Cannabis for Chronic Pain

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Learning Objectives

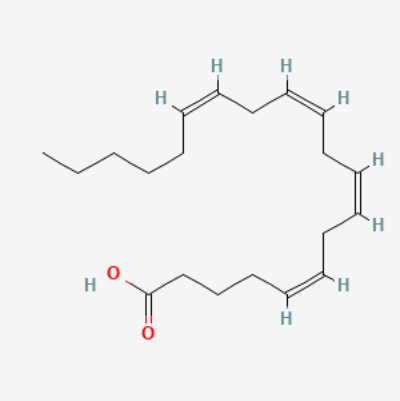
- Name components of the endocannabinoid system and their putative role in pain signaling
- Evaluate the evidence supporting the use of cannabinoids for chronic pain

Conflicts & Disclosures

- Dr. Rzasa Lynn has received grant/research support from the Colorado Department of Public Health & Environment, National Institutes of Health and US Department of Defense

Endocannabinoid System

- Endogenous cannabinoids
  - Chemically similar to arachidonic acid
    - Arachidonoylethanolamide (AEA) aka anandamide
    - 2-arachidonoylglycerol (2-AG)
- Enzymes and proteins for EC synthesis, degradation and re-uptake
- G-protein-coupled receptors



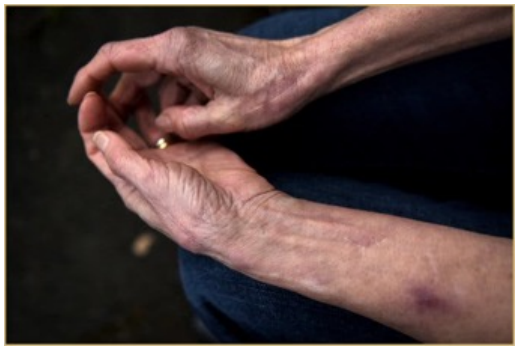
AEA synthesis involves different enzymes that 2-AG synthesis

Degradation: oxygenation or hydrolysis
AEA: Fatty-acid amide hydrolase (FAAH)
2-AG: Monoacylglycerol lipase
Both: oxygenation by COX-2, lipoxygenases or CYP450 enzymes

Katz-Talmor D (2018) Nat Rev Rheumatol 14(8): 488-498

Endocannabinoid Degradation and Pain

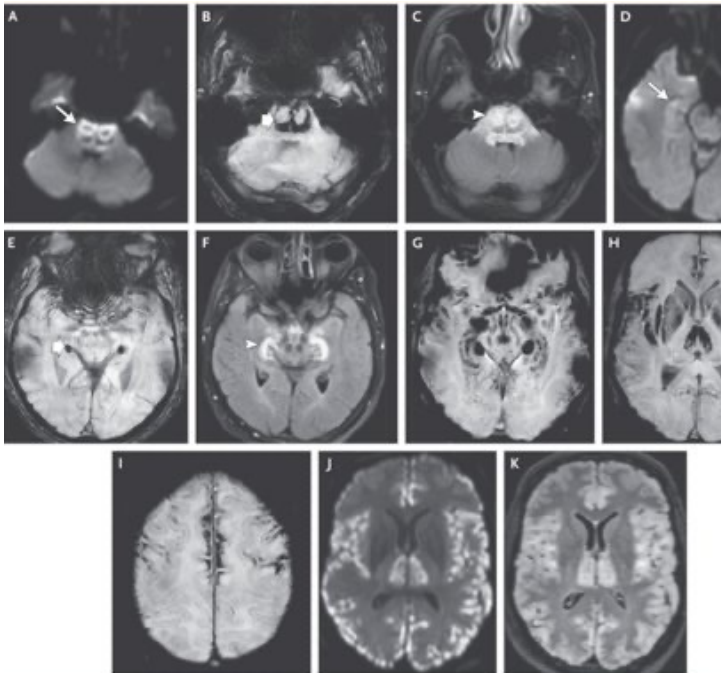
- 71 year old Scottish woman who doesn't feel pain
- Described childbirth as feeling like "a tickle"
- Often takes the smell of burning flesh to alert her to burns while cooking
- Also doesn't recall having ever felt depressed or scared
- Physicians were stunned when she felt almost no pain after painful orthopedic surgery
- Found to have genetic mutation that disrupts FAAH functioning
- Results in significantly elevated levels of anandamide in her blood



Endocannabinoid Degradation and Pain

Could a FAAH inhibitor have therapeutic effects for anxiety, chronic pain in humans?

- Portuguese company developed the compound BIA 10-2474, which inhibits FAAH
  - 2016: Phase I clinical trial in France in healthy volunteers
  - Resulted in 1 death and 5 hospitalizations due to "deep, necrotic, and hemorrhagic lesions in the brain[s]"



Endocannabinoid System

- G-protein-coupled receptors
  - CB1
    - Expressed on nerve axons and presynaptic terminals
    - Also in thyroid, adrenals, liver, adipose tissue, GI tract, reproductive organs and immune cells
    - Expressed in CNS
  - CB2
    - Expressed on immune cells
      - (but also chondrocytes, osteocytes, fibroblasts, and DRG as well as microglia)
    - "Peripheral" cannabinoid receptor

- Cannabinoids also interact with other receptors
  - TrpV1: ligand-gated cation channel
  - "CB3" aka G protein-coupled receptor 55 (GPR55)
  - Peroxisome proliferator-activated recaptor-α (PPARα)
    - Fatty-acid-activated transcription factor

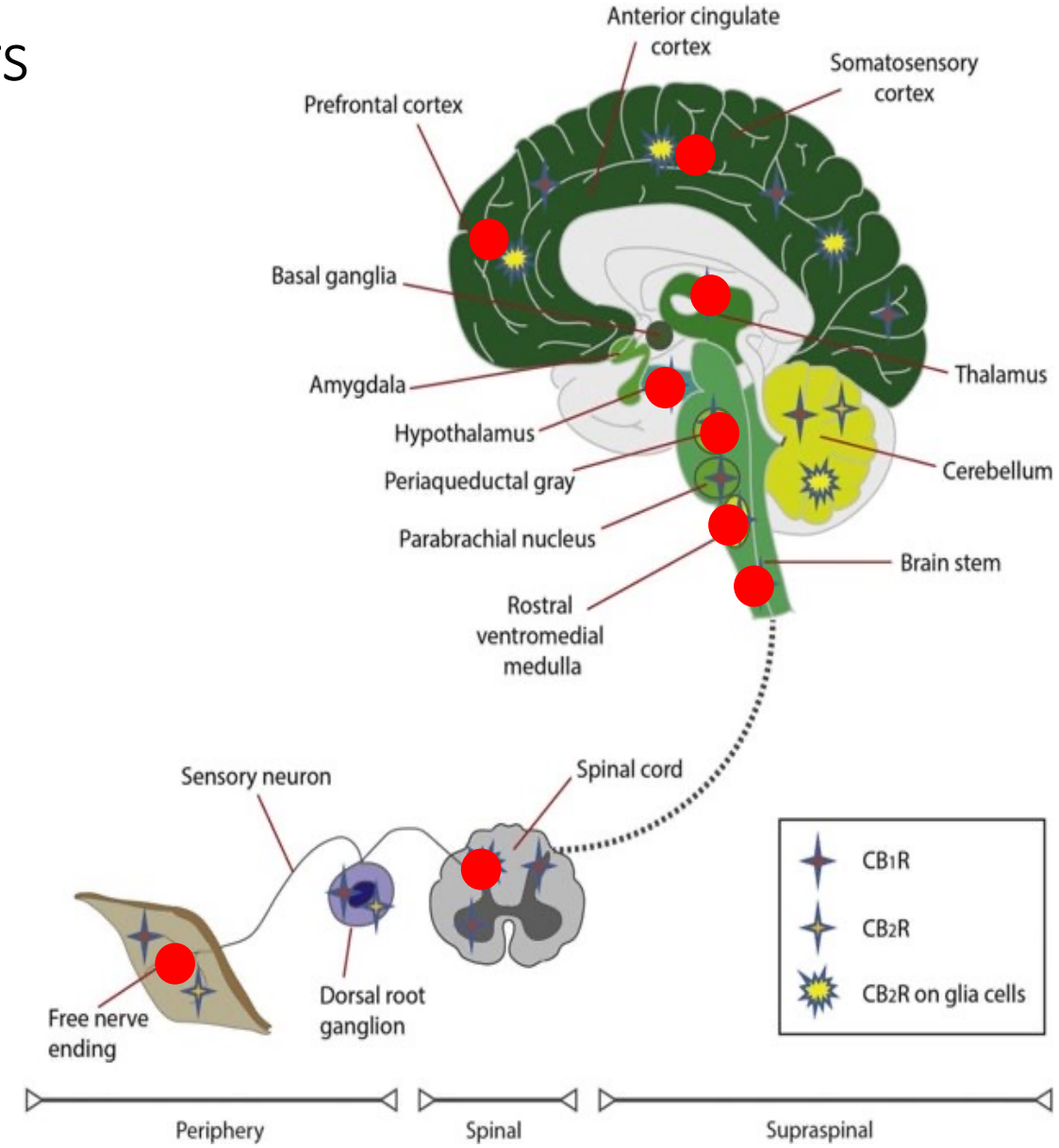
Katz-Talmor D (2018) Nat Rev Rheumatol 14(8): 488-498

Cannabinoid Receptors in the Pain Pathway

Periphery
- CB1: peripheral sensory nerve endings
- CB1 and CB2: dorsal root ganglion (DRG)

Spinal Cord
- CB1: dorsolateral funiculus, surroundings of the central canal, superficial dorsal horn
- CB2: glial cells highly restricted to lumbar spinal cord

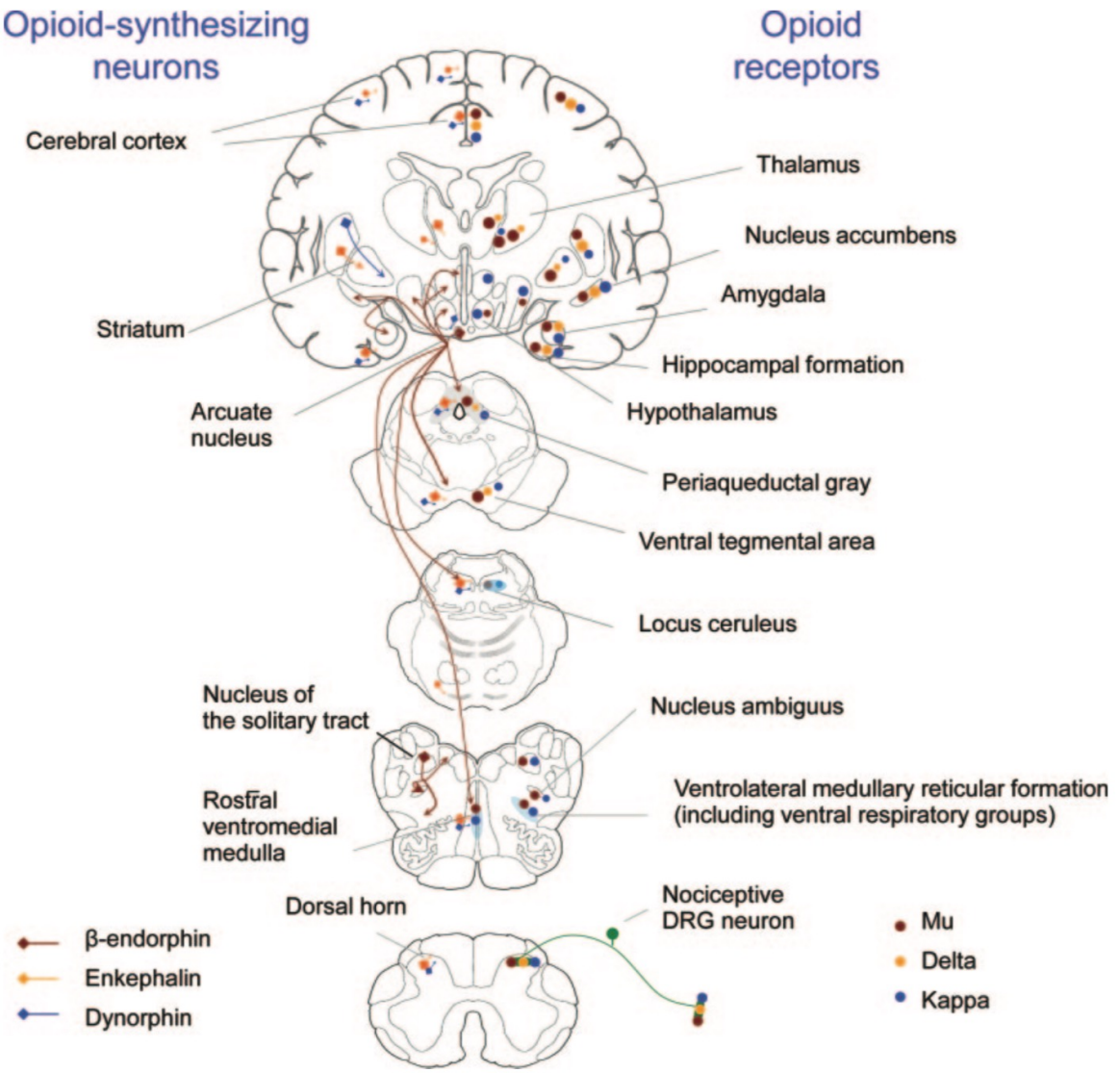
Supraspinal Sites
- CB1: many areas of the brain involved in pain processing, perception, and modulation
- CB2: brain stem, glial cells in the cerebellum and cortex.



Pain and Cannabinoids

University of Colorado Anschutz Medical Campus

Starowicz and Finn. Advances in Pharmacology Vol 80, 2017

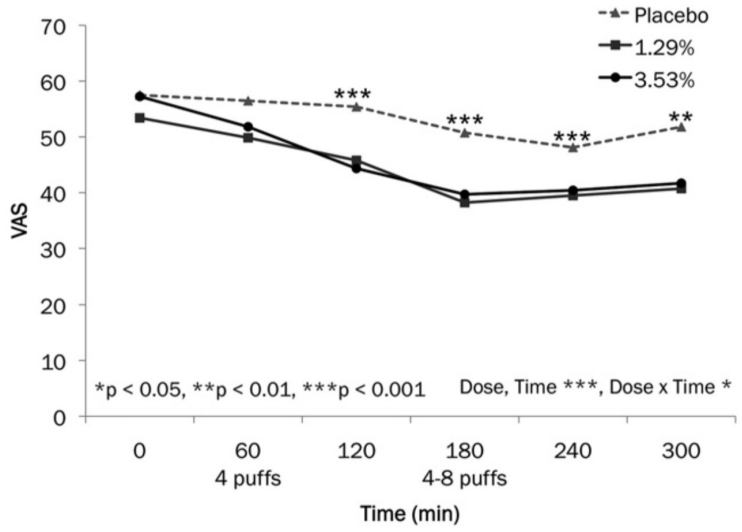

Opioid-synthesizing neurons
Opioid receptors
Cerebral cortex
Thalamus
Nucleus accumbens
Amygdala
Striatum
Hippocampal formation
Arcuate nucleus
Hypothalamus
Periaqueductal gray
Ventral tegmental area
Locus ceruleus
Nucleus of the solitary tract
Nucleus ambiguus
Rostral ventromedial medulla
Ventrolateral medullary reticular formation (including ventral respiratory groups)
Dorsal horn
Nociceptive DRG neuron
β-endorphin
Enkephalin
Dynorphin
Mu
Delta
Kappa

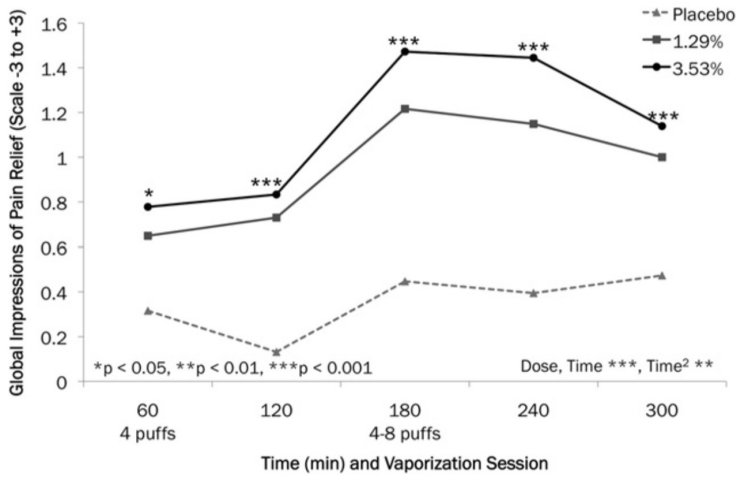
Cannabinoids and Pain: Pre-Clinical Studies

- Genetic and pharmacologic approaches confirm the modulation of pain by cannabinoids
  - Mice lacking FAAH have enhanced thermal analgesia and reduced nociceptive behaviors
  - Cannabinoids induce anti-nociception when directly injected into brain areas thought to have a role in nociception (eg PAG, RVM)
- Administration of cannabinoid receptor agonists has analgesic efficacy in pre-clinical models of pain
  - Similar to morphine analgesia
  - Positive effects in mechanical, inflammatory, and neuropathic pain models

Cannabis and Pain: Clinical Trials
Wilsey et al (2013)

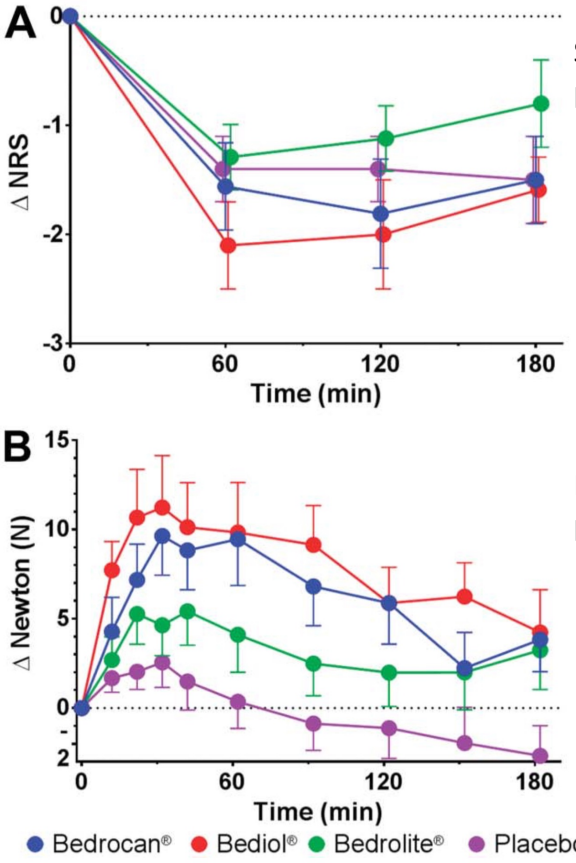
- Pain outcomes:
  - Spontaneous pain (VAS)
  - Global Impression of Change
  - Heat pain threshold
  - Neuropathic pain scale (0-11 pts)
  - Allodynia (VAS)





Cannabis and Pain: Clinical Trials
Van de Donk et al 2018

- 20 female patients with **fibromyalgia** completed the protocol
- Double-blind, placebo-controlled crossover
- Compared the effect of vaporized cannabis
  - High THC, low CBD (22% THC, 1% CBD)
  - Balanced (6.3% THC, 8% CBD)
  - Low THC, high CBD (<1% THC, 9% CBD)
  - Placebo
- Pressure pain and Electrical pain



Spontaneous pain

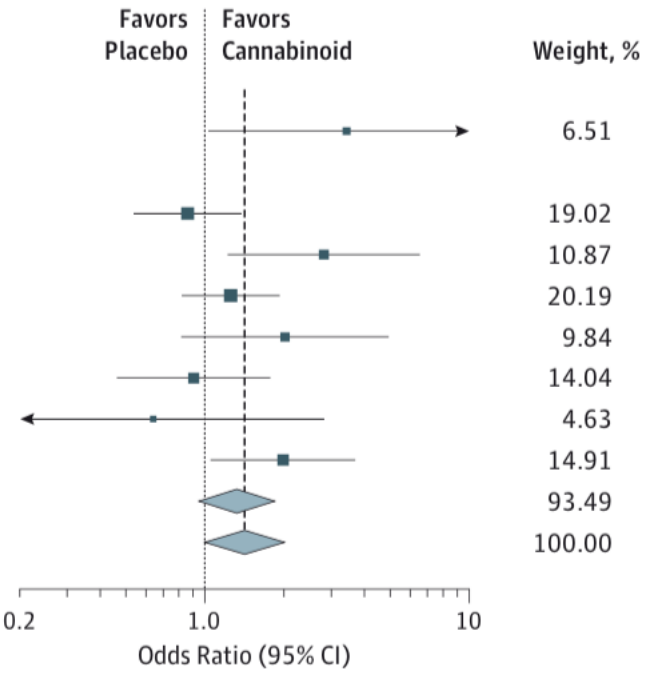
Pressure pain

Whiting, 2015
Meta-analysis of Cannabis for Chronic Pain

- Pooled studies of cancer pain and non-cancer pain

Figure 2. Improvement in 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)

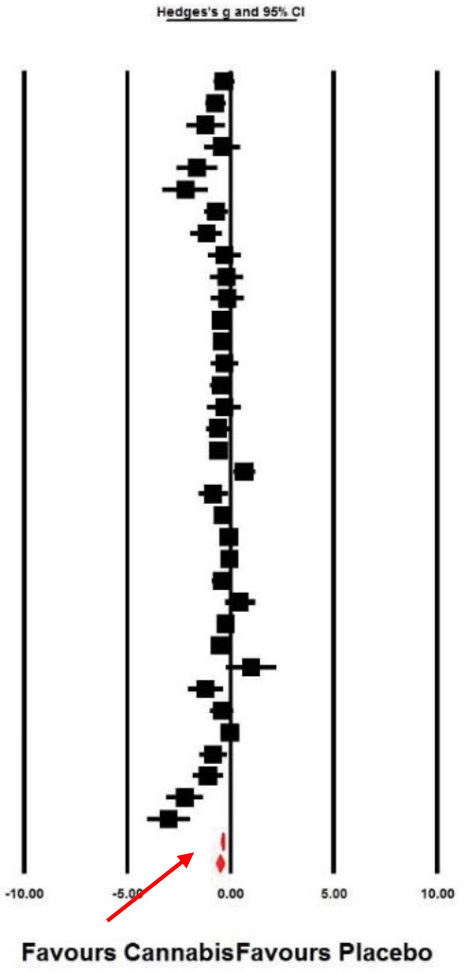


- OR 1.4 vs placebo for 30% pain reduction

Aviram, 2017
Meta-analysis of Cannabis for Acute & Chronic Pain

- Pooled studies of cancer pain and NCNP, acute and chronic

Model	Study name	Outcome	Hedges's g	Lower limit	Upper limit	p-Value
	Noyes 1975al	THC10mg vs. Placebo	-0.316	-0.789	0.157	0.190
	Noyes 1975all	THC 20mg vs. Placebo	-0.753	-1.240	-0.266	0.002
	Noyes 1975bl	THC 5mg vs. Placebo	-1.202	-2.120	-0.283	0.010
	Noyes 1975bll	THC 10mg vs. Placebo	-0.418	-1.267	0.432	0.335
	Noyes 1975blll	THC 15mg vs. Placebo	-1.622	-2.600	-0.643	0.001
	Noyes 1975blV	THC 20mg vs. Placebo	-2.196	-3.276	-1.115	0.000
	Staquet 1978a	NIB 4mg vs. Placebo	-0.716	-1.254	-0.177	0.009
	Staquet 1978b	NIB 4mg vs. Placebo	-1.183	-1.941	-0.425	0.002
	Wade 2003a	THC 2.5mg vs. Placebo	-0.289	-1.066	0.488	0.466
	Wade 2003b	CBD 2.5mg vs. Placebo	-0.190	-0.964	0.585	0.631
	Wade 2003c	THC\CBD 2.5mg vs. Placebo	-0.158	-0.932	0.616	0.689
	Berman 2004a	GW-2000-02 (THC) vs. Placebo	-0.473	-0.773	-0.173	0.002
	Berman 2004b	GW-1000-02 (sativax) vs. Placebo	-0.419	-0.712	-0.125	0.005
	Wade 2004	Sativax vs. Placebo	-0.303	-0.945	0.340	0.356
	Rog 2005*	Sativax vs. Placebo	-0.492	-0.980	-0.004	0.048
	Wissel 2006	Nabilone 1mg vs. Placebo	-0.309	-1.118	0.500	0.454
	Blake 2006	CBM vs. Placebo	-0.629	-1.151	-0.107	0.018
	Nurmikko 2007*	Sativax vs. Placebo	-0.589	-0.982	-0.196	0.003
	Frank 2008	Nabilone 2mg vs. Dihydrocodeine 240mg	0.652	0.154	1.150	0.010
	Skrabek 2008	Nabilone 0.5mg vs. Placebo	-0.837	-1.535	-0.138	0.019
	Wilsey 2008	3.5+7% cannabis cigarete vs. Placebo	-0.402	-0.727	-0.078	0.015
	Ware 2010a	2.5% cannabis cigarete vs. Placebo	-0.082	-0.494	0.330	0.697
	Ware 2010b	6% cannabis cigarete vs. Placebo	-0.057	-0.469	0.355	0.786
	Ware 2010c	9.4% cannabis cigarete vs. Placebo	-0.451	-0.884	-0.017	0.042
	Selvarajah 2010*	Sativax vs. Placebo	0.445	-0.272	1.162	0.224
	Johnson 2010a*	THC 2.7mg vs. Placebo	-0.237	-0.636	0.162	0.244
	Johnson 2010b*	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.499	-0.897	-0.102	0.014
	Rintala 2010	Dronabinol vs. Diphenhydramine	0.975	-0.224	2.173	0.111
	Toth 2012	Nabilone 1-4mg vs. Placebo	-1.216	-2.030	-0.401	0.003
	Pini 2012	Nabilone 0.5mg vs. Ibuprufen 400mg	-0.431	-0.973	0.111	0.119
	Langford 2013a	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.045	-0.273	0.182	0.696
	Langford 2013b	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.844	-1.472	-0.216	0.008
	Wallace 2015a	1% THC vaporizer vs. Placebo	-1.103	-1.831	-0.376	0.003
	Wallace 2015b	4% THC vaporizer vs. Placebo	-2.228	-3.096	-1.359	0.000
	Wallace 2015c	7% THC vaporizer vs. Placebo	-3.001	-4.000	-2.003	0.000
Fixed			-0.411	-0.494	-0.327	0.000
Random			-0.541	-0.715	-0.367	0.000



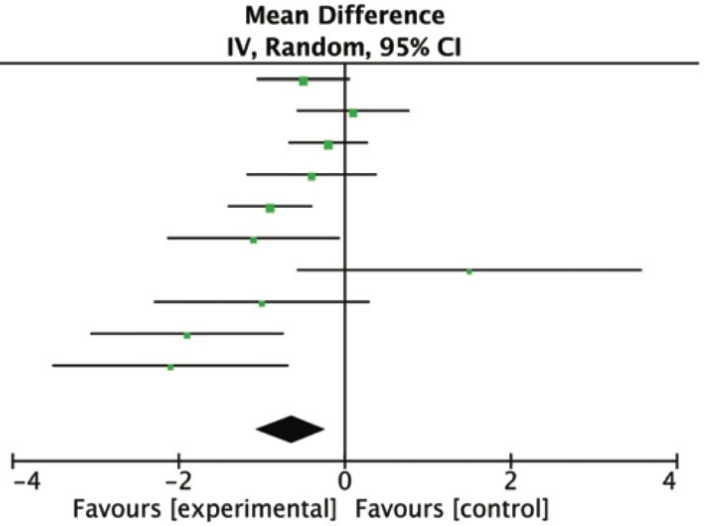
x*= Parallel design.

Meng, 2017
Meta-analysis of Cannabis for Chronic Pain

- Chronic Neuropathic Pain
  - Minimum study duration of 2 weeks

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Berman 2004 (Ref #22)	6.1	1.4	48	6.6	1.4	48	14.1%	−0.50 [−1.06, 0.06]
Frank 2008 (Ref #23)	6	2.4	96	5.9	2.4	96	12.6%	0.10 [−0.58, 0.78]
Langford 2013 (Ref #13)	4.5	2.2	167	4.7	2.3	172	15.2%	−0.20 [−0.68, 0.28]
Lynch 2014 (Ref #14)	6	1.2	18	6.4	1.2	18	11.3%	−0.40 [−1.18, 0.38]
Nurmikko 2007 (Ref #15)	5.8	1.4	63	6.7	1.5	62	14.8%	−0.90 [−1.41, −0.39]
Rog 2005 (Ref #16)	3.9	2.1	34	5	2.2	32	8.6%	−1.10 [−2.14, −0.06]
Selvarajah 2010 (Ref #17)	4	2.9	15	2.5	2.9	15	3.3%	1.50 [−0.58, 3.58]
Svendsen 2004 (Ref #19)	4	2.7	24	5	1.8	24	6.6%	−1.00 [−2.30, 0.30]
Toth 2012 (Ref #20)	3.5	1.3	13	5.4	1.7	13	7.6%	−1.90 [−3.06, −0.74]
Turcotte 2015 (Ref #21)	3.5	1.4	8	5.6	1.4	7	5.9%	−2.10 [−3.52, −0.68]
Total (95% CI)			**486**			**487**	**100.0%**	**−0.65 [−1.06, −0.23]**

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 22.59$, df = 9 (P = 0.007); $I^2 = 60\%$
Test for overall effect: Z = 3.07 (P = 0.002)



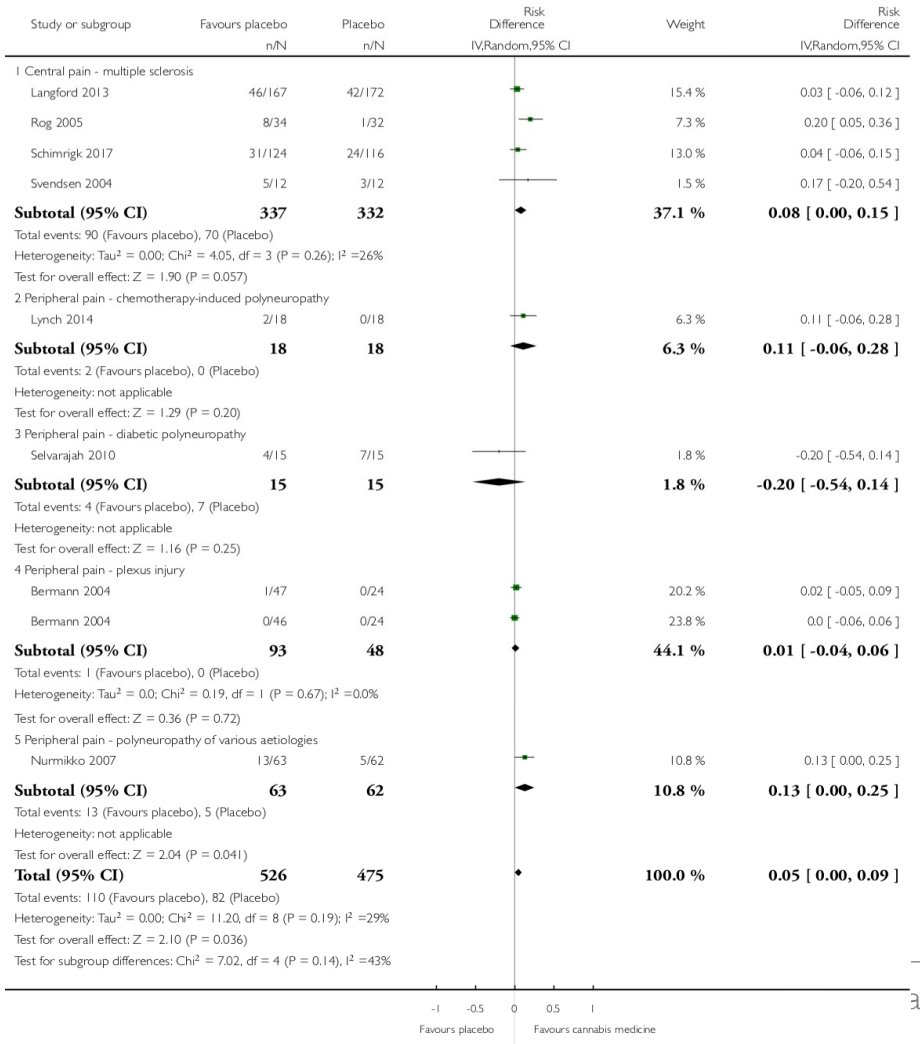
- Positive effect, but clinically small
  - mean difference vs placebo or dihydrocodeine: -0.65 points on NRS scale (95% CI, -1.06 to -0.23)

Mücke, 2018
Meta-analysis of Cannabis for Chronic Pain

- Neuropathic Pain Cochrane Review
  - Treatment duration ≥ 2 weeks, ≥ 10 patients per arm

- For 50% reduction in pain, NNTB = 20
- For **30% reduction in pain**, NNTB = 11

- Nervous system adverse events NNTH = 3;
- Psychiatric disorder adverse events NNTH = 10
- Study withdrawal due to AE NNTH = 25



Study or subgroup	Favours placebo n/N	Placebo n/N	Risk Difference IV,Random,95% CI	Weight	Risk Difference IV,Random,95% CI
1 Central pain - multiple sclerosis					
Langford 2013	46/167	42/172		15.4 %	0.03 [-0.06, 0.12]
Rog 2005	8/34	1/32		7.3 %	0.20 [0.05, 0.36]
Schimrigk 2017	31/124	24/116		13.0 %	0.04 [-0.06, 0.15]
Svendsen 2004	5/12	3/12		1.5 %	0.17 [-0.20, 0.54]
Subtotal (95% CI)	**337**	**332**		**37.1 %**	**0.08 [0.00, 0.15]**
Total events: 90 (Favours placebo), 70 (Placebo)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 4.05, df = 3 (P = 0.26); I^2 =26%					
Test for overall effect: Z = 1.90 (P = 0.057)					
2 Peripheral pain - chemotherapy-induced polyneuropathy					
Lynch 2014	2/18	0/18		6.3 %	0.11 [-0.06, 0.28]
Subtotal (95% CI)	**18**	**18**		**6.3 %**	**0.11 [-0.06, 0.28]**
Total events: 2 (Favours placebo), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.29 (P = 0.20)					
3 Peripheral pain - diabetic polyneuropathy					
Selvarajah 2010	4/15	7/15		1.8 %	-0.20 [-0.54, 0.14]
Subtotal (95% CI)	**15**	**15**		**1.8 %**	**-0.20 [-0.54, 0.14]**
Total events: 4 (Favours placebo), 7 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.16 (P = 0.25)					
4 Peripheral pain - plexus injury					
Bermann 2004	1/47	0/24		20.2 %	0.02 [-0.05, 0.09]
Bermann 2004	0/46	0/24		23.8 %	0.0 [-0.06, 0.06]
Subtotal (95% CI)	**93**	**48**		**44.1 %**	**0.01 [-0.04, 0.06]**
Total events: 1 (Favours placebo), 0 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.19, df = 1 (P = 0.67); I^2 =0.0%					
Test for overall effect: Z = 0.36 (P = 0.72)					
5 Peripheral pain - polyneuropathy of various aetiologies					
Nurmikko 2007	13/63	5/62		10.8 %	0.13 [0.00, 0.25]
Subtotal (95% CI)	**63**	**62**		**10.8 %**	**0.13 [0.00, 0.25]**
Total events: 13 (Favours placebo), 5 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.04 (P = 0.041)					
Total (95% CI)	**526**	**475**		**100.0 %**	**0.05 [0.00, 0.09]**
Total events: 110 (Favours placebo), 82 (Placebo)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 11.20, df = 8 (P = 0.19); I^2 =29%					
Test for overall effect: Z = 2.10 (P = 0.036)					
Test for subgroup differences: Chi^2 = 7.02, df = 4 (P = 0.14), I^2 =43%					

University of Colorado Anschutz Medical Campus

abinoids

PAIN

Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies

Emily Stockings[a,*], Gabrielle Campbell[a], Wayne D. Hall[b,c], Suzanne Nielsen[a], Dino Zagic[a], Rakin Rahman[a], Bridin Murnion[d,e], Michael Farrell[a], Megan Weier[a], Louisa Degenhardt[a]

- 104 studies identified
  - 47 RCTs (24 parallel, 23 cross-over)
  - 57 observational
  - Total 9,958 participants
  - 48 studied neuropathic pain
  - 7 studied fibromyalgia
  - 48 for other CNCP
  - 1 arthritis

- Nabiximols (Sativex)
  - In the UK, approved for MS spasticity
  - In Canada, also approved for MS neuropathic pain
- Nabilone
  - oral synthetic cannabinoid, mimics THC
    - Schedule II
  - FDA approved for n/v with chemotherapy
- Oral THC
  - Extract
  - Synthetic: dronabinol (Marinol [cap] or Syndros [liquid])
    - Anorexia and weight gain in AIDS
    - Chemo n/v
- Whole flower, inhaled (smoked or vaporized)

https://www.bayer.ca/omr/online/sativex-dhcpl-lapds-04-01-2005-en.pdf
Pain 159 (2018) 1932–1954. https://www.bayer.ca/omr/online/sativex-pm-en.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018677s011lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/205525Orig1s000Approv.pdf

Cannabis for CNCP: 2018 Meta-analysis

- Overall, cannabinoids were more likely than placebo to produce a 30% reduction in pain or significant reduction in pain intensity

BUT

- These effects were **SMALL**
  - For 30% reduction in pain, OR 1.46 (95% %CI 1.16-1.84)
    - 29.0% achieved this with cannabinoids vs 25.9% with placebo
      - However in observational studies, the pooled prevalence of 30% pain reduction was 72%
  - Change in pain intensity standardized mean difference was only -0.14 vs placebo (95%CI -0.20 to -0.08)

    = reduction of **2.9mm on 100mm VAS**!
  - The longer the intervention, the smaller the effect
    - Single-administration and very short term (<4 weeks) studies remained significant, but longer studies >13 weeks, did not

Cannabis for CNCP: 2018 Meta-analysis

- No significant effect on physical functioning
- No difference in emotional functioning, nor depression or anxiety symptoms specifically
- 2x greater risk of study withdrawal, for any reason, if receiving cannabinoid
  - 3.47x odds of withdrawing due to AE
  - Those receiving placebo were more likely to withdraw due to lack of effects
- 2.33x greater risk of adverse events vs placebo
  - Dizzines (OR 5.52), cognitive or attention disturbance (OR 5.67), confusion and disorientation (OR 5.35)

Cannabis for CNCP: 2018 Meta-analysis

- Number Needed to Benefit: 24
  - 24 patients have to be exposed for 1 to achieve 30% reduction in pain
  - WAY higher than other analgesics
    - For neuropathic pain, previous studies show NNTB
      - Strong opioids: 4.3
      - Pregabalin: 7.7
      - TCAs: 3.6
- Number Needed to Harm: 6
  - 1 out of every 6 patients will experience an AE
    - Similar to opioids

Cannabinoid Opioid Interactions

- Cannabinoids and opioids share many effects:
  - analgesia, catalepsy, hypothermia, motor depression, hypotension, immunosuppression, sedation and reward effects
- Both CB and opioid receptors (OR) primarily located presynaptically. Activation inhibits neurotransmitter release
  - Similar intracellular signaling via G protein activation
- Similar distribution of CB and OR in spinal cord dorsal horn and brain
  - μOR and CB1 co-localize at the first synaptic contact for afferent peripheral nociceptive neurons
  - Both are abundant in caudate putamen, dorsal hippocampus, and substantia nigra, also found in more moderate levels in other brain areas processing pain
- CB2 activation produces antinociception via peripheral release of endogenous opioids (analgesia blocked by local administration of opioid antagonist)
- Co-administration of cannabinoids and opioids enhances antinociception

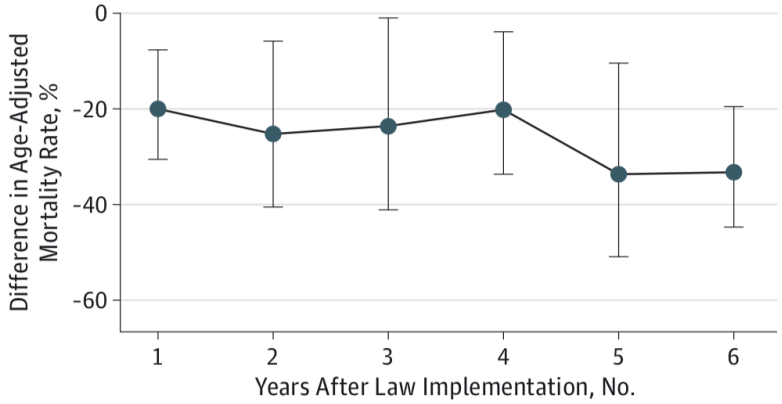
Cannabinoid Analgesic Effects: Opioid Sparing in Pre-Clinical Models

- Numerous studies show opioid sparing effects when cannabinoids are co-administered with opioids in animal models of acute and chronic pain.
  - Meta-analysis of pre-clinical animal models:
    - Median effective dose (ED50) of morphine is **3.6 times lower** when administered in combination with THC than alone.
    - The ED50 for codeine administered with THC is **9.5 times lower** than the ED50 for codeine alone.

Nielsen et al. Neuropsychopharmacology 2017 Vol 42.

Cannabis and Opioids – Population Data

- Opioid analgesic overdose death rates from 1999-2010 were lower in states with medical cannabis (MC) laws
- Reduction increased over time following MC legislation

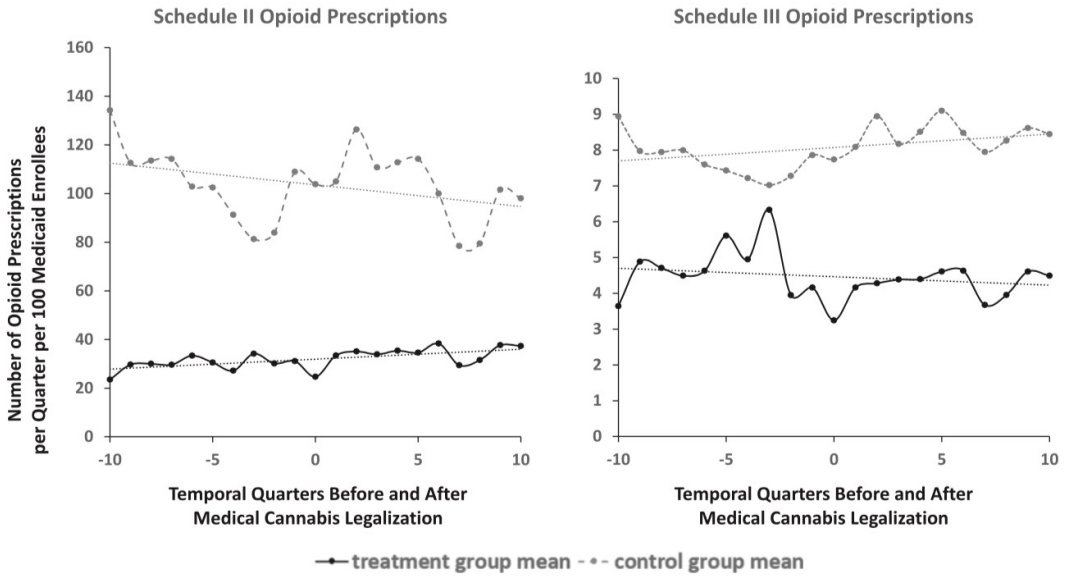


- States with MC laws saw decrease in opioid prescriptions filled in Medicare database from 2010-2015
  - Most significant for hydrocodone and morphine (17.4% and 20.7% reductions)
- MC laws were associated with a 5.88% lower rate of opioid prescribing in Medicaid database
- In a sample of patients with commercial insurance (n=4,840,562) 2006-2014, MC legalization was associated with lower odds of:
  - Any opioid use (OR 0.95; 0.94-0.96)
  - Chronic opioid use (OR 0.93; 0.91-0.95)
  - High risk opioid use (OR 0.96; 0.94-0.98)

Bradford,et al. 2018 JAMA Intern Med 178, 667-672. Wen et al 2018. JAMA Intern Med 178. Shah 2019. J Gen Intern Med 34, 1419-1426

Population Studies of Cannabis and Opioids

- Liang, 2018: MC and opioid among Medicaid enrollees 1993-2014: NO association with change in Schedule II opioid prescribing (oxycodone, morphine)
- MC legalization was associated with 29.6% (p=0.03) reduction in number of prescriptions, 29.9% (p=0.02) reduction in dosage for Schedule III opioids (codeine, buprenorphine)



- Differences between medical cannabis use and non-medical cannabis use
- Liang (2019) NSDUH data
  - **All** cannabis use associated with higher rate of Rx opioid **misuse**
  - Only **non-medical** cannabis use associated with **opioid use disorder**

Survey Studies of Cannabis and Opioids for Pain: Medical Cannabis Consistently Reduces Opioid Use

- Survey participants overwhelmingly (97%) report medical cannabis (MC) facilitates reduction in opioid use; MC alone more effective for pain than opioid+MC (Reiman, 2017)
- 76.7% or respondents to survey of New England dispensary members reported reducing opioid use since starting MC (Piper, 2017)
- Among respondents to an online survey in states where MC is legal, 53% reported substituting MC for opioids, 22% for BZDs (Boehnke, 2019)
- Respondents in longitudinal survey of Israeli patients obtaining MC registration reported 42% reduction in opioid use at 12-month time point vs baseline (Aviram, 2021)

Observational Studies of Cannabis and Opioids for Pain

- Haroutounian, 2016: followed 206 patients in Israeli pain clinic when starting MC
  - 44% of patients discontinued opioids at 6 months
  - No significant change in opioid dose among those who continued using opioids
- Meng, 2021: followed 757 Canadian patients starting MC for chronic pain
  - Proportion of participants using opioids fell by half at 12 months (BUT huge reduction in participants from baseline (n=104), missing data)
- Campbell, 2018: longitudinal observational cohort of Australian patients with chronic non-cancer pain prescribed opioids (Pain and Opioids IN Treatment)
  - N=1514 at baseline, at 4-year follow-up, 295 (24%) participants had used cannabis for pain
  - Compared with non-users, patients who used cannabis had:
    - greater pain severity
    - greater pain interference
    - lower pain self-efficacy
  - No evidence that cannabis use reduced prescribed opioid use or increased discontinuation

Cannabis and Opioids for Pain: Clinical Trials – Abrams et al (2011)

- Enrolled 21 patients with chronic pain on chronic opioid therapy (morphine or oxycodone)
- Diverse pain conditions: musculoskeletal NOS (7), post-trauma (4), arthritis (2), peripheral neuropathy (2), cancer, fibromyalgia, migraine, multiple sclerosis, sickle cell disease, and thoracic outlet syndrome (1 each)
- Inhaled vaporized cannabis (3.56% THC) up to TID for 5 days

  No change in opioid AUC

Table 2 Pain by study day

		Day 1	Day 5	Difference	Percentage change
	n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Overall	21	39.6 (35.8, 43.3)	29.1 (25.4, 32.8)	−10.7 (−14.4, −7.3)	−27.2 (−45.5, −8.9)
Morphine	11	34.8 (29.4, 40.1)	24.1 (18.8, 29.4)	−11.2 (−16.5, −6.0)	−33.7 (−63.8, −3.5)
Oxycodone	10	43.8 (38.6, 49.1)	33.6 (28.5, 38.6)	−10.3 (−14.8, −5.8)	−21.3 (−47.0, 5.3)

CI, confidence interval.

Cannabis and Opioids: Clinical Data

BMJ Open

Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis of randomised and observational studies

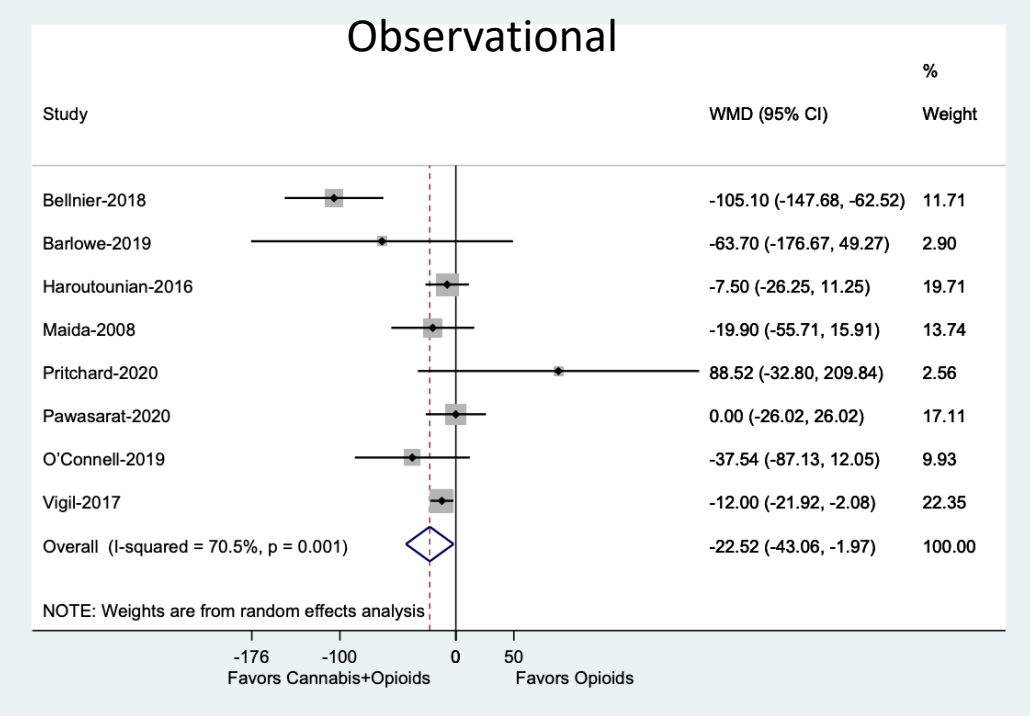
Atefeh Noori,[1,2] Anna Miroshnychenko,[1] Yaadwinder Shergill,[1] Vahid Ashoorion,[1] Yasir Rehman,[1] Rachel J Couban,[2] D Norman Buckley,[3] Lehana Thabane ,[1] Mohit Bhandari,[1,4] Gordon H Guyatt,[1] Thomas Agoritsas,[1,5] Jason W Busse [1,3,6,7]

- 2021 meta-analysis found only 18 publications (RCTs or observational studies) reporting the impact of medical cannabis initiation on opioid use for chronic pain
- 5 RCTs, 13 observational
  - All 5 RCTs and 3 observational enrolled only **cancer pain**
  - All RCTs administered isolated or synthetic cannabinoids
  - All RCTs instructed patients to maintain prescribed pain med doses

Cannabis and Opioid Use for Pain (Noori): Opioid Use

- Minimal change in opioid use in RCTs (WMD -3.4MME, 95% CI -12.7 – 5.9)
- Data from 8 observational studies suggests adding cannabis may reduce opioid use in CNCP (WMD -22.5 MME, 95% CI -43.06 – -1.97)

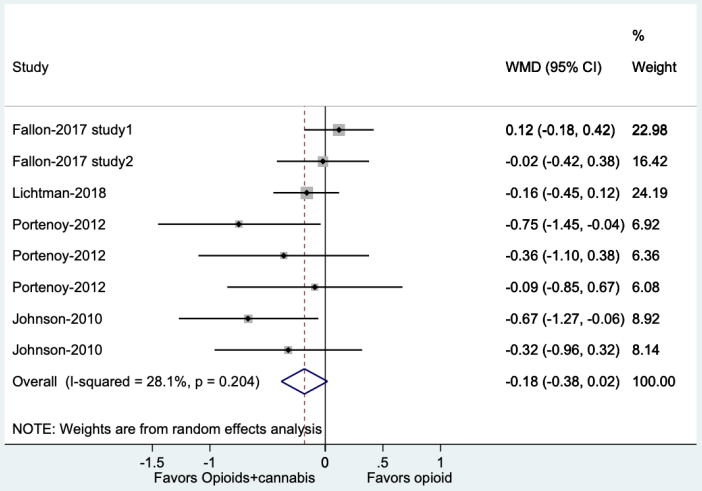
  1 study found over half of patients with low back pain stopped all opioid use at median follow-up of 6.4 years



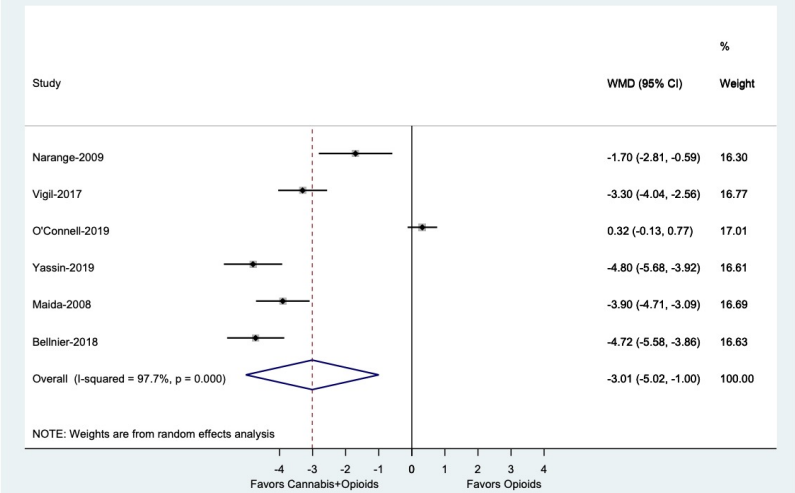
Cannabis and Opioid Use for Pain (Noori): Pain

- Trivial to no difference in pain in the RCTs vs large decrease in observational studies

RCTs



Observational



Cannabinoids Are Opioid Sparing: Clinical Studies

Cannabis use results in self-reported reductions in opioid use for pain in observational studies

Low quality evidence of reduced opioid requirement after initiation of short-term smoked/vaporized cannabis

Higher quality studies have not found an opioid sparing effect

Important limitations in translating findings from pre-clinical studies to clinical practice

- Heterogeneous populations
- Sub-population of responders?

A little perspective….

- EtOH is also an analgesic!
  - Most studies show that alcohol can reduce pain
  - Mean BAC of 0.08% (3-4 cocktails) slightly increases pain threshold (level at which pain first detected) but reduces pain intensity ratings by the equivalent of 1.25 points on 0-10 NRS
    - In one study, the equivalent of 2 cocktails produced an analgesic effect comparable to that of ~10mg SQ morphine

Horn-Hoffman, 2015; Thompson, 2017; Woodrow, 1988