Medical Cannabis ... Clinical and Legal Considerations in the Emergency Department

Christine Roussel, PharmD, BCOP
Director of Pharmacy, Doylestown Hospital

Disclosures

• No financial Disclosures Relevant to the Cannabis Industry

• Program Director, Medical Cannabis Education Course,
  Philadelphia College of Pharmacy, University of the Sciences
Outline

• Endocannabinoid System
• Cannabis Pharmacology and Formulations
• Clinical Considerations and Adverse Effects

Disclaimer

• Cannabis is currently not FDA approved for any condition
• Cannabis is currently DEA Schedule 1 (Federal) under the Controlled Substance Act of 1970
  • No currently acceptable medical use
  • High Potential for abuse
• Investigational use only
  – IND applications must receive triple agency approvals: National Institute of Drug Abuse (NIDA) / DEA / FDA
  – Product for Federal Research is Sole Source through NIDA (Unless Import permission is granted)
Cannabinoids as antioxidants and neuroprotectants

US Government Owns Patent

“Cannabinoids are found to have particular application as neuroprotectants, for example limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson’s disease and HIV dimension”

US Government Grows Cannabis and Supplies it to Patients

1977 – 1993 Federal Compassionate IND (n=13)
Grown by University of Mississippi & NIDA

Pictures by Irvin Rosenfield, author My Medicine. Used with Permission.
Nerve Communication

1. Neurotransmitters Synthesized and stored in vesicles until ready to release

2. Neurotransmitter Binding to Corresponding Receptor

3. Initiates Downstream Effects

Neuro Signal Transmission Across the Synaptic Cleft

- Glutamate
- GABA
- Acetylcholine
- Norepinephrine
- Dopamine
- 5-HT3
- Cholecystokinin

Image by C. Roussel
1. Too much activity

2. Endocannabinoids (Anandamide, 2-AG) synthesized on demand for immediate release

3. Binding at the CB1 Receptor stabilizes vesicles to decrease neurotransmitter release

Endocannabinoid Signaling is Retrograde Inhibition

CB1 Receptors

CB1 – Primarily in Brain
- NOT significant in brainstem (RR,HR)

Other Locations
- Adipocytes
- Endocrine and Exocrine Glands
- Liver
- Heart, Vascular Smooth Muscle Cells

Cannabinoid Pharmacology in CNS
- Parasympathetic
- Anti-Nociceptive
- Neuroprotection
- Neuroplasticity

Human brain after injection of radio tracer to show the regional distribution of CB1R

**CB2 Receptors**

- Signally ↓ release of activators and sensitizers

Immunomodulation:
- Monocytes and Macrophages
- B-cells and T-cells

Liver, Spleen, Tonsils
Central & Enteric Nervous System
Endocrine and Exocrine Glands

---

**Medical Cannabis vs Marijuana**

*Cannabis sativa*

- Plant reliably grown and handled
- Good Manufacturing Practices
- Assayed, Labeled and Dated for cannabinoids and terpene content
- Proven absence of typical contaminants:
  - Mold / Yeast
  - Pesticides
  - Heavy Metals
  - Residual Solvents

**Same plant – With Different Chemovars**

- **Cannabis Sativa**
  - **Hemp – Fiber Type**
    - Tall, thick stalk
  - **Drug Type (aka Cannabis, Marijuana)**
    - THC + Cannabinoids
    - Terpenes
  - **Fiber**
  - **Oil**
  - **Food / Feed**

Industrial Hemp: stalk and seeds are used for textiles, paper, food, detergents, building materials (excludes flower)
THC Content < 0.3 – 1.5%
Not Scheduled

Cannabis / Marijuana: medicinal / recreational use of cannabinoids
THC content – 5 – 15+%
DEA Controlled Substance

---

**Seed to Sale Tracking**

Pictures by C. Roussel
“Genetic tools weed out misconceptions of strain reliability in *Cannabis sativa*”

No consistent genetic differentiation between the widely held perceptions of Sativa and Indica *Cannabis* types.

Instances were found where samples within strains are not genetically similar

Schwabe A and McGlaughlin M. Genetic tools weed out misconceptions of strain reliability in 1 *Cannabis sativa*: Implications for a budding industry. bioRxiv preprint first posted online May, 28, 2018. NOT PEER REVIEWED
Cannabis: Entourage Effect

- THC (tetrahydrocannabinol)
- CBD (cannabidiol)
- THC-A (Tetrahydrocannabinolic acid)
- CBC (Cannabichromene)
- CBG (cannabigerol)
- CBN (Cannabinol)
- THCV (Tetrahydrocannabivarin)
- Limonene
- Pinene
- Myrcene
- Linalool
- Linalool
- ß-Caryophyllene

Cannabinoids
Flavonoids
Lipids
Terpenes
Sterols

Endocannabinoids (Anandamide, 2-AG)
**TETRAHYDROCANNABINOL (THC)**

- Partial Agonist of CB1 and CB2
- Euphoria
- Analgesia (primary Pain relief molecule)
- Muscle Relaxant
- Anxiolytic (low dose) -> Anxiogenic (higher doses)

![Image by C. Roussel](image1)

**ADVERSE EFFECTS**

**Psychoactivity vs Psychotoxicity**
- Impaired cognition
- Difficulty concentrating
- Memory Impairment

Dizziness, Weakness
Increase risk of falls
Tachycardia
Vasodilation, Hypotension
Addiction (1 in 10 chronic recreational users)
Hypothermia

Caution in patients with unstable mental health conditions (especially bipolar disorder and schizophrenia)

![Image by C. Roussel](image2)
**Cannabidiol (CBD)**

- Enhances natural endocannabinoid activity
- inhibits anandamide hydrolysis
- Agonist at 5-HT (anti-nausea) and TRPV1 (Pain relief)
- Potent Immune Modulator = Strong Anti-Inflammatory Activity
- Anti-seizure
- Neuroprotective
- Decrease negative effects of THC (anxiety, memory impairment, psychoactivity)

*Image by C. Roussel*

**ADVERSE EFFECTS**

- Diarrhea
- Headache
- Suppress Appetite
- Stimulating (trouble sleeping) .... Somnolence
- Drug Interactions

*World Health Organization: Cannabidiol Critical Review*
TERPENES

**LINALOOL**
- Sedative
- Anxiolytic
- Analgesic
- Modulate GABA and Glutamate

**MYRCENE**
- Analgesic
- Anti-Inflammatory via PGE-2
- Anti-Convulsant
- Skeletal Muscle Relaxant

**ß CARYOPHYLLENE**
- Select CB2 Agonist
- Analgesic
- Gastric Protective
- Anti-Inflammatory via PGE-1

**PINENE**
- Anti-Inflammatory
- Bronchodilator
- Acetylcholinesterase Inhibitor (Aids memory)

---


---

**THC Inhalation**

Bioavailability is Variable due to smoking dynamics (10 – 60%)
- Depth of inhalation
- Duration of Breath Holding
- Temp of Vaporizer

Good For Titration and break through because of rapid effects

Import to Teach:
- Patient Proper Technique
- To wait 5-10 minutes between inhalations during titration

---


MacCullum C and Russo E. Practical considerations in medical cannabis administration and dosage. *European Journal of Internal Medicine.* 2018; 53-19
Cannabis (THC) Oral Administration

- Onset 30 – 120 min
- ↑ Inter/Intra Patient Variable Absorption
- Absorption ↑ w/ high fat meal
- Duration 4 – 8 hours
- *Up to 24 hours dose dependent
- Lower Peak [THC]
- ↑ [11-Hydroxy-THC]
  - Longer T1/2
  - More potent analgesic activity
  - More lipophilic

After Administration of 2.5 mg Dronabinol


Oral Mucosal Products

By Passes Liver Metabolism
Onset 15 – 60 mins
Inhalation

- Higher Doses that exceed therapeutic threshold in most patients
- Poor Ability to Dose
- Don’t confuse Recreational and Medical

Delivers smaller Doses
Able to measure dose
More Appropriate for Medicinal Use

CBD Routes of Administration

**Oral CBD**
- bioavailability is between 13% and 19%
- significant first-pass metabolism
- Absorption ↑ w/ high fat meal
- Sublingual

**Aerosolized CBD**
- rapid peak plasma concentrations in 5–10 minutes
- higher bioavailability than oral administration

**Rectal or Vaginal Suppositories**
- Increased bioavailability: higher absorption + less first pass metabolism

**Topical**


WHO 2018 Cannabidiol Critical Review
Considerations in Dosing ... Patient Self-Titration

Patient Education

Higher Doses -> Increased ADRs
Possible Decrease in efficacy

Finding Optimal Dose
“The Sweet Spot”
Minimal Side Effects

Start Low, Go Slow
Sub-psychoactive dosing
Cannabis Sensitization

Rooted in the Concept:
Less is Really More!

Want Upregulation of
Endocannabinoid receptors....
(Not down regulation)

Medical Goals of Therapy:

Symptom Management vs. Disease Modification

- Pain
- Spasticity
- Inflammation
- Sleep Disorders
- Nausea / Vomiting
- Appetite
- Anxiety / Depression
THC:CBD Chemotypes or Ratios

Psychoactivity

THC-predominant Ex. 50:1, 19:1, 16:1

Balanced = Intermediate Ex. 1:1, 4:1

CBD-dominant Ex. CBD Only, 1:>20

Psychoactivity is Dose Dependent and can be affected by tolerance and setting.

Psychoactivity is dose dependent and can be affected by tolerance and setting.

Average [THC] in DEA specimens 1995 - 2014

“All things are poisons, for there is nothing without poisonous qualities. It is only the dose which makes a thing poison.” – Paracelsus

ECS and the Gastrointestinal Tract

ECS regulates energy balance & food intake, acting both in brain & GI tract

- Anandamide (AEA) is mediator of hunger in intestines
- Starvation increases AEA levels & CB1 expression
- THC increases food uptake via CB1 activation

Anandamide on CB receptors in adipose tissue stimulates lipogenesis. Increased adiposity, insulin resistance

Inhibit nausea and vomiting

---

ECS in the Gastrointestinal Tract and affects of Cananbiniods

THC = Direct activation of CB1 receptors
- Analgesia
- ↓ gastric acid secretion
- ↓ contractility
- ↓ motility
- ↓ formation of gastric mucosal lesions through enhanced intestinal epithelial barrier functions
- Stimulates hunger sensation

CBD = targets upregulated CB2 receptors
- Anti-inflammatory
- Control fluid accumulation
- ** controls hunger **
Cannabis Hyperemesis Syndrome

- THC and CBD both have antiemetic properties low doses ... but high doses associated with.....

- Cyclic periods of vomiting and, often, epigastric pain.
  - Improvement by hot showering or bathing

- Typically remitted within 2–3 days after cessation of cannabis.

- Possible resistant to usual antiemetics
  - consider haloperidol or lorazepam
  - Fluid and electrolyte replacement

Handbook of Cannabis and Related Pathologies Cannabis. Chapter 48 Hyperemesis Syndrome. Bonnet, U.

---

ENDOCANNABINOIDS IN THE RESPIRATORY SYSTEM

**Short-term (Acute) cannabis smoking**

- Bronchodilation and consistent
- Improve specific airway conductance
- ↑ peak flow measurements
- ↑ forced expiratory volume (FEV1)
- Reverse bronchospasm in methacholine challenges

**Heavy habitual smokers of cannabis alone**

- Symptoms of chronic bronchitis (cough and sputum)
- Histopathological bronchial mucosa abnormalities (destruction of ciliated epithelial cells, increase mucus secreting surface epithelial cells)
- Not associated with increased lung cancer

Cardio-pulmonary exchange transfers cannabinoids to blood then brain
Smoke may irritate large air passages of lungs, throat, windpipe

Dries mucous membranes of mouth and nasal passages

---

Cardiovascular Effects of “Marijuana”

SUPINE ↑ SYSTOLIC AND DIASTOLIC BLOOD PRESSURE

↓ Time to ANGINA

Increased Risk of Myocardial Infarction with Inhaled Cannabis Population Analysis

4.8-fold higher risk of MI within first hour after Inhaling Product

- 124 / 3882 patient cohort
- Patients with history of MI, marijuana use ≥ once a week associated with 3 x ↑ Risk of Death

Increased CVD in cannabis users

- 316,397 of > 20 million

Marijuana not associate with increased CVD

- 4286 with h/o marijuana use

Pacher, et al. Cardiovascular effects of and synthetic cannabinoids: The good, the bad and the ugly, Nature Reviews Cardiology, Online 2017 Sept
### SELECT PHYTOCANNABINOIDS

<table>
<thead>
<tr>
<th>Cannabinoid</th>
<th>Areas of Investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBD-A</td>
<td>Cannabidiolic acid</td>
</tr>
<tr>
<td></td>
<td>Anti-emetic, anti-anxiety</td>
</tr>
<tr>
<td>THC-A</td>
<td>Tetrahydrocannabinolic acid</td>
</tr>
<tr>
<td></td>
<td>Anti-inflammatory effects via antagonism of tissue necrosis factor alpha (TNF-α); anti-emetic, anti-convulsant, clinical trial on-going for diabetes</td>
</tr>
<tr>
<td>CBN</td>
<td>Cannabinol</td>
</tr>
<tr>
<td></td>
<td>1/10th the psychoactive potency, sedative, antibacterial, inhibition of keratinocytes in psoriasis</td>
</tr>
<tr>
<td>CBC</td>
<td>Cannabichromene</td>
</tr>
<tr>
<td></td>
<td>anti-inflammatory, anti-fungal, anandamide reuptake inhibitor</td>
</tr>
<tr>
<td>CBG</td>
<td>Cannabigerol</td>
</tr>
<tr>
<td></td>
<td>DGABA uptake inhibitor, antibacterial, inhibition of keratinocytes in psoriasis</td>
</tr>
</tbody>
</table>


---

### Synthetic Cannabinoids

(i.e. K2, Spice, Crazy Monkey, Chill Out)

- Developed to study the endocannabinoid system
- Up to 200 times more potent than plant based cannabis products
  - **Extreme Potency = Extreme Toxicities**
- Vaporizers, E-cigarettes, plant products sprayed with chemicals to burn
- 2015 – 7,797 toxic exposures reported
  - 25% of events in children 13 to 18 years old

Neurologic symptoms:
- Agitation, coma, seizures, toxic psychosis, hallucinations
Synthetic Cannabinoids
Extreme Potency = Extreme Toxicities

Organ Function
• Severe nausea / vomiting, acute kidney injury, respiratory depression, death, Cardiac Symptoms

Bleeding ... contamination with Brodifacoum
• 2018 – 320 cases of severe bleeding and abnormal coagulation

Cannabis Use Disorder (CUDIT-SF)
How often in the past 6 months:
1. Did you find you were unable to stop using cannabis once you had started?
2. Have you devoted a great deal of your time to getting, using or recovering from cannabis?
3. Have you had a problem with memory or conversation after using cannabis?

Never(0) Less than monthly (1) Monthly (2) Weekly (3) Daily (4)
CUD present with > 2

Ratio of Average [THC]:[CBD] in DEA specimens


Defining Products

USP Expert Panel on Cannabis
- Botanical Identification
- Chemical Analysis & Contaminants
- Monograph Development

Cannabis Strain Analysis. Steep Hill Labs. All rights reserved. Reprinted with permission.
I can add a white square over the company name in the bottom of the circle.

Not sure what size you want my references

Roussel, Christine, 8/18/2018
### US Approval and DEA Schedule

<table>
<thead>
<tr>
<th>Product</th>
<th>US Approval</th>
<th>DEA Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dronabinol (Marinol)</td>
<td>1985</td>
<td>Solid = III; Liquid = II</td>
</tr>
<tr>
<td>Nabilone (Cesamet)</td>
<td>2006</td>
<td>II</td>
</tr>
<tr>
<td>Cannabidiol (Epidiolex)</td>
<td>2018</td>
<td>V</td>
</tr>
<tr>
<td>Nabiximols (Sativex) (1:1 THC: CBD)</td>
<td>NOT APPROVED</td>
<td>I (listed as such in NDA)</td>
</tr>
</tbody>
</table>

---

### Slow Titration Decreases Adverse Effects

- The focus is on maintaining / establishing favorable endocannabinoid tone
- Most Adverse Effects are early and transient
- Goal is avoid patients ever feeling uncomfortable
- Safety profile is improved by going slow and Low

---

Drug Interactions: Cannabis Effects on Other Drugs

**Potentiate the Effects of Other CNS Depressants**
- Alcohol, Opioids, Benzos, Muscle Relaxers

**Cardiac Effects**
- Amphetamines

**CYP Interactions 2C19, 2C9, 3A4**
- Cancer
- HIV
- Anti-Seizure

Oral Chemotherapy Food and Drug Interactions: A Comprehensive Review of the Literature Segal EM 2013

---

Cannabidiol Drug Interaction Examples

**Case Report**
- Patient INR Stable between 2-3 on Warfarin at dose of 7.5 mg/day
- Initiated CBD 15 mg/kg/day and the **INR went to 7**!!
- Warfarin dose was lowered

Dronabinol US Package Insert Contains Cautions when use with warfarin


**Multiple Pediatric Patient Study**
- Initiation of Cannabidiol led to average 60% in clobazam concentrations and average 500% increase in clobazam's active metabolite concentrations in blood.
- Additional studies show interactions Depakote

Drug Interactions
Effects of other drugs on Cannabis

<table>
<thead>
<tr>
<th>Increase Effects of Cannabis (2-3 times higher levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
</tr>
<tr>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Antifungal Drugs</td>
</tr>
<tr>
<td>Diltiazem</td>
</tr>
<tr>
<td>Fluvastatin</td>
</tr>
<tr>
<td>Certain HIV Drugs</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decrease Effects of Cannabis (50% less Cannabis Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
</tr>
<tr>
<td>St. Johns Wort</td>
</tr>
<tr>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Phenytoin</td>
</tr>
</tbody>
</table>

Nabiximols Summary of Medicinal Product Characteristics, European Medicines Agency 3/15


• No current evidence of that oral CBD administration in humans results in clinically relevant THC-like subjective or physiological effects, or appreciable plasma concentrations of THC or its metabolites.

• At present no public health problems related to misuse, abuse or dependence, including no concern related to “driving under the influence”
Dependence & CBD

• In a human physical dependence study, administration of cannabidiol 1500 mg/day (750 mg 2x daily) to adults for 28 days did not produce signs or symptoms of withdrawal over 6-week period after drug discontinuation

• Suggests that cannabidiol (CBD) does not produce physical dependence


• However, cannabis dependence & withdrawal symptoms are reported in the literature.

• Thus THC (and/or minor cannabinoids) are driving the neuroadaptation that results in a withdrawal syndrome


https://www.drugabuse.gov/publications/research-reports/marijuana/references
# Heterogeneity of State MMJ Programs

<table>
<thead>
<tr>
<th>Regulation = Patient Safety</th>
<th>Licensed HCP + State Regulated Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budtenders + State Regulated Production</td>
<td>CBD falls within the MMJ program if purchased at dispensaries OR if state specifically allows high CBD, low THC products to be sold</td>
</tr>
</tbody>
</table>

## State Allowed Home Grown

## Illegally Obtained

---

## Physicians Cannot Prescribe Medical Marijuana

**Physicians may NOT:**
- Order a patient to consume/obtain or order the dispense of a CS I

**Physicians Can:**
- Discuss treatment options, Pros/Cons (including cannabis products)
- Recommend that a patient consider the use of cannabis for symptoms

The court held that what it regarded as physicians' "legitimate need to discuss with and to recommend to their patients all medically acceptable forms of treatment" outweighs the government's "legitimate interest in suppressing and controlling the flow of dangerous drugs and controlled substances within the United States."

Where Does Cannabidiol Fit?

People who benefit from Cannabidiol

- Seizure Disorders
- Chronic Pain
- Hypertension
- Fibromyalgia, Lupus, Lyme Disease
- Stroke Victims

FREE TRIAL

BENEFITS of CANNABIDIOL that have been clinically validated:

Permission not requested from this company that fills my email full of cannabis spam and false information that has not been requested!!

Sign in a window of a vape shop 0.1 miles from a Police Station

DEA – Marijuanan Extract Rule (MER)
Cannabidiol considered CS I (Dec 2016)

- New drug code established for marijuana extracts = Schedule 1
  - An extract containing 1 or more cannabinoids that has been derived from any plant of the genus Cannabis, other than the separated resin (whether crude or purified) obtained from the plant.

- For practical purposes, all extracts that contain CBD will also contain at least small amounts of other cannabinoids.

- Hemp Industry Association contested this, but was denied by court

https://www.deadiversion.usdoj.gov/schedules/marijuana/m_extract_7350.html
Agricultural Improvement Act of 2018 (aka Farm Bill) and HEMP

- Allows for legal cultivation of Hemp for growers registered with the state and the Department of Agriculture.
- Hemp removed from the Controlled Substance Act
- Allows interstate commerce of legally grown hemp or hemp products
- **Does not supersede the Food Drug and Cosmetic Act**
- Does not prohibit the ability to promulgate Federal regulations and guidelines that relate to the production of hemp

The term ‘hemp’ means the plant Cannabis sativa L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis.

www.congress.gov/115/bills/hr2/BILLS-115hr2enr.pdf

CANNABIDIOL: FOOD DRUG AND COSMETIC ACT HAS AUTHORITY

Unlawful under the FD&C Act to introduce food containing added CBD or THC into interstate commerce, or to market CBD or THC products as, or in, dietary supplements, regardless of whether the substances are hemp-derived. This is because both CBD and THC are active ingredients in FDA-approved drugs and were the subject of substantial clinical investigations before they were marketed as foods or dietary supplements.

- https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628988.htm
Labelling Accuracy of Cannabidiol containing Products obtained on Internet

• Using +/- 10% for label accuracy of CBD content (n=84)
  • 43% over label
  • 26% under label
  • 31% on label

• 18 / 84 samples (22%) contained detectable THC
• THC contamination detected as high as 6.43 mg/mL


THE FDA ACTIVITY

"introduction of a misbranded drug into interstate commerce is a violation “

“intended for treatment of one or more diseases that are not amenable to self-diagnosis or treatment without the supervision of a licensed practitioner. Therefore, it is impossible to write adequate directions for a layperson to use your products safely for their intended purposes.”

<table>
<thead>
<tr>
<th>Product</th>
<th>State</th>
<th>Purchase Website</th>
<th>Product Size (mg)</th>
<th>Lab Results (mg)</th>
<th>Lab Results % (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemp Honey 21% Cannabidiol Oil</td>
<td>CA</td>
<td>hempolive.com</td>
<td>1g 21% CBD</td>
<td>negative for cannabinoid</td>
<td>negative for cannabinoid</td>
</tr>
<tr>
<td>Hemp Honey CBD Tangerine - Blueberry &amp; Cream</td>
<td>CA</td>
<td>hempolive.com</td>
<td>15ml</td>
<td>negative for cannabinoid</td>
<td>negative for cannabinoid</td>
</tr>
<tr>
<td>CBD Oil Extract Capsules</td>
<td>WA</td>
<td>pulsarid.net</td>
<td>300mg CBD</td>
<td>negative for cannabinoid</td>
<td>negative for cannabinoid</td>
</tr>
</tbody>
</table>

Warning Letters
2015
• 6 companies ->18 products
2016
• 8 companies -> 24 products
2017
• 4 companies
2018
• 1 company
Store in a local Mall ....
Selective Reinforcement?

In North Dakota, Police
Targeting CBD Deferred to DEA
Marihuana Extract Rule

• Information for Health Care Professionals Cannabis (marihuana, marijuana) and the cannabinoids Prepared by Health Canada. February 2013
• Mead A. The legal status of cannabis (marijuana) and cannabidiol (CBD) under U.S. law. *Epilepsy Behav.* 2017 May;70(Pt B):288-291.