Cannabinoids in Harm Reduction: Physiology and Clinical Applications

NAADAC Annual Conference 2016

Dustin Sulak, D.O.
Learning Objectives

1. Describe the basic function of endocannabinoid physiology in the CNS and its involvement in the regulation of addiction.

2. Summarize the preclinical and clinical research on the use of exogenous cannabinoids in the treatment of addiction.

1. Feel comfortable discussing cannabinoid therapeutics with patients and understand the potential uses of cannabinoids in the clinical setting.
• 3 locations:
  – Falmouth, Maine
  – Manchester, Maine
  – Burlington, Massachusetts
• 18,000+ total patients
• 16 medical providers
• Medical cannabis consultations, integrative family medicine, osteopathy, functional medicine, mind-body medicine, and more.
Cannabis analytics:
- High performance liquid chromatography (HPLC) for cannabinoids
- Gas chromatography (GC) for terpenes and residual solvents
Medical cannabis works best with education.

Through our program, you will learn:

- How to find your optimal cannabis dosage
- How to use cannabis therapeutically, without the high
- How to become more sensitive to cannabis
- How to control unwanted side effects

Get started
Overview

1. Neurophysiology of endocannabinoid signaling related to addiction
2. Cannabinoid therapeutics in addiction and harm reduction
3. Clinical considerations in cannabinoid medicine: dosing and delivery
Part 1: **ENDOCANNABINOID PHYSIOLOGY**
## Health Conditions Influenced By Cannabinoids

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<th>ADD/ADHD</th>
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<td>Crohn's</td>
<td>Nausea</td>
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Why does one herb help so many different conditions?

The Endocannabinoid System
Endocannabinoid synthesis is an adaptive response to cellular stress, aimed at re-establishing cellular homeostasis.

Pubmed search results for “endocannabinoid”
1993: 10 citations
2016: 7,296 citations
“...modulating endocannabinoid system activity may have therapeutic potential in almost all diseases affecting humans, including obesity/metabolic syndrome; diabetes and diabetic complications; pain; neurodegenerative, inflammatory, cardiovascular, liver, gastrointestinal and skin diseases; psychiatric disorders; cachexia; cancer; and chemotherapy-induced nausea and vomiting, amongst many others.”

Cannabinoid Receptors
The Cannabinoid Receptors: CB1 and CB2

secondary structure

tertiary structure
Cannabinoid Receptors

CB1 located in:
- CNS
- Testes, uterus
- Adipose tissue
- Connective tissue
- Endocrine glands
- Exocrine glands
- Leukocytes
- Spleen
- Heart
- GI tract
- Liver

CB2 located in:
- Monocytes
- Macrophages
- B-cells
- T-cells
- Liver
- Spleen
- Tonsils
- CNS
- Enteric nervous system

(McPartland, 2008)
CB Receptors Evolved 600 Million Years Ago

human  monkey  rat  mouse  finch  newt  Fugu fish  sea squirt

Drosophila, Apis

McPartland, 2006
Cannabinoid Receptors Can Activate Different G Protein Subtypes

- $G_0$ – ion channels
- $G_i$ – inhibits adenylate cyclase
- $G_s$ – stimulates adenylate cyclase

- Depends on which agonist activates the receptor: “agonist trafficking”
- An assortment of keys opens the same lock, but the door opens into different rooms

(Glass, 1999)
Agonist Trafficking

THC inhibits Ca\(^{++}\) channels

Go

HU-210

WIN55,212

anandamide

Gi inhibits adenylate cyclase

Gs stimulates adenylate cyclase

(Glass, 1999)
CB1 Receptor Distribution in Human Brain

(Terry et al. 2010)
CB2 Receptor Distribution

(Ahmad, 2013)
Endogenous and Exogenous Cannabinoids
Endogenous Cannabinoid Ligands: The Endocannabinoids

Anandamide (AEA)
Devane, Mechoulam et al., 1992

2-arachidonoylglycerol (2-AG)
Mechoulam et al., 1995
Sugiura et al., 1995
Endogenous Cannabinoid Ligands:
The Endocannabinoids

Anandamide (AEA) and 2-arachidonoylglycerol (2-AG):
- Retrograde messengers in nervous system.
- Autocrine or paracrine mediators elsewhere.
- Synthesized “on demand” from cell membrane precursors (arachidonic acid derivatives) and immediately released.
- Degraded by enzymatic hydrolysis
  - AEA -> fatty acid amide hydrolase (FAAH)
  - 2-AG -> monoacylglycerol lipase (MAGL)

(McPArtland, 2008)
Numerous Other Endogenous Cannabinoids

7, 10, 13, 16-docosotetraenylethanolamide ("anandamide" 22:4, n-6)

Homo-7,10,13,16-docosotetraenylethanolamide (62,112,142-docosatrienylethanolamide, "anandamide" 20:3, n-6)

Vidoramine (O-arachidonylethanolamine)

Noladin ether (2-arachidonoylglyceryl ether)

NADA (N-arachidonoyldopamine)

(Kogan 2006)
Other Endocannabinoid Targets

- **GPR55** (Ryberg, 2007) (Staton, 2008)
- **TRPV1** “capsaicin receptor” (Ross, 2003)
- **PPARs**: Peroxisome proliferator-activated receptors (O’sullivan, 2007)
- **Voltage-gated ion channels**
  - Ca2+, Na+, and various types of K+ channels
- **Ligand-gated ion channels**
  - 5-HT3 and nicotinic ACh receptors. (Oz, 2006)
Phytocannabinoids: Δ9-THC

- THC mimics AEA and 2-AG by acting as an partial agonist at CB1 and CB2.
- Antagonism more likely at CB2, and in CB1 when ECS is down-regulated. (Pertwee, 2008)

- THC produces rewarding effects in
  - humans (Hart et al., 2005),
  - non-human primates (Tanda et al., 2000)
  - rodents (Braida et al., 2004)
Synthetic Cannabinoids, Some With Ultrapotency

Δ⁹-THC
Roxane Labs
Kᵢ CB1 = 41 nM

Nabilone
Eli Lilly
Kᵢ = x1.8 THC

Levonantradol
Pfizer
Kᵢ = x38 THC

CP 55,940
Pfizer
Kᵢ = x44 THC

HU-210
Pharmos
Kᵢ = x600 THC

WIN 55,212-2
Sterling Winthrop
Kᵢ = x1.7 THC
THC: Low and acute doses -> ECS
Upregulation

• THC increases the production of endocannabinoids in brain cells. (Burstein, 1995)
• THC upregulated CB1 receptors in mouse spinal cords. (Cichewicz, 2001)
• Acute dose of THC increased cannabinoid receptor affinity in rats. (Oviedo, 1993)
• Sub-therapeutic doses of THC enhance the pain relief imparted by endocannabinoids in rats. (Suplita 2008)
• After cannabis use, CB1 & CB2 receptor mRNA are increased in peripheral blood cells (Nong et al., 2002; Rotter et al., 2013)
CB Receptor Downregulation

1. Persistent agonism
2. Phosphorylation by GRK or PKC
3. Binding by β-arrestin
4. Receptor pulled into a clathrin-coated pit
5. Endosome internalization

(Hsieh, 1999)
Endocannabinoid Basics: Summary

- CB1 and CB2 receptors found throughout the body
- Anandamide (AEA) and 2-AG synthesized on-demand for homeostatic functions
- Complex effects of cannabinoids due to agonist trafficking and overlap with other systems
CB1 Receptor Distribution in CNS

- Most common G protein coupled receptor in the brain
- Highest densities:
  - hippocampus
  - cerebral cortex
  - cerebellum
  - amygdaloid nucleus
  - basal ganglia
- Accounts for effects:
  - short-term memory
  - cognition
  - mood and emotion
  - motor function
  - nociception.
- Virtually absent in brainstem cardiorespiratory centers – no lethal overdose

Glass, 1997
Burns, 2007
Cannabinoid Activity in the Nervous System: Retrograde Signaling
Depolarization-Induced Suppression of Excitation

• Action potential from depolarized neuron arrives at axon terminal and opens voltage-gated calcium channels.

• Ca^{2+} influx releases glutamate vesicles, glutamate diffuses across synaptic cleft to activate receptors in postsynaptic cell.

(Wilson & Nicholl, 2002)
• **Strong stimulus** of presynaptic cell increases glutamate release, which upregulates other glutamate receptors in the post-synaptic cell.

• Upregulated glutamate receptors open Ca\(^{2+}\) channels in the post-synaptic cell.

(Wilson & Nicholl, 2002)
- $\mathrm{Ca}^{2+}$ influx into post-synaptic cell stimulates the synthesis and release of 2-AG.

- 2-AG diffuses retrograde to presynaptic CB1, which closes presynaptic $\mathrm{Ca}^{2+}$ channels and stops vesicle release.

(Wilson & Nicholl, 2002)
Depolarization-Induced Suppression of Inhibition

- Ca\(^{2+}\) influx into post-synaptic cell stimulates the synthesis and release of 2-AG.

- 2-AG diffuses retrograde to presynaptic CB1, which closes pre-synaptic Ca\(^{2+}\) channels and stops vesicle release.

(Wilson & Nicholl, 2002)
Neural Protection

- AEA and 2-AG are endogenous neuroprotective agents produced by the nervous system upon both chemical and mechanical trauma. (Mechoulam, 2002)
- $\Delta 9$-THC, CBD, AEA, 2-AG, and HU-210 all decrease glutamate excitotoxicity. (Baker, 2003)
  - Reduce seizure activity
  - Limit infarct size post-stroke
- Cannabinoids effective at reducing and preventing perinatal brain injury (reviewed in Fernández-Álvarez et al., 2013)
CANNABINOIDS AS ANTIOXIDANTS AND NEUROPROTECTANTS

Inventors: Aidan J. Hampson, Irvine, CA (US); Julius Axelrod, Rockville, MD (US); Maurizio Grimaldi, Bethesda, MD (US)

Assignee: The United States of America as represented by the Department of Health and Human Services, Washington, DC (US)

Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

Appl. No.: 09/674,028
PCT Filed: Apr. 21, 1999

OTHER PUBLICATIONS
Carlini et al., “Hypnotic and Anti-epileptic Effects of Can-
Glutamate in Drug Addiction

• All drugs of abuse appear to modulate glutamatergic transmission, albeit by different mechanisms.
• Results in long-lasting neuroplastic changes in the brain that may contribute to the perseveration of drug-seeking behavior and drug-associated memories.
• ↓ Glut = ↓ reward, reinforcement, relapse-like behavior
• ↑ Glut = ↑ extinction of drug-seeking behavior

(Reviewed in Gass & Foster Olive, 2008)
Fig. 3.
Sagittal section of the rodent brain showing neuroanatomical interactions between glutamate and mesolimbic dopamine systems. The “reward circuit” is hypothesized to consist of dopamine-synthesizing cell bodies in the VTA that project rostrally to innervate the NAcc, Amyg and FC, as well as other regions such as the portions of the CPU and ventral pallidum (not shown). This mesolimbic reward pathway is robustly innervated by glutamate-containing neurons. Dopamine-containing cell bodies in the VTA receive glutamatergic input from the PPT, LDT, Amyg and FC. The NAcc receives a host of glutamatergic innervation from the FC, Hipp, Thal, and Amyg. The FC receives glutamatergic input from the Hipp, Thal and Amyg. Drawing adapted from the atlas of Franklin and Paxinos [906]. Abbreviations: Amyg, amygdala; CPU, caudate-putamen (dorsal striatum); FC, frontal cortex; Hipp, hippocampus; LDT, laterodorsal tegmentum; NAcc, nucleus accumbens; PPT, pedunculopontine tegmentum; Thal, thalamus; VTA, ventral tegmental area.
Mechanisms By Which Cannabinoids Modulate Neural Plasticity

- Depolarization-induced suppression of excitation (DSE)
- Depolarization-induced suppression of inhibition (DSI)
- Long-term potentiation (LTP)
- Long-term depression (LTD)
- Neurogenesis
  - pCREB: phosphorylated cAMP response element-binding protein
  - BDNF: brain-derived neurotrophic factor

(Fishbein, 2012)
(Lovinger, 2008)
The ECS in Reward and Addiction Behavior

Ubiquitous ECS regulation of

- **Primary rewarding effects of cannabinoids, nicotine, alcohol, and opioids**
  - Mostly via release of endocannabinoids in the VTA
- The common mechanisms underlying drug addiction and relapse to drug-seeking behavior
  - Modulation of motivational effects of drug-related environmental stimuli

Many drugs of abuse, including cannabinoids, opioids, alcohol, and nicotine, can alter levels of endocannabinoids in selected brain regions.

Cannabinoids and Reward

• Phyto-, synthetic and endogenous cannabinoids can produce rewarding effects in humans and laboratory animals. (Fattore et al., 2001; Hart et al., 2005; Justinova et al., 2005; Seely et al., 2012)

• CB1 receptors are present in brain areas involved in reward processes, and their activation produces rewarding effects per se and also increases those of drugs of abuse (Vlachou and Panagis, 2014).
The ECS modulates the ability of drugs and drug-associated cues to reinstate drug-seeking behavior in animal models of relapse (reviewed in Fattore et al., 2007).

CB1 receptor stimulation can elicit relapse to
- Cannabinoid seeking (Spano et al., 2004; Fattore et al., 2010)
- Heroin seeking (De Vries et al., 2003; Fattore et al., 2003, 2005)
- Nicotine seeking (Gamaleddin et al., 2012)

All effects are attenuated or fully prevented by pretreatment with the CB1 antagonist rimonabant.
Alcohol and the ECS

Down-regulation of CB1 function by chronic alcohol intake

• Probably results from the persistent CB1 stimulation by anandamide and 2-AG, the synthesis of which is increased in the limbic forebrain by chronic alcohol treatment.

(Gonzalez et al., 2002).
Alcohol and the ECS

• In humans, alcohol dependence has been associated with a down-regulation of CB1 receptors (Vinod et al., 2010).
• Ethanol dampens the effects of the ECS, except perhaps in areas involved in reward and motivation to self-administer this substance of abuse. (Reviewed in McPartland, 2014)
Nicotine and ECS

- CB1 receptor agonists decrease nicotine somatic withdrawal signs in mice.  
  (Balerio et al., 2004)

- FAAH inhibition blocks nicotine self-administration and prevents nicotine-induced reinstatement in rats. 
  (Scherma et al., 2008; Muldoon et al., 2013)
THC Protective Against Meth

Methamphetamine-induced neurotoxicity in the caudate putamen and prefrontal cortex can be attenuated by pre- and post-treatment with THC (Castelli et al., 2014).
Cannabinoid Deficiency Syndromes?

In human studies, ECS deficiencies have been implicated in:

- Schizophrenia
- Migraine
- Multiple sclerosis
- Huntington’s
- Parkinson’s
- Irritable bowel syndrome
- Anorexia
- Chronic motion sickness
- Fibromyalgia (Dunnett, 2007)
- Menstrual symptoms (Dunnett, 2007)

(reviewed in McPartland, 2014 and Russo, 2004)
Cannabinoid Deficiency Syndromes?

Cannabinoid receptor polymorphisms have been associated with:

- Happiness (Matsunaga, 2014)
- Schizophrenia Subtypes (Ujike, 2001)
- Body Mass Index (Gazzerro, 2006)
- Central Obesity (Jaeger, 2008)
- ADHD and PTSD (Lu, 2008)
ECS Polymorphisms

- Functional mutations in the CNR1 and FAAH genes are related to marijuana, cocaine, alcohol, heroin, and nicotine dependence (reviewed in Lopez-Moreno et al., 2012).

- Most compelling association: C385A SNP, found in the human FAAH gene and in homozygous form is over-represented in subjects with problem drug use (Hariri et al., 2009).
  - lower threat-related amygdala reactivity
  - higher reward-related reactivity
  - less anxiety
  - higher impulsivity
Endocannabinoid Neurophysiology Summary

• Retrograde synaptic transmission
• Regulation of glutamate activity
  – Neuroprotection & neuroplasticity
  – Reward, reinforcement, extinction of drug-seeking behavior
• ECS Regulation of
  – Primary rewarding effects
  – Motivational effects of environmental stimuli
• Dysfunction in the ECS associated mental health outcomes
Part 2:
CANNABINOID THERAPEUTICS IN ADDICTION
Cannabis Dependence

• Lifetime risk of dependence
  – Cannabis 9%
  – Stimulants (other than cocaine) 11%
  – Alcohol 15%
  – Cocaine 17%
  – Heroin 23%
  – Nicotine 32%

• Highest risk of cannabis dependence:
  – Poor academic achievement, deviant behavior in childhood and adolescence, rebelliousness, poor parental relationships, parental history of drug and alcohol problems.

Anthony, 2006
Anthony et al. 1994
Cannabis Withdrawal

• Common cannabis withdrawal symptoms (heavy users)
  – Anger or aggression
  – Decreased appetite or weight loss
  – Irritability
  – Anxiety
  – Restlessness
  – Sleep difficulties, including strange dreams

• Symptoms appear 1-2 days after cessation and resolve in 1-2 weeks

Reviewed in Budney et al. 2004, Haney 2005
Drug Interactions

- THC - CYPs 2C9, 3A4
- CBD - CYPs 2C19, 3A4
- CBN - CYPs 2C9, 3A4

“low risk of clinically significant drug interactions with most use, but specific human data are lacking.”

Drug Interactions

Use caution in patients who are taking:

- Warfarin (check INR, usually not significant change)
- Statins (max dose)
- Erythromycin, Azole antifungals
- Stimulants (works well for some, can increase paranoia and psychiatric side effects in others)
- Anticholinergics
  - (McPartland et al., 2008)
Medical Cannabis Side Effects

- Dizziness
- Dry mouth
- Nausea
- Fatigue
- Sleepiness
- Euphoria
- Depression
- Vomiting
- Diarrhea
- Disorientation
- Anxiety
- Confusion
- Impaired balance
- Hallucination
- Paranoia

Number Needed to Prevent: Schizophrenia

- This study used findings from a recent meta-analysis which report an adjusted risk ratio (RR) of 2.1 (95% CI 1.5–2.8) between ‘heavy cannabis use’ and psychosis outcome compared to non-users, combined with epidemiologic data.

- Lowest NNP: Men, heavy use, age 20-24 yrs
- NNP=2800 [90% CI 2018–4530]
- Other results were higher

Hickman et al., 2009
Many Phytocannabinoids Are Non-psychototropic Yet Therapeutic
CBD Mechanism of Action

- Very low affinity for CB1 and CB2 receptors
- Antagonizes CB1 & CB2 agonists
- Allosteric modulation of CB1
- Non-competitive inverse agonist

(Zhornitsky & Potvin, 2012; Laprairie et al. 2015; Morales et al., 2016)
Herbal Synergism: THC + CBD

Cannabidiol (CBD)

– Antagonizes undesirable effects of THC such as intoxication, sedation and tachycardia

– Enhances the analgesic, anti-emetic, and anti-carcinogenic properties of THC.

CBD Mechanism of Action

- Antagonizes
  - GPR55
  - alpha-1 adrenergic
  - μ-opioid receptors
  - Adenosine receptors
- Activates
  - 5-HT$_{1A}$ serotonergic
  - TRPV1–2 vanilloid receptors
- Inhibits uptake
  - noradrenaline
  - dopamine
  - serotonin
  - GABA
  - anandamide
- Inhibits activity of fatty amide hydrolase (FAAH) and numerous other enzymes
- Acts on mitochondria Ca$^2+$ stores
- May block low-voltage-activated (T-type) Ca$^2+$ channels
- May stimulate activity of the inhibitory glycine-receptor
- CBD lacks hedonic properties on its own (Parker et al., 2004)

(reviewed in Zhornitsky, 2012)
FAAH Inhibition

- Pharmacotherapies targeting endocannabinoid degrading enzymes are less likely to cause tolerance and dependence than direct CB1 receptor stimulation.

- Repeated anandamide administration in FAAH-KO mice causes smaller CB1 receptor down-regulation and desensitization and shows lesser dependence liability than repeated THC (Falenski et al., 2010)
CBD and Addiction: Nicotine

Inhaled CBD reduces cigarette consumption in tobacco smokers

- n=24 RCT CBD vaporizer vs placebo
- ~40% reduction in CBD group
- no change in placebo

(Morgan et al., 2013)
CBD and Addiction: Heroin

- CBD for heroin self-administration in rats
  - CBD specifically inhibited reinstatement of cue-induced heroin seeking
  - CBD (5 mg/kg and 20 mg/kg i.p.) did not reduce heroin self-administration behavior. (Ren et al., 2009)

**Figure 1.** CBD effects on heroin self-administration. (a) Rats readily maintained stable self-administered heroin from approximately the sixth training session. (b, c) CBD (5–20 mg/kg, i.p.) did not affect the number of lever presses (b) or locomotor activity (c) during maintenance of heroin self-administration. Data represent mean ± SEM; n = 7–9/group.

**Figure 2.** CBD inhibits cue-induced heroin-seeking behavior. (a) CBD reduced the number of active lever presses induced by exposure to a stimulus light cue 24 h before testing (a) and 2 weeks following last repeated CBD injection (b; 5 mg/kg, daily during the final 3 d of heroin self-administration maintenance; 3×/d). Data represent mean ± SEM; n = 7–9/group. *p < 0.05, **p < 0.01, ***p < 0.001 versus vehicle.
CBD vs. Amisulpride RCT

(Leweke et al., 2012)
CBD vs. Amisulpride RCT

(Leweke et al., 2012)
CBD vs. Amisulpride RCT

(Leweke et al., 2012)
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<td>Labiglani (89), Dreher (90), De Vry (36)</td>
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<td>Motor neurone disease (ALS) (increased survival, function)</td>
<td>+</td>
<td>+</td>
<td>Raman (81), Abood (82)</td>
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CBD for Cannabis Withdrawal: Case Report

• 19yo woman, user since age 13
• Severe withdrawal symptoms, unable to quit
• Treated with CBD for 10 days at 300-600mg/d.
• Daily symptom assessments demonstrated the absence of significant withdrawal, anxiety, and dissociative symptoms during the treatment. (Crippa et al., 2013)
Nabiximols for Cannabis WD

- DBRCT, n=51 DSM-IV cannabis-dependent treatment-seekers
- New South Wales, Australia
- 6-day regimen of nabiximols (max daily dose 86.4mg THC + 80mg CBD) vs placebo
- Standardized psychosocial interventions during a 9-day admission.

Allsop et al., 2014
Figure 2. Mean Change From Baseline in Withdrawal Score for Overall Withdrawal Scores and for Symptoms That Were Significantly Suppressed by Nabiximols

Overall Withdrawal Score

Irritability

Craving

Depression

Figure 3. Retention in Withdrawal Treatment

Allsop et al., 2014
CBD+THC Abuse Potential

• Single-dose, randomized, double-blind, crossover study
• n=23 heavy cannabis users
• Nabiximols (CBD:THC ~1:1 oromucosal spray) vs dronabinol (synthetic THC capsule)
• Subjective and cognitive/psychomotor abuse potential measures administered over 24-hr post-dose
• 10mg CBD + 10mg THC lower than 20mg THC on most measures (P<0.05)
• 20mg CBD + 20mg THC lower than 20mg THC but statistically significant on only some measures.

Schoedel et al., 2011
CBD + THC Abuse Potential

• In nabiximols clinical trials, intoxication scores have been low and euphoria reported by only 2.2% of patients.
• Tolerance has not occurred, abrupt withdrawal has not resulted in a formal withdrawal syndrome. (Robson, 2011)
• Nabiximols has not been abused or diverted to any degree in more than 30,000 patient-years of recorded usage. (Russo et al., 2015)
Cannabis in Opioid Addiction
Cannabinoid-Opioid Synergy

- Opioid and cannabinoid receptors are both present in pain signaling regions of the brain and spinal cord.
- Opioid and cannabinoid signaling pathways interact with each other.
- Administering cannabinoids with opioids results in a greater than additive antinociceptive (anti-pain) effect.

reviewed in Cichewicz, 2004
Cannabinoid-Opioid Synergy: Tail Flick Test in Mice

Smith et al. 1998

THC 20mg/kg + morphine       morphine-only

MPE = maximum possible effect

Smith et al. 1998
Cannabinoid-Opioid Synergy Human Trial

• 21 patients with chronic pain on sustained release opioids
  – Oxycodone mean 62mg BID or morphine mean 53mg BID
• Cannabis (NIDA supplied, 3.56% THC) vaporized 3x daily, inpatient setting
• Pain significantly decreased: 27% (95% CI 9.46)

(Abrams et al. 2011)
Can Cannabis Be Used To Replace Opioids in Chronic Pain Patients?
Cannabis For Treatment-Resistant Chronic Pain

- Open-label, longitudinal ~7 months, n=176
  - 73 on opioids at baseline
- 20g cannabis monthly: smoked, cookies, or olive oil extract
- Patients given titration instructions – up to 3x/day
- Subjects encouraged to attempt gradual dose reduction of other analgesics, especially opioids
- Results:
  - Improvements in pain and pain-related quality of life scores
  - 44% of those taking opioids discontinued

Haroutounian et al., 2016
Medical Cannabis Associated With Decreased Opioid Use in Chronic Pain Patients

- Cross-sectional retrospective survey of 244 medical cannabis patients with chronic pain in Michigan
- Medical cannabis use associated with
  - 64% decrease in opioid use (n=118)
  - Decreased number and side effects of medications
  - Improved quality of life (45%)

Boehnke et al. 2016
Summary of Survey Data Maine 2016

• 1074 responders (48% female)
  – 70% had used opioids >3 months
  – 50% had used medical cannabis in combination w/ opioids

• 542 cannabinoid-opioid cotreatment
  – 39% stopped opioids completely
    • 73% for >1 year
  – 39% reduced dose
Summary of Survey Data Maine 2016

- 542 cannabinoid-opioid cotreatment
  - 47% reported ≥40% pain reduction
  - 80% reported improved function
  - 87% reported improved quality of life
Is It Safe To Use Cannabis and Opioids Together?
Is It Safe To Use Cannabinoids and Opioids Together?

- Opioid and cannabinoid receptors are co-distributed in pain centers.
- Cannabinoid receptors have low density in brainstem cardiorespiratory centers.
- Combination increases therapeutic index of opiates!

(Reviewed in Cichewicz, 2004)
Retention of Opioid Efficacy

- Opioid receptor proteins are upregulated in the spinal cord of chronic combination-treated animals.
- Mice treated with low doses of THC and morphine in combination demonstrate avoidance of tolerance to the opioid with retention of the antinociceptive effect.
- Cannabinoid and opioid receptors are co-localized in brain areas important for morphine abstinence: nucleus accumbens, septum, striatum, PAG and amygdaloid nucleus.

(reviewed in Cichewicz, 2004)
Public Health Impact of Opioid Prescriptions

• 44 people in the United States die every day from prescription painkiller overdose.

• Almost 7,000 people are treated in emergency departments every day for using prescription opioids in a manner other than as directed.

• One in 20 people in the United States, ages 12 and older, used prescription painkillers non-medically in 2010.

Data from cdc.gov
Public Health Costs of Opioid Prescriptions: Federal CDC Data

• Sales of opioids quadrupled between 1999 and 2010.

• Between 2000 and 2014 the rates of death from prescription-opioid overdose nearly quadrupled.

• Enough opioids prescribed in 2010 to medicate every American adult with a standard pain treatment dose of 5 mg of hydrocodone taken every 4 hours for a month.

Data from cdc.gov
Do Opioids Help Chronic Pain?

“Evidence is insufficient to determine the effectiveness of long-term opioid therapy for improving chronic pain and function.”

- 34 studies analyzed, ≥ 18yo, ≥ 3 months chronic pain and opioid Rx
- No studies evaluated long-term (>1 year) outcomes related to pain, function, or quality of life:
  - opioid vs. placebo, opioid vs. no opioid therapy, opioid vs. non-opioid therapy
- Increased risk for serious harms associated with long-term opioid therapy: overdose, opioid abuse, fractures, myocardial infarction, and markers of sexual dysfunction

Chou et al., Ann Intern Med. 2015
States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate compared with states without medical cannabis laws.


<table>
<thead>
<tr>
<th>Independent Variable</th>
<th>Percentage Difference in Age-Adjusted Opioid Analgesic Overdose Mortality in States With vs Without a Law</th>
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<tbody>
<tr>
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<td>Primary Analysis</td>
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<tr>
<td></td>
<td>Estimate (95% CI)</td>
</tr>
<tr>
<td>Medical cannabis law</td>
<td>-24.8 (-37.5 to -9.5)e</td>
</tr>
<tr>
<td>Prescription drug monitoring program</td>
<td>3.7 (-12.7 to 23.3)</td>
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<tr>
<td>Law requiring or allowing pharmacists to request patient identification</td>
<td>5.0 (-10.4 to 23.1)</td>
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<tr>
<td>Increased state oversight of pain management clinics</td>
<td>-7.6 (-19.1 to 5.6)</td>
</tr>
<tr>
<td>Annual state unemployment rate</td>
<td>4.4 (-0.3 to 9.3)</td>
</tr>
</tbody>
</table>
“[C]onsistent with other studies of the liberalization of cannabis laws, medical cannabis laws do not appear to increase use of the drug.”

Gorman & Huber, 2006
Cannabis Laws and The Youth

“There is no evidence of a differential increase in past-month marijuana use in youth that can be attributed to state medical marijuana laws”


"[T]he results of this study showed no evidence for an increase in adolescent marijuana use after the passage of state laws permitting use of marijuana for medical purposes. ... [C]oncerns that increased marijuana use is an unintended effect of state marijuana laws seem unfounded."

Cannabis Treats Symptoms Of Opioid Withdrawal

- Nausea, vomiting, diarrhea, cramping
- Muscle spasm
- Anxiety, agitation, restlessness
- Insomnia
- Runny nose, sweating
THC Reduces Withdrawal & Cannabis Use Improves Naltrexone Treatment Retention

- n=60, 8 weeks, long-acting naltrexone injection at 1 & 4 weeks
- Dronabinol (THC) 30mg/day vs placebo for 6 weeks.
- 100% of cannabis users received second injection
- 46% of non-cannabis users received second injection

(Bisaga et al., 2015)
Cannabis Improves Naltrexone Treatment Retention

• Days in treatment (mean):
  – Intermittent cannabis use = 113 days
  – Consistent cannabis use = 68 days
  – Abstinent = 47 days

• Intensive behavioral therapy helped the consistent cannabis group but not the abstinent group.

(Raby et al., 2009)
CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016

previously (30). Clinicians should not test for substances for which results would not affect patient management or for which implications for patient management are unclear. For example, experts noted that there might be uncertainty about the clinical implications of a positive urine drug test for tetrahydrdocannabinol (THC). In addition, restricting
I am 38 years old and I struggled with opiate and alcohol addiction for about 15 years. Long hours as a chef and a couple of minor surgeries where I was prescribed opiates, led me to become dependent on them to get through my day. Pretty soon I was fully consumed by addiction.

Even after going to 2 detoxes and a 28 day rehab in 2010, I still struggled to stay clean for the next 2 years. The 12 step meetings that I was going to several times a week discouraged cannabis use, so I tried to do it their way and didn’t use any. That didn’t work and led to several relapses. In 2012, I decided to start using a little bit of cannabis before bed to help me get a good nights sleep, and when I was getting stressed, angry, etc. It was very effective in keeping me centered and on the path to recovery, although I didn’t feel comfortable (and still don’t) sharing this with fellow addicts at meetings.

I had been a cannabis smoker on and off since I was 18, and always enjoyed the effects. In the throes of my opiate addiction however, I got out of the routine of regular cannabis using. I believe that this is because cannabis use tends to magnify my own problems and shortcomings in my mind when I use it, and no drug addict wants to take such an honest look at themselves.

As of right now I have been free of active addiction since January 2012. I have also been a patient of Integr8 Health since 2012. Cannabis is the only thing that I am currently prescribed, and the only substance that I use for pain, stress, etc. I don’t know if I would be here today, and sober, if it wasn’t for cannabis. I use cannabis throughout the day and before bed, and live a happy, healthy, productive life with my wife and 2 daughters.
I took opiates for 15 years, along with various forms of Benzo's. I had legitimate pain, I fractured my back in 3 places when I was about 19. I healed from the initial injury, but the pain got worse over the next few years, to the point where I was drinking to get by. I had an uncanny knack for being able to walk into a doctors office and get almost anything I asked for due to my injury. Anyway, I took opiates to the tune of 2 Oxycontin 80's & 12 mg Dilaudids for a PRN.

At some point it wasn't just about the pain anymore, it had become more about the addiction. In retrospect, the opiates were only working on the emotional pain, not the physical pain. So to make the long story short, I've been to detox 27 times since I was 27, I've been in three 30-day rehabs, from here to Ohio. I tried halfway houses, suboxone treatment etc. It's been 21 months since my first visit to your office, and I literally have not used an opiate since. Thank You.

p.s. I truly believe that medical marijuana has saved my life.
Harm Reduction: Medical Cannabis As An Exit Drug

• n=350 medical cannabis patients, self-report (Reiman 2009)
  – 40% have used cannabis as a substitute for alcohol
  – 26% as a substitute for illicit drugs
  – 66% as a substitute for prescription drugs.

• n=404 medical cannabis patients, self-report (Lucas et al., 2012)
  – 41% have used cannabis as a substitute for alcohol
  – 36% as a substitute for illicit drugs
  – 68% as a substitute for prescription drugs.

• The most common reasons given for substituting were:
  – less adverse side effects
  – better symptom management
  – less withdrawal potential
Therapeutic Use of Cannabis by Crack Addicts in Brazil

- 25 male patients age 16-28 strongly addicted to crack, followed for 9 months
- 17 (68%) reported using cannabis to cease using crack
  - Decreased anxiety and WD Sx's
  - Less urge to use crack & seek people whom they had previously joined to use crack
  - Increased sleep and weight gain
  - Improved socialization
- 4 lost to follow up, 4 unable to abstain from crack.

Labigalini et al., 1999
Crack Heads and Root Daughters

Ethnographic study of 33 current or former crack using women:

• “It mek you meditate an’ have an interest away from crack.”
• “. . . when you want crack you should smoke a spliff instead.”
• “. . . nuff time me would use crack but (ganja) mek me t’ink twice.”
• “. . . herb helps me not want to smoke.”
• “If you’re trying to stop and you smoke weed, you nah wan de rock. With two spliff, I can resist crack.”

(Dreher 2002)
Part 3: CLINICAL CONSIDERATIONS IN CANNABINOID MEDICINE
Clinical Dosing Terminology

- Tetrahydrocannabinol (THC)
- Cannabidiol (CBD)
- Δ⁹-THC Acid (THCA)
Dosing By The Milligram

Oral dosing range effective in my practice:
0.015mg/kg/day – 30mg/kg/day
(e.g. 1mg - 2,100mg daily for 70kg adult)

Monkeys treated with oral THC at 9,000mg/kg survived (Rosenkrantz et al., 1975)
Biphasic Dose-Response
Multiphasic Dose-Response

Example: THC & Locomotor activity in rats

(Sañudo-Peña et al, 2000)

Fig. 1. Dose-curve of systemic administration of Δ⁹-tetrahydrocannabinol effects on horizontal activity in rats. There is an increase in activity with relatively low doses (1–2 mg/kg) of the cannabinoid receptor agonist.
Nabiximols for Opioid-Treated Cancer Patients With Poorly Controlled Chronic Pain

Randomized, placebo-controlled, graded-dose trial, n=263, 9 weeks. (Portenoy et al, 2012)

Figure 4. Analysis of change from baseline in NRS average pain score.
Widening of Therapeutic Window

- Cannabis-naïve patients demonstrate more frequent adverse effects (Hall et al. 2003)
- Regular users demonstrate less psychotomimetic, perceptual altering, amnestic, and endocrine effects. (D'Souza et al., 2008)
- THC can widen its own therapeutic window
  - Heterogeneous tolerance-building to various effects. (reviewed in Pertwee, 2004)
  - Therapeutic effects may be more resistant to tolerance development than side effects. (De Vry et al., 2004)
The same medicine can cause opposite responses in different individuals.

- Anxious subjects tended to become less anxious. More euphoric, non-anxious individuals tended to become somewhat more anxious. (Abel, 1971)
- Sedation vs stimulation
- Appetite stimulant vs suppressant
Bidirectional Effects

• The same medicine can cause opposite responses in the same individual:
  – Different doses (Hollister, 1986)
  – Different settings – stress environments can precipitate adverse emotional responses (Gregg et al, 1976)

• Different cannabis cultivars or cannabinoid ratios can cause opposite responses in the same individual
Dosing: New to Cannabis

1. Start sub-therapeutic.

2. Increase to minimal noticeable dose for 3 days.

3. Increase to effective therapeutic dose on day 4.
New User Dosing Tips

• Starting dose:
  – Tincture or oil 1-2mg 3x daily
  – Vapor 1-2 puffs 3x daily

• Choose initial CBD:THC ratio based on symptoms and goals, adjust later.
  – 1:1 is broadly effective and well-tolerated.

• Track and document response

• Combine with activities and diet that stimulate endocannabinoid system
Inner Inventory: Self-Awareness Tool

Breath  Body  Mood
Non-Psychoactive Strategies

- Low dose THC after widening therapeutic window
- CBD:THC ratio > 3:1
- Acidic (raw) cannabinoids
- Topical delivery
Dosing: Experienced User

1. Sensitization Protocol: 6 days
2. Try switching from inhalation to oromucosal delivery
3. Mitigate side effects and enhance benefits – adjust strain or CBD:THC ratio
Sensitization Protocol

1. Day 1-2: 48 hours cannabis abstinence
   - Endocannabinoid enhancing activities: exercise, omega-3 and -6 PUFAs, probiotics, massage, osteopathic manipulation, acupuncture, stress reduction (reviewed McPartland et al, 2014)

2. Day 3-5: Reintroduce Cannabis
   - Titrate to minimal therapeutic effect BID-TID for 3 days
     • Inhaled: 1 puff every 5 min
     • Tincture or PO: start at 1/10 of previous dose, gradually increase
     • Opportunity to practice self-awareness “Inner Inventory”

3. Day 6: Resume PRN dosing to previous therapeutic efficacy or better
Cannabinoid Sensitization Protocol

- 6-day specific protocol to reduce dose with equivalent or improved efficacy
- 90% of participants decrease dosage
- Average dosage decrease: 56%

Data from patient email survey n=48
Delivery Methods

• Inhalation: Vaporizing, smoking
  – Strength: rapid onset, easy dose titration, non-invasive parenteral (anti-emetic), easy to judge response
  – Weakness: narrow therapeutic window, respiratory irritation, more cardiovascular side effects, higher abuse potential, shorter duration
  – Clinical Utility: abrupt onset conditions (e.g. migraine, panic attack, flashbacks, cyclic vomiting episode), breakthrough symptoms
  – Bioavailability varies widely: 10-35% (reviewed in Grotenhermen, 2003)
Delivery Methods: Inhalation
Delivery Methods

• Oromucosal (tincture, oil)
  – Strength: intermediate onset, easy dose titration
  – Weakness: variable onset and effects if swallowed vs held in mouth, not fast enough onset for some conditions, palatability
  – Clinical Utility: broadly applicable, good for cannabis-naïve patients

• Enteral (capsules, edible, tincture if swallowed)
  – Strength: convenient, long duration
  – Weakness: erratic bioavailability, slow onset, first-pass metabolism, most common to be used inappropriately and to cause adverse effects, may be more psychoactive, non-homogenous products
  – Clinical Utility: baseline dosage, insomnia
Delivery Methods: Oromucosal and Enteral
Delivery Methods

• Topical (salves, liniments)
  – Strengths: non-psychoactive at most doses, anti-pruritic and analgesic, anti-inflammatory, muscle-relaxant
  – Weakness: little research
  – Clinical Utility: eczema, psoriasis, arthritis, trigger points

• Transdermal (patch)
  – Strengths: convenient, likely high bioavailability, low abuse potential
  – Weakness: slow onset, may be difficult to achieve correct dosage
  – Clinical Utility: personal preference, need for consistent dosing, avoid first-pass metabolism

• Rectal
  – Strengths: potentially higher bioavailability and faster onset than oral with less psychoactive effects, avoid first-pass metabolism
  – Weakness: inconvenient, formulation can affect absorbability
  – Clinical Utility: end-of-life, pelvic and low back symptoms
Dear Healthcare Provider,

This document provides a succinct overview of the clinical information you’ll need to safely care for patients who elect to use medical cannabis. If you’re interested in learning more about the emerging field of cannabinoid medicine, please visit Healer.com.

Sincerely,

Dustin Sulak, D.O.
Founder, Healer.com
Thank You!
Dustin Sulak, D.O.

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