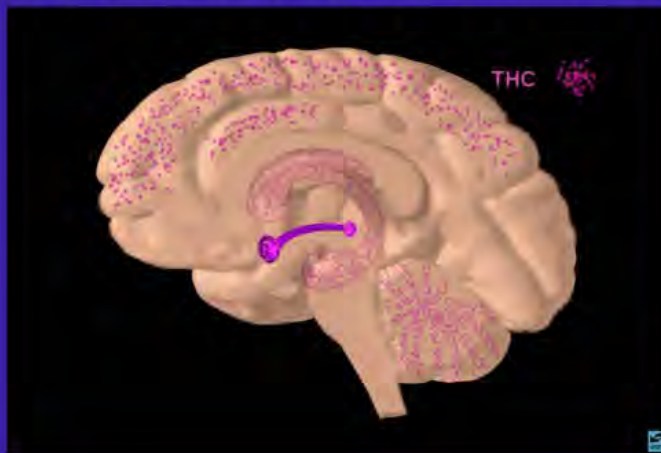


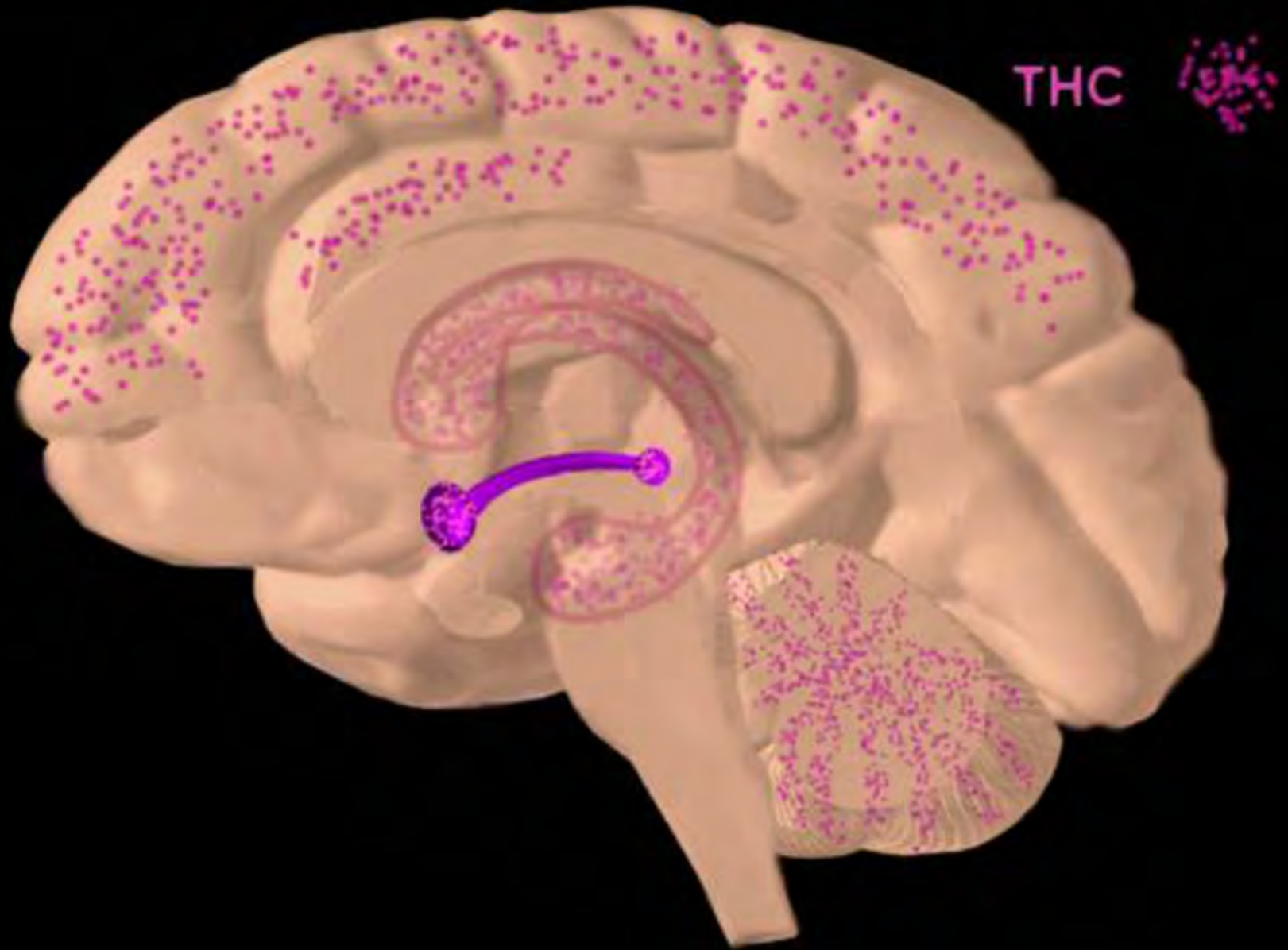
Cannabis

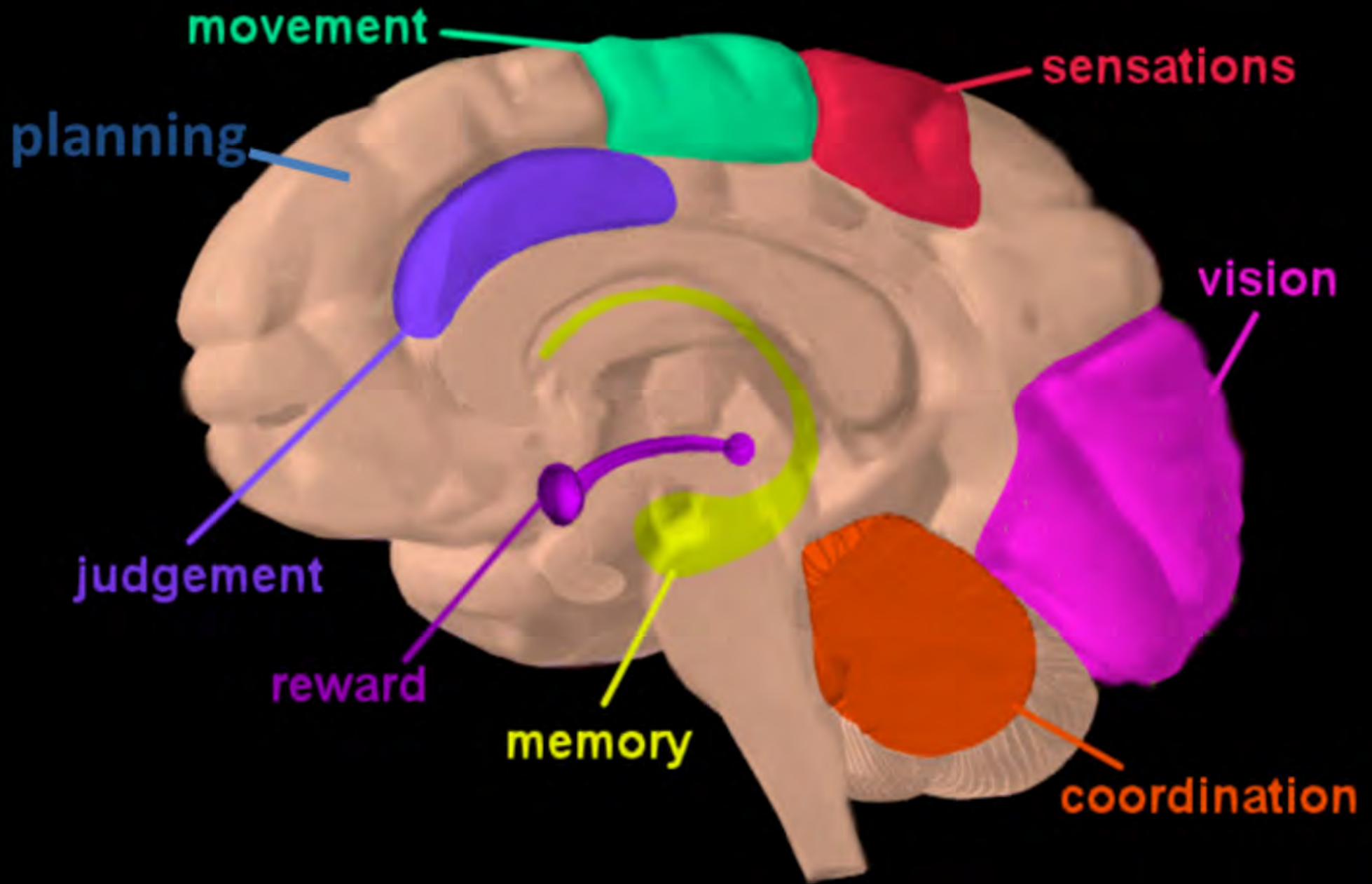
- Marijuana plant, *Cannabis sativa*, contains >500 compounds, ~100 cannabinoids
- Cannabinoids appear in the resinous glands and flowering tops of the plant
- Cannabinoids are lipophilic
 - dissolve in fat, not soluble in water
- Δ -9-tetrahydrocannabinol (THC) is marijuana's principal psychoactive cannabinoid
- Marijuana potency is due to the concentration of THC

Brain Areas Affected by Marijuana

- Cannabinoid receptors (CB1 and CB2) interact with exogenous and endogenous cannabinoids (anandamide and 2-AG)
- Hippocampus, cerebellum, cerebral cortex, basal nuclei, specifically nucleus accumbens, ventral tegmental area (i.e., “the reward pathway”), and amygdala
- Control of memory, attention, motor function, cognition, emotion, reward, and mood regulation

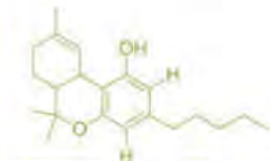






Acute Effects of Marijuana

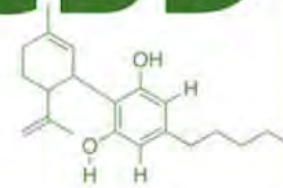
- **Positive Affect: Increased euphoria**
- **Negative Affect: Increased or decreased anxiety**
- **Cognitive impairment: judgment and decision-making, memory, and attention**
- **Also: Increased appetite, tachycardia, impaired motor coordination, and reaction time**



THC

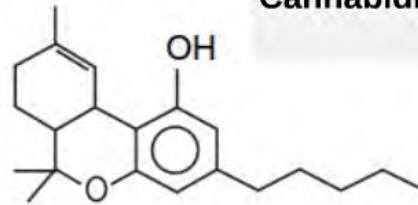


CBD



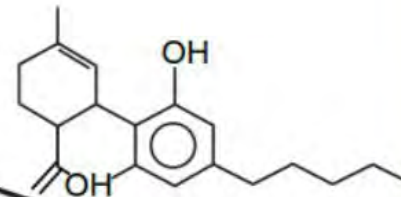
<http://thehempoilbenefits.com/cbd-oil-high>

Cannabidiol (CBD) is a non-psychoactive cannabinoid implicated in medicinal benefits



- Reward
- Drug seeking
- Anxiety (+/-)
- Sensitivity to other drugs of abuse

Δ-9-THC



- Reward
- Drug seeking
- Anxiety
- Sensitivity to other drugs of abuse

CBD

Hurd et al 2015

Increasing potency of THC

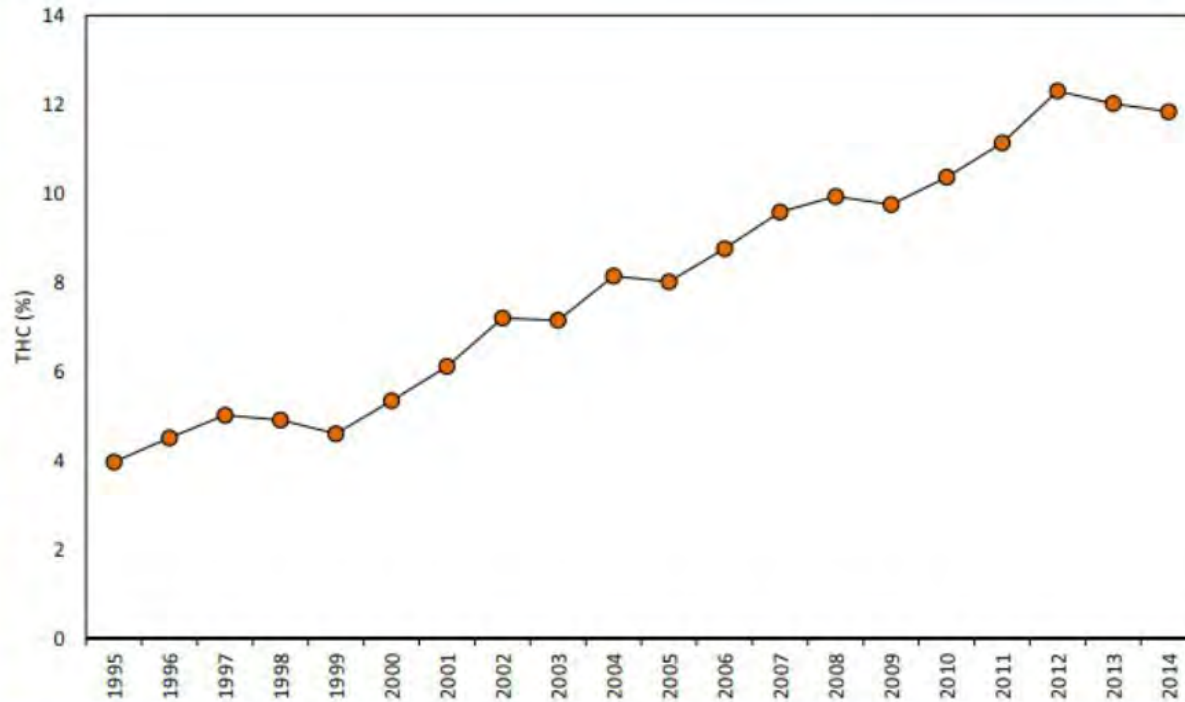


Figure 1. Average Δ^9 -tetrahydrocannabinol (THC) concentration of Drug Enforcement Administration specimens by year, 1995–2014.

EISOHLY, M. A., MEHMEVIC, Z., FOSTER, S., GON, C., CHANDRA, S., & CHURCH, J. C. (2016). Changes in cannabis potency over the last 2 decades (1995–2014): analysis of current data in the United States. *Biological psychiatry*, 79(7), 613-619.

- THC potency has increased steadily over time, while CBD has decreased
- Average potency higher in states with recreational laws: ~ 30% in Colorado



Marijuana Concentrates



CRUMBLE

Dried oil with a honey-comb like consistency



BADDER/BUDDER

Concentrates whipped under heat to create a cake-batter like texture



SHATTER

A translucent, brittle, & often golden to amber colored concentrate made with a solvent



DISTILLATE

Refined cannabinoid oil that is typically free of taste, smell & flavor. It is the base of most edibles and vape cartridges



CRYSTALLINE

Isolated cannabinoids in their pure crystal structure



DRY SIFT

Ground cannabis filtered with screens leaving behind complete trichome glands. The end-product is also referred to as kief



ROSIN

End product of cannabis flower being squeezed under heat and pressure



BUBBLE HASH

Uses water, ice, and mesh screens to pull out whole trichomes into a paste-like consistency

<https://www.marijuana.com/news/2017/07/dabs-wax-and-concentrates-710-is-national-hash-day/>

- "Dabbing" refers to vaporizing concentrated forms of marijuana at high temperatures
- THC level upwards of 80% (Mehmedic et al., 2010)
- Very little peer-reviewed research, but risks include: fire/burns from use of butane, higher likelihood of dependence/withdrawal, acute psychosis, effects on memory





Rates of poison control center calls for unintentional pediatric marijuana exposures more than **tripled** in states that decriminalized marijuana before 2005

In Colorado from 2011 through 2013, marijuana-related emergency department visits increased by 57%

"state lawmakers should consider requirements, such as child-resistant packaging, warning labels, and public education, when drafting marijuana legislation to minimize the effect on children"

Data are from the National Poison Data System (NPDS), which contains information from the human poison exposure case phone calls taken by all 56 poison centers across the country. Single-substance, unintentional exposures in children aged 9 years and younger from January 1, 2005, to December 31, 2011 were included as cases.

Prevalence and patterns among pregnant U.S. women

3.9% past-month users (60% increase since 2002)

Prevalence highest among 18-25 year olds (7.47%)

70% of women believe there is little risk from using cannabis 1-2x/week

69% of dispensaries in Colorado recommend cannabis for nausea and vomiting during pregnancy

Associations with maternal outcomes

Increased odds of anemia

Possible effects on pregnancy implantation and placentation

More negative attitudes toward pregnancy

Associations with offspring outcomes

Lower birthweight

Increased likelihood of need for NICU

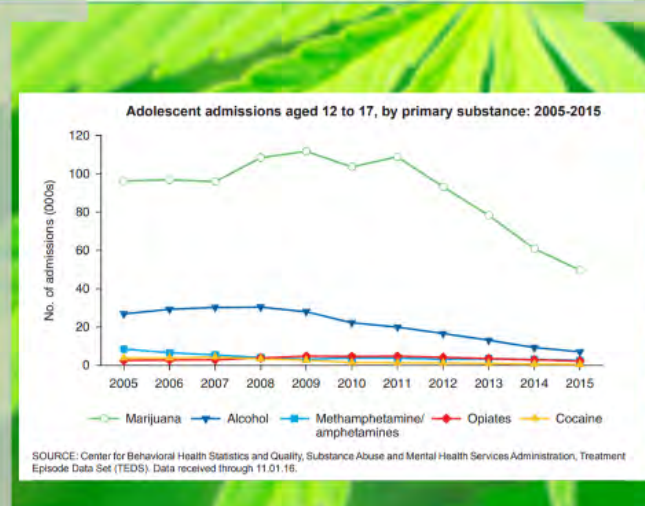
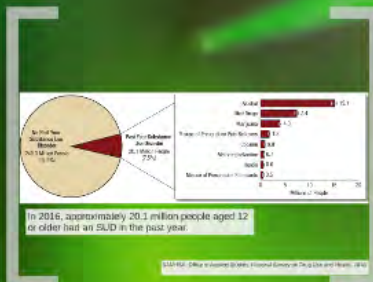
Impeded brain development

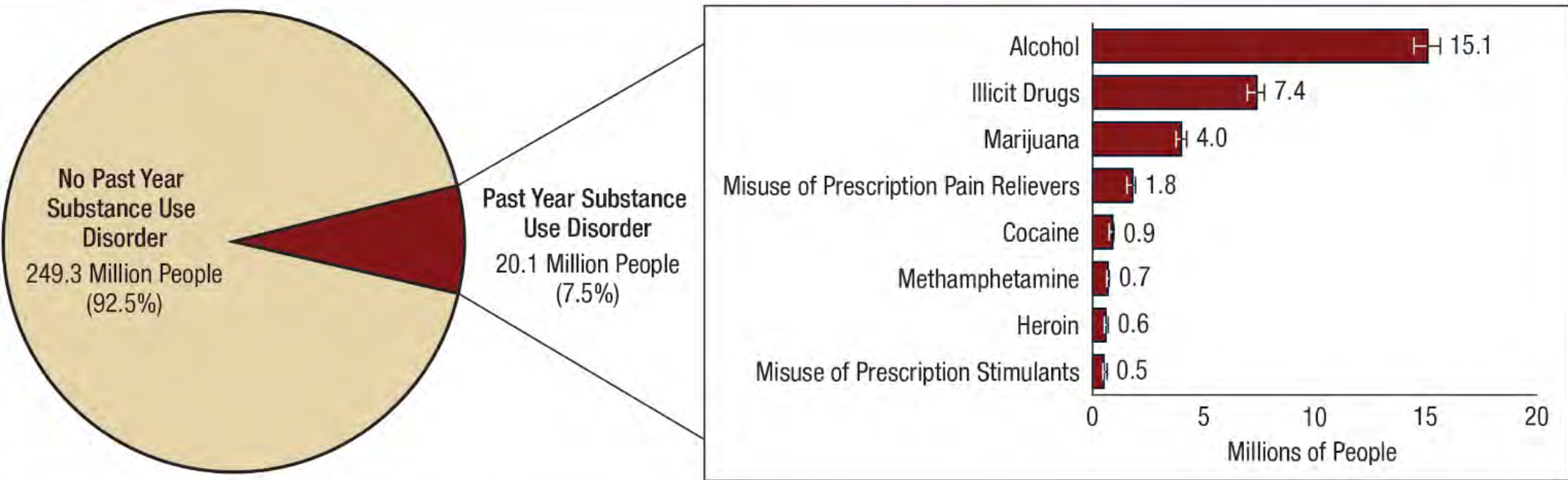
Behavioral and neurocognitive problems including earlier initiation and substance use



Is Marijuana Addictive?

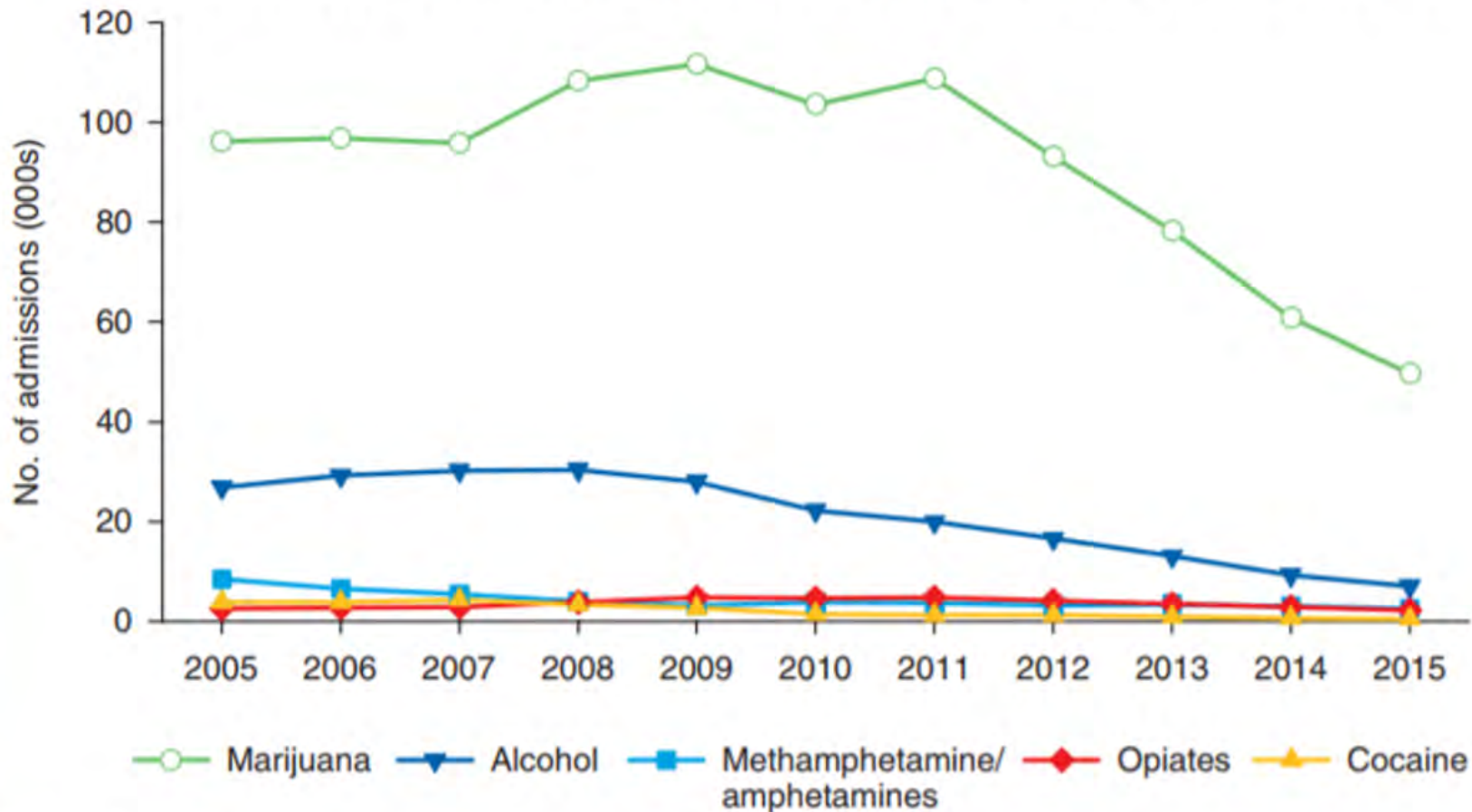
- Dependence among those who have ever experimented with marijuana: 9%
- Those who start using as teenagers: 17%
- Daily users: 25-50%
- Treatment admissions (ages 12+): 17% for marijuana





In 2016, approximately 20.1 million people aged 12 or older had an SUD in the past year.

Adolescent admissions aged 12 to 17, by primary substance: 2005-2015



SOURCE: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Treatment Episode Data Set (TEDS). Data received through 11.01.16.

Cannabis Withdrawal

- **Core symptoms: increased craving, depressed mood, irritability, anxiety, sleep disturbance, decreased food intake, restlessness, anger, and upset stomach**
- **44% of cannabis dependent users report severe craving when abstinent and relapse due to craving**
- **Onset: days 1-3 after cessation. Peak: days 2-6. Resolves within 10-14 days**

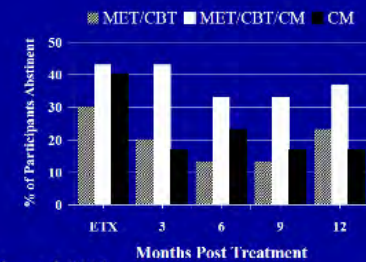
Treatment of Cannabis Use Disorder

Behavioral treatments are efficacious Motivational Enhancement Therapy (MET) + Cognitive-Behavioral Treatment+ Contingency Management (CM)

- No FDA-approved pharmacological treatment
- A range of medications have been tested with humans
 - Cannabinoid substitutes (agonists): dronabinol and nabilone
 - Dronabinol reduced cannabis withdrawal in human laboratory studies and in outpatient clinic but RCT results were not compelling
 - Nabilone (long-lasting cannabinoid agonist) is more promising for reducing cannabis withdrawal and relapse (still need RCT)

Relapse rates at about 65%, similar to alcohol and tobacco cessation treatment
For adolescents, relapse rates are higher

Motivational Incentives Improve Outcomes
Contingency Management (CM)



Budney et al. (2006)





Driving and Marijuana

- Marijuana doubles the risk of motor vehicle crashes (MVC) and fatalities
- Marijuana-positive drivers involved in fatal MVCs increased after marijuana legalization in CO and in CA
- Marijuana causes impairment of psychomotor skills related to driving
- Marijuana-intoxicated drivers unsuccessfully attempt to compensate for impairment

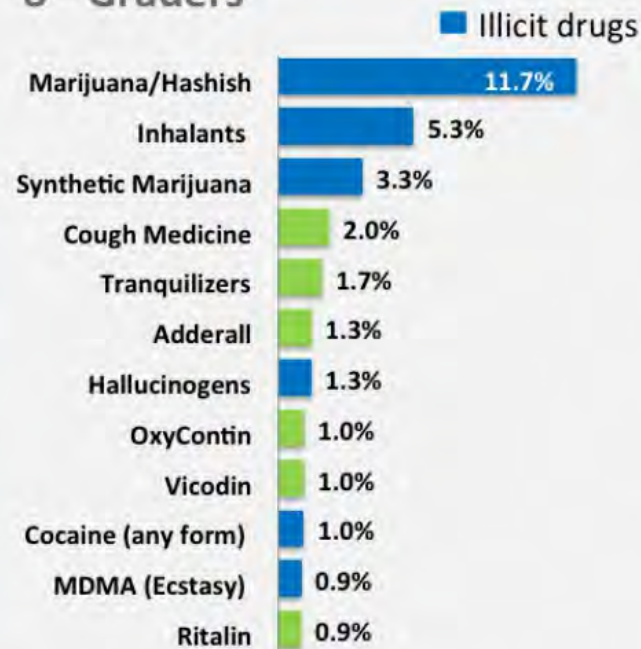


What Do Marijuana Users Say?

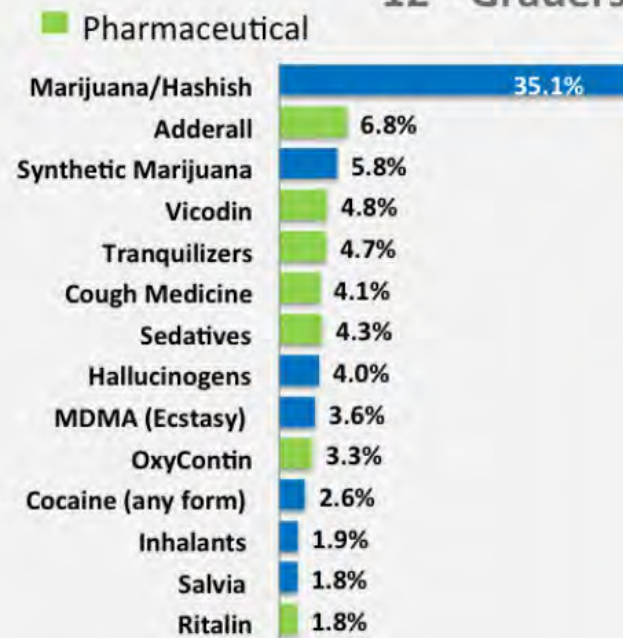
- Most marijuana users have driven after smoking marijuana (83%) or while smoking marijuana (78%)
- Marijuana users endorse low perceived risk, and negligible perceived impairment or even safer driving after marijuana use
- *"When I drive after smoking, I am more careful (65%) or as careful (33%) as when driving sober" e.g. more careful not to speed (70%)*
- More positive or permissive driving-related peer norms and attitudes predict greater likelihood of driving under the influence of marijuana and smoking marijuana while driving

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

8th Graders



12th Graders




* Only 12th graders surveyed about sedatives use

Source: University of Michigan, 2014 Monitoring the Future Study

- Regular marijuana use in adolescence leads to impairment in neural connectivity in adulthood and neurotoxic effects
- Significant decline in IQ (8 pts) from childhood to age 38 (over 20 years) with persistent use, particularly if use starts in adolescence (< age 18)
- Regular marijuana use: poor school performance and drop out; then linked with lower income, unemployment, lower satisfaction with life

Meier et al., 2012 PNAS; Volkow et al., 2014 NEJM



The background of the slide features a row of four bottles of alcohol (two clear, two dark) and a cannabis leaf on the right side. The text is overlaid on a white semi-transparent box.

Marijuana and Alcohol

- Comorbidity: 68% of individuals with current CUD meet criteria for AUD
- Combined use increases cognitive and psychomotor impairment; significantly higher THC blood levels when used with alcohol
- Marijuana use is associated with increased risk of AUD onset and persistence over the course of three years (NESARC data) Weinberger, Platt, Goodwin, 2016
- Marijuana use during treatment for AUD is associated with lower abstinence post-treatment and at 1 year and with alcohol-related problems at 1 year (Project COMBINE data)

Subbaraman, Metrik, Patterson, Swift, 2017, *Addiction*; Subbaraman, Metrik, Patterson, Stout, *Drug and Alcohol Dependence*, in press

Daily Patterns of Marijuana and Alcohol Co-Use

Examined daily associations between marijuana and alcohol use and how these differed by CUD and AUD diagnosis
TLFB interview of 127 Veterans over 180 days (22,860 observations)

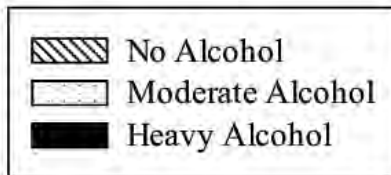
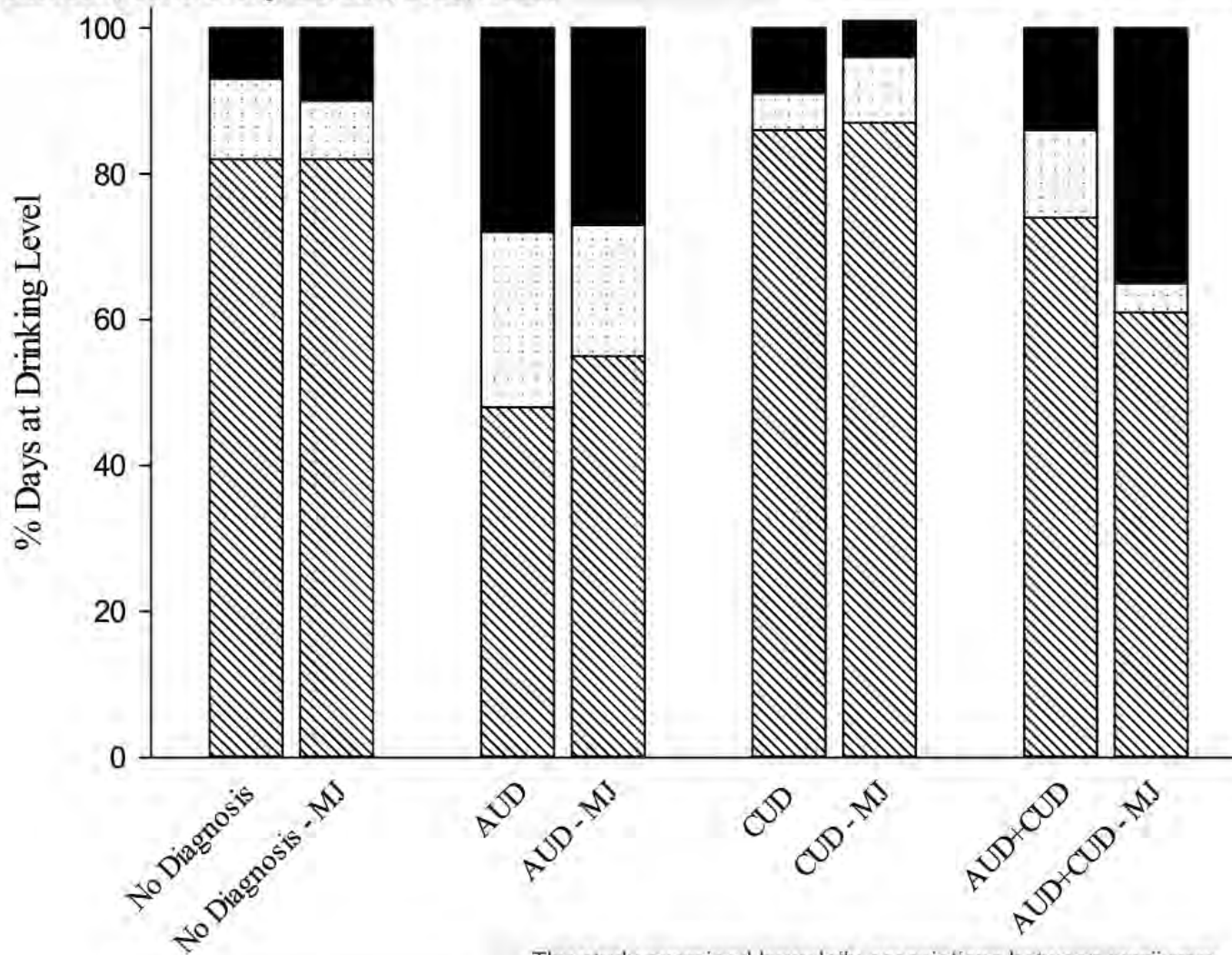
37% with DSM-5 CUD

40% with DSM-5 AUD

15% both CUD + AUD

Multilevel modeling analysis showed that participants were more likely to drink heavily (5/4+ drinks for men/women) vs moderately (1-4/3 drinks) (OR = 2.34) and moderately vs not drinking (OR=1.61) on marijuana use days relative to non-use days.

Metrik, Gunn, Jackson, Sokolovsky, Borsari, 2018, ACER



The study examined how daily associations between marijuana and alcohol use differed as a function of cannabis use disorder (CUD) and/or alcohol use disorder (AUD) diagnosis. Heavy drinking was more likely to occur on days when marijuana was also used among individuals with AUD and AUD+CUD, but not among those with only CUD. Alcohol interventions need to address marijuana use as a risk factor for heavy drinking and AUD.

Bars with MJ = marijuana use days; other bars represent non-marijuana days

Project RADAR

Table 2. Group differences between medicinal and recreational cannabis users in diagnoses, cannabis-related problems, reasons for using marijuana, and other health-related and substance use outcomes.

	Medicinal Users	Recreational Users	Unadjusted for		Adjusted for	
	(n = 66)	(n = 77)	frequency of use	frequency of use	F	η^2
	M (SD)	M (SD)	t-test	d		
% of cannabis use days past 6 months	64.49 (37.17)	20.82 (33.65)	7.37***	1.23	-	-
% of cannabis use days in past month	70.10 (39.22)	19.83 (35.38)	8.06***	1.35	↓	↓
% of alcohol use days in past month	14.49 (23.32)	31.86 (30.90)	3.74***	0.63	5.48*	.04
% heavy drinking days in past month	7.73 (20.53)	16.41 (23.78)	2.32*	0.39	2.51	.02
No. of alcohol drinks/week, past month	5.62 (12.42)	11.86 (14.11)	2.79**	0.47	2.78	.02
% of drug use days in past month ^a	3.23 (13.13)	4.76 (16.38)	0.61	0.10	1.60	.01
Cannabis-related problems	2.85 (4.07)	1.61 (2.65)	2.18*	0.36	0.48	.00
Reasons for using cannabis						
Enjoyment	3.55 (1.11)	3.15 (1.26)	1.10*	0.34	0.05	.00
Conformity	1.24 (0.51)	1.40 (0.77)	1.44	0.24	0.18	.00
Coping	2.28 (1.11)	1.73 (1.12)	2.94**	0.49	0.64	.00
Experimentation	1.66 (0.91)	1.89 (1.00)	1.40	0.24	0.00	.00
Boredom	2.23 (1.23)	2.23 (1.18)	0.00	0.00	1.45	.01
Alcohol	1.33 (0.52)	1.97 (1.11)	4.33***	0.74	7.62**	.05
Celebration	2.32 (1.17)	2.28 (1.23)	0.21	0.03	0.65	.00
Social anxiety	2.26 (1.17)	1.67 (1.04)	3.22**	0.53	1.40	.01
Relative low risk	2.82 (1.42)	2.07 (1.12)	3.51**	0.58	3.71	.02
Sleep	3.51 (1.16)	2.16 (1.32)	6.47***	1.09	17.05***	.09
SF-36 physical health score	63.28 (21.74)	73.73 (18.67)	3.09**	0.52	4.09*	.03
SF-36 mental health score	49.80 (23.60)	61.62 (22.06)	3.09**	0.52	2.87	.02
Global PSQI score	10.97 (4.00)	9.08 (4.12)	2.77**	0.47	2.95	.02
Satisfaction with Life Scale	15.68 (6.8)	18.42 (7.46)	2.27*	0.38	1.25	.01

Notes. Heavy drinking days = four or more drinks per day for females and five or more drinks per day for males; ^a = past month drug use was endorsed by 14 medicinal cannabis users and 14 recreational cannabis users; *p < .05, **p < .01, ***p < .001

Metrik, Bassett, Aston, Jackson, & Borsari (in press). *Translational Issues in Psychological Science*

- NIDA-funded prospective (1 year) study of the trajectories of marijuana use, related problems, cannabis use disorders and comorbid affective disorders among post-9/11 returning Veterans
- N = 361 (mean age = 33; 95% male; 81% White)
- 40% past year cannabis use (with 20% frequent weekly use); 60% lifetime no past year use

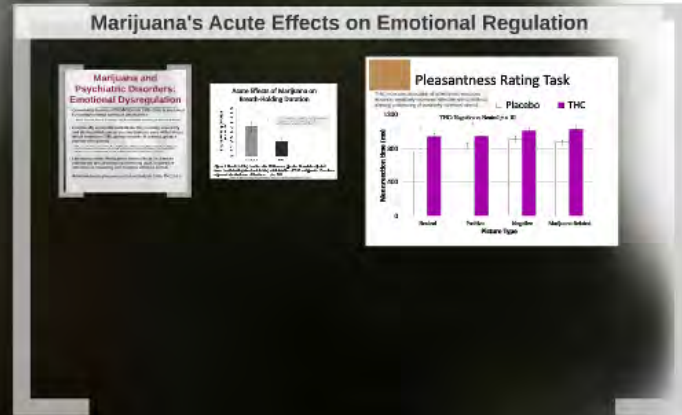
Metrik, Jackson, Bassett, Zvolensky, Seal, & Borsari (2016). *Psychology of Addictive Behaviors*.

Medical marijuana users drink less often and have less alcohol problems than recreational marijuana users



Project RADAR

State	Year	Medical Marijuana	Recreational Marijuana
Alaska	2008	Yes	No
Arizona	2009	Yes	No
Arkansas	2012	Yes	No
California	2003	Yes	Yes
Colorado	2000	Yes	Yes
Connecticut	2003	Yes	No
Delaware	2010	Yes	No
District of Columbia	2000	Yes	Yes
Florida	2010	Yes	No
Georgia	2015	Yes	No
Hawaii	2000	Yes	Yes
Illinois	2012	Yes	No
Indiana	2013	Yes	No
Iowa	2008	Yes	No
Kansas	2016	Yes	No
Kentucky	2014	Yes	No
Louisiana	2015	Yes	No
Maine	2009	Yes	No
Maryland	2013	Yes	No
Massachusetts	2009	Yes	No
Michigan	2008	Yes	No
Minnesota	2002	Yes	No
Mississippi	2017	Yes	No
Missouri	2018	Yes	No
Montana	2018	Yes	No
Nebraska	2016	Yes	No
Nevada	2001	Yes	Yes
New Hampshire	2013	Yes	No
New Jersey	2010	Yes	Yes
New Mexico	2009	Yes	No
New York	2009	Yes	Yes
North Carolina	2012	Yes	No
North Dakota	2015	Yes	No
Ohio	2016	Yes	No
Oklahoma	2016	Yes	No
Oregon	2000	Yes	Yes
Rhode Island	2008	Yes	No
Tennessee	2014	Yes	No
Texas	2015	Yes	No
Utah	2018	Yes	No
Vermont	2004	Yes	No
Virginia	2013	Yes	No
Washington	2000	Yes	Yes
West Virginia	2014	Yes	No
Wisconsin	2013	Yes	No
Wyoming	2014	Yes	No



Marijuana and Psychiatric Disorders: Emotional Dysregulation



Marijuana Use in Veterans

- Marijuana use among Veterans is increasing
 - Increases post-deployment after military separation (~34% in past month among OEF/OIF)
- Of OEF/OIF/OND Veterans, 23% have PTSD and 20% screen positive for depression
- PTSD is the most prevalent co-occurring psychiatric disorder among veterans with CUD presenting to VHA, at 29%
- PTSD+CUD Comorbidity associated with greater PTSD symptom severity, decreased likelihood of CUD cessation, and worse PTSD and CUD clinical outcomes



- Patients report using marijuana to cope with PTSD symptoms of hyperarousal, negative affect, and sleep disturbances
- PTSD = inability to extinguish fear and anxiety
- PTSD exposure therapy (repeated exposure to fear-linked cues to produce extinction); however, extinguished fear often re-emerges
- Endocannabinoids play significant role in the etiology of PTSD and stress modulation
- Activation of CB system may regulate extinction learning and retention (animal studies and now human acute THC administration study): facilitated fear extinction-prevented recovery of fear 24 h later
 - CB system may be a promising target (very preliminary)
- No published RCTs of marijuana for PTSD

Source: Neuropharmacology 2013; 64: 396-402

Marijuana and Psychiatric Disorders: Emotional Dysregulation

- Comorbidity between PTSD/MDD with CUD (36%) is explained by coping-oriented cannabis use motives

Metrik, Jackson, Bassett, Zvolensky, Seal, Borsari (2016). Psychology of Addictive Behaviors.

- Emotionally vulnerable individuals (high anxiety sensitivity and distress intolerance) use marijuana to cope with distress, which maintains CUD, greater severity of craving, greater number of problems

Farris, S.G., Metrik, J., Bonn-Miller, M.O., Kahler, C.W., Zvolensky, M.J. (2016). Anxiety sensitivity and distress intolerance as predictors of cannabis dependence symptoms, problems, and craving: the mediating role of coping motives. Journal of Studies on Alcohol and Drugs, 77, 889-897.

- Laboratory study: Marijuana's acute effects on distress intolerance and attentional processing (bias in selective attention) of rewarding and negative affective stimuli
- Within-subjects placebo-controlled study (n = 89), THC 3.0%

Acute Effects of Marijuana on Breath-Holding Duration

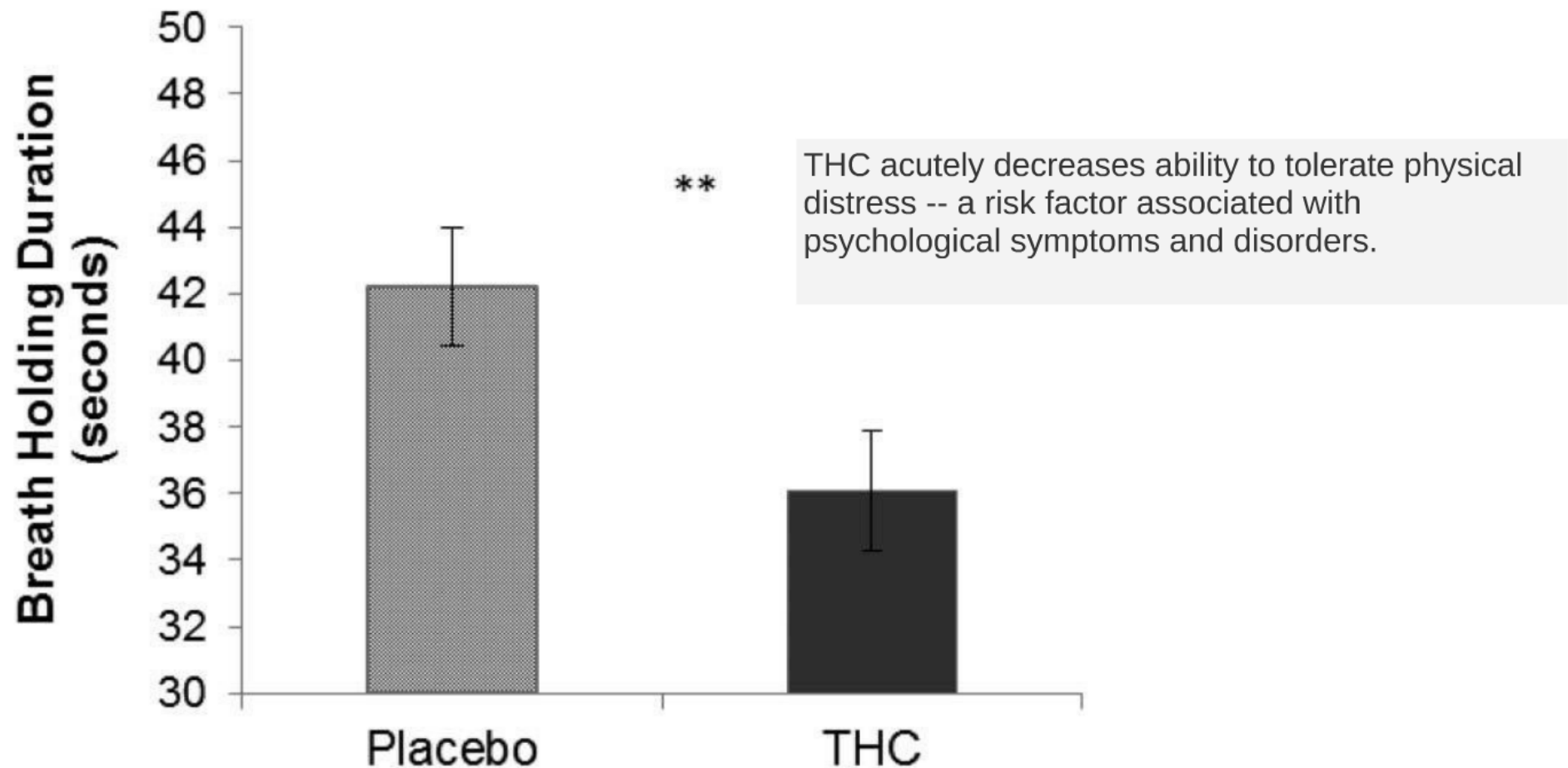


Figure 1. Breath-holding duration after THC versus placebo. Covariate adjusted mean breath-holding duration following administration of THC and placebo. Error bars represent standard error of the mean. $**p < .001$.

The Endocannabinoid System as a Target of Pharmacotherapy

Glaucoma

- evidence of transient decrease in intraocular pressure
- standard treatments are more effective

Epilepsy

- Insufficient evidence on using cannabis botanicals
- Increasing evidence of CBD as effective antiepileptic agent
- Epidiolex (GW Pharma), a liquid formulation of highly purified plant-derived cannabidiol (CBD), pediatric epilepsy syndromes. Positive results of US Phase 3 clinical trial in treatment of Dravet Syndrome – a rare and severe form of epilepsy in children with no FDA-approved treatments.

Sativex® has now been launched in 15 countries (including the UK, Canada, Spain, Italy and Germany) and approved in a further 12 (by rx).

Inflammation

- Cannabinoids (THC & CBD) have substantial antiinflammatory effects
- CBD is a useful target for rheumatoid arthritis and inflammatory diseases of the gastrointestinal tract (e.g., ulcerative colitis, Crohn's) as it lacks psychoactive effects

AIDS-anorexia/wasting syndrome

- marijuana improves appetite and weight gain (FDA-approved cannabinoid tx)
- no long-term evidence of sustained effect of marijuana on AIDS morbidity/mortality



Nausea

- THC may be effective antiemetic agent in chemotherapy (FDA-approved cannabinoid tx)
- patients report relief from nausea

Chronic Pain

- Marijuana is effective in neuropathic pain even at low levels of THC (1.29%)
- Marijuana and dronabinol are both effective in decreasing pain sensitivity

Multiple sclerosis

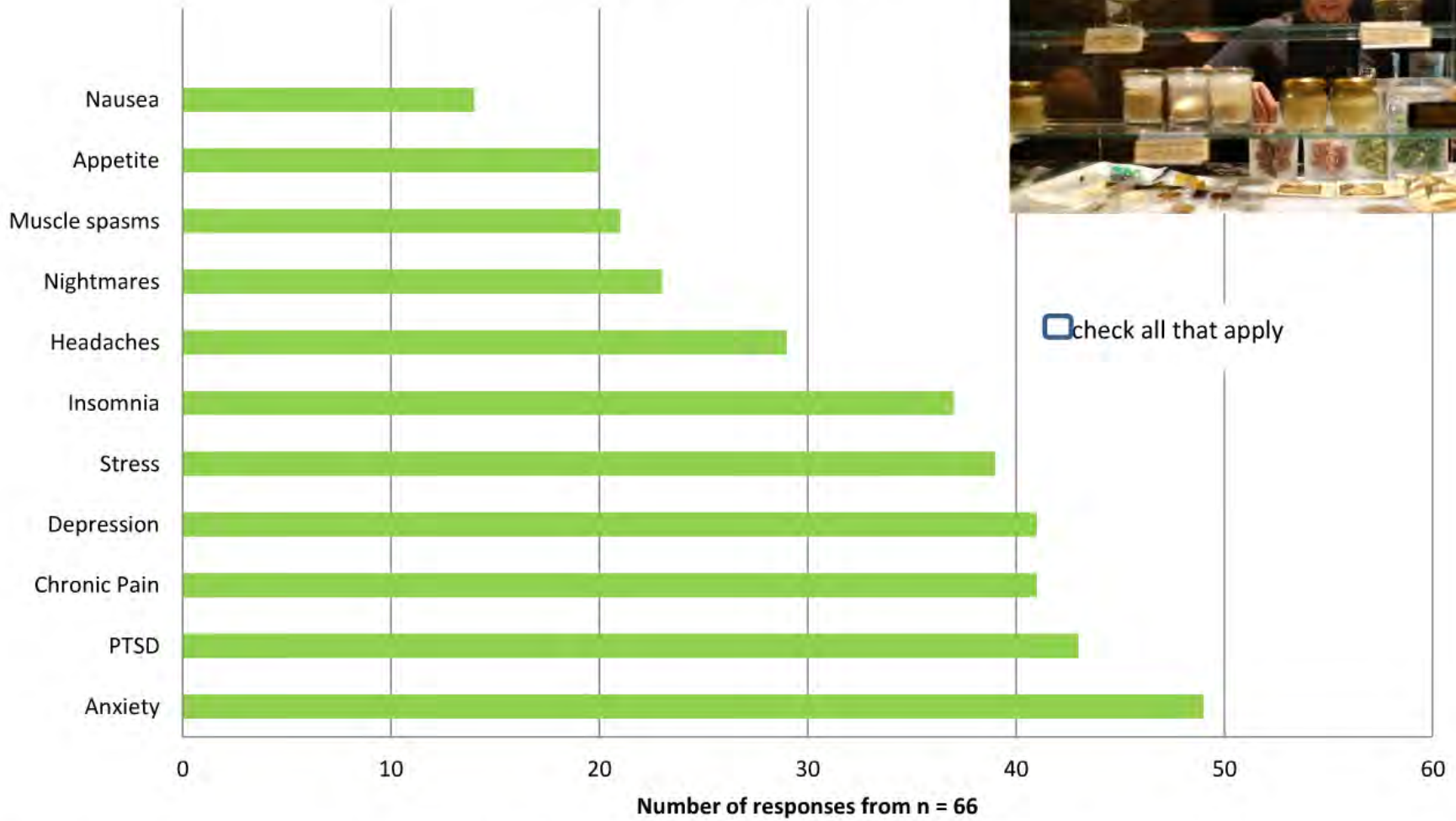
- Nabiximols (Sativex®, GW Pharma), oromucosal spray of THC+CBD, effective for neuropathic pain, disturbed sleep, and spasticity in MS (Phase 3 clinical trials in the US). Also nabilone and dronabinol
- Nabiximols is now also in development in the US for cancer pain (Phase 3 clinical trials)

HIGH QUALITY EVIDENCE

Research focused on compounds that modulate the endocannabinoid system will lead to novel therapeutic approaches in a number of diseases for which current treatments do not fully address the patients' need.

Sources:
JAMA. 2015; 313 (24): 2474-83 and JAMA. 2015;313(24):2456-2473
N ENGL J MED 2014; 370 (23): 2219-27.
Marijuana and Cannabinoids: A Neuroscience Research Summit by the NIH

What condition(s) led you to seek out medical marijuana?

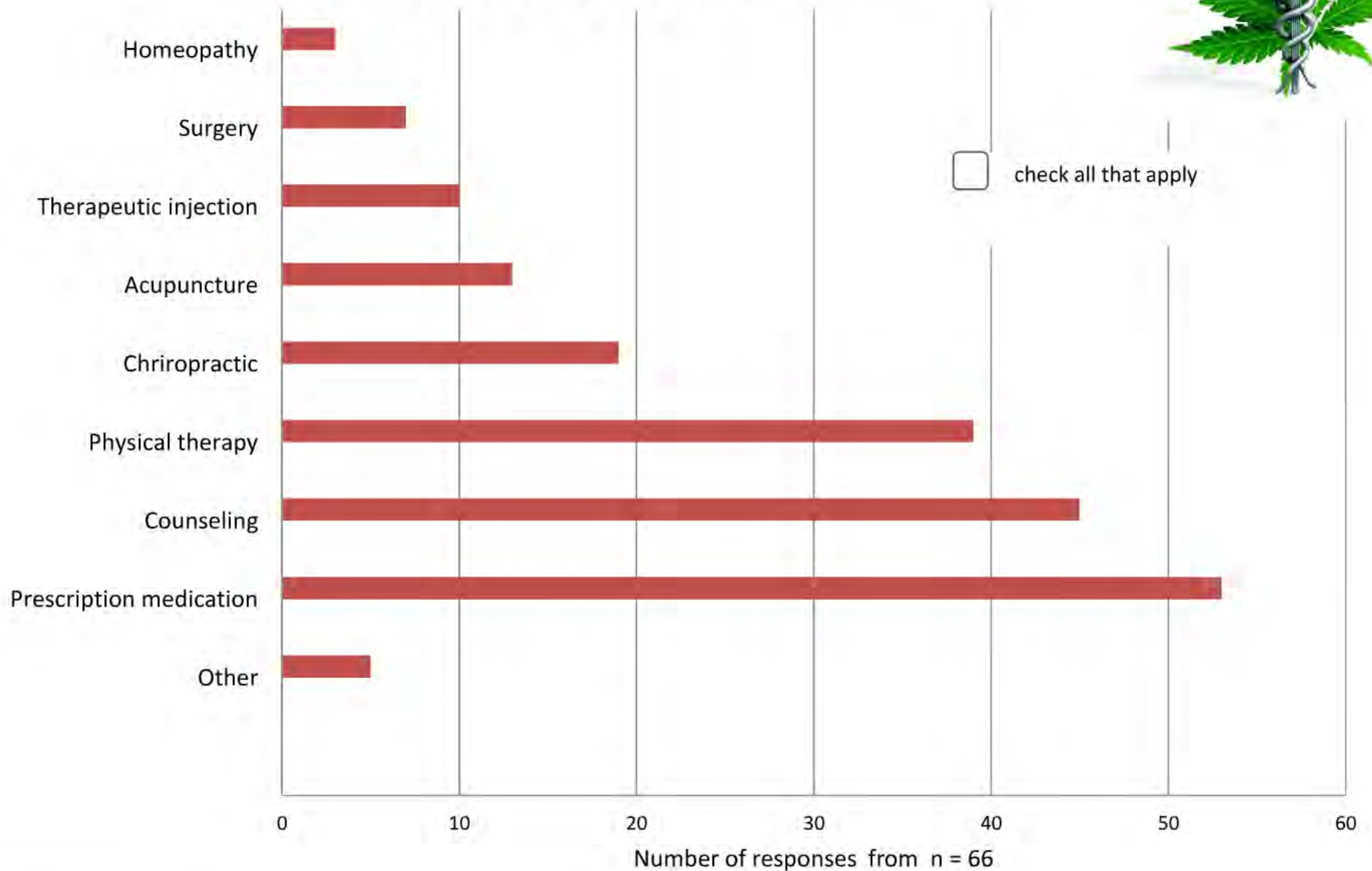


check all that apply

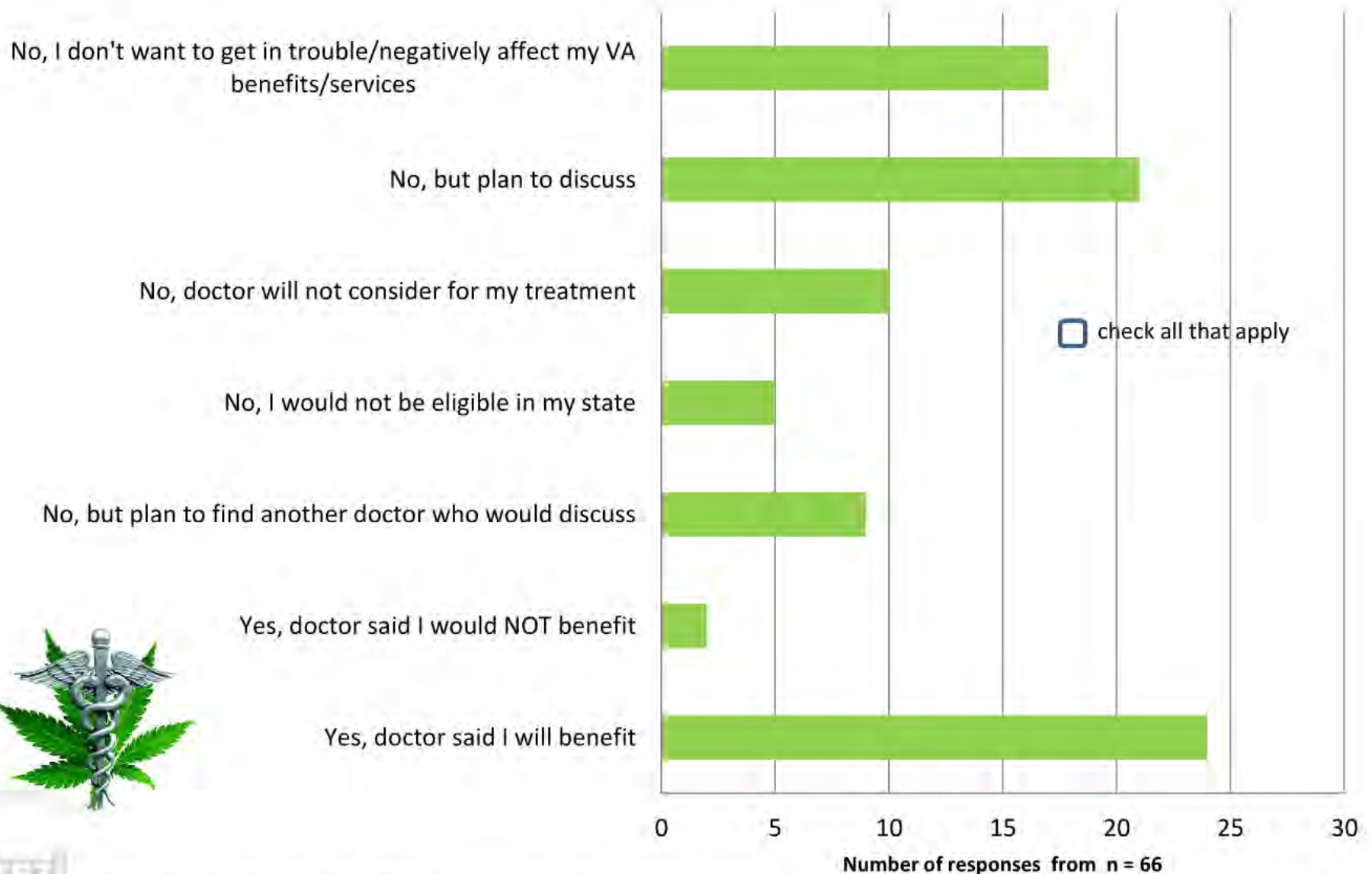
How well has marijuana helped your condition(s)?



Have you tried any of these treatments for your medical condition?



Have you discussed using medical marijuana with your doctor?

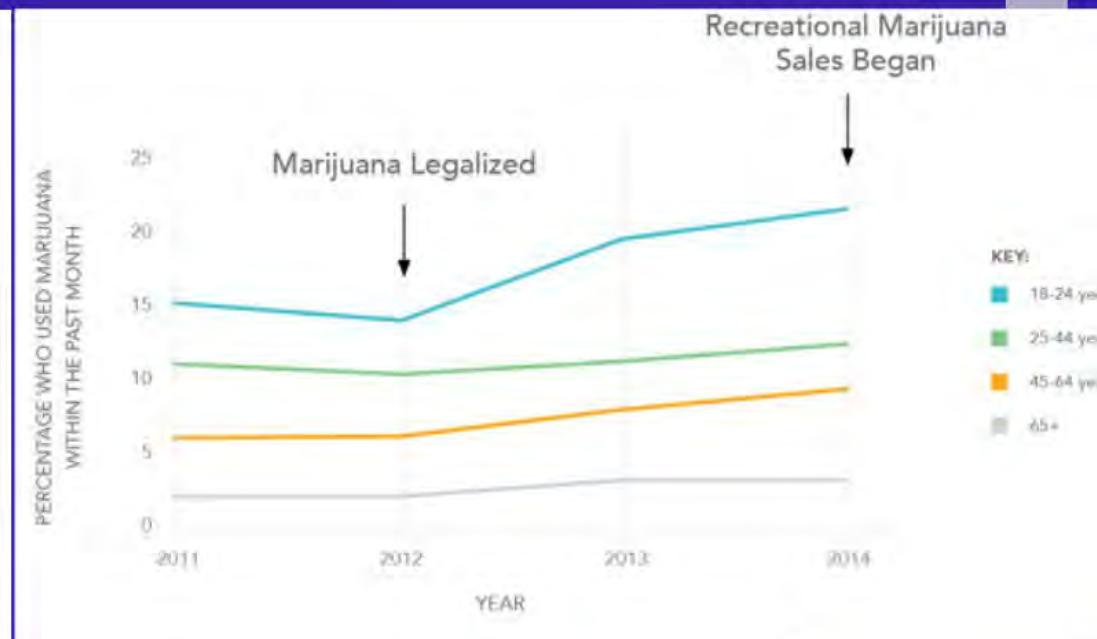
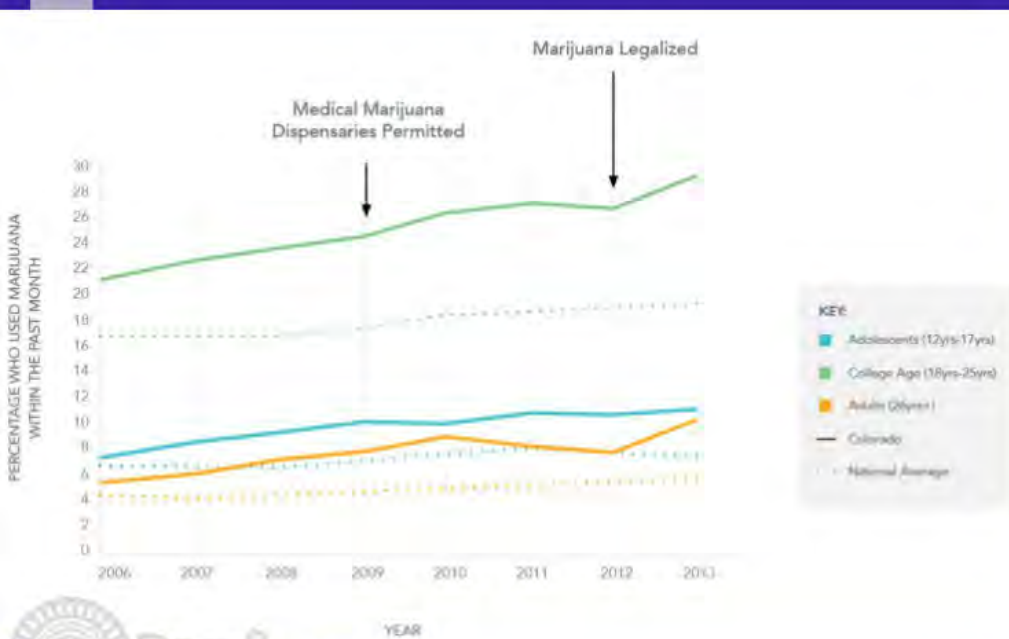


Evidence-Based Recommendations for Lowering Risk from Marijuana Use

1. Abstain
2. Delay initiation of use
3. Use marijuana with low THC content
4. Avoid synthetic cannabinoids
5. Alternative (to smoking) method of delivery (i.e., vaping)
6. Reduce frequency of use to occasional
7. Avoid driving within at least 6 hours of use
8. Avoid use if positive family history for psychosis, SUD, or if pregnant
9. Do not mix with alcohol

Data from WA and CO

- States with medical marijuana laws have higher rates of cannabis use and cannabis use disorder (Cerdá et al., 2012)
- Increasing use among young adults (Hall & Lynskey, 2016)
- Increased potency in states with medical marijuana laws (Sevigny et al., 2014)



Legalizing Marijuana in Rhode Island: Lessons learned from other states

- Potency likely to increase: regulating THC content?
- May reduce racial disparity in arrests
- Frequency of use likely to increase among current users, young adults
- Unintentional access to minors
- Motor-vehicle accidents and deaths



Behavioral economics of marijuana use

Price elasticity of illegal versus legal cannabis: a behavioral economic substitutability analysis

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The study used a behavioral economic approach to inform price policy for legal cannabis by investigating the effects of cannabis legalization on use of cannabis from illegal sources.

How will legalization impact the illegal cannabis market? Will illegal cannabis serve as a substitute for legal cannabis?

A substitution-based marijuana purchase task assessed estimated cannabis consumption from concurrently available legal (a dispensary) and illegal (a dealer) sources. Prices of the two options were reciprocally either held constant (\$10/gram) or escalated (\$0–\$60/gram). Adult cannabis users who were at least 21 years old from US states with legalized recreational cannabis ($n = 724$; mean age = 34.13; 52% female; 74% Caucasian) were recruited using online crowdsourcing.

Optimizing pricing policy on legal cannabis

Legal cannabis was considered a superior commodity to illegal cannabis, as indicated by increased unconstrained demand for legal cannabis that was 29% higher than illegal cannabis and price elasticity that was 43% lower for legal cannabis (less elastic) compared to illegal cannabis.

The presence of legal cannabis substantially decreased demand for illegal cannabis, but the reverse effect was significantly different and much smaller.

Conclusions: introduction of legal cannabis into the market is likely to disrupt and potentially reduce illegal purchases unless the price of the legal product is too high.

Pricing policy will need to be optimized to maximize the benefits of a legally regulated cannabis marketplace. Lawmakers will need to 'thread the needle' of identifying the best prices to both suppress the contraband market (avoid over-pricing) and not inadvertently encourage greater use (avoid underpricing). This will vary across regions and over time, but the current data suggest \$8–\$14/gram would optimize the balance.

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