Cannabis/Cannabinoids for Treating Opioid Us Disorder

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Disclosures

- Paid consultant to Zynerba Pharmaceuticals and Canopy Health Innovations

- Advisory board member for FSD Pharma

Cannabis and the Opioid Epidemic

TIONS SEARCH

THE BALTIMORE SUN

PR. 28, 2017 BREAKING SPORTS MARYLAND BUSINESS OPINION OBITS ENEWSPAPER ADVERTISING

Maryland legislators propose using marijuana to treat heroin addiction

1. Cannabis Strains That Help Treat Generalized Pain

All hail ACDC, one of the most effective painkilling strains out there du
punch of cannabinoids CBD and THC. As a general rule, cannabis strai
of both THC and CBD tend to make the best pain medicines, and ther
CBD strains out there offering similar chemical profiles as ACDC.

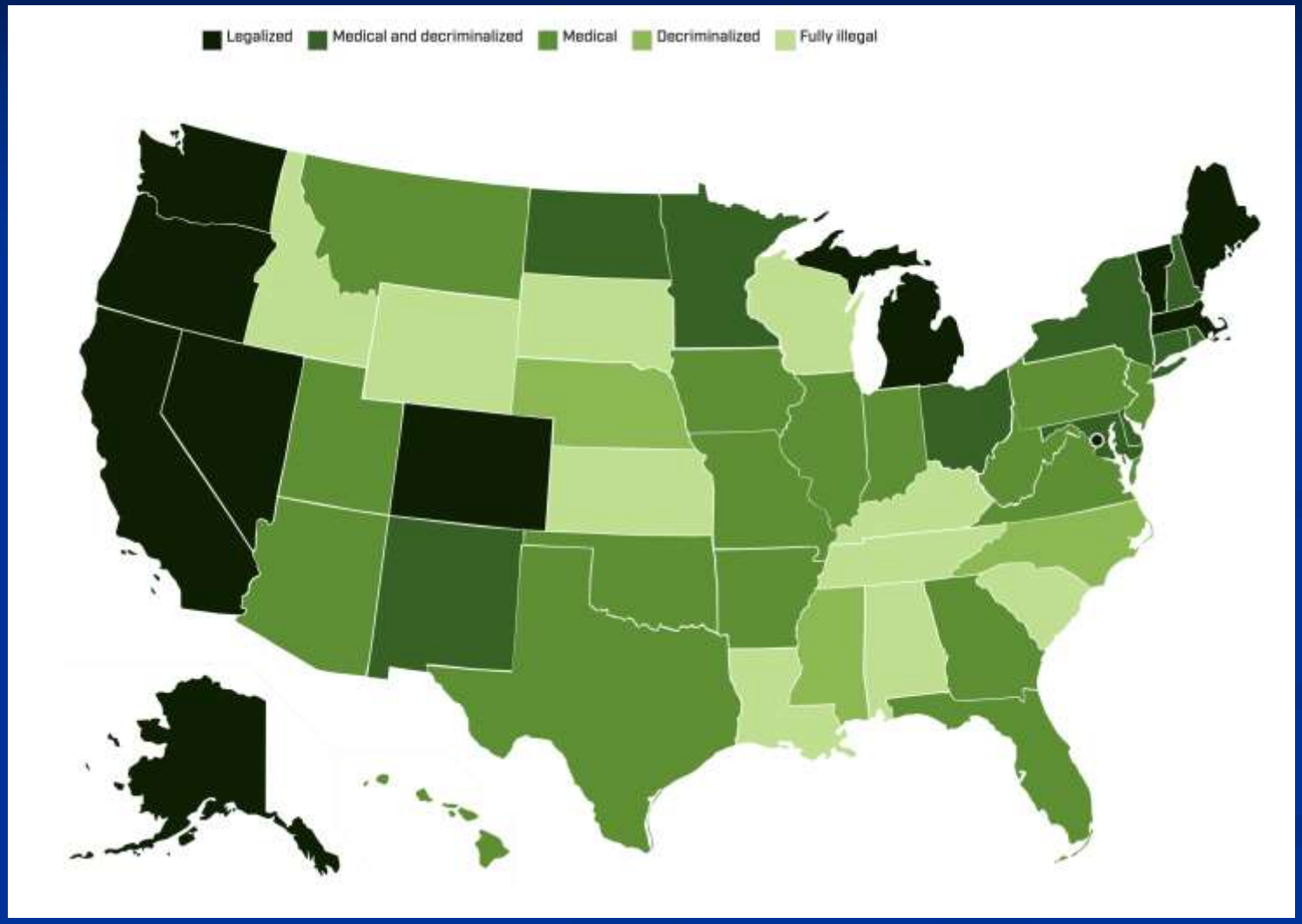
Marijuana Relieves Chronic Pain, Research Shows

Three Puffs a Day Helped People With Nerve Pain, Study Finds

Brief History of Cannabis and Politics

- Controversy has surrounded social acceptance/legality of cannabis throughout history
- Health benefits expounded in 1800s, included in U.S. Pharmacopeia, tinctures available legally
- Banned as part of Marihuana Tax Act in 1937, and continued with Controlled Substances Act in 1970
- California enacted the first medical cannabis law in 1996, in opposition to Federal Law

Current State Laws

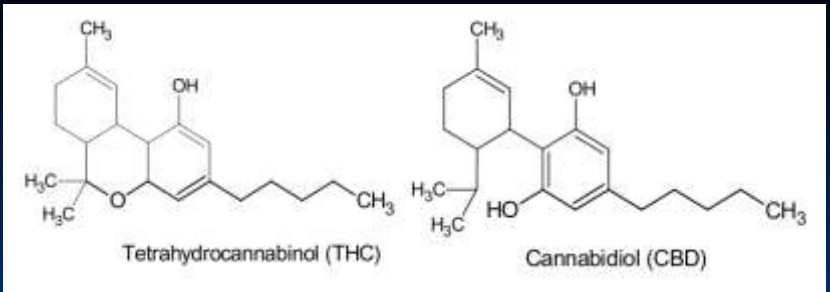


Hemp is federally legal

Cannabis Vs. Cannabinoids

- Cannabis is a complex chemical entity
- Over 100 botanically derived phytocannabinoids, each of which can be synthesized or isolated
- Hundreds of synthetic cannabinoids
- Diverse pharmacology
- Pharmaceutical vs. botanical
- Cannabis vs. hemp

THC Vs. CBD

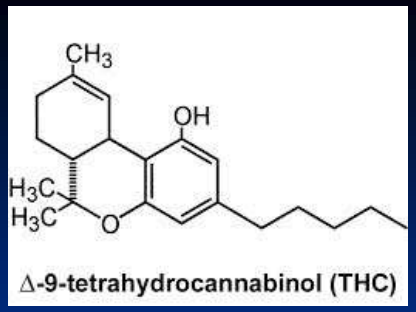


- THC drives most of the hallmark effects of cannabis ("high" feeling, increased appetite, memory difficulties)
- Partial agonist at CB1 and CB2 receptor
- CBD does not produce the same "high" as THC, no abuse liability via oral route, but does produce drug effects
- Different and complex pharmacology
- CBD does NOT mitigate most effects of THC
- Several other cannabinoids that we know little about

Minor Cannabinoids

- CBG - Cannabigerol
- CBN - Cannabinol
- CBC - Cannabichromene
- THC-V - Tetrahydrocannabivarin
- THCA – Acid form of THC
- CBDA - Acid form of CBD
- Also terpenoids and flavonoids

Cannabinoid pharmacology



Δ-9-tetrahydrocannabinol (THC)

- THC: Partial agonist at CB1 and CB2 receptors
- CBD: Allosteric modulator at CB1/CB2; mu- and delta-opioid receptors; partial agonism at 5HT1a
- CBG: Weak partial agonist at CB1 and CB2; GABA uptake inhibition
- CBN: Partial agonist at CB1 and CB2, less affinity than THC
- THC-V: Dose-dependent CB1 agonism/antagonism

Opioid Receptors

Mu: responsible for euphoric and analgesic effects, distributed throughout brain and spinal cord

Kappa: Antagonize mu activity, produce some analgesia but also dysphoric effects

Delta: Heavily expressed in basal ganglia and neocortex; believed to modulate mood, analgesic effects uncertain

Sigma: Limited analgesic effects but associated with emotions

Cannabinoid - Opioid Similarities

- Comparable receptor distribution in CNS
- Pre-synaptic g-protein coupled receptors - inhibit neurotransmitter release
- Acute administration of agonists induce analgesia, catalepsy, hypothermia, motor depression, hypotension, immunosuppression, and sedation
- Agonists increase DA release in reward pathway

Cannabinoid - Opioid Cross-Talk

- Cross-tolerance demonstrated in most, but not all preclinical studies of anti-nociception
- Antagonist-precipitated withdrawal and withdrawal attenuation across drug types
- Substitution across drug types for self-administration and reduction with antagonist
- Mixed results for behavioral and neurobiological correlates; species and region specific

Cannabinoid - Opioid Cross-Talk

- Exogenous opioid analgesic effects unchanged in CB1 KO mice; opioid models of dependence reduced, but self-administration and place preference still acquired
- Cannabinoid models of dependence reduced in mu-opioid KO mice
- THC, but not anandamide, increased dynorphin release in spinal cord: THC-induced analgesia may have kappa- and possibly delta-opioid mechanism

Cannabinoid - Opioid Cross-Talk

- Evidence of additive or synergistic analgesia in rodents with sub-threshold doses of cannabinoids and opioids; what about other endpoints?
- Chronic opioid and cannabinoid exposure alters endogenous ligands for the opposing system in region/species/drug specific manner

  Acute cannabinoid agonists shown to increase synthesis and release of endogenous opioids

Pre-Clinical Summary

- Neurobiological interaction between cannabinoid and opioid systems
- Both induce analgesia and there is evidence of substitution effects
- Mechanism of analgesia appears to be different
- Some evidence of cross-system modulation in pre-clinical models of drug dependence
- Variability in results across studies

Clinical/Epi Studies: Abrams et al., 2011

- Vaporized cannabis effects (up to 32mg THC) 3x/day for 4 days on pain and opioid metabolism
- 11 morphine and 10 oxycodone maintained patients with assorted chronic pain conditions

Table 1 Participant characteristics

	Morphine group	Oxycodone group
n	10	11
Women	4	6
Caucasian	8	9
Mean age (range)	42.9 (33–55)	47.1 (28–61)
Mean opioid dose (mg) (range)	62 Twice daily (10–200)	53 Twice daily (10–120)
Mean pain score day 1 (95% CI)	34.8 (29.4, 40.1)	43.8 (38.6, 49.1)

CI, confidence interval.

Table 2 Pain by study day

		Day 1	Day 5	Difference	Percentage change
	n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Overall	21	39.6 (35.8, 43.3)	29.1 (25.4, 32.8)	−10.7 (−14.4, −7.3)	−27.2 (−45.5, −8.9)
Morphine	11	34.8 (29.4, 40.1)	24.1 (18.8, 29.4)	−11.2 (−16.5, −6.0)	−33.7 (−63.8, −3.5)
Oxycodone	10	43.8 (38.6, 49.1)	33.6 (28.5, 38.6)	−10.3 (−14.8, −5.8)	−21.3 (−47.0, 5.3)

CI, confidence interval.

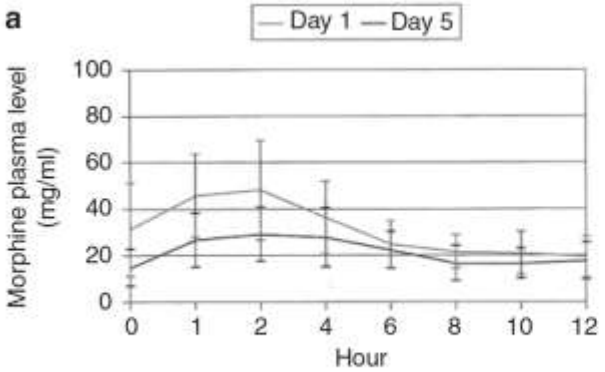


Figure 1 Plasma concentration–time curves for sustained-release (**a**) morphine and (**b**) oxycodone before and after exposure to inhaled cannabis.

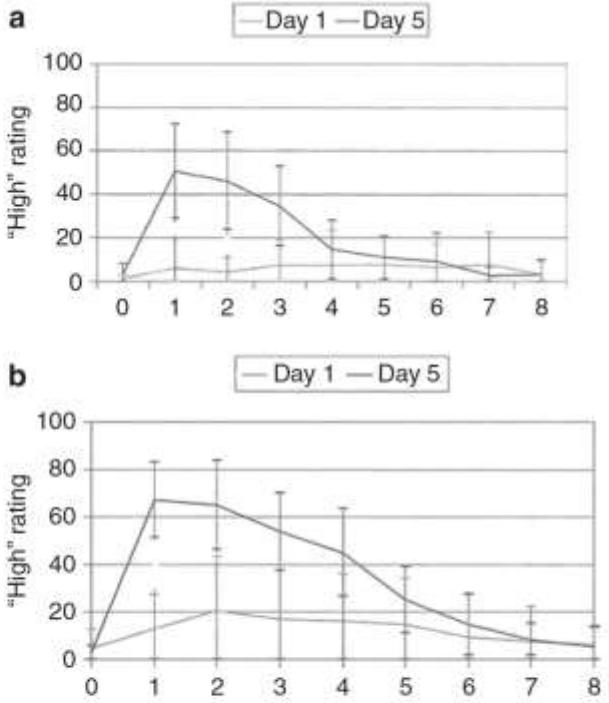
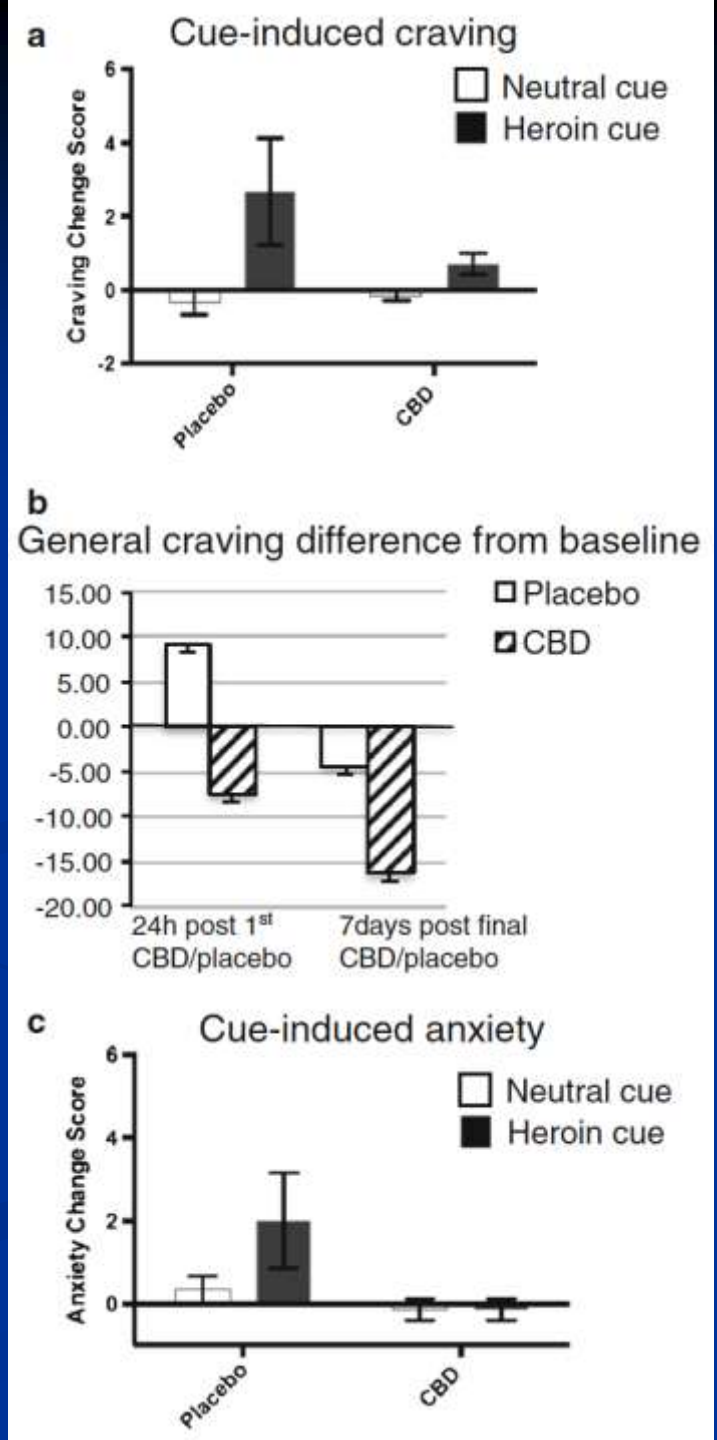


Figure 2 Subjective highs experienced when cannabis was combined with (**a**) morphine and (**b**) oxycodone on day 5.

maximal morphine concentration was longer during cannabi

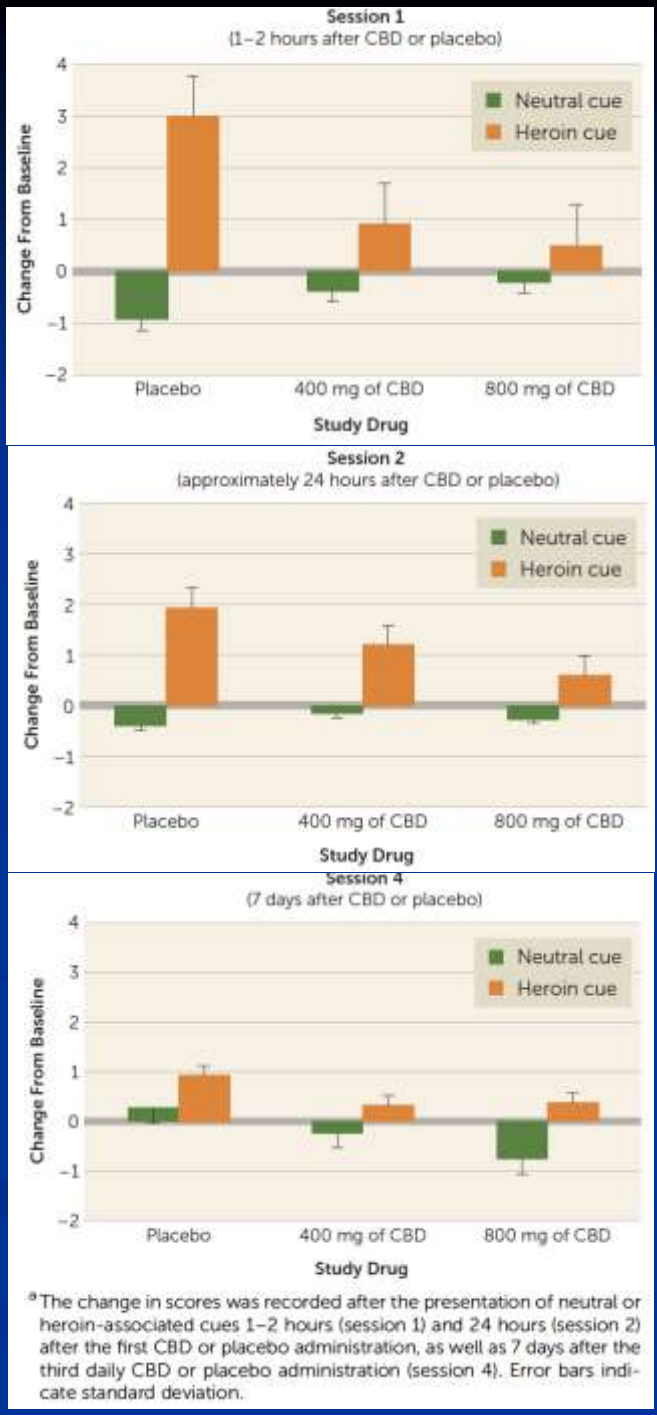
Hurd et al., 2015

- Pilot study of CBD on craving for heroin and cue-reactivity in dependent adults
- 400 to 800mg administered to 6 participants



Hurd et al., 2019

- Assessed cue-induced craving and anxiety at multiple time points in abstinent Ss with OUD
- Reduced craving (24 hrs) and anxiety (1-2 hrs) after acute and repeat dosing
- No impairment, few AEs



[a] The change in scores was recorded after the presentation of neutral or heroin-associated cues 1–2 hours (session 1) and 24 hours (session 2) after the first CBD or placebo administration, as well as 7 days after the third daily CBD or placebo administration (session 4). Error bars indicate standard deviation.

Gruber et al., 2016

- 11 adults beginning use of medicinal cannabis through Mass state program; 7 for chronic pain
- Baseline evaluation followed by 3-mo follow-up after initiation of cannabis use
- 42% reduction in opioid use observed
- Improvements in depression, sleep, QOL, and cognitive function also observed; reductions in benzodiazepines, mood stabilizers, and antidepressants.

Bachhuber et al 2014/Shover et al 2019

- Evaluated opioid overdoses by state law with regards to medicinal use of cannabis
- Initial study found lower opioid overdose mortality in states with versus without medical cannabis
- Follow-up study showed a reversal of this trend
- Correlational, cannot control for other factors

Shi et al., 2017

- Rate of hospital admissions related to cannabis and prescription opioids up 300% from 1997 – 2014
- Medical cannabis law implementation reduced opioid dependence admissions 23% and prescription opioid overdose admissions by 13%
- Medical cannabis laws had no impact on cannabis-related hospitalizations
- Correlational, cannot control for other factors

Degenhardt et al., 2015

- Community sample of 1514 individuals prescribed opioids for chronic non-cancer pain
- 16% had used cannabis for pain, 6% in past month
- 25% said they would use cannabis if given access
- Cannabis users were younger, had greater pain, more pain-related problems, had been taking opioids for longer, using higher doses, and were more non-adherent with their opioid use, had a greater history of other drug abuse and psychiatric problems

Piper et al., 2017

- Convenience sample of 1514 individuals recruited from New England dispensaries; online survey
- Respondents indicated cannabis was effective for pain following trauma, menstrual/abdominal pain, back/neck pain, neuropathic pain, cancer pain, and post-surgical pain
- 41% of those who used opioids (N=215) reported a significant reduction in opioid use following initiation of cannabis; 35% reported slight reduction

Clinical/Epidemiological Summary

- Some evidence of substitution of cannabis for opioids or reduction of opioid use for pain
- CBD potential for reduction of craving/anxiety
- THC potential for reduction of withdrawal
- Other cannabinoids/terpenes???
- A lot of uncontrolled studies; most focused on pain; no controlled trials for treatment of OUD

Clinical Trials Design and Measurement

- At what stage of OUD are we intervening?
- What is the product?
- How will the product be used?
- What is the benchmark for comparative efficacy and safety?
- What are key safety and feasibility concerns?
- Is this a federally legal drug, or a Schedule I drug?

At what stage of OUD do we intervene?

- Replace opioids with cannabis for pain to prevent OUD onset among prescription opioid users
- Suppress opioid withdrawal
- Reduce craving/relapse prevention
- Promote cannabis as a substitute for illicit opioids (harm reduction approach)
- Each of these questions requires a completely different design and primary endpoint

What is the product?


AM:
Cannabis Sativa Patch
Cannabis Sativa Patch
PM:
Cannabis Indica Patch
Cannabis Indica Patch


Pineapple
Cannabis Sativa


WHITE ASH
PINEAPPLE


BEYOND MARS
YUMMY GUMMY

“Medicinal” Cannabis Preparations

- Many very high potency (THC)/multi-dose
- Unknown exactly what constituents of plant material remain in extracts/oils
- Dosing challenges across routes/products
- Cannabinoid content typically not labeled, can be incorrect
- QC oversight is inadequate; lack of standards
- Appropriate placebo for clinical trials?

How will the product be used?

- There is very little basis for selecting any particular route of admin, dose, or product type
- Short-term (e.g. nicotine patch) or long-term (e.g. methadone) use?
- Will cannabinoid therapies be used in conjunction with other treatments? If so, which ones?
- Multiple cannabinoid product types?
- Are we developing a pharmaceutical or just looking to replace opioids

What is the benchmark for comparison?

- Cannabis vs placebo?
- Cannabis vs methadone/buprenorphine?
- Cannabis vs naltrexone?
- Cannabis vs benzos?
- Cannabis vs lofexedine, tramadol, kratom, etc.
- Cannabis vs psychosocial treatment
- Cannabis vs cannabis + psychosocial tx

What are key safety/feasibility concerns?

- Opioid overdose
- High rate of psychiatric comorbidity
- Tolerance to cannabis effects over time
- Cannabis Use Disorder
- Cannabis quality control issues
- AEs associated with cannabis use
- Drug-drug interactions

Quality Control Issues

- Manufacturing largely unregulated, state rules differ, little enforcement of compliance
- Potency/dose variability for all products
- Labs for testing impeded by DEA, no standards
- Multiple studies show product label inaccuracy and contaminants in retail products

Cognition

- Cannabis use associated with decreased memory, attention, IQ
- Altered brain structure
- Age of onset important

- Unclear if effects are reversed with abstinence
- Correlations only; cannot infer causality
- Functional significance not well established

Regulation of Cannabinoids

- Cannabis, CBD, and multiple synthetic cannabinoids are in Schedule I of CSA
- Hemp derived CBD is legal via Farm Bill
- THC is in Schedules I, II, and III of the CSA
- Terpenes are legal and most are GRAS (oral only)
- Epidiolex is Schedule V
- INCREDIBLY difficult to do Phase 2 or larger trials with Schedule I drug

Key Trial Types

- Pre-clinical mechanism-oriented
- Longitudinal observational
- Human lab – dose finding; models of efficacy
- Outpatient RCTs
- Phase 4 type monitoring

Key Trial Design Features

- GMP standardized product/dose flexibility
- Randomized; Placebo controlled
- Comparison with evidence-based positive control
- Foundational psychosocial treatment
- Powered for sex differences
- Of sufficient duration with follow-ups to evaluate long-term health impacts/relapse

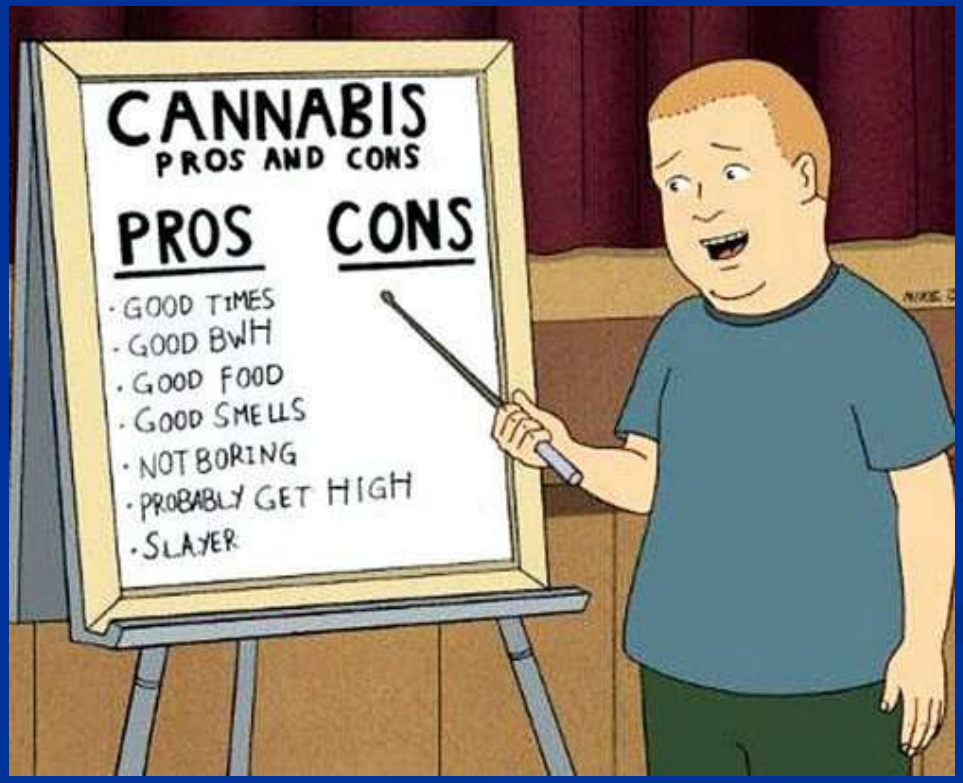
Inclusion/Exclusion

- Comorbid psychiatric disorders a concern
- Cannabis use history
- Cardiovascular health
- Use of other medications
- Pregnancy

Key Outcome Measures

- Cannabis medication vs other cannabis use
- Acceptability of the study drug/retention
- Opioid use, craving, withdrawal and overdose
- Other medication/drug use/SUD severity
- Adverse events
- Health (mental and physical)
- Quality of life/functioning/pain/sleep
- Healthcare utilization?

Can Cannabis Help With the Opioid Epidemic?



What Do We Know?

- Cannabis is a complex “drug” and differences are observed across species, dose, and pain type
- It is neither benign, nor an ideal medicine; Harm vs. benefit depends on case and circumstance
- Observational studies suggest it is relatively safe and associated with reduced opioid use
- Controlled clinical trials indicate its effectiveness as an analgesic is modest at best; no trials of OUD where opioid use is primary outcome

What Do We Need To Know?

EVERYTHING

Where Do We Go From Here?

- Pre-clinical work evaluating potential mechanisms and opioid-cannabinoid interactions
- Observational studies of cannabinoid-opioid substitution
- Appropriate product standards in cannabis
- Minimization of unwanted effects
- Comparative efficacy trials on appropriate endpoints with regulated medications
- Increased risk of OD vs meth/bup/ntx big concern

Thanks and Contact Info

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