

Medical Cannabinoids for the Management of Chronic Noncancer Pain

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Disclosures

- Grants: CanniMed
- Consulting:
 - CHI Inc
 - Emmes

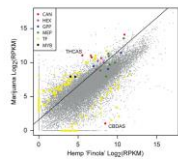
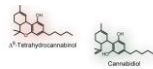
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van Bel et al. *Genome Biology* 2017, 18:102
<http://genomebiology.com/2017/18/1/102>



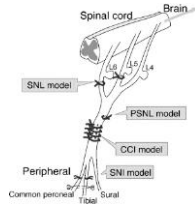
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The draft genome and transcriptome of *Cannabis sativa*



Cannabinoids are effective in all peripheral neuropathic pain models

- Nerve injury
 - Chronic constriction injury
 - Sciatic nerve ligation
 - Brachial plexus avulsion
 - Trigeminal neuralgia
- Diabetes
 - Streptozotocin
- Chemotherapy
 - Paclitaxel
 - Cisplatin
 - Vincristine
- HIV neuropathy



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...and in other pain models

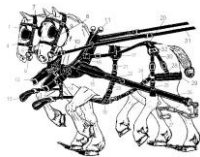
- Spinal cord injury
- Multiple sclerosis
- Cancer pain
- Osteoarthritis
- Visceral pain
- Inflammatory, nociceptive pain
- Muscle pain



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Defining the cannabinoid system

- Exogenous compounds
 - Phytocannabinoids
 - THC, CBD, combinations
 - Synthetic cannabinoids
 - Nabilone, dronabinol
 - K2, "spice"
- Endogenous cannabinoids
 - Anandamide
 - 2-arachidonyl glycerol
- Receptor targets
 - CB1, CB2, TRPV1, PPAR, 5-HT, other...

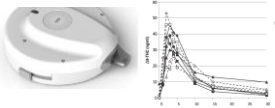
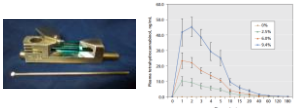


Smoked cannabis for chronic neuropathic pain: a randomized controlled trial

Mark A. Ware MBBS, Tongtong Wang PhD, Stan Shapiro PhD, Ann Robinson RN, Thierry Ducourt MSc, Thao Huynh MD, Ann Gama PhD, Gary J. Bennett PhD, Jean-Paul Collet MD PhD

25 mg herbal cannabis; 0, 2.5, 6, 9.4% THC
Single inhalation using pipe, 3 times daily
N=23 neuropathic pain patients

15 mg herbal cannabis; 19% THC
Single inhalation using inhaler
N=10 neuropathic pain patients



There is conclusive or substantial evidence that cannabis or cannabinoids are effective:

- For the treatment of chronic pain in adults (cannabis) (4-1)
- As anti-emetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids) (4-3)
- For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids) (4-7a)



Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2017. *The health effects of cannabis and cannabinoids: Current state of evidence and recommendations for research*. Washington, DC: The National Academies Press.

The National Academies of SCIENCES • ENGINEERING • MEDICINE

Prescription cannabinoids

- Dronabinol (Δ-9 tetrahydrocannabinol – THC) (2.5 - 10mg)
 - Oral capsule
 - Approved for **chemotherapy-induced nausea and vomiting and anorexia associated with HIV/AIDS**
- Nabilone (0.25 - 1.0mg)
 - Oral capsule
 - Approved for **chemotherapy-induced nausea and vomiting**
- Nabiximols (2.7mg THC + 2.5mg CBD)
 - Oromucosal spray
 - Approved in Canada for **multiple sclerosis-associated neuropathic pain, spasticity and advanced cancer pain**

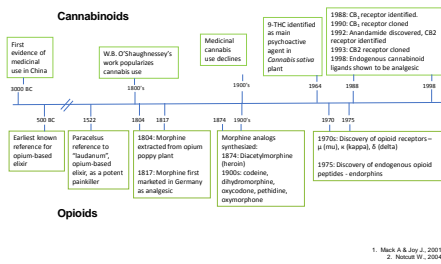
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Safety concerns

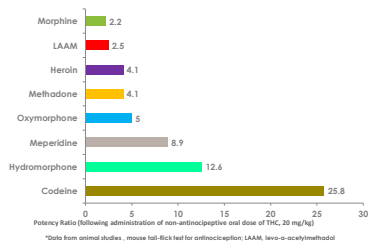
- Brain development
- Psychosis
- Cannabis use disorder
- Cognitive function
- Driving
- Drug interactions
- Anxiety/depression
- Cardiovascular effects
- Pregnancy/lactation
- Lung
- ...

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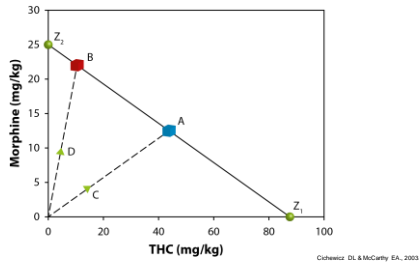
Cannabinoids and Opioids: Historical Perspective



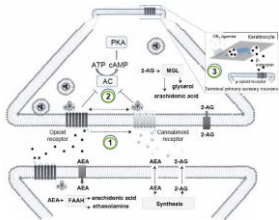
Opioid Sparring Effects of THC



Cannabinoid-Opioid Synergism



Opioid/cannabinoid receptor interactions



- Three main hypotheses related to opioid and cannabinoid interactions:
- ① Indirect interaction and alterations of the cannabinoid system after exposure to opioids
 - ② Interaction at their signal-transduction mechanisms
 - ③ Direct interaction at the receptor and release and/or synthesis of endogenous opioid peptides by cannabinoids

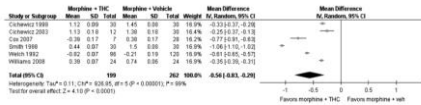
Diwanetz J & Beaulieu P. 2010.

“Over the past year, I have put almost 40 patients on medical cannabis, usually oil, almost all with neuropathic pain ...I am very impressed with its efficacy and utility as an opioid-sparing medication. I tell patients that once they are on the cannabis oil, I will help them slowly bring down their opioids...A very few have said it did nothing for them, but 90-95% have been helped tremendously.”

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Review Article
Opioid-Sparing Effect of Cannabinoids: A Systematic Review and Meta-Analysis

Suzanne Nielsen^{1,2,3}, Pamela Sabioni⁴, Jose M Trigo⁵, Mark A Ware⁶, Brigit D Beta-Stablein⁶,
 Bradin Pharoos⁶, Nicholas Lintzeris⁶, Kok Eng Khoo⁶, Michael Farrell⁶, Andrew Strain⁶ and Bernard Le Fell⁶



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Opioid Sparing Effects of Cannabinoids: Case series

- Case report* of patient with familial Mediterranean fever
 - 10yr history of chronic relapsing pain and inflammation of gastrointestinal origin; morphine, codeine, buprenorphine, dextropropoxyphene all had little effect
- Oral cannabis administered for 3 weeks of active treatment, with placebo administered in between, on background morphine therapy (30 mg BID, MS Contin; rescue dosage using 10 mg morphine)
 - Significant reduction in morphine use, as measured by a reduction in use of rescue dosage analgesic tablets
- Patient was able to maintain similar pain scores (4.8 – 6.2 on the VAS scale) during active and placebo weeks

*Uncontrolled data

Hodson A, et al., 1997.

Opioid Sparing Effects of Cannabis

- Three case studies* where patients used small doses of smoked marijuana in combination with an opioid
- Patients were able to decrease the dose of opioid by 60–100% as compared to before the regular use of smoked marijuana
- With the introduction of smoked marijuana, each patient reported better pain control

*Uncontrolled data

Lynch ME & Clark AJ, 2003.

Conclusion

-
- Cannabinoids emerging as valid option for refractory chronic pain management
 - Innovative solutions to opioid crises needed
 - Cannabinoid-opioid synergy deserves attention
 - Clinical trials challenging to design but necessary to conduct

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