Marijuana 101:
What an internist needs to know

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Conflicts of Interest

- None

Learning objectives

- List main components of cannabis and their physiological effects
- Describe evidence for use in pain and nausea
- List possible risks of cannabis use

Public Health Symposium March 7, 2014
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What is cannabis?

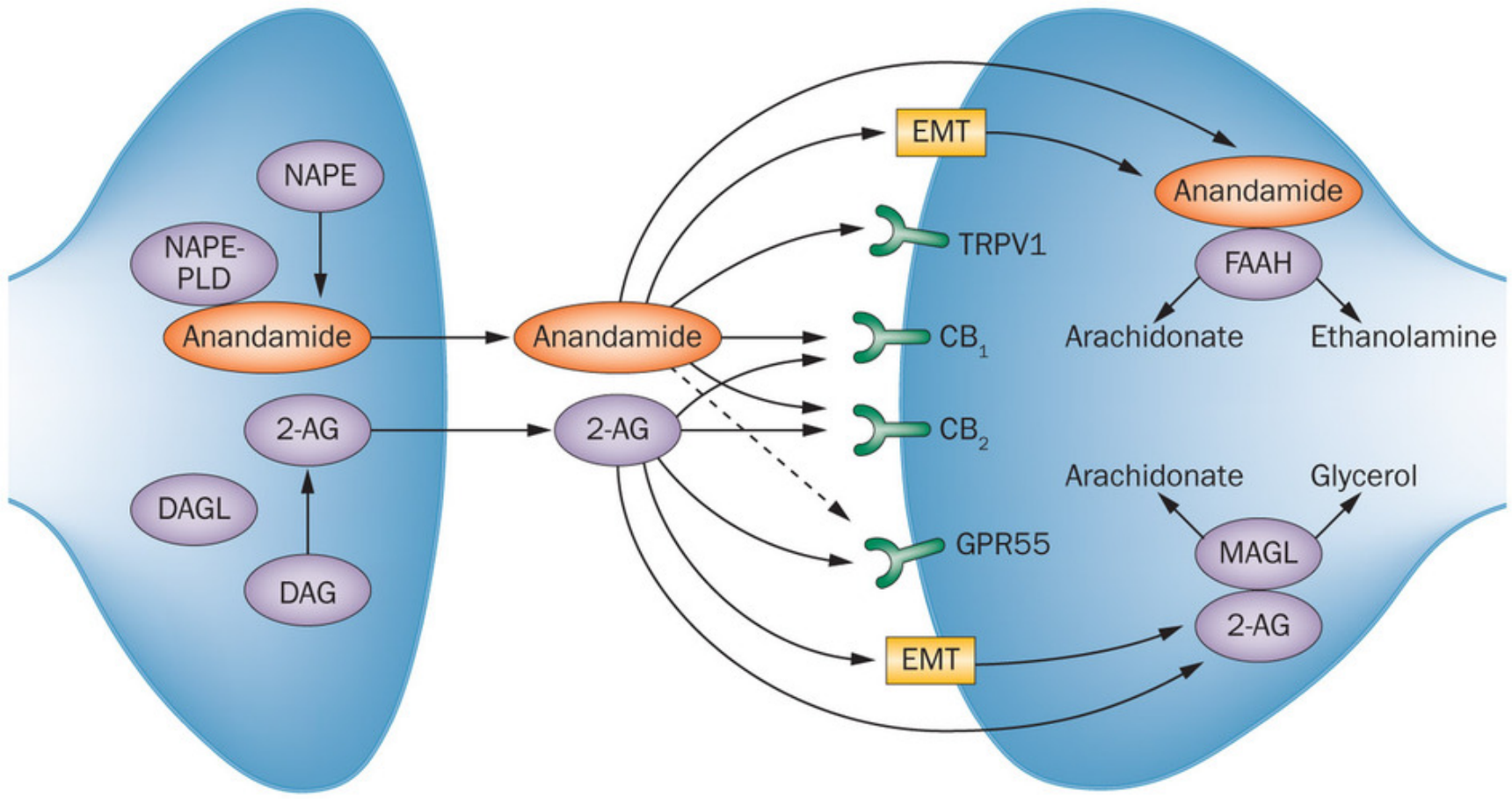
- Cannabis refers to the dried flower tops of the cannabis plant.
- Indica, Sativa, and Ruderalis
- Cannabis contains over 600 chemicals, about 80 of which are considered cannabinoids.
- Others are terpinoids and non psychoactive chemicals related to plant growth.

Main chemical components

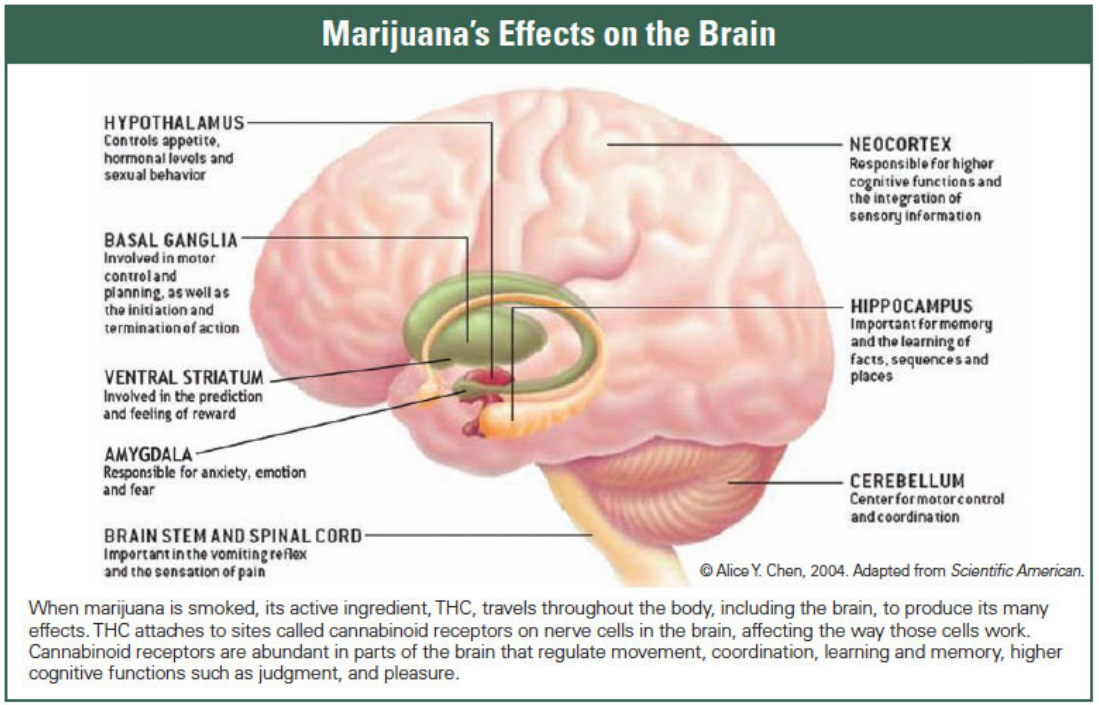
- The rock star: THC
- The silent hero: CBD
- The goofy side kicks: CBN, CBG, THCV, THCA, CBDA
- Back up dancers: Terpinoids

www.denverpost.com accessed 12/14/14

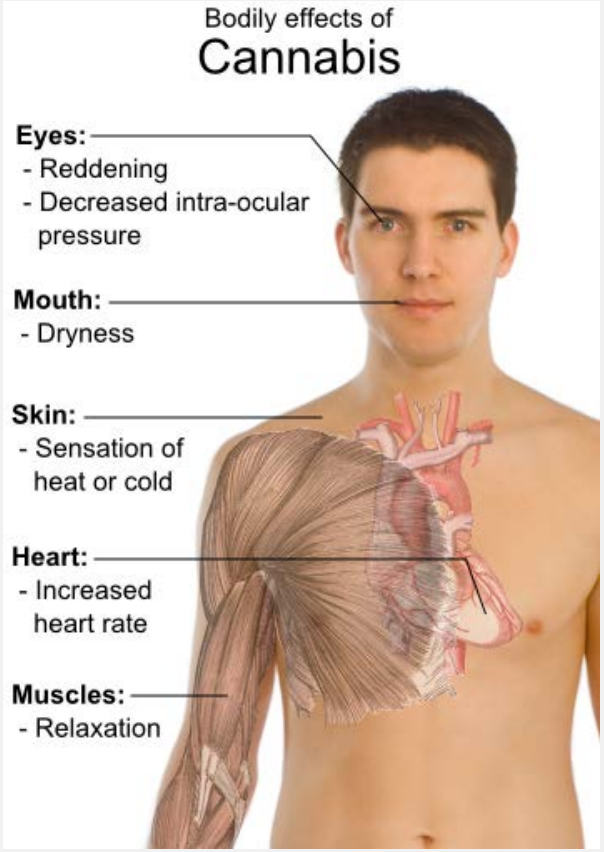
Endocannabinoid system



Marijuana's physiologic effects

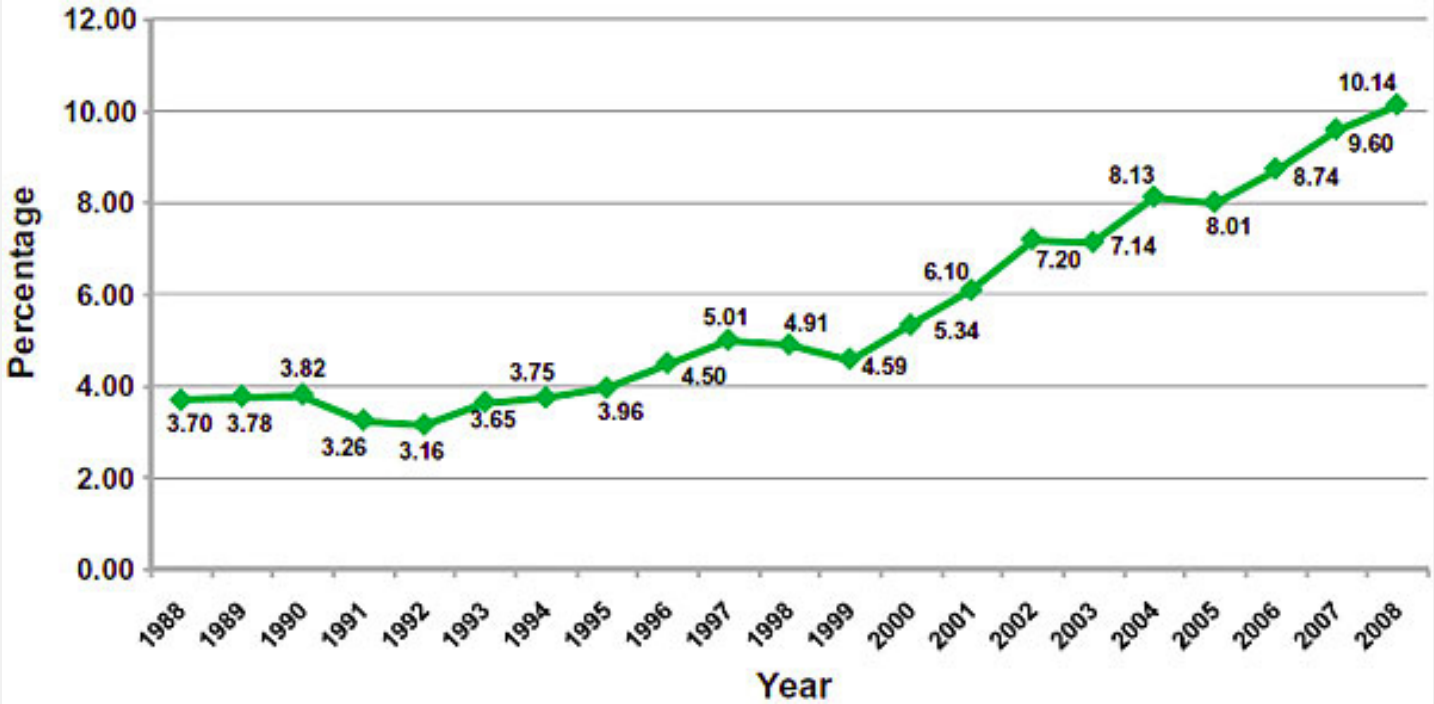


When marijuana is smoked, its active ingredient, THC, travels throughout the body, including the brain, to produce its many effects. THC attaches to sites called cannabinoid receptors on nerve cells in the brain, affecting the way those cells work. Cannabinoid receptors are abundant in parts of the brain that regulate movement, coordination, learning and memory, higher cognitive functions such as judgment, and pleasure.



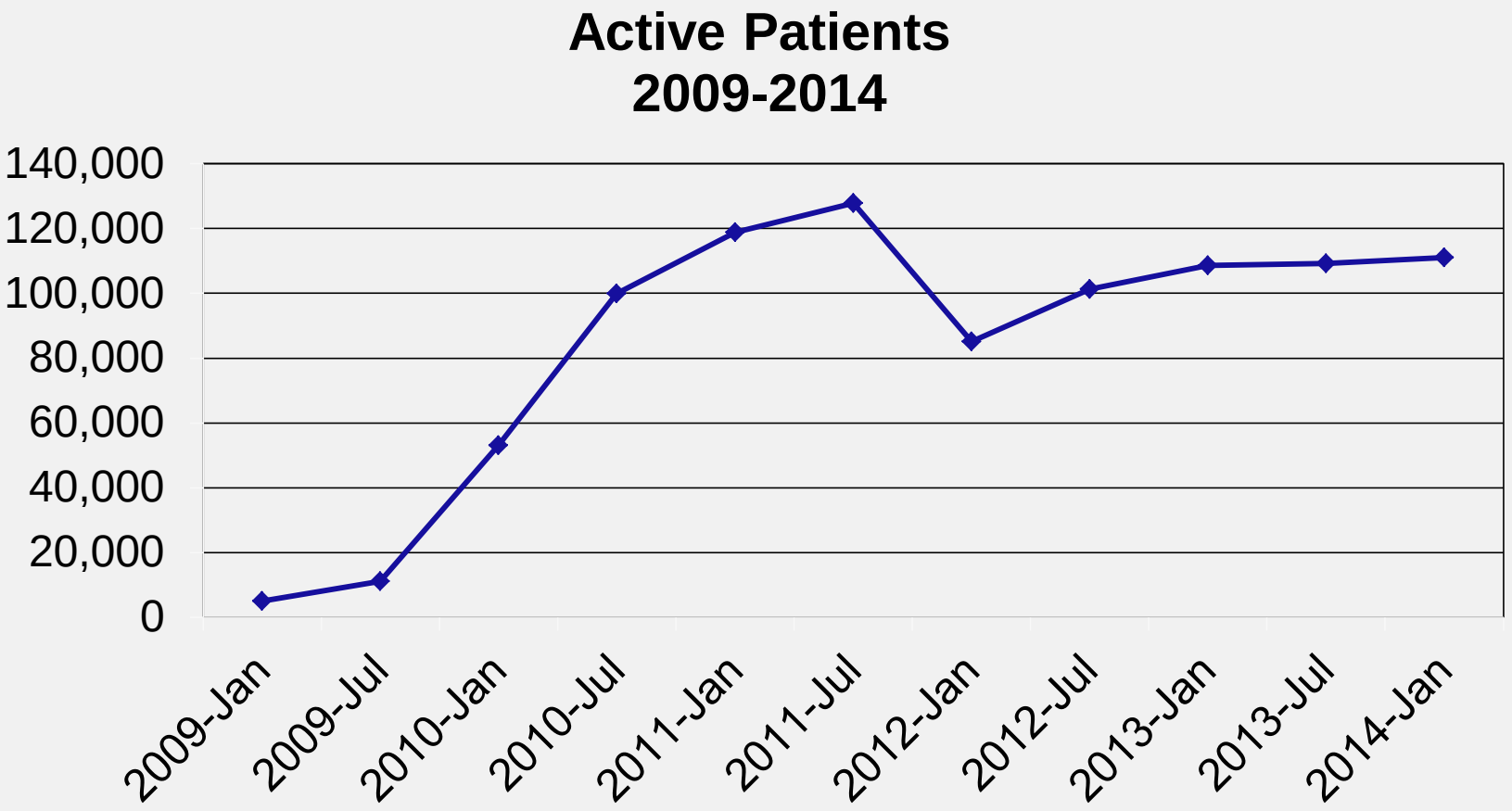
www.drugabuse.gov/publications/marijuana-abuse/how-does-marijuana-produce-its-effects
Accessed March 3, 2014

THC concentration is increasing



Routes of administration

Colorado Medical Marijuana Registry



Colorado Reported Conditions

Condition	Number	Percent*
Severe Pain	103,825	94%
Muscle Spasms	14,714	13%
Severe Nausea	11,023	10%
Cancer	3,079	3%
Seizures	2,098	2%
Cachexia	1,165	1%
Glaucoma	1,113	1%
HIV/AIDS	657	1%

*Does not add to 100% as some patients report more than one condition
MMWR Monthly Report – December 31, 2013

Does it do *anything* helpful?

Pain

Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review

Fiona A Campbell, Martin R Tramèr, Dawn Carroll, D John M Reynolds, R Andrew Moore, Henry J McQuay

- Five single-dose trials in cancer patients (9 total studies)
- Cross-over designs, single dose studies
- Cannabinoids as effective as codeine 50-120 mg
- Adverse events were common
- Problems: does not address smoked products, chronic use, adjunctive use

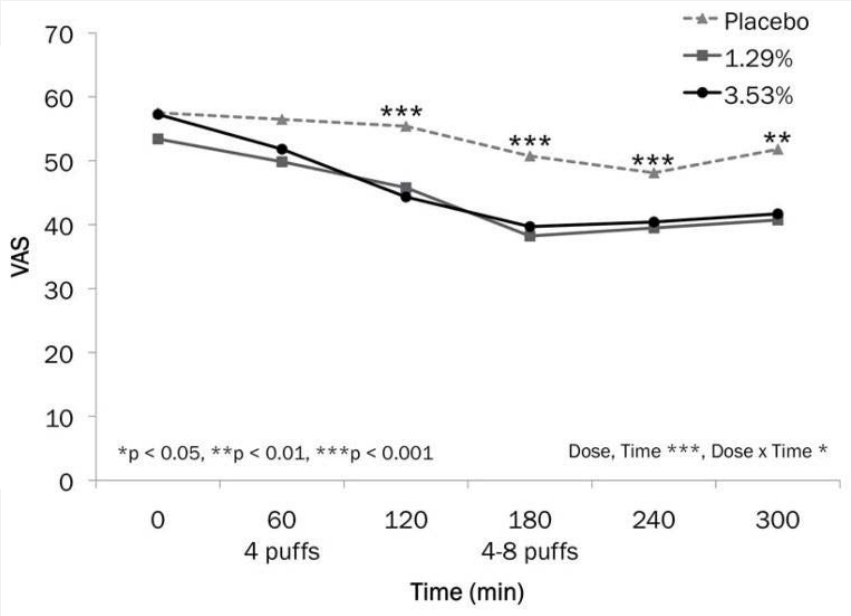
BMJ 2001; 323: 1-6

Cannabis for neuropathic pain

Pairwise comparisons of the effects of four potencies of smoked cannabis on average daily pain

	Potency, % of THC, mean difference (95% CI)							
Potency, % of THC	**0**		**2.5**		**6.0**		**9.4**	
0	–	–	–	–	–	–	–	–
2.5	−0.13	(−0.83 to 0.56)	–	–	–	–	–	–
6.0	−0.09	(−0.78–0.60)	0.04	(−0.64 to 0.73)	–	–	–	–
9.4	−0.71	(−1.40 to −0.02)	−0.58	(−1.27 to 0.11)	−0.63	(−1.30 to 0.06)	–	–

Note: CI = confidence interval, THC = tetrahydrocannabinol.



Smoked

Vaporized

CMAJ. 2010; 182: E694–E701
J Pain. 2013; 14: 136–148.

Placebo controlled pain trials

Patients	Route	THC%	Better than placebo?
HIV neuropathy	Smoked	3.56	Yes
Neuropathic	Smoked	2.5-9.4	Yes
Neuropathic	Vaporized	1.29-3.53	Yes
Multiple sclerosis muscle stiffness	Cannabis extract	--	Yes
MS pain	Smoked	4	Yes

Neurology 2007; 68:515-21. CMAJ. 2010; 182: E694–E701. J Pain. 2013; 14: 136–148. J Neurol Neurosurg Psychiatry. 2012;83:1125-32.. CMAJ 2012; 184: 1143–1150.

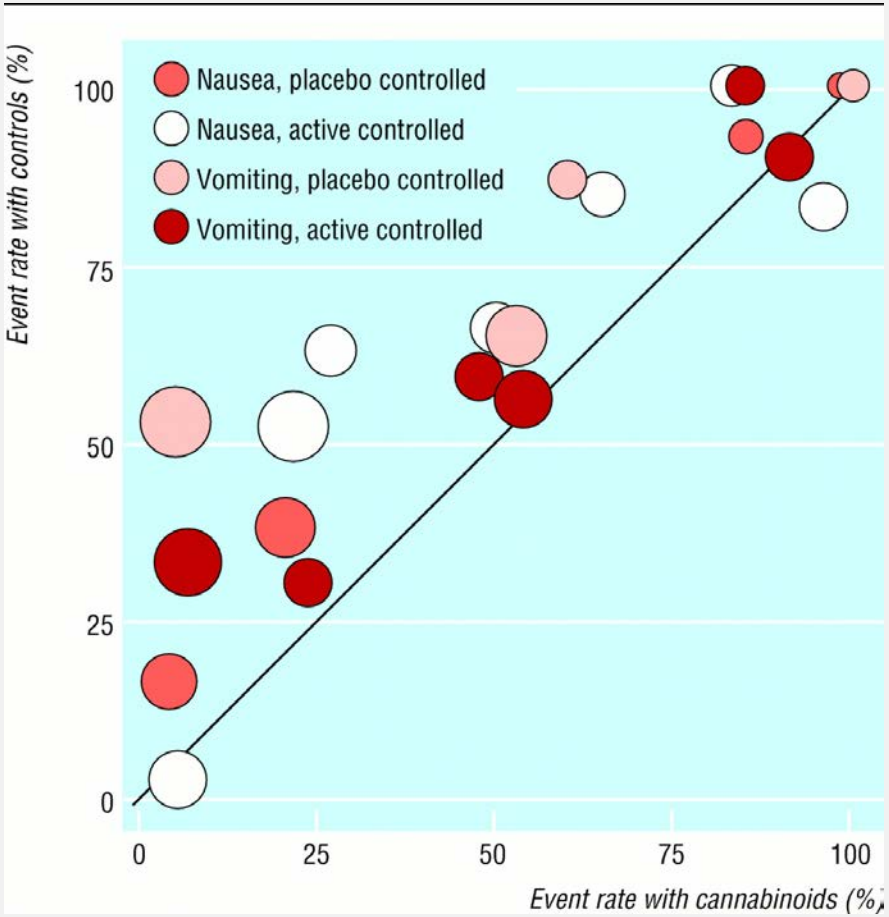
Nausea & Vomiting

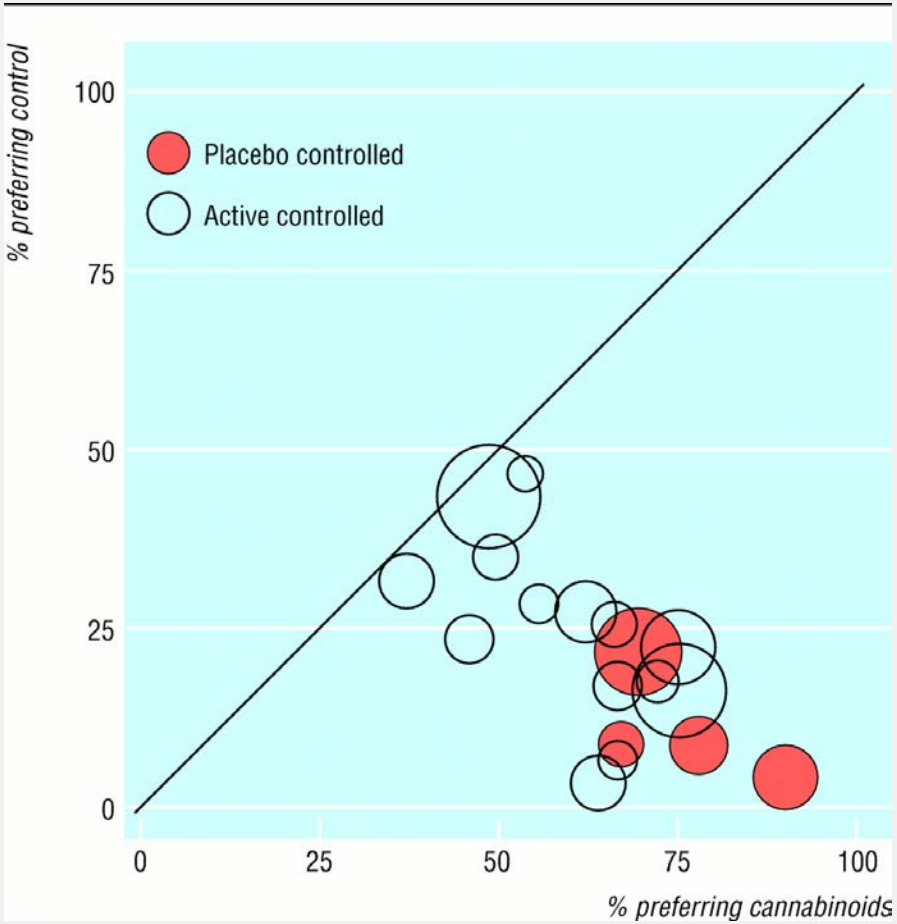
Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review

Martin R Tramèr, Dawn Carroll, Fiona A Campbell, D John M Reynolds, R Andrew Moore, Henry J McQuay

- 198 reports whittled to 30 evaluable trials
- Efficacy data on 1366 patients
- Average trial size was 46 patients
- 83% of trials used a cross over design
- Nabilone (16), dronabinol (13), levonantradol (1)
- All evaluated acute CINV

BMJ 2001; 323: 1-8


Nausea, placebo controlled
Nausea, active controlled
Vomiting, placebo controlled
Vomiting, active controlled
Event rate with controls (%)
Event rate with cannabinoids (%)
0
25
50
75
100


Placebo controlled
Active controlled
% preferring control
% preferring cannabinoids
0
25
50
75
100

Cannabis extract for N/V

Proportion of patients reaching secondary or exploratory end points

	CBM *n*= 7	Placebo *n*= 9	Difference (%) (95% CI)
No delayed emesis	5 (71.4%)	2 (22.2%)	49.2 (1.0, 75.0)
No delayed nausea[*]	4 (57.1%)	2 (22.2%)	34.9 (−10.8, 66.3)
No significant delayed nausea[†]	5 (71.4%)	4 (44.4%)	27.0 (−18.0, 59.7)
Not valued	1[‡] (14.3%)	–	

Br J Clin Pharmacol. 2010;70:656-63

Herbal cannabis for non-chemo N/V

Cannabinoid hyperemesis

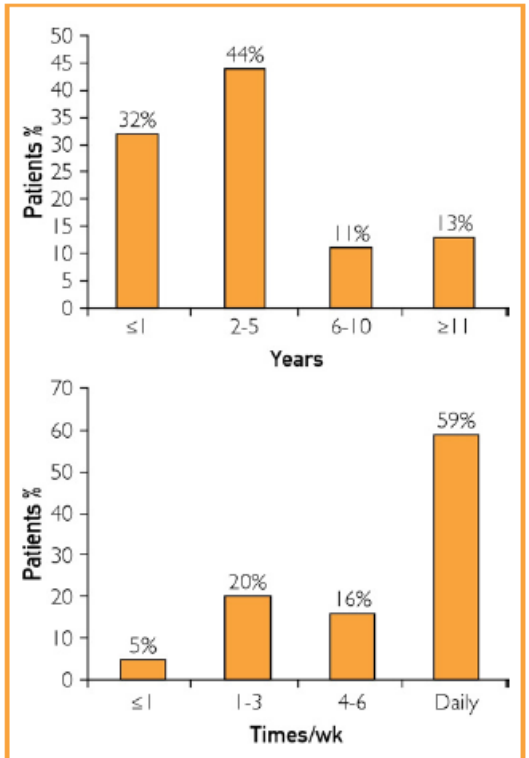


FIGURE. Duration of cannabis use before onset of symptoms (top) and frequency of cannabis use per week (bottom).

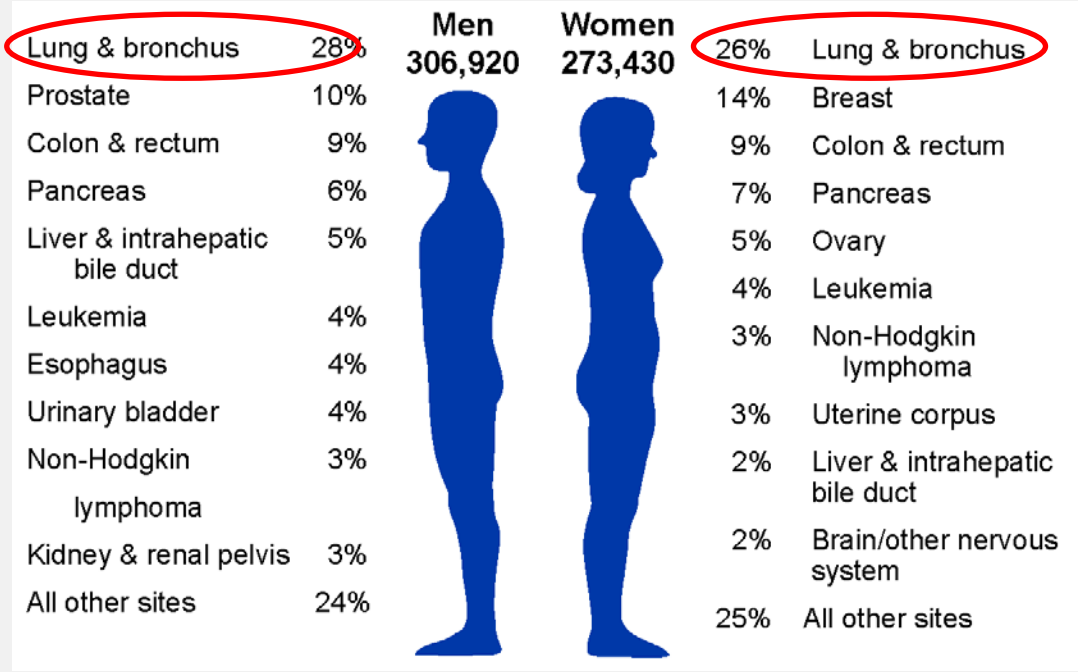
TABLE 3. Clinical Manifestations of Cannabinoid Hyperemesis in 98 Patients

Symptom	No. (%) of patients
Nausea	98 (100)
Emesis	98 (100)
Time of symptoms (n=75)	
Morning	53 (71)
Postprandial	16 (21)
During defecation	6 (8)
Abdominal pain	84 (86)
Location of pain (n=75)	
Epigastric	46 (61)
Periumbilical	17 (23)
Diffuse	4 (5)
Other	8 (11)
Description of pain (n=48)	
Burning	13 (27)
Crampy	14 (29)
Sharp	11 (23)
Other	10 (21)
Bowel habits (n=95)	
Diarrhea	22 (23)
Constipation	7 (7)
Both	2 (2)
Normal	64 (67)
Relief with hot showers (n=57)	
Yes	52 (91)
No	5 (9)

Mayo Clin Proc. 2012;87:114-9.

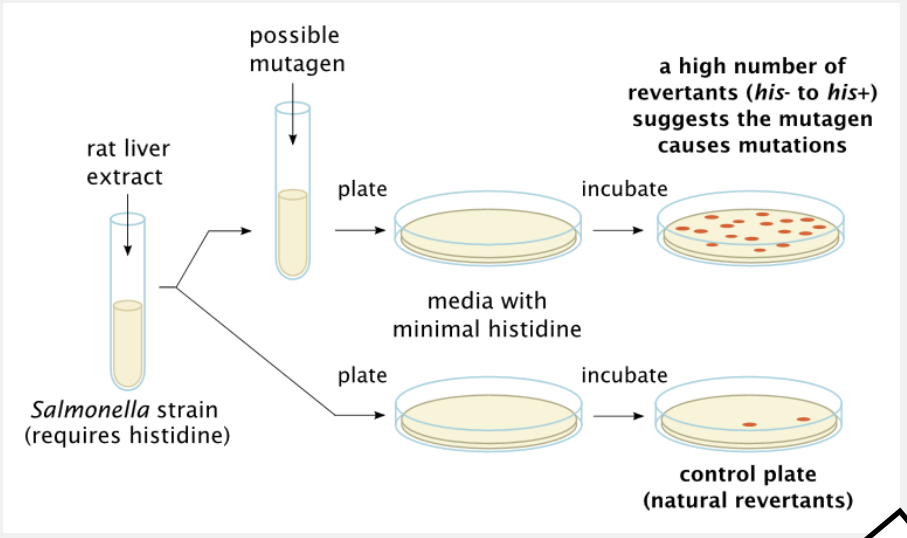
What are the risks?

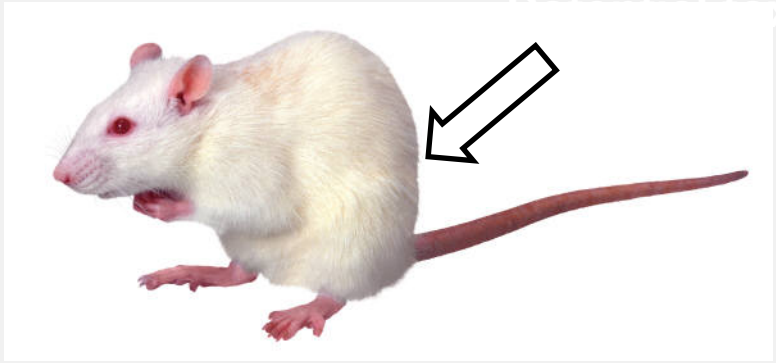
Cannabis and cancer



Separate the weed from the chaff

Cannabinoid vs. cannabis smoke



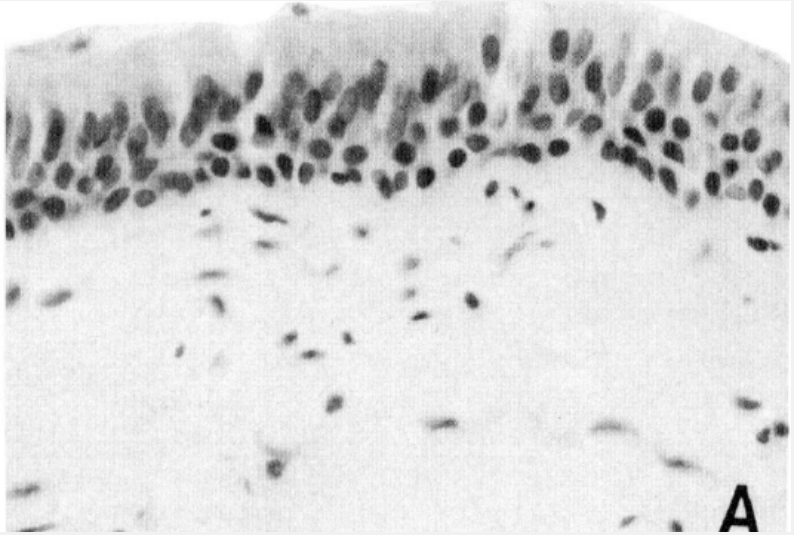


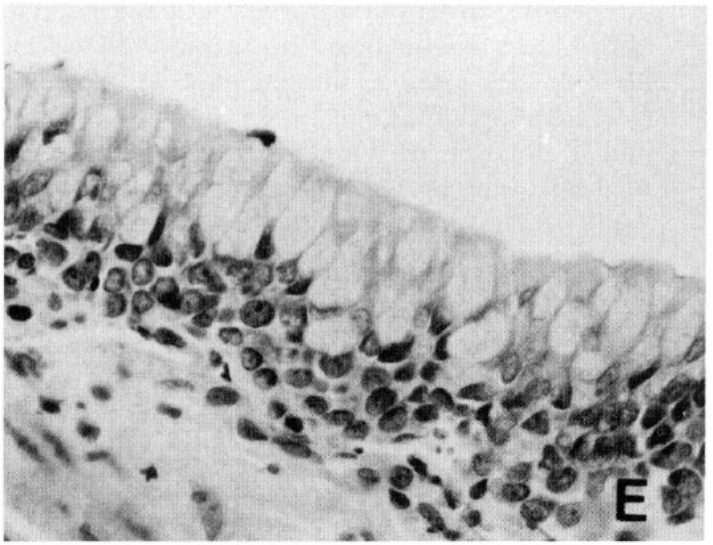
Cannabinoids:
Not mutagenic/carcinogenic

Cannabis smoke:
Mutagenic/carcinogenic

Cannabis Smoke

- Similar carcinogens to tobacco smoke
- Increased tar compared to tobacco smoke
- Causes pre-cancerous changes to respiratory mucosa





Fligiel et al. Chest 1997.
Maertens et al. Chem Res Toxicol 2009.

Lung Ca: Swedish Military Study

- Longitudinal study of 49,321 men
- Conscripted 1969-1970
- Assessed for baseline health factors
- Followed until 2009

Callaghan et al. Cancer Causes Control 20

Risk adjusted for tobacco smoking

Cannabis smoking	Crude HR (95% CI)	Tobacco-adjusted HR (95% CI)	Fully adjusted HR (95% CI)
Never (reference)	1	1	1
Ever	1.9 (1.3-2.75)	1.25 (0.85-1.83)	1.25 (0.84-187)
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 (0.21-20.9)	0.68 (0.21-2.16)
11-50 times	2.69 (1.26-5.74)	1.68 (0.78-3.62)	1.69 (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)
1-10 cigs/day	2.29 (1.48-3.57)		
>10 cigs/day	5.16 (3.45-7.73)		

Callaghan et al. Cancer Causes Control 201

Other studies

Study	Findings	Limitations
Hashibe (2006)	OR 0.62 (NS)	Young age pts, unmeasured confounders
Mehra (2006)	NS	Systematic review
Berthiller (2008)	OR 2.4	Inconsistent tobacco reporting
Aldington (2008)	RR 5.7 in highest uses adjusted for tobacco	Limited cases (79)

Hashibe M et al. Cancer Epi Biomark Prev. 2006. Mehra et al. Arch Int. Med. 2006
Berthiller J et al. J Thoracic Oncol 2008. Aldington et al. Eur Respr J 2008.

Meta-analysis: lung cancer

- Multi-site: US, Canada, UK, New Zealand
- Matched controls (2985)/cases (2159)
- No association between marijuana and cancer
  - Habitual vs. occ/never: OR 0.96
  - >10 joint years vs non-habitual/never: OR 0.88

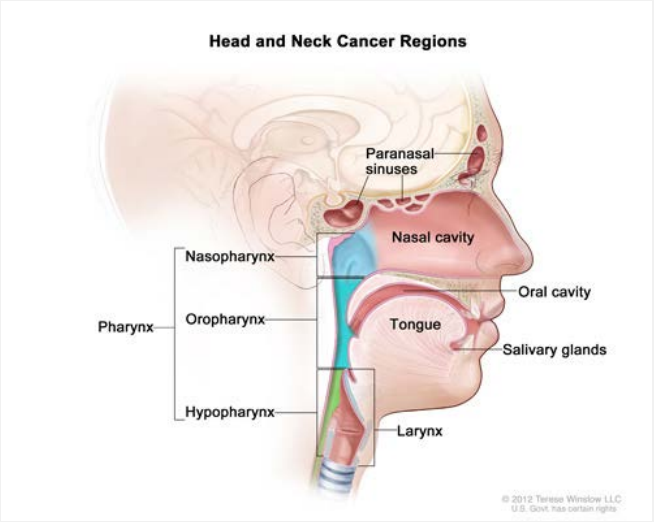
Int J Cancer. 2015;136:894-903

Head and Neck Cancer

- Major risk factors
  - Tobacco
  - Alcohol
  - Human papillomavirus (HPV) infection
- Previous studies have been mixed

INHANCE Consortium

- Over 2000 patients and 7800 controls
- Multiple sites in US and Latin America
- Mixed prospective and case-control



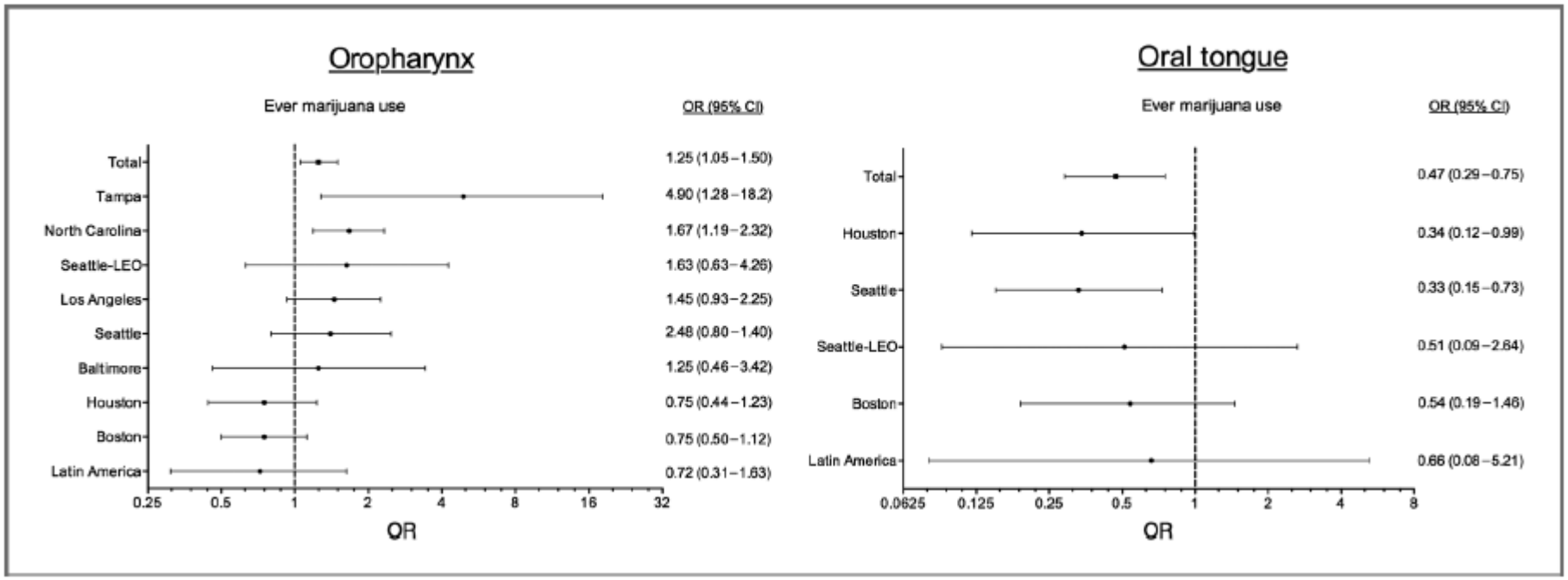
Marks MA et al. Cancer Epi Biomark Prev 2013.
www.cancer.gov

Marijuana and oropharynx cancers

Table 3. Association of marijuana use and oropharyngeal[a] cancer among never tobacco smokers/never drinkers versus ever smoker/drinkers in the INHANCE Consortium

	Never tobacco smokers and never drinkers			Ever tobacco smokers and/or ever drinkers				
Marijuana use variables	Cases	Controls	aOR (95% CI)[b]	Cases	Controls	aOR (95% CI)[b]	ROR (95% CI)	RERI (95% CI)
Ever use								
Never	103	732	1.0	981	3,232	1.0		
Ever	11	41	2.11 (0.97–4.62)	386	1,102	1.47 (1.24–1.73)	0.58 (0.28–1.26)	−0.48 (−1.43–0.47)
P (interaction by study)			0.011			<0.001		
Frequency of use (per week)[c]								
Never	103	732	1.0	981	3,232	1.0		
≤3	8	33	2.35 (0.92–5.99)	227	741	1.48 (1.21–1.81)	0.59 (0.24–1.43)	−0.42 (−0.79–−0.04)
>3	2	6	1.61 (0.31–8.50)	127	274	1.57 (1.23–2.01)	0.79 (0.15–4.14)	−0.53 (−4.77–3.71)
Missing	1	2		32	87			
P_{trend}			0.117			<0.001		
P (interaction by study)			0.004			<0.001		
Duration of use, y[c]								
Never	103	732	1.0	981	3,232	1.0		
≤10	7	31	1.82 (0.72–4.62)	179	610	1.27 (1.03–1.56)	0.63 (0.26–1.54)	−0.43 (−1.12–0.26)
>10	3	9	2.66 (0.63–11.24)	160	400	1.66 (1.32–2.09)	0.60 (0.12–2.97)	−0.28 (−1.77–1.21)
Missing	1	1		47	92			
P_{trend}			0.080			<0.001		
P (interaction by study)			0.032			<0.001		
Cumulative exposure (joint-year)[c]								
Never	103	732	1.0	981	3,232	1.0		
>0–1	5	29	1.57 (0.53–4.66)	107	462	1.27 (0.98–1.64)	0.70 (0.25–1.54)	−0.34 (−0.67–−0.01)
2–10	3	7	2.83 (0.66–12.1)	125	289	1.66 (1.29–2.12)	0.66 (0.12–3.46)	−0.53 (−1.88–1.13)
>10	2	3	3.94 (0.59–26.3)	81	183	1.48 (1.10–1.99)	0.30 (0.05–1.05)	−2.25 (−10.4–5.9)
Missing	1	2		73	168			
P_{trend}			0.037			<0.001		
P (interaction by study)			0.027			<0.001		

Marks MA et al. Cancer Epi Biomark Prev 201



Marks MA et al. Cancer Epi Biomark Prev 201

HNSCC Risk and Marijuana Use

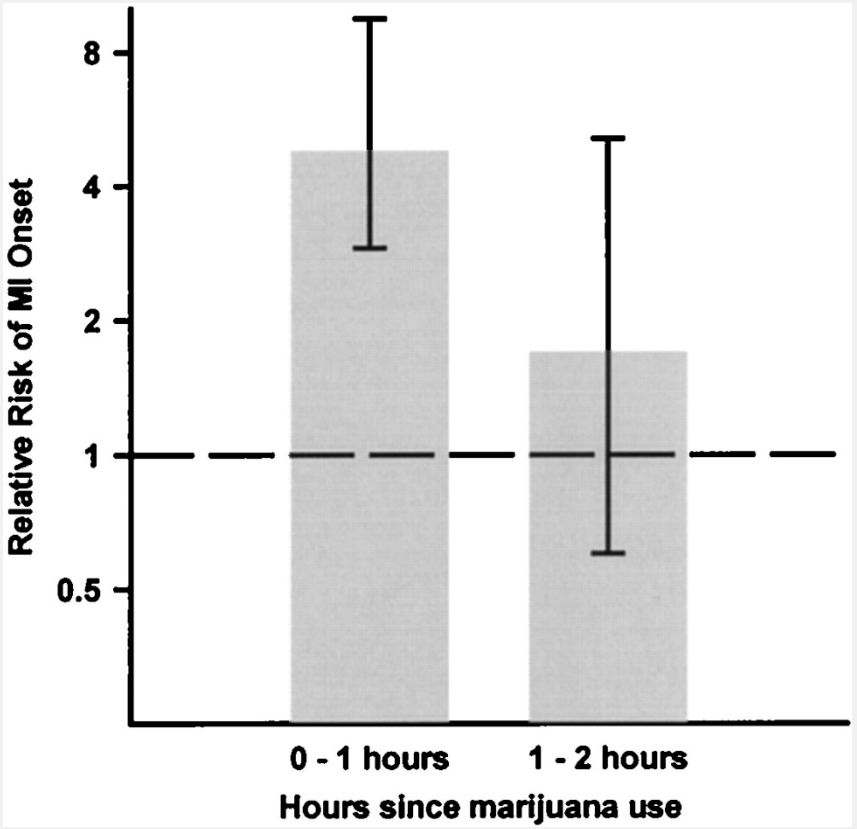
- Risk varies with location
  - Increased in oropharynx cancer (24%)
  - Decreased in oral tongue (53%)
- Dose dependent
- Oropharynx results may be confounded by HPV status

Marks MA et al. Cancer Epi Biomark Prev 2013

Marijuana and Heart Disease

Relative risk of myocardial infarction onset after smoking marijuana.

- 3882 patients with acute MI
- average 4 days after MI
- 124 (3.2%) reported smoking marijuana in prior year, 37 within 24 hours, and 9 within 1 hour of MI symptoms.
- A rare trigger of MI



Mittleman M et al. Circulation 2001;103:2805-2809

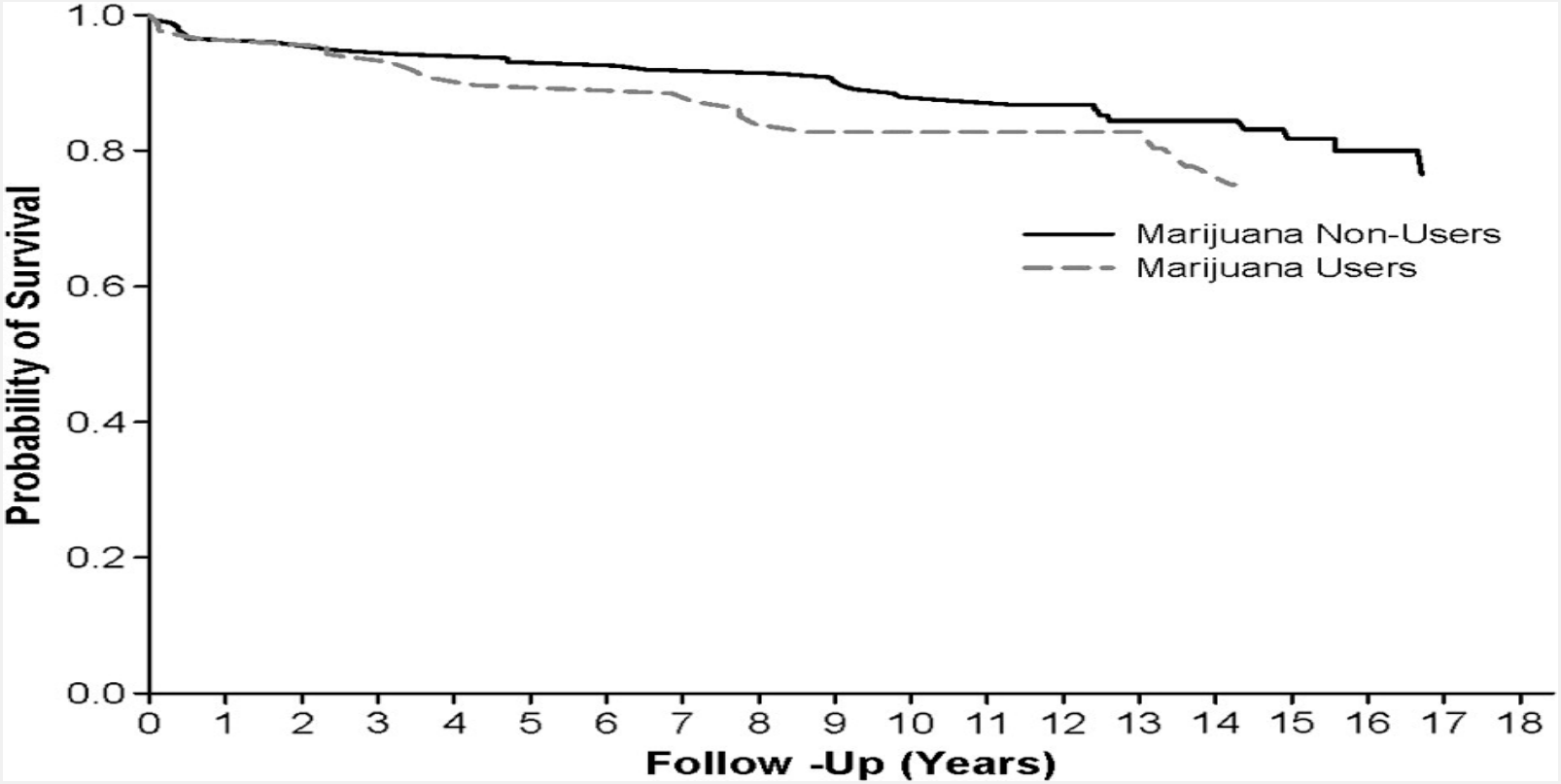
Marijuana and Mortality Following MI

- 1913 MI patients
- Mean f/u 3.8 yrs
- 52 users in prior year
- 317 deaths

	Marijuana use		*P*
	No	**Yes**	
Number	**1861**	**52**	
Deaths	**310**	**7**	
RR			
Adjusted model	**1.0**	**3.0**	**.009**
	Ref	**(1.3-7.0)**	

The adjusted model included age, sex, body mass index, marital status, race, income, education, physical activity, current smoking, former smoking, tea intake, usual and binge alcohol intake, medical history (previous AMI, congestive heart failure, diabetes, hypertension, and non-cardiac comorbidity), receipt of thrombolytic therapy, and medication use (aspirin, β-blockers, calcium-channel antagonists, ACE inhibitors, digoxin, diuretics, and hypolipidemic agents).

Mukamal, et al. Am Heart J 2008;155:465e470.



Kaplan-Meier estimates of post-MI survival among 87 marijuana users and 174 propensity-matched nonusers.

Marijuana use and long-term mortality among survivors of acute myocardial infarction

Cannabis, Ischemic Stroke, and Transient Ischemic Attack: A Case-Control Study

- Consecutive stroke patients (160), 18 to 55 years, compared with control patients (160) matched for age, sex, and ethnicity & admitted to hospital without cardiovascular or neurological diagnoses.

Table 2. Comparison Between Stroke and TIA Patients and Controls

	Stroke/TIA Patients	Control Participants	Total	*P* Value
Men:women	100:60	94:66	320	0.492*
Age, mean (SD), y	44.8 (8.5)	44.8 (8.7)		0.979†
Ethnicity				
European New Zealand	83	88	171	
Māori	22	19	41	
Pacific	24	25	49	0.910*
Current smoking	60	33	93	0.001*
Cannabis use	25	13	38	0.038*

*χ^2 test; and †*t* test test.

Adjusted for tobacco use, no association (OR, 1.59; 95% CI 0.71–3.70).

Barber PA, et al. Stroke. 2013;44:2327-2329.

Marijuana and Lung Disease

Marijuana and Lung Diseases

Review of 89 published papers from largely human studies concerning potential associations between marijuana smoking and pulmonary consequences.

Taskin. Ann Am Thorac Soc 2013;10:239–247.

Table 1. Effects of regular use of marijuana alone on chronic respiratory symptoms and lung function in comparison with nonsmoking control subjects

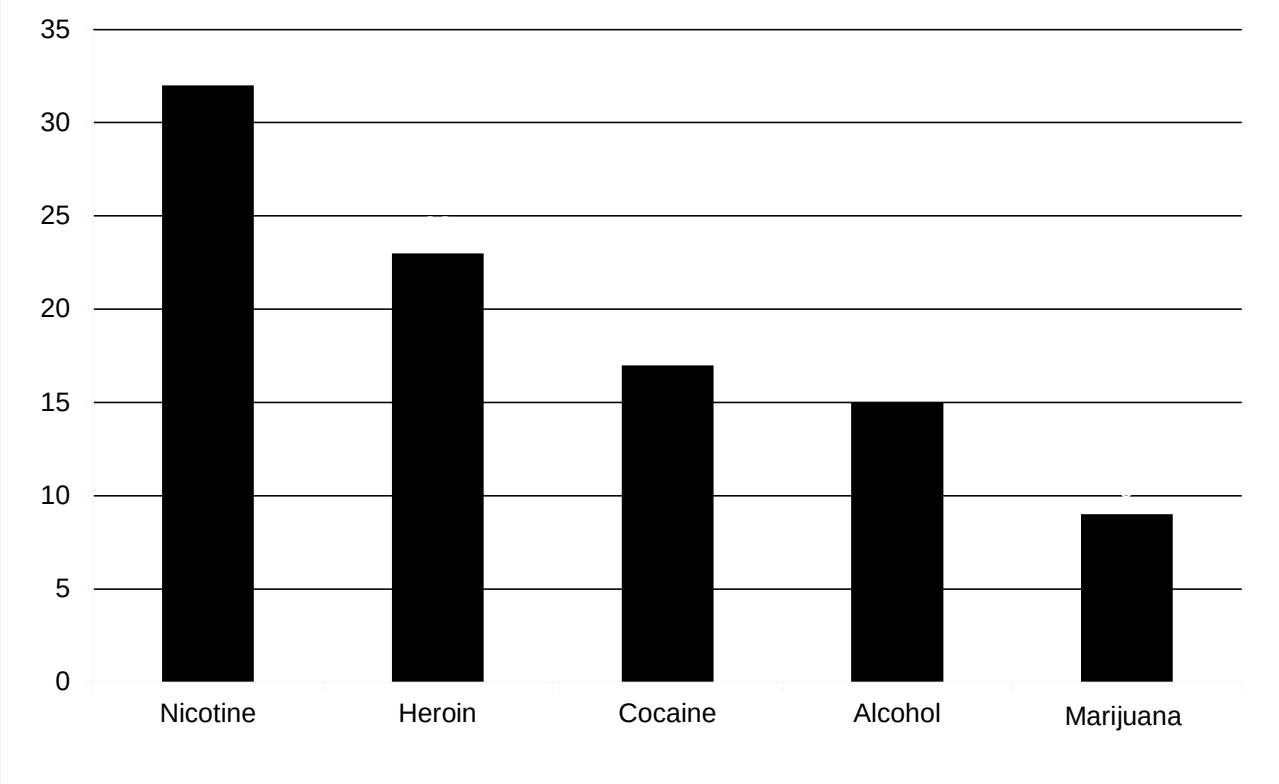
Symptoms
Increased prevalence of chronic cough or sputum (17, 18, 20–22), wheezing (17, 18, 20–22), and shortness of breath (20)
Increased incidence of acute bronchitic episodes (17) or clinic visits for acute respiratory illness (19)
Lung Function
No difference in FEV_1 or FVC (17, 20, 21)
Increase 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)

Definition of abbreviations: D_{LCO} = single-breath diffusing capacity for carbon monoxide; FRC = functional residual capacity; Raw = airway resistance; RV = residual volume; SGaw = specific airway conductance; TLC = total lung capacity.

Taskin. Ann Am Thorac Soc 2013;10:239–247.

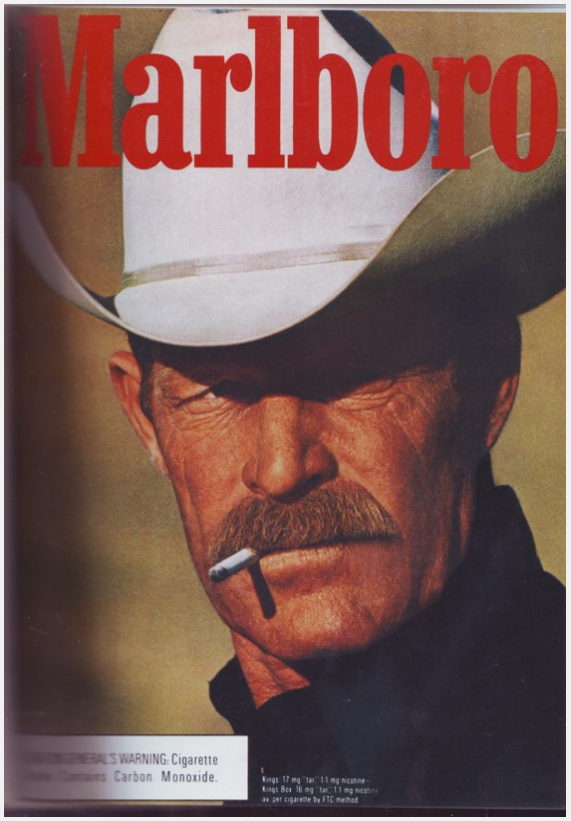
Marijuana and Drug Dependency

Lifetime dependence risk with use



Hall and Degenhardt (2009), Lancet 374:1383-1391

Physical withdrawal



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Mean withdrawal scale (MWS)=13

MWS =13.2

Budney et al. (2008), J Substance Abuse Treatment 35:362-368

Marijuana and Neuropsychology

Some cause for concern

- 2003 meta-analysis: learning/memory changes
- Twin study: slight decrease in intelligence
- New Zealand: worse cognition, esp. in adolescent onset use
- Increased risk of psychosis
  - Earlier onset psychosis (2.7 yrs)
  - More likely to develop psychosis (OR 1.41)

Int Neuropsychol Soc. 2003;9:679. Psychol Med. 2004;34:1239. Proc Natl Acad Sci U S A. 2012;109:E2657-64. Lancet. 2007;370:319. Arch Gen Psychiatry. 2011;68:555.

The Colorado Perspective

- Lots of dispensaries: 497 medical, 292 retail
- Edibles present a particular challenge
- Possibly increased health care burden
  - Estimated 1-2% of U. Colorado Hosp ER visits
  - Marijuana-related burns
  - Increased marijuana N/V (prev ratio 1.92)
  - Accidental ingestions among children

Moshe, Zane, Heard. JAMA 2014
JAMA Pediatr. 2013;167:630-633

What to tell patients

- A lot of the risks/benefits are not known
- Keep it away from children
- Be wary with adolescents
- Be careful with edibles

Conclusions

- Marijuana is composed of numerous cannabinoids: TCH and CBD are most important
- Good data as a pain med, limited for other symptoms
- No clear association with cancer or cardiopulmonary disease
- Associated with dependence