Scientific and Clinical Perspectives on Cannabis Use: A Q&A Puff through the Literature

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October 25, 2017

Disclosures

- We have no relevant disclosures

Case 1

Tom is brought to our office by his girlfriend, Jenn. He is a 19 year old student in his first year at UCLA. He uses alcohol and cannabis most days, reason for his partner bringing him in. Tom claims that the use of these substances do not cause him any difficulties. He has been consuming almost daily since being a freshman in high school and he has it under control, to the point that he was even accepted into UCLA.

Case 1.

Jenn states Tom has dropped half of his classes this quarter. He wakes up each morning and the first thing he does is look for his marijuana pipe, and this continues throughout the day, maybe smoking 4 or 5 times. He drinks almost every night but does not “need an eye-opener” in the morning. He stopped drinking a couple of times for about a week, but quickly started again after going to parties. On multiple occasions he has driven after having 5 or 6 beers or smoking marijuana and this scares her. She has never seen him use any other drugs.

Case 1.

- Does Tom have a substance use disorder (SUD) and to what?

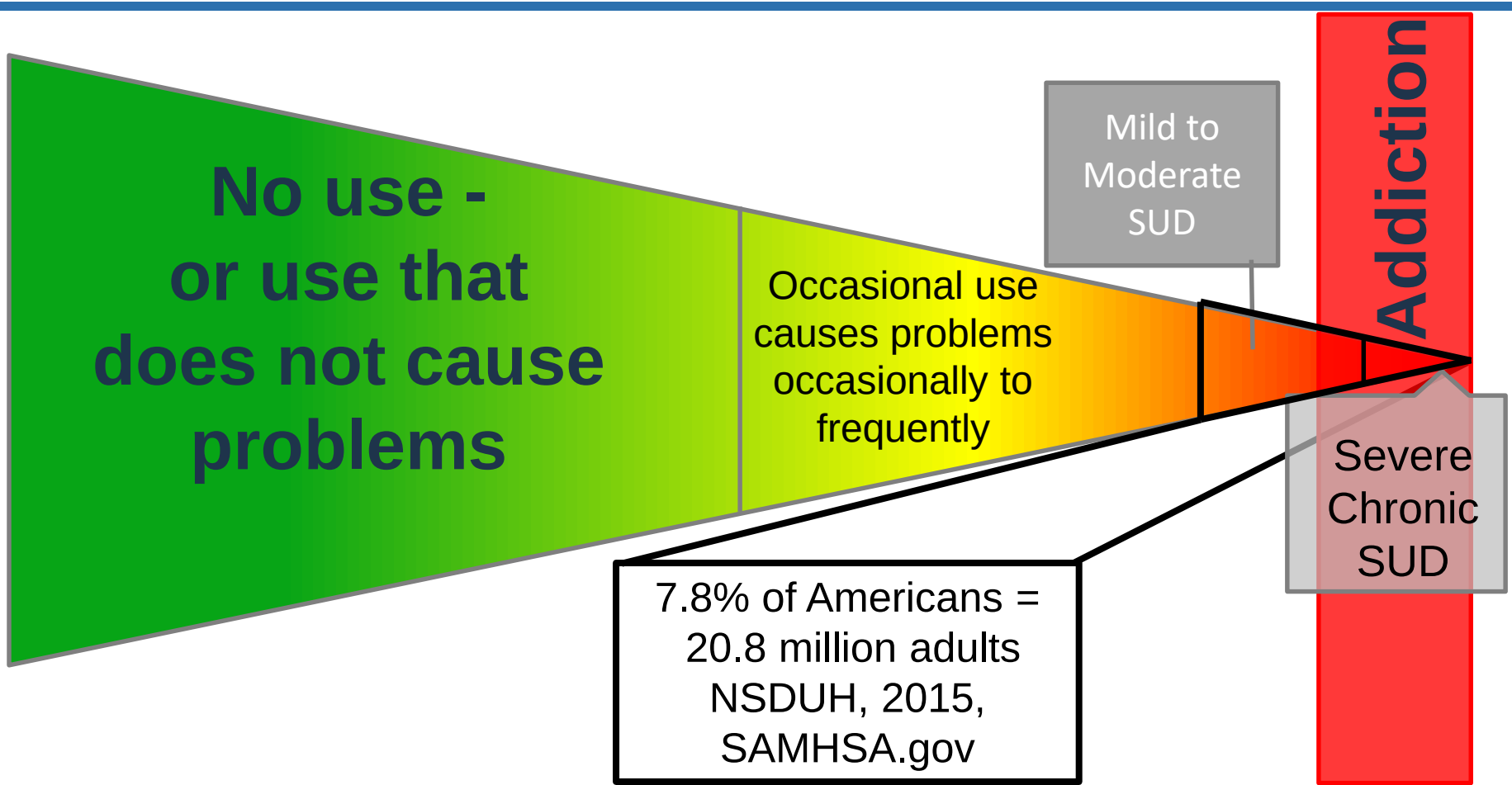
A. No, he is an average college student

B. Yes, he has a SUD but only to marijuana

C. Yes, he has a SUD but only to alcohol

D. Yes, he has a SUD to both marijuana and alcohol

Definitions of a Spectrum: Substance Use to SUD



DSM-5 Definition: Substance Use Disorder

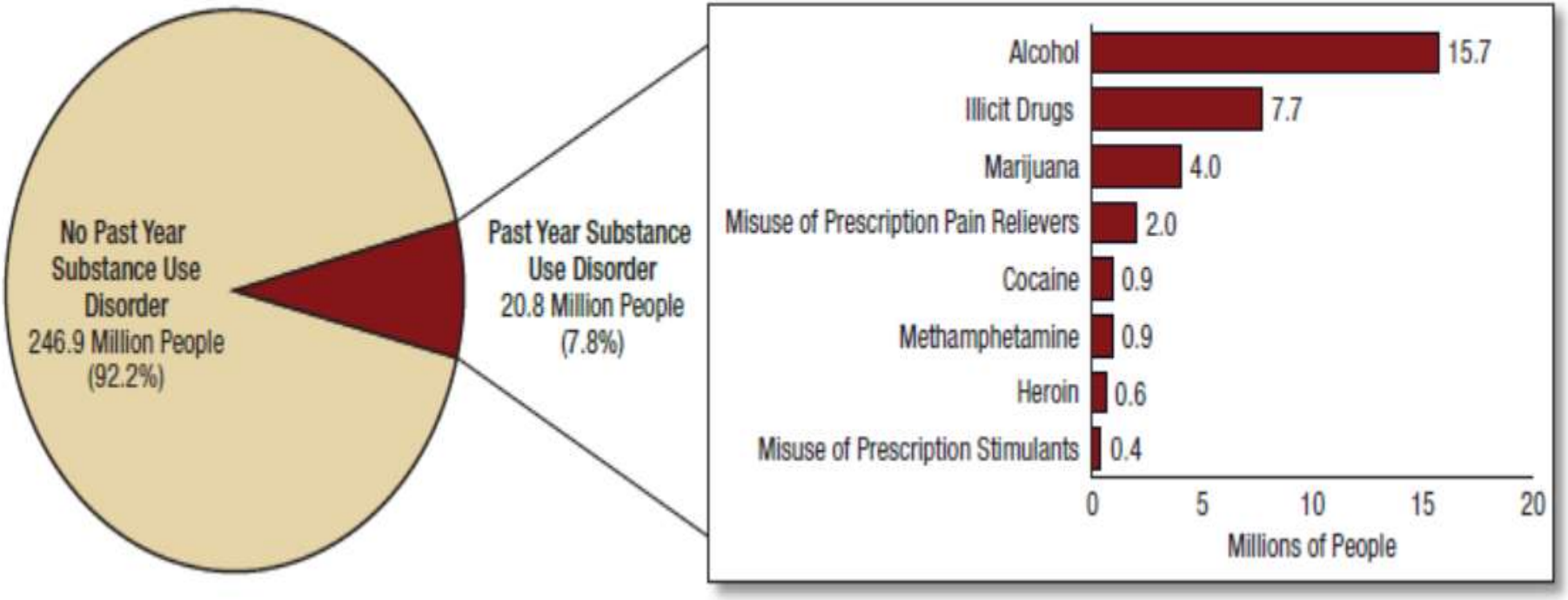
Maladaptive pattern of use, *clinically significant impairment or distress* and 2+ of the following in the same 12-month period:

1. Tolerance
2. Withdrawal
3. Used for longer periods than intended
4. Can't cut down or quit
5. Time spent getting, using or recovering
6. Give up social, work or fun activities
7. Craving or a strong desire or urge to use a substance
8. Continued use despite knowledge of negative consequences
9. Failure to fulfill major role obligations
10. Use in physically hazardous situations
11. Continued use despite social and interpersonal problems

Mild = 2-3 criteria; Moderate = 4-5 criteria; Severe = 6+ criteria

Substance Use Disorder Prevalence, 2015

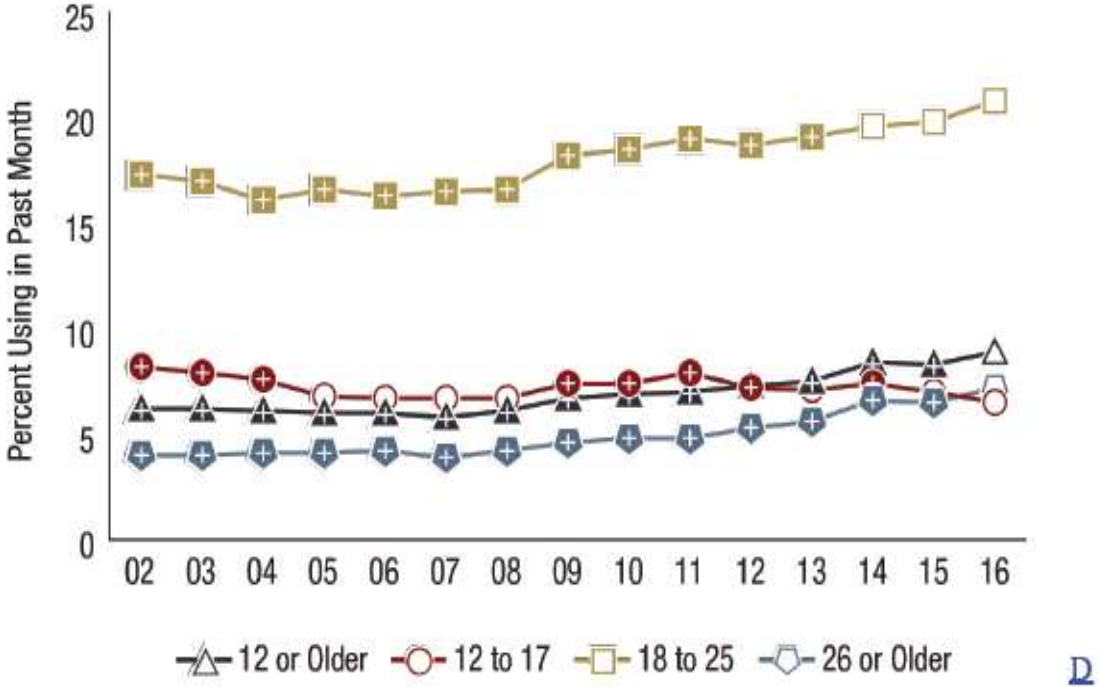
Figure 27. Numbers of People Aged 12 or Older with a Past Year Substance Use Disorder: 2015



www.samhsa.gov

Epidemiology: Current Use

Figure 17. Past Month Marijuana Use among People Aged 12 or Older, by Age Group: Percentages, 2002-2016

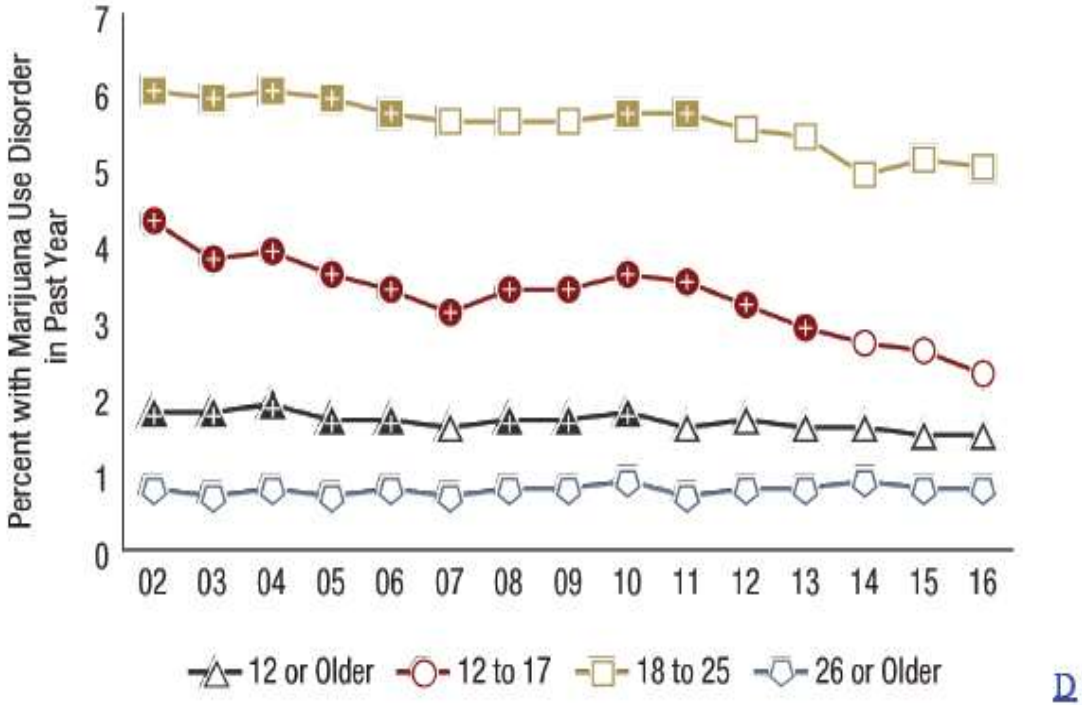


[+] Difference between this estimate and the 2016 estimate is statistically significant at the .05 level.

SAMHSA.gov; NSDUH, 2016

Marijuana Use Disorder

Figure 37. Marijuana Use Disorder in the Past Year among People Aged 12 or Older, by Age Group: Percentages, 2002-2016



+ Difference between this estimate and the 2016 estimate is statistically significant at the .05 level.

SAMHSA.gov; NSDUH, 2016

Case 1.

Tom is enrolled in a substance use treatment program. After 1 year of counseling and group therapy, he has been able to cut down his drinking, only rarely drinking in social situations. He has stopped drinking and driving. He is fully enrolled this quarter in all of his classes. He broke up with Jenn, things just didn't work out, but is very grateful to her for bringing him initially in. He does continue to smoke marijuana but only at nights. He occasionally will eat THC bars during the day. He doesn't want to quit. He feels it helps him relieve the stress of his school work.

Cannabis Species

sativa

indica

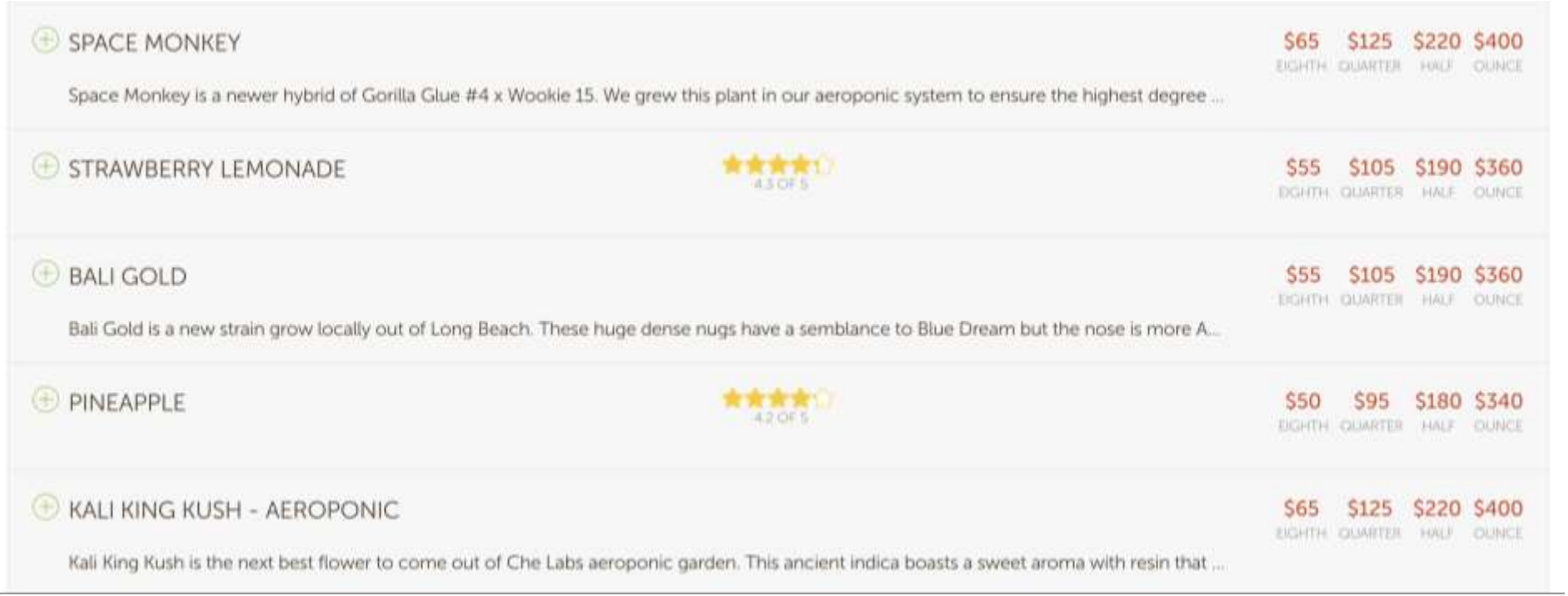
ruderalis

Cannabis Species

Cannabis Products

- Flower/bud
- Edibles
- Vaporizer
- Concentrates
  - Hash/wax/dabs
- Capsules/pills
- Sprays/tinctures

Cannabis Prices



		EIGHTH	QUARTER	HALF	OUNCE
SPACE MONKEY		$65	$125	$220	$400
Space Monkey is a newer hybrid of Gorilla Glue #4 x Wookie 15. We grew this plant in our aeroponic system to ensure the highest degree ...					
STRAWBERRY LEMONADE	4.5 OF 5	$55	$105	$190	$360
BALI GOLD		$55	$105	$190	$360
Bali Gold is a new strain grow locally out of Long Beach. These huge dense nugs have a semblance to Blue Dream but the nose is more A...					
PINEAPPLE	4.2 OF 5	$50	$95	$180	$340
KALI KING KUSH - AEROPONIC		$65	$125	$220	$400
Kali King Kush is the next best flower to come out of Che Labs aeroponic garden. This ancient indica boasts a sweet aroma with resin that ...					

Case 2.

Tom is now in his 3rd year of college at UCLA. He continues to smoke marijuana daily. And he has been doing well in school. He is now brought in by his girlfriend Pam. She is concerned because Tom is now trying other forms of marijuana. He was in downtown LA and got some “legal marijuana” at a corner store. It came in a little package called K2. She doesn’t like him using this because he goes into a blank stare for hours or sometimes gets really agitated.

Case 2.

What should you advise?

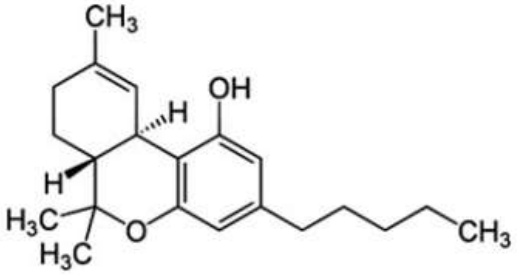
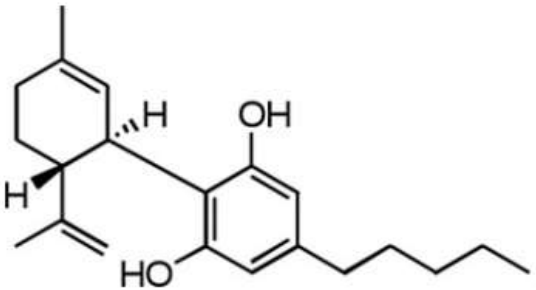
A. He is using a legal form of marijuana, so it is probably safe for him to continue

B. It is probably the increase in THC what is causing Tom's symptoms, he should probably just cut back or switch to a strain containing more CBD

C. He is using synthetic marijuana, a much more dangerous form, he should definitely stop

D. He has been smoking any form of marijuana to long, he should stop all marijuana containing products

Active Compounds in Cannabis

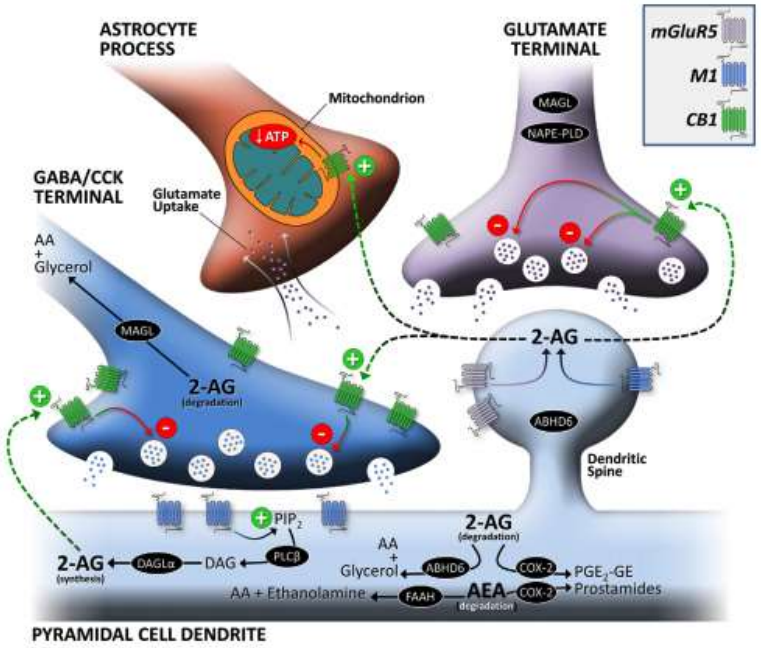
Cannabinoid Type	Chemical Structure	Pharmacological Actions	Potential Targets
Δ^9-Tetrahydrocannbinol (Δ^9-THC)		Anticonvulsant Euphoria Psychoactive Analgesic Cognitive modulation Reduces muscle spasms Reduces nausea Stimulates appetite	CB_1 partial agonist CB_2 partial agonist TRPA1 agonist TRPV2 agonist TRPM8 antagonist $\alpha_1\beta$Gly enhancer 5-HT_{3A} antagonist PPAR-γ activator GPR18 agonist GPR55 agonist
Cannabidiol (CBD)		Anticonvulsant Analgesic Anti-inflammatory Antitumorigenic Neuroprotective Reduces nausea Immune modulation	CB_1 ligand CB_2 ligand TRPA1 agonist TRPV1-3 agonist TRPV4 agonist TRPM8 antagonist 5-HT_{3A} antagonist

Reddy DS, Golub VM. J Pharmacol Exp Ther 357:45–55 2016

Endocannabinoid Receptors: CB1/CB2

Endocannabinoid System

- Anandamide and AG-2



Biol Psychiatry. 2016 Apr 1;79(7):516-25.

CB1 Locations:

- Cortex
- Basal ganglia
- Hippocampus
- Cerebellum
- Spinal cord
- Vagal nerve
- Fat (adipocytes)
- Liver
- Pancreas
- Skeletal muscle

CB2 Locations:

- Immune cells
- Macrophages
- CNS
- Vascular

J Neuroendocrinol. 2008 May;20 Suppl 1:10-4

Endocannabinoid Receptors: CB2

Cell type	Effect of CB_2 activation
Immune cells	
Macrophages	diminished release of NO, IL-12p40 and TNFα
Macrophages	prevented ROS production and secretion of TNFα and CCL2
B and T cells	affected B and T cell differentiation, and the balance of pro-inflammatory to anti- inflammatory cytokines
Macrophages	increased secretion of the anti- inflammatory cytokine, IL-10
Macrophages (Kupffer cells)	inhibited LPS-induced NF-kB activation

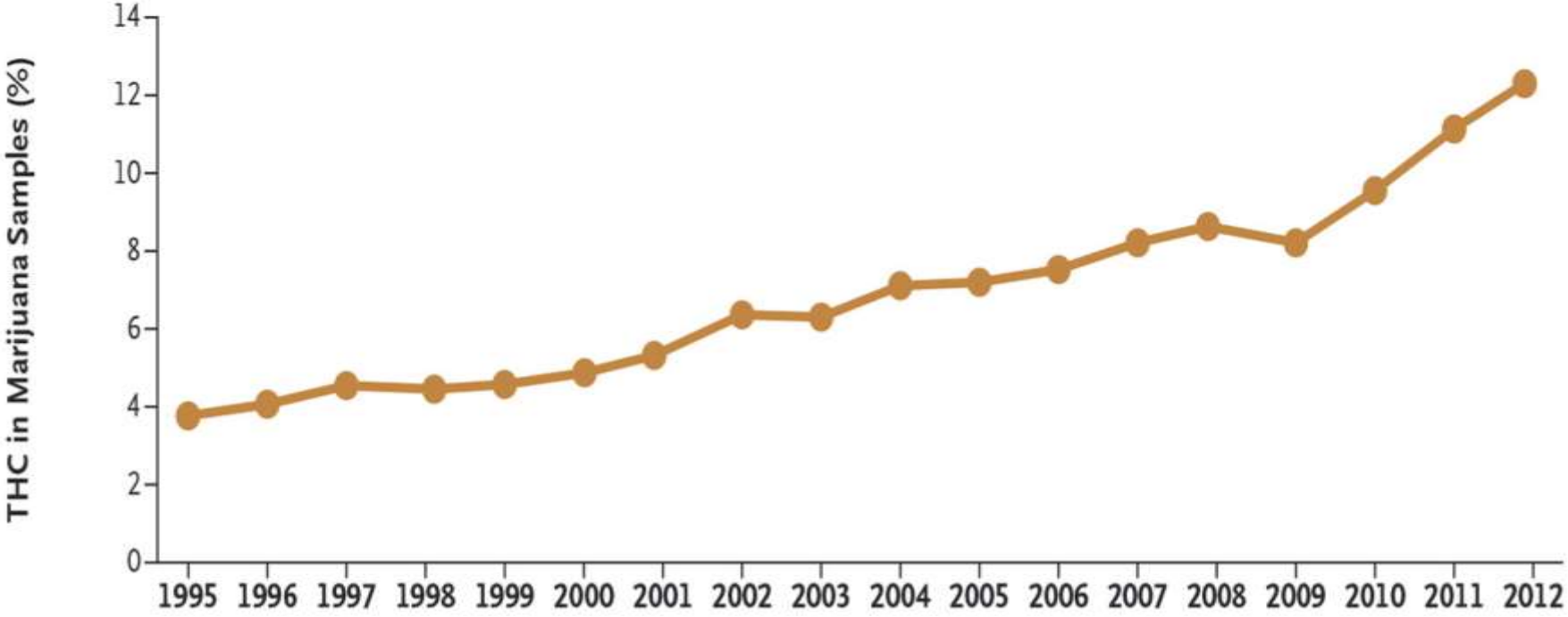
J Neuroimmune Pharmacol. 2013 June ; 8(3): 608–620

Endocannabinoid Receptors: CB2

Cell type	Effect of CB_2 activation
Neuroimmune	
Microglia	diminished levels of IL-1β, IL-6 and TNFα
Microglia	inhibited release of TNFα
Microglia	diminished expression of CD40
Glia	enhanced release of the anti-inflammatory factors, IL-4 and IL-10
Microglia	inhibited TNFα production, p38 MAPK activation and NADPH oxidase (NOX) activation
Microglia	interfered with expression of CCR2 and iNOS
Microglia	inhibited migration of microglial cells to HIV Tat protein

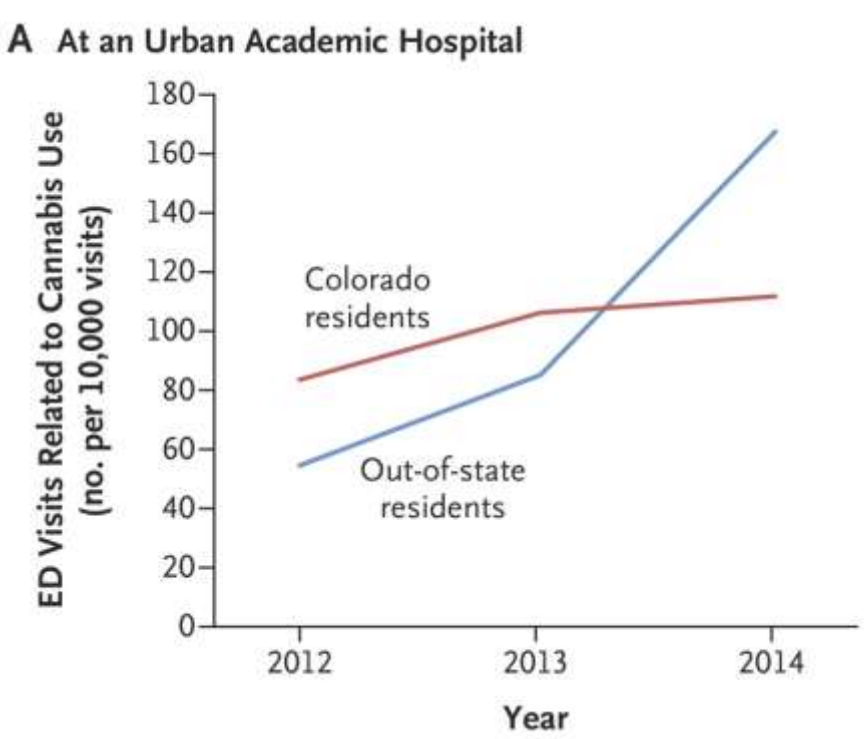
J Neuroimmune Pharmacol. 2013 June ; 8(3): 608–620

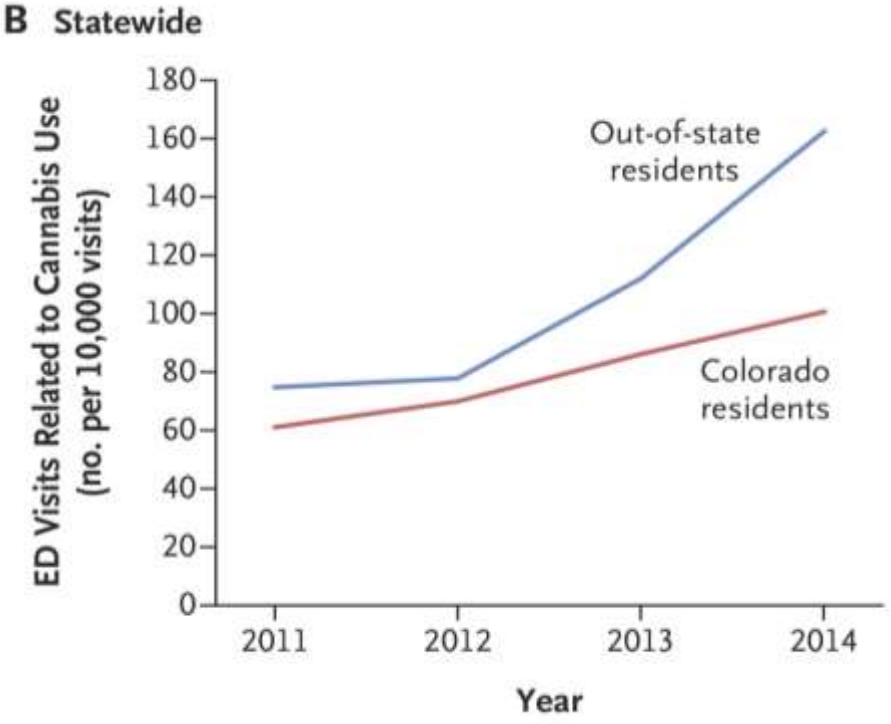
Potency of THC over Time



Volkow N et al. N Engl J Med 2014; 370:2219-2227

ED Visits in Colorado: Early Legalization





Volkow N et al. N Engl J Med 2014; 370:2219-2227

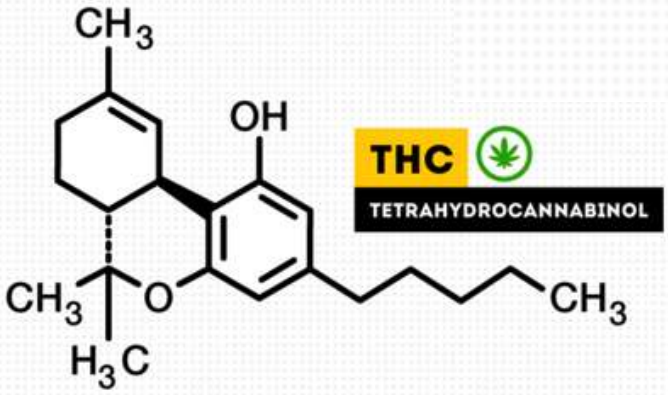
Synthetic Marijuana (Cannabinoids)

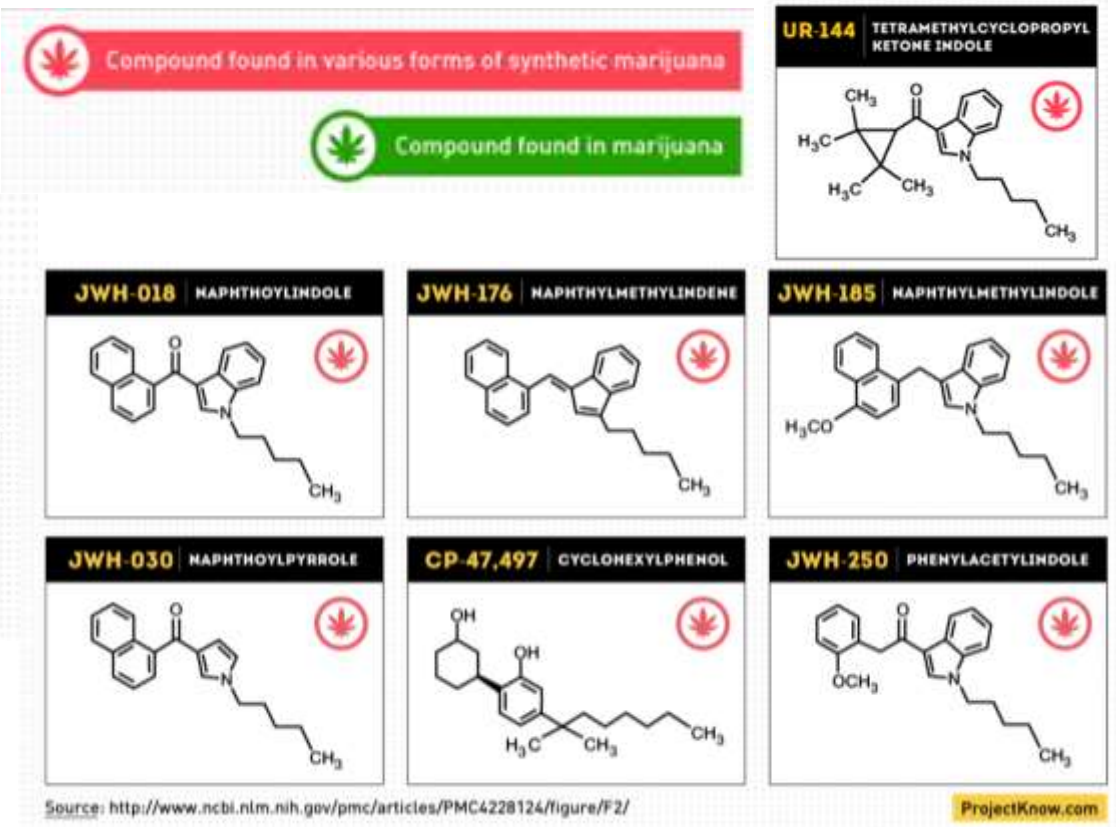
- Also known as K2, spice, AK-47 among many other brands
- Structurally distinct from THC
- High affinity for CB1 receptors
- Caused:
  - Zombie-like outbreak in NYC (AMB-FUBINACA)[1]
  - Multiple overdoses in LA (Skid row)
    - 2016 Senate Bill 139: Crime to possess synthetic cannabinoids
  - Seizures
  - ED visits

[1] N Engl J Med 2017; 376:235-242

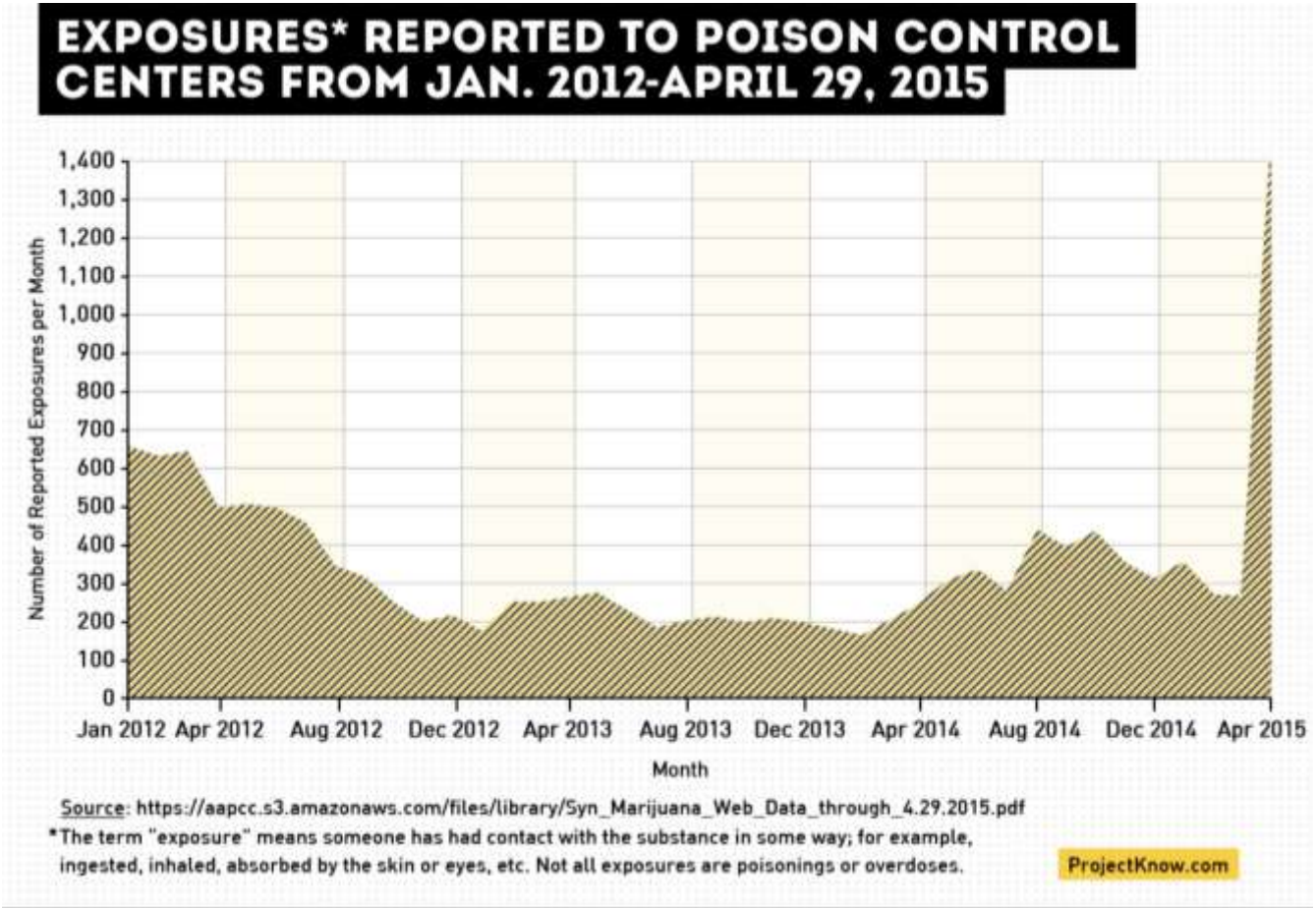
Synthetic Marijuana

Synthetic Marijuana: Chemical Structure





Synthetic Marijuana Exposures



Case 3.

Tom, now 29, has graduated and has been working at a successful firm. Things didn't work out with Pam, but he has been dating Jim for the past 4 years. Tom continues to smoke every night, but never before work. Jim is concerned that he has been smoking for so long know.

- For sure it has some negative effect on his brain? - Jim asks – Like its gotta' affect his intelligence or 'cause him to be schizo' or bipolar, right?

Case 3.

What effects does marijuana use have on mental health or behavior?

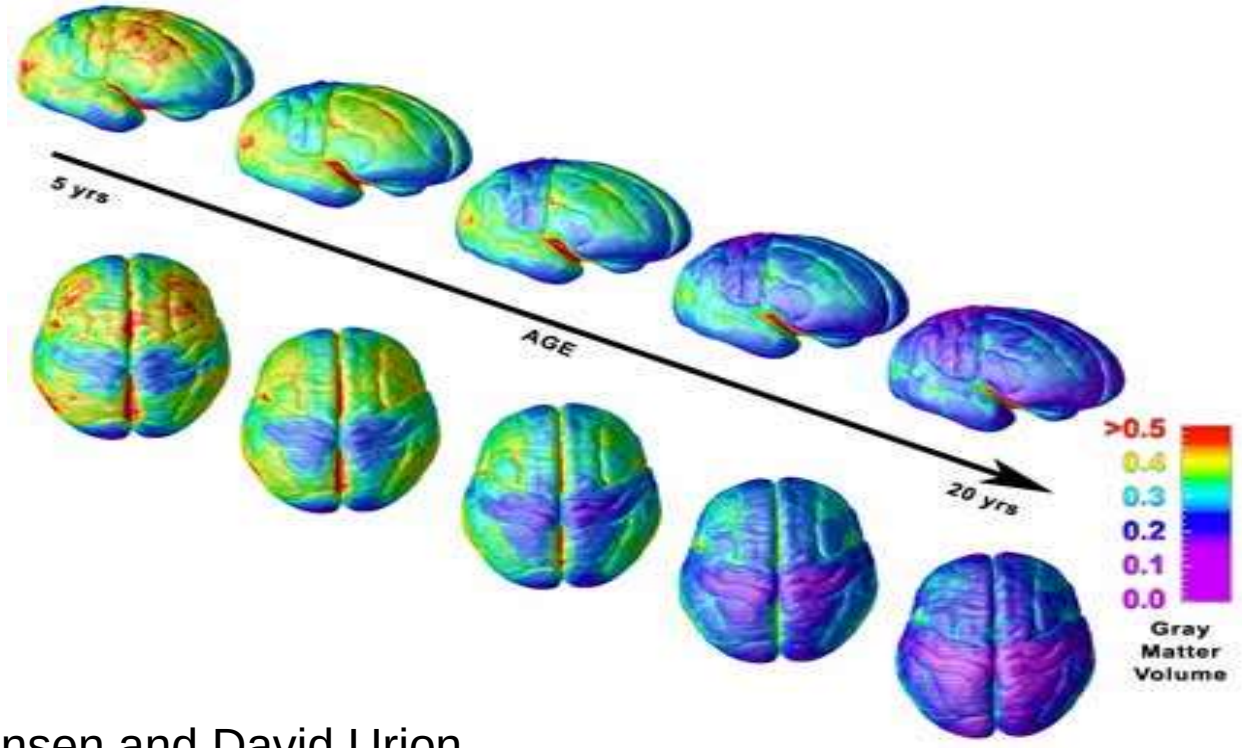
A. Marijuana use has an irreversible negative effect on IQ

B. Marijuana use has been associated with bipolar disease

C. Marijuana use has been associated with schizophrenia

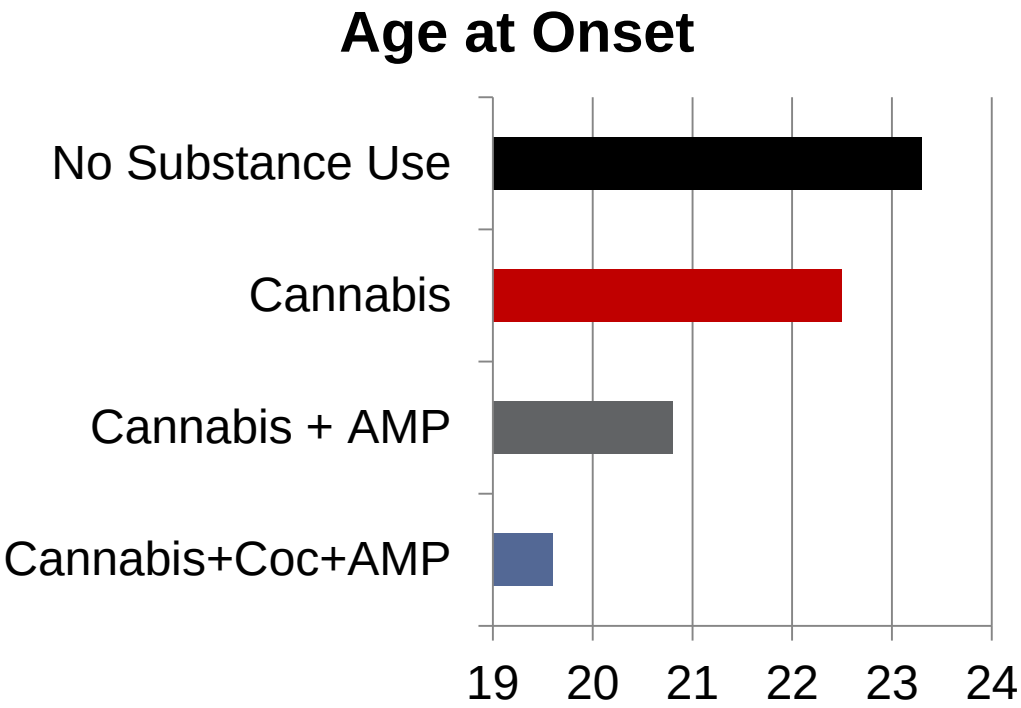
D. Marijuana use has been associated with increased sexual risk behavior

Brain Development



Frances Jensen and David Urion

Substances and Incident Schizophrenia



Power BD et al., 2013. *Aust N Z J Psychiatry. 47*:51-8. [N=167]

Replication of this finding from large cohort [N=785] of Dutch patients (Dekker et al., 2012)

In 63.5% of cannabis using patients, most intense period of use preceded incident break by 1+ years.

Effect not as consistent for depression disorders (Manrique-Garcia et al., *BMC Psychiatry* 2012

Substances and Incident Bipolar

In 118 Australian first episode psychotic mania, substance use (cannabis) and forensic issues were predictive for males; sexual abuse and trauma for females (Cotton et al. *BMC Psychiatry.* 2013 Mar *13*:82)

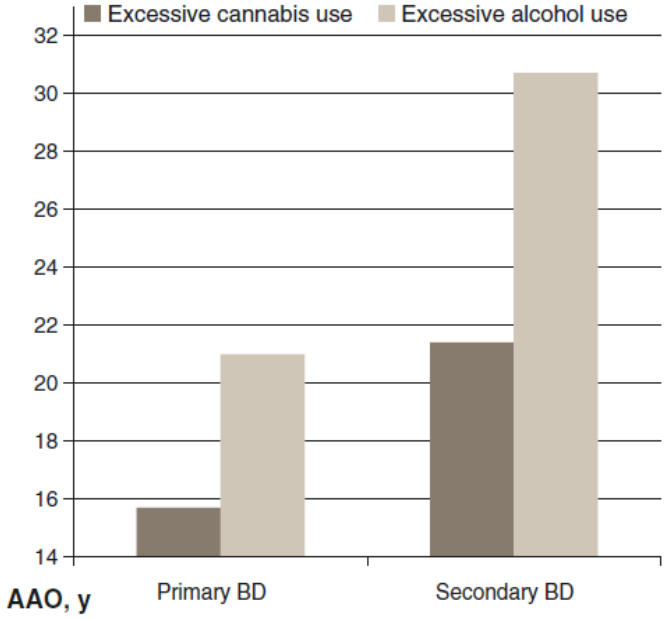


Fig. 1 The relationship between age at onset (AAO), sequencing and type of substance use. *y* years

Lagerberg et al., 2011, *Eur Arch Psychiatry Clin Neurosci. 261*:397-405

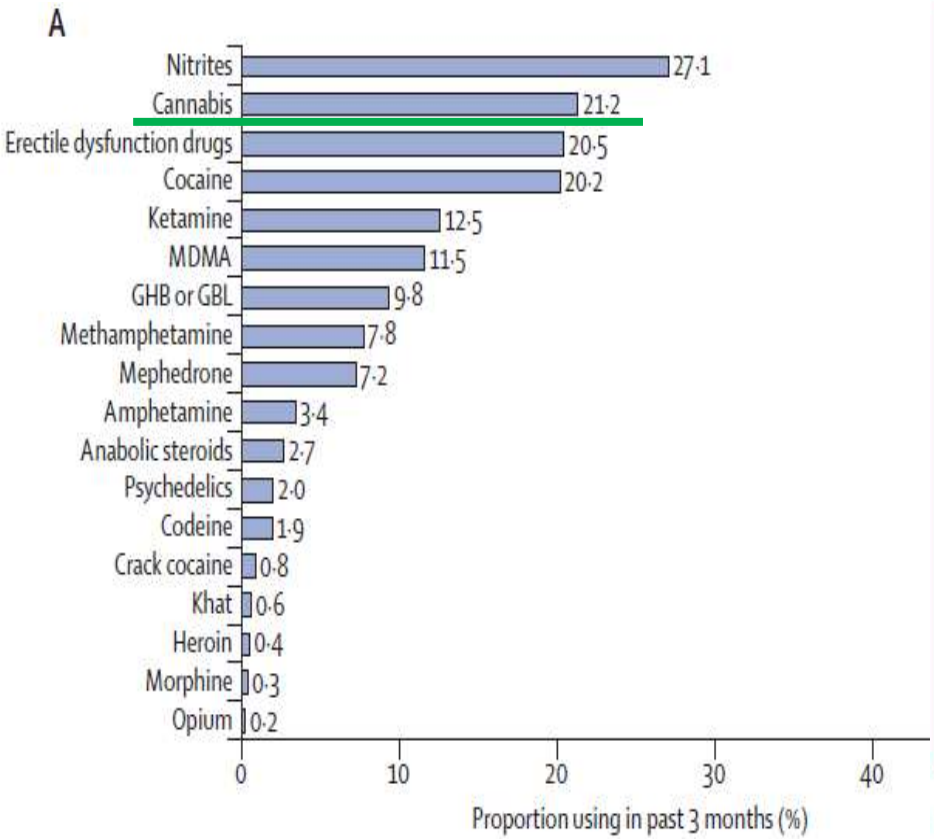
Dunedin Study: IQ and Marijuana

Table 1. IQ before and after cannabis use

	N	% male	Age 7–13 full-scale IQ	Age 38 full-scale IQ	Δ IQ effect size*
Persistence of cannabis dependence					
Never used, never diagnosed	242	38.84	99.84 (14.39)	100.64 (15.25)	0.05
Used, never diagnosed	479	49.48	102.32 (13.34)	101.25 (14.70)	−0.07
1 diagnosis	80	70.00	96.40 (14.31)	94.78 (14.54)	−0.11
2 diagnoses	35	62.86	102.14 (17.08)	99.67 (16.11)	−0.17
3+ diagnoses	38	81.58	99.68 (13.53)	93.93 (13.32)	−0.38
Persistence of regular cannabis use					
Never used	242	38.84	99.84 (14.39)	100.64 (15.25)	0.05
Used, never regularly	508	50.59	102.27 (13.59)	101.24 (14.81)	−0.07
Used regularly at 1 wave	47	72.34	101.42 (14.41)	98.45 (14.89)	−0.20
Used regularly at 2 waves	36	63.89	95.28 (10.74)	93.26 (11.44)	−0.13
Used regularly at 3+ waves	41	78.05	96.00 (16.06)	90.77 (13.88)	−0.35

Meier et al., *PNAS, 2012*

ASTRA: Substance Use and Sex Risks



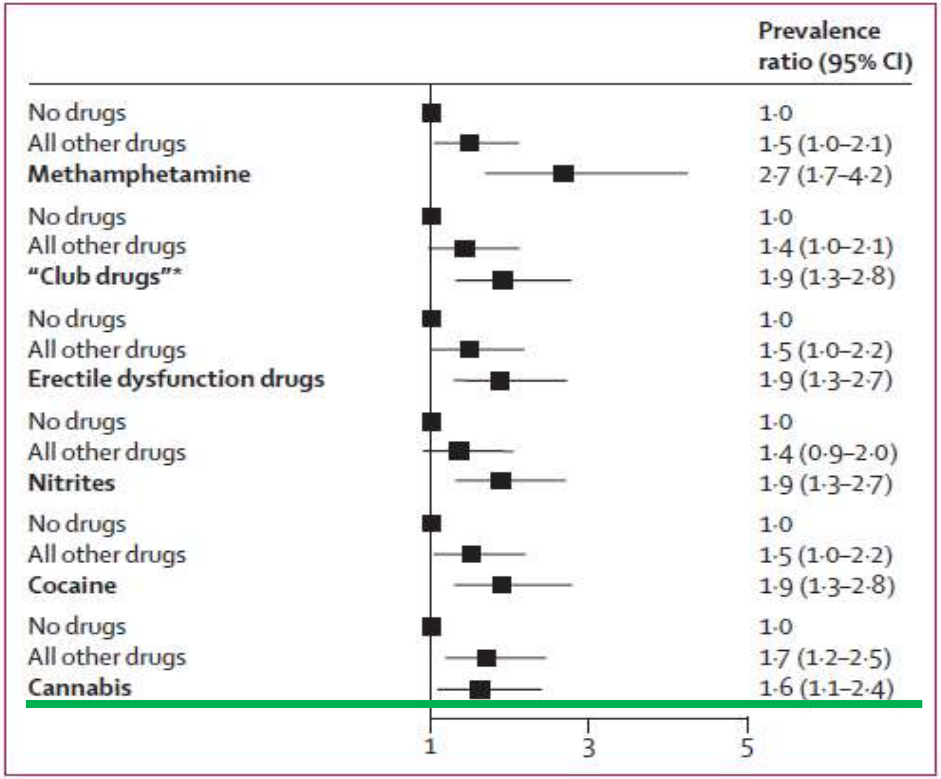


Figure 3: Adjusted prevalence ratios for the association of use of specific drugs in the past 3 months with higher-HIV-risk condomless sex with a serodiscordant partner

Daskalopoulou et al., 2014, *Lancet HIV,* Oct;1(1):e22-31

Case 4.

Tom, now 35, has been gaining weight. He has been working a lot and has been promoted. He has been going to several work lunches and meetings where they always have donuts. Things didn't work out with Jim, he thinks it was because of his weight gain.

People have told him he has been gaining weight from all the marijuana he has been smoking, and that he will probably get diabetes.

Case 4.

Is Tom's weight gain from his marijuana use? Is he at increased risk for diabetes?

A. Of course, marijuana -> munchies -> weight gain -> diabetes
B. No, marijuana has an anti-inflammatory effect protecting him from diabetes
C. It will make him gain weight, but not get diabetes
D. I don't know.

Cannabis Use and Cardiometabolic Risk Factors, NHANES

n=6281

Dependent variables	Past use		Current use	
	Mean	SE	Mean	SE
Insulin (μU/mL)	−0.046	0.027	−0.116**	0.037
HOMA-IR	−0.059	0.030	−0.108**	0.039
Glucose (mg/dL)	−1.503	0.866	1.324	1.472
Triglycerides (mg/dL)	−0.009	0.022	0.022	0.035
HDL-C (mg/dL)	−0.110	0.503	0.726	0.621
BMI (kg/m^2)	0.051	0.223	−0.771*	0.340
Waist (cm)	0.475	0.528	−2.120*	0.885
SBP (mm Hg)	−1.045	0.560	0.251	0.785
DBP (mm Hg)	0.080	0.448	0.513	0.672

DBP = diastolic blood pressure; SBP = systolic blood pressure; SE = standard error.
*$p < .05$; **$p < .01$.

Annals of Epidemiology 25 (2015)

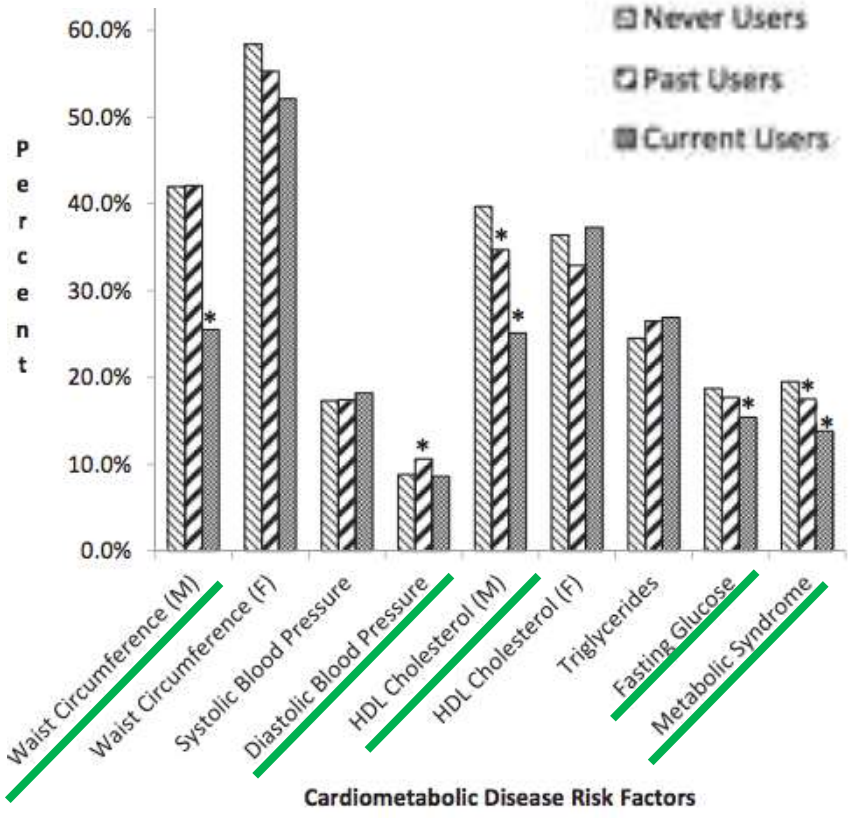
Cannabis Use and Metabolic Syndrome, NHANES

n=3051

Variable	Marijuana use Odds ratio (95% CI)	
	(A) Years of use	(B) Regular user
Metabolic syndrome	**1.05** (1.01, 1.09)	0.25 (0.06, 1.02)
Abdominal obesity	1.03 (0.99, 1.07)	0.42 (0.13, 1.36)
Hypertension	**1.05** (1.02, 1.09)	**0.26** (0.10, 0.67)
Hyperglycemia	1.02 (0.98, 1.06)	0.50 (0.13, 1.89)
Hypertriglyceridemia	**1.03** (1.01, 1.06)	0.76 (0.15, 3.97)
Low HDL cholesterolemia	1.02 (0.99, 1.05)	0.54 (0.18, 1.55)

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 10S (2016) S89–S95

Cannabis Use and Metabolic Syndrome, NHANES

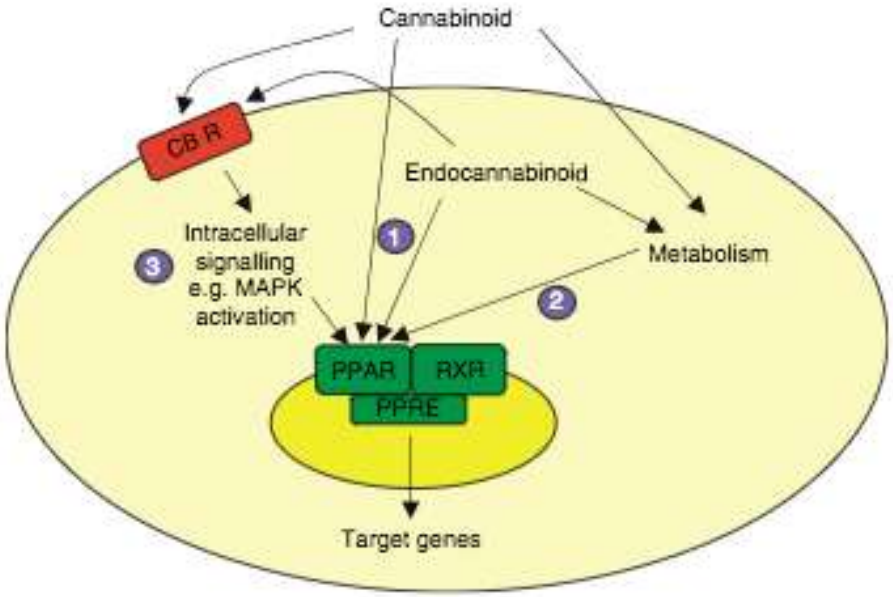


n=8478	Metabolic Syndrome AOR (95% CI)
Overall sample	
Past use	0.76 (0.57-1.02)
Current use	0.69 (0.47-1.00)
Emerging adults	
Past use	0.62 (0.30-1.27)
Current use	**0.46 (0.24-0.89)**
Adults	
Past use	1.14 (0.81-1.61)
Current use	1.05 (0.70-1.56)
Middle-aged adults	
Past use	**0.61 (0.40-0.91)**
Current use	**0.49 (0.25-0.97)**

Reference Group = Never Used Marijuana

Am J Med. 2016 Feb;129(2):173-9.

Cannabinoids have Gone Nuclear: PPAR receptors



PPARγ	PPARα	PPARβ
	Synthetic ligands	
TZDs	WY-14643	L-165041
JTT-501 (isoxazolidinedione)	Clofibrate	GW-501516
GW-7845	Gemfibrozil	NSAIDs (antagonist)
CDDO	Nafenopin	—
BADGE (antagonist)	Bezafibrate	—
LG-100641 (antagonist)	Fenofibrate	—

Br J Pharmacol. 2016 Jun; 173(12): 1899–1910.
PPAR Res. 2007; 2007: 23513.

Case 5

Guess what's new? Tom, now 45, has a new partner, Lyn. They are planning to get married. He has been doing great at work. He has been named Chief Executive. Both Tom and Lyn are concerned as the prior Chief Executive suddenly died of a heart attack. Despite continuing to smoke marijuana, he checked his blood pressure at Vons and it was 149/95. It is similar in your office. He is the heaviest you have ever seen him. His BMI is 29. You screen him for diabetes but his HgbA1c is 5.2% (normal <6.5%).

Case 5.

Given his new diagnosis of hypertension, what would you recommend in regards to his marijuana use?

A. You just told me that marijuana was anti-inflammatory and decreases his risk of metabolic syndrome. He should continue.

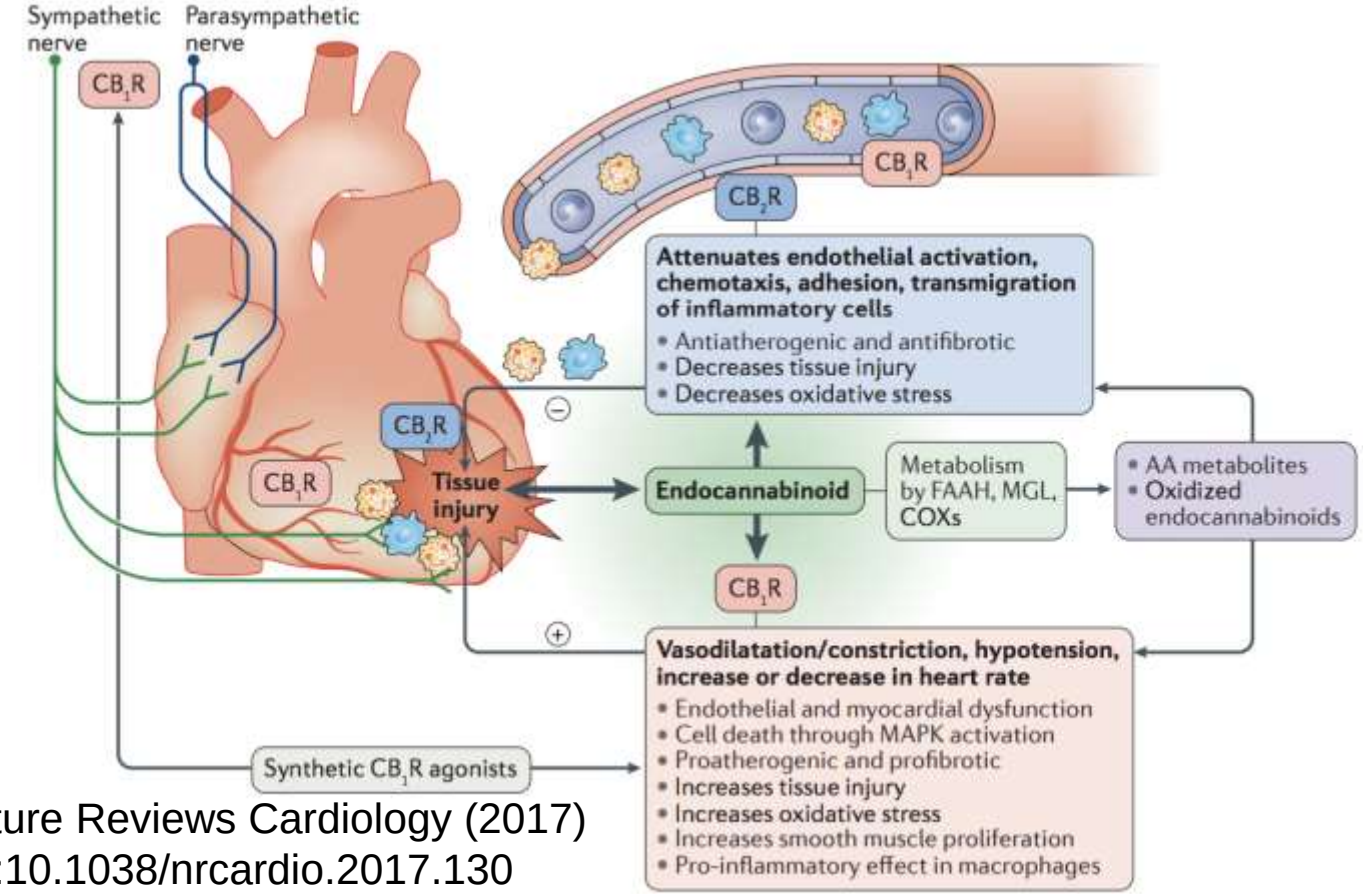
B. Marijuana decreases blood pressure, it might be best if he smokes more to get a more pronounced therapeutic effect

C. He should stop. Marijuana is associated with hypertensive mortality.

Acute Cardiovascular Effects of THC

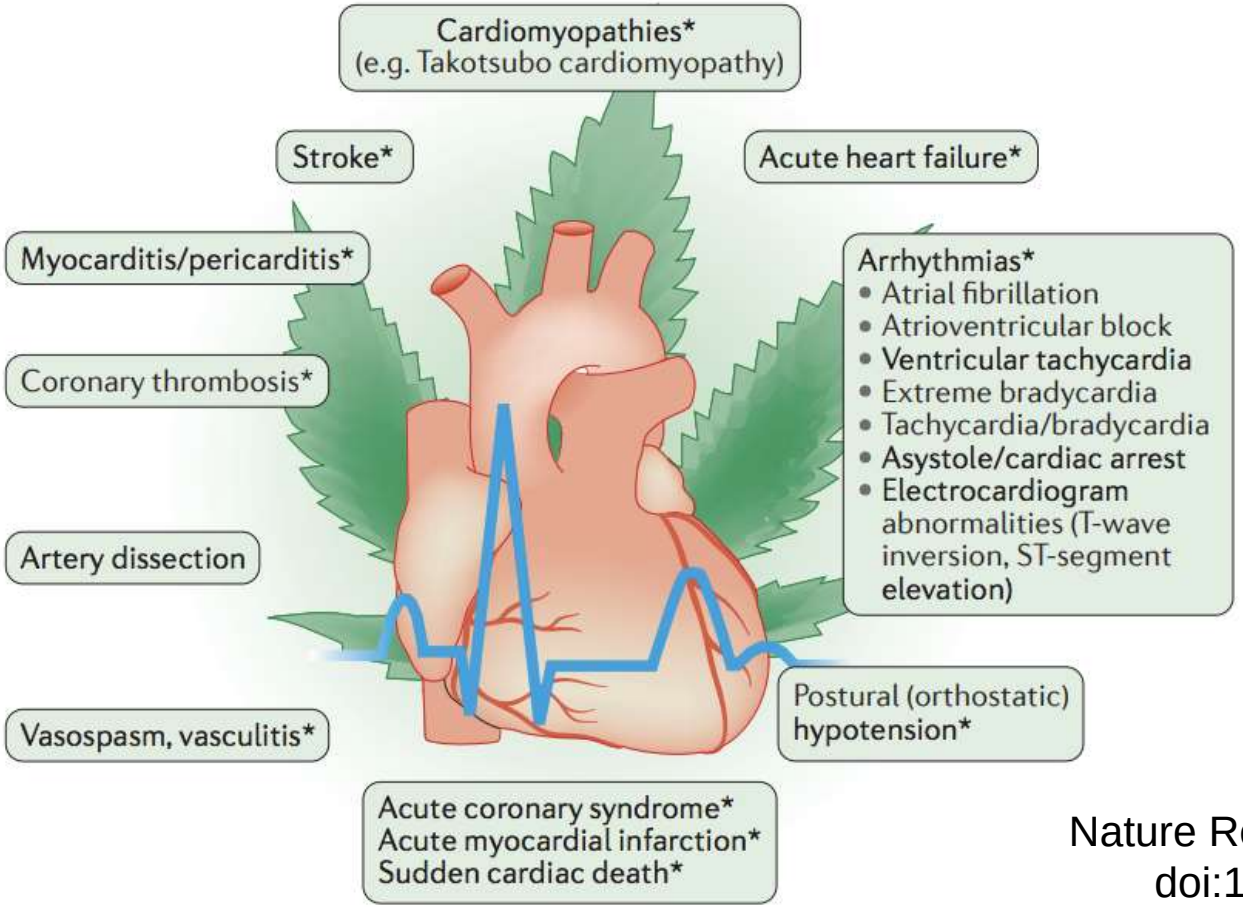
- Increased heart rate
- Orthostatic hypotension
- Increased cardiac output
- Reductions in left ventricular ejection time
- Increases in venous carboxyhemoglobin levels

Cardiovascular effects of THC/Endocannabinoids



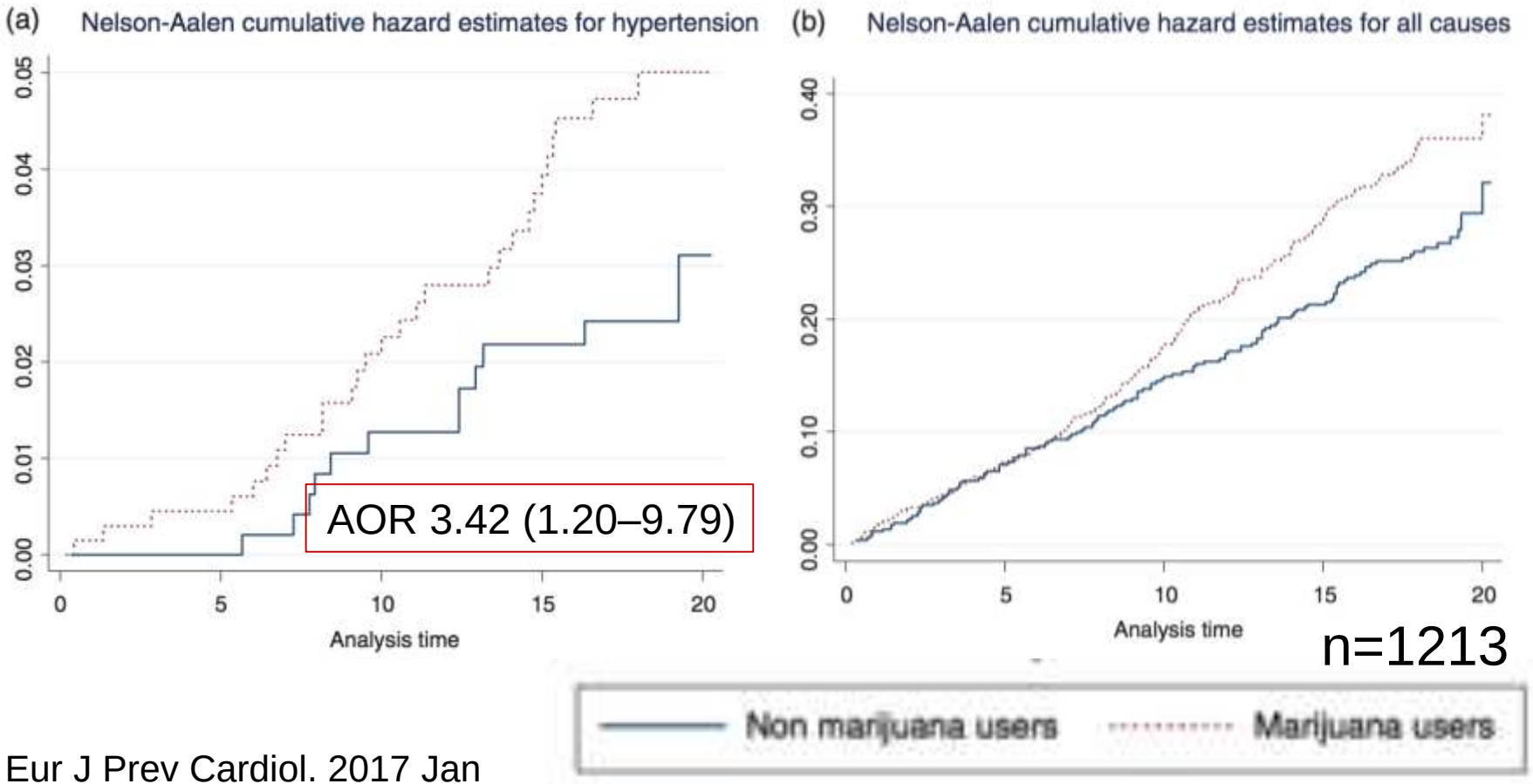
Nature Reviews Cardiology (2017)
doi:10.1038/nrcardio.2017.130

Clinical Syndromes Associated with Cannabis



Nature Reviews Cardiology (2017)
doi:10.1038/nrcardio.2017.130

Hypertensive Mortality, NHANES



Eur J Prev Cardiol. 2017 Jan

Case 6.

It didn't work out between Tom and Lyn. He is 65 and has retired. He didn't take our recommendation to stop smoking marijuana given his high blood pressure. Since retiring he actually smokes more. He did get on an intensive exercise program and lost 20 pounds (BMI now 24) and has been very adherent to two blood pressure medications (BP consistently 120s/80s). Over the last few months he has been noticing he is more fatigued when doing his exercises. He has a mild cough in the morning and wonders if he could have COPD. He sees commercials for inhalers all day on TV (his new hobby). He also asks if he could have lung cancer, as his dad, a smoker, died in his 60s of lung cancer.

Case 6.

Does marijuana cause COPD or lung cancer?

A. Of course it can cause both.

B. Probably only causes COPD, it doesn't have the carcinogens tobacco has

C. It only causes lung cancer

D. He has nothing to worry about, tobacco causes these, marijuana is a gift from the Aztecs

Airway Effects of Cannabis Smoking

Symptoms
Increased prevalence of chronic cough or sputum (17, 18, 20–22), wheezing (17, 18, 20–22), and shortness of breath (20)
Increased incidence of acute bronchitic episodes (17) or clinic visits for acute respiratory illness (19)

Lung Function
No difference in FEV_1 or FVC (17, 20, 21)
Increase in FVC (23, 27, 29)
Increase in FEV_1 (23)
Decrease in FEV_1/FVC (18, 20)
No difference in single-breath nitrogen washout measures (17, 25)
No differences in FRC, TLC, or RV (17, 21)
Increases in FRC, TLC, and RV (27)
Increase in Raw and decrease in SGaw (17, 25, 27)
No difference in D_{LCO} (17, 21, 27)

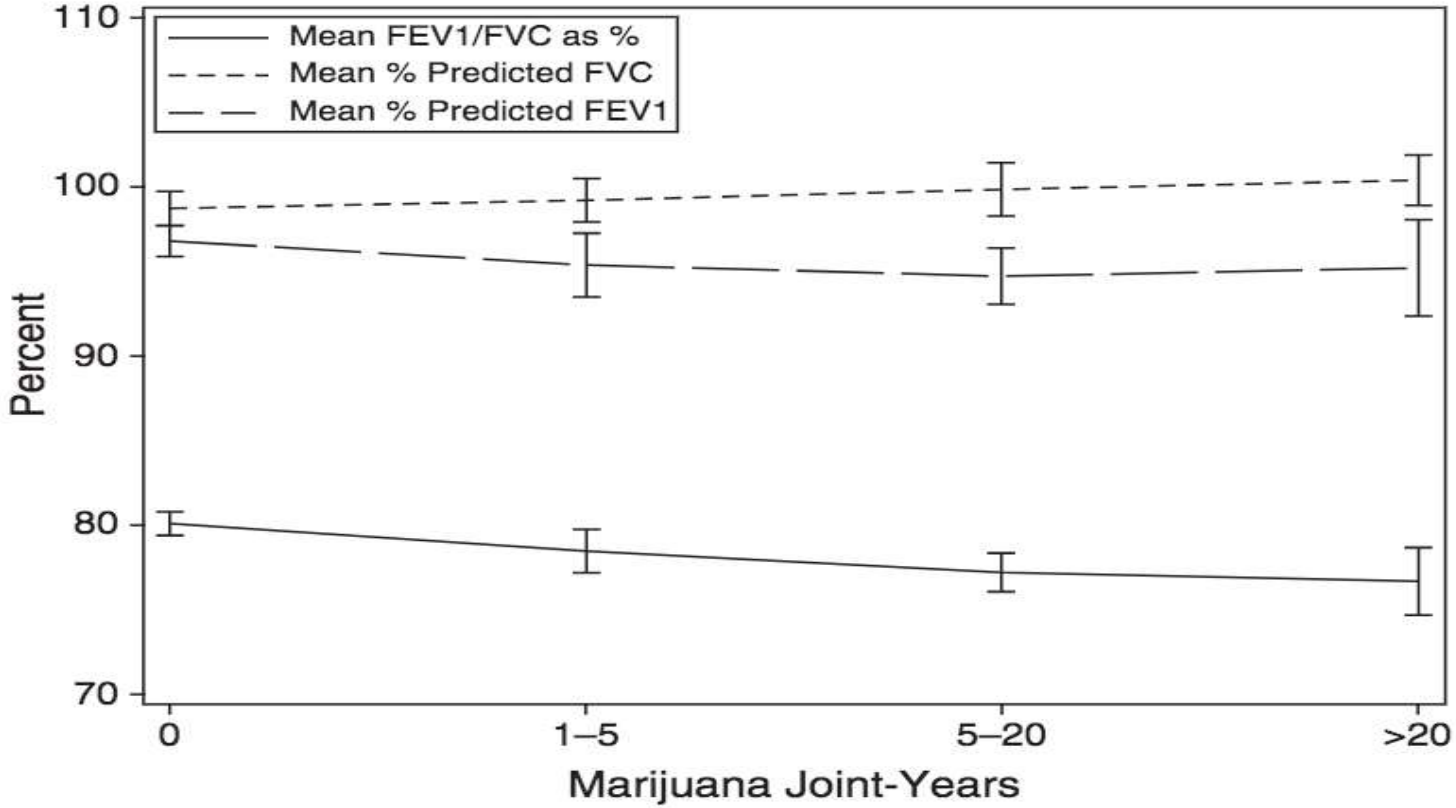
Ann Am Thorac Soc. 2013 Jun;10(3):239-47.

FEV1/FVC < 70%, NHANES 2009-2010 (n=2,956)

Variable	OR (95% CI)	*P* Value
Joint-years		
>20	2.1 (1.1–3.9)	0.02
5–20	1.2 (0.8–1.8)	0.4
1–5	1.1 (0.7–1.6)	0.8
0	Reference	NA
Tobacco pack-years		
>20	2.9 (1.9–4.3)	<0.0001
5–20	1.8 (1.3–2.7)	0.001
1–5	1.9 (1.1–3.4)	0.02
0	Reference	NA
Female	0.7 (0.5–1.0)	0.07
Increasing age, yr	1.1 (1.0–1.1)	<0.0001
White race	1.5 (1.0–2.3)	0.04
History of asthma	3.6 (2.5–5.3)	<0.0001
History of chronic bronchitis	0.5 (0.2–1.2)	0.1
History of emphysema	2.9 (0.7–11.3)	0.1

Ann Am Thorac Soc. 2015 Feb;12(2):135-41.

FEV1/FVC < 70%, NHANES 2009-2010 (n=2,956)

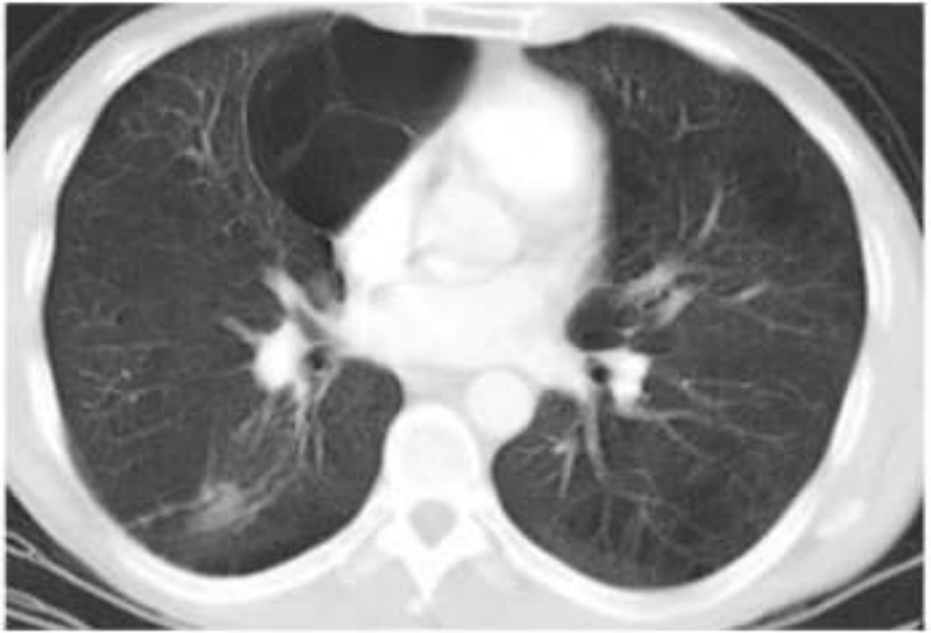


FVC

FEV1/FVC

Ann Am Thorac Soc. 2015 Feb;12(2):135-41.

Bong Lung: Apical Bullous Disease



Respirology (2008) 13, 122–127

Cancer and Cannabis: Is there a Link? (n=1040)

Cancer type (marijuana use)	Cases, *N*	Controls, *N*	Crude OR (95% CL)	Adjusted OR (95% CL)	
				Model 1	Model 2
Oral cancer					
Never	57	294	1	1	1
>0 to <1 joint-years	25	138	0.93 (0.56, 1.6)	0.86 (0.51, 1.5)	0.93 (0.53, 1.6)
1 to <10 joint-years	11	34	1.7 (0.80, 3.5)	1.5 (0.68, 3.1)	1.5 (0.68, 3.5)
≥10 joint-years	9	21	2.2 (0.96, 5.1)	2.0 (0.82, 4.7)	1.8 (0.69, 4.7)
Pharyngeal cancer					
Never	30	294	1	1	1
Ever	13	193	0.66 (0.34, 1.3)	0.61 (0.30, 1.2)	0.92 (0.41, 2.1)
Laryngeal cancer					
Never	7	296	1	1	1
Ever	6	193	1.3 (0.44, 4.0)	0.97 (0.31, 3.0)	1.2 (0.26, 5.5)
Esophageal cancer					
Never	14	293	1	1	1
Ever	9	192	0.98 (0.42, 2.3)	0.92 (0.37, 2.2)	0.79 (0.30, 2.1)
Lung cancer					
Never	91	291	1	1	1
>0 to <1 joint-years	10	136	0.24 (0.12, 0.47)	0.26 (0.13, 0.53)	0.44 (0.21, 0.92)
≥1 joint-years	9	55	0.52 (0.25, 1.1)	0.63 (0.29, 1.4)	1.1 (0.48, 2.6)

Cancer Epidemiol Biomarkers Prev. 2006 Oct;15(10):1829-34.

Cannabis Use and Lung Cancer (n=44,257)

Table 4 Crude and adjusted hazard ratios (HRs) and 95 % CIs for lung cancer ($n = 179$) among 44,257 conscripts, in relation to lifetime frequency of cannabis-use categories

Cannabis smoking	Crude HR (95 % CI)	Tobacco-adjusted[a] HR (95 % CI)	Fully adjusted[b] HR (95 % CI)
Never (reference)	1.0	1.0	1.0
Once	2.07 (1.06–4.06)	1.48 (0.75–2.91)	1.52 (0.77–3.01)
2–4 times	0.95 (0.39–2.33)	0.65 (0.26–1.58)	0.66 (0.27–1.62)
5–10 times	1.02 (0.32–3.20)	0.66 (0.21–2.09)	0.68 (0.21–2.16)
11–50 times	2.69 (1.26–5.74)	1.68 (0.78–3.62)	1.68 (0.77–3.66)
More than 50 times	3.72 (1.96–7.06)	2.24 (1.17–4.29)	2.12 (1.08–4.14)

Cancer Causes Control. 2013 Oct;24(10):1811-20

20,679* Physicians say "LUCKIES are *less irritating*"

"It's toasted"

Your Throat Protection against irritation against cough

The Doctors behind the Doctor

● Magical penicillin . . . the amazing "mitis" . . . and now the new streptomycin . . . Thank the men of research medicine for these . . . and for all the other valuable aids they have placed in the doctor's "little black bag."

Biochemists and bacteriologists . . . pathologists and physiologists . . . whatever the field of research . . . they are, first and foremost, *doctors!* And, like all doctors, they are tirelessly devoting their lives to the cause of human health and happiness.

According to a recent Nationwide survey:

MORE DOCTORS SMOKE CAMELS THAN ANY OTHER CIGARETTE

Case 7.

Remember Tom? Well, that fatigue? He wound up having high-risk localized prostate cancer. He underwent radiotherapy and androgen deprivation therapy. After his diagnosis, he quit smoking marijuana. Now close to 80, he had severe hip pain. An MRI showed metastatic lesions in his iliac bone and L2 and L5. His pain was so severe he was started on oxycodone ER 10 mg every 12 hours and hydrocodone/acetaminophen PRN for breakthrough pain. He tells you that he started using a vaporizer pen for inhaling cannabis that he gets at his local dispensary. Since, he has decreased his oxycodone use to only once a day and never takes his hydrocodone. You confirm this on the CURES website.

Case 7.

What should we advise in regards to his pain management?

A. Stop the cannabinoid and return to the original narcotic pain protocol.

B. Suggest using dronabinol instead of the vaporizer.

C. Continue using the cannabinoid and his pain medications with frequent follow-up visits to monitor safety.

D. Undergo detoxification of all narcotics and seek treatment for addiction if he is unable to stop using the cannabinoid.

Cannabis as an Opioid-Sparing Agent

Medication Type	Use Before Initiation of Cannabis, n/N (%)	Use After Initiation of Cannabis, n/N (%)
Opioids	119/184 (65)	33/184 (18)
Nonsteroidal anti-inflammatory drugs	115/184 (62)	38/184 (21)
Disease-modifying antirheumatic drugs	15/184 (8)	3/184 (2)
Antidepressants	72/184 (39)	25/184 (14)
Serotonin–norepinephrine reuptake inhibitors	13/184 (7)	3/184 (2)
Selective serotonin reuptake inhibitors	34/184 (18)	8/184 (4)
Other	69/184 (38)	40/184 (22)

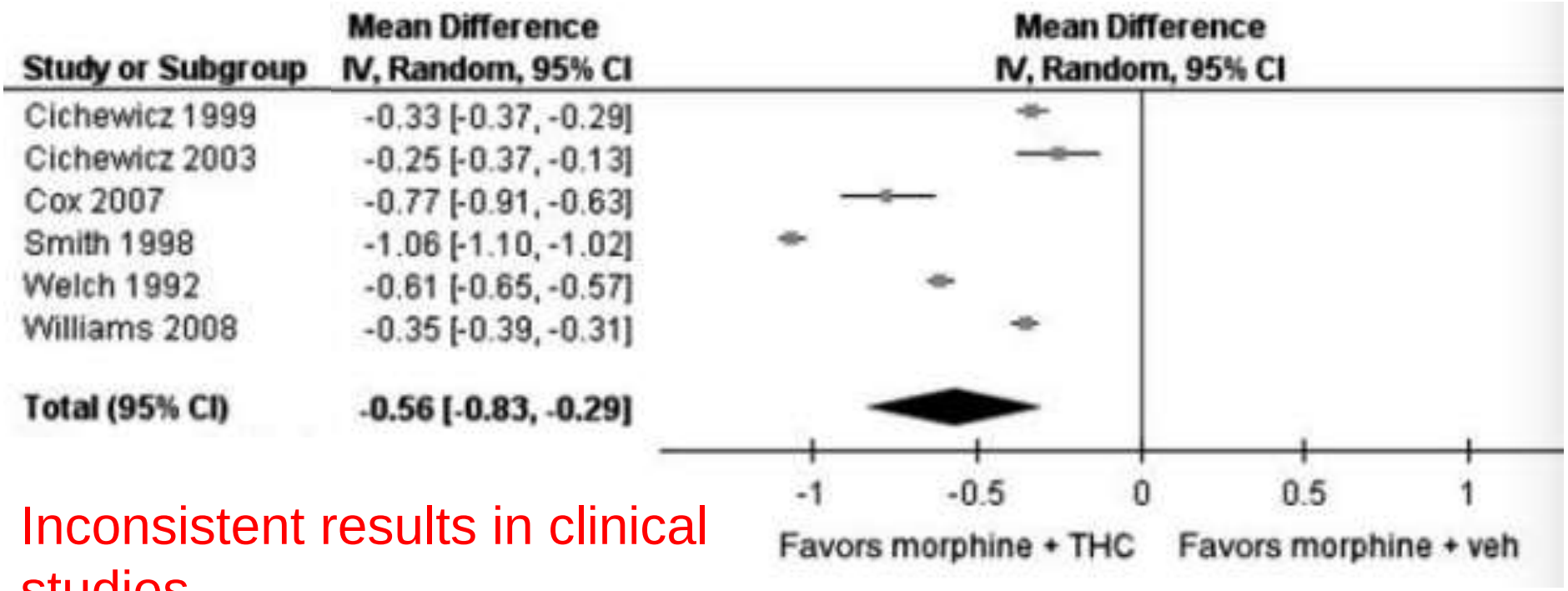
J Pain. 2016 Jun;17(6):739-44.

Cannabis as an Opioid-Sparing Agent

Outcome of Interest	CP (N = 185)
FM score	9.16 (5.42) n = 185
Opioid use change (−100% to +100%)	−64% (45%) n = 118
Degree to which side effects of medication affect daily function before using medical cannabis; scale from 1 (no effect) to 10 (significant effect)	6.51 (2.88) n = 136
Degree to which side effects of medication affect daily function after using medical cannabis; scale from 1 (no effect) to 10 (significant effect)	2.79 (2.39) n = 136
Change in medication side effects after initiation of cannabis	−3.72 (3.42) n = 136
Number of medication classes used (before cannabis use)	2.38 (1.44) n = 184
Number of medication classes used (after cannabis use)	1.81 (.95) n = 184
Change in quality of life (−100% to +100%)	+45% (29%) n = 180

J Pain. 2016 Jun;17(6):739-44.

Cannabis as an Opioid-Sparing Agent: Pre-Clinical Studies



Inconsistent results in clinical studies.

Neuropsychopharmacology (2017) 42, 1752–1765

Pharmaceutical Cannabinols

- Dronabinol (Marinol)
  - Anorexia in AIDS
  - Chemotherapy induced nausea and vomiting
- Nabilone (Cesamet)
  - Nausea and vomiting associated with chemotherapy
  - Spasticity in multiple sclerosis *
  - Behavioral disturbances in patients with Alzheimer's disease *
  - Chronic pain *
- Nabiximols (Sativex, approved in Canada, oral spray)

Case 8.

Given his battle with metastatic prostate cancer, Tom, 85, has difficulty with his activities of daily life. He is admitted to a nursing facility. In the facility, he continues to smoke marijuana. He has made friends with other marijuana smoking residents. One day many of the residents smoke out of the same “bong”. Weeks later, three of the residents, including Tom are hospitalized due to nightly fevers, weight loss, and hemoptysis.

Case 8.

What infections are associated with marijuana use?

A. Aspergillus

B. Tuberculosis

C. Penicillium

D. All of the above

Culture Results: Netherlands (*Letter)

Result	Cigarettes (n = 98)	Marijuana (n = 7)
Positive culture for molds	63 (64)	7 (100)
CFU/g	200-300	10^4-10^7
Aspergillus fumigatus	36 (37)	2 (28)
Aspergillus flavus	1 (1)	1 (14)
Aspergillus terreus	3 (3)	0
Aspergillus glaucus complex	17 (17)	0
Penicillium species	3 (3)	6 (86)

*Data are presented as No. (%) unless otherwise indicated.

JAMA. 2000;284(22):2875.

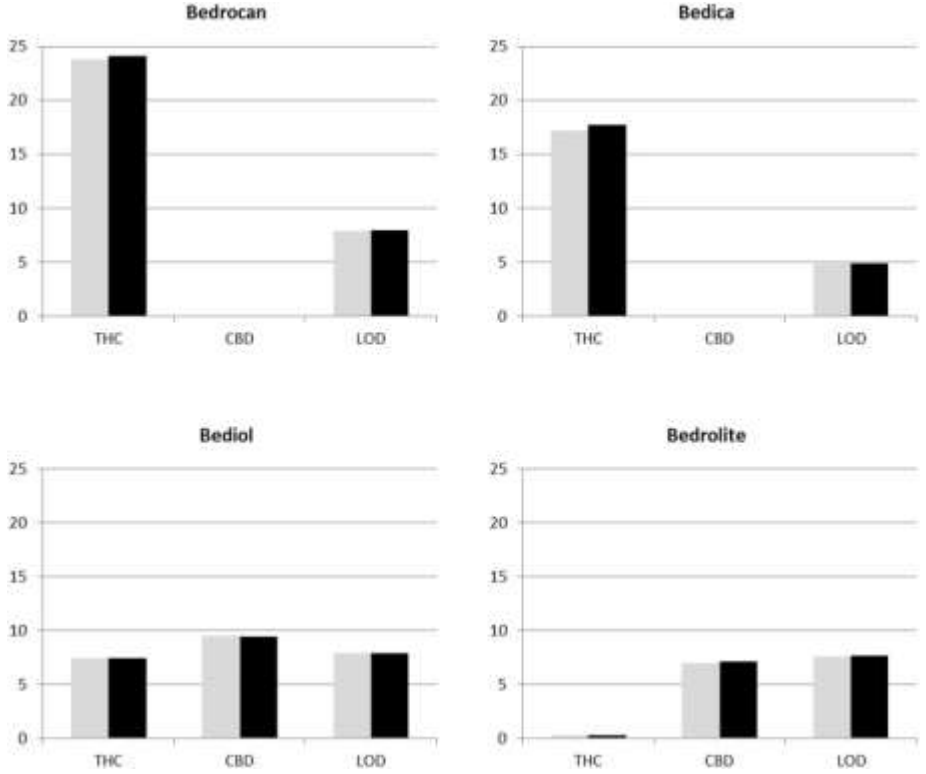
Invasive Aspergillosis and Marijuana

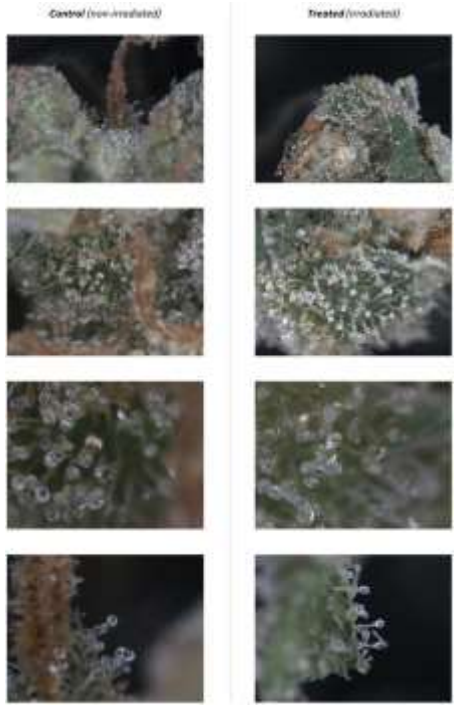
Case report	Patient characteristics	Medications	Neutropenia	Course
Chest. 1988 Aug;94(2):432-3.	34 y/o M CML s/p BMT, GVHD	Cyclosporin, prednisone, ketoconazole and gamma globulin	Not reported	Died, tx amphotericin and investigational drug
Transplantation. 1996 Jun 27;61(12):1771-4.	48 y/o M renal transplant, 30 days post-op		WBC 11,700 cells/mm3 (82% segs, 0.6% bands)	Survivied, amphotericin and itraconazole
Leuk Lymphoma. 2001 Nov-Dec;42 (6):1433-7.	46 y/o M AML	Idarubicin, cytosine arabinoside and etoposide	WBC 62,000/ml with 81% blast	Survived, amphotericin
J Clin Oncol. 2008 May 1;26 (13):2214-5.	65 y/o M colorectal CA, mets to lung and pelvis	Capecitabine, irinotecan, and bevacizumab every 3 weeks	Normal: PMN 5.2 × 109/L, WBC 7.9 × 109/L	Survived, tx voriconazole

Aspergillosis and Marijuana in "Immunocompetent" Hosts

Case report	Patient characteristics	Condition	Aspergillosis disease type	Course
J Toxicol Pharmacol 2017; 1:004	46 y/o M with hypertension and chronic cough	30 pack/year history	Spiculated mass measuring 4 cm × 1 cm × 1.2, found to be fungus ball	VATS, voriconazole
Mediterr J Hematol Infect Dis. 2011; 3(1): e2011005.	47 y/o M	39 pack/year history Rheumatoid arthritis on prednisolone	Fungus ball	VATS, posaconazole
Mediterr J Hematol Infect Dis. 2011; 3(1): e2011005.	35 y/o M	Tetralogy of Fallot 680 joint/year history	Chronic cavitary aspergillosis	Voriconazole, died
Chest 2010	31 y/o M	No known history	Neuroaspergillosis	Surgical resection, tx voriconazole

Sterility: Gamma-Irradiation





Hazekamp. Front Pharmacol. 2016; 7: 108.

Cannabis and Tuberculosis

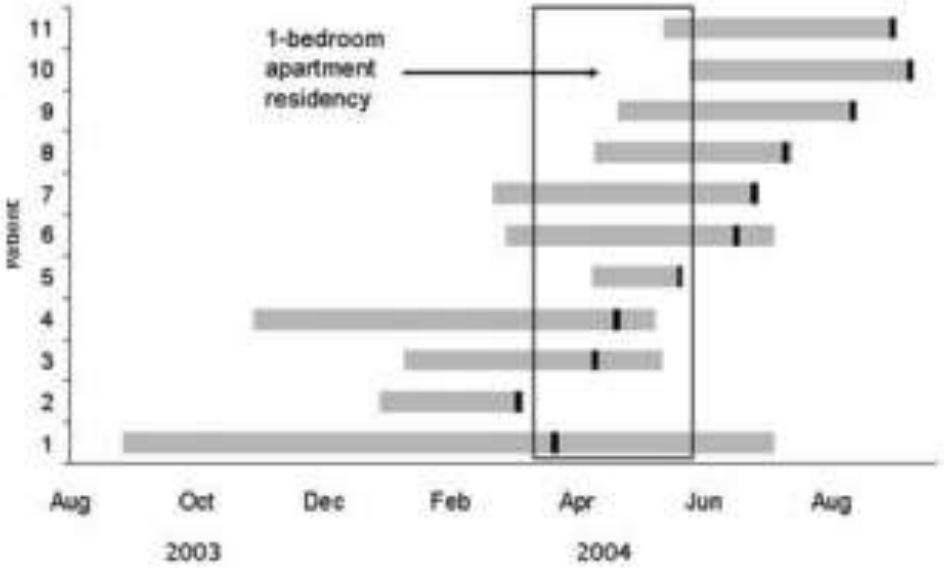


Figure. Infectious periods of tuberculosis patients. Vertical black bars indicate treatment start dates.

Emerg Infect Dis. 2006 Jul;12(7):1156-9.

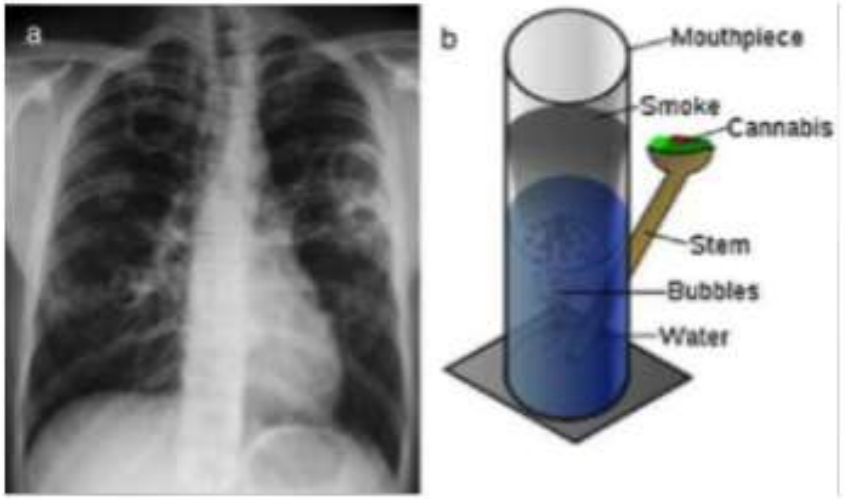


Figure 1 (a) Chest X-ray with multiple cavitation lung lesions (case 1). (b) Diagram of a bong in operation..

Intern Med J. 2013 Apr;43(4):456-8.

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CBD and Epilepsy

The NEW ENGLAND JOURNAL of MEDICINE

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Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D.,

Cannabis and Epilepsy

Table 2. Primary Efficacy End Point of Percentage Change in Convulsive-Seizure Frequency in Each Trial Group.*

Variable	Cannabidiol	Placebo	Adjusted Median Difference (95% CI)	P Value†
			percentage points	
No. of convulsive seizures per mo — median (range)				
Baseline	12.4 (3.9 to 1717)	14.9 (3.7 to 718)		
Treatment period	5.9 (0.0 to 2159)	14.1 (0.9 to 709)		
Percentage change in seizure frequency — median (range)	−38.9 (−100 to 337)	−13.3 (−91.5 to 230)	−22.8 (−41.1 to −5.4)	0.01

N Engl J Med 2017;376:2011-20.

Low Risk Cannabis Use Guidelines

(1) The most effective way to avoid cannabis use–related health risks is abstinence

(2) Avoid early age initiation of cannabis use (i.e., definitively before the age of 16 years)

(3) Choose low-potency tetrahydrocannabinol (THC) or balanced THC-to-cannabidiol (CBD)–ratio cannabis products

(4) Abstain from using synthetic cannabinoids

(5) Avoid combusted cannabis inhalation and give preference to nonsmoking use methods

Am J Public Health. 2017 Aug;107(8):e1-e12

Low Risk Cannabis Use Guidelines

- (6) Avoid deep or other risky inhalation practices
- (7) Avoid high-frequency (e.g., daily or near-daily) cannabis use
- (8) Abstain from cannabis-impaired driving
- (9) Populations at higher risk for cannabis use–related health problems should avoid use altogether
- (10) Avoid combining previously mentioned risk behaviors (e.g., early initiation and high-frequency use).

Am J Public Health. 2017 Aug;107(8):e1-e12

Summary

- Cannabis use is frequent among the adolescent and adult population
- Substance use disorder only affects of subset of users
- Many different genus, strains and ways of consuming marijuana exist
- The psychoactive effects of marijuana are mediated through THC and interaction of CB1 receptors
- CB2 receptors may provide an immune-modulating effect
- Synthetic cannabinoids are potent agonist of the CB1 receptor and produce potent effects. Sale and possession are illegal in California.

Summary

- Cannabis use is associated with earlier schizophrenia diagnosis and first manic episodes
- Likely has no long term effect on IQ
- Regular cannabis use may have a protective metabolic effect
- Cannabis use was associated with higher hypertensive mortality
- No strong evidence for cannabis use and COPD or lung cancer. But beware.
- Evolving role in treatment of refractory epilepsy

Summary

- THC may have an opioid sparing effect in treatment of chronic pain
- Several pharmaceutical CB1 agonists exist (dronabinol, nabiolone, nabiximols)
- Cannabis smoking has been linked to cases of aspergillosis (immunosuppressed) and tuberculosis
- Overall, methodological issues of studies make definite conclusions difficult

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