The Endocannabinoid System and Harm Reduction with Cannabis

Gregory Gerdeman, PhD
Mary Lynn Mathre, RN, MSN, CARN
Cannabis is real medicine

• Cannabis is safe medicine

• Studying cannabis led to discovery of the ENDOCANNABINOID SYSTEM (ECS)
  • Cannabinoid receptors (activated by THC)
  • Endogenous THC-like cannabinoid signaling molecules (endocannabinoids)
  • Endocannabinoid metabolic enzymes

• ECS is a “master regulator” of human physiology
Effects of cannabis in the brain are undeniably the root of human attraction and aversion – both – to this plant that has been cultivated and utilized as medicine for longer than any historical record.
A timeline of major discoveries in the research of cannabis and the cannabinoids

1964 – Gaoni and Mechoulam isolate $\Delta^9$-THC from hashish

1980’s – “Tetrad” test of cannabinoid effects is developed, and used to test synthetic analogs.

1988 – CB1 cannabinoid receptor is identified.

1992 – Anandamide is discovered as first endocannabinoid
The focus of cannabis research in the 2\textsuperscript{nd} half of the 20\textsuperscript{th} century was not so even-handed.

- **How does marijuana make someone...**
  
  - Stoned
  
  - Lazy
  
  - **Addicted** (including to other drugs)
  
  - Violent!!!
  
  - **Mentally impaired** for life... brain damage model
    (THC as neurotoxin)
  
  - Insane (paranoid **schizophrenia**)
Mainstream scientific conceptions of the endocannabinoid system are now well beyond the exclusive domain of drug abuse research ...

Endocannabinoid signaling as a synaptic circuit breaker in neurological disease
István Katona & Tamás F Freund
Endocannabinoids as guardians of the nervous system

Physical trauma or seizure activity rapidly and significantly elevates endocannabinoids in the brain.

Administering endocannabinoids to animals:

• attenuates many kinds of chemically or electrically induced seizure activity

• reduces the extent and severity of brain injury following experimentally inflicted head wounds

• reduces the severity of inflammation that naturally follows brain injury, and which has enormous clinical consequence for recovery
What about drug abuse and addiction?

Prevailing NIDA-funded paradigm is exclusively one of risk, abuse and addiction.

Yet, clinical use of cannabis to successfully treat drug abuse has a long history that includes esteemed doctors.

Results of preclinical animal research in the modern NIDA era are also utterly inconsistent with labeling cannabis simplistically as a “dangerous and addictive drug” and having “no accepted medical use.”
Uptake of [18F]MK-9470 in human brain

Prominence in reward centers and circuits relevant to addiction

Burns H. D. et.al. *PNAS* 2007;104:9800-05

It’s all much more complicated than dopamine

Principal neurotransmitters:
- Glutamate – excitatory (+)
- GABA – inhibitory (-)

Dopamine – can enhance or decrease excitability

Dopamine is much more than a “pleasure signal”

Research into dopamine as a trigger to reward and addiction has helped drive neuroscience outside the addiction paradigm.

- Action selection
- Motivated behavior
- Motor programs / sensorimotor integration
- Implicit memory (procedural, non-declarative)
  **AND**
- Addiction as a pathology of habit formation

Neuropsychopharm Reviews 35: 217-238
Neurocircuitry of addiction

It’s all much more complicated than dopamine

Principal neurotransmitters:
- Glutamate – excitatory (+)
- GABA – inhibitory (-)

Dopamine – acetylcholine – peptides

Endocannabinoids regulate ALL of the above

As dopamine drug-abuse model expanded foundational understanding of how the brain works, research into cannabis as a drug of abuse is leading to similar revolutions in understanding nervous system function, and homeostatic wellbeing.

Major findings
- Endocannabinoids and retrograde synaptic signaling
- ECS mitigates neuroinflammation
- THC is anomalous as a drug of abuse

---

eCB signaling provides negative feedback to excitatory synapses.

- blocks excitotoxicity and seizures
- regulates information processing
  - mechanisms of learning & memory

- including the circuitry of pleasure/reward and decision-making

eCB signaling also acts to DISINHIBIT certain neurons by tuning down inhibitory synapses

- regulates information processing
  - mechanisms of learning & memory
  - filtering and gain at synapses

Gerdeman & Schechter (2010) in *The Pot Book*
An excitatory glutamatergic synapse

**Excitotoxicity**

An EXCITATORY synapse is formed when an axon terminal EXCITES its target cell to elicit a response.

Presynaptic axon release site

Postsynaptic target dendrite (or cell body)


http://www.nature.com/nm/journal/v14/n9/extref/nm.f.1869-S1.swf
Multiple cannabinoid pathways to brain resilience and repair

**Excitotoxicity** (cell damage due to excessive excitation and calcium signaling)

**Reactive oxygen species (ROS) and nitrosylation**
- cannabinoids as antioxidants

**Microglial activation**

**Pro-inflammatory cytokines**

**Vasodilation and cerebral perfusion**

**Neurogenesis** – growth of new neurons from neuronal stem cells
Synaptic modulation by endocannabinoids
Intrinsic defense against excitotoxicity

A mechanism intrinsic to numerous circuit-level processes of learning & memory

**Encoding of explicit, declarative memory.**
- Episodic memory, spatial orientation
- Involving hippocampus

**Consolidation and extinction of behavioral habits, procedural memory**
- Stimulus-response behavior in rodent models
- Automatic routines, resistant to devaluation.
  - These kinds of S-R habits are facilitated by amphetamines
  - Impaired by blocking CB1 cannabinoid receptors, **BUT**
  - **NOT** facilitated by exogenous cannabinoids
    - *Extinction or unlearning* of S-R habits is *also* hampered by blocking CB1 receptors.
  - Involving OFC, striatum and mesolimbic dopamine systems (basal ganglia)

**Neurobiological axis of stress**
- Fear perception and its translation into acute HPA stress responses
- Terminating the HPA stress response (long loop cortisol feedback)
- Extinguishing fearful/traumatic memories
- Involving PFC, amygdala, hypothalamus
So, is cannabis an addictive drug ... how does ECS fit the drug abuse paradigm?

Conditioned Place Preference (CPP)

THC and synthetic cannabinoids are found to be anomalous compared to typical drugs of abuse.

Many studies fail to find place preference or instead find place aversion to CBs.

Positive CPP results, when found, are narrowly dose dependent.

(Panagis, et al., 2007)

Parker et al. (2004) : CPP to stimulants reversed by THC or CBD or rimonabant!

eCBs are important for the neural encoding and/or recall of behavioral context!
Drug abuse paradigms... how does ECS fit?

Self-administration

Drug of interest (i.e., THC or synthetic CB1 agonist)

Again, CB agonists are highly atypical... most methods requiring drastic restraint (esp. in mice), food or water deprivation, prior cocaine self-admin, or a combination of these. (Panagis, et al., 2007)

But see studies by S. Goldberg, Z. Justinova and colleagues.
But, why? Cannabis is often a rewarding experience in humans!

Studying the ECS in detail is revealing:

- insight into how cannabis is rewarding (how it’s different from the dopamine model)
- neurobiology of why dependence/addiction CAN occur
- how frequent is a “cannabis dependence disorder” (DSM V)

  • Genetic variation in ECS genes (FAAH, CNR1) may contribute susceptibility to addiction
    • and anxiety
    • and depression (drug-resistant)

By far the most compelling theme that has emerged from cannabis addiction research – and most consistent across groups – is the evidence that endocannabinoid signaling modulates cue-induced relapse to the seeking of OTHER drugs.
Reinstatement of drug seeking

Protocol:

Subjects learn to self-administer drug whenever a CUE indicates drug availability.
Reinstatement of drug seeking

Protocol:

Subjects learn to self-administer drug whenever a CUE indicates drug availability.

Followed by...

*Prolonged abstinence*

No cue.
Lever pressing yields no drug.
Drug seeking behavior is *extinguished.*
Reinstatement of drug seeking

Protocol:

Subjects learn to self-administer drug whenever a CUE indicates drug availability.

Followed by...

Prolonged abstinence
No cue.
Lever pressing yields no drug.
Drug seeking behavior is extinguished.

Reinstatement
Pretreating animals with CB1-acting compounds BLOCK reinstatement of drug seeking in many studies.

To seek or not to seek?
**Reinstatement of drug self-administration**

CB1 receptors are found to be necessary for conditioned (cue-directed) reinstatement of drug seeking behaviors.

- *A model of relapse in drug addicts*

Consistent for numerous psychostimulant drugs of abuse:

- Cocaine (De Vries, *Nat Med*, 2001)
- Sucrose and nicotine (De Vries, *Behav Brain Res*, 2005)

  * also blocked relapse with THC*

CBD found to block heroin reinstatement (Ren, *J. Neurosci*. 2009)

Neurobiological Interactions Between Stress and the Endocannabinoid System

Maria Morena1,2, Sachin Patel3, Jaideep S Bains1,4 and Matthew N Hilln1,2,5

1Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada; 2Mathison Centre for Mental Health Research and Education, University of Calgary, Calgary, AB, Canada; 3Department of Molecular Physiology and Biophysics and Psychiatry, Vanderbilt Institute, Vanderbilt-Kennedy Center for Research on Human Development, Vanderbilt University Medical Center, Nashville, TN, USA; 4Department of Physiology and Pharmacology, University of Calgary, Calgary, AB, Canada; 5Departments of Cell Biology and Anatomy and Psychiatry, University of Calgary, Calgary, AB, Canada

ARTICLE
Received 22 Aug 2014 | Accepted 23 Jan 2015 | Published 3 Mar 2015
DOI: 10.1038/ncomms7395

FAAH genetic variation enhances fronto-amygdala function in mouse and human
Take home: In translating to clinical reality, do not oversimplify...

The human reward circuitry is not a simple on/off switch, even in the addicted brain.

Nonetheless the circuits of stress, reward, habit learning and relapse to compulsive drug seeking are finely modulated by eCB signaling... targeting this system makes at least as much sense as other pharmacotherapeutics developed by targeted medicinal chemistry.

Need to study human populations and real world controlled use of cannabis as a treatment modality

What about the risks?

All pharmacotherapies have risks and must be compared to the danger of the patient's condition.
Numerous recent studies seem to find that the presence of CBD can mitigate or eliminate some risks of THC identified in lab models of chronic use.

According to preclinical research, CBD as a regulator might:
• elevate eCB levels in extracellular fluid
• block or inhibit THC actions at CB1 as an allosteric antagonist

Other preclinical findings relevant to ECS and addiction from human genomics.

Polymorphisms in CNR1 or FAAH might predict:
• substance use disorders
• anxiety disorders, or forms of stress
• depression or other affective disorders

This field is young, but serious... the practice of nursing should be at the forefront of acquiring and implementing new knowledge.
Cannabis as an “exit drug” for the treatment of addictions

Observational human research supports it
- Jamaican “roots daughters” study (Dreher)
- Therapeutic use of cannabis by crack addicts in Brazil (Labigalini)
- Cannabis as a substitute for alcohol and other drugs (Reiman, Mikurya, Lucas)
- Preclinical animal models create a powerful proof of concept for the use of CBD-containing cannabis for the prevention of relapse in treatment seeking addicts.
- This must be talked about more seriously... as seriously as any risk of cannabis addiction *per se*
The Endocannabinoid System and Harm Reduction with Cannabis

Gregory Gerdeman, PhD
Mary Lynn Mathre, RN, MSN, CARN
Opioid Use

- Americans, constituting only 5% of the world’s population,
- have been consuming 84% of the global oxycodone (Oxycontin) consumption,
- and 99% of the global hydrocodone (Vicodin, Lortab) consumption.

CDC, 2016
Opioid Overdoses

• Opioid overdose epidemic – 16,651 prescription opioid overdoses and 3036 heroin overdoses in 2010 (WHO)
• Immunosuppressive effects of opioids may increase morbidity from infectious diseases, autoimmune diseases, and cancer
• Newly approved Zohydro ER (pure hydrocodone) – 5-10 X stronger than Vicodin

Made by Alkermes: Maker of Vivitrol (naltrexone extended release) – used to treat addictions
OPIOID STATISTICS AND ITS IMPACT

◆ Almost 2 million Americans are opiate dependent
◆ 259 million opiate prescriptions written in 2012
◆ 4 in 5 heroin users started with opiate prescriptions
◆ 40 Americans die each day from prescription opioids
◆ For 2013 economic burden of opioid epidemic is estimated to be $78.5 billion
Long term use of Opioids

• 2015 review showed no evidence to support long term use of opioids for pain management

• Increased risk of harm from long term use of opioids: overdose, opioid abuse, fractures, heart attacks, and sexual dysfunction
Long–term Use of Cannabis

• 2016 study of 176 pain patients using cannabis at 6 months follow-up
• Improved pain management and functional outcomes
• Reduced use of opioids by 44%
  – Haroutounian, S et al.
Cannabinoids 101

- **Phyto**cannabinoids (e.g. THC, CBD, CBN) are produced by cannabis.

- **Endogenous** cannabinoids (e.g. anandamide) are termed endocannabinoids, made within the body.

- **Synthetic** cannabinoids (e.g. dronabinol, HU-210) have been developed.
Non-THC Components of Cannabis

- Δ9-tetrahydrocannabinol (THC) is the primary psycho-active ingredient of cannabis
- Secondary compounds may enhance the beneficial effects of THC
- Other cannabinoid and non-cannabinoid compounds may reduce THC-induced anxiety, anticholinergic effects and immunosuppression
- Terpenoids and flavonoids may increase cerebral blood flow, enhance cortical activity, kill respiratory pathogens and provide anti-inflammatory activity
Non-psychotropic Cannabinoids
Cannabis Synergism: The Entourage Effect

• “This type of synergism may play a role in the widely held (but not experimentally based) view that in some cases plants are better drugs than the natural products isolated from them.” (Mechoulam & Ben-Shabat 1999)

• “The whole is greater than the sum of its parts.” (McPartland)
Cannabinoids and Pain

• Continuous descriptions of cannabis as an analgesic throughout history
• Brain regulates pain and processes the pain experience occurring elsewhere in the body
• Endocannabinoids centrally regulate our interpretation of the pain phenomenon
• Endocannabinoids also work directly in the periphery to curb the pain sensation
Cannabinoids and Pain

• Elevated levels of the CB1 receptor - like the opioid - are found in areas of the brain that modulate nociceptive processing
• CB1 and CB2 agonists have peripheral analgesic actions
• CBs may also exert anti-inflammatory effects
• Analgesic effects not blocked by opioid antagonists
THC and Analgesia

• In cancer trial, oral THC 20 mg was comparable to codeine 120 mg (5mg THC = 30mg codeine)
• Cannabinoid-induced analgesia appears linked to opioid system
• Cannabinoids act on the kappa and delta receptors, while opioids act on the mu receptors and the mu receptors can be enhanced by cannabinoids
• Cannabinoid analgesic effects not blocked by opioid antagonists
THC and Opioid Interactions

• Animal studies show:
  – THC + opioids are synergistic in analgesic effects
  – When combined can decrease tolerance to opioids
  – When combined can decrease physical dependence of opioids
  – When THC is introduced to a mouse that developed tolerance to opioids, the effectiveness of the opioids is restored

• Cichewicz DL et al, 1999; Cichewicz & Welch, 2013
Cannabis and Opioid Interactions

- Study of 21 pain patients on sustained release oxycodone or morphine adding vaporized cannabis:
- Lowers plasma level of the opioids but yields a statistically significant reduction in pain
Cannabis Can Reduce Opioid Use

• 2014 study looked at death certificate data from 1999-2010
• showed a 24.8% decreased mortality rate from opioids in the 23 states with medical cannabis laws compared to the other states
• It was a progressive decrease over time
• Conclusion: Medical cannabis laws are associated with significantly lower state-level opioid OD mortality rates.
  – Bachhuber et al.
Cannabis Can Reduce Opioid Use

• Michigan study: retrospective survey of 244 chronic pain patients at a dispensary from 11/2013 to 2/2015
• 64% lower opioid use
• Increased quality of life
• Fewer medication side effects and medications used
  • Boehnke et al., 2016
Cannabis May Decrease Opioid Use

• 2016 published study of 68,394 drivers from 18 states who died within one hour after a traffic accident from 1999-2013.
• Reduction of opioid use in the medical cannabis states
• Opioid presence was reduced by 50% in drivers aged 21-40 years.
  – Kim et al, 2016, AJPH
Decrease in Medicare Part D

- 2016 study from U of GA
- Review of all prescriptions filled by Medicare Part D from 2010 – 2013
- Results: Decreased use of prescription drugs for which cannabis could serve as a clinical alternative in states with medical marijuana laws
  - Bradford & Bradford
Cannabis – Harm Reduction

• A 2013 study of cannabis use during induction of methadone treatment
• Associated with decreased symptoms of opiate withdrawal.
• Potential role for cannabis during methadone induction.

— Scavone JL, Sterling RC, Wienstein, SP & Bockstaele EJ (Farber Institute for Neurosciences at Thomas Jefferson University, Philadelphia)
Cannabis – Harm Reduction

• 2009 study at NY State Psychiatric Institute
• Higher retention in naltrexone treatment for heroin addiction seen with cannabis users
• (Naltrexone is an opioid receptor antagonist used in heroin addiction and alcoholism treatment)
  – Raby WN et al.
When used in conjunction with opiates, cannabinoids lead to a greater cumulative relief of pain, resulting in a reduction in the use of opiates (and associated side-effects) by patients in a clinical setting. Additionally, cannabinoids can prevent the development of tolerance to and withdrawal from opiates, and can even rekindle opiate analgesia after a prior dosage has become ineffective."

— Lucas, P. 2012

Cannabis + Opioids for Pain Management

• Using cannabis with opioids is safer
• Cannabis + opioids work synergistically
• Cannabis slows the tolerance to opioids
• Cannabis can treat opioid withdrawal symptoms
• Cannabis can serve as a harm reduction medication for persons with an opioid use disorder
Silver Bullet vs. Natural Medicine

- Single drugs – more potent effect, usually more side effects
- Poly pharmacy – medications added to deal with side effects of medications
- Natural plant medicine – synergy among the constituents
Use of Cannabis with Opioids

• Opiate sparing effect
• Helps prevent nausea that sometimes accompanies opioids
• No constipation with cannabis
• Acts as an anti-depressant
• Acts as an anti-inflammatory agent
• No significant withdrawal symptoms
• Helps with sleep
CDC Guideline for Prescribing Opioids

• “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 tetrahyrdocannabinol (THC).” (#10 of the recommendations)
CDC Guideline for Prescribing Opioids

• “Clinicians should not dismiss patients from care based on a urine drug test result because this could constitute patient abandonment and could have adverse consequences for patient safety, potentially including the patient obtaining opioids from alternative sources and the clinician missing opportunities to facilitate treatment for substance use disorder.” (#10 of the recommendations)
Key Points

• We have an epidemic of overdose deaths caused by opioids
• Cannabis works synergistically with opioids
• Most patients with chronic pain will decrease their use of opioids when they have access to cannabis
• Cannabis is a harm reduction medication for pain management and opioid use disorder
How to reduce harm from Cannabis

• Organically grown
• Start low and go slow with dosing
• Vaporize rather than smoke
• If smoke – limit breath holding, clean pipe daily
• Caution with edibles – SLOW onset
• If not home grown – Need a known source with testing
• De-schedule the plant; Regulate cannabis products
References

References cont.

References cont.

References cont.

Websites

• www.patientsoutoftime.org
• www.medicalcannabis.com
• www.themedicalcannabisinstitute.org
• www.americancannabisnursesassociation.org
• http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881
• http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm CDC Guideline for Prescribing Opioids for Chronic Pain – United States, 2016