Cannabis:

Basic Biology and Implications for Medicine and Mental Health

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Disclosures

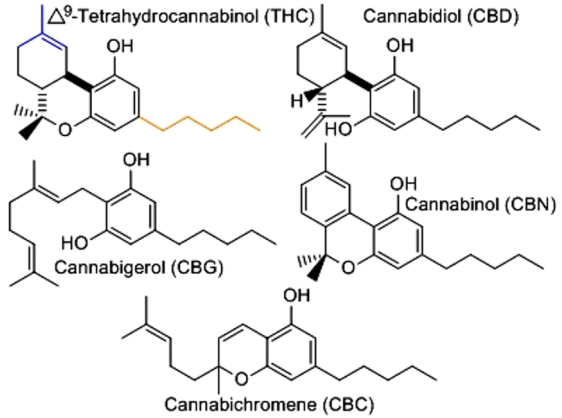
- Research Contract H. Lundbeck A/S
- Scientific consultant for Psy Therapeutics

Outline

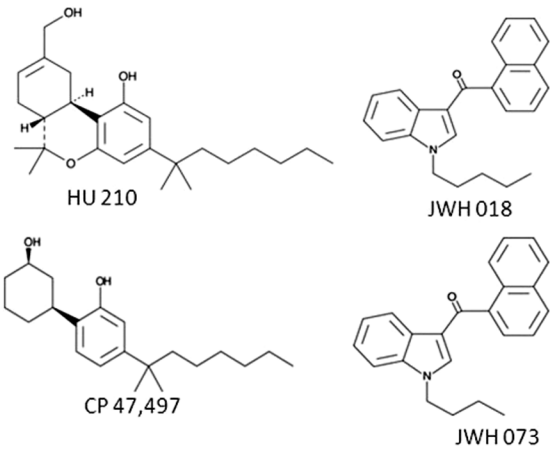
- Cannabis, cannabinoids and endocannabinoid
- Medical Cannabis Introduction
- Cannabis and Pain
- Cannabidiol and Epilepsy
- Cannabis Adverse Effects
- Problem Cannabis Use
- Cannabis and Mental Health Outcomes: focus on Schizophrenia

The Basics

Natural vs. Synthetic



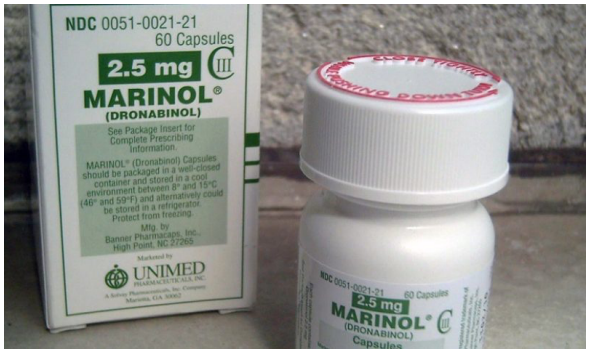
Marijuana, hashish



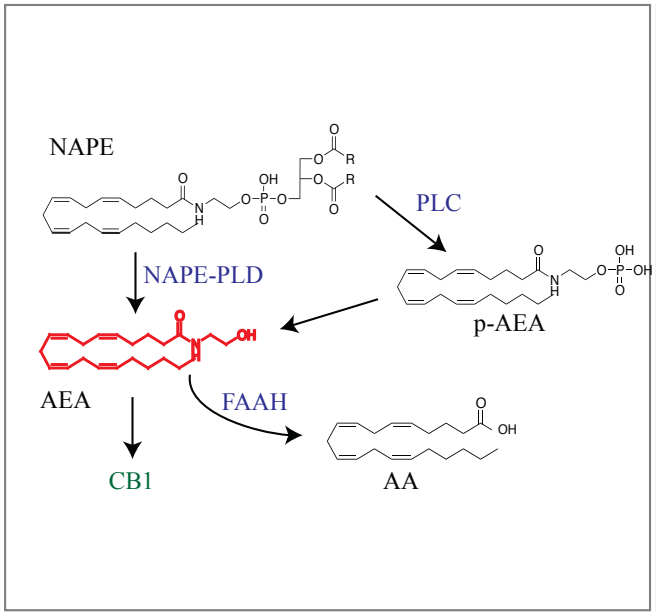
Spice, spike 99, K2

Cannabinoids

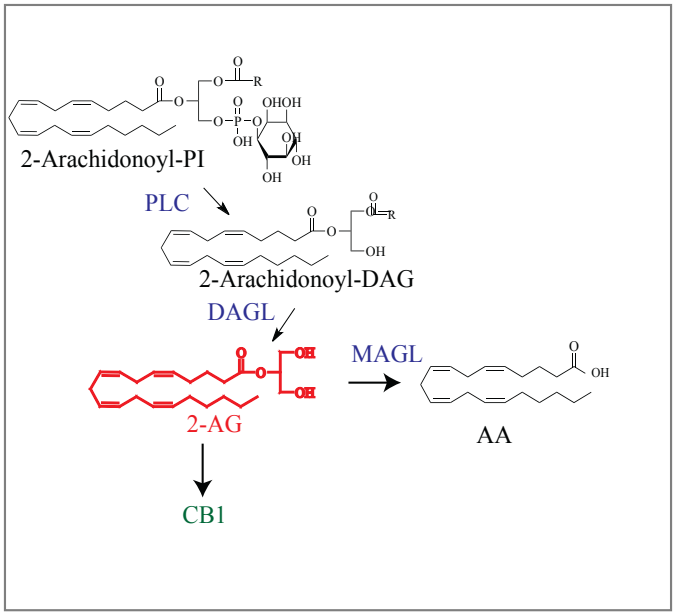
Cannabinoids



Endogenous cannabinoids

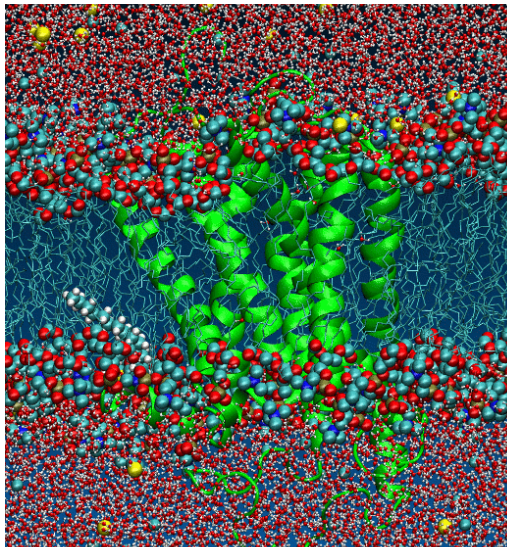


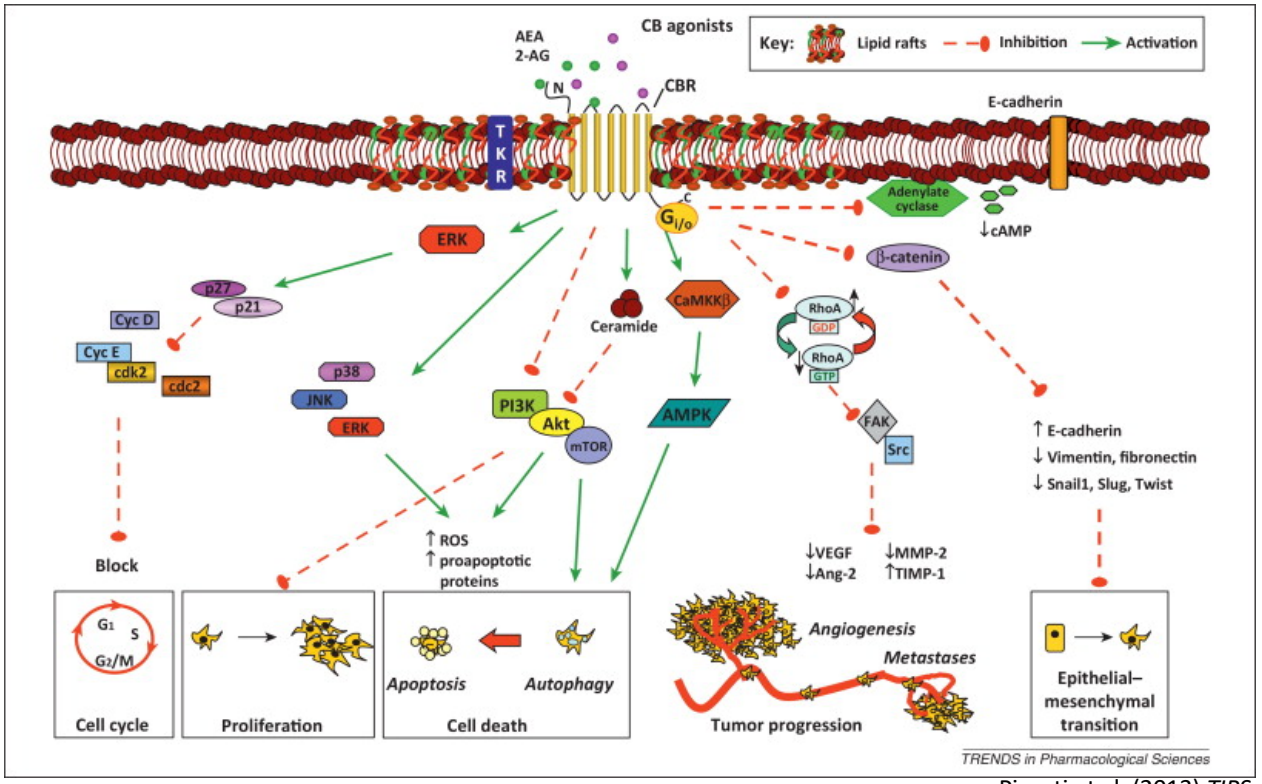
Anandamide (AEA)



2-arachidonoylglycerol (2-AG)

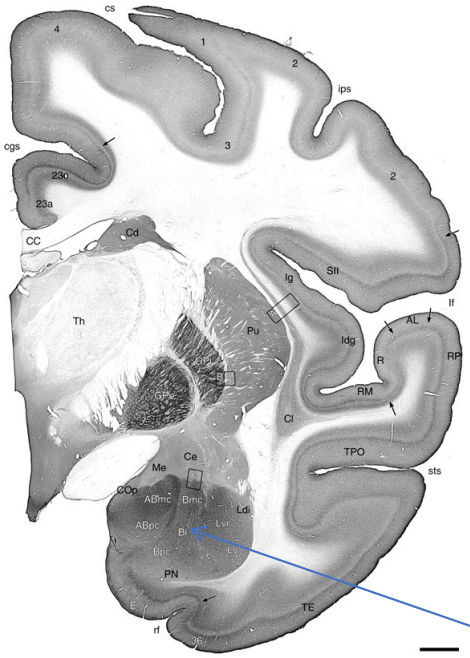
Cannabinoid Receptors





Pisanti et al. (2013) *TIPS*

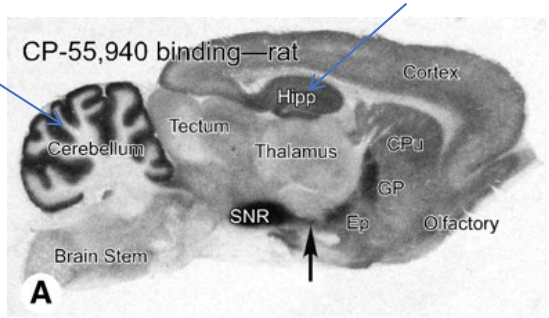
Cannabinoid Receptors

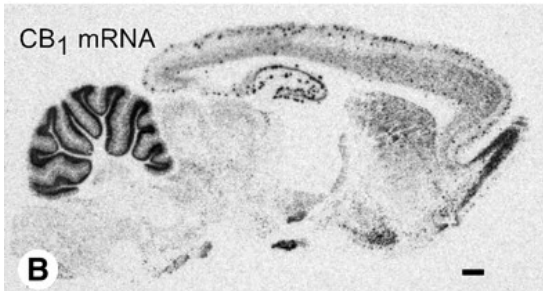


Eggan and Lewis, 2010

Ataxia

Memory problems

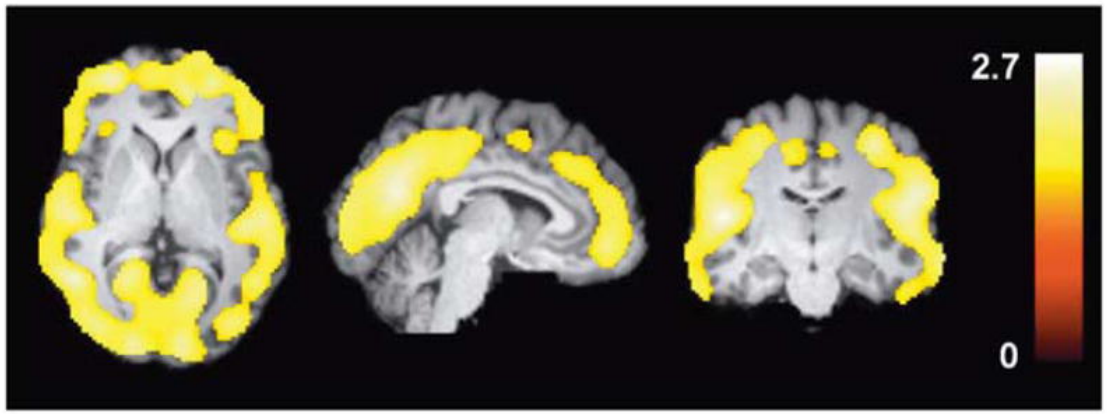


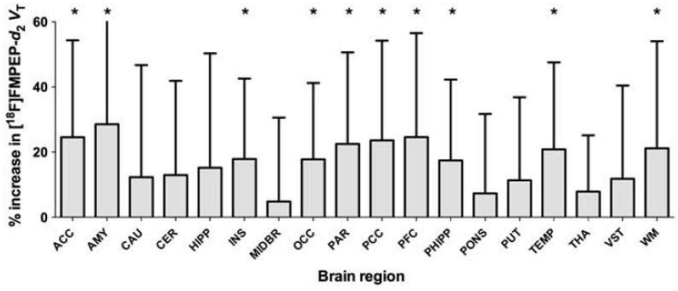


Freund et al., 2003

Mood changes

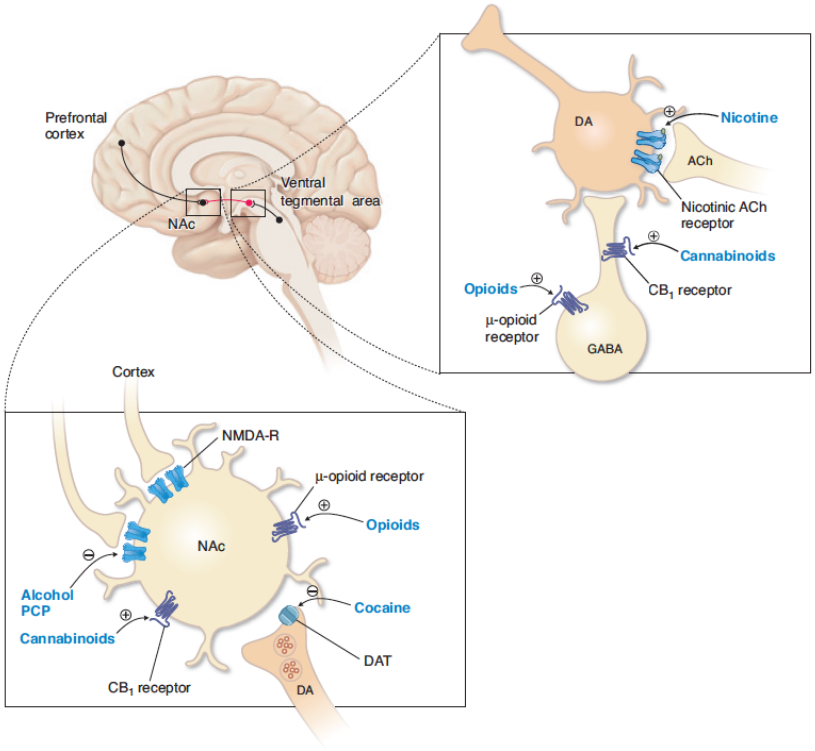
CB1 receptor desensitization in humans

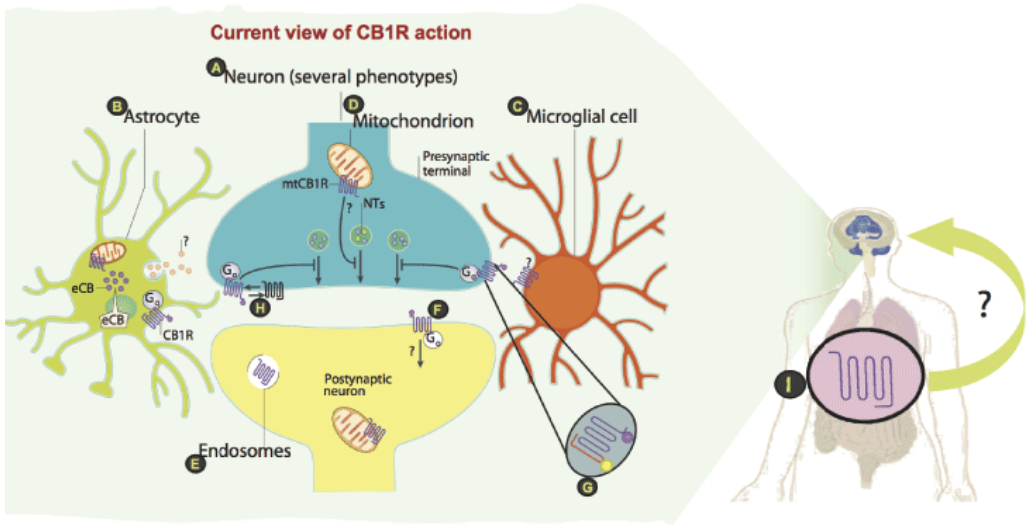




Hirvonen et al. 2012

Synaptic Effects of Cannabinoids





Medical Cannabis: What, Where, Why and How

What

FDA-APPROVED CANNABINOID MEDICATIONS IN THE UNITED STATES

SYNTHETICALLY DERIVED MEDICATIONS		
Marinol (pill) and Syndros (solution)	Dronabinol (active ingredient; synthetic THC)	Indications: ■ Stimulate appetite to counteract weight loss in patients with AIDS or cancer. ■ Mitigate nausea and vomiting associated with chemotherapy.
Cesamet	Nabiolone (active ingredient; chemical structure similar to THC)	Indications: ■ Mitigate nausea and vomiting associated with chemotherapy.
BOTANICAL EXTRACT FROM THE CANNABIS PLANT		
Epidiolex (solution)	CBD (purified form)	Indications: ■ Seizures associated with severe forms of epilepsy (Lennox-Gastaut syndrome and Dravet syndrome).

Abbreviations: AIDS, acquired immune deficiency syndrome; CBD, cannabidiol; FDA, US Food and Drug Administration; THC, tetrahydrocannabinol.
From US Food and Drug Administration[5]; Orrange S.[6]

Nierengarten (2019), Contemp. Ped.

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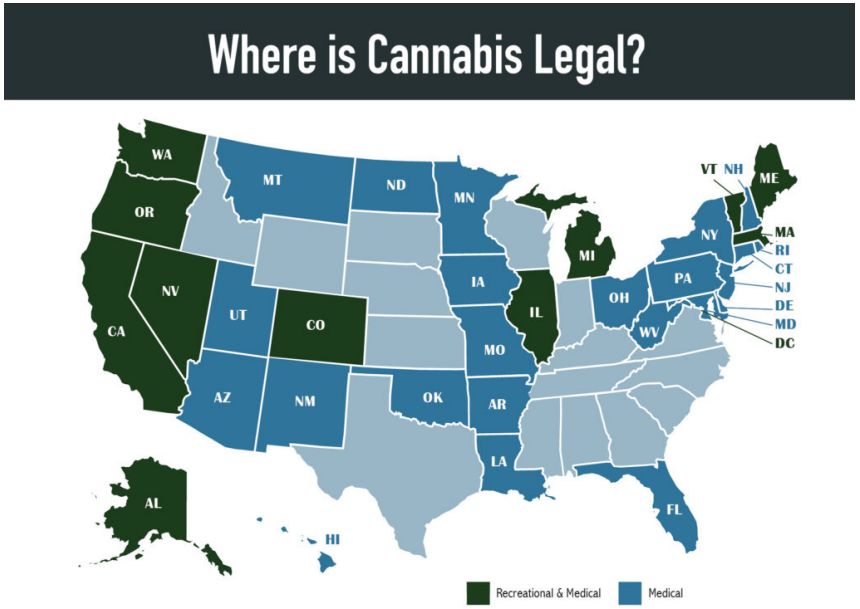
What

- In adults with chemotherapy induced nausea and vomiting, oral cannabinoids are effective antiemetics.
- In adults with chronic pain, patients who were treated with cannabis or cannabinoids are more likely to experience a clinically significant reduction in pain symptoms
- In adults with multiple sclerosis (MS) related spasticity, short-term use of oral cannabinoids improves patient-reported spasticity symptoms.
- For these conditions the effects of cannabinoids are modest; for all other conditions evaluated there is inadequate information to assess their effects.

Where



Recreational & Medical	
Alaska	Michigan
California	Nevada
Colorado	Oregon
Illinois	Vermont
Maine	Washington
Massachusetts	Washington, D.C.

Medical Only			
Arizona	Hawaii	New Hampshire	Oklahoma
Arkansas	Louisiana	New Jersey	Pennsylvania
Connecticut	Maryland	New Mexico	Rhode Island
Delaware	Minnesota	New York	Utah
Florida	Missouri	North Dakota	West Virginia
Iowa	Montana	Ohio	

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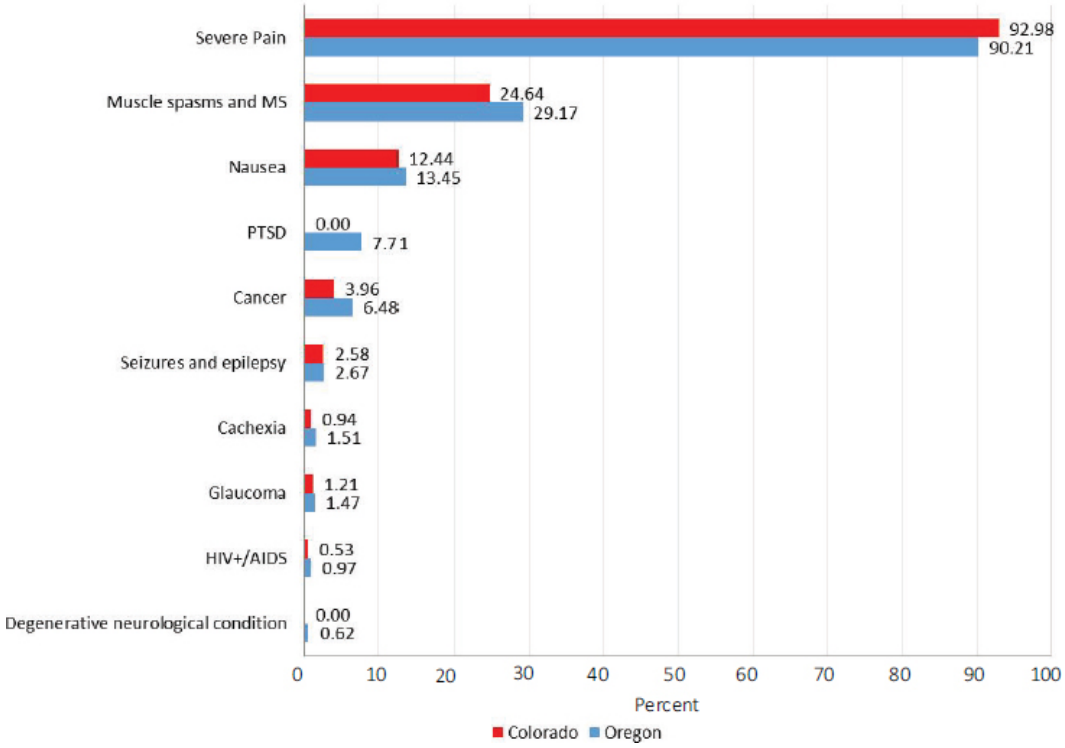
Why



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How

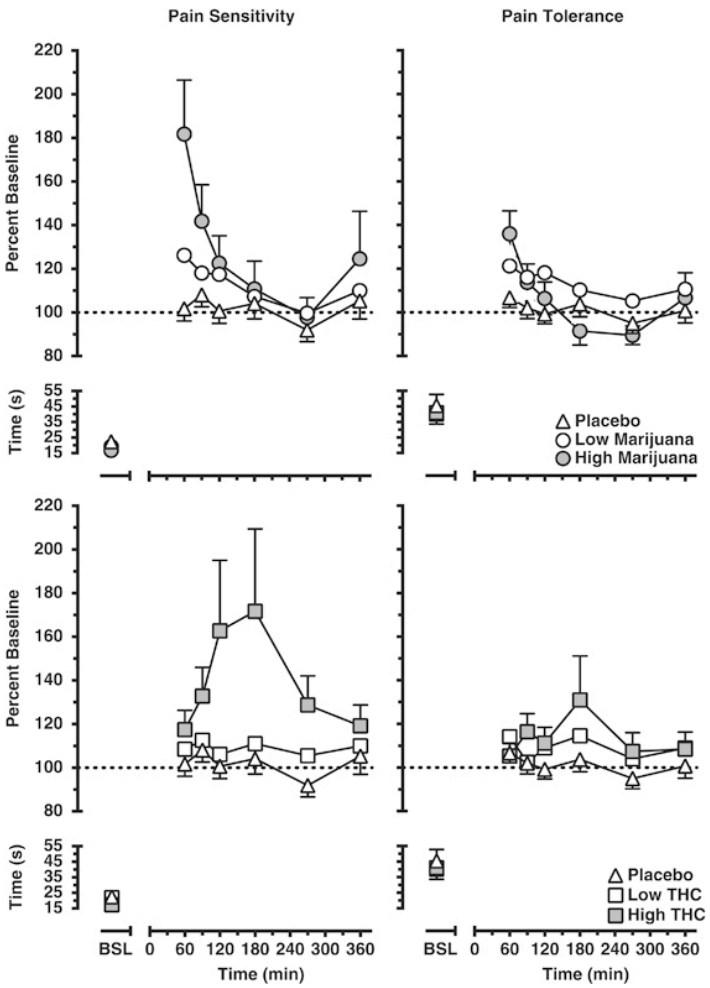
Table 2 Differences between inhaled and oral cannabinoid administration

Characteristics	Inhaled	Oral
THC and CBD concentrations in available products sold in Canada	THC: <1–30%; CBD: <1–20%	THC: <1–30 mg/mL (maximum concentration); CBD: <1–25 mg/mL or more (no maximum concentration)
Titration characteristics	Quick titration	Lengthier titration
Ease of dosing	More challenging with higher potency strains	More precise with standardized preparations (oils, tinctures)
average bioavailability of THC	10–25%	10% (variable 6–20%)
Active metabolites	Δ9-THC > 11-OH-THC	Δ9-THC < 11-OH-THC
Psychoactivity	THC-mediated	THC-mediated*
First onset of effects	3–10 minutes	60–90 minutes
Peak concentration	2–10 minutes	1–3 hours
Peak psychoactive effects: euphoria, depersonalization, sensory perceptions	15 minutes	3 hours
Peak cognitive effects: short-term memory, attention, concentration	15 minutes	5 hours
Duration of effects	2–4 hours	8–12 hours or more
Dosing frequency	5–6/day	1–3/day

*, 11-OH THC may be more psychoactive than Δ 9 THC.

Cannabis and Pain

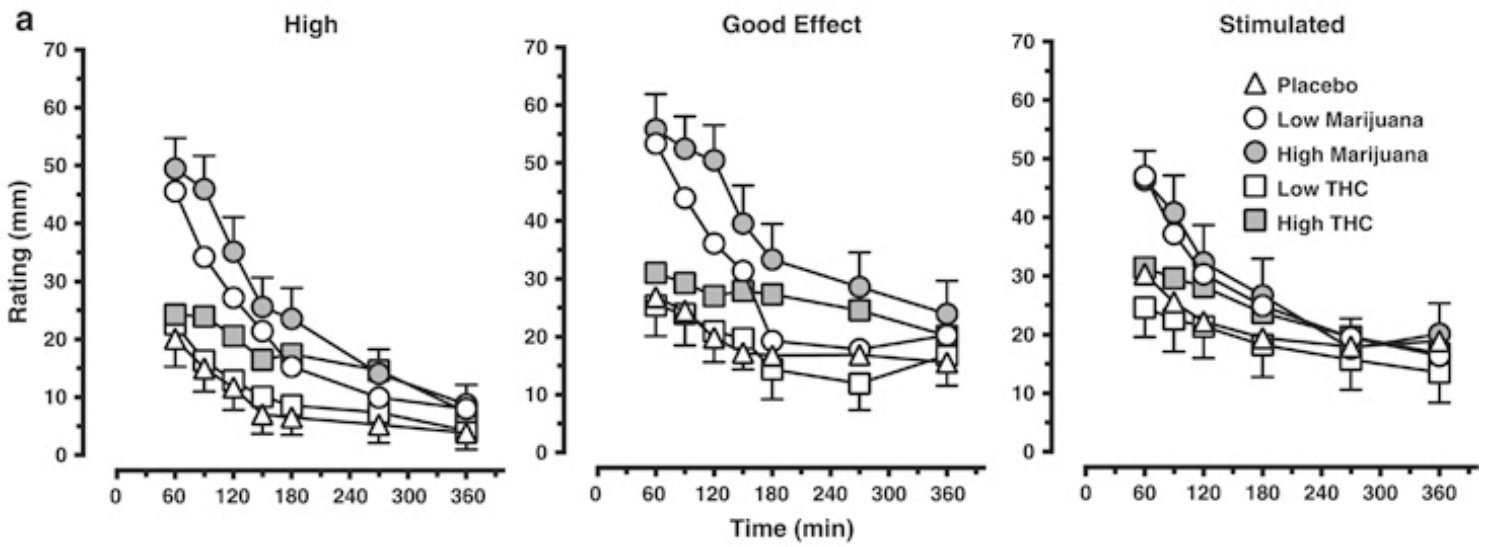
Cannabis and Pain in Human Experimental Studies



Both smoked marijuana and oral THC reduce pain sensation in a CPT laboratory pain model

Cooper et al. (2013). *NPP*

Cannabis and Pain in Human Experimental Studies

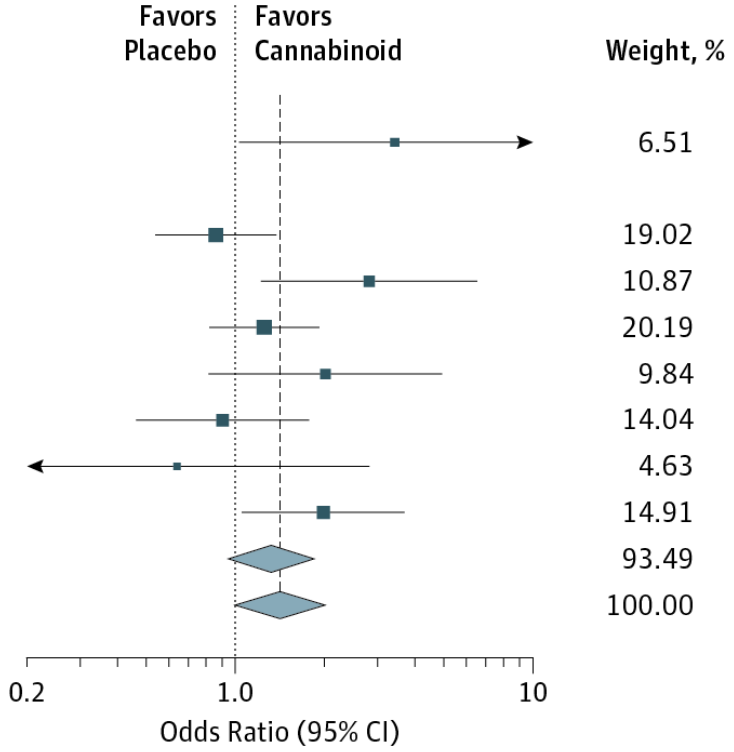


Only smoked active marijuana resulted in significant “high” sensation

Cooper et al. (2013). *NPP*

Chronic Pain

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)
Tetrahydrocannabinol (smoked)					
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)
Nabiximols					
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)
Subtotal $I^2 = 44.5\%$, ($P = .0.94$)	241	660	209	660	1.32 (0.94-1.86)
Overall $I^2 = 47.6\%$, ($P = .0.64$)	254	685	215	685	1.41 (0.99-2.00)



There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity

Whiting et al. (2015), *JAMA*

Table 2. Summary of Evidence of the Benefits of Cannabis in Populations With Chronic Pain

Pain Type	Studies	Findings	Strength of Evidence*	Comments
Neuropathic	11 low-ROB studies; combined *N* = 593: 4 of smoked THC (28, 31, 33, 39); combined *N* = 150 3 of vaporized THC (36, 40, 47); combined *N* = 97 3 of nabiximols (24, 27, 42); combined *N* = 312 1 of oromucosal spray delivering THC or THC+CBD (43); *N* = 34 1 unclear-ROB study of nabiximols (26); *N* = 30 1 high-ROB trial (35); *N* = 125	Studies did not find a clinically significant between-group difference on continuous pain scales, but a higher proportion of intervention patients had clinically significant pain relief up to several months later In a meta-analysis of 9 studies, intervention patients were more likely to report ≥30% improvement in pain (combined RR, 1.43 [95% CI, 1.16–1.88]; I^2 = 38.6%; *P* = 0.111)	Low	Few patients enrolled in most low-ROB studies; inconsistent results; marked differences among studies in dosing and delivery mechanism; brevity of study duration; low applicability to formulations available in dispensaries
Cancer	2 unclear-ROB trials; combined *N* = 596; 177–360 per study: 1 of nabiximols (25) 1 of nabiximols and THC oromucosal spray in separate groups (23) 1 high-ROB trial of THC capsules (34), *N* = 10	No consistent clinically significant effects on pain	Insufficient	Small number of studies; methodological flaws, including high attrition, lack of clarity about randomization and blinding procedures, and use of nonstandard outcome measures

From: The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General HarmsA Systematic Review

Ann Intern Med. 2017;167(5):319-331. doi:10.7326/M17-0155

Table 2. Summary of Evidence of the Benefits of Cannabis in Populations With Chronic Pain

Pain Type	Studies	Findings	Strength of Evidence*	Comments
Other/mixed	1 unclear-ROB trial of nabiximols for rheumatoid arthritis (21); *N* = 58 1 high-ROB trial of EPC002A (orally ingested 99% THC) for abdominal pain (46); *N* = 65 3 cohort studies of mixed forms of cannabis (smoked, orally ingested, vaporized) for fibromyalgia (48), inflammatory bowel disease/Crohn disease (49), and nociceptive and/or neuropathic pain (50)	Small improvements in pain	Insufficient	Larger observational study had high attrition

From: The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General HarmsA Systematic Review

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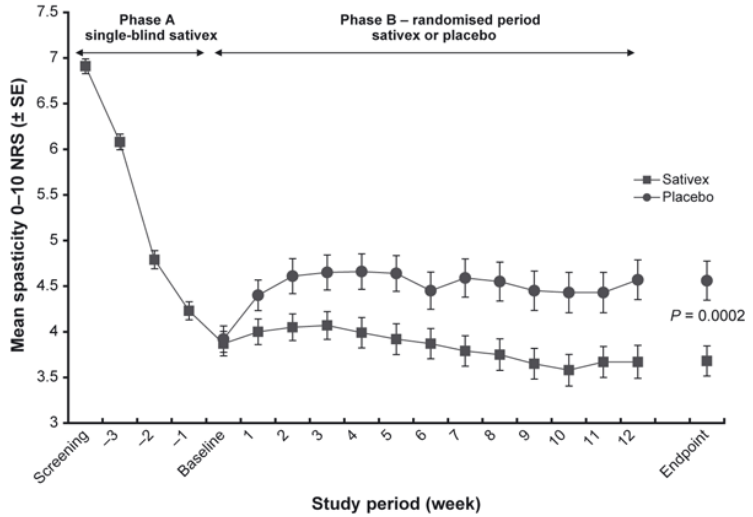
Multiple Sclerosis

Produced and marketed by GW Pharmaceuticals. Approved in the UK for the treatment of pain and spasticity associated with MS

Extracted from pharma grown cannabis in the UK.

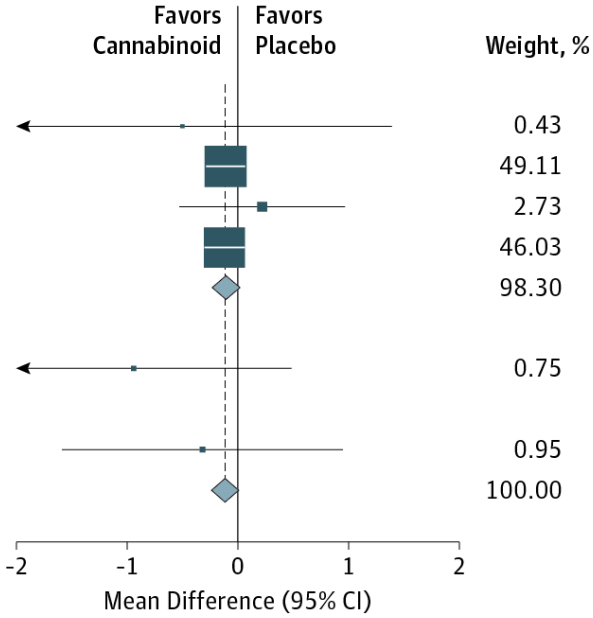
Sublingual preparation of THC:CBD in a 1:1 ratio. Also contains >100 trace cannabinoids



Novotna et al. (2015), *E. J. Neurol.*

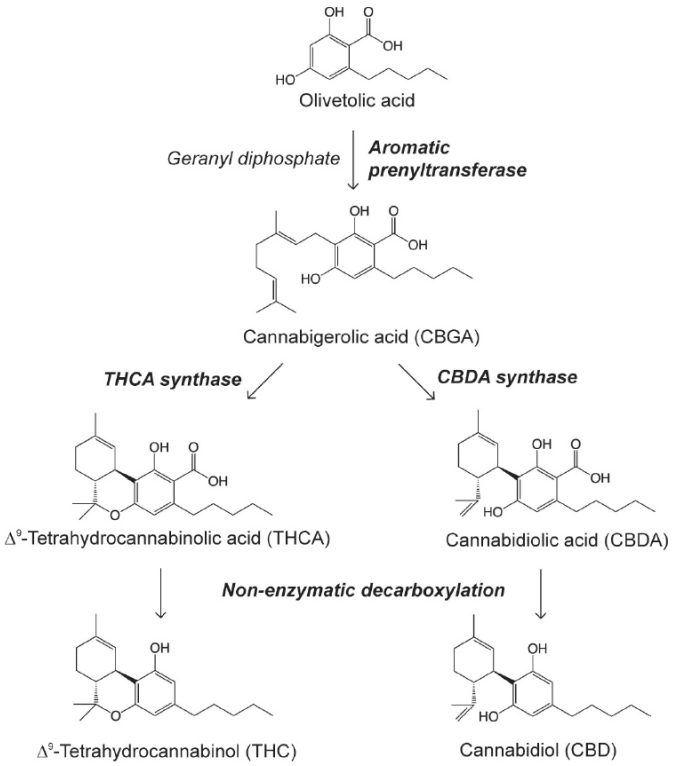
Multiple Sclerosis

Score Change With Cannabinoid vs Placebo by Study	Cannabinoid		Placebo		Mean Difference (95% CI)
	No. of Patients	Mean (SD) Score Change	No. of Patients	Mean (SD) Score Change	
Nabiximols					
Collin,[125] 2010	156	-3.3 (9.25)	160	-2.8 (7.81)	-0.50 (-2.39 to 1.39)
Collin,[127] 2007	114	-.64 (.56)	63	-.53 (.58)	-0.11 (-0.29 to 0.07)
Wade,[129] 2004	73	-.37 (2.51)	70	-.59 (2.04)	0.22 (-0.53 to 0.97)
Berman,[87] 2007	40	-.13 (.43)	44	-.01 (.42)	-0.12 (-0.30 to 0.06)
Subtotal $I^2 = 0.0\%$, ($P = .82$)	383		337		-0.11 (-0.23 to 0.02)
Dronabinol					
Zajicek,[131] 2003	197	-1.86 (7.95)	207	-.92 (6.56)	-0.94 (-2.37 to 0.49)
Tetrahydrocannabinol/cannabidiol					
Zajicek,[131] 2003	207	-1.24 (6.6)	207	-.92 (6.56)	-0.32 (-1.59 to 0.95)
Overall $I^2 = 0.0\%$, ($P = .80$)	590		544		-0.12 (-0.24 to 0.01)



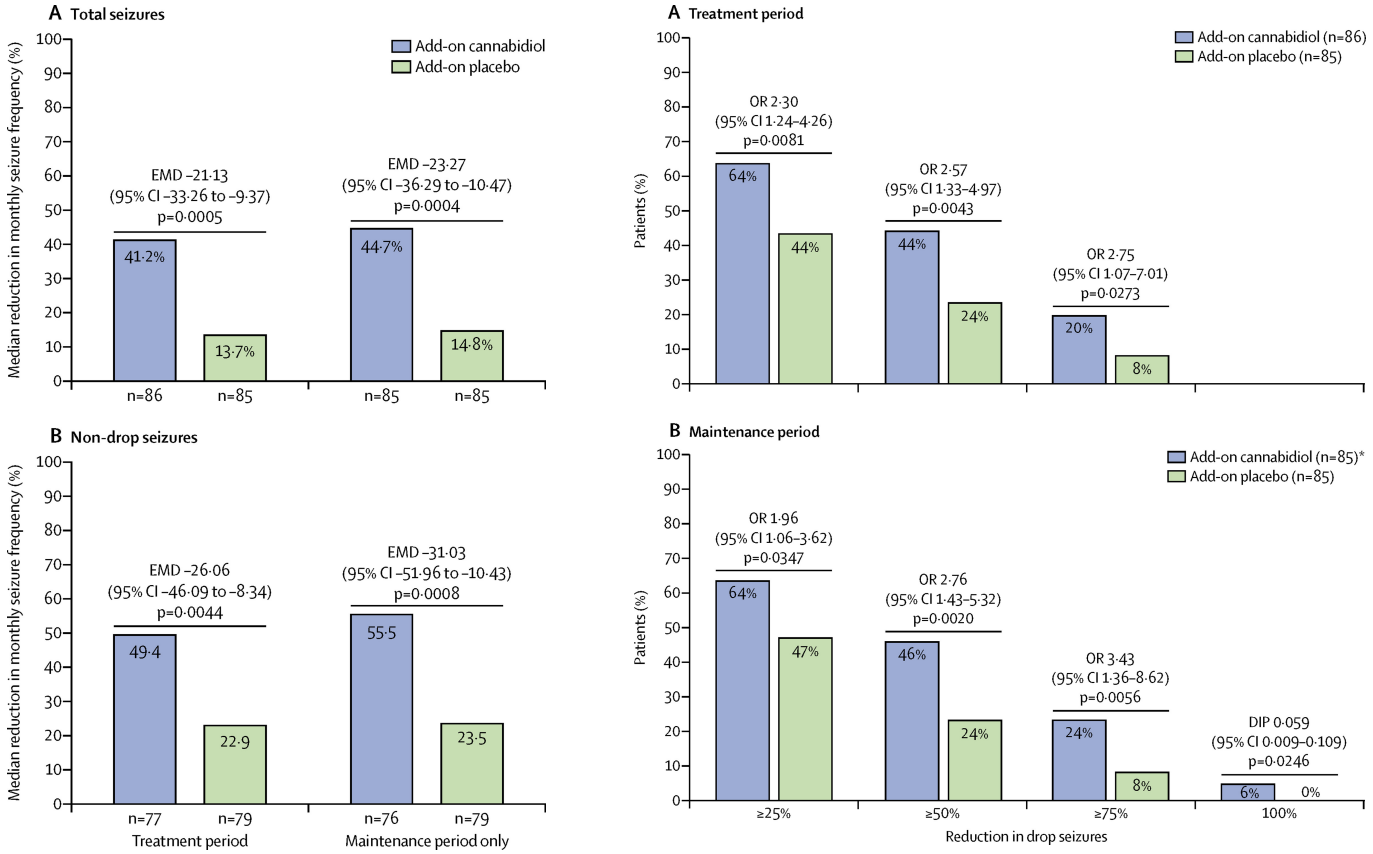
Whiting et al. (2015), *JAMA*

Cannabidiol and Epilepsy



Cannabidiol and Epilepsy

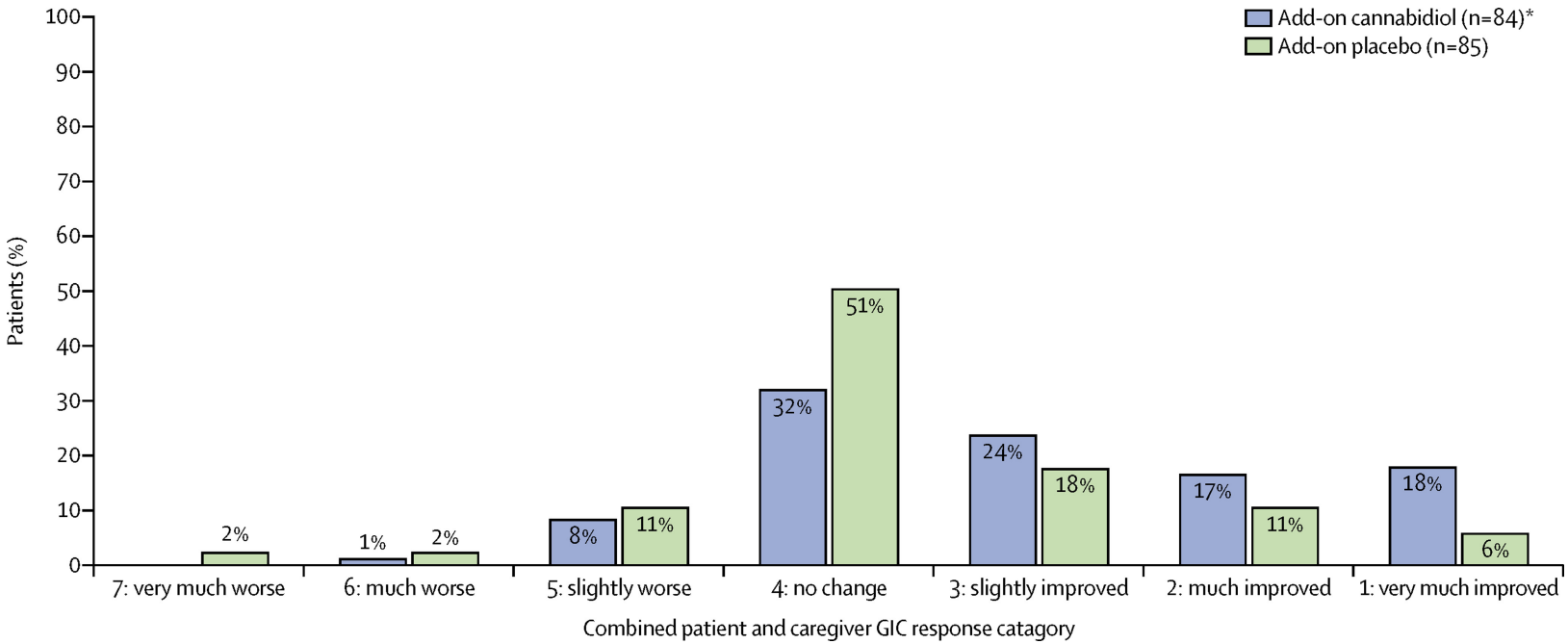
20 mg/kg



A randomised, double-blind, placebo-controlled, phase 3 trial at 24 clinical sites in the USA (n=17), the Netherlands (n=1), and Poland (n=6). Eligible patients were aged between 2 and 55 years, with a clinical diagnosis of Lennox-Gastaut syndrome

Thiele et al. (2018), *The Lancet*

Cannabidiol and Epilepsy



Thiele et al. (2018), *The Lancet*

Adverse Effects and Problemed Use

Table 3. Summary of Evidence for the Harms of Cannabis in Chronic Pain and General Adult Populations

Outcome	Studies	Findings	Strength of Evidence*	Comments
General AEs	2 systematic reviews (10, 11) and 1 observational study of chronic pain (50)	Cannabis-based treatments associated with higher overall risk for short-term, nonserious AEs.	–	Consistent findings except for serious AE
Motor vehicle accidents	Meta-analysis (51) of 21 observational studies; combined *N* = 239 739	Increase in collision risk (OR, 1.35 [95% CI, 1.15–1.61]).	Moderate	Small but significant increase in risk seen consistently across numerous sensitivity analyses and after adjustment in meta-regression analyses
Medical AEs				
Pulmonary function	2 low-ROB prospective cohort studies (52, 53) with 20–32 y follow-up; combined *N* = 6053 1 systematic review (54) of 5 observational studies (3 cohort, 2 cross-sectional); combined *N* = 851	In young adults, low levels of cannabis smoking did not adversely affect lung function over about 20 y A previous meta-analysis of 5 studies found no increased risk for pulmonary adverse effects (OR, 0.80 [95% CI, 0.46–1.39])	Young adults: moderate Older adults: no evidence	2 well-done prospective cohort studies, but limited information about effects of heavy use and no information in older or multimorbid populations
Cardiovascular effects	2 high-ROB observational studies: 1 case–crossover (55), *N* = 3882; 1 cohort (56), *N* = 2097	Cannabis use at time of MI not associated with mortality after mean 12.7-y follow-up, but longitudinal use not assessed Risk of MI within 1 h of cannabis use significantly elevated compared with periods of nonuse, but finding may be inflated by recall bias (OR, 4.8 [95% CI, 2.9–9.5])	Insufficient	Recall bias; inadequate controlling for confounders; lack of longitudinal exposure data
Lung cancer	1 patient-level meta-analysis (57) of 6 case–control studies; combined *N* = 2150 1 high-ROB cohort study (58); *N* = 49 231	Meta-analysis found no association between light cannabis use and lung cancer	Low	Recall bias; mostly light users, few heavy users; large cohort study had no information about exposure over time

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Head/neck/ oral cancer	Meta-analysis (59) of 9 case–control studies; combined *N* = 5732	No association between cannabis use and cancer (OR, 1.02 [95% CI, 0.91–1.14]); generally consistent across studies and no evidence of dose-response	Low	Imprecise exposure measurement with potential recall bias; ever-use among studies ranged from 1%–83%
Testicular cancer	Meta-analysis (60) of 3 high-ROB case–control studies; combined *N* = 719	Increased cancer risk for weekly users compared with never-users seen with nonseminoma cancer but not seminoma cancer (OR, 1.92 [95% CI, 1.35–2.72])	Insufficient	Potential confounding from recall bias and tobacco use
Transitional cell cancer	1 high-ROB VA case–control study (61); *N* = 52	Risk of cancer with >40 joint-years cannabis use vs. none (OR, 3.4; unadjusted *P* = 0.012).	Insufficient	1 very small case–control study with several methodological flaws
Mental health AEs				
Suicidal behaviors	1 meta-analysis (62) of 4 observational studies	Significantly increased odds of suicide with any cannabis use (OR, 2.56 [95% CI, 1.25–5.27])	Insufficient	Inconsistent results; inadequate exposure ascertainment and adjustment for confounding
Mania	1 meta-analysis (63) of 2 prospective studies	Increased incidence of new-onset mania symptoms among populations without diagnosis of bipolar disorder (OR, 2.97 [95% CI, 1.80–4.90])	Low	Small number of studies; exposure not well-characterized in 1 study, but other was large community-based cohort study also showing dose–response effect
Psychosis	1 systematic review (64) 8 studies (65-71, 74) including patients without psychotic symptoms at baseline: 3 low ROB, 3 medium ROB, 2 high ROB	History of cannabis use associated with increased risk for psychotic symptoms	Low	Consistent evidence from large observational studies and some evidence of increased risk with higher levels of use; consistent with data from small experimental studies suggesting risk of acute psychosis in some patients; magnitude of risk unclear and not specifically studied in chronic pain populations
Cognitive effects	2 systematic reviews (72, 73)	Active long-term cannabis use associated with small negative effects on all aspects of cognition Mixed, inconsistent findings on long-term effects in past users.	Moderate Insufficient (past use)	Consistent data from large number of studies on effects on active long-term use, but inconsistent findings from smaller number of studies regarding effects in those who abstained and no data available specifically in chronic pain populations

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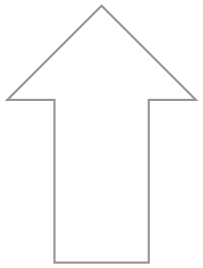
Problem Cannabis Use

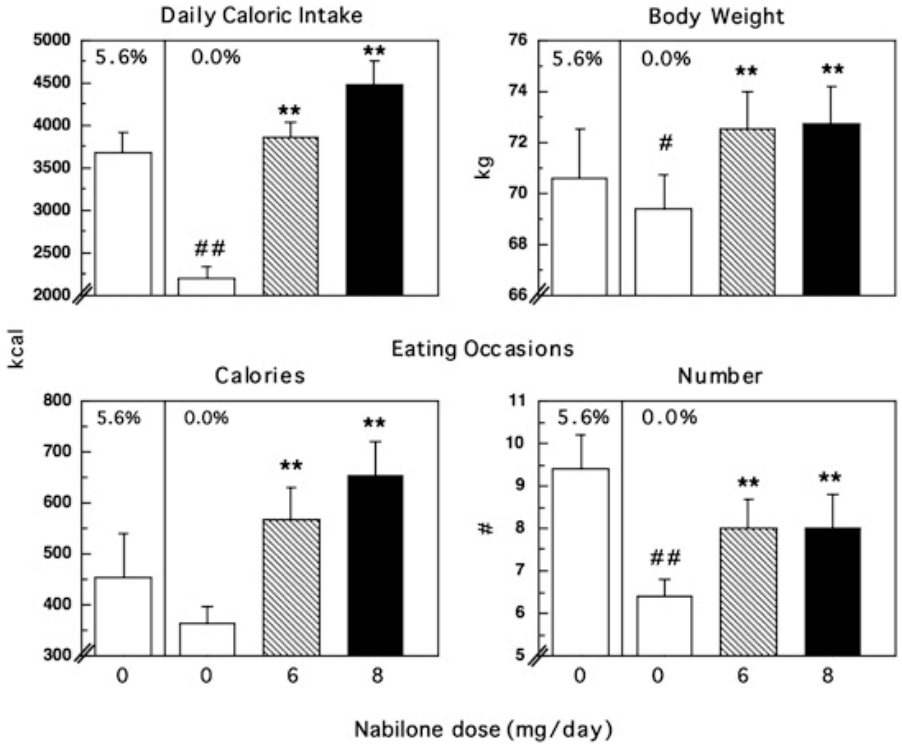
- 4.2 million Americans reported experiencing symptoms in the past year that would qualify them for cannabis use disorder.

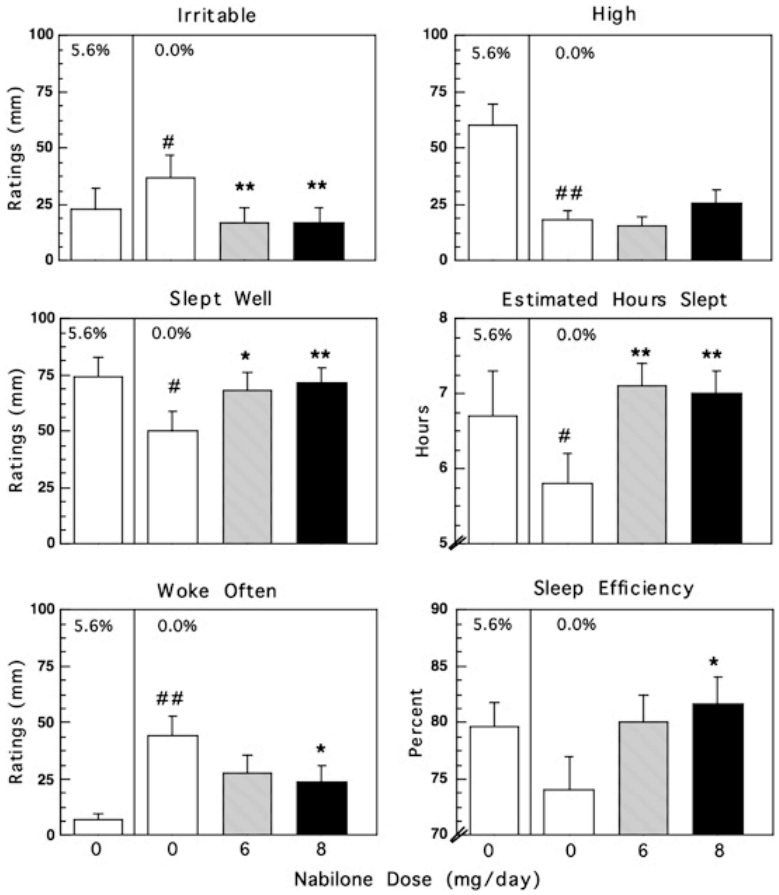
- Risk factors include:
  - **Initiating cannabis use at a young age.**
  - Being male and smoking cigarettes.



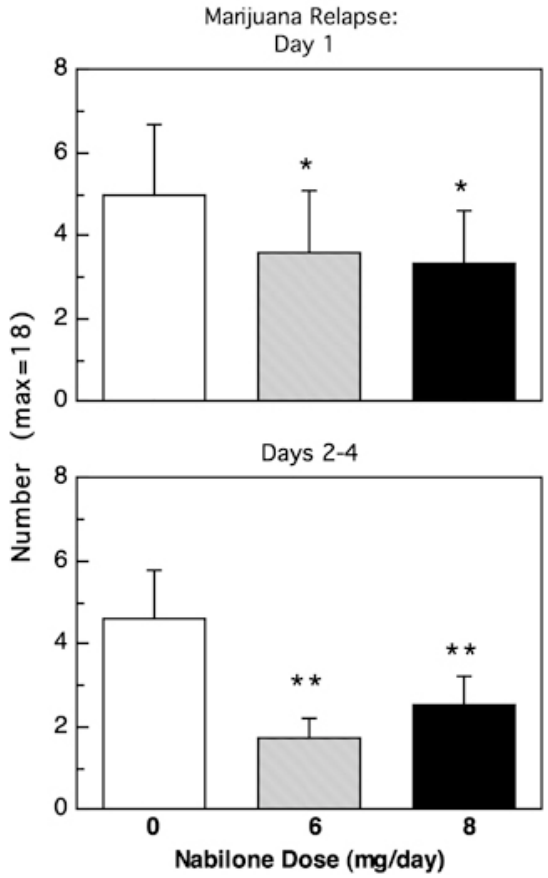
Greater frequency of cannabis use also increases likelihood of developing problem cannabis use.

Cannabis Withdrawal and Dependence Treatment



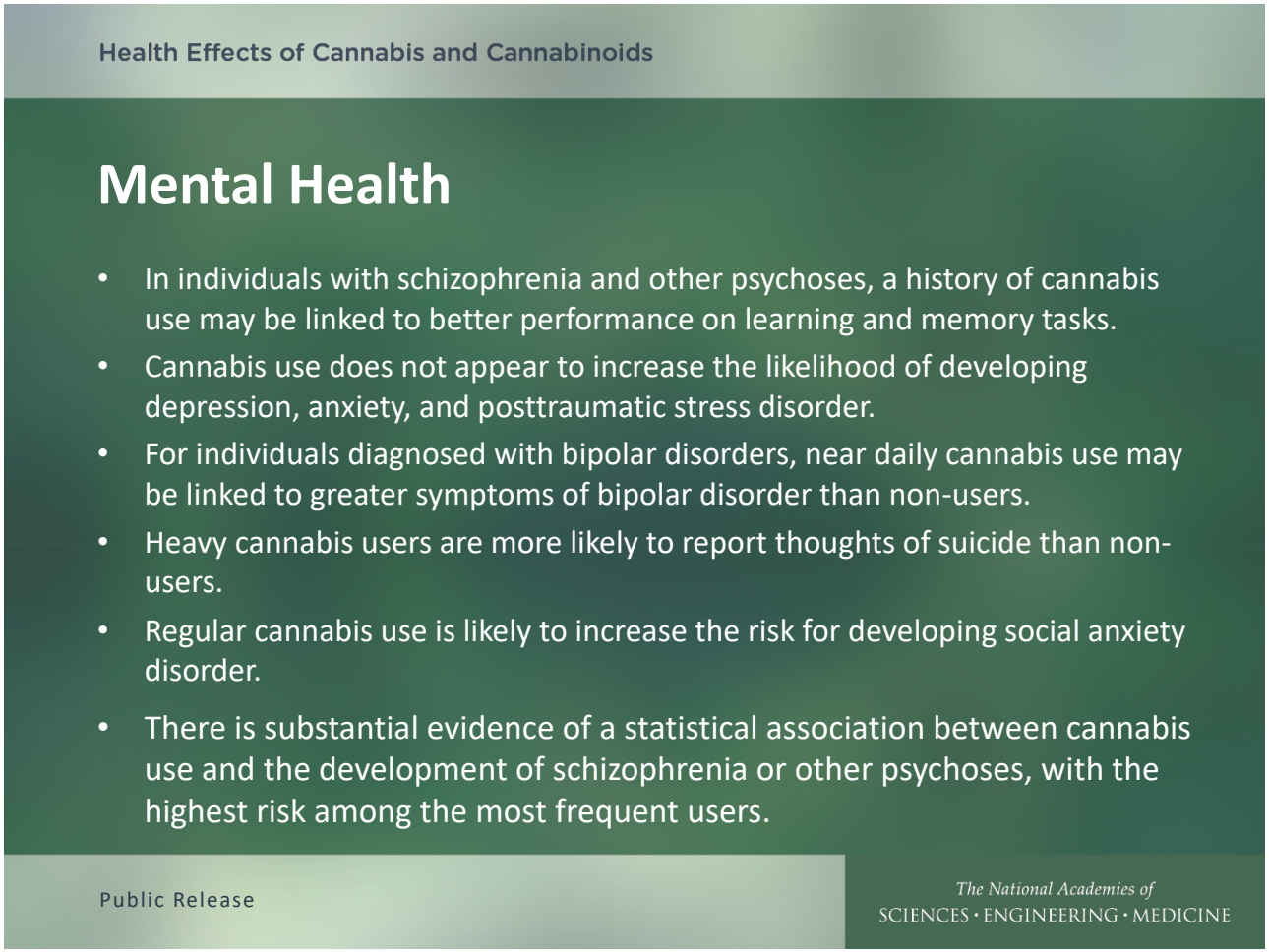


Marijuana Withdrawal and Dependence Treatment

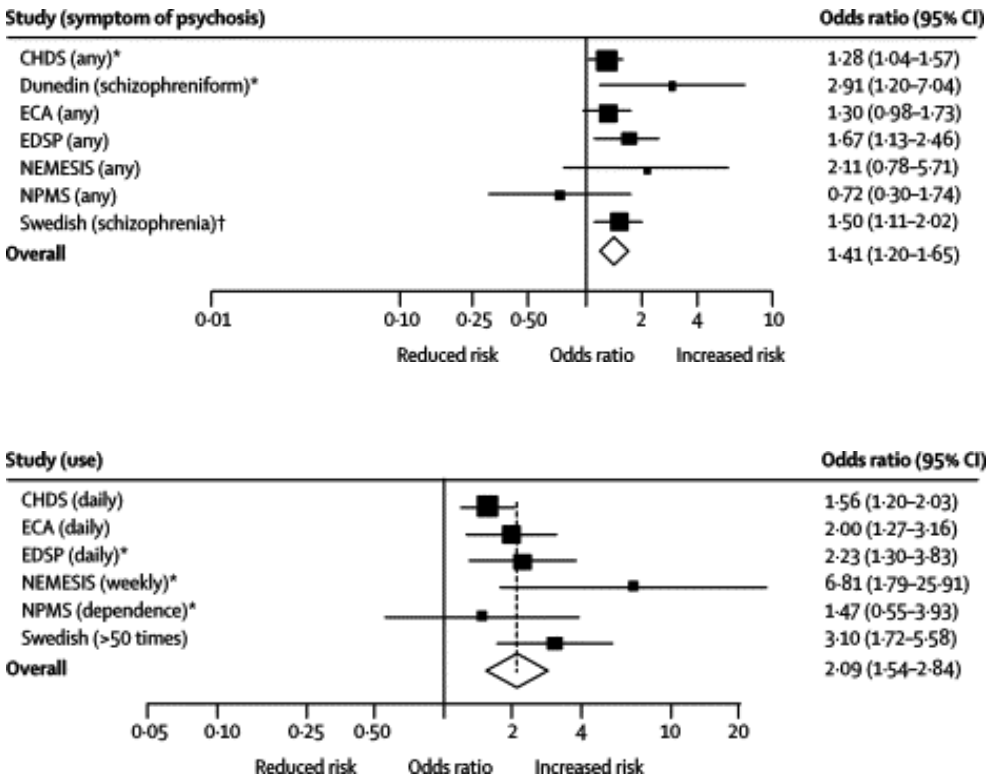


Mirtazapine (30 mg/day) and quetiapine (200 mg/day) substantially reversed withdrawal-related disruptions in sleep and food intake, yet did not decrease cannabis relapse in the laboratory, while baclofen (60, 90 mg/day) had little effect on any measure (Haney et al., 2010; Cooper et al., 2012).

Cannabis Use and Mental Health Outcomes

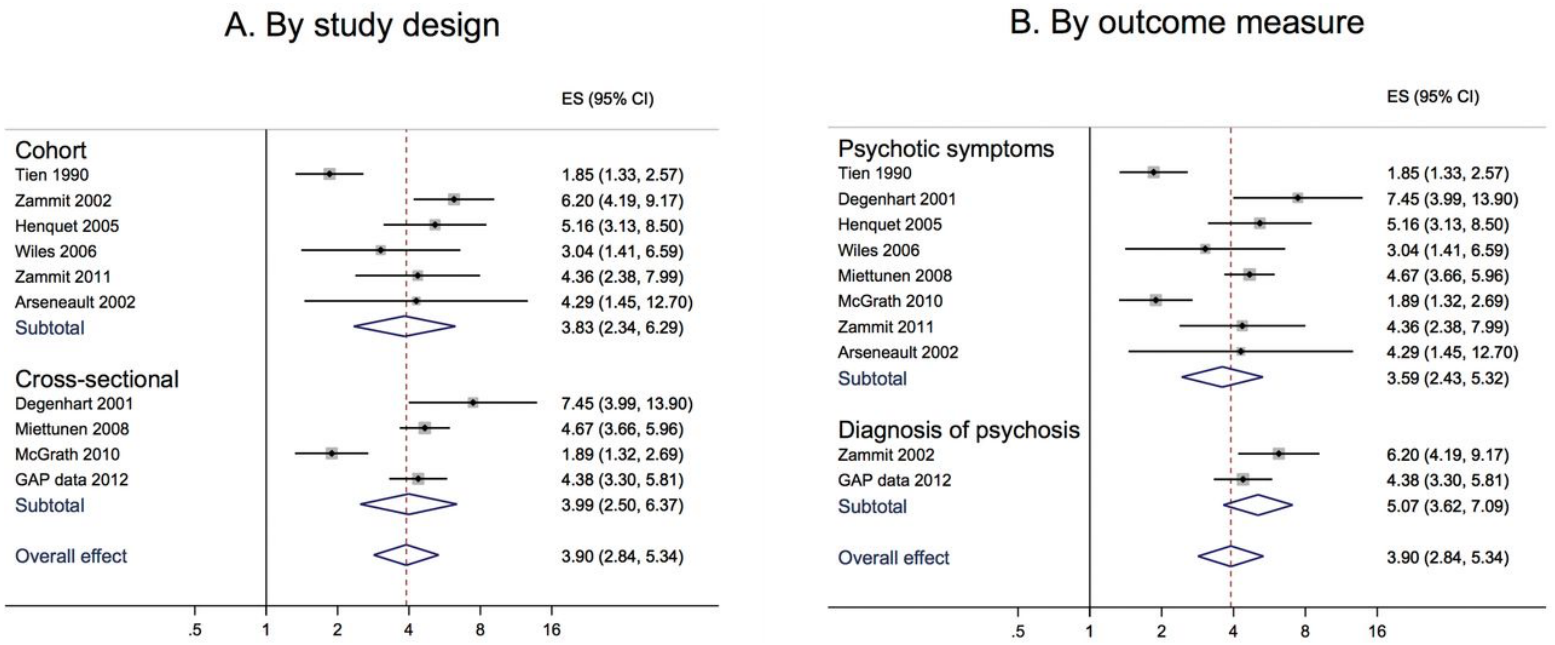


Cannabis use as a risk factor for schizophrenia



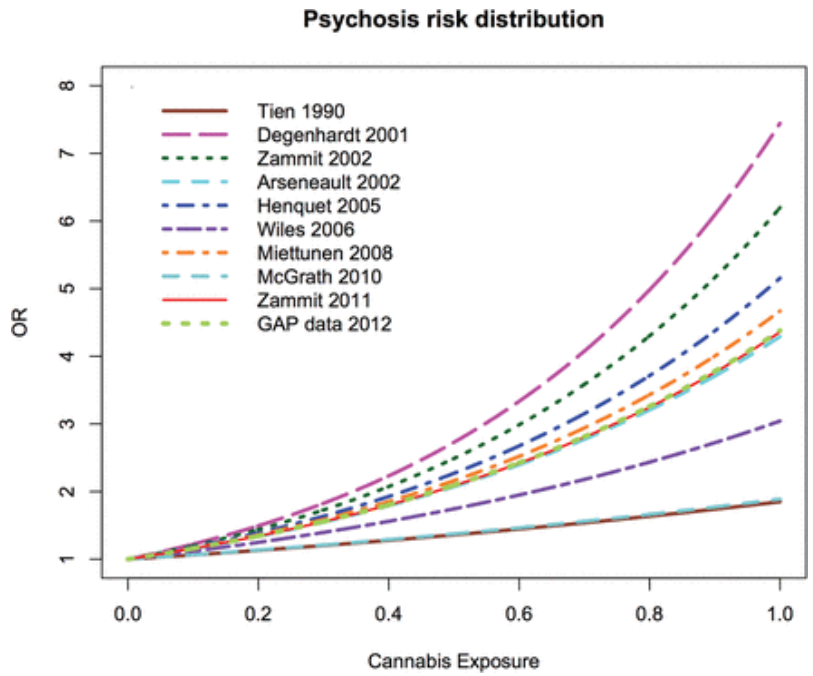
Moore et al., 2007

Cannabis use as a risk factor for schizophrenia



Marconi et al., 2016

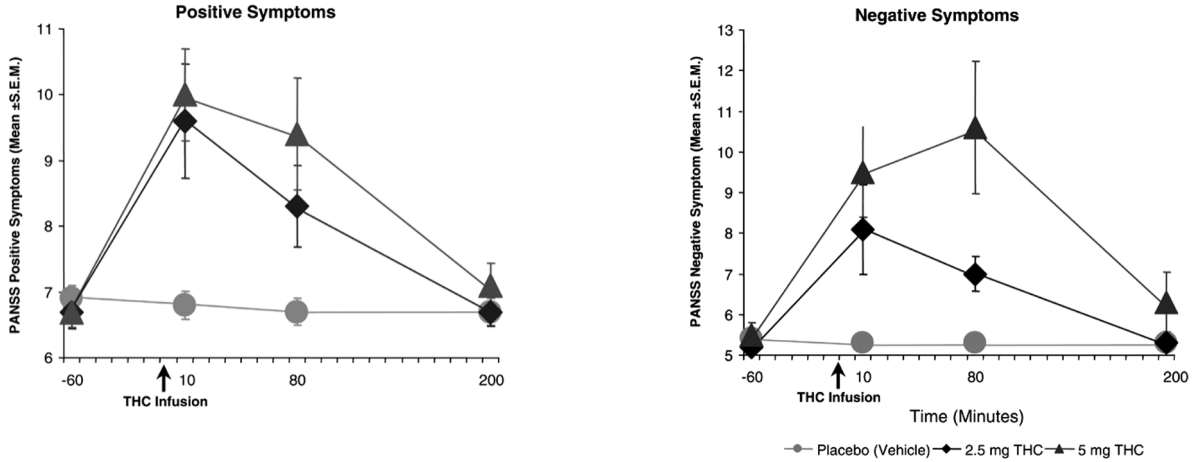
Cannabis use as a risk factor for schizophrenia



Marconi et al., 2016

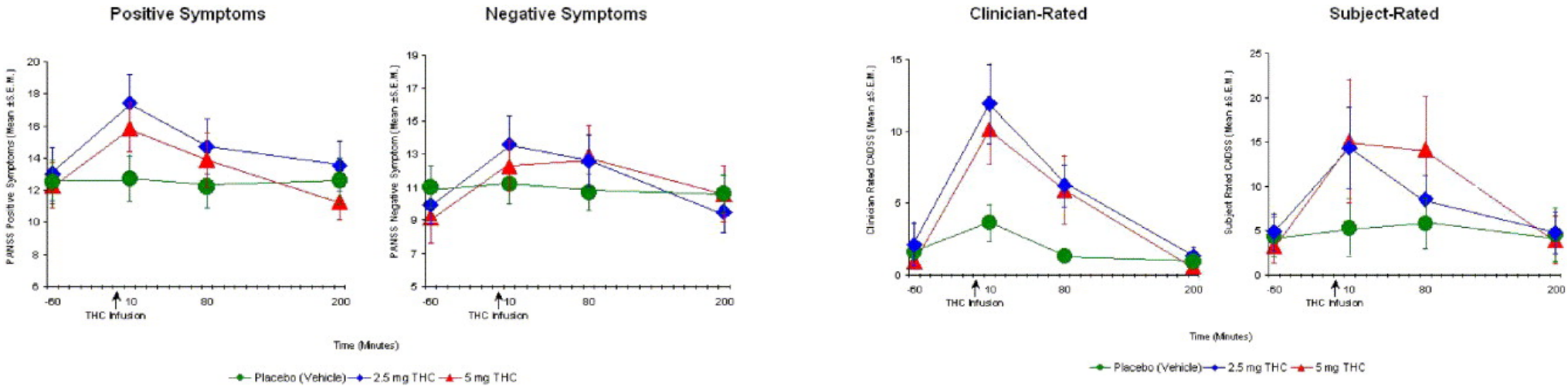
THC use and psychotic symptoms

- "The positive symptoms induced by Δ^9-THC included suspiciousness, paranoid and grandiose delusions, conceptual disorganization, and illusions. It also produced depersonalization, derealization, distorted sensory perceptions, altered body perception, feelings of unreality and extreme slowing of time. Δ^9-THC produced negative symptoms including blunted affect, reduced rapport, lack of spontaneity, psychomotor retardation, and emotional withdrawal."

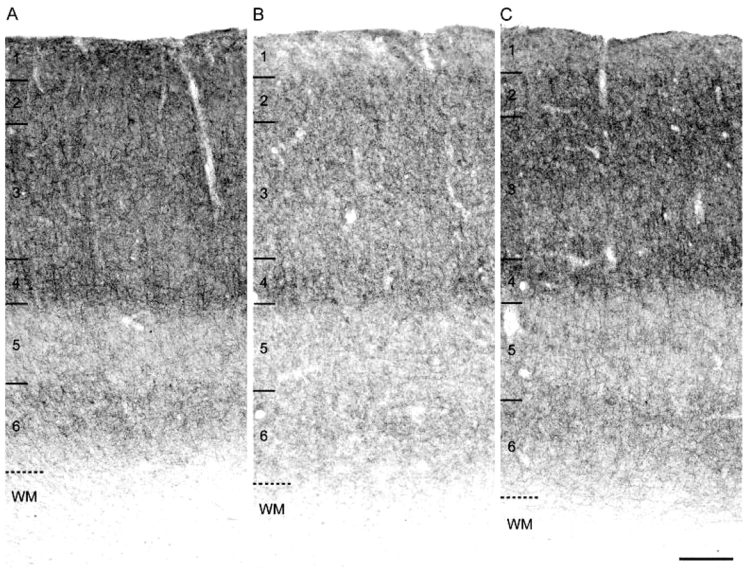


D'Souza et al., 2004

THC worsens psychotic symptoms in schizophrenia



Dysregulation in endocannabinoid signaling in schizophrenia



Eggan et al. 2010

Patients with schizophrenia have reduced CB1 receptors in the prefrontal cortex compared to controls and depressed patients

Summary

- Medical and recreational use of cannabis is growing
- Medical professionals should be educated on the biology, efficacy and adverse effects of cannabinoids
- Efficacy of cannabinoids for the treatment of pain is present but weak and has significant limitations in terms of types of cannabis used and length and quality of trials
- Cannabidiol was recently approved for treatment of Seizures
- Physical AEs of cannabis use are limited
- Mental health consequences are present but causal relationships between cannabis use and mental health consequences is very limited