Cannabis and Your Patient: The Good, The Bad, and The Ugly

Thomas Kupiec, Ph.D.
ARL Bio Pharma
Disclosures

Employee of ARL Bio Pharma
Learning Objectives

At the conclusion of this program, the participating Healthcare provider will understand:

• Define Pharmacodynamics and Pharmacokinetics of Marijuana

• Define the Medical Implications of Marijuana Including:
  – THC and CBD

• Identify Marijuana and its Implications in Healthcare
Medical Marijuana
(MM)
History of Use

- 400 AD: First Medicinal Use (China)
- 1851: Included in USP
- 1937: Marihuana Tax Act Restricted Sales/Use
- 1942: Removed from USP

Bridgeman MB and Abazia, DT. Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting. Pharmacology and Therapeutics. 2017;42(3):180-188
History of Use

• 1970: Prohibition Under Controlled Substances Act (CSA)
• 1996: California first state to legalize
• 2017: Decriminalized in 21 states and D.C.

Recreational use legalized in 8 states

Bridgeman MB and Abazia, DT. Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting. Pharmacology and Therapeutics. 2017;42(3):180-188
Chemical Entity vs Cultivar

• Chemical Entity
  Based on chemical profile

• Cultivar (variety)
  Domesticated Plants
  Breeding and genetic stabilization

• “Skunk #1”, “Haze”, “Northern Lights”,
  “AK47”, “Bubblegum”, “White Widow

3 Main Cultivars

- *Cannabis sativa*
  - Higher THC content
  - Stimulating, uplifting, energizing and creativity enhancing
  - Better at treating depression, headaches, nausea and loss of appetite

Department of Health
3 Main Cultivars

- *Cannabis indica*
  - Higher CBD content
  - Relaxing, sedating, pain reducing
  - Better at treating pain, inflammation, muscle spasms, epilepsy, glaucoma and insomnia

3 Main Cultivars

• *Cannabis ruderalis* (Higher CBD content)

Cannabis Pharmacology

Tetrahydrocannabinolic acid-A (THCA-A) → Heat → Tetrahydrocannabinol (THC)

Heat → Cannabidiolic acid (CBDA) → Heat → Cannabidiol (CBD)

Bridgeman MB and Abazia, DT. Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting. *Pharmacology and Therapeutics*. 2017;42(3):180-188
Endogenous Cannabinoid Agonists

• Anandamide (AEA)

• 2-arachidonoylglycerol (2-AG)

Endogenous Cannabinoid Agonists

- Originate from cell membranes
- Not stored in synaptic vesicles
- Cleaved into arachidonic acid and:
  - Ethanolamine (AEA)
  - Glycerol (2-AG)
- Arachidonic acid linked to prostaglandins

Brain CB1 Receptors:
- Periaqueductal gray
- Raphe nuclei
- Central-medial thalamic nuclei


Bushlin I, Rozenfeld R, and Devi LA. Cannabinoid-opioid interactions during neuropathic pain and analgesia. *Current Opinion in Pharmacology.* 2010;10-80-86
Neural Distribution of CB1 Receptors

CB1 Receptors are Also Found Within the Superficial Dorsal Horn of the Spinal Cord


Distinct Cannabinoid Mechanisms

- THC potently binds $\text{CB}_1$ receptors in the CNS resulting in its euphoric effects\(^1-^3\).
- CBD has very poor affinity for $\text{CB}_1$ receptors and lacks euphoric effects\(^1,^2,^5\).

Neural Effects of CB1 Receptors

• Activation of CB1 Receptors Produces:
  Anti-nociception
  Hypothermia and Sedation
  Hypotension
  Inhibition of Intestinal Motility
  Motor depression

CB1 Receptors Beyond the CNS

- CNS
  - Appetite ↑
  - Cerebral Dilation ↑
  - Core body temperature ↓

- Cardiovascular System
  - Heart rate ↓
  - Blood pressure ↓
  - Myocardial contractility ↓
  - Coronary dilation ↑

- Liver
  - Lipogenesis Cerebral Adipogenesis ↓
  - Adiponectin ↑
  - Plasma triglyceride ↑
  - HDL cholesterol ↓

- Adipose Tissue
  - Insulin and leptin resistance ↑
  - Glucose tolerance ↓
  - Thermogenesis ↓

- Skeletal Muscle

(Pacher et al 2008)

Department of Health
• CB2:
Mainly expressed in the immune system and hematopoietic cells

Immuno-modulation effects

Signal Transduction Pathways

• CB1 receptors are G-protein coupled receptors that couple to $G_{\alpha i}$ and inhibit cAMP production

• Activate MAP kinases

• Inhibit calcium channels and activate of potassium channels

THC

- CB1 >>> CB2 partial agonist
  - ↑ appetite, cerebral dilation
  - ↓ core temperature, heart rate, myocardial contractility
- Psychoactive
  - 11-OH-THC 4x more potent
- Lipophilic
- Anti-inflammatory, neuro-protective
- Anti-nausea, analgesia

CBD

- Non-psychoactive
- Inhibits formation of 11-OH-THC
  Mitigates psychoactive effects of THC
  Enhances therapeutic effects of THC
- Inhibits adenosine uptake
- Inhibits release of pro-inflammatory cytokines
- Potent CYP2D6 and CYP3A1 inhibitor

- Meta-analysis suggests clinical improvement in seizure frequency for certain seizure disorders

Pharmacokinetics

• Inhalation

Onset of ~90 seconds with peak at 3-10 minutes

Easier to titrate

Cleared in 3 hours

Similar carcinogens and bronchial irritants as cigarette smoking

Pharmacokinetics

- Oral

  Onset of 90 minutes with peak at 1-6 hours
  Half life is 20-30 hours
  Low and erratic GI bioavailability with first past metabolism
  50% of the THC is metabolized before entering systemic circulation

  “Start low and go slow”

Blood Cannabinoids vs “high” (After Smoking 2 Marijuana Joints)
Drug Interaction Concerns

- Interactions may exist between medical marijuana and other drugs

- CYP2C9 and 3A4 play a significant role in the primary metabolism of THC

  3A4 inhibitors will ↑ THC concentrations

- CYP2C19 and 3A4 are responsible for CBD metabolism

Bridgeman MB and Abazia, DT. Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting. *Pharmacology and Therapeutics*. 2017;42(3):180-188
Routes of Administration

• Common:
  Inhalation: Smoking and vaporization
  Edibles
• Others
  Topical
  Rectal

Oral: Oro-mucosal/sublingual
Dosage Forms

- Herbal/joints
- Chemically-extracted concentrates
  - Has varying amounts of THC
- Resin
- Edibles, tinctures, oils
- Lozenges, lollipops
- Prescription oral products
Common Forms and Routes of Administration

- **Common modes of administration**
  - Inhalation (smoking, vaporization)
  - Oral
  - Oro-mucosal or Sublingual
  - Topical, Rectal

- **Common formulations**
  - Herbal cannabis, Resin
  - Chemically-extracted concentrates
  - Edibles, Tinctures
  - Lozenges, Lollipops, Nabiximols
  - Prescription cannabinoids (dronabinol, nabilone)

Department of Health
Quality Control Concerns

• May be contaminated with harmful fungi and bacteria (McPartland, et. al.)

• Pesticides may leave residues (Sullivan, et. al.)

• Quality control standards for cultivation, drying, packaging, and analytical testing

  Should be more strictly enforced


Chemical Extraction Concerns

- Extraction processes may leave behind residual solvents
- E-cigarette formulations often contain propylene glycol
  Carbonyls (e.g. formaldehyde) may form when vaporizing
- Extraction may remove medically beneficial terpenoids

Department of Health
CBD Purification Concerns

• Positive marijuana tests for CBD users

• Quality control

  Sensitivity and specificity of assays for testing purposes

• 0.3% vs 0.1% THC content
Current U.S. FDA Approved Drugs

• Dronabinol (Marinol) – May 1985

THC (2.5, 5, or 10mg) - $200

Chemo related nausea/vomiting

AIDS-associated anorexia

Dronabinol, nabilone, and cannabidiol monographs. Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; October 8, 2018
Current U.S. FDA Approved Drugs

• Nabilone (Cesamet) – December 1985

THC (1mg) – $2,000

Chemo related nausea/vomiting

Dronabinol, nabilone, and cannabidiol monographs. Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; October 8, 2018
Current U.S. FDA Approved Drugs

- Cannabidiol (Epidiolex) – June 2018

CBD (100 mg/mL; 100 mL) – $14.82 per 1 mL

Lennox-Gestault Syndrome

Dravet Syndrome

Dronabinol, nabilone, and cannabidiol monographs. Lexi-Comp, Inc. (Lexi-Drugs™). Lexi-Comp, Inc.; October 8, 2018
Products Outside the U.S.

- Nabiximols (Sativex) – THC/CBD

Oro-mucosal Spray

Multiple Sclerosis and Cancer Pain
Products Outside the U.S.

- Canasol:
  - Available in Jamaica
  - Ophthalmic Drops
Disadvantages of THC Only Products

• Lack constituents that mitigate side effects:
  
  CBD
  
  Terpenoids

• Harmful effects more likely in the elderly and frail
Disadvantages of THC Only Products

• Dronabinol Adverse Effects
  Lethargy and Dizziness
  Anxiety and Paranoia
  Seizure risk
  Depersonalization

• Additional Nabilone Adverse Effects:
  Dry mouth
Clinical Applications
Substantial Evidence For...

• MM is effective for

  Treatment of chronic pain in adults

  Chemotherapy-induced nausea and vomiting

  Improving patient-reported spasticity symptoms in multiple sclerosis

Synergy with Opiate Use

- Cannabinoids act as opioid sparing agents

Lower Doses

Fewer Side Effects

Synergy with Opiate Use

- MM use associated with
  64% Decrease in Opioid Use (n=118)
- Decreased Number of Medications
- Fewer Side Effects
- Improved Quality of Life (45%)

CBD Decreases Inflammation in Multiple Sclerosis

- Modified the deleterious effects of inflammation
- CBD decreased the transmigration of blood leukocytes to decrease inflammation
- Improves MS associated motor deficits

Neuropathic Pain

• A single inhalation of 25 mg smoked cannabis of three times daily for 5 days

  Reduced pain intensity

  Improved sleep

  Well tolerated

• Neuropathic pain reduction was modest compared to gabapentin and pregabalin

Glaucoma

- Recent review by the American Society of Glaucoma indicated that marijuana does lower intraocular pressure for 3-4 hours requiring frequent administration

- ASG does NOT recommend for treatment of glaucoma due to the short duration of effectiveness

Jampel H. J Glaucoma. 2010 Feb; 19(2):75-6
Anti-emesis

• Systematic review and meta-analysis found cannabinoids were superior to conventional drugs

• Chemotherapy-induced nausea and vomiting
  Dronabinol: Statistically and clinically more effective than neuroleptics
  Nabilone: Clinically but not statistically more effective

THC/CBD Decreases Inflammation

THC/CBD Decreases Inflammation

Adverse Effects

- Addiction risk increases
- Mental illness risk with early exposure
- Cognitive development deficits
- Development of respiratory problems

Review Article of Adverse Effects

- Possible gateway drug
- Motor vehicle accidents increase 2-fold after marijuana use
- E.R. visits have increased yearly due to marijuana use

<table>
<thead>
<tr>
<th>Effect</th>
<th>Overall Level of Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction to marijuana and other substances</td>
<td>High</td>
</tr>
<tr>
<td>Abnormal brain development</td>
<td>Medium</td>
</tr>
<tr>
<td>Progression to use of other drugs</td>
<td>Medium</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Medium</td>
</tr>
<tr>
<td>Depression or anxiety</td>
<td>Medium</td>
</tr>
<tr>
<td>Diminished lifetime achievement</td>
<td>High</td>
</tr>
<tr>
<td>Motor vehicle accidents</td>
<td>High</td>
</tr>
<tr>
<td>Symptoms of chronic bronchitis</td>
<td>High</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Low</td>
</tr>
</tbody>
</table>

Risk Factors for MM Use Problems

• Using MM at Earlier Ages
• Increases in Frequency of MM Use
• Male Sex
• Cigarette Smoking
• **Stimulant Treatment for ADHD is NOT a Risk Factor**

MM as a Possible Gateway Drug

• Moderate evidence suggests a relationship between MM use and other substance use disorders:
  
  Alcohol
  
  Tobacco
  
  Other illicit drugs

Cannabis Use and Risk of Prescription Opioid Use Disorder in the U.S.

Cannabis use appears to increase risk of developing non-medical prescription opioid use and opioid use disorder.


NESARC—National Epidemiological Survey on Alcohol and Related Conditions; wave 1 was conducted in 2001 and 2002, and wave 2 in 2004 and 2005.
Federal Law

• Marijuana is a Schedule I under the Controlled Substances Act of 1970

Recreational or Medical

• According to the DEA, Schedule I means:
  “No Currently Accepted Medical Use”
  “High Potential for Abuse”
Hemp Farming Act: Proposed 2018

• Redefines Hemp to include all derivatives, extracts, and cannabinoids with THC ≤ 0.3%

• Hemp removed from the CSA
  THC and derivatives remain Schedule I

• State may cultivate hemp independent of federal research programs if passed

Further Information

The legal status of cannabis (marijuana) and cannabidiol (CBD) under U.S. law

Alice Mead, J.D. LL.M.*

GW Pharmaceuticals, Inc., 5800 Armada Dr., Suite 210, Carlsbad, CA 92008, United States

ARTICLE INFO

Article history:
Received 20 October 2016
Revised 13 November 2016
Accepted 14 November 2016
Available online 4 February 2017

Keywords:

ABSTRACT

In the United States, federal and state laws regarding the medical use of cannabis and cannabinoids are in conflict and have led to confusion among patients, caregivers, and healthcare providers. Currently, cannabis is legal for medical purposes in 50% of the states, and another seventeen states allow products that are high in cannabidiol (CBD) and low in THC (tetrahydrocannabinol) for medical use. Many of these artisanal products are sold in dispensaries or over the internet. However, none of these products has been approved by the Food and Drug Administration (FDA). Understanding how federal laws apply to clinical research and practice can be challenging, and the complexity of laws has led to a lack of rigorous scientific evaluation in the legal status of CBD. This paper...
Further Information

Cannabis and Cannabinoid Research
Volume 3.1, 2018
DOI: 10.1089/can.2018.0030

PERIODICAL

Open Access

Regulatory Status of Cannabidiol in the United States: A Perspective

Jamie Corroon\textsuperscript{1,2,*} and Rod Kight\textsuperscript{3}

Abstract
Cannabidiol (CBD) is 1 of > 100 cannabinoids found in Cannabis sativa L. (Cannabis spp. or Cannabis). Despite its complex and rapidly evolving regulatory status in the United States, projected retail sales of CBD products—hemp, cannabis and pharmaceutical—are as high as $1.9 billion by 2020. CBD products can currently be purchased online, over the counter, and at cannabis-specific dispensaries throughout most parts of the country, despite the fact that CBD is presently deemed a Schedule I controlled substance by the U.S. Drug Enforcement Administration and renounced as a dietary supplement ingredient by the U.S. Food and Drug Administration (FDA). These products are largely unregulated, and are being used predominantly to treat specific medical conditions...
Summary- Medical Marijuana

• THC is primary psychoactive component of cannabis with higher affinity for CB1 and CB2 receptors

• CBD is the non-psychoactive component that can mitigate the THC side effects

• Quality Control Concerns- MM and CBD
Summary- Medical Marijuana

• CB1 receptors are found in the CNS
• CB2 receptors are found in the immune system
• There are many routes of administration and many dosage forms with different pharmacokinetic parameters
Summary- Medical Marijuana

• MM has demonstrated benefit in chemotherapy-induced nausea and vomiting and chronic pain and spasticity symptoms in multiple sclerosis

• MM remains federally illegal, and the DOJ reserves the right to enforce law at any time
Acknowledgements

• Scott Schaeffer, D.Ph., DABAT, Managing Director of Oklahoma Poison and Drug Information

• Kelly M. Standifer, Ph.D., Professor and Department Chair of Pharmaceutical Sciences of University of Oklahoma College of Pharmacy

• Joy Woods, Pharm.D. Candidate 2019

• Quy Nguyen, Pharm.D. Candidate 2019

• Jacob Haddock, Pharm.D. Candidate 2019
Need More Information?

Thomas Kupiec
President and CEO, ARL Bio Pharma
tkupiec@arlok.com
405-271-1144
References


2. Russo, E. Cannabis in India: Ancient lore and modern medicine. *GW Pharmaceuticals*. March 2006 DOI: 10.1007/3-7643-7358-X_1


References