Weighing Risks and Benefits of Cannabis in Treatment of Chronic Pain

Brant Hager, MD

Associate Professor of Psychiatry

University of New Mexico

Disclosure

- No conflicts of interest to disclose

Learning Objectives

By the end of this talk, participants should be able to:

- Appreciate basic cannabinoid neurobiology pertaining to anti-nociception
- Cite relative efficacies of cannabinoids, opioids, duloxetine, pregabalin, and NSAIDs in chronic pain
- Engage in collaborative decision making with patients requesting diagnostic certification for medical cannabis

Points of Departure

- Majority of cannabis-related literature focuses on its risks as a recreational or use disorder substance
- Minority of cannabis-related literature focuses on its therapeutic uses
- Similarities and differences remain unclear between people who use cannabis primarily recreationally vs. primarily medically
- Most studies of therapeutic uses of cannabis utilize pharmaceutically prepared cannabinoids
- Cannabinoid content of medical cannabis preparations differs *prima facie* from that of researched preparations
- Cannabinoids other than THC and CBD remain underrepresented in therapeutic literature
- Terpenes remain underrepresented in therapeutic literature

Cannabinoid Receptors

- CB1
  - Inhibitory G protein coupled
  - Brain, spinal cord, peripheral nerves
  - Astrocytes
  - Adipocytes, liver, pancreas, skeletal muscle
- CB2
  - Inhibitory G Protein Coupled
  - Immune and Inflammatory Cells
  - Brain, spinal cord
    - Unclear role under normal physiologic conditions
- TRPV (aka “Ionotropic Cannabinoid Receptors”)
  - Afferent nociception

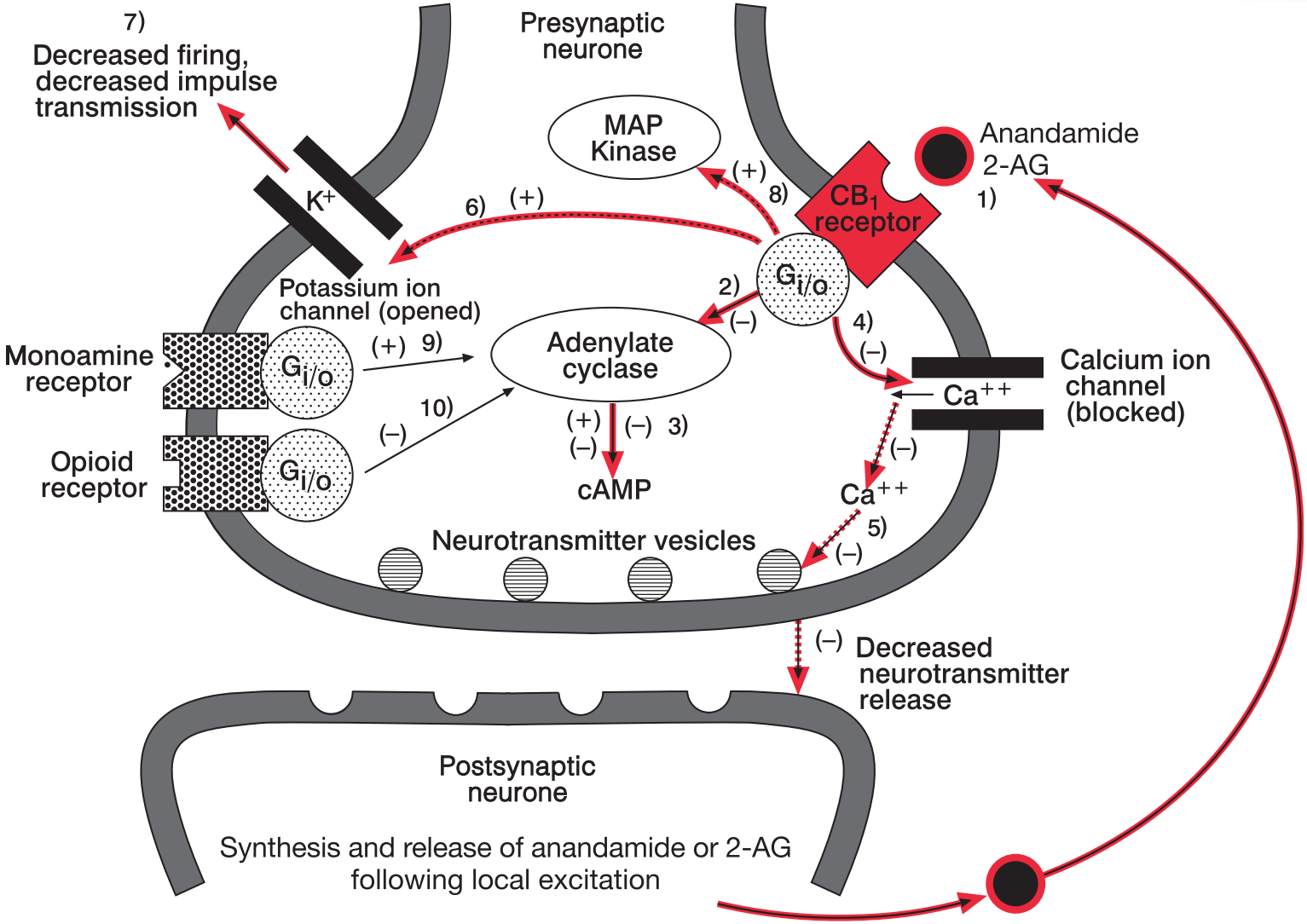
Ashton 2015, Piomelli 2015, Palazzo 2010

Endogenous Cannabinoids

- 2-AG
  - CB1 / CB2 agonist
  - Rapid release
  - Retrograde synaptic messenger
  - Metabolized by COX-2, MGL
- Anandamide
  - CB1 / CB2 agonist
  - Slow release
  - Paracrine / autocrine Messenger
  - Metabolized by FAAH

Piomelli 2015

Endogenous Cannabinoid Functions with CB1 Receptor Binding

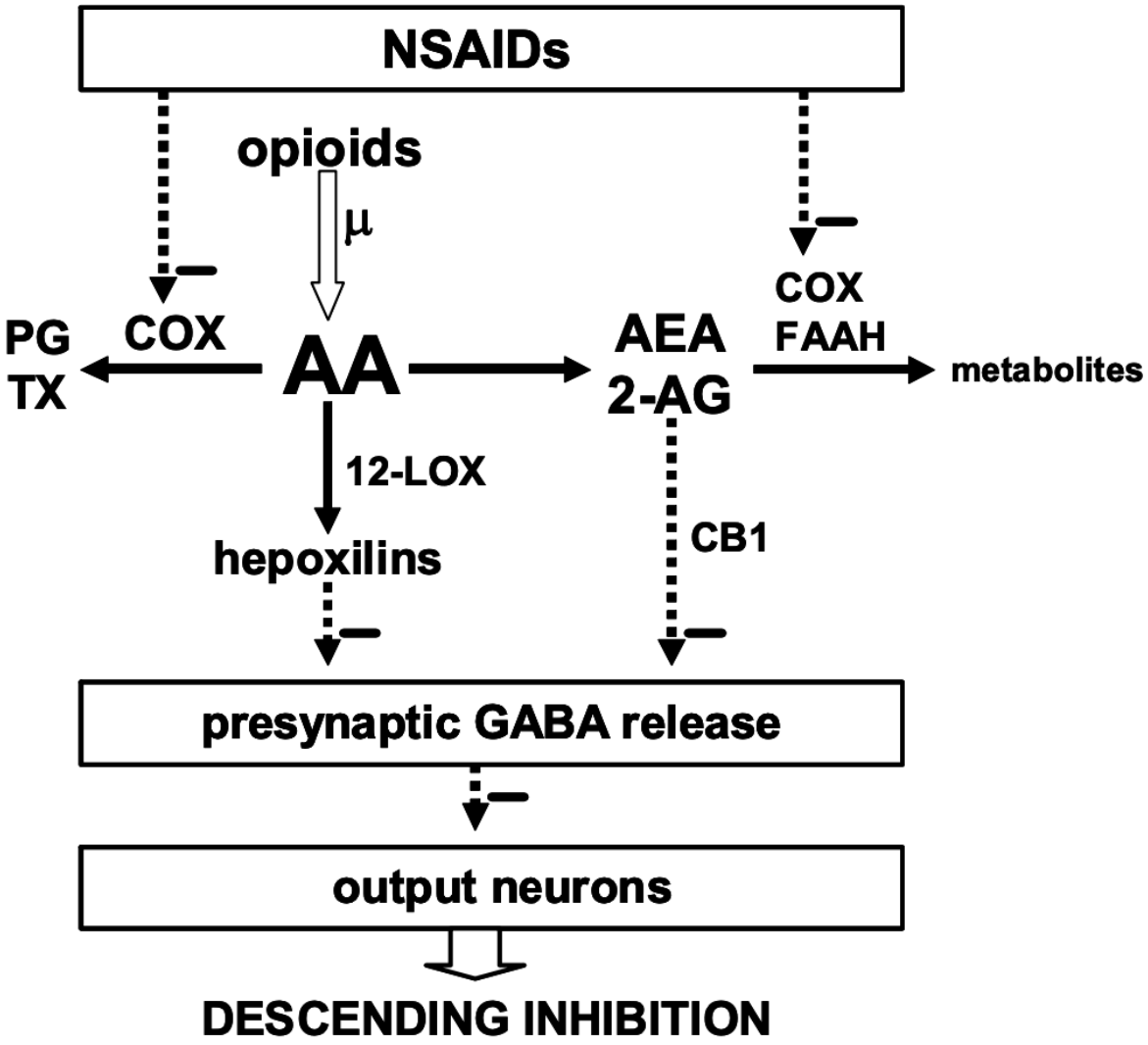


Cannabinoid Mechanisms in Anti-Nociception (Animal Models)

- Inhibition of peripheral mast cell degranulation via CB2 receptors
- Inhibition of dorsal root ganglion capsaicin sensitive fibers via CB1 receptors
- Decreased noxious stimulus firing of dorsal root ganglion wide dynamic range neurons via CB1 receptors
- Decreased spinal cord NMDA receptor activation via CB1 receptors
- Promotion of stress-induced analgesia via periaqueductal gray matter CB1 receptor activation

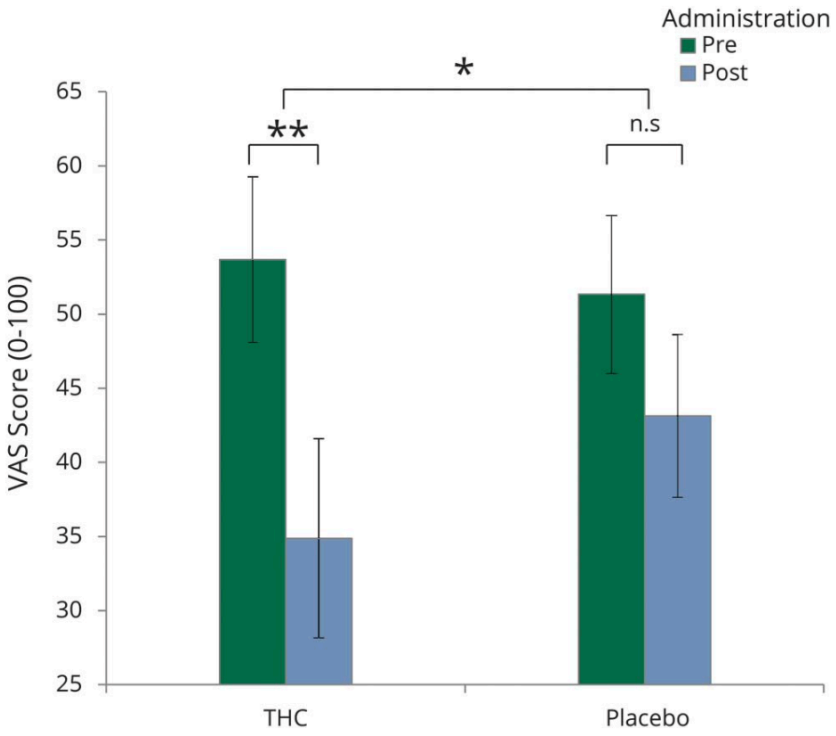
Richardson 2000

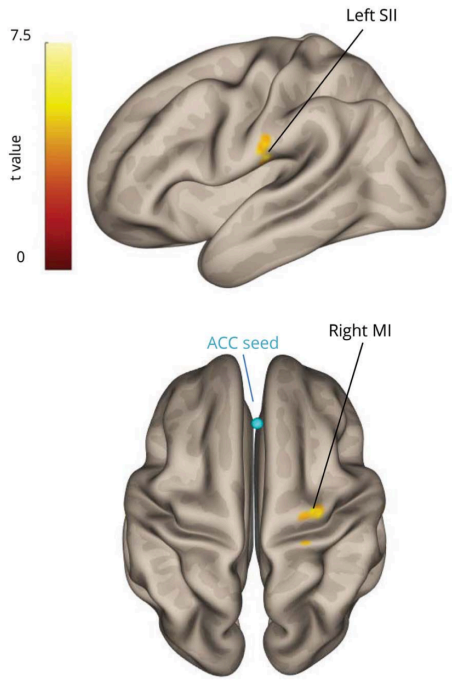
Endocannabinoids Facilitate Descending Modulation of Pain in PAG and RVL

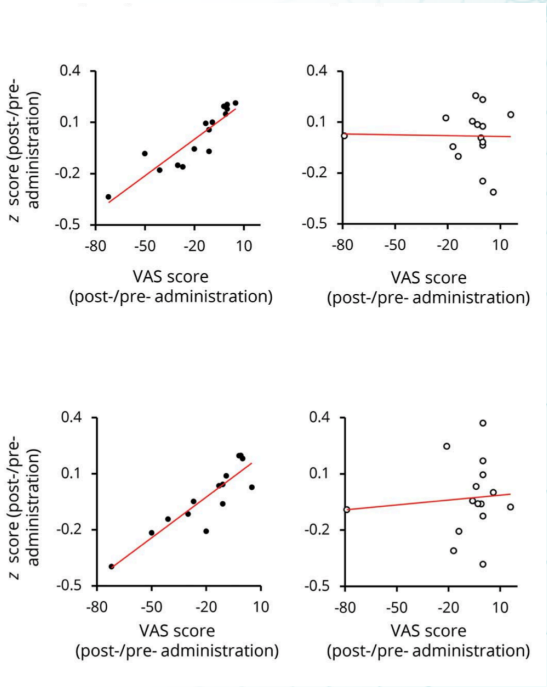


Venegas 2010

THC Induced Functional Dysconnectivity Correlates with Neuropathic Pain Analgesia in Humans







Cannabinoids

- Phytocannabinoids
  - THC: CB1 / CB2 partial agonist
  - CBD: Blocks CB1 / CB2 agonists, 5HT1A agonist, α1 / α3 glycine agonist, inhibits anandamide breakdown, sundry transporter targets
  - Others: CBC, CBG, CBV, CBN
- Synthetic Cannabinoids
  - Nabilone: CB1 / CB2 partial agonist
  - “Spice”, “K2”: CB1 / CB2 full agonists

Piomelli 2015, Bih 2015, Devinsky 2014, Russo 2011

Other Neuropsychiatric Effects of Cannabinoids

- Acute THC
  - Induces psychotic symptoms
  - Increases SCR fluctuations and amplitude to fearful faces
  - Impairs verbal learning, short term memory, working memory, attention
  - Increases striatal dopamine 2%-5%
- Chronic THC
  - Induces psychotic symptoms
  - Reduces glutamate levels
  - Reduces GABA levels
  - Decreases hippocampal volume and gray matter concentration
  - Downregulates cortical CB1 receptors

Skosnik 2016, Fusar-Poli 2009, Broyd 2016

Other Neuropsychiatric Effects of Cannabinoids

- Acute CBD
  - Attenuates THC-induced psychotogenic effects
  - Attenuates THC-induced verbal memory impairment
  - Decreases SCR fluctuations to fearful faces
  - Decreases L amygdala activation to fearful faces
- Chronic CBD
  - Attenuates THC-induced hippocampal decreased volume and THC-induced decreased gray matter concentration
  - Attenuates THC-induced psychotic symptoms

Sherif 2016, Lorenzetti 2016

Clinical Cannabis Intoxication

- Euphoria
- Calmness
- Appetite increase
- Sociability increase
- Time perception alteration
- Color perception heightened
- Cognitive impairment
- Judgment impairment
- Motor coordination impairment
- Panic
- Paranoia
- Hallucinations
- Conjunctival injection, dry mouth, tachycardia

Clinical Cannabis Withdrawal

- Irritability, anger, aggression
- Nervousness, anxiety
- Insomnia, disturbed dreams
- Appetite decrease
- Restlessness
- Depressed mood
- Abdominal pain, tremors, sweating, f/c, headache

Recreational Cannabis Use

- Past year use, 2016
  - 12-17: 12%
  - 18-25: 33%
  - 26-29: 26%
  - 40-44: 10%
  - ≥65: 3%
- Cannabis use disorder
  - 12-month prevalence 1.5%
  - Lifetime prevalence 8.5%
  - 9% of first-time recreational cannabis users eventually develop use disorder

SAMHSA 2017, Lopez-Quintero 2011, Stinson 2006

Recreational Cannabis Use Correlates

- Recreational cannabis use at baseline associated with subsequent
  - Alcohol use disorder OR 2-5
  - Tobacco use disorder OR 2
  - Opioid use disorder OR 2
  - Major depressive disorder OR 2
  - Bipolar disorder OR 3
  - Schizophrenia OR 2-3
- Several psychiatric disorders at baseline associated with increased risk of subsequent recreational cannabis useand cannabis use disorder

Gorelick 2021, Stinson 2006

Recreational Cannabis Use Correlates

- Lower birth weight
- Increased attention and behavioral problems in offspring
- Poorer cognitive, academic, vocational outcomes
- ~2x increased risk MVA
- Increased risk acute MI
- Increased risk ischemic stroke
- Exacerbation of PTSD
- Exacerbation of schizophrenia, bipolar Disorder, depression
- 2-5 x increased risk suicide

Hall 2015; Wilkinson 2015; National Academies of Sciences 2017

Statistical Note

- Number needed to treat (NNT)
  - 1/absolute risk reduction
- Number needed to harm (NNH)
  - 1/absolute risk increase
- Standardized mean difference (SMD)
  - (treatment effect – comparator effect / std dev)
- Weighted mean difference (WMD)
  - Mean accounting for relative weight of each contributing measure

Statistical Note

- Small SMD (0.2-0.5)
  - Inhaled corticosteroids COPD FEV1 (SMD 0.36)
  - Antidepressants acute depression (SMD 0.31)
- Medium SMD (0.5-0.8)
  - ACE-I systolic BP (SMD 0.5)
  - Antidepressants dysthymia (SMD 0.52)
- Large SMD (>0.8)
  - Metformin diabetes HgA1C (SMD 0.97)
  - Electroconvulsive tx acute depression (SMD 0.9)
- Most treatments for chronic medical conditions have small to medium effect sizes

Leucht 2012, Kuhn 2014, Kho 2002

Summary Efficacy of Cannabinoids for Chronic Pain

- Reduction in pain vs. placebo
  - ≥30% reduction in pain
    - OR 1.37 (1.14-1.64)
    - NNT 11
  - 10-Point numeric rating scale
    - WMD 0.46 (0.11-0.8)
- Cancer pain: SMD 0.76
- Non-cancer pain: SMD 0.53
  - Neuropathic pain: SMD 0.53
- Nixed trials in fibromyalgia
- Mostly negative trials in MS-related pain
- No trials in osteoarthritis pain

Allan 2018, Whiting 2015

Summary Efficacy of Cannabinoids for Chronic Pain

- Vast majority of studies use THC alone, nabilone alone, or THC plus CBD
- Very few studies of cannabis flower or extracts
- Very few studies of CBD alone
- Adverse effects vs. placebo
  - Any: OR 3.03
  - Serious: OR 1.41
  - Withdrawal due to adverse effects: OR 2.94
  - Dizziness: NNH 5
  - Sedation: NNH 5
  - Confusion: NNH 15
  - Dissociation: NNH 20

Allan 2018, Whiting 2015

Adverse Effects and ORs vs. Placebo

Individual AEs		
Dizziness	41 (4243)	5.09 (4.10-6.32)
Dry mouth	36 (4181)	3.50 (2.58-4.75)
Nausea	30 (3579)	2.08 (1.63-2.65)
Fatigue	20 (2717)	2.00 (1.54-2.62)
Somnolence	26 (3168)	2.83 (2.05-3.91)
Euphoria	27 (2420)	4.08 (2.18-7.64)
Depression	15 (2353)	1.32 (0.87-2.01)
Vomiting	17 (2191)	1.67 (1.13-2.47)
Diarrhea	17 (2077)	1.65 (1.04-2.62)
Disorientation	12 (1736)	5.41 (2.61-11.19)
Asthenia	15 (1717)	2.03 (1.35-3.06)
Drowsiness	18 (1272)	3.68 (2.24-6.01)
Anxiety	12 (1242)	1.98 (0.73-5.35)
Confusion	13 (1160)	4.03 (2.05-7.97)
Balance	6 (920)	2.62 (1.12-6.13)
Hallucination	10 (898)	2.19 (1.02-4.68)
Dyspnea	4 (375)	0.83 (0.26-2.63)
Paranoia	4 (492)	2.05 (0.42-10.10)
Psychosis	2 (37)	1.09 (0.07-16.35)
Seizures	2 (42)	0.91 (0.05-15.66)

Whiting 2015

In Comparison

- Chronic non-cancer pain
  - Opioids vs. placebo
    - 10cm visual analog scale
      - WMD 0.69 (0.56-0.82)
- Low back pain
  - NSAIDs vs. placebo
    - 10cm visual analog scale
      - WMD 0.7 (0.3-1.1)
- Painful diabetic neuropathy
  - Pregabalin vs. placebo
    - ≥30% reduction in pain
      - 300mg: RR 1.1, NNT 22
      - 600mg: RR 1.2, NNT 10

Busse 2018, Enthoven 2016

In Comparison

- Painful diabetic neuropathy
  - Pregabalin vs. placebo
    - ≥50% reduction in pain
      - 300mg: RR 1.3, NNT 22
      - 600mg: RR 1.4, NNT 7.8
  - Duloxetine 60mg vs. placebo
    - ≥50% reduction in pain
      - RR 1.5
      - NNT ~5
    - 10-Point numeric rating scale
      - WMD 0.96

Busse 2018, Enthoven 2016, Lunn 2014

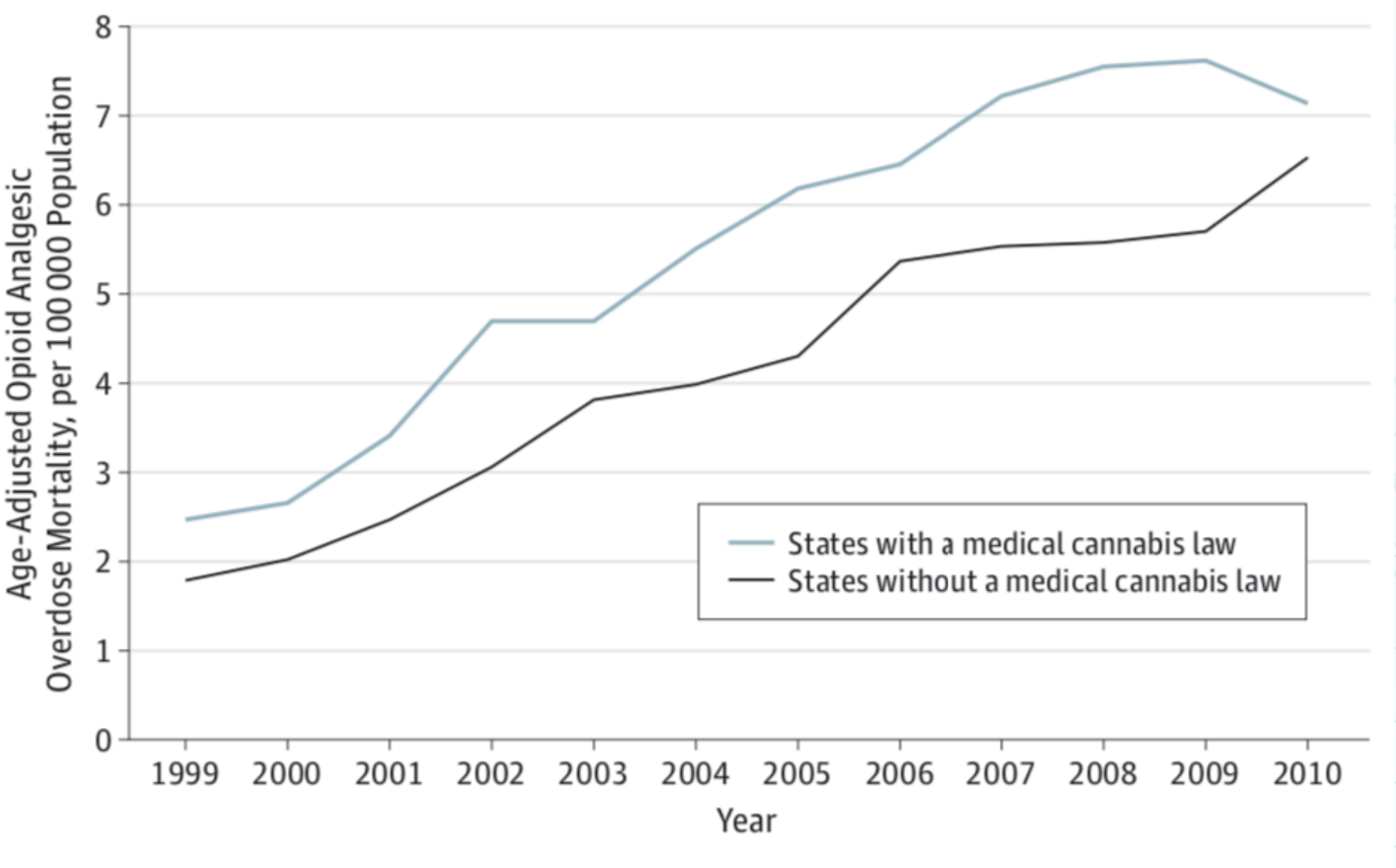
In Comparison

- Neuropathic pain (mixed causes)
  - Tramadol ~400mg vs. placebo
    - ≥50% reduction in pain
      - RR 2.2
      - NNT 4.4

Outstanding Questions

- Does medical cannabis reduce risk of opioid overdose?
- Does medical cannabis reduce opioid use?
- Does medical cannabis treat opioid withdrawal?

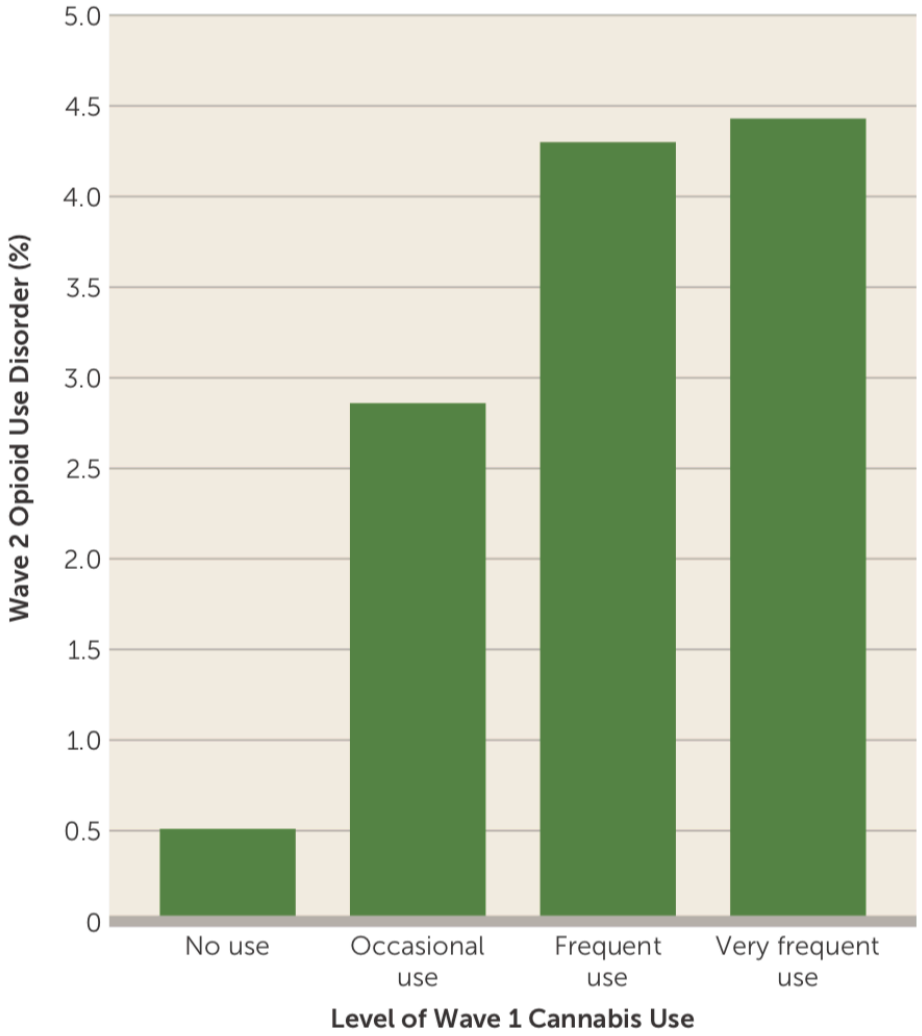
Medical Cannabis Laws and Opioid Overdose Deaths (Ecological)



Bachhuber 2014

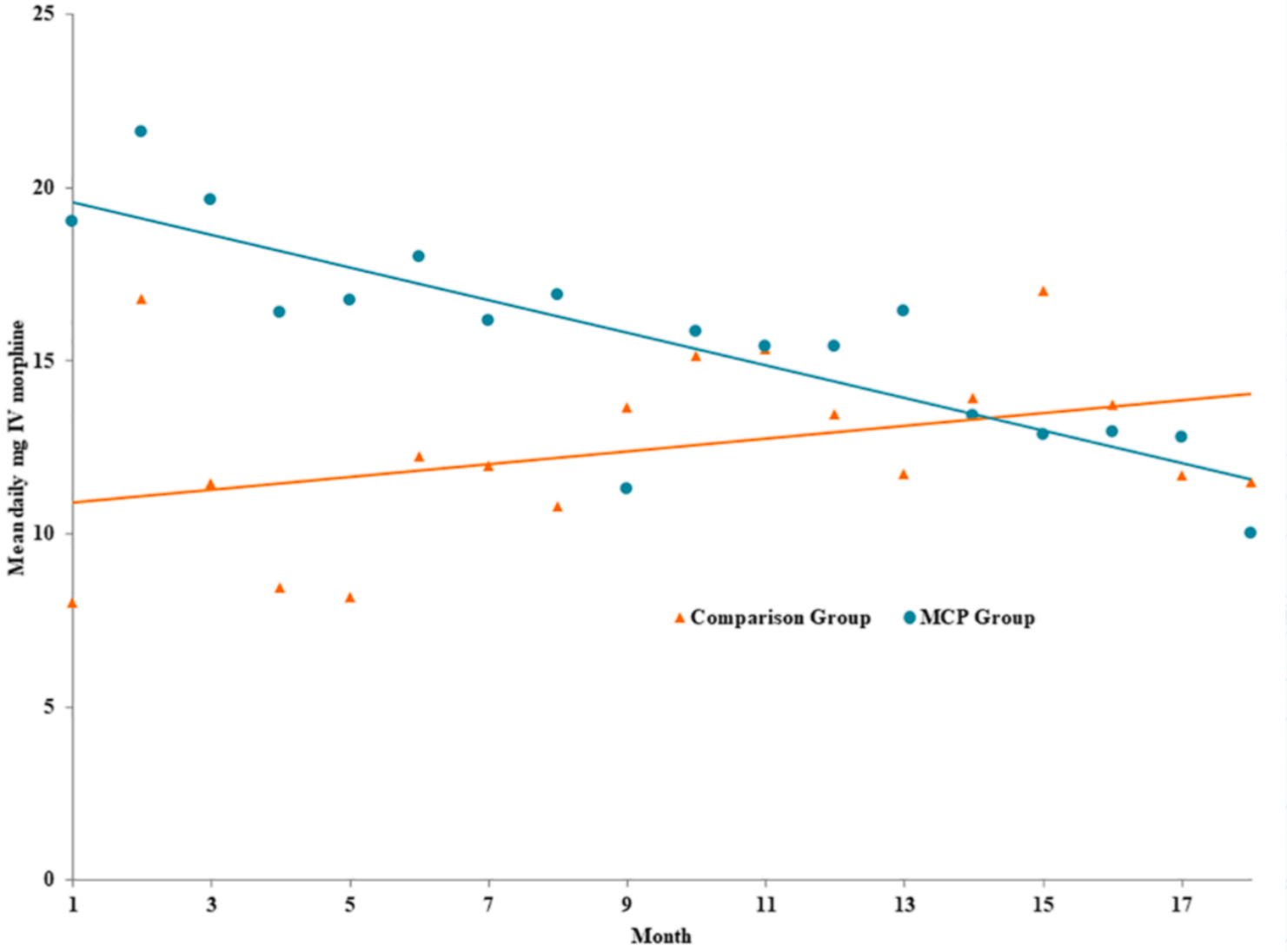
Recreational Cannabis Use and Incident Rx Opioid Use Disorder (Longitudinal)

FIGURE 1. Level of Wave 1 Cannabis Use and Incident Wave 2 Prescription Opioid Use Disorder in the NESARC[a]



Olfson 2018

Medical Cannabis Program and Rx Opioid Doses (Uncontrolled Observational)



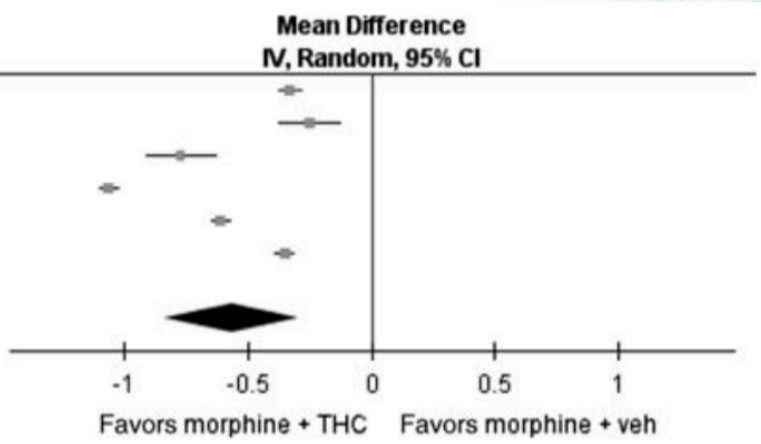
Vigil 2017

Cannabinoids and Opioid Sparing

- Extensive rodent data of opioid sparing effect

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]**

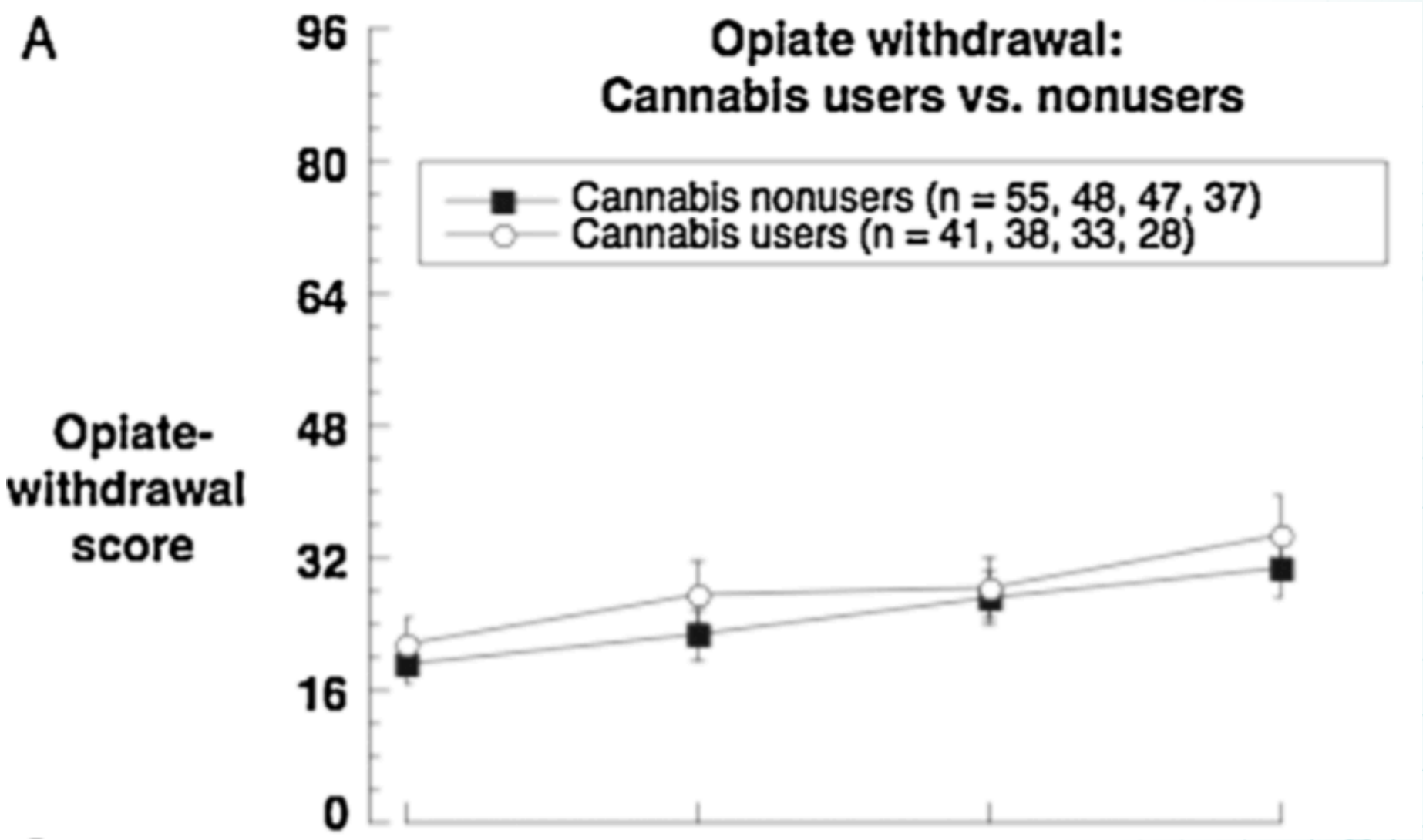
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 926.85$, df = 5 ($P < 0.00001$); $I^2 = 99\%$
Test for overall effect: $Z = 4.10$ ($P < 0.0001$)



- Only 1 of 9 human clinical studies shows evidence of opioid sparing effect

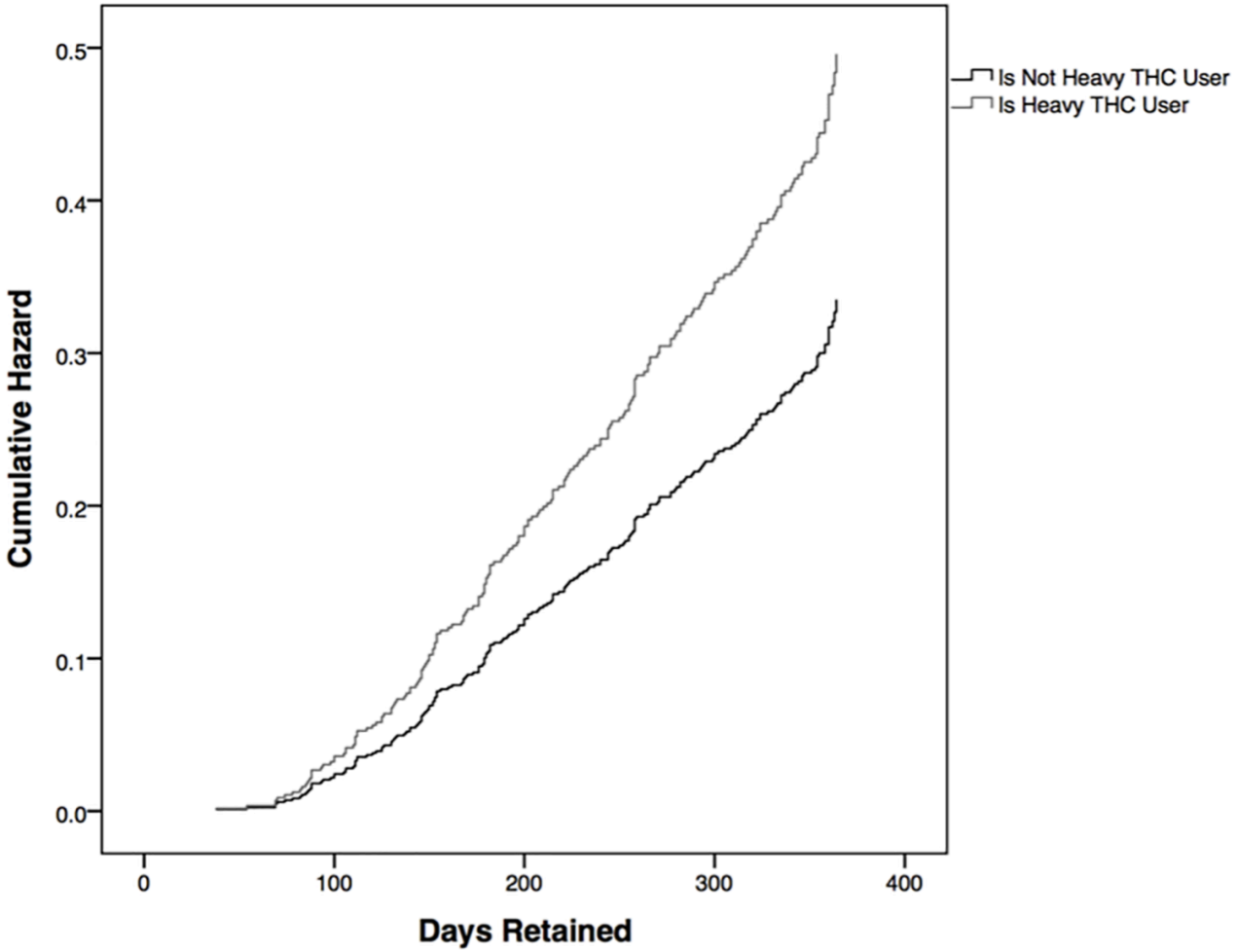
Nielsen 2017

Cannabis in Opioid Withdrawal (Observational)



Epstein 2015

Cannabis Use Correlates with Opioid Replacement Treatment Dropout



Franklyn 2017

Proposed Relative Contraindications and Cautions for Medical Cannabis

- Contraindications
  - Cannabis use disorder
  - Schizophrenia
  - Bipolar disorder
  - Suicidality
  - Use prior to full neurodevelopment
- Cautions
  - PTSD
  - Depression
  - Non-cannabis substance use disorder
  - High cardiovascular risk
  - High cerebrovascular risk
  - Chronic bronchitis (for smoked cannabis)

Proposed Harm Reduction Strategies

- Provide collaborative education and monitoring of possible risks
  - Request patients refrain from driving while cannabis effects are active
- Collaborate with patients on strain selection
- Inquire about THC and CBD percentages of utilized strains
- Encourage CBD supplementation to counteract psychotogenic and adverse neuroanatomic effects
- Continue concomitant pursuit of standard pain rehabilitation and palliation strategies

Summary

- THC containing preparations demonstrate modest benefit in treatment of chronic pain, mostly in neuropathic pain and cancer pain
- Adverse effects of THC containing preparations are common and in keeping with known intoxication syndrome
- Adverse correlates of recreational cannabis well documented
- Studies of THC preparations likely do not reflect demographics of recreational cannabis use or available strains of medical cannabis
- Risk stratification and harm reduction encouraged

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