

The Role of Cannabinoids in Acute & Chronic Pain Treatment

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The History & Science of Medicinal Cannabis

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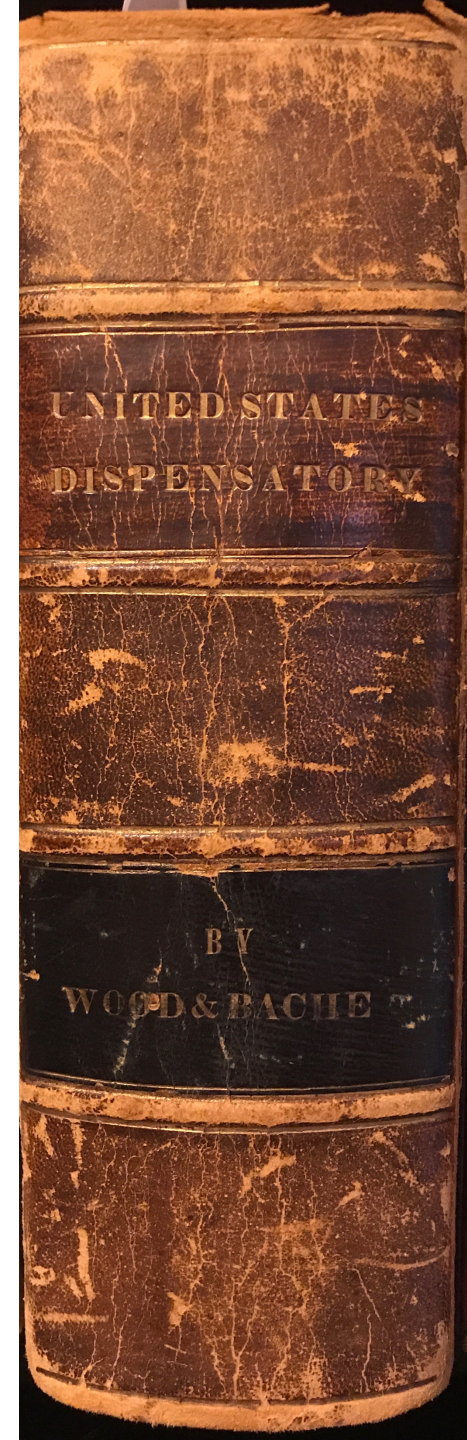
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History of Medicinal Cannabis

- China, 1st century: rheumatic pain, constipation...
- India: sedative, anxiolytic, anticonvulsant, analgesic...
- 1839: Dr. William O'Shaughnessy
- U.S. Dispensatory 1845: analgesic in place of opium
- Late 19th/Early 20th Century:
 - migraine, neuralgia, dysmenorrhea, acute rheumatism, dental pain
 - multiple patent medicines
- Removed from pharmacopoeia in 1942
 - Against advice of the AMA
- 1996: California prop 215



Cannabinoid Refers to a Variety of Compounds

- Endocannabinoids
 - Endogenous cannabinoids
- Phytocannabinoids
 - Derived from cannabis plants
- Synthetic



Medicinal Cannabis: Cannabinoid Pharmaceuticals



THC schedule 1

Nabiximols (Sativex)
Not FDA approved in
US;
Canada & Europe:
Cancer pain, spasticity



Nabilone
(Cesamet)
schedule II
FDA approved for:
chemo nausea

Dronabinol
(Marinol)
schedule III
FDA approved
for: HIV wasting
& chemo nausea



Cannabinoid MOA

- **Cannabinoid Receptors**

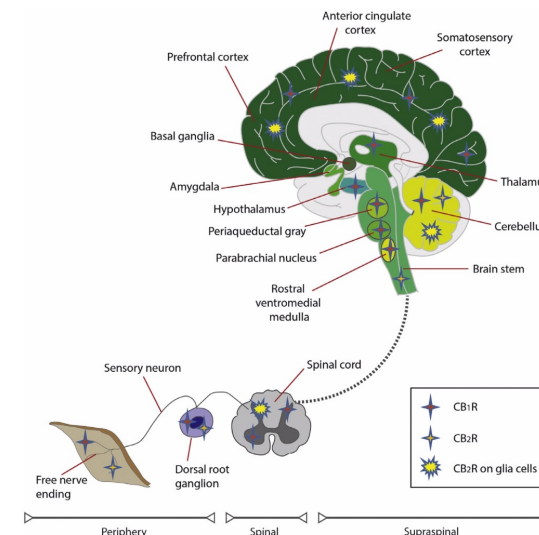
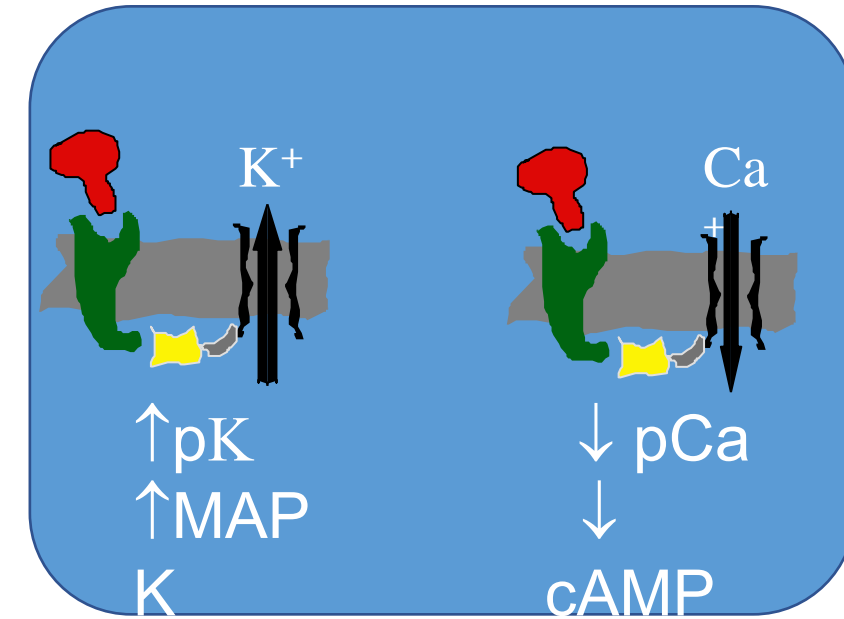
- G-protein coupled

- **CB1: neuromodulatory**

- CNS & PNS
 - ↓ Terminal excitability - PNS
 - ↓ Evoked postsynaptic excitation - CNS
- Pain processing centers: dorsal horn, amygdala, Periaqueductal grey, RVM

- **CB2: immunomodulatory**

- monocytes, B/T-cells, mast cells
 - ↓ Inflammatory cell mediator release
 - ↓ Plasma extravasation
 - ↓ Sensitization of afferent terminals



THE ENDOCANNABINOID SYSTEM

Implicated in processes such as pain, perception,
mood, memory and reward.

To provide that we:

EAT



SLEEP



RELAX



FORGET



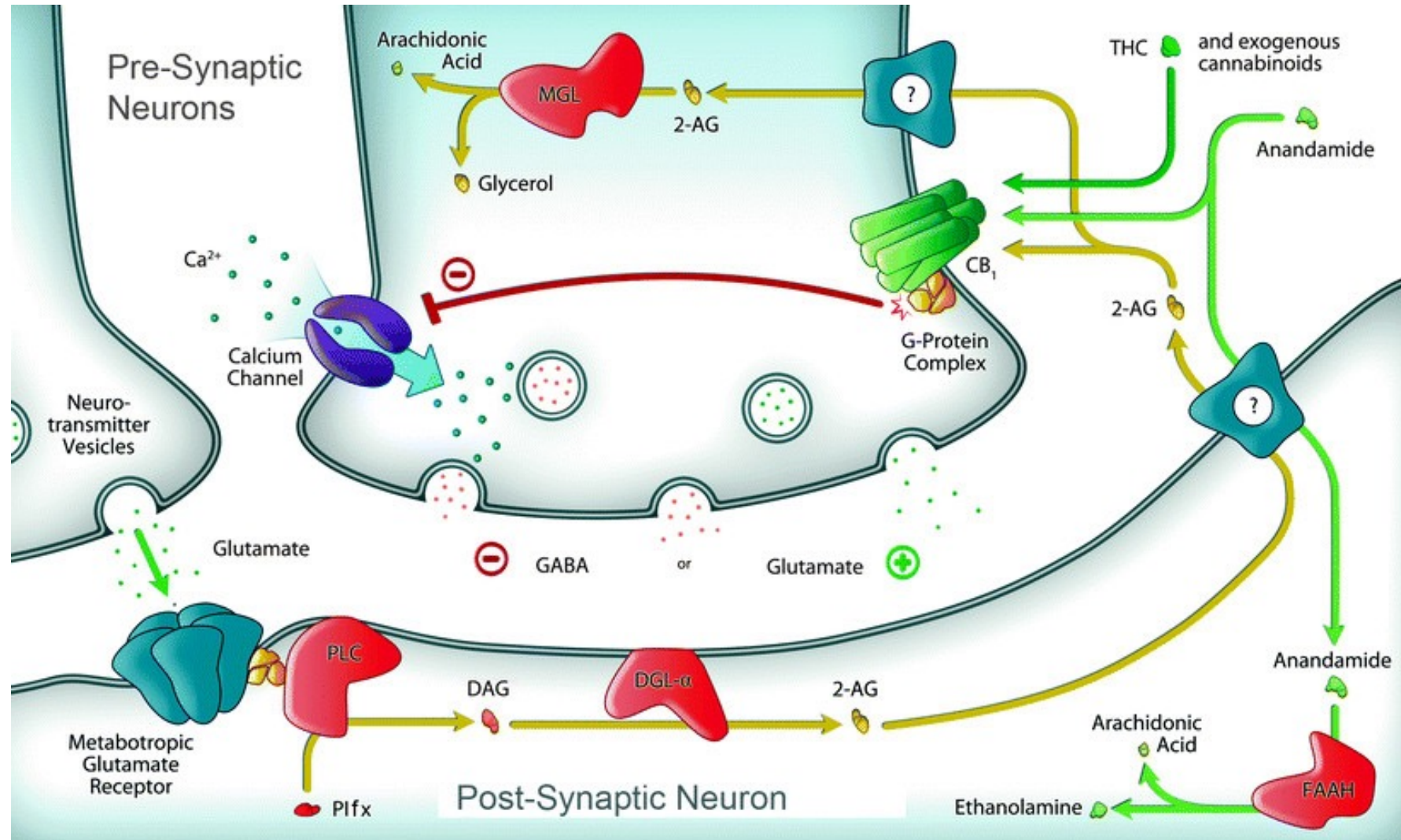
PROTECT



Di Marzo V, Piscitelli F, Mechoulam R (2011) Cannabinoids and
endocannabinoids in metabolic disorders with focus on diabetes. Handbook of
Experimental Pharmacology: 75–104.

Endocannabinoid Signaling System

Pre and Post Synaptic Modulation



THC

- **analgesic** effects of in humans.
- **anxiolytic** (dose related).
- **anti-inflammatory** effects.
- Agonist at both **CB₁** and **CB₂**
- modulate **dopamine mechanisms**
- **Low Dose** can be effective- CBD may “synergize” and allow for lower dosing

Cannabidiol

- **No studies** reporting analgesic effects of CBD in humans.
- CBD has been shown to have **anxiolytic** effects. (5HT_{1A})
- CBD has been shown to have **anti-inflammatory** effects. (GPR55)
- CBD has been shown to increase AEA levels (support eCS function).
- CBD may **modulate dopamine mechanisms** in the ventral tegmental area (related to addiction)
- Dose is relatively high compared to THC (100s of milligrams)
- Shown to modulate the psychoactivity of THC, slow metabolism (prolong the effect)

Medicinal Cannabis: Evidence for Chronic Pain

- Pre-Modern use for pain
- Experimental Pain
- Modern studies of pain

THC: Shown Effective in Pre-Clinical Peripheral Neuropathic Pain Models

Nerve injury

- Chronic constriction injury
- Sciatic nerve ligation
- Brachial plexus avulsion
- Trigeminal neuralgia

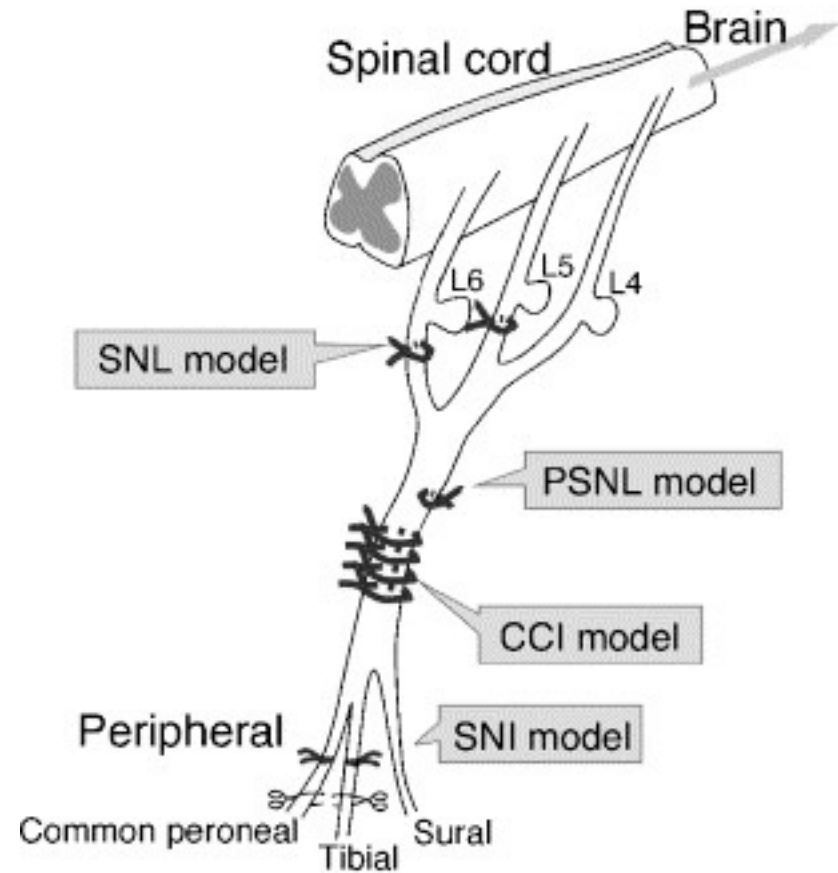
Diabetes

- Streptozotocin

Chemotherapy

- Paclitaxel
- Cisplatin
- Vincristine

HIV neuropathy



[Pharmacology & Therapeutics](#)

[Volume 109, Issues 1–2](#), January 2006, Pages 57–77

...and in other pain models

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



Systematic Review Cannabinoids Chronic Non-Cancer Pain

Lynch ME, Campbell F. Br
J Clin Pharmacol. 2011
Nov;72(5):735-44.

BJCP British Journal of Clinical Pharmacology

Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials

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Keywords:
cannabinoids, chronic non-cancer pain, neuropathic pain, systematic review

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Accepted Article:
21 March 2011

Fifteen of the eighteen trials that met the inclusion criteria demonstrated a significant analgesic effect of cannabinoid as compared with placebo and several reported significant improvements in sleep. There were no serious adverse effects. Adverse effects most commonly reported were generally well tolerated, mild to moderate in severity and led to withdrawal from the studies in only a few cases.

This article is linked to a themed issue in the British Journal of Pharmacology on Respiratory Pharmacology. To view this issue visit <http://dx.doi.org/10.1111/bjph.2011.163.issue-1>

Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis.

[4, 5] there is increasing attention on their potential role in the management of pain [6–9]. A previous systematic review done a decade ago identified the need for further randomized controlled trials (RCTs) evaluating cannabinoids in the management of chronic pain indicating that there was insufficient evidence to introduce cannabinoids into widespread use for pain at that time [10]. A subsequent review identified a moderate analgesic effect but indicated this may be offset by potentially serious harm [11]. This conclusion of serious harm mentioned in the more recent review is not consistent with our clinical experience. In addition there have been a number of additional

ment guidelines for reporting systematic reviews that evaluate health care interventions [12].

Systematic search
A literature search was undertaken to retrieve RCTs on the efficacy of cannabinoids in the treatment for chronic pain. The databases searched were: PubMed, Embase, CINAHL (EBSCO), PsycInfo (EBSCO), The Cochrane Library (Wiley), ISI Web of Science, ABI Inform (Proquest), Dissertation Abstracts (Proquest), Academic Search Premier (EBSCO), Clinical Trials.gov, TrialsCentral.org, individual pharmaceutical company trials sites for Eli Lilly and GlaxoSmithKline.

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Br J Clin Pharmacol / 72:5 / 735–744 / 735

Meta-Analysis Chronic Non-Cancer Pain

- Andreae et al (2015 *J Pain*)
 - Inhaled cannabis for neuropathic pain
 - 5 RCT studies included
 - Odds ratio of 30% reduction 3.2 with NNT of 5.5
- Stockings et al, (2018 *J Pain*)
 - 104 RCT and observational studies, mixed CNCP (half were neuropathic pain)
 - Mixed cannabis types and delivery routes
 - Evidence of 30% reduction in pain vs placebo; no evidence of 50% reduction
 - Conclusion: limited evidence benefit vs harm

Andreae et al. Pain. 2015 Dec;16(12):1221-1232

Stockings et al. Pain. 2018 Oct;159(10):1932-1954

RCTs of Smoked Cannabis in Pain

Author /Year	N=	Indication	Duration/type	Outcome
Abrams 2007	50	HIV neuropathy	5 days/DB	Positive: Decreased pain and hyperalgesia
Wallace 2015	16	Diabetic Peripheral Neuropathy	Single dose/DB/ Crossover	Positive: Decreased pain
Wilsey 2008	38	Neuropathic pain	Single dose/DBC	Positive: Decreased pain w/ highest dose, but significant psychoactive effects
Ellis 2009	34	HIV neuropathy	5 days/DB	Positive: Improved pain vs placebo,
Wilsey 2016	42	Spinal cord injury	Single dose/crossover	Positive: Decreased pain, no difference between low and high dose

RCTs of Synthetic Cannabinoids in Pain

Author/ Year	N=	Agent	Indication	Duration/type	Outcome
Karst 2003	21	Ajulemic acid	Neuropathic pain	7 day crossover	Positive: Decreased pain
Svendsen 2004	24	Dronabinol	Neuropathic pain in MS	15-21 days/DBC	Positive: Median numerical pain and relief improved
Narang 2008	30	Dronabinol	Chronic pain	3 doses, 1 day/DB	Positive: Total pain relief improved with 10 and 20 mg. AEs prominent
Ware 2010	31	Nabilone	Fibromyalgia	2 weeks/DBC	Negative: No effect on pain; sleep improved
Frank 2008	96	Nabilone	Neuropathic pain	14 weeks/DBC vs dihydrocodeine	Negative: DHC more effective with fewer AE

RCTs of Cannabis-Based Medicines in Neuropathic Pain

Author/ Year	N=	Agent	Indication	Duration/Type	Outcomes
Wade 2004	20	Nabixmols	Neurogenic pain	2 week crossover	Positive: Decreased pain
Berman 2004	48	Nabixmols vs THC	Brachial Plexus Avulsion	6 wks in 3 two- week arms	Positive: Decreased pain
Rog 2005	66	Nabixmols	Central neuropathic pain of MS	5 weeks	Positive: Decreased pain
Nurmikko 2007	125	Nabixmols	Peripheral neuropathic pain	5 weeks	Positive: Decreased pain and allodynia
Ernst 2005	65	Cannador	Post Herpetic neuralgia	4 weeks	Negative: No benefit
Zajicek 2003	419	Cannador	Pain in MS	15 weeks	Positive: Decr spasm-related pain, No decr in Spasms

RCTs of Cannabis-Based Medicines in Cancer Pain

Author/ Year	N=	Agent	Indication	Duration/type	Outcome
Noyes 1975	36	Oral THC	Cancer Pain	Rand, DB, Crossover, Single dose; vs codeine	Equivocal: Decreased pain similar to codeine; high dose cannabis >AE than codeine
Johnson 2010	117	Nabixmols	Cancer Pain	2 weeks, Rand, DB, Parallel	Positive: Decreased pain
Portenoy 2012	360	Nabixmols	Cancer Pain	5 weeks, Rand, DB, PC, Parallel	Positive: Decreased pain in low and middle dose

Medicinal Cannabis: Evidence for Acute Pain

- Studies of cannabinoids and acute pain
- Effects of chronic cannabis use on acute pain and anesthesia

Cannabinoids & Acute Pain: Retrospective Studies

Dronabinol in THA & TKA

- Retrospective (81 cases, 162 controls)
- Dronabinol 5mg bid
- Results:
 - Decreased cumulative opioid use in dronabinol group
 - Reduced LOS in dronabinol group
 - No difference in NRS

Dronabinol for Acute Pain of Traumatic Injuries

- Retrospective matched cohort study (33 cases, 33 controls) in pts with traumatic injury
- Dronabinol dosing avg 11mg/day, started 48 hrs after admission
- Results:
 - Cases: reduced opioid consumption (-79 (20) MME, $p<0.001$)
 - No change in NRS pain scores
 - Controls: opioid consumption was unchanged (-9 (20) MME, $p=0.63$)

RCT Evidence for Cannabinoids in Acute Pain

Study	Year	# Subjects	Drug (dose)	Comparator	Route	Effect vs placebo=
Beaulieu et al	2006	30	Nabilone (1-2mg)	ketoprofen 50mg, placebo	Oral	Negative
Buggy et al	2003	40	THC (5mg)	placebo	Oral	Equivalent
Jain et al	1981	56	Levonantradol (1.5, 2, 2.5, 3mg)	placebo	IM	Positive
Kalliomaki et al	2013	120	AZD1940 (800 mcg)	Naproxen 500, placebo	Oral	Equivalent
Levin et al		340	Nabilone (0.5mg)		Oral	Equivalent
Ostenfeld et al	2011	92	GW842166 (100mg, 800mg)	Ibuprofen, placebo	Oral	Equivalent
Guillaud et al	1983	100	Levonantradol (1-2mg)	Pethidine 1mg/kg IM, placebo	IM	Equivalent
Seeling et al	2006	100	Dronabinol (5mg)	placebo	Oral	Equivalent

Cannabinoids and Acute Pain: Review

Analgesic efficacy of cannabinoids for acute pain management after surgery: a systematic review and meta-analysis

Faraj W Abdallah ¹, Nasir Hussain ², Tristan Weaver,² Richard Brull ³

- Eight RCTs (924 patients) and four observational studies (4259 patients)
- Primary outcomes: 1) cumulative OME; 2) pain severity at 24 hours
- Heterogeneous drugs, doses, routes of delivery, timing
- Insufficient data for difference in OME or pain at 24 hrs
- Trend towards increased pain at 12 hrs; No difference pain/OME other time points

Chronic Cannabis Use: Perioperative Effects

Post-Op Pain & Sleep

- Retrospective Cohort Study: Orthopedic Surgery Outcomes
- 155 cannabis users matched with 155 non- users
- Higher NRS rest and movement post-op
- Higher incidence of severe post-op pain
- Higher incidence of sleep interruption

Post-Op Pain & Opioid Use

- Retrospective Cohort Study: IBD Surgery
- 42 cannabis users matched with 312 non-users
- Higher OME in cannabis group
 - Not significant after adjusting for age/pre-op opioid use



Liu et al. Anesth Analg. 2019; 129(3)

Jamal et al. Eur J Anesth. 2019;
36:705-715

Chronic Cannabis Use: Perioperative Effects

Post-Op Pain & Opioid Use

- Prospective Cohort: Orthopedic Surgery Jamaica
- 41 cannabis users & 32 non-users
- Higher PACU analgesic requirement
- Higher PACU pain scores at 1 hour post-op

Propofol Induction

- Prospective randomized single-blind trial
- 30 cannabis users vs 30 non-users
- No difference in propofol dose to achieve BIS <60
- Higher dose propofol to achieve successful LMA insertion

Chronic Cannabis & Perioperative Risk

Perioperative Risk

- Cannabis Use Disorder Dx Code
- No difference on composite perioperative outcome
- Odds of periop MI 1.88 times higher

ANESTHESIOLOGY

Cannabis Use Disorder and Perioperative Outcomes in Major Elective Surgeries

A Retrospective Cohort Analysis

Akash Goel, M.D., M.P.H., Brandon McGuinness, M.D.,
Naheed K. Jivraj, M.B.B.S., M.Sc.,
Duminda N. Wijesundera, M.D., Ph.D.,
Murray A. Mittleman, M.D., Dr.P.H.,
Brian T. Bateman, M.D., M.Sc., Hance Clarke, M.D., Ph.D.,
Lakshmi P. Kotra, B.Pharm. (Hons), Ph.D.,
Karim S. Ladha, M.D., M.Sc.

ANESTHESIOLOGY 2020; 132:625–35

The Clinical Practice of Medical Cannabis

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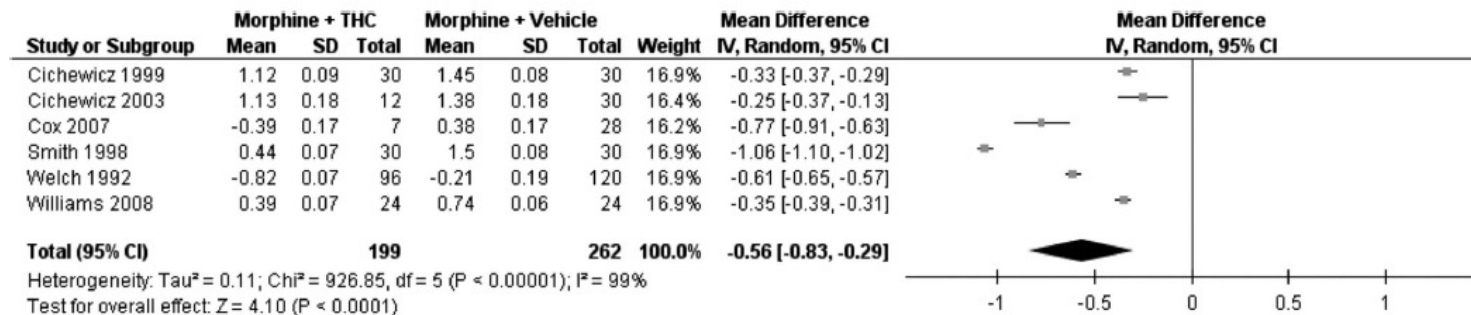


Suzanne Nielsen^{*,1,2}, Pamela Sabioni³, Jose M Trigo³, Mark A Ware⁴, Brigid D Betz-Stablein⁵,
Bridin Murnion^{6,7}, Nicholas Lintzeris^{2,6}, Kok Eng Khor⁸, Michael Farrell¹, Andrew Smith⁹ and Bernard Le Foll³

Neuropsychopharmacology (2017), 1–14

19 preclinical studies: 14 studied THC and 10 other synthetic agonists of CB₁R

- Pain outcome: Tail-flick and hotplate tests
Morphine (17), codeine (3), buprenorphine, fentanyl oxycodone, hydromorphone, methadone, LAAM, meperidine and pentazocine (1-2)
- 90% demonstrated significant synergistic effect on hot plate latency.
2 studies showed duration of effect was extended with co-administration of low dose opioid and cannabinoid.



The median effective dose of morphine/codeine was 3.6/9.5 times lower when given in combination with THC compared to when morphine was administered alone

Cannabinoid/Opioid System Interactions

- Animal studies indicate a contribution of the opioid system in cannabinoid reward, reinforcement and dependence
 - Opioid agonists facilitate while antagonist reduce self administration of cannabinoids
 - Naloxone induces cannabinoid withdrawal while co-administration prevents dependence
 - Opioids attenuate cannabinoid withdrawal
- Opioid modulation in humans less clear

Effect of Medical Cannabis Laws on Opioid use: The Good and the Bad



The Good



Population studies are emerging suggesting that medical marijuana patients are substituting marijuana for opioids

Lucas, Psychoactive Drugs, 2012

Lucas Addict Res Theory, 2013

Lucas, Int J Drug Policy, 2017

Reiman, Harm Reduct, 2009

Original Investigation

Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999-2010

Marcus A. Bachhuber, MD; Brendan Saloner, PhD; Chinazo O. Cunningham, MD, MS; Colleen L. Barry, PhD, MPP

Table. Association Between Medical Cannabis Laws and State-Level Opioid Analgesic Overdose Mortality Rates in the United States, 1999-2010

Independent Variable ^a	Percentage Difference In Age-Adjusted Opioid Analgesic Overdose Mortality In States With vs Without a Law		
	Primary Analysis	Secondary Analyses	
	Estimate (95% CI) ^b	Estimate (95% CI) ^c	Estimate (95% CI) ^d
Medical cannabis law	-24.8 (-37.5 to -9.5) ^e	-31.0 (-42.2 to -17.6) ^f	-23.1 (-37.1 to -5.9) ^e
Prescription drug monitoring program	3.7 (-12.7 to 23.3)	3.5 (-13.4 to 23.7)	7.7 (-11.0 to 30.3)
Law requiring or allowing pharmacists to request patient identification	5.0 (-10.4 to 23.1)	4.1 (-11.4 to 22.5)	2.3 (-15.4 to 23.7)
Increased state oversight of pain management clinics	-7.6 (-19.1 to 5.6)	-11.7 (-20.7 to -1.7) ^e	-3.9 (-21.7 to 18.0)
Annual state unemployment rate ^g	4.4 (-0.3 to 9.3)	5.2 (0.1 to 10.6) ^e	2.5 (-2.3 to 7.5)

^a All models adjusted for state and year (fixed effects).

^b $R^2 = 0.876$.

^c All intentional (suicide) overdose deaths were excluded from the dependent variable; opioid analgesic overdose mortality is therefore deaths that are unintentional or of undetermined intent. All covariates were the same as in the primary analysis; $R^2 = 0.873$.

^d Findings include all heroin overdose deaths, even if no opioid analgesic was

involved. All covariates were the same as in the primary analysis. $R^2 = 0.842$.

^e $P \leq .05$.

^f $P \leq .001$.

^g An association was calculated for a 1-percentage-point increase in the state unemployment rate.

Medical marijuana policies and hospitalization related to marijuana and opioids

- Hospital discharges 1997-2014
 - Medical Marijuana Policies associated with:
 - No change in Marijuana dependence or abuse discharges
 - 23% reduction in Opioid dependence or abuse discharges
 - 13% reduction in Opioid pain reliever overdose discharges
- Shi, Y. Drug and Alcohol Dependence, 2017

Association Between Prescribing Patterns for Opioids in Medicare Part D and the Implementation of State MCLs

- Doses of opioids filled in Medicare D from 2010– 2015
- Average of 23.08 million daily doses of any opioid dispensed/year across states
- Multiple regression analysis found fewer daily doses in states with MCLs
 - Active dispensaries – 3.742 million reduction
 - Home cultivation – 1.792 million reduction
- Largest effect seen on hydrocodone

Cannabis Use Associated with Decreased Opiate Use

- A retrospective cross-sectional survey of patients with chronic pain
 - 64% decreased opioid use
 - Decreased side effects of medications
 - Improved quality of life
- Boehnke et al. J Pain, 17:739, 2016



Recreational Marijuana Legalization and Prescription Opioids in Medicaid Patients

- Prescription drug utilization 2010-2017
- 3 population-adjusted variables: # opioid prescriptions, total MME, related Medicaid spending
- Legalization associated with Schedule III but not II opioid reduction:
 - Reduction in # prescriptions – 32%
 - MME – 30%
 - Spending on schedule II opioids – 31%



Shi, publication pending, 2018

The BAD



Cannabis use and risk of prescription opioid use disorder

- Logistic regression models to assess associations between cannabis use (2001-2002) and nonmedical prescription opioid use and prescription opioid use disorder (2004-2005) using DSM-IV criteria.
- Cannabis use, → Increase nonmedical prescription opioid use and opioid use disorder
- Adults with pain and cannabis use → Increase nonmedical opioid use

Effect of cannabis use in chronic pain patients prescribed opioids

- 4 year prospective, national, observational cohort study in chronic pain patients on opioids
- 1514 included in the study
 - 24 % reported using cannabis
 - Compared to no cannabis used:
 - > pain severity score
 - > pain interference score
 - > generalized anxiety disorder severity score
 - No evidence that cannabis use reduced prescribed opioid use or increased rates of opioid discontinuation

Cannabis:

Conditioned Placed Preference vs. Aversion

- High dose THC produces CPA
- Lower doses of THC produces CPP
- Human cannabis smokers also report opposing effects

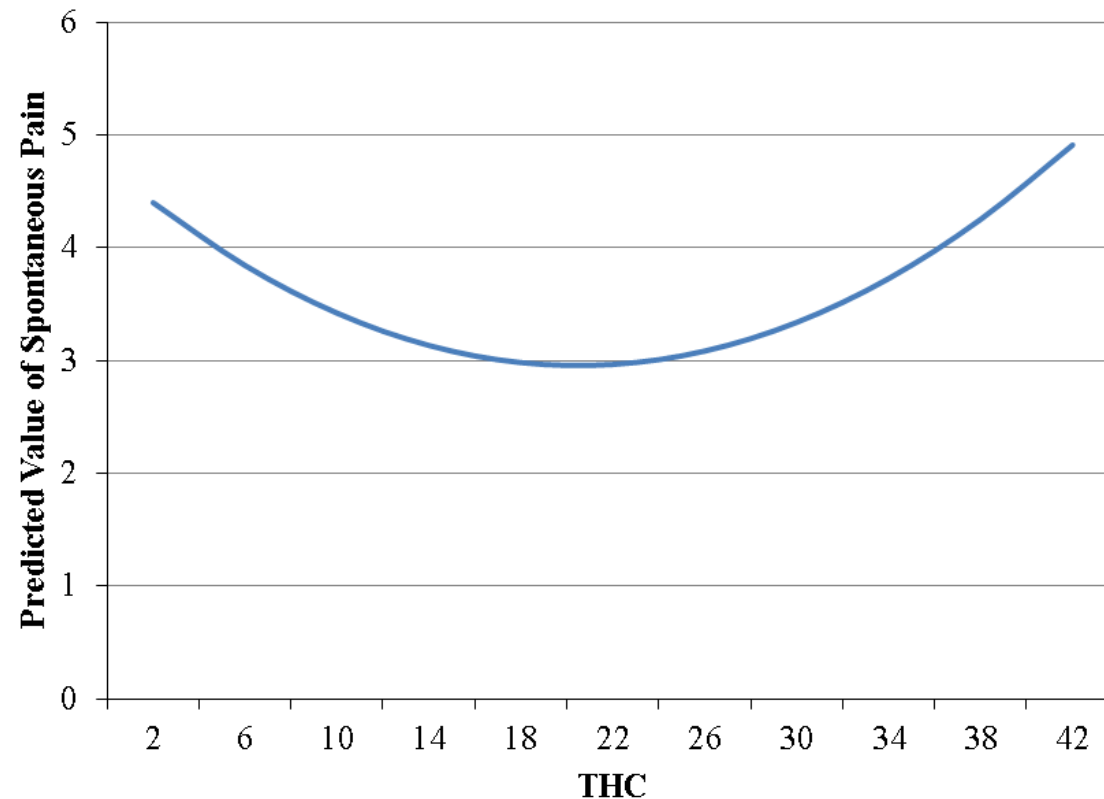
*Braida D, Pozzi M, Cavallini R, Sala M
Neuroscience. 2001; 104(4):923-6
Cheer JF, Kendall DA, Marsden CA
Psychopharmacology (Berl). 2000 Jul;
151(1):25-30.*

*Reilly D, Didcott P, Swift W, Hall W
Addiction. 1998 Jun; 93(6):837-46.*



THC Plasma Levels and Pain Relief

Therapeutic window of pain relief occurs between 16-31 ng/ml plasma level of THC



Bi-phasic effects

THC in “naïve” patients

2-5 mg: anxiolytic/ analgesic

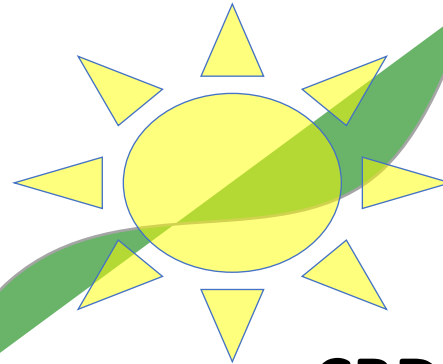
10-15 mg: paranoia

20-25 mg: psychosis, sedation,
nociception

Low dose: Stimulation

eCB deficiency:

migraine,
fibromyalgia
Chronic anxiety,
osteoporosis



CBD

15 mg: ‘alertness’

4 mg/kg is “sedative” (adult)

160 mg increased sleep duration

400 mg induced ‘sedation’

> 400 mg is antipsychotic

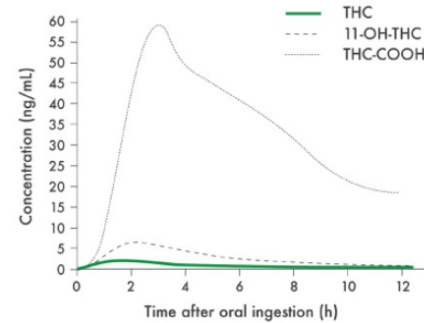
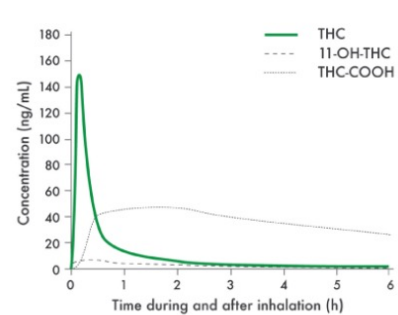
High dose: Inhibition

eCB excess:

schizophrenia
CB1 mutations?
sub abuse,
obesity, ADD,
Parkinson,
Metabolic
Syndrome

Cannabis Pharmacology and Dosing

- Inhalation
- Ingestion
- Topical
 - patients mostly report very little benefit



Grotenhermen F. Clin Pharmacokinet. 42, 2003



Primary benefit from THC

There is no human data to support CBD as an analgesic

- Patients report little to no benefit



CBD may help reduce drug craving AND/OR
decrease the psychoactivity of THC

Dosing Guidelines: Clearing the Smoke

- Self-titration : Patients adapt dosing to balance pain benefit with side-effect profile. Liquids work best: tincture or “oil”.
- Start at low milligram dose of THC and gradually increase over 10-14-day trial. (0.5-2 mg- individualized per patient)
- Patients develop tolerance to psychoactive effects of cannabis over a period of days, without concomitant tolerance to the benefits.
- THC-mediated side effects such as fatigue, tachycardia and dizziness are avoidable when starting dose is low and titration is slow.
- Less can be more; lower dose is often more effective, a higher dose can be less effective. (biphasic effects)

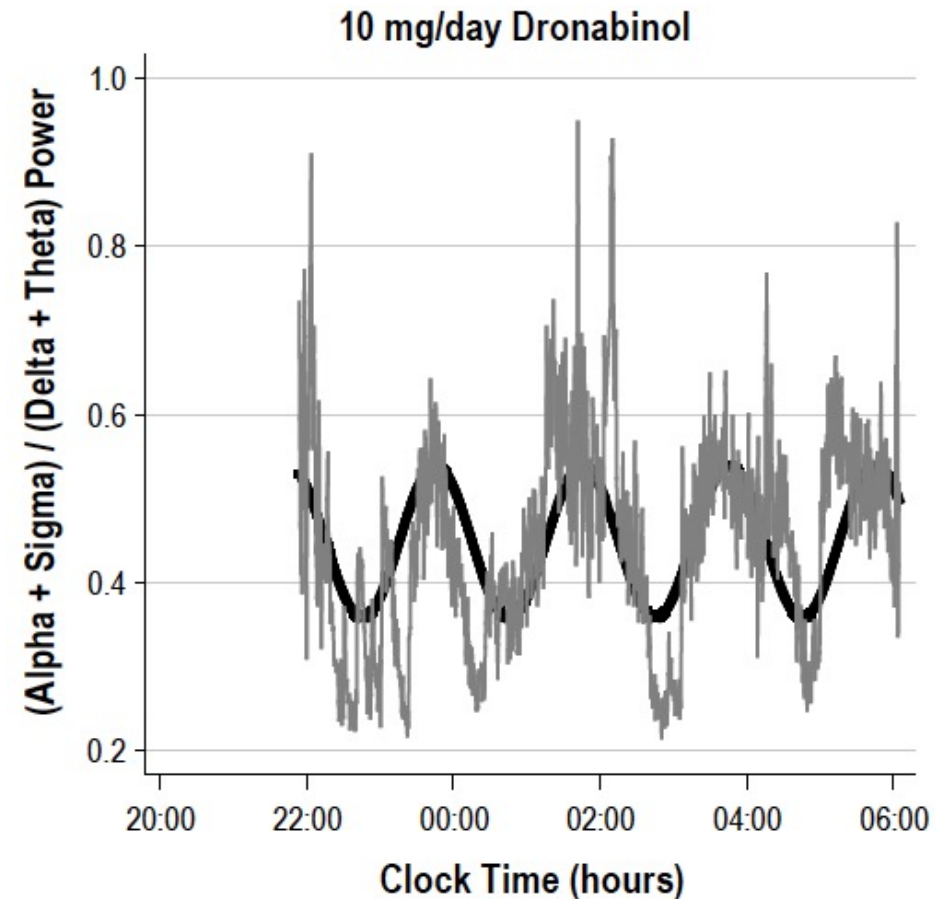
Cannabis Product Testing in California

- Bureau of Cannabis Control
 - All cannabis harvested and all products manufactured on or after 1/1/2018 shall be tested according to Title 16 of the California Code of regulations
 - Testing will include:
 - Cannabinoids, moisture, residual solvents, pesticides, microbial impurities, homogeneity of edibles, foreign materials, terpenoids, mycotoxins, heavy metals

Cannabis and Obstructive Sleep Apnea

Pharmacotherapy of Apnea by Cannabimimetic Enhancement, the *PACE*
Clinical Trial: Effects of Dronabinol in Obstructive Sleep Apnea

- N=20 subjects: 2.5 mg THC;
10 mg THC and placebo
- Dronabinol was safe and well-tolerated for OSA
- Decreased Sleep Latency
- Reduced AHI
- Strengthened ultradian rhythm



Take-home

- Low THC cannabis is producing synergistic and antinociceptive effects in our patient population
- Pain relief is occurring with relatively low dose THC, minimizing side-effects.
- Cannabis provides a therapeutic strategy to enhance the analgesic effects of opioids, allowing for opioid-tapering



A mild euphoria or sense of well-being can play an important therapeutic role for patients faced with the despair of chronic pain and the loss of function that accompanies it.

THE END

