Cannabinoids act on many of the same pain pathways as opioids

Endogenous neurotransmitters

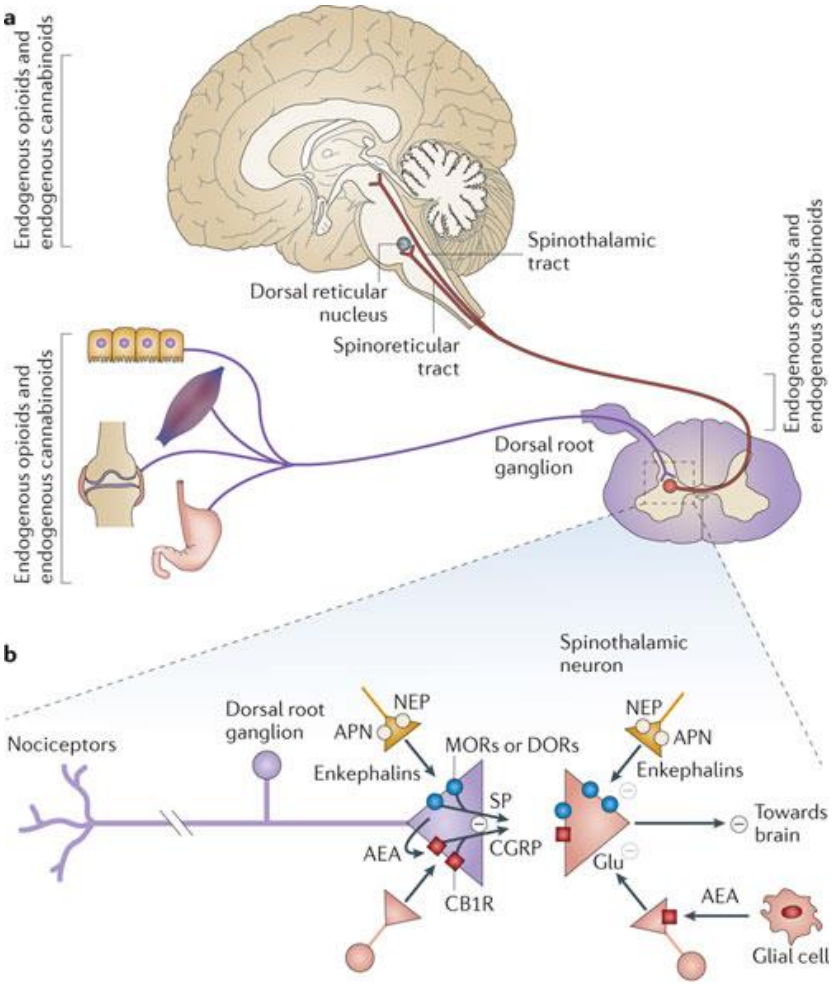
- opioids (enkephalins) -> opioid receptors
  endocannabinoids (anadamide) -> cannabinoid receptors

Similar locations of these receptors:

- Peripheral nocioceptive nerves (source of pain)
- In the sensory neuron transduction pathway
- In the descending modulatory pathways

With a key difference…

although CB receptors are found in similar pain circuits as opioids, their absence in the brainstem makes them safer than opioids.



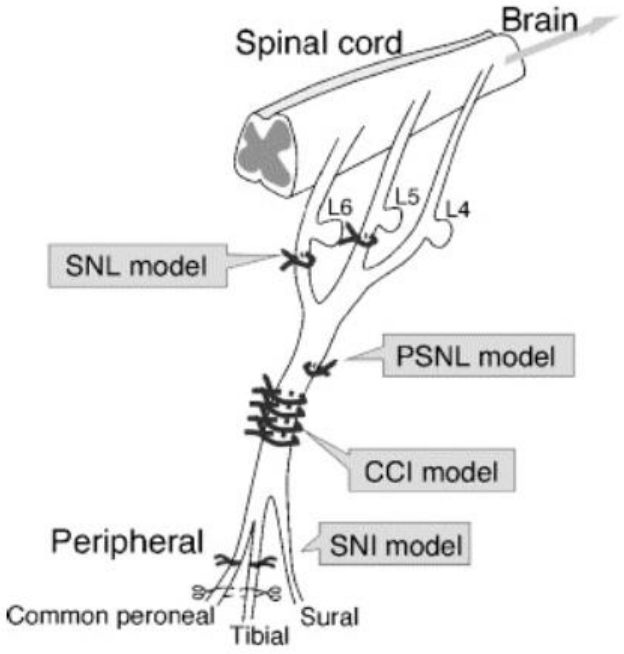
Roques BP, et al. Inhibiting the breakdown of endogenous opioids and cannabinoids to alleviate pain, 2012

http://www.nature.com/nrd/journal/v11/n4/full/nrd3673.html

Nature Reviews | Drug Discovery

Cannabinoid agonists are effective in all peripheral neuropathic pain models

- Nerve Injury
  - Sciatic nerve ligation (SNL and PSN
  - Sciatic nerve injury (CCI, SNI)
- Diabetes
  - Streptozotocin
- Chemotherapy
  - Paclitaxel, Cisplatin
- HIV neuropathy



Pharmacology & Therapeutics
Volume 109, Issues 1–2, January 2006, Pages 57–77

Bouhassira D, Attal N. Translational neuropathic pain research: A clinical perspective. Neuroscience (2016), http://dx.doi.org/10.1016/j.neuroscience.2016.03.029

Cannabis provide an adjunct for opioids for treatment of pain

Individuals with chronic pain requiring opioids (musculoskeletal, post-traumatic, arthritic, peripheral neuropathy, cancer, fibromyalgia, migraine, MS, sickle cell disease, TOS).

Table 1 Participant characteristics

	Morphine group	Oxycodone group
n	10	11
Women	4	6
Caucasian	8	9
Mean age (range)	42.9 (33–55)	47.1 (28–61)
Mean opioid dose (mg) (range)	62 Twice daily (10–200)	53 Twice daily (10–120)
Mean pain score day 1 (95% CI)	34.8 (29.4, 40.1)	43.8 (38.6, 49.1)

CI, confidence interval.

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.

Synergistic effects with opioids, providing pain relief with lower opioid doses and with less side effects. Did not change opioid blood levels.

Abrams DI, et al. Cannabinoid-opioid interaction in chronic pain. *Clinical Pharmacology & Therapeutics*. 90(6):844-51, 2011 Dec.

GW pharmaceuticals phase 3 trials of nabiximols (Sativex) show benefit for cancer pain

- Randomized 360 subjects to placebo or one of three experimental groups
- Best results with 4 sprays per day (10mg THC / 10 mg CBD)
- Higher doses were not well-tolerated
  - more adverse events
  - higher drop-out rates.

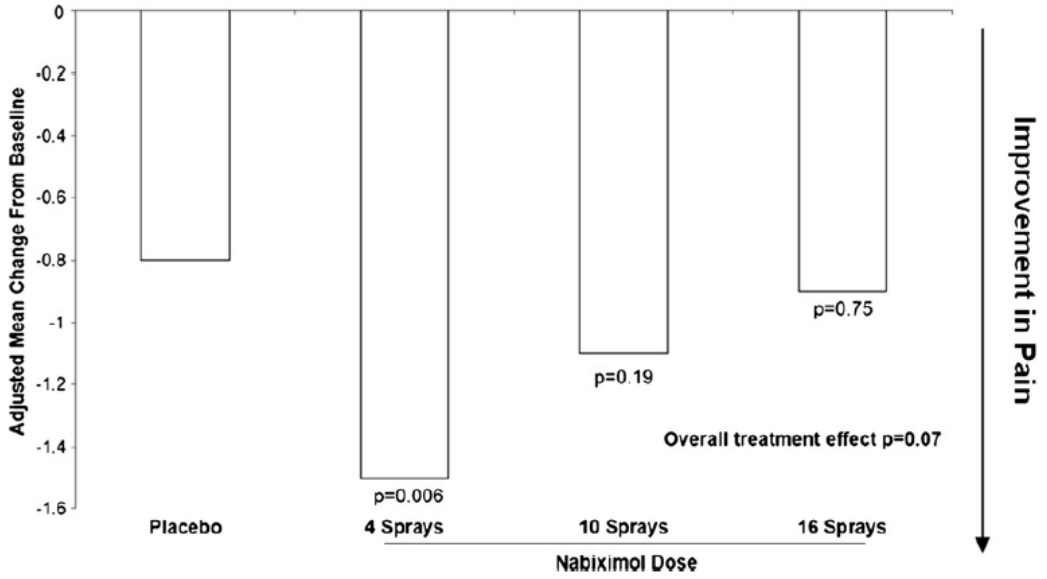


Figure 4. Analysis of change from baseline in NRS average pain score.

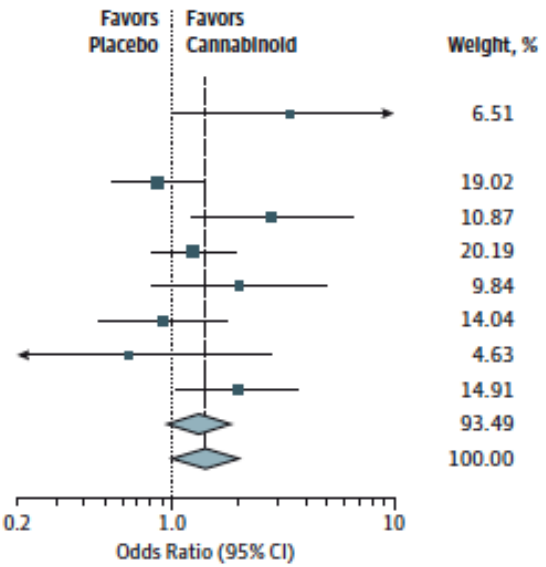
Portenoy RK, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012 May;13(5):438-49. doi: 10.1016/j.jpain.2012.01.003.

JAMA meta-analysis = highest level of evidence for cannabis in treatment of chronic pain

- Meta-analysis provides compilation of data from randomized clinical trials (RCTs) comparing cannabinoids to placebo for chronic pain and other conditions.
- Also provides best available information about potential for adverse events (AEs) with cannabis [1].
- Includes 28 studies of chronic pain (63 reports, 2454 individual participants)

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)



Odds indicate 30% or greater improvement in pain with cannabinoid compared with placebo, stratified according to cannabinoid. The square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal lines indicate 95% CIs. The blue diamond data markers represent the subtotal and overall OR and 95% CI. The vertical dashed line shows the summary effect estimate, the dotted shows the line of no effect (OR = 1).

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358

Patients with chronic pain successfully substitute medical cannabis for opioids

- Online survey of 244 medical cannabis patients with chronic pain to examine whether medical cannabis changed individual patterns of opioid use
- N=184 analyzed
- Found that cannabis was associated with
  - Decrease in opioid use (64%)
  - Improved quality of life (45%)

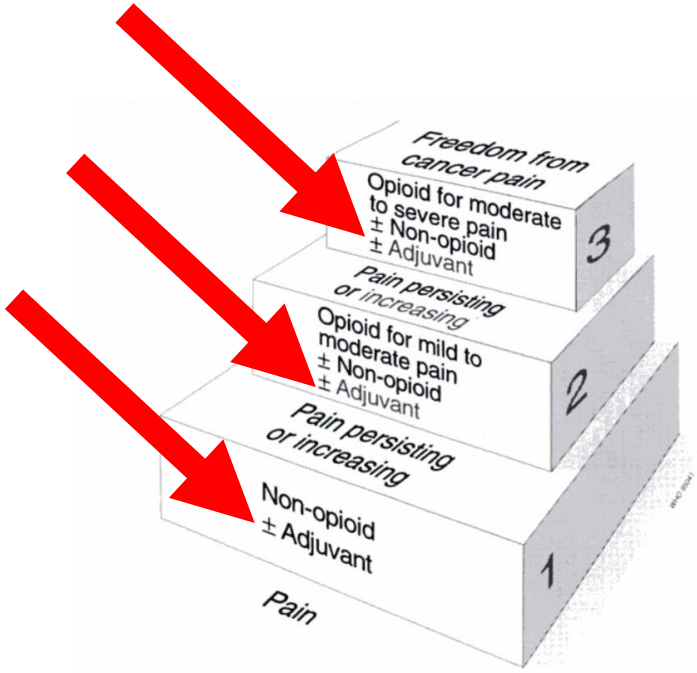
Medication type	Use before initiation of cannabis (n/N)	Use after initiation of cannabis (n/N)
Opioids	119/184 (65%)	33/184 (18%)
NSAIDs	115/184 (62%)	38/184 (21%)
Disease-modifying antirheumatic drugs (DMARDs)	15/184 (8%)	3/184 (2%)
Anti-depressants	72/184 (39%)	25/184 (14%)
Serotonin–norepinephrine reuptake inhibitors (SNRIs)	13/184 (7%)	3/184 (2%)
Selective serotonin reuptake inhibitors (SSRIs)	34/184 (18%)	8/184 (4%)
Other	69/184 (38%)	40/184 (22%)

NOTE. Study participants reported using fewer medication classes of all categories after initiation of cannabis.

1. Boehnke KF, et al. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. J Pain. 2016 Jun;17(6):739-44. doi: 10.1016/j.jpain.2016.03.002. PMID: 27001005

Cannabis is considered an beneficial adjuvant at all steps of analgesic ladder

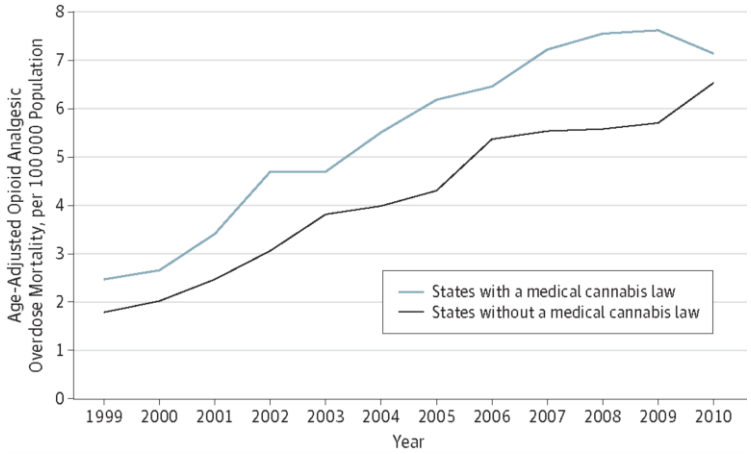
- Synergistic actions between cannabinoids and opioids can lower dose of opioids needed to control pain
- Cannabis-based medicine containing both THC and CBD appears to be more effective and better tolerated than synthetic THC (dronabinol)
- Modified WHO analgesic ladder includes cannabinoids as adjuvant medications that may be considered at all steps of treatment of cancer or other chronic pain [1]



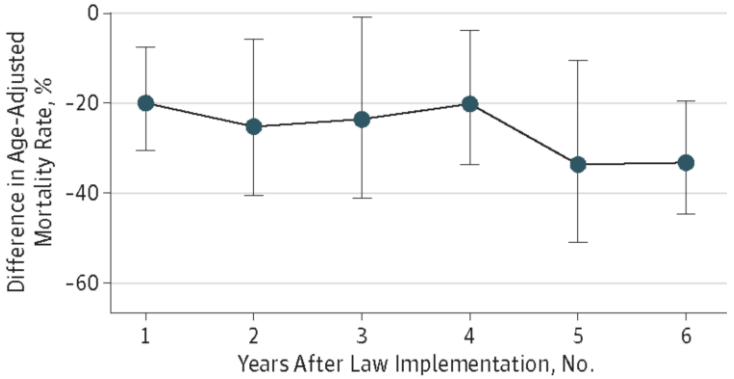
[1] Vargas-Schaffer, G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. Can Fam Physician. 2010 Jun; 56(6): 514–517. PMCID: PMC2902929

States with medical cannabis laws have significantly lower state-level opioid overdose mortality rates

- A time-series analysis was conducted of medical cannabis laws and state-level death certificate data in the United States from 1999 to 2010; all 50 states were included.
- Reported age-adjusted opioid analgesic overdose death rate per 100 000 population in each state.
- Regression models were developed including state and year fixed effects, the presence of 3 different policies regarding opioid analgesics, and the state-specific unemployment rate.
- Results showed states with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, −37.5% to −9.5%; *P* = .003) compared with states without medical cannabis laws.
- The association between medical cannabis laws and opioid analgesic overdose mortality in each year after implementation of the law strengthened over time
- Concluded that medical cannabis laws are associated with significantly lower state-level opioid overdose mortality rates.



Mean Age-Adjusted Opioid Analgesic Overdose Death Rate. States with medical cannabis laws compared with states without such laws in the United States, 1999-2010.



Association Between Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in Each Year After Implementation of Laws in the United States, 1999-2010. Point estimate of the mean difference in the opioid analgesic overdose mortality rate in states with medical cannabis laws compared with states without such laws; whiskers indicate 95% CIs.

Bachhuber MA et al. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. JAMA Intern Med. 2014 Oct;174(10):1668-73.

States with medical cannabis laws have fewer fatal crashes involving opioids

- Columbia University scientists analyzed traffic fatality data from 18 U.S states (1999-2013).
- States that passed medical marijuana laws saw an *overall reduction in fatal crashes involving drivers who tested positive for opioids*.
- Authors expect the adverse consequences of opioid use to decrease over time in states where medical marijuana use is legal, as individuals substitute marijuana for opioids in the treatment of severe or chronic pain.

Kim JH, et al.State Medical Marijuana Laws and the Prevalence of Opioids Detected Among Fatally Injured Drivers. Am J Public Health. 2016 Sep 15:e1-e6. [Epub ahead of print]