# The Role of Cannabinoids in Chronic Pain Treatment

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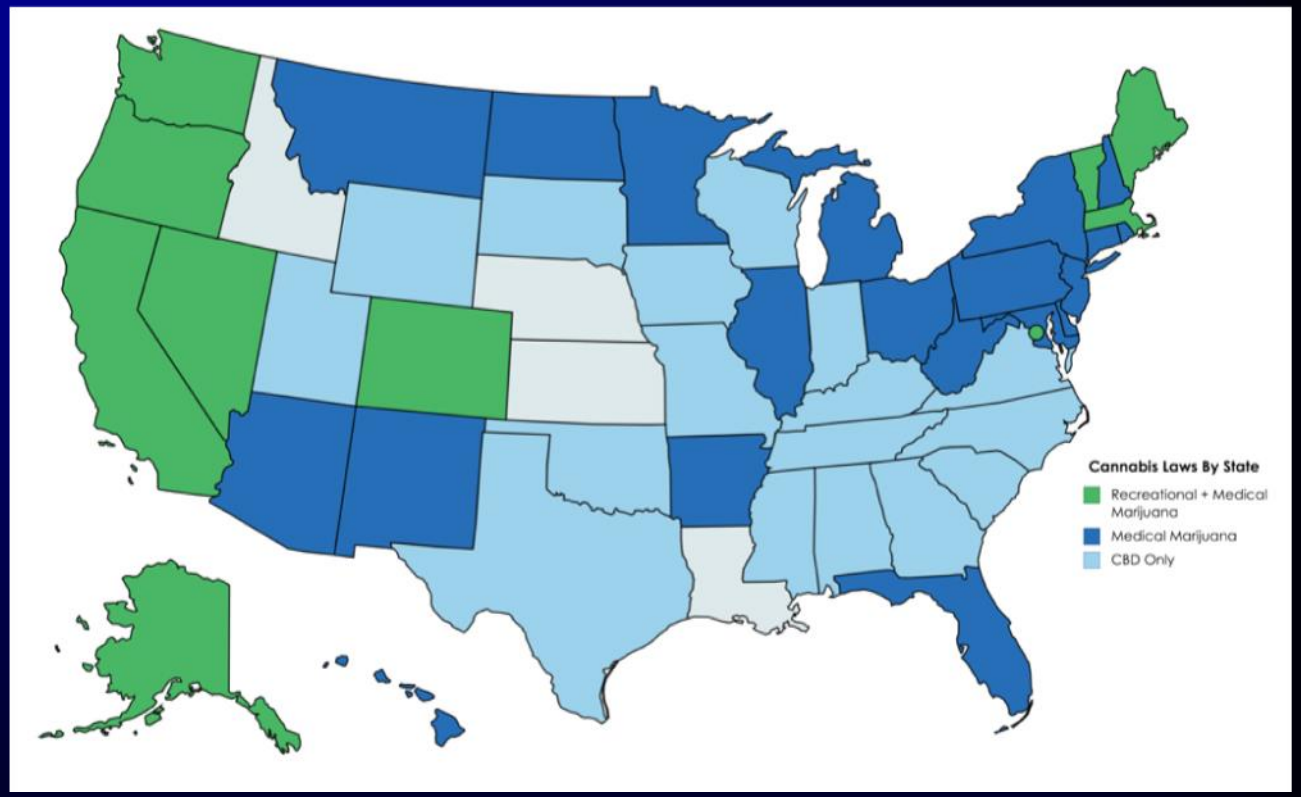
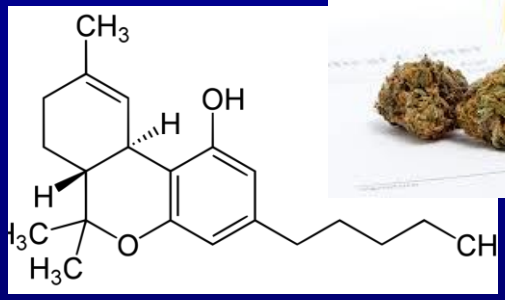
# Map of U.S. Marijuana Legalization

- Medical:
  - 29 states & DC
- Recreational & Medical:
  - 9 states & DC
- CBD Only:
  - 17 states

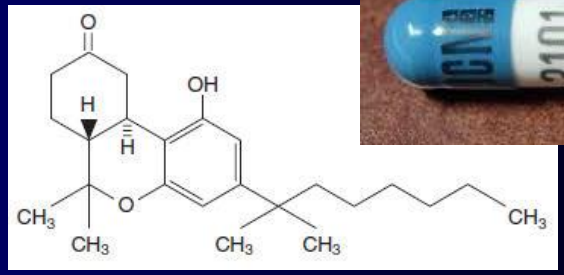



As of May 2018

# Medicinal Cannabis: Cannabinoid Pharmaceuticals

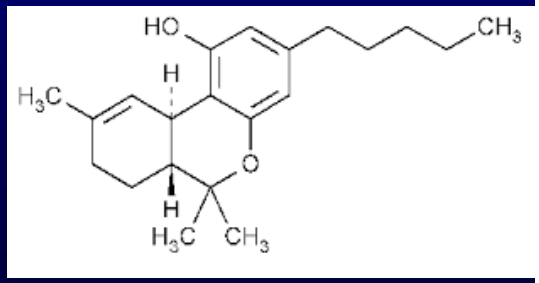



**THC** schedule 1





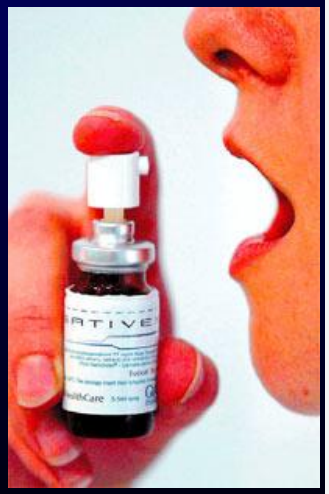
**Nabilone** (Cesamet)
schedule II
FDA approved for:
chemo nausea

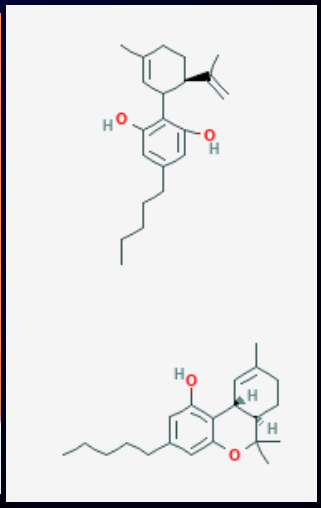




**Dronabinol** (Marinol)
schedule III
FDA approved for: HIV wasting & chemo nausea

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





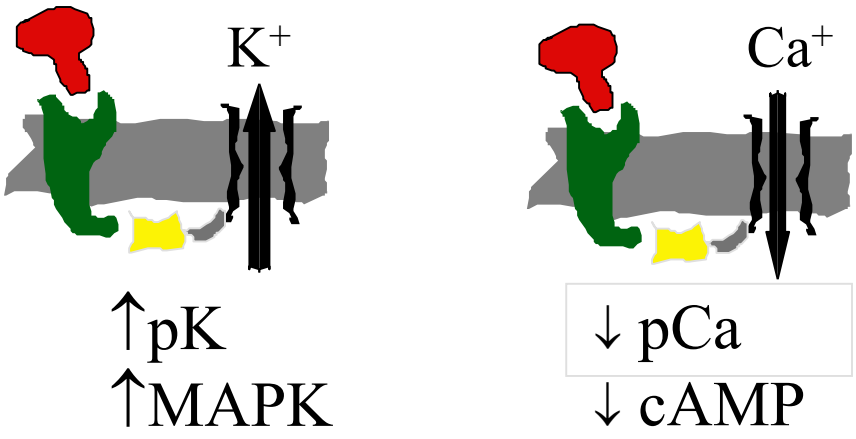
# CANNABINOIDS

Two cannabinoid (CB) receptors: CB1/CB2

G protein coupled superfamily 7 TM

-positively to potassium channels and mitogen active protein kinase (MAPK)

-negatively to N-type and P/Q-type calcium channels and adenylate cyclase (responsible for THC psychoactive effects)



# CANNABINOID TARGETS

**Peripheral** Cells: monocytes,B/T and mast cells

CB2-r:

↓Inflammatory cell mediator release

↓Plasma extravasation

↓Sensitization of afferent terminals

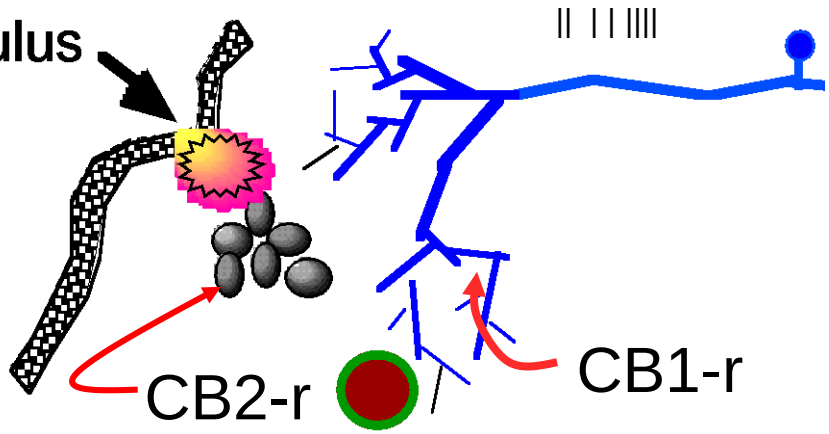
**Peripheral terminal of Primary afferent.**

CB1-r:

↓Terminal excitability

↓Release of pro-inflammatory terminal peptides

CB-r agonists: reduction of elevated terminal excitability otherwise induced by local injury and inflammation.



# CANNABINOID TARGETS

## Spinal Dorsal Horn

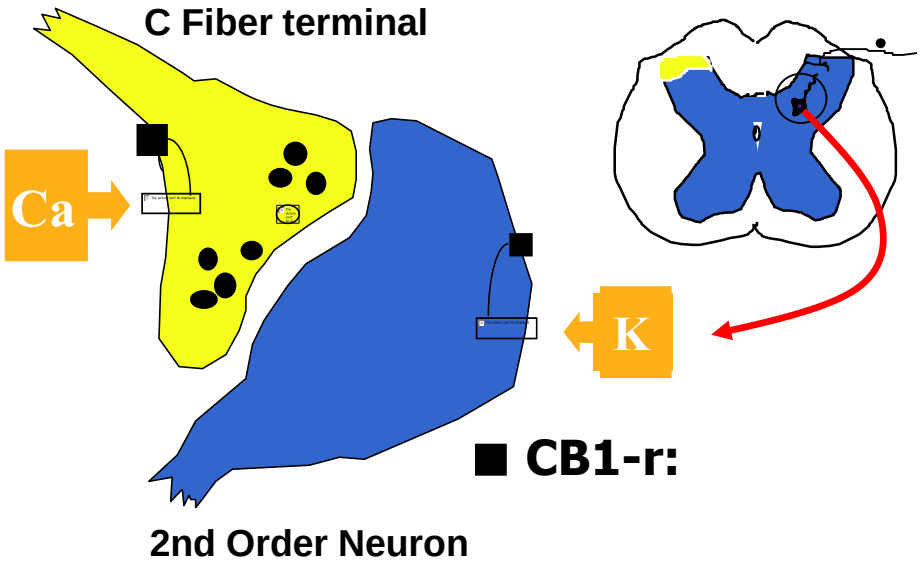
CB1-r: (intrathecal)

*Presynaptic* - Terminals of small primary afferents (peptidergic and non peptidergic)..partial colocation with TRPV-1-r
Agonist: ↓N/P/Q-VSCC →↓ neurotransmitter release

*Post synaptic* - neurons: (mRNA): Lam I-V, X
Agonist: ↑K Ch → hyperpolarization →↓ excitability

CB1-r/ CB2-r:
*Non neuronal cells* (??)

CB1 agonists: reduction of afferent evoked excitation of dorsal horn nociceptive neurons.



# CANNABINOID TARGETS

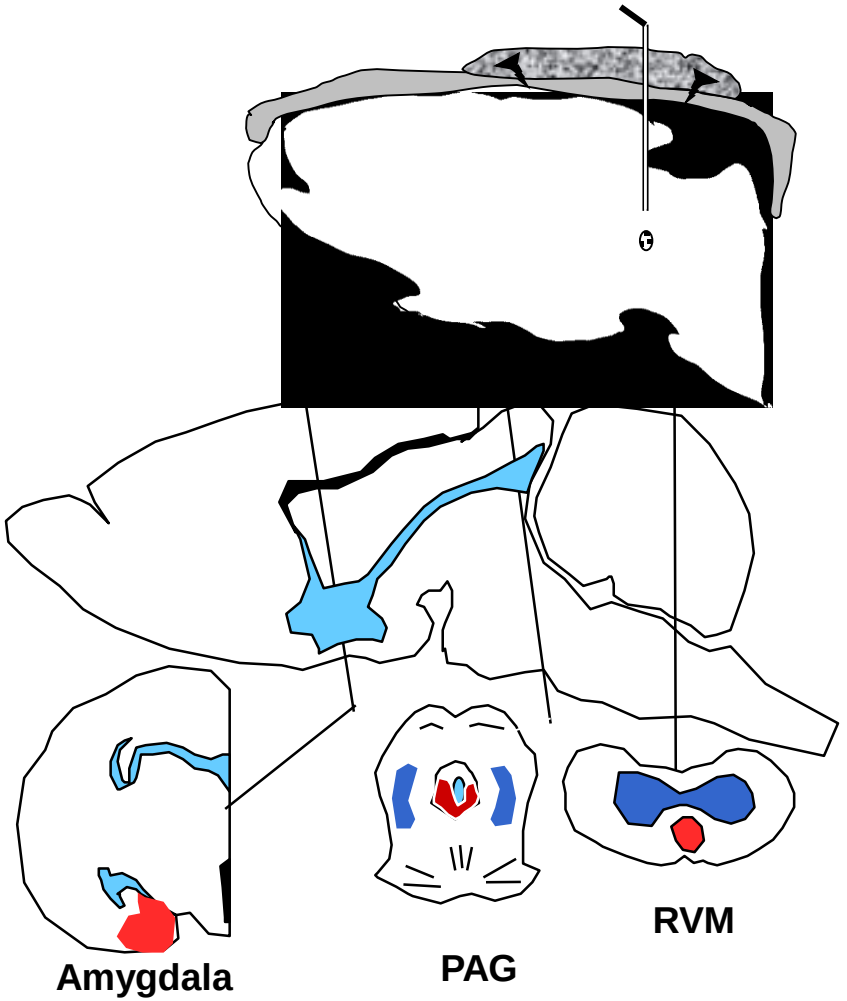
## Supraspinal Sites

CB1-r (microinjection)

*Basolateral Amygdala*

*Periaqueductal gray*

*Rostroventral Medulla*




Local effects upon nociceptive processing

Activation of bulbospinal pathways…regulating dorsal horn excitability

CB1 agonists: reduction of afferent evoked excitation of dorsal horn nociceptive neurons.

# Cannabinoid Refers to a Variety of Compounds

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

# THE ENDOCANNABINOID SYSTEM

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

**To provide that we:**

**EAT**

**SLEEP**

**RELAX**

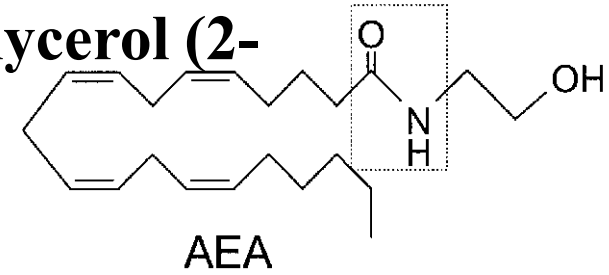
**FORGET**


**PROTECT**

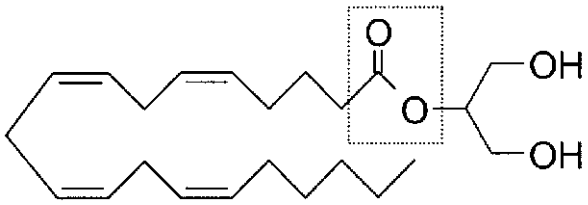
Di Marzo V, Piscitelli F, Mechoulam R (2011) Cannabinoids and endocannabinoids in metabolic disorders with focus on diabetes. Handbook of Experimental Pharmacology: 75–104.

# Endogenous Cannabinoid Ligands: The Endocannabinoids Lipid transmitters

**Anandamide (AEA) and 2-arachidonoylglycerol (2-AG):**




AEA

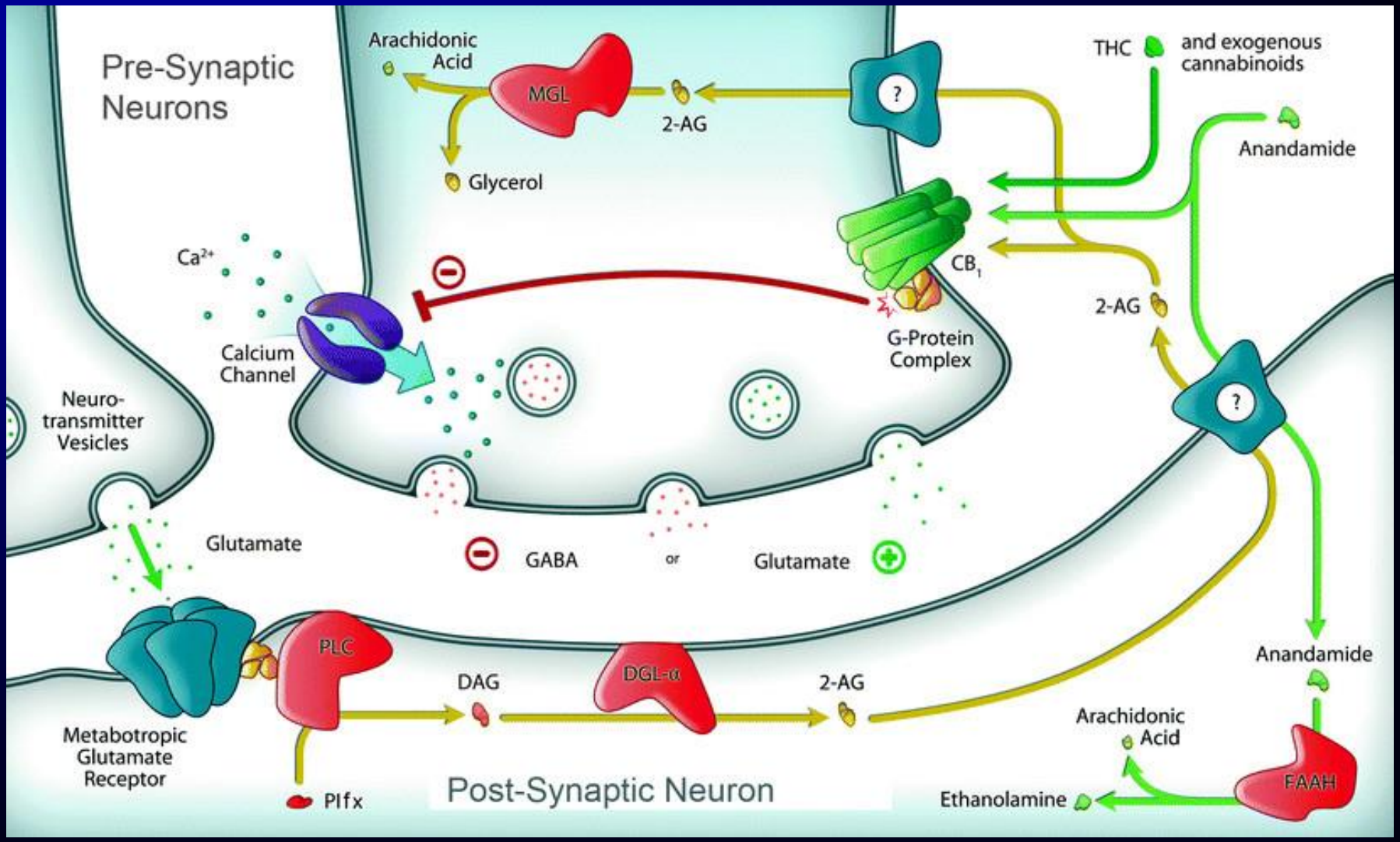



2-AG

- **Synthesized "on demand"**
- **Autocrine or paracrine mediators**
- **Retrograde messengers on neurons**
- **Degraded by enzymatic hydrolysis**
  - **AEA > FAAH)**
  - **2-AG > MAGL)**

(McPartland, 2008)

# Endocannabinoid Signaling System



# Medicinal Cannabis: Evidence for Pain

- Pre-Modern use for pain
- Experimental Pain
- Modern studies of pain
  - Limited & small studies
  - Best evidence: neuropathic pain
  - Wide variation in study product

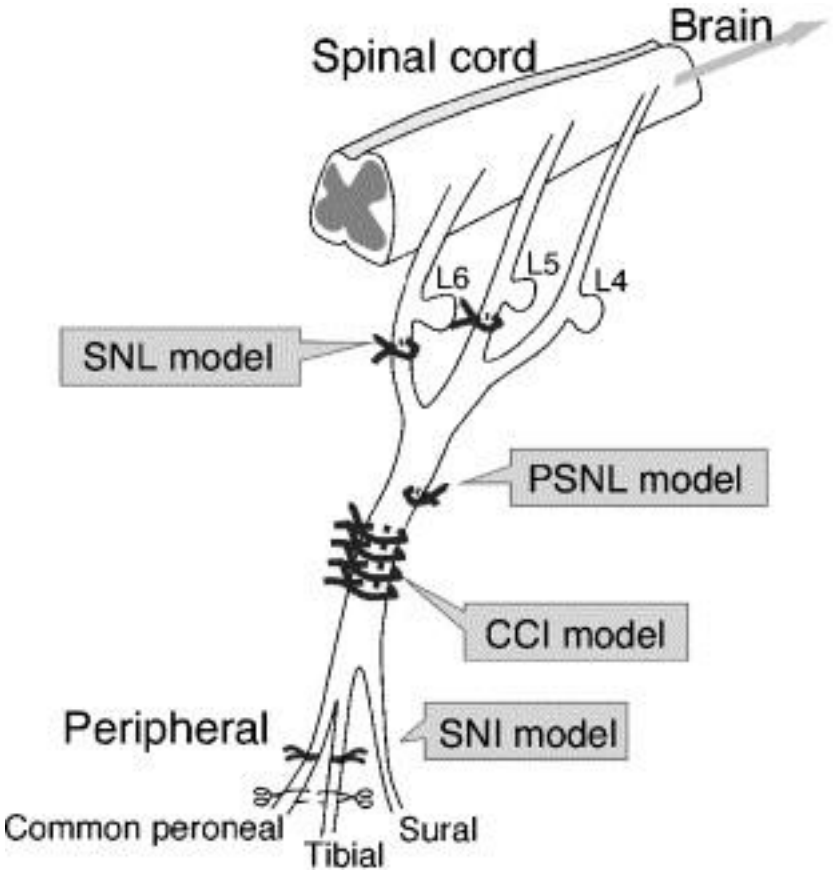
# THC shown to be effective in all peripheral neuropathic pain models

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

Diabetes
- Streptozotocin

Chemotherapy
- Paclitaxel
- Cisplatin
- Vincristine

HIV neuropathy




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

Image from Nature Reviews Immunology 2007 http://www.nature.com/nri/journal/v7/n9/fig_tab/nri2153_F3.html

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

Received
20 December 2010
Accepted
7 March 2011
Accepted Article

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/bph.2011.163.issue-1

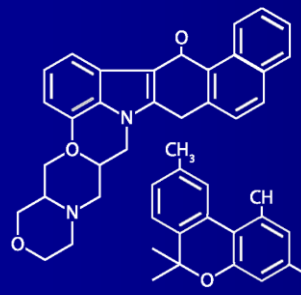
Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis.

[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.



# CMCR

Center for Medicinal Cannabis Research
University of California

**Founded in 2000** (State of California SB 847): ***The longest-running*** *clinical cannabis research center in the United States*

Mission: To facilitate high quality scientific studies to ascertain the safety and efficacy of cannabis and cannabinoid products and examine alternative forms of administration. More broadly, to determine the health effects of cannabis.

**Director:** I. Grant, MD; **Co-Directors:** T. Marcotte, PhD & J.H. Atkinson, MD
**Investigators:** David Grelotti, MD; Robert Fitzgerald, PhD; Mark Wallace, MD; Kristin Cadenhead, MD; Ron Ellis, MD, PhD; Emily Gray, MD; Brook Henry, PhD; Walter Kaye, MD; Alysson Muotri, PhD; Fatah Nahab, MD; William Perry, PhD; Nathaniel Schuster, MD; Gabriel Silva, PhD; Ji Sun, PharmD; Doris Trauner, MD; Jared Young, PhD

## Resources

- Guidance regarding regulatory pathways, study design, protocol standardization
- Data management/information systems
- Lab analyses (cannabinoids, endocannabinoids), specimen repository/processing
- Facilities and equipment, e.g., negative pressure rooms for administration of inhaled cannabis, driving simulation rooms, clinical exam rooms, cognitive testing

# CMCR Clinical Studies completed

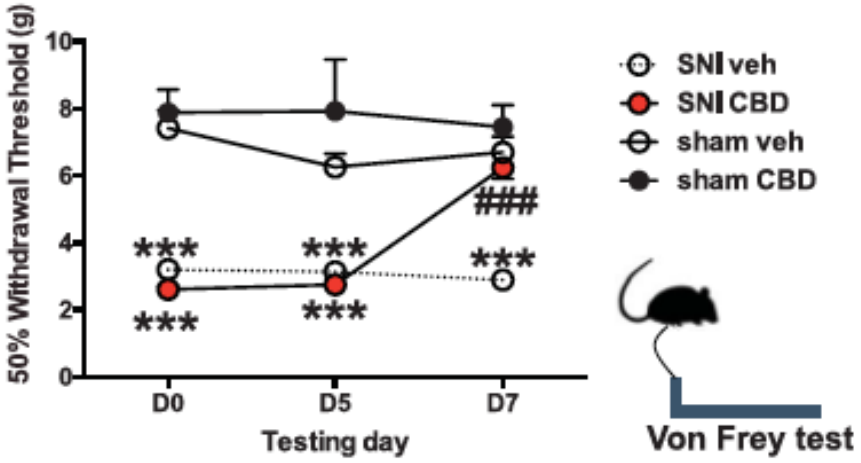
| SITE | DISORDER | DESIGN | N | DOSE (% THC) | Result |
|---|---|---|---|---|---|
| UCSD<br>Mark Wallace | Healthy Volunteers<br>(Experimentally-Induced Pain) | Crossover<br>RCT | 15 | 0%, 2%, 4%, 8% | + |
| UCSF<br>Donald Abrams | HIV Neuropathy,<br>Experimental Pain | Parallel Groups<br>RCT | 50 | 0%, 3.5% | + |
| UCSD<br>Ronald Ellis | HIV Neuropathy | Crossover<br>RCT | 28 | 0%, 1-8% | + |
| UCD<br>Barth Wilsey | Neuropathic Pain,<br>Experimental Pain | Crossover<br>RCT | 33 | 0%, 3.5%, 7% | + |
| UCD<br>Barth Wilsey | Neuropathic Pain | Crossover<br>RCT | 39 | 0%, 1.29%, 3.53%<br>(Vaporized) | + |
| UCSD<br>Jody Corey-Bloom | MS Spasticity | Crossover<br>RCT | 30 | 0%, 4% | + |
| UCSD<br>Mark Wallace | Diabetic Neuropathy | Crossover<br>RCT | 16 | 0%, 2%, 4%, 7% | + |

# CBD in pain

**Cannabidiol modulates serotonergic transmission and reverses both allodynia and anxiety-like behavior in a model of neuropathic pain**

PAIN

Sciatic Nerve Injury model; IV administration




**Plant-Based Cannabinoids for the Treatment of Chronic Neuropathic Pain**

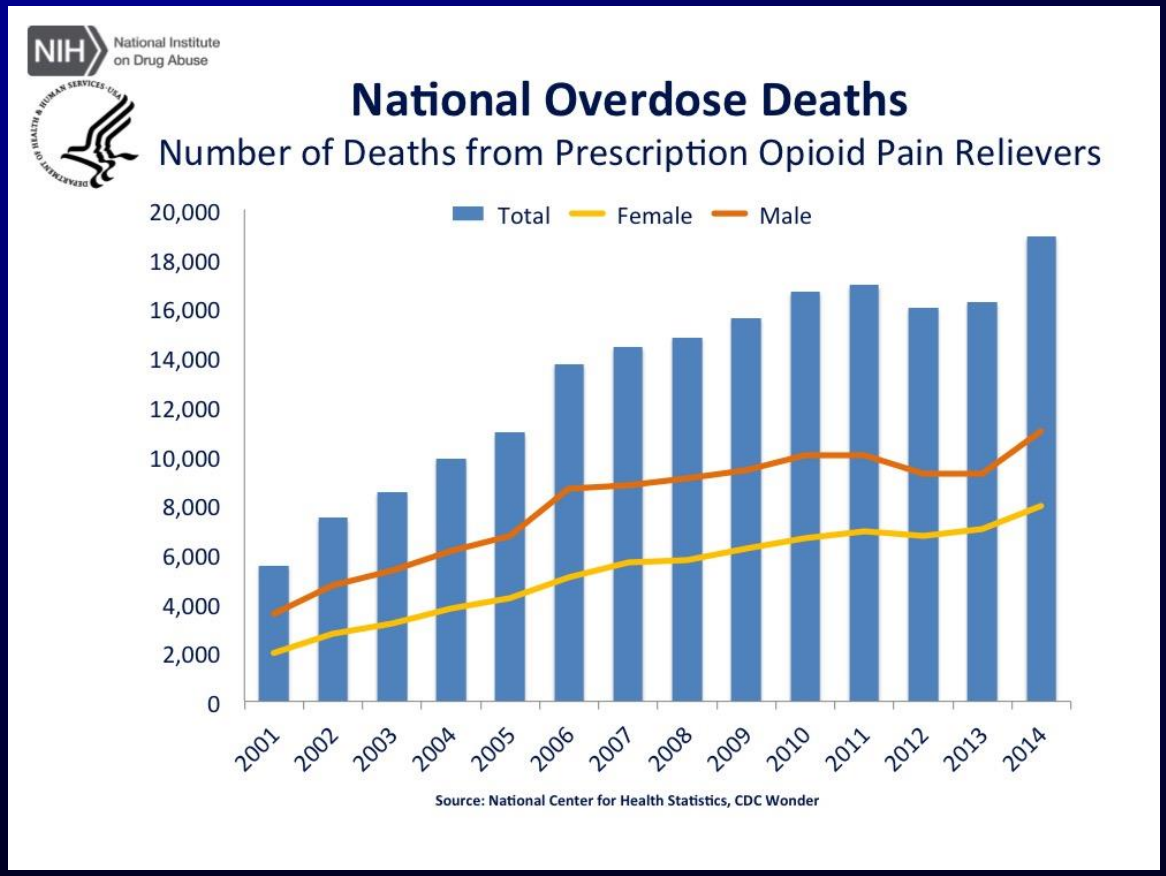
Sherelle L. Casey * and Christopher W. Vaughan

*Medicines* 2018, *5*, 67; doi:10.3390/medicines5030067

3. The Clinical Evidence for Cannabinoid Efficacy against Neuropathic Pain Is Poor

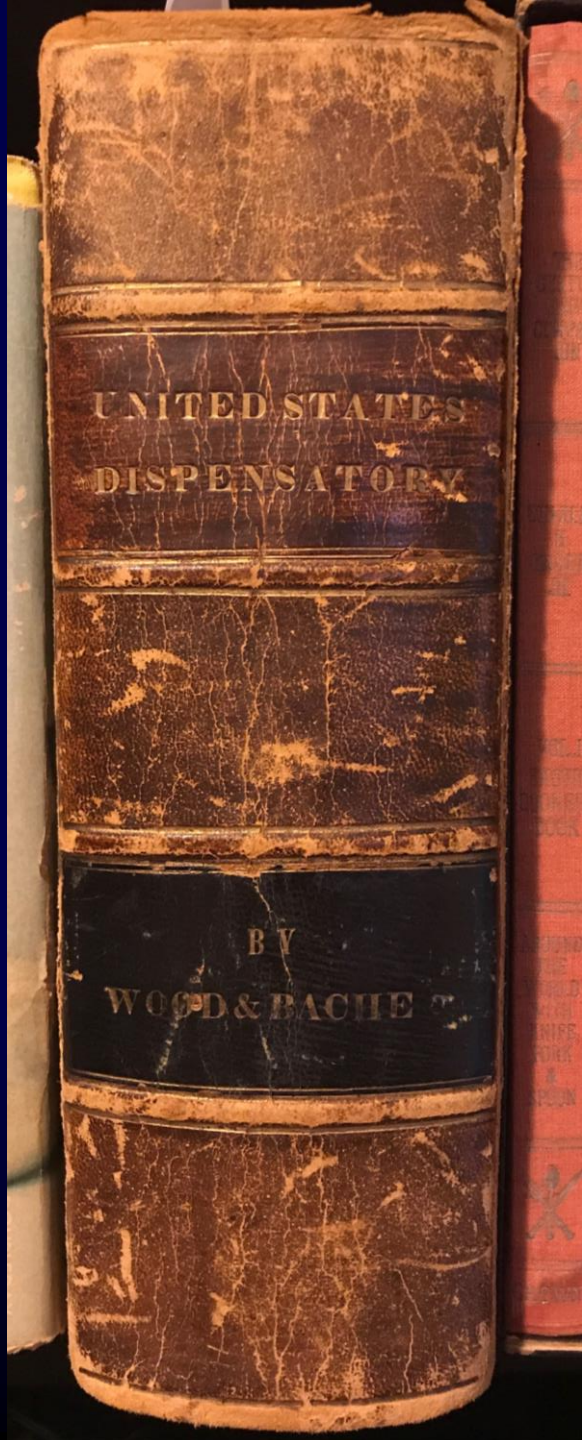
cannabidiol has a maximal analgesic effect (efficacy) that is only half of that observed for THC

# Prescription Opioid Deaths Continue to Rise



# 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



# AMA Policy Statement on MCT

**Amended AMA Policy:**

**AMA Policy Statement on Cannabis H-95.998:**

Our AMA believes that (1) cannabis is a dangerous drug and as such is a public health concern; (2) ~~sale of cannabis should not be legalized; (3)~~ public health based strategies, rather than incarceration, should be utilized in the handling of individuals possessing cannabis for personal use; and ~~(4)~~ (3) additional research should be encouraged.

# History of Opioids

- Opioids described favorably by ancient Sumerians and Egyptians (c 3400-1300 BC)
- Greek descriptions (c 460 BC) of harmful effects of opioids
- Galen recommended opium as a cure for many conditions (c AD 150-210)
- Opium introduced to China by Arab traders (c AD 400)
- Opium disappeared from European history record for 200 years (c AD 1300)
- Late 17th–18th centuries: reports of opium abuse described
- Sertürner (1803) synthesized morphine
- Wright synthesized heroin (1874)

# History of Opioids

- Early 20th century: Restriction of opioids
  - morphine addiction grows
  - "morphine maintenance" clinics proliferate
  - harsh legislation severely limits opioid availability
- 1960s–1990s: Rejustification of opioid use
  - growth of hospice and palliative care movements
  - growth of patients' rights movement
  - JCAHO guidelines
  - controlled clinical trials show opioid efficacy for acute and cancer pain
  - data suggest addiction potential possibly overstated
  - DEA, FDA, Federation of State Medical Boards, APS, AAPM, ASAM, ACR, AGS
    - all issue guidelines supporting appropriate use of opioids for chronic pain
- 1990s: **THE OPIOID CRISIS BEGINS**

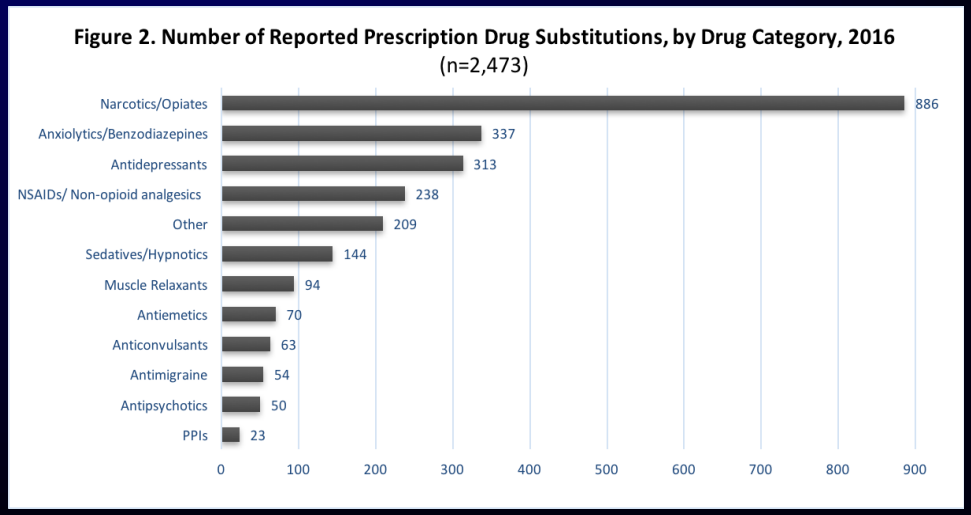
# Cannabis as a Substitute for Prescription Drugs

Jamie Corroon, ND, MPH; Laurie K Mischley ND MPH PhD; Michelle Sexton ND

- ‘‘Have you have ever used cannabis as a substitute for prescription drugs?’’ 46% responded “Yes” (n=2864)
  - A total of 2,473 substitutions were reported, or approximately 2 drug substitutions each
- Most common classes of drugs:
  - narcotics/opiates 35.8%
  - anxiolytics/benzodiazepines 13.6%
  - antidepressants 12.6%
  - NSAIDS 9.6%

**Females: 6x more likely**
**Medical Users: 4.6x more likely**
**Pain, anxiety and depression 1.3x**

Journal of Pain Research 2017:10 989–998



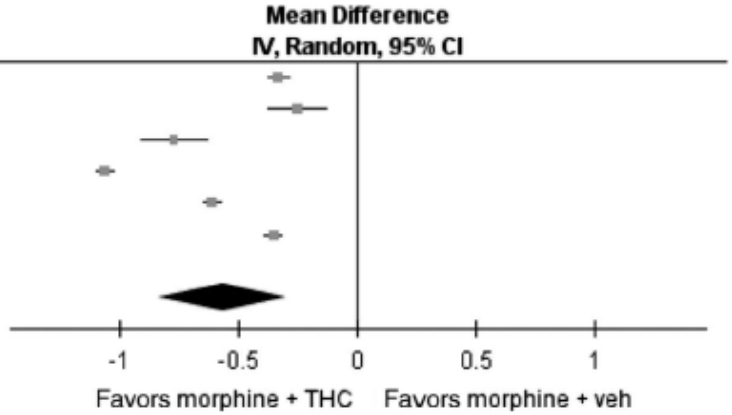
# Opioid-Sparing Effect of Cannabinoids: A Systematic Review and Meta-Analysis

"Cannabinoids, when co-administered with opioids, may enable reduced opioid doses without loss of analgesic efficacy."

| Study or Subgroup | Morphine + THC Mean | SD | Total | Morphine + Vehicle Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Cichewicz 1999 | 1.12 | 0.09 | 30 | 1.45 | 0.08 | 30 | 16.9% | -0.33 [-0.37, -0.29] |
| Cichewicz 2003 | 1.13 | 0.18 | 12 | 1.38 | 0.18 | 30 | 16.4% | -0.25 [-0.37, -0.13] |
| Cox 2007 | -0.39 | 0.17 | 7 | 0.38 | 0.17 | 28 | 16.2% | -0.77 [-0.91, -0.63] |
| Smith 1998 | 0.44 | 0.07 | 30 | 1.5 | 0.08 | 30 | 16.9% | -1.06 [-1.10, -1.02] |
| Welch 1992 | -0.82 | 0.07 | 96 | -0.21 | 0.19 | 120 | 16.9% | -0.61 [-0.65, -0.57] |
| Williams 2008 | 0.39 | 0.07 | 24 | 0.74 | 0.06 | 24 | 16.9% | -0.35 [-0.39, -0.31] |
| **Total (95% CI)** | | | **199** | | | **262** | **100.0%** | **-0.56 [-0.83, -0.29]** |

Heterogeneity: Tau² = 0.11; Chi² = 926.85, df = 5 (P < 0.00001); I² = 99%

Test for overall effect: Z = 4.10 (P < 0.0001)




**Reduced Opioid requirements when co-administered with cannabinoid (THC)**

# 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

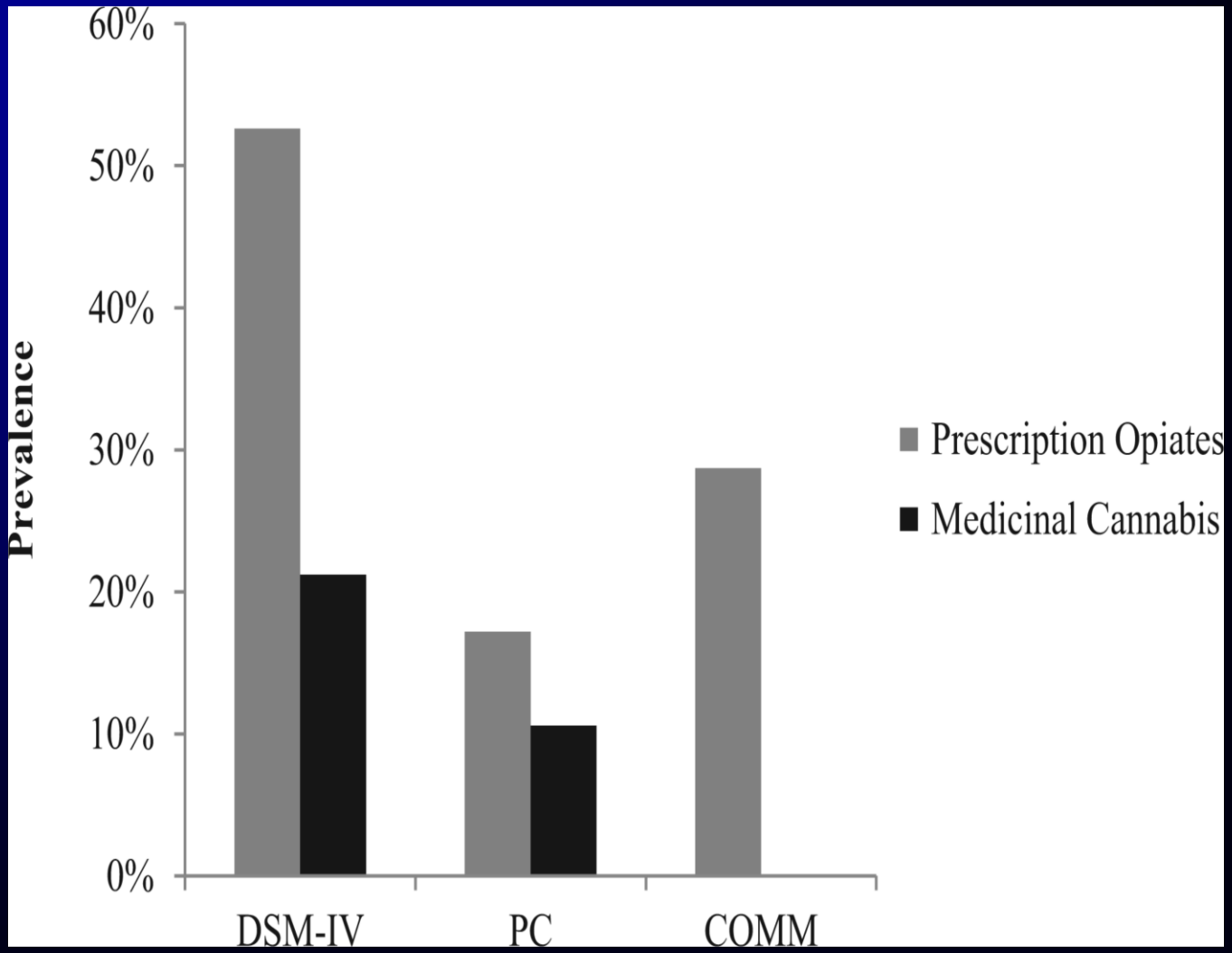
Cooper ZV, Haney M. Int Rev Psychiatry, 2009, 104-112

# Cannabis:
## Abuse Potential

- Although cannabis abuse is prevalent, animal studies show that cannabinoids do not seem to be as robust as other agents (heroine, cocaine, nicotine)

Cooper ZV, Haney M. Int Rev Psychiatry, 2009, 104-112

# Problematic Opioid vs Cannabis Use: Pain Patients




Feingold et al. Pain Med 2017;18(2):294-306

# Cannabis Tolerance

- With chronic cannabis use, tolerance develops to the physiological (i.e. cardiovascular) and subjective (i.e. highness) effects.

*Benowitz NL, Jones RT J Clin Pharmacol. 1981 Aug-Sep; 21(8-9 Suppl):214S-223S.*
*Hart CL, Haney M, Ward AS, Fischman MW, Foltin RW Drug Alcohol Depend. 2002 Aug 1; 67(3):301-9.*

# Cannabis:
## Dependence and Withdrawal

- Abrupt termination in habitual users results in withdrawal symptoms similar to opioids
- Dependent on the dose of THC consumed
  - Less likely to occur or symptoms less with lower dose consumption

*Haney M, Hart CL, Vosburg SK, Nasser J, Bennett A, Zubaran C, Foltin RW Neuropsychopharmacology. 2004 Jan; 29(1):158-70.*

# 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, Pyschoactive 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

| | Percentage Difference in Age-Adjusted Opioid Analgesic Overdose Mortality in States With vs Without a Law | | |
|---|---|---|---|
| | Primary Analysis | Secondary Analyses | |
| Independent Variable[a] | 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 hydrodocone

JAMA Int Med, 2018

# 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

Olfson, Am J Psychiatry, 2018

# 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

Campbell, Lancet Public Health, 2018

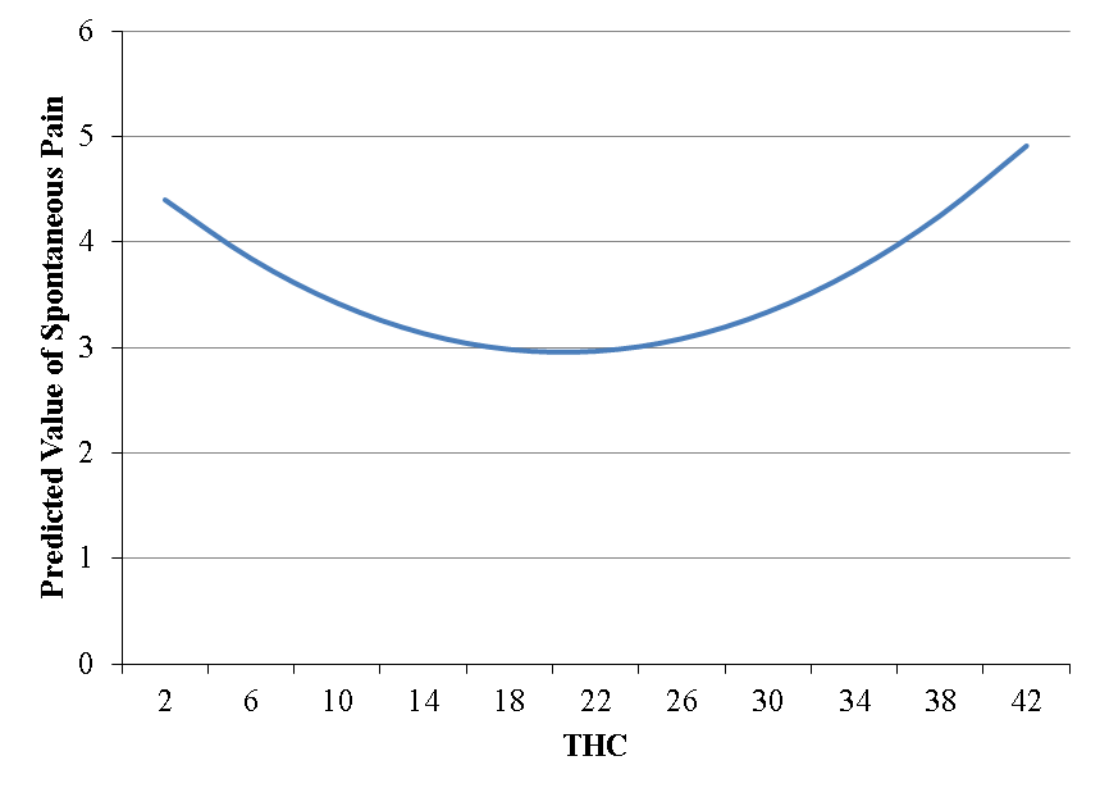
# Cannabis:
## Conditioned Placed Preference vs. Aversion

- 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



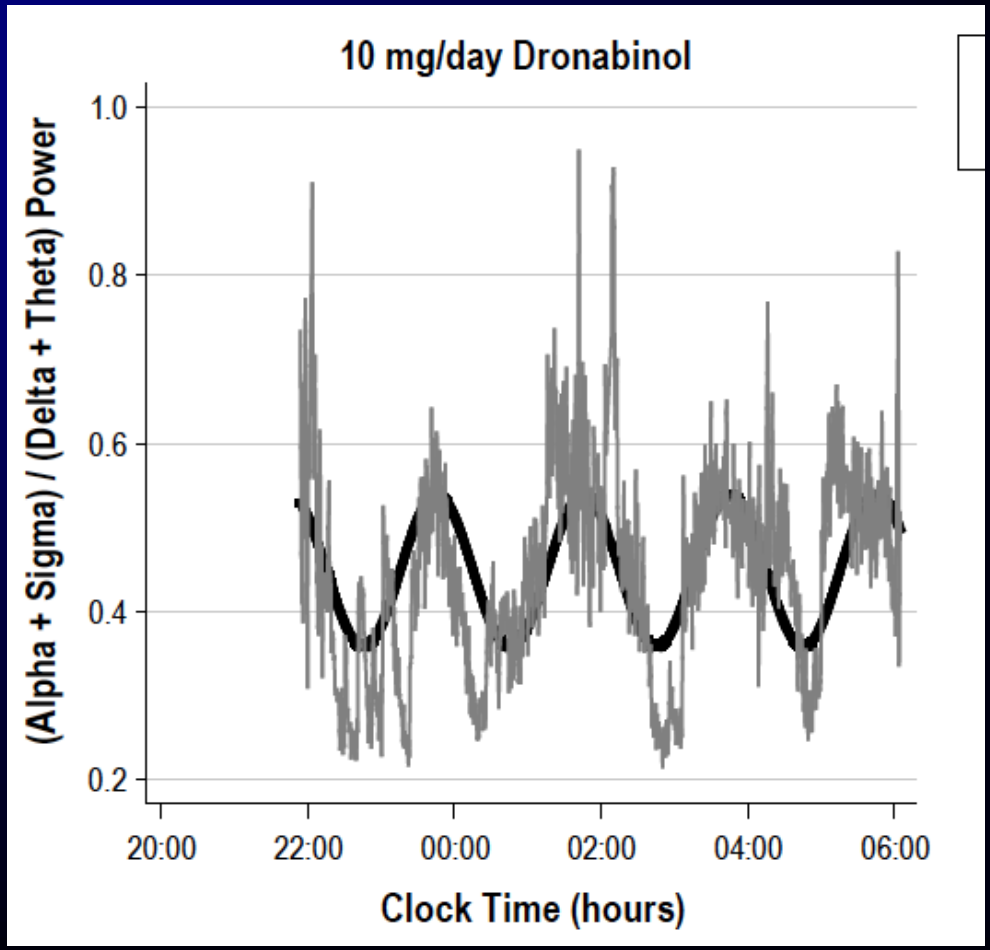
# Cannabinoids and Sleep

- Not much known about the effects on sleep
- THC and CBD biphasic and different doses affect sleep differently
- THC alone had no effect on sleep quality
- Low dose CBD is stimulating and reduced stage 3 and wakefulness
- High dose CBD is sedating
- No studies on combination therapy

**Nicholson A, et al. J Clin Pharmacol, 2004, 3:305-313

## 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




Journal of Clinical Sleep Medicine, Vol. 10, No. 1, 2014

# Patient Selection and Monitoring
## Still Unclear and Unanswered Questions

- Should they be as strict as opioids?
- Role of UDT
- Role of Patient Agreements
- Concurrent use of opioids or wean first
- Dosing

# UCSD Pain Clinic Approach to Medical Marijuana

- Failure of conservative therapies
  - Consider before chronic opioids
- Provide authorization via the DPH application
- Dosing consultation
- If using chronic opioids, start wean first
  - Consider introducing cannabis during wean for compliant patients
- Follow up: document type and dose if known
- Consider UDT

# THE END


I'M IN PAIN. CAN YOU GIVE ME SOME MEDICAL MARIJUANA?
WE'RE AGAINST IT. IT LEADS TO UNINTENDED CONSEQUENCES.
FLORIDA MEDICAL ASSO.
I'M PRESCRIBING OXYCONTIN INSTEAD.
SOUTH FLORIDA SUN SENTINEL
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