High in the Sky with CAMA: Medical Marijuana and CBD

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Disclosures

• All treatments discussed are off-label, not FDA approved for pain or migraine, and may be ILLEGAL in some states.

• Stock: ACB, APHA, TRTC, MJNA

• Advisory Board: Theranica Bio-Electronics
Goals

• Review historical timelines leading to current legal landscape and legal implications of medical cannabis use

• Discuss the major phytocannabinoids CBD and THC, define the terpenes, and describe strain (chemovar) differentiation

• Summarize evidence for cannabinoid use in pain and HA

• Provide clinical use highlights and suggestions

• Summarize potential harms and adverse effects of cannabis and cannabinoids
History

• Ancient medical uses dating back thousands of years

• 1839: Dr. William Brooke O’Shaughnessy
  - Introduced Western world to “Indian hemp” (Cannabis indica) after professorship in Calcutta, India
  - Advocated for analgesic and muscle relaxant
Late 19\textsuperscript{th}/early 20\textsuperscript{th} century:

- Cannabis-based preparations:
  - Listed in US Dispensatory 1845
  - North America: Bristol-Meyers Squib, Davis, Eli Lilly

- Many prominent physicians prescribed for episodic/chronic daily HA, migraine, acutely/preventively
• “The headache to which I wish to draw attention is of a dull, continuous or sub continuous character, attended sometimes with paroxysmal exacerbations”

• “...may last weeks, months or even years”

• Describes a regimen of increasing bid doses of cannabis.

• 1915: “Father of modern medicine” Sir William Osler
  - Cannabis for migraine in his textbook The Principles and Practice of Medicine
  - When treating migraine, “Cannabis indica is probably the most satisfactory remedy...”

• 1930s: Harry Anslinger
  - Led Federal Bureau of Narcotics (early DEA)
  - Associated psychosis, addiction, violent crime to marijuana use
  - “Drug of abuse used by minority, low income communities”
• **Marihuana Tax Act of 1937**
  - AMA strongly opposed
  - Large fines / prison w/ cannabis involvement

• **1941: Cannabis preparations taken off US Pharmacopoeia and National Formulary**

• **Controlled Substances Act of 1970**
  - Changed cannabis to Schedule 1 drug
• DEA won’t reschedule from “most dangerous” Schedule 1 classification
  - Claim “No accepted medicinal use”

• Hinders federal funding for research to prove or disprove Schedule 1 claims of “no medicinal use”

• “Stuck” here since
The Paradox

- US Government/Department of Health and Human Services
  - 2003: Awarded patent (US Patent #6,630,507) for “cannabinoids as antioxidants and neuroprotectants”

- FDA approved 3 cannabinoids for medicinal purposes
  - Dronabinol (Marinol®): THC
  - Nabilone (Cesamet®): THC
  - Epidiolex: CBD
So... the DEA says cannabis has no medicinal qualities, and won't reschedule...

But the FDA approved 3 cannabinoid medications...

And the government owns a patent for medical uses of cannabinoids...

So... the DEA says cannabis has no medicinal qualities, and won't reschedule...

My brain just broke. I can’t handle this maaaaan...
Legal access

• 1996: CA 1st state to pass Compassionate Use Act
  - Allowed legal use of marijuana for medicinal purposes

• Legalized MMJ is growing
  - Medical:
    • 33 states (AK, AR, AZ, CA, CO, CT, DE, FL, HI, IL, LA, ME, MD, MA, MI, MN, MO, MT, ND, NH, NJ, NM, NY, NV, OH, OK, OR, PA, RI, UT, VT, WA, WV) + Washington DC
  - Recreational (“Adult use”):
    • 11 states (AK, CA, CO, IL, MA, ME, MI, NV, OR, VT, WA) + Washington DC
Medical Cannabis Programs

• Qualifying conditions vary by state

• State Medical Board certifies doctors to “recommend” MMJ (Certificate to Recommend; CTR)

• Physician confirms qualifying condition and signs “recommendation” form for potential benefit from MMJ

• State issues licenses for: cultivators ➔ processors ➔ testing ➔ dispensaries (state pharmacy board oversees)
However…

• Under the CSA (Controlled Substances Act):
  - Cannabis remains Schedule I drug

  - Doctors can’t "prescribe" cannabis; only "recommend"
    • 1st Amendment protects discussion of MMJ pros/cons

  - Interstate travel w/ any amount of cannabis or plant extract (including CBD products w/ THC >0.3%) violates federal law
    • Federal drug trafficking; stiff penalties of prison time and fines

  - Patients and providers participating in state MMJ programs are in “technical” violation of federal law
• 2009: Justice Department sent a memorandum to federal prosecutors:
  - Should be no federal prosecution of MMJ pts + providers if following state law

• 2013: Cole Memorandum sent to US Attorney Generals:
  - Reinforced that Justice Department would not enforce federal prosecution in legal states following their laws

• 1/2018: Cole Memorandum rescinded by AG Jeff Sessions

• 4/2018 on: President Trump reinforced support in protecting MMJ states from federal prosecution if following state laws
We’re really hungry for some science. Can we talk about that?
Endocannabinoid System

• Widely distributed throughout CNS and PNS

• Plays a role in many regulatory physiological processes across all organ systems

• Plays a strong role in pain pathways

• Comprised of cannabinoid receptors and endocannabinoids
• Cannabinoid 1 (CB1) receptors
  - Central > peripheral nerve terminals
  - Most abundant G-protein coupled receptor in brain; also abundant in spine and GI system
  - Modulates many inhibitory/excitatory neurotransmitters

• Cannabinoid 2 (CB2) receptors:
  - Peripheral tissues > central tissues
  - Strong role in immune and hematopoietic systems
• Ligands (Endocannabinoids)
  - Arachidonic acid derivatives
  - Synthesized on-demand
  - Upregulate or downregulate presynaptic neurotransmitter release

• Two primary endocannabinoids:
  - N-arachidonoyl ethanolamine (anandamide; AEA)
    • Primary mediator of endocannabinoid signaling
    • Partial agonist CB1 >> CB2 receptors
    • Partial agonist TRPV1 receptors (capsaicin)
  - 2-arachidonoyl glycerol (2-AG)
    • Full agonist CB1/CB2
Fascinating, but tell me more about this "Cannabis" plant…
PHYTOCANNABINOIDS

- Cannabis contains:
  - > 100 **phytocannabinoids**
  - ≈ 200 **terpenes**
  - > 540 distinct compounds in 18 chemical classes
    - Flavonoids, terpenes, phenols, amino acids, vitamins, proteins, steroids, nitrogenous compounds, enzymes, glycoproteins, simple alcohols, hydrocarbons, ketones, aldehydes, fatty acids, simple esters and lactones, pigments, and others
THC (9-tetrahydrocannabinol)

- Causes cannabis psychoactive qualities (“high”)

- Analgesic / anti-inflammatory effects
  - 20x more anti-inflammatory than ASA
  - 2x as anti-inflammatory as hydrocortisone

- Potent anti-emetic

- Primary MOA
  - Partial agonist CB1 > CB2 receptors
  - Wide range of other receptor involvement
• THC serum clearance rates
  - THC $\frac{1}{2}$-life: 4 hrs
  - Active 11-OH-THC metabolite $t_{1/2}$ 36 hrs
  - Inactive THC-COOH metabolite $t_{1/2}$ 55 hrs

• THC metabolized by CYP 3A4, 2C9, 2C19

• 2 Prescription forms of synthetic THC
  - Dronabinol: Schedule III
    • FDA approved: N/V w/ chemo, AIDS-associated anorexia/weight loss
  - Nabilone: Schedule II
    • FDA approved: N/V w/ chemo
THC Detection

• **Blood:**
  - Few hours to 1-2 days after single use
  - Heavy users (multiple times/day), up to a week

• **Saliva:**
  - Appears in 1 hour, detectable 1-2 days

• **Urine:**
  - 5-12 days after one time use
  - 11-18 days when used 2-4 days/week
  - 33-48 days when used 5-6 days/week
  - Around 50-65 days if used daily (stored in adipose tissue)

• **Hair:**
  - 90 days, some hair follicle tests can go back years
CBD (Cannabidiol)

• Non-intoxicating (no “high”); no dependence/withdrawal

• Non-sedating
  - Some CBD studies contained sedating components; trace THC, minor cannabinoids, terpenes (ie. myrcene, attributed to “couch lock”).

• 11/2017 World Health Organization (WHO)
  - “In humans, CBD exhibits no evidence for abuse or dependence potential, and there is no evidence of public health related problems associated with the use of pure CBD”

• 1/2018 World Anti-Doping Agency (WADA) removed CBD from prohibited list, no longer banning use by athletes
• Powerful analgesic and anti-inflammatory effects
  - Anti-inflammatory effect several hundred x more than ASA

• Minimal affinity for CB1 or CB2 receptors
  - (-) allosteric modulator (noncompetitive CB1 antagonist)
  - Neutralizes (-) THC side effects

• >65 molecular receptor targets and >80 MOA identified

• ½-life: 2–5 days chronic oral use, 1.4-10.9 h oromucosal spray, 24 h IV, 31 h smoking
Epidiolex

• Purified cannabis derived CBD; 100 mg/ml
  - FDA approved 6/2018 for LGS/Dravet syndrome ages ≥ 2
  - Schedule V
  - 2.5 mg/kg bid (5 mg/kg/day) -10 mg/kg bid (20 mg/kg/day)

• Dose-related transaminase elevations:
  - Overall 13% (CBD) vs. 1% (placebo)
    • Majority of ALT elevation:
      • High 20/mg/kg/day dose
      • In combo w/ valproate > clobazam
        • Only 3% elevated when not combined
Epidiolex

- Most common adverse effects in ≥10%:
  - Somnolence, decreased appetite, diarrhea, fatigue, malaise, asthenia, rash, insomnia

- At 10 mg/kg/day dose:
  - Purity ≈ 98% CBD
  - **BUT** contains <0.15% THC, traces other cannabinoids, terpenes
    - Likely influence side effects > CBD
Epidiolex

- Metabolism: Liver and gut
  - CYP3A4, CYP2C19 (enzyme inhibitor)

- May increase levels of certain meds; **warfarin**, macrolides, Ca channel blockers, benzos, cyclosporine, antihistamines, **antidepressants**, **antipsychotics**, antiretrovirals, Clobazam, some statins, others
So is CBD safe?

• We now have rigorous CBD safety data from Epidiolex BUT…

• CBD dosing w/ Epidiolex significantly higher than available OTC strengths, not completely pure CBD

• Currently no clear dosing threshold to interact w/ P450
  - Likely much higher doses needed than typical OTC strengths

    - Sativex studies (whole plant CBD rich SL spray) found no interactions with CYP enzymes with 40 mg CBD
So is CBD legal?
• Agriculture Improvement Act (Farm Bill): 12/2018
  - Legalized agricultural growth and use of hemp (cannabis strains containing ≤ 0.3% THC) and hemp derivatives (CBD); removed from CSA

• 5/2019: TSA allowed travel with CBD products with ≤ 0.3% THC, or FDA-approved products

• Cannabis strains and CBD oils with > 0.3% THC still considered marijuana
  - Illegal federally
  - Require medical marijuana card for use
  - Illegal to cross state lines
OTC CBD Products

• Full spectrum or “whole plant”:
  - Most popular
  - Most likely to provide “entourage effects”
  - Contain everything the cannabis plant contains
  - CBD, trace THC (should be ≤0.3% per Federal law) terpenes, flavonoids

• Broad spectrum:
  - Full Spectrum without trace THC

• CBD Isolate:
  - CBD isolated from trace THC and all plant contents
• The problem: Currently no regulations of quality control and dosing standardization

• The 2018 Farm Bill preserves FDA’s authority to regulate products containing cannabis or cannabis-derived compounds

- FDA regulations pending (and needed)… stay tuned
- 84 CBD products analyzed from 31 companies
- 40 oils, 20 tinctures, 24 vaporization liquids

CBD Content
- 43% had > advertised CBD
- 26% had < advertised CBD
- 31% were accurate (≈70% inaccurately labeled!!)

Frequency of mislabeling
- Vaporization liquid: 88% (12% accurate)
- Tinctures: 75% (25% accurate)
- Oil: 55% (45% accurate)
- **THC detected** (up to 6.43 mg/mL) in 21.4% (should be <0.3%)
13 CBD products tested across Los Angeles and NJ

- 5 had no traceable CBD
- Only 1 had advertised amount of CBD
- 2 close to advertised CBD
- 4 had significantly less than advertised
- 1 had more than advertised
- 2 had high THC (3 mg), when supposed to be 0
- 1 CBD gel caps product contaminated with deadly strain of *E. Coli* (shiga toxin)
- 2 had potentially dangerous levels of ethanol
Terpenes (Terpenoids)

- Found in cannabis, herbs, plants, essential oils, fruits, vegetables

- Differing flavors, aromas between cannabis strains, plants, herbs
  - Limonene (citrus), Pinene (pine, conifer), Linalool (lavender)

- Many medicinal benefits, including anti-inflammatory, analgesic

- Work synergistically w/ cannabinoids for therapeutic effects, strain characteristics:
  - “Cannabis entourage effects”
Cannabis Strains: Historical (Outdated) Cultivar Classification

- **Cannabis sativa**
  - Uplifting, energetic, euphoric, spacey, better for day use
  - High THC, Low CBD

- **Cannabis indica**
  - Calming, relaxing, sedative, better for night use
  - More balanced mix, moderate THC, higher CBD

- **Hemp/Ruderalis strains**
  - Low/no THC, high CBD
  - CBD oils, industrial uses, no psychoactivity

*HOWEVER: Biochemical studies show strain names are often inaccurate in distinguishing CBD/THC content*
Cannabis Chemovars (Chemotypes): Newer classification

- More scientific classification
- Allows medicinal users find a chemical profile better matching pharmacological needs
- Most strains used today:
  - Hybrid strains genetically cross-bred for standardized CBD, THC, terpenes, minor cannabinoid content
- Type I-III
Type I – THC-predominant

- High THC (>0.3%); generally >10-20%
- Low CBD (<0.5%); generally < 2%
- Intoxicating, associated with recreational > medical use
- Moderately-heavily psychedelic with changes in perception and sensory awareness
- Can produce significant physiological changes in HR + BP
- Can intensify relief from symptoms like nausea or pain
Type II – Balanced THC and CBD

• High THC (>0.3%); generally 3%-10%
• High CBD (>0.5%); generally 1%- 14%
• Intoxicating to a much lesser degree than Type I
• Mildly-moderately psychedelic w/ possible changes in perception and sensory awareness
• Can be more effective at treating symptoms with less neg side effects
Type III – CBD-predominant

- Low THC (<0.3%); generally 0%-1%
- High CBD (>0.5%); generally 5%-20% +
- Low to no intoxication
- Little to no cognitive impairment; but possible mild effects in sensitive users, depending on THC %
- High CBD strains: 1:1-1:5 THC:CBD; Pure CBD strains: >1:10–1:50 THC:CBD
Evidence for Cannabis and Cannabinoids in Chronic Pain

My back really hurts doc. Can I get some of that “medical marijuana”?
• Neurobiology of cannabinoids and pain
  - CB1 receptors dense in CNS + PNS pain pathways
    • Periaqueductal gray (PAG) matter
    • Rostral ventrolateral medulla (RVM)
    • Dorsal primary afferent and substantia gelatinosa spinal cord regions, spinal interneurons
    • Peripheral nerves/nociceptors
    • Other brain regions including amygdala, cerebral cortex, hippocampus, substantia nigra pars reticulata, basal ganglia, globus pallidus (internal and external segments), cerebellar molecular layer

- CB2 receptor mediates inflammation and pain
• 348 patients in MI MMJ certification clinic
  - Recertification (current users) vs. 1st time applicants

• 87% (303/348) seeking MMJ for chronic pain relief
  - Consistent w/ most registries

• Recertification (153) vs. 1st time applicants (195)
  - Lower current pain levels (p=.04)
  - Higher mental health (p<.05)
  - Higher physical functioning (p<.01)

• Systematic review of 18 RCTs of cannabis/cannabinoids for chronic non-cancer pain
  - 83% (15/18) statistically significant + analgesic effects


• 11 additional RCTs of cannabis/cannabinoids in chronic non-cancer pain since prior review
  - 64% (7/11) statistically significant + analgesic effects

• Systematic review of 38 RCTs of cannabis/cannabinoids in chronic pain
  - 71% (27/38) statistically significant + analgesic effects


• Systematic review and meta-analysis of 79 trials of cannabis/cannabinoids for medicinal use (28 chronic pain)
  - Conclusion: Moderate-quality evidence to support use for chronic pain and spasticity

• Reviewed
  - 6 trials involving 325 patients w/ chronic pain
  - 6 trials involving 396 patients w/ neuropathic pain
  - 12 trials involving 1600 patients w/ MS

• Conclusion
  - Marijuana use for chronic pain, neuropathic pain, and spasticity due to MS is supported by high-quality evidence

• Number needed to treat (NNT) for pain benefit with cannabinoids estimated \( \approx 3.4 \)

• 2014: Canadian Pain Society revised consensus statement recommending cannabinoids as 3\(^{rd}\) level therapy for chronic neuropathic pain

• 2017: National Academies of Sciences, Engineering, and Medicine published:
  - “The use of cannabis for the treatment of pain is supported by well-controlled clinical trials, and there is substantial evidence that cannabis is an effective treatment for chronic pain in adults”.
Evidence for Cannabis and Cannabinoids in Headache Disorders
- CSF of chronic migraineurs compared w/ normal controls:
  - ↓AEA, ↑CGRP, ↑NO levels
  - Endocannabinoid deficiency in chronic migraine, fibro, IBS??

- AEA inhibits dural blood vessel dilatation from migraine triggers:
  - Neurogenic, CGRP, electrical stimulation, capsaicin, NO
  - Reversed by cannabinoid antagonists

- AEA modulates CGRP release via TRPV1 pathways

- CB1 activity suppressed cortical spreading depression
- CB1 activation in brainstem (VPAG, RVM, DRN):
  
  - Inhibits nociceptive trigeminovascular responses
  
  - Modulated via serotonergic system
    - **5HT1B/1D receptor** plays a role (triptan receptor)
    - 5HT1B/1D antagonists inhibit CB1 responses
  
  - Modulates DRN serotonergic firing
  
  - \(\downarrow\) basal trigeminal neuronal tone in TNC
Case reports, case series, surveys, 1 retrospective review, 2 prospective trials containing a control group

- Chronic headaches (4)
- Migraine including chronic migraine (18)
- Medication overuse headache (1)
- Cluster headache (4)
- Idiopathic intracranial hypertension (IIH) (1)
- Multiple sclerosis (MS) associated trigeminal neuralgia (1)

- Prophylaxis in chronic migraine or chronic cluster
- 200 mg 0.4% THC / 9% CBD in a 200 mL 50% fat emulsion PO

- Chronic migraine (n = 79) prophylaxis
  - Amitriptyline 25 mg/day vs. THC/CBD 200 mg/day x 3 months
  - 40.4% improvement w/ THC/CBD 200 mg vs. 40.1% w/ Amitrip

- Chronic cluster (n = 48) prophylaxis
  - Verapamil 480 mg/day vs. THC/CBD 200 mg/day x 1 month
  - THC/CBD 200 mg prophylaxis minimal to no benefit
• For acute pain attacks, additional acute dosing of THC/CBD 200 mg allowed in both groups

- Chronic migraine
  • Decreased pain intensity by 43.5%

- Chronic cluster
  • Same acute benefit as migraine, but ONLY w/ hx childhood migraine

- Retrospective study of cannabis use in migraine
- Chart review of 121 adults from 2 MMJ specialty clinics in CO
- Physician recommendation for acute and/or preventive treatment with MMJ
- Primary outcome: mean # of migraines/month at initial vs. follow-up visits
Mean migraines/month ↓ from 10.4 to 4.6 (P < .0001)
- 103 (85.1%) had ↓ frequency of migraines/month
- 15 (12.4%) had same migraines/month
- 3 (2.5%) had ↑ migraines/month

- Electronic survey to 16,675 Tilray medicinal cannabis patients
- 2,032 patients analyzed; Male: 1271 (62.6%), Female: 758 (37.3%)
- Pain syndromes accounted for 42.4% (n = 861) overall
- HA: primary symptom treated w/ cannabis in 505 (25%)
  - ID Migraine questionnaire: 445/505 (88%) of HA patients + (high probability of migraine)
  - Hybrid strains most preferred
  - Most preferred strain: High THC/THCA, low CBD/CBDA w/ β-caryophyllene and β-myrcene as predominant terpenes
• 272 (54%) of 505 HA pts substituted prescriptions w/ cannabis
  - 118 (43.4%) opiates/opioids (73% substituted in chronic pain pts)
  - 106 (39%) antidepressant/anti-anxiety
  - 57 (21%) NSAIDs
  - 22 (8.1%) triptans
  - 21 (7.7%) antiseizure
  - 19 (7%) muscle relaxers
  - 1 (0.4%) ergots

• Quantity used: 11.4 g/week, 1.7 g/day, 0.66 g/treatment

• Frequency used: 6.4 days/week, 3.9 times/day
Cannabis As A Potential Opioid Alternative?
• CB1 receptors
  - 10 x more concentrated than mu-opioid receptors in brain
  - Co-localize w/ opioid receptors in many pain regions
  - Sparsely populate CP centers in brainstem
    • Lack of respiratory depression w/ cannabinoids

• Cannabinoids enhance release of endogenous opioids

• Abundant literature describing “opioid-sparing effect” of cannabinoids
• Cannabinoids combined w/ opiates show:
  - ↑ pain relief
  - ↓ opiate use and dose requirements
  - ↓ tolerance to opiates
  - ↓ withdrawal from opiates
  - Rekindling of opiate analgesia after prior dosage becomes ineffective

• Growing literature suggesting MMJ as tool in opioid detoxification and weaning

- Assessed 13 states w/ MMJ 1999-2010
  - 24.8% ↓ mean annual opioid overdose mortality vs. states without MMJ (p = .003)
  - ↓ in opioid overdose mortality each year after law implementation strengthened over time
- 33.7% ↓ by year 5

- Large meta-analysis: 17 of 19 studies w/ good evidence of synergistic effects from opioid + cannabinoid

- Median effective dose (ED50) of morphine w/ THC: 3.6 times \( \downarrow \) than ED50 of morphine alone

- ED50 for codeine administered w/ THC: 9.5 times \( \downarrow \) than ED50 of codeine alone

- Conclusion: Robust evidence of opioid-sparing effect of cannabinoids

- Chronic pain pts on daily morphine or oxycodone
  - Added vaporized cannabis dosing
- Pain significantly ↓ (average 27%) after combining
- No effect on plasma opioid levels


• Chronic pain pts using MMJ + opioids:
  - ↓ opioid use
  - Improved pain and functional outcomes
  - Improvement in quality of life
  - Better side profiles
Dosing and Clinical Use
• Smoked
  - **Fastest onset**: 5-10 mins
  - **Shortest duration**: 2-4 hrs

• Vaporized
  - Pharmacokinetics same as smoking
  - Heated to where cannabinoid vapors form, below point of combustion where irritating respiratory smoke/toxins produced
• Oral
  - **Slowest onset:** 60-180 mins
  - **Longest duration:** 6-8 hrs
  - Foods such as “gummies”, brownies, oils, butters, cookies, teas

• Oromucosal, Tinctures, Sublingual
  - **Onset:** 15-45 mins
  - **Duration:** 6-8 hrs

• Oromucosal: Nabiximols (Sativex®)
  - Standardized tincture of cannabis:
    • THC (2.7 mg), CBD (2.5 mg), cannabinoids, terpenes
  - Approved in 29 countries for variable chronic pain syndromes, MS spasticity
• **Topical (ointments, creams, lotions)**
  - Variable onset and duration (can last 6-8 hrs)
  - No psychoactive effects
  - Variable range of potency
  - Only local effects, very limited data or evidence

• **Rectal**
  - Dose and vehicle dependent
  - High bioavailability of THC (52-61%)

• **Intramuscular and intravenous**
  - Limited studies
• Inhaled / orally ingested cannabis averages
  - **1-3 g/day**, 10-20 g/week*

  - Use of high dose THC strains > 5 g/d suggest possible tolerance or misuse, and usually unjustified

  - **2-4 times per day**


**THC Dosing**

- 1-2.5 mg: good starting dose
  - Start qhs, increase 1-2.5 mg every few days qhs or daytime until benefit or side effects

- 5 mg: many experience benefit without excess side-effects

- 10 mg: produces side effects for most

- 15 mg or more: may cause psychedelic side effects

- 0.5-1 g cannabis cigarette $\approx$ 0.5-5 mg THC (can be much higher)

- Total THC dose should be $< 20\text{-}30 \text{ mg/day}$ to limit adverse effects and tolerance

- Use preferably w/ CBD
CBD Dosing

- Undefined, variable between products
- Often 5-60 mg qd-tid, titrated to effect
- High doses likely needed for pain and inflammation
- No established dosing guidelines or max doses established
  - Doses of 400-600 mg/day showed benefit in anxiety
  - Doses of 600-800 mg/day showed benefit in psychosis
  - Doses up to 2500 mg/day (25-50 mg/kg) have been used in epilepsy
General Use Recommendations

• Start low, go slow, stay low
  - Promotes tolerance to THC psychoactive effects

• Use low dose THC

• Use CBD + THC together
  - CBD attenuates (-) THC side effects

• 15-20% CBD w/ <1% THC good start

• CBD predominant preparations working/daytime

• THC predominant preparations after work/qhs
General Use Recommendations

• Long acting oral formulations for chronic conditions and symptoms

• Vaporization add-on prn episodic symptom exacerbations

• Avoid driving for:
  - 4 hrs after inhaled cannabis
  - 6 hrs after ingested cannabis
  - 8 hrs if euphoria experienced

ADVERSE EFFECTS
• Side effects influenced by:
  - Dose
  - Method of administration
  - Patient tolerance
  - Strain of cannabis and ratios of THC, CBD, cannabinoids, terpenes
  - Production quality control (toxins, fungus, bacteria, heavy metals, etc.)

• Many studies inconclusive or contradictory
Most Common (most from THC)

- Sedation / Lethargy
- Dizziness
- Dry mouth
- Increased appetite
- Impaired concentration
- Slowed reaction time
- Impaired short term memory
- Altered perception of time
- Heightened sensory awareness
- Incoordination/ataxia
- Anxiety with high doses
- Short term memory problems
- Euphoria
- Dysphoria
- Paranoid thinking
- Dissociation
- Bronchitis/coughing w/ smoking
Dysphoria/Paranoia:
https://youtu.be/V1kTZRcKZ6Y

Euphoria:
https://youtu.be/OQSNhk5ICTI
• **Overdose**
  - No documented deaths from overdose or use
  - Typically from high THC content and oral dosing
  - **Signs:**
    • Tachycardia
    • Confusion
    • Panic attack
    • Extreme paranoia
    • Hallucinations
Cardiovascular

- Effects (primarily THC)
  - Tachycardia / arrhythmia
  - Increased cardiac output/work load
    - Demand ischemia
- Impaired vasomotor reflex
  - Orthostatic hypotension
  - Supine hypertension
- Increased carboxy-hemoglobin
  - Increased myocardial O2 demand
- Increased catecholamine levels
Cardiovascular

• Literature review: 147 cases cannabis associated MI
  • 93% male, mean age 42 (17-53)
  • 38% within 24 hours of cannabis use
  • 70% also tobacco smokers
  • 6-38% had CV risk factors

Cardiovascular

- **Case-crossover study** (pts serve as own control) of 3,882 pts hospitalized for MI

- **4.8 fold increase in MI risk within 1 hr** of smoking cannabis. No increased risk after 1 hr.
  - 124 (3.2%) smoked cannabis in preceding 1 yr
  - Only 9 smoked in hour before

Cardiovascular

- **Prospective cohort 65,171 pts** (15-49 yrs)

- Relative risk of MI, stroke, or all CV disease **not** increased in cannabis users

Postulated mechanisms of cannabis associated stroke:

- Altered cerebral autoregulation
  - Studies have shown both ↓ and ↑ cerebral blood flow
- Reversible vasospasms/vasculitis
- Secondary from cardiac effects (THC)
Cerebrovascular

- Literature review: 71 cases of **ischemic stroke** in cannabis users
  - **86% male, mean age 36** (15-63)
  - **76.5%** occurred **during use or 30 mins after**
  - 23.5% 24 hours after use
  - **34%** also used **other substances**
  - 53.5% posterior circulation
  - **43%** presented w/ **RCVS**

Cerebrovascular

• Reviewed **all reported cases** of cannabis/cannabinoid neurovascular events 1964 - Nov 2016

• **98 cases** cannabinoid-associated stroke reported
  - **85** in cannabis use (**73 ischemic**, 4 TIA, 4 hemorrhagic, 4 unspecified)
    • **RCVS 30%** (n=26)
  - **13** in synthetic cannabinoids (8 ischemic, 5 hemorrhagic)

Wolff V, Jouanjus E. Strokes are possible complications of cannabinoids use. Epilepsy Behav. 2017 May;70(Pt B):355-363.
Cerebrovascular

- Of 85 cannabis associated strokes
  - M:F : 3.7:1, Mean age 33 (15-63)

- Cannabis used w/ tobacco 69%, alcohol 29%, illicit drug or vasoactive substances 12% cases

- Chronic cannabis smokers 86% cases

- Anterior 53% > Posterior 37% > Both 4% circulation

- 32% (n=23) of ischemic stroke had RCVS
  - Posterior 48% > Anterior 30% > Both 13%
  - Predominantly young men
Peripheral Vascular

• Cannabis arteritis (CA), <100 cases

• Looks like thromboangiitis obliterans (Buerger’s disease)
  - Inflammatory / occlusive disease small + medium vessels
  - Predominantly young men, tobacco smokers
  - Lower limbs primarily involved

• Co-abuse of cannabis and tobacco in almost all cases
  - Common contaminant arsenic hypothesized
Cannabis Hyperemesis Syndrome (CHS)

- **Clinical**
  - Cyclical nausea/vomiting, diffuse abdominal pain, frequent hot showers
    - Episodes 24-48 hrs, up to 7-10 days
    - Recur with re-exposure

- High-dose, high-THC regular cannabis use

- Can be confused with CVS. Differentiated by:
  - Chronic cannabis use
  - Frequent hot bathing produces temporary relief
CHS

• Etiology (not fully understood)
  - Dysregulation of endogenous cannabinoid system by downregulation of CB1 receptors

- In GI tract may slow gastric motility, causing hyperemesis

- Genetic differences in cytochrome P450 system

- TRPV1 interacts with endocannabinoid system
  • AEA partial agonist at TRPV1
  • Capsaicin receptor
  • Activated by heat (hot showers/bath)
CHS

• Treatment
  - **Cannabis cessation!**
  - Supportive therapy w/ fluid resuscitation
  - Capsaicin 0.075% topical
    • Abdomen, back of arms, areas that hot water gives symptom relief
  - Antipsychotics: Haloperidol, Olanzapine
  - Conventional antiemetics, antihistamines, serotonin antagonists, benzos limited use
  - Avoid opiates
Addiction and Dependence

• Comparative addiction rates
  - Tobacco 32%
  - Heroin 23%
  - Cocaine 17%
  - Alcohol 15%
  - Cannabis 9% (17% when used in adolescence, 25-50% adolescents using daily)

• Tolerance develops faster with high potency (high THC) cannabinoids
- **DSM-5** recognizes 5 cannabis-associated disorders:
  - Cannabis Use Disorder
  - Cannabis Intoxication
  - Cannabis Withdrawal
  - Other Cannabis-Induced Disorders
    - Cannabis Intoxication Delirium
    - Cannabis Induced Psychotic Disorder
    - Cannabis Induced Anxiety Disorder
    - Cannabis Induced Sleep Disorder
  - Unspecified Cannabis-Related Disorder

- **Cannabis Use Disorder**
  - 3-4% meet criteria
  - Mild, mod, severe criteria (work, home, social, tolerance, withdrawal, etc.)
  - Prevalence decreases w/ age
  - **Highest**: ages 18-29 (4.4%); **Lowest**: ages 65 and older (0.01%)
Cannabis Withdrawal

- Associated with heavy chronic use, daily or near daily use for > a few months

- Starts in 24 hrs, peak day 3, last 1-2 weeks

- 3+ of the following within 1 week of cessation:
  - Irritability, anger or aggression
  - Nervousness or anxiety
  - Sleep difficulty (insomnia, nightmares)
  - Decreased appetite or weight loss
  - Restlessness
  - Depressed mood
  - At least one: abdominal pain, shakiness/tremors, sweating, fever, chills, headache
Neuropsychological

- Use during adolescence when brain is still pruning, and organizing itself have shown detrimental effects

- Some evidence of decreased IQ w/ heavy use in teens to adulthood (primarily before age 18)


- **Rigorous review** of relevant scientific research published since 1999 for **100 research conclusions**

- **>10,000 studies**, highest preference to **systematic reviews from 2011-2016** and **“high quality primary research”**
CONCLUSIONS FOR: THERAPEUTIC EFFECTS

• There is **conclusive or substantial evidence** that cannabis or cannabinoids are effective:

  - For the treatment for **chronic pain** in adults
  
  - Anti-emetics in the treatment of chemotherapy-induced nausea and vomiting
  
  - For improving patient-reported MS spasticity symptoms
CONCLUSIONS FOR: CARDIOMETABOLIC RISK

• Limited evidence of:
  - Triggering of acute MI
  - Ischemic stroke or subarachnoid hemorrhage

• No evidence to support or refute chronic cannabis use and:
  - Increased risk of acute MI
CONCLUSIONS FOR: PSYCHOSOCIAL

• Moderate evidence:
  - Impairment in the cognitive domains of learning, short-term memory, and attention with acute cannabis use

• Limited evidence for sustained abstinence and:
  - Persistent impairments in cognitive domains of learning, memory, and attention
CONCLUSIONS FOR: MENTAL HEALTH

• Substantial evidence:
  - Development of schizophrenia or other psychoses (in those at risk); highest risk among the most frequent users

• Moderate evidence for increased:
  - Symptoms of mania and hypomania in bipolar
  - Risk of depressive disorders
  - Incidence of suicidal ideation and suicide attempts (higher incidence in heavier users)
  - Incidence of suicide completion
  - Incidence of social anxiety disorder
CONCLUSIONS FOR: INJURY AND DEATH

- **Substantial evidence:**
  - Increased risk of MVAs
    - Simulated driving/flying studies w/ cannabis: Impaired attention, time/distance estimations

- **Moderate evidence:**
  - Increased risk of overdose, especially among pediatric populations (edibles)

- **No** or insufficient evidence:
  - All-cause mortality
  - Death due to cannabis overdose
CONCLUSIONS FOR: PRENATAL, PERINATAL, AND NEONATAL EXPOSURE

• Substantial evidence between maternal cannabis smoking and lower birth weight

• Lactation
  - Amount reaching infant very low
  - Unknown effects
  - Recommended to not use in either pregnancy or breastfeeding
Conclusions

• Cannabis for treatment of chronic pain in adults is supported by well-controlled clinical trials w/ substantial evidence. This may infer potential benefit in headache disorders, but studies are lacking.

• Many cannabinoids and terpenes have strong anti-inflammatory and analgesic properties.

• Knowledge of adverse effects is important in patient selection.

• Data are needed to determine most effective ratios of cannabinoids, terpenes, and other compounds (entourage effects) for chronic pain, headache, and other medical disorders.


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