# The Role of Cannabinoids in Acute & Chronic Pain Treatment

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# The History & Science of Medicinal Cannabis

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# Financial disclosure

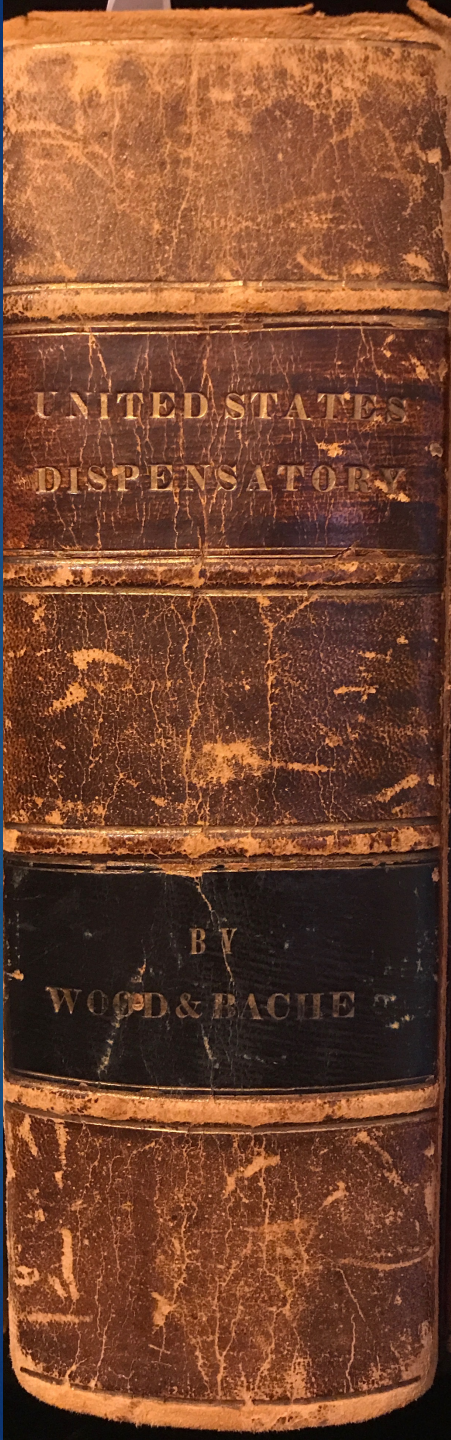
- UC San  receives educational grants for fellow salary& education from Medtronic, Boston Scientific,  Abbott, and Nevro
- We will discuss off-label usage of FDA approved medications

# Learning Objectives

- Explain the difference in evidence between THC and CBD in chronic pain
- Explain the difference in evidence between cannabinoids for acute pain and chronic pain

# 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

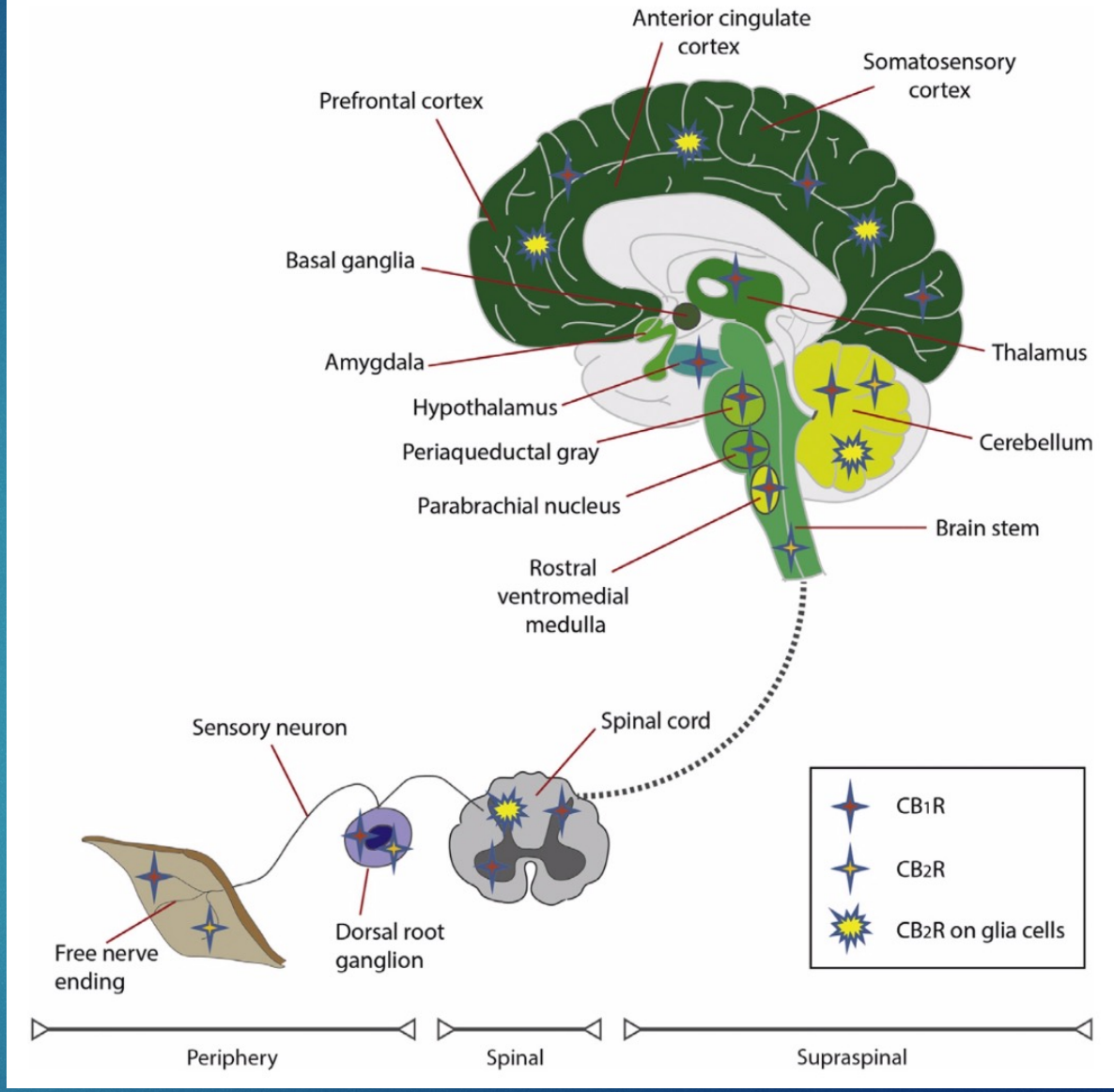

**Nabilone** (Cesamet)
schedule II
FDA approved for:
chemo nausea

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

**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




Starowicz K, Finn D. Cannabinoids and Pain: Sites and Mechanisms of Action. In Advances in Pharmacology; Vol 80; 2017: 437-475

# THE ENDOCANNABINOID SYSTEM

**Implicated in processes such as pain, perception, mood, memory and reward.**
**To provide that we:**

**EAT**

**SLEEP**

**RELAX**

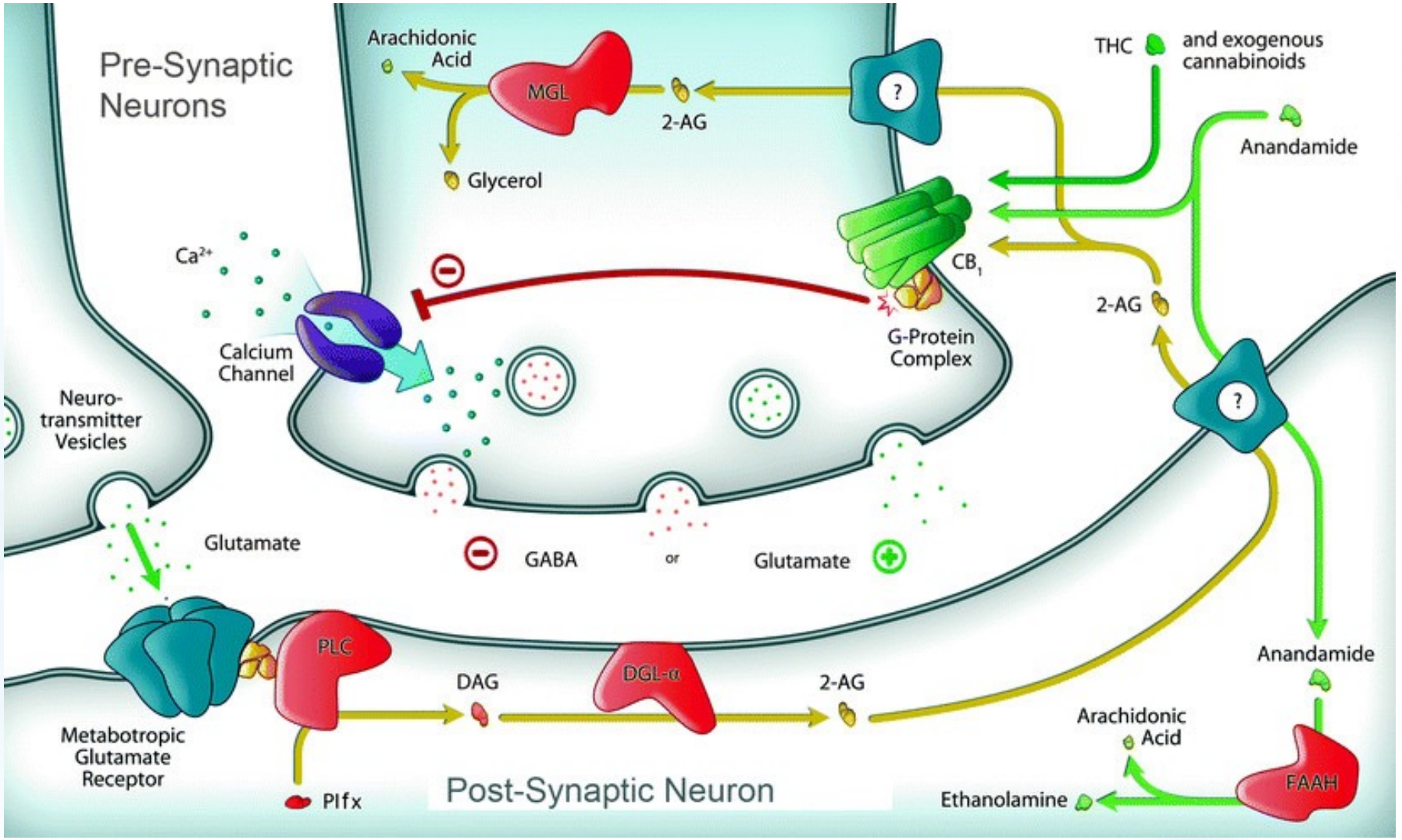
**FORGET**


**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



# Cannabidiol

- **No studies** reporting analgesic effects of CBD in humans.
- CBD has been shown to have **anxiolytic** effects. ($5HT1_A$)
- 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)

# THC

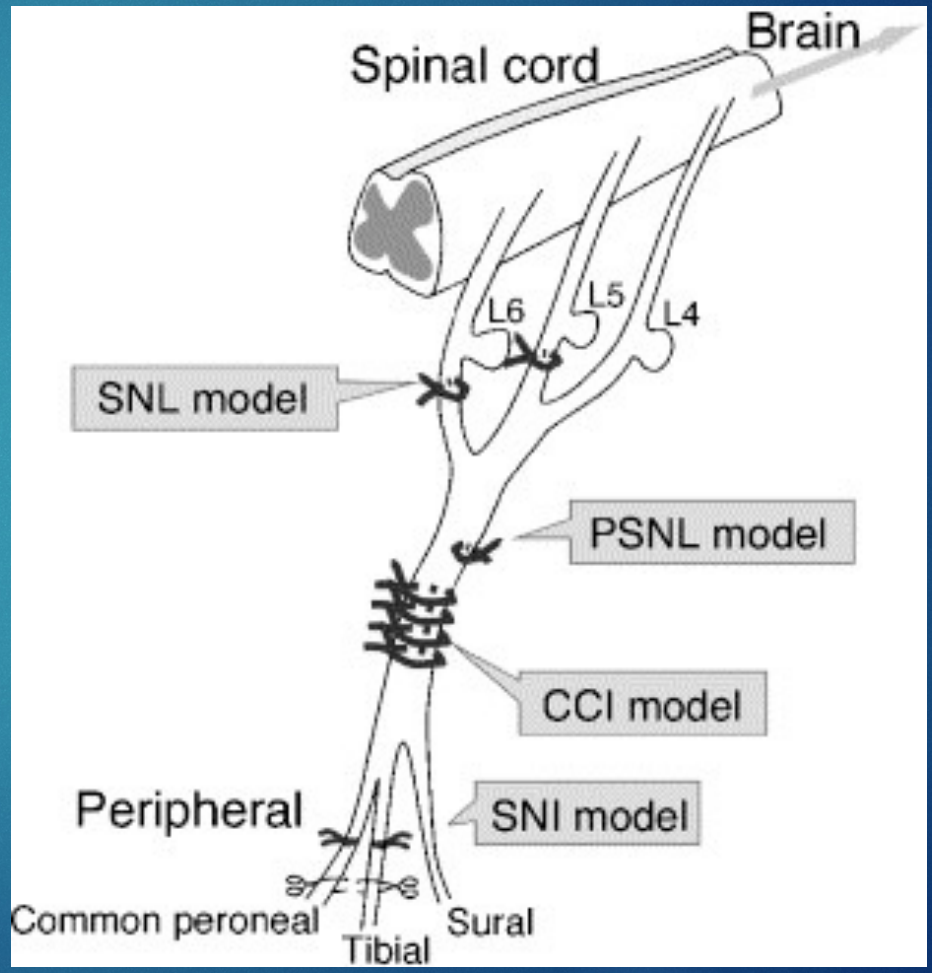
- **analgesic** effects of in humans.
- **anxiolytic** (dose related).
- **anti-inflammatory** effects.
- Agonist at both **$CB_1$ and $CB_2$**
- modulate **dopamine mechanisms**
- **Low Dose** can be effective- CBD may "synergize" and allow for lower dosing

# 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



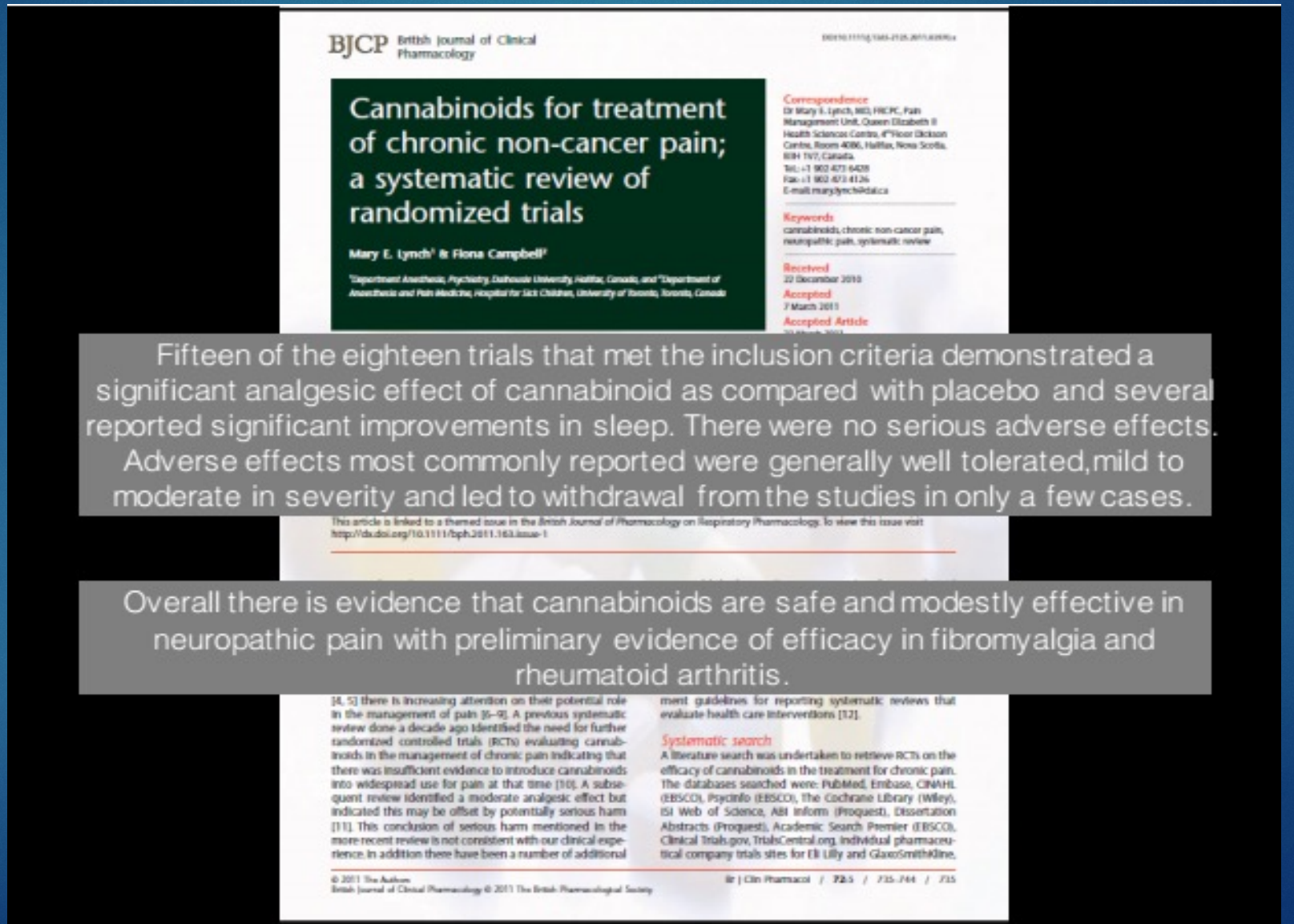

Pharmacology & Therapeutics. Volume 109, Issues 1–2, January 2006, Pages 57–77

# …and in other pain models

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

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

# Systematic Review Cannabinoids Chronic Non-Cancer Pain



BJCP British Journal of Clinical Pharmacology

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

Mary E. Lynch & Fiona Campbell

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.

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

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

# Meta-Analysis Chronic 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
- Barakji et al (2023 *PLoS One)*
  - Cannabis vs placebo for (any) pain
  - 65 RCT studies included
  - Reduced pain & improved sleep (stat signf, but not clinically signif)
- McParland et al, (2023 *RAPM*)
  - 8 RCT Cannabinoids on sleep & neuropathic pain
  - Improved sleep and pain; incr risk of daytime somnolence, dizziness, nausea

Andreae et al. Pain. 2015 Dec;16(12):1221-1232
Stockings et al. Pain. 2018 Oct;159(10):1932-1954
Barakji et al. Plos One. 2023 Jan 30;18(1)
McParland et al. RAPM. 2023 Apr;48(4):180-190

# RCTs of Inhaled Cannabis in Pain

| Author/ Year | N= | Indication | Duration/type | Outcome |
|---|---|---|---|---|
| Abrams 2007 | 50 | HIV neuropathy (vaporized cannabis) | 5 days/DB | **Positive:** Decreased pain and hyperalgesia |
| Wallace 2015 | 16 | Diabetic Peripheral Neuropathy (vap cannabis) | Single dose/DB/ Crossover | **Positive:** Decreased pain |
| Wilsey 2008 | 38 | Neuropathic pain (vaporized cannabis) | Single dose/DBC | **Positive:** Decr pain w/ highest dose, but significant psychoactive effects |
| Ellis 2009 | 34 | HIV neuropathy (vaporized cannabis) | 5 days/DB | **Positive:** Improved pain vs placebo, |
| Wilsey 2016 | 42 | Spinal cord injury (vaporized cannabis) | Single dose/crossover | **Positive:** Decr pain, no difference between low and high dose |
| Abrams 2020 | 23 | Sickle Cell Disease (vaporized cannabis) | TID x 5 days/DB crossover | **Negative:** No statisc signf change in pain or pain interference |
| Almog 2020 | 27 | Neuropathic pain/CRPS (metered inhaler 0.5mg & 1mg THC) | Single dose, Rand DB, PC, crossover 3 arm | **Positive**: 1mg dose signf reduc pain vs placebo |

# 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 | Periph neuropathic pain | 5 weeks | **Positive:** Decreased pain and allodynia |
| Ernst 2005 | 65 | Cannador | PHN | 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 Neuropathic Pain

| Author/ Year | N= | Agent | Indication | Duration/type | Outcome |
|---|---|---|---|---|---|
| Zubcevic 2023 | 118 | Oral THC, oral CBD, oral THC/CBD | Neuropathy, PHN, Perip nerve injury | 8 weeks rand, DB, 4 arm | **Negative**: no diff from placebo |
| Chaves 2020 | 17 | THC oil | Fibromyalgia | 8 weeks, Rand, DB, PC | **Positive**: signif dif on FIQ scores (pain, feel good, do work, fatigue) |

# 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 | Nabiximols | Cancer Pain | 2 weeks, Rand, DB, Parallel | **Positive**: Decreased pain |
| Portenoy 2012 | 360 | Nabiximols | Cancer Pain | 5 weeks, Rand, DB, PC, Parallel | **Positive:** Decreased pain in low and middle dose |
| Lichtman 2018 | 397 | Nabiximols | Cancer Pain | Phase 2/3, rand, DB, PC, self titr 2 wk, 3 wk tx phase | **Negative:** primary end pt not met; multiple secondary end pts met in US grp |

# 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, $p=0.63$)

Hickernell TR et al. The Journal of Arthroplasty 2018, 33:3637-3641

Trauma Surg Acute Care Open. 2020 Feb 9;5(1)

# 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

Abdallah FW, et al. Reg Anesth Pain Med 2020;45:509–519.

# 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

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

**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

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

Jefferson et al. J Psychoactive Drugs. 2013; 45(3)

**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

Flisberg et al. Eur J Anesth. 209;0 26:192-195

# 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. Wijeysundera, 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*

# ASRA Perioperative Guidelines

## Question/Recommendation

- 1) Should surgery patients be screened for cannabis use?
  - Universal screen for cannabinoid use; Include type, freq, & last use
  - No rec for universal UDS
- 2) Evidence to continue or stop cannabinoids or delay surgery?
  - Counsel pts on risks of periop cannabinoids
  - Delay elective surgery for intoxication
  - Delay elective surgery for at least 2 hrs after smoking due to incr risk of MI;
  - Other routes of administration & elective surgery weigh risks of periop CV events
- 3) Chronic cannabinoid & opioid use, do you taper cannabinoids?
  - Counsel freq users re: post-op pain risk;
  - No rec made re: tapering
- 4) Specific concerns re: chronic use in parturients?
  - Counsel pregnant pts re: risks to fetus/neonate and discourage use during pregnancy/immediate post-partum
- 5) Should doses of anesthetics & analgesics be adjusted?
  - consider adj induction/maint doses based on clinical presentation/timing of last cannabinoid use

Shah S, Schwenk ES, Sondekoppam RV, *et al*. ASRA pain medicine consensus guidelines on the management of the perioperative patient on cannabis and cannabinoids. *RAPM*. Jan 2023

# ASRA Perioperative Guidelines

## Question/Recommendation

- 6) Does acute or chronic cannabis use req adjustment of vent settings to accommodate for possible V/Q mismatch, or other pathology?
  - Oral cannabinoids don't require adj of vent settings;
  - Chronic inhaled use may require vent setting adj c/w obstructive lung disease
  - Insufficient evidence re: acute use
- 7) Any special post-op considerations?
  - No rec for additional post-op monitoring but rec incr vigilance for cardiac/neurovascular events;
  - Rec multimodal analgesia
- 8)Any considerations for chronic cannabinoid + opioid use and should opioid Rx post-op be adjusted?
  - Opioids should be administered when indicated for post-op pain with incr vigilance
  - Insufficient evidence to rec adjusting post-op opioid regimen
- 9) How does cannabis withdrawal present and evidence for treatment
  - Counsel pts re: risk of CWS and monitor for withdrawal
  - Consider using dronabinol for CWS

Shah S, Schwenk ES, Sondekoppam RV, *et al*. ASRA pain medicine consensus guidelines on the management of the perioperative patient on cannabis and cannabinoids. *RAPM*. Jan 2023

# The Clinical Practice of Medical Cannabis

MARK S. WALLACE, M.D.
PROFESSOR OF ANESTHESIOLOGY
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Review Article

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

Suzanne Nielsen[*,1,2], Pamela Sabioni[3], Jose M Trigo[3], Mark A Ware[4], Brigid D Betz-Stablein[5], Bridin Murnion[6,7], Nicholas Lintzeris[2,6], Kok Eng Khor[8], Michael Farrell[1], Andrew Smith[9] and Bernard Le Foll[3]

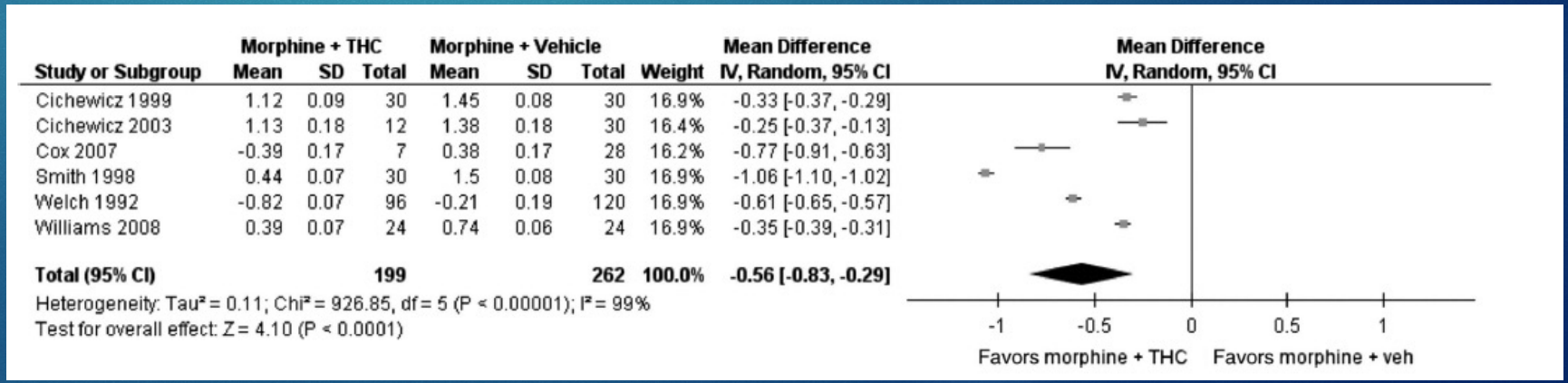
Neuropsychopharmacology (2017), 1–14

**19 preclinical studies: 14 studied THC and 10 other synthetic agonists of $CB_1R$**

- 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



| 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: $Tau^2 = 0.11$; $Chi^2 = 926.85$, df = 5 ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: $Z = 4.10$ ($P < 0.0001$)

Mean Difference
IV, Random, 95% CI

-1 -0.5 0 0.5 1

Favors morphine + THC Favors morphine + veh

# 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

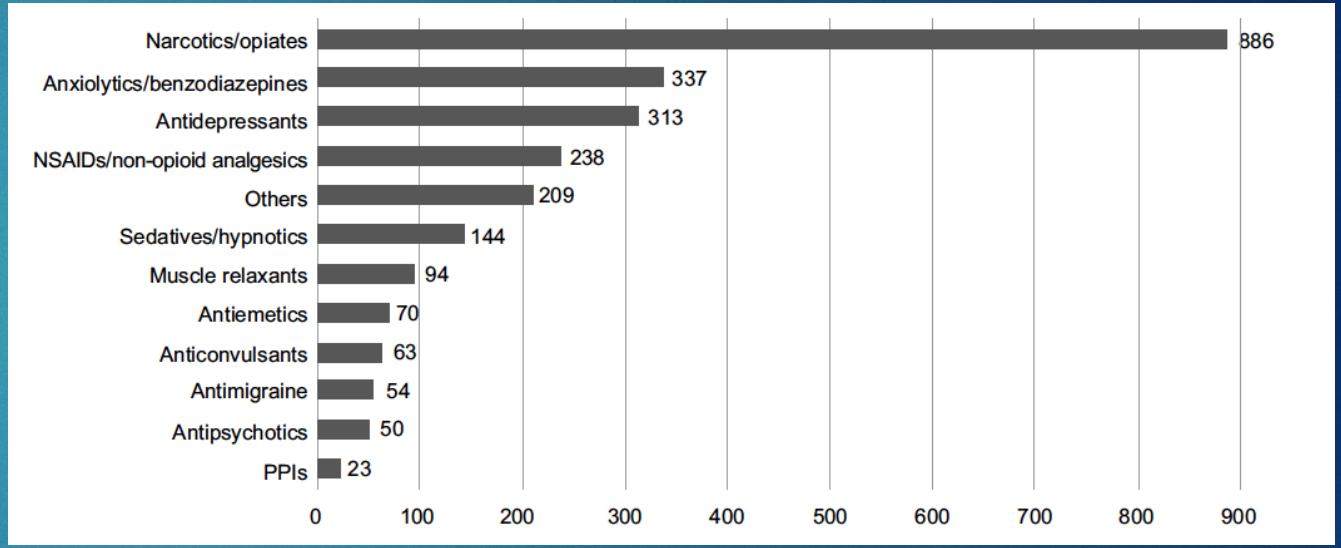
Cooper ZV, Haney M. Int Rev Psychiatry, 2009, 104-112

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

# The Good

# Cannabis as a substitute for prescription drugs – a cross-sectional study

46% reported substitution of Rx drugs (1248/2774)




- The odds of reporting substituting were 4.59 (95% CI, 3.87–5.43) greater among medical cannabis users compared with non-medical users
- 1.66 (95% CI, 1.27–2.16) greater among those reporting use for managing the comorbidities of pain, anxiety and depression

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

Research

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; $R^2 = 0.873$.

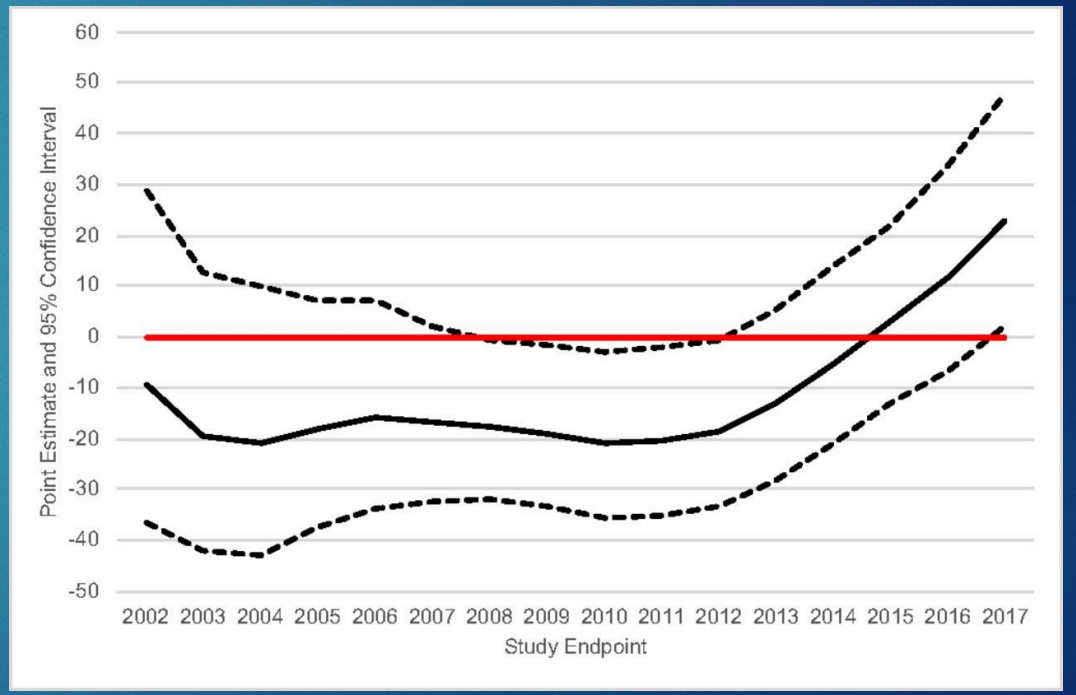
[d] Findings include all heroin overdose deaths, even if no opioid analgesic was involved. All covariates were the same as in the primary analysis. $R^2 = 0.842$.

[e] $P \leq .05$.

[f] $P \leq .001$.

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

**Canges in point estimate and 95% CI of association between medical cannabis law and age-adjusted opioid overdose death rate by the last year included in the analysis since 1999.**




Chelsea L. Shover et al. PNAS 2019;116:26:12624-12626

## 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

# 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

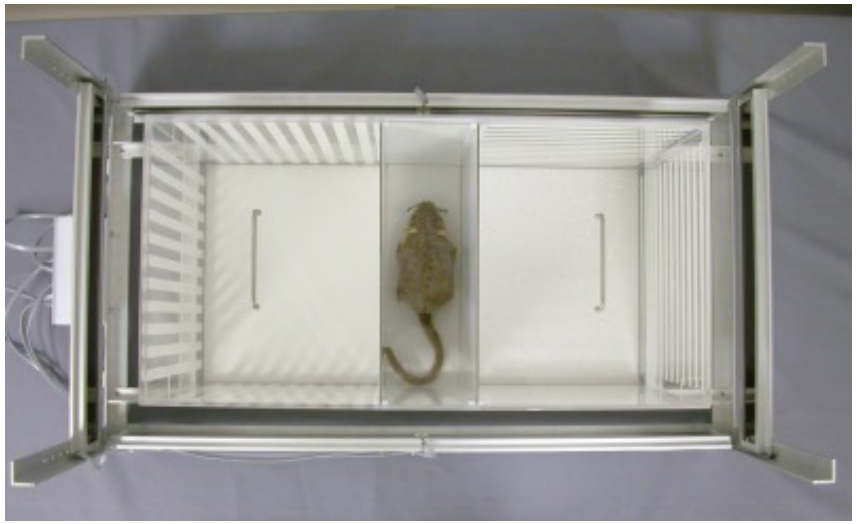
# Effect of cannabis use in chronic pain patients prescribed opioids

- 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



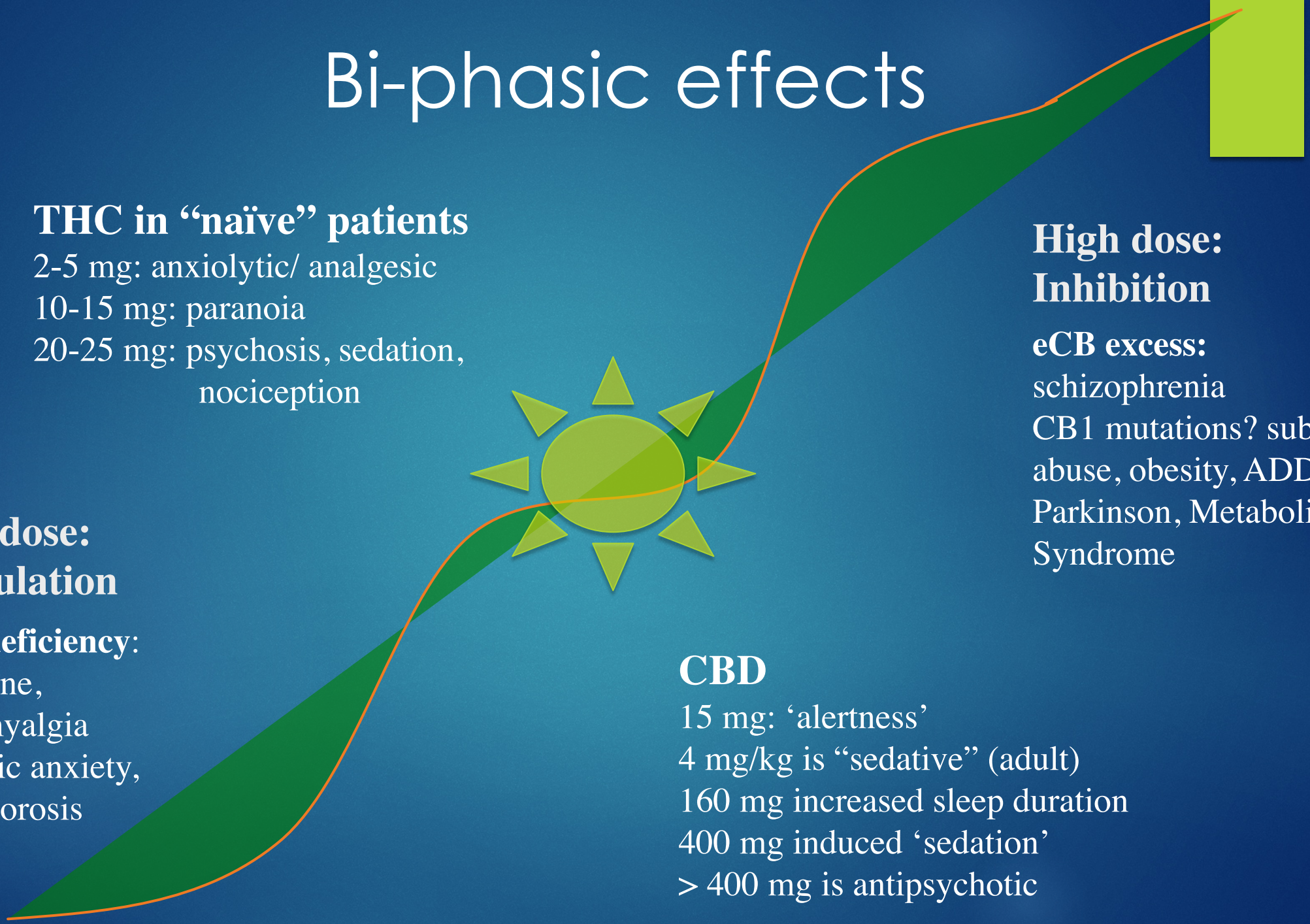

*Braida D, Pozzi M, Cavallini R, Sala M Neuroscience. 2001; 104(4):923-6*

*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.*

# Bi-phasic effects

**THC in "naïve" patients**
2-5 mg: anxiolytic/ analgesic
10-15 mg: paranoia
20-25 mg: psychosis, sedation, nociception



**High dose: Inhibition**

**eCB excess:**
schizophrenia
CB1 mutations? sub abuse, obesity, ADD, Parkinson, Metabolic Syndrome

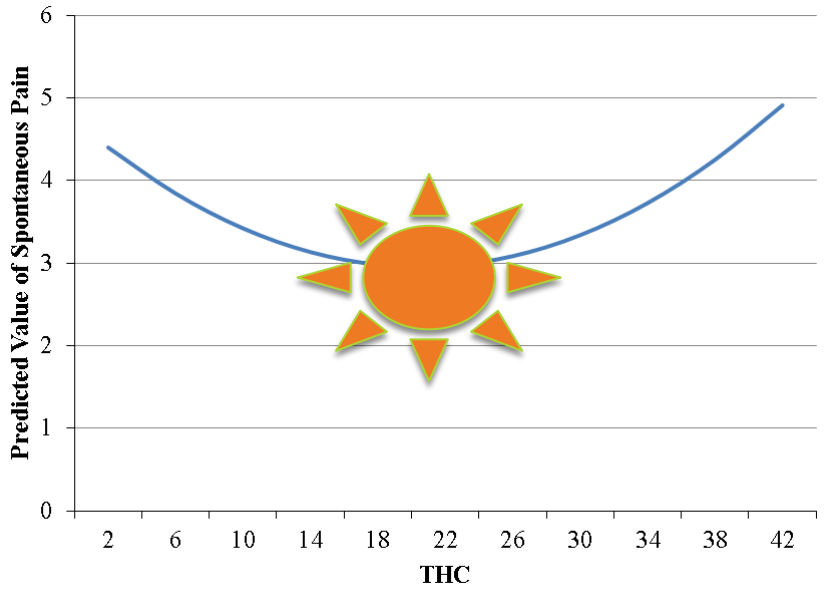
**Low dose: Stimulation**

**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

# THC Plasma Levels and Pain Relief

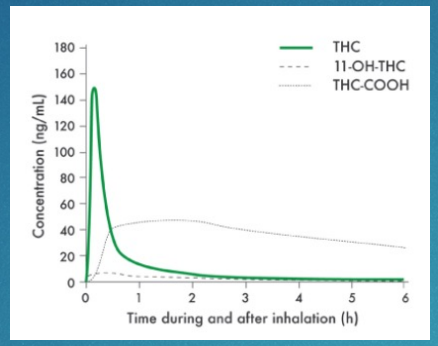
Therapeutic window of pain relief occurs between 16-31 ng/ml (plasma level of THC)

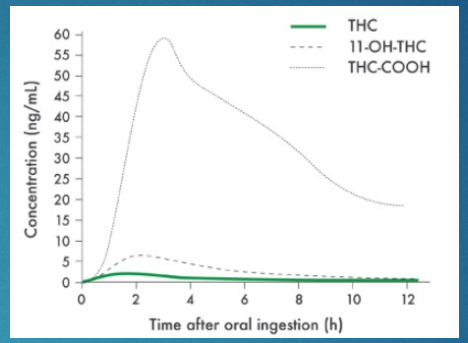



Wallace et al, J Pain, 2020

# Cannabis Pharmacology and Dosing

- Inhalation
- Ingestion
- Topical




Grotenhermen F. Clin Pharmacokinet. 42, 2003

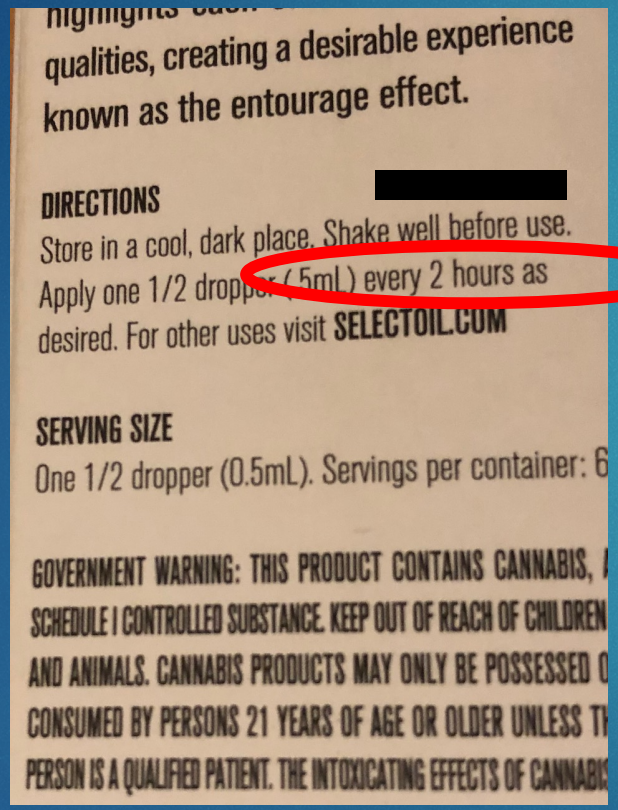

**Primary benefit from THC**

There is no human data to support CBD as an analgesic

- Patients report little to no benefit
- Placebo controlled study showed no benefit of CBD in acute low back pain (Bebee, Med J Aust, 2021)
- Hi dose CBD has shown elevated LFTs

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

# Pitfalls for Patients


qualities, creating a desirable experience known as the entourage effect.

**DIRECTIONS**

Store in a cool, dark place. Shake well before use. Apply one 1/2 dropper (.5mL) every 2 hours as desired. For other uses visit **SELECTOIL.COM**

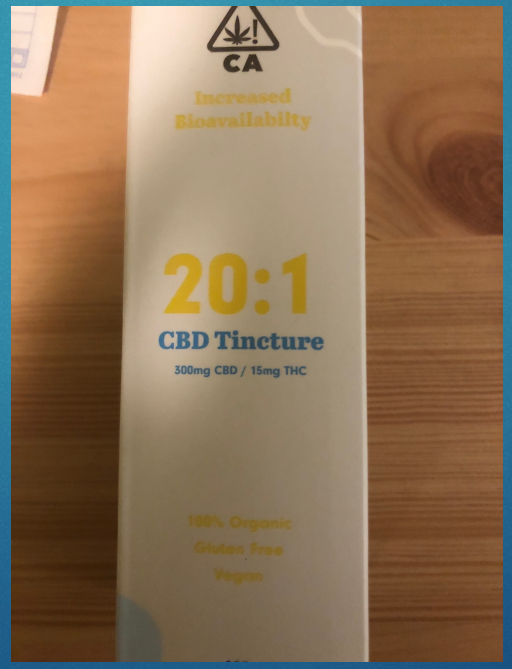
**SERVING SIZE**

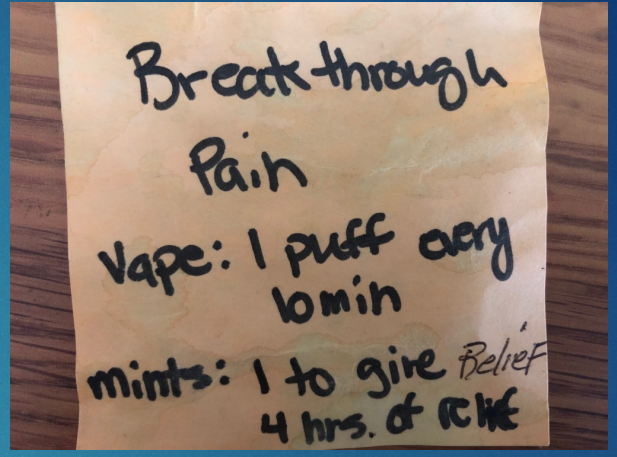
One 1/2 dropper (0.5mL). Servings per container: 6

GOVERNMENT WARNING: THIS PRODUCT CONTAINS CANNABIS, A SCHEDULE I CONTROLLED SUBSTANCE. KEEP OUT OF REACH OF CHILDREN AND ANIMALS. CANNABIS PRODUCTS MAY ONLY BE POSSESSED O CONSUMED BY PERSONS 21 YEARS OF AGE OR OLDER UNLESS TH PERSON IS A QUALIFIED PATIENT. THE INTOXICATING EFFECTS OF CANNABIS

Conflicts of interest on behalf of retail salespersons.

**Hemp:**
**Full Spectrum**
**Isolate**
**Broad Spectrum**




Shifts in potency 60-85% (10x)

# Inhalation

1) **Temperature** of the vaporizer: start with 175 C. and increase incrementally by 5 degrees at a time.

2) **Potency** (ratio of CBD to THC flower)

3) **Duration and number** of inhalations

# Oral Dose titration*

**Day (increase as needed, to tolerance)**
Day 1: 1.25 mg (THC) twice per day.
Day 4: Increase to 2.5 mg twice per day
Day 7: Increase to 3.75 mg twice per day
**Night**
2.5 mg (THC) - directly upon getting into bed
After 3 nights, if no improvement in sleep / pain, increase to 5 mg

* typically 1:20 ratio with CBD daytime; 1:1 ratio at nighttime

# Contamination

# Heavy Metals

PLoS One. 2015 Sep 25;10(9)
**Strategies to Reduce Tin and Other Metals in Electronic Cigarette Aerosol.**

- Nano-metal particles from the heated coil
  - Tin, copper, cadmium, nickel, aluminum titanium, zinc

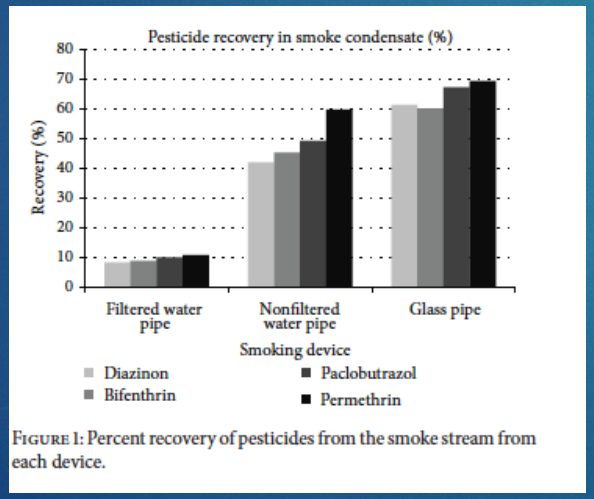



FIGURE 1: Percent recovery of pesticides from the smoke stream from each device.

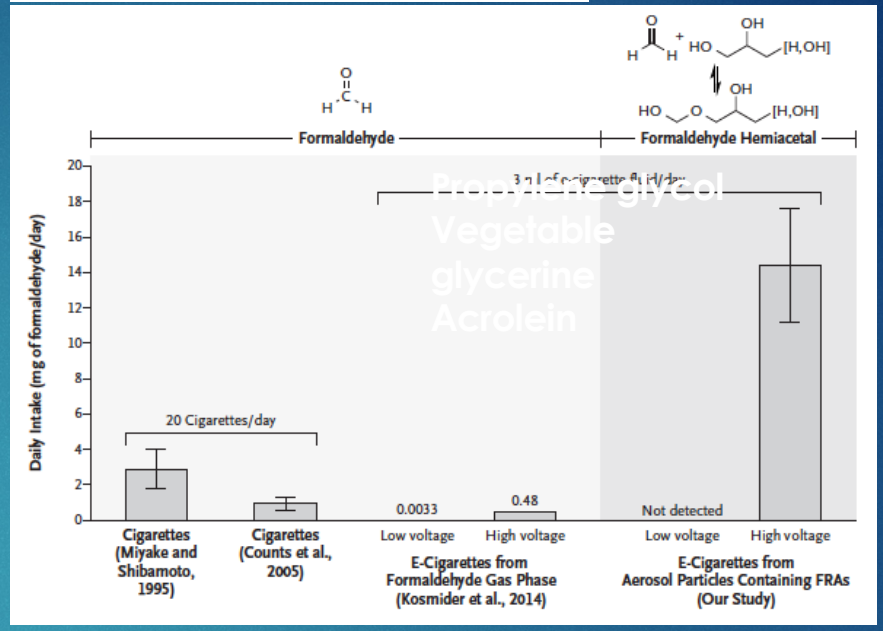
**Determination of Pesticide Residues in Cannabis Smoke**

Nicholas Sullivan, Sytze Elzinga, and Jeffrey C. Raber

Journal of Toxicology
Volume 2013, Article ID 378168, 6 pages
http://dx.doi.org/10.1155/2013/378168

## Hidden Formaldehyde in E-Cigarette Aerosols

N ENGL J MED 372;4 NEJM.ORG JANUARY 22, 2015




## Pesticides, aflatoxins, residual solvent

**"Pesticide Contamination of Cannabis in the Legal Market"**
Ethan Russo, 2016 ICRS

- 22 concentrates
- 4 flower
- 84.6% tested positive for pesticides
- Many had multiple contaminants

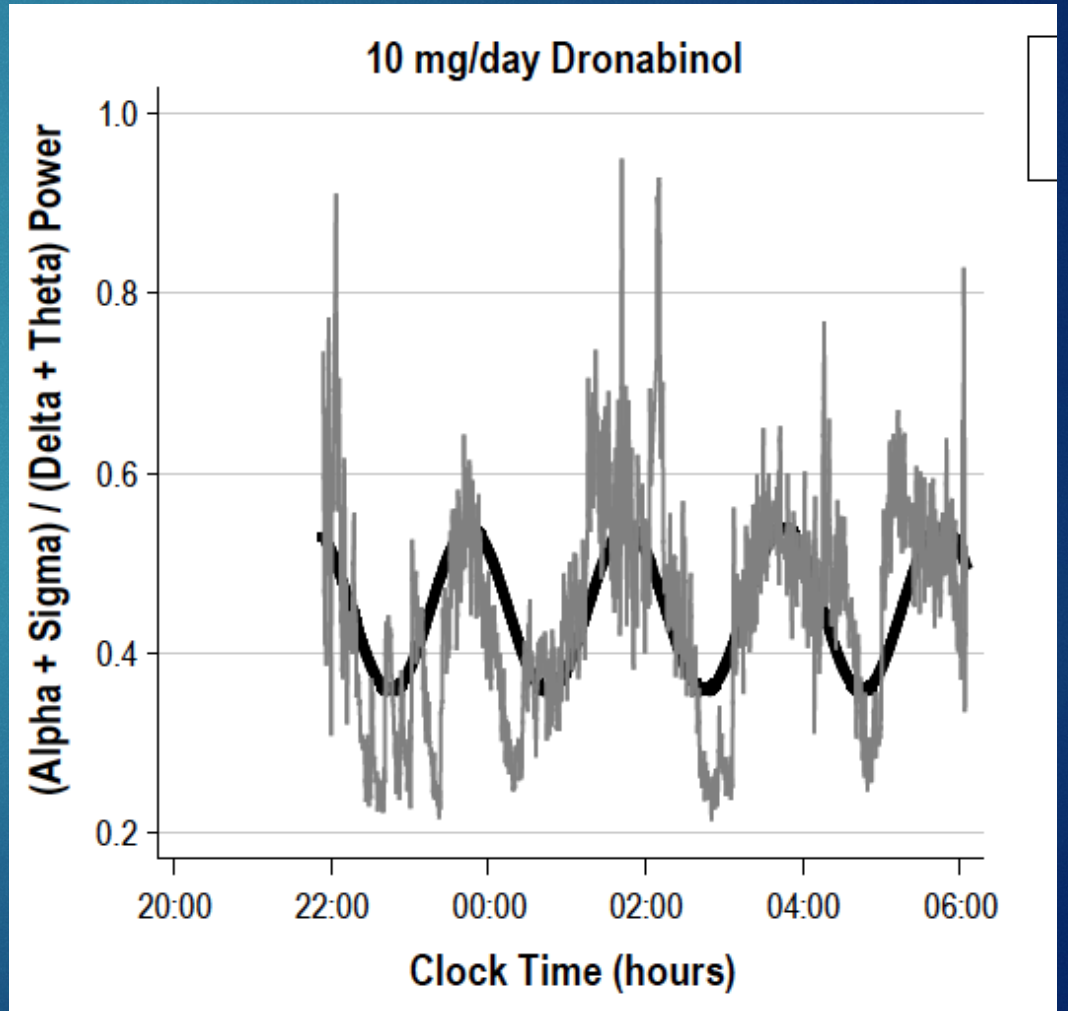
# Cannabis Product Testing in California

- 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, myocotoxins, heavy metals

# Cannabis and Obstructive Sleep Apnea

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

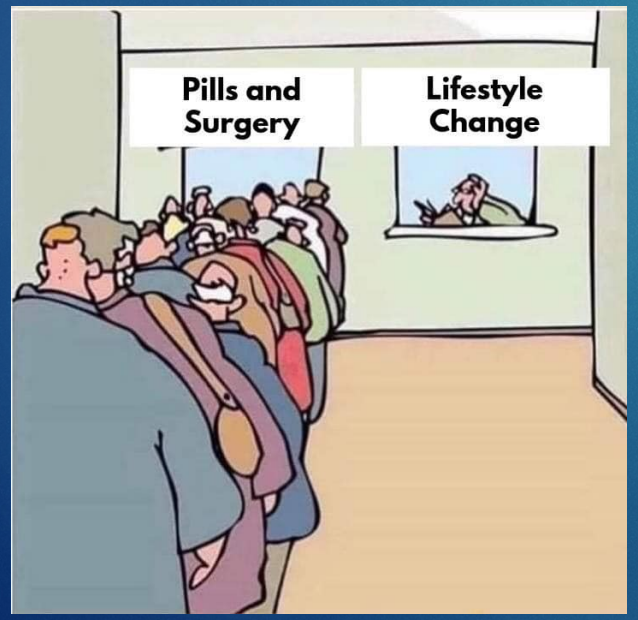
- N=20 subjects:  2.5 mg THC; 10 mg THC and placebo
- Dronabinol was safe and well-tolerated for OSA
- Decreased Sleep Latency
- Reduced AHI
- Strengthened ultradian rhythm




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

# 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.


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.


Study: More senior citizens using pot...
REALLY FEELING MY JOINTS TODAY...
ME, TOO!
DAVE GRANLUND© www.davegranlund.com

# THE END