Medical Cannabis for Health Professionals

Ray Bailey BPharm, R.Ph.
Educational Objectives

- Explain the mechanisms of action and pharmacological properties of Cannabis, including administration, dosing and formulations
- Identify disease states where Cannabis has shown efficacy and define particularly in Cancer patients
- Discuss adverse drug reactions, drug interactions and required monitoring
- Outline the history of Medical Cannabis use
- Discuss the Pharmacist role in counseling patients and caregivers and legal implications
- Discuss the Federal Prohibition and the impact on Clinical Research and Pharmacist involvement
What is Cannabis (Marijuana)

- The Cannabinoids – Some 113 identified to date
  - Delta-9-THC (Tetrahydrocannabinol)
  - Cannabidol (CBD) Charlotte’s Web
  - Cannabigerol Acid – Chemical precursor to THC and CBD
  - Cannabinol (CBN) Most prevalent chemical compound
  - Cannabichomene (CBC)
- Terpenoids – Produce Marijuana distinct aroma
- Flavonoids – over 20 known

- Cannabis most common routes of administration
  - Smoked either rolled or in pipes
  - Ingested in many edible forms
  - Vaporized in a variety of marketed devices
The Endocannabinoid System

- The Endocannabinoid System is the largest neural pathway in the human body – responsible for total body homeostasis (Pain baseline theory)
- Receptors first identified in 1992 – CB1 and CB2 and distributed throughout the central nervous and immune systems
- First naturally occurring endocannabinoids isolated
  - Anandamide stimulates CB1 receptor site as does THC
  - 2-AG stimulates CB2 receptor site as does CBD
- Endocannabinoids serve as the primary messenger across the synapse and is thought to affect the release (modulation) of neurotransmitters. Their role in the synapse is more important and far more complex than previously thought. Much more research is needed.
- The proper endocannabinoid “tone” is associated with general well-being
A Biological System of Endocannabinoids Neurotransmitters and Receptors

CB1 RECEPTORS ARE LOCATED IN CELLS OF THE:
- Brain/CNS/Spinal cord (CB1)
- Cortical regions (CB1): neocortex, pyriform cortex, hippocampus, amygdala
- Cerebellum (CB1)
- Brainstem (CB1)
- Basal ganglia (CB1): globus pallidus, substantia nigra par, reticulata
- Olfactory bulb (CB1)
- Thalamus (CB1)
- Hypothalamus (endocrine-brain link CB1)
- Pituitary (CB1)
- Thyroid (endocrine gland (CB1))
- Upper Airways (of mammals CB1)
- Liver (CB1): kupffer cells (macrophage immune cells), hepatocytes (liver cell), hepatic stellate cells (fat storage cell)
- Adrenals (endocrine gland CB1)
- Ovaries (gonads and endocrine gland CB1)
- Uterus (myometrium CB1)
- Prostate (CB1): epithelial and smooth muscle cells
- Testes (gonads and endocrine gland CB1): Leydig cells: sperm cells

CB1 AND CB2 RECEPTORS ARE LOCATED IN CELLS OF THE:
- Eye (CB1 and CB2)
- Retinal pigment epithelial/RPE cells
- Stomach (CB1 and CB2)
- Heart (CB1 and CB2)
- Pancreas (CB1 and CB2)
- Digestive tract (CB1 and CB2)
- Bone (CB1 and CB2)

Non-CB1 and non-CB2 are located in cells of the:
- Blood vessels: epithelial cells of arterial blood vessels (non-CB1 and non-CB2)

CB2 receptors are located in cells of the:
- Lymphatic and Immune system
  - Spleen (CB2)
  - Thymus (CB2)
  - Tonsils (CB2)
  - Blood (CB2) lymphocytes

Non-Immune cell CB2 receptors are found in the Skin keratinocytes
Phytocannabinoids

- More than 545 chemical constituents produced within the cannabis plant
- Phytocannabinoids are cannabinoids produced by the cannabis plant in the form of carboxylic acids:
  - THCA
  - CBDA
- Upon heating, or gradually warming up to room temperature over time, these cannabinoids are converted to their chemically neutral more widely known forms THC and CBD
- It is in this neutral form that THC become psychoactive to humans
- Now thought that cannabinoids work in concert with each other, along with terpenes to produce differences in medicinal and psychoactive effects
The Highly Studied Cannabinoids

- **THC**
  - Certain stains can produce up to 25% of the plants dry weight in THC
  - Primary psychoactive constituent of cannabis
  - Potent anti-inflammatory and analgesic
  - Is neuroprotective and reduces intraocular pressure, spasticity and muscle tension
  - No activity in the brain stem thusly impossible to lethally overdose. LD50 unknown

- **CBD**
  - Most common phytocannabinoid in fiber cannabis (hemp) and second most common in drug cannabis varieties
  - Due to Project CBD, High-CBD cannabis varieties have reemerged. Some with a 20:1 CBDA to THCA concentration
  - Seems to be more neuroprotective with little or no psychoactive effects
  - GW Pharma has drug in clinical trials which is combination of THC and CBD called Sativex (sublingual spray) Available in Europe and Canada
  - CBD compounds used in Israel for strokes patients in place of tPA
  - FDA has recently approved CBD based Epidiolex for 2 forms of severe childhood epilepsies

- Committee Report Health Effects of Marijuana
- Current State of Evidence
- Recommendations for Research
- MARIE C. McCORMICK (Chair), Sumner and Esther Feldberg Professor, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA
Figure 1. Pharmacological actions of non-psychotropic cannabinoids (with the indication of the proposed mechanisms of action).

Abbreviations: $\Delta^8$-THC, $\Delta$-tetrahydrocannabinol; $\Delta^8$-THC, $\Delta$-tetrahydrocannabinol; CBN, cannabindol; CBD, cannabidiol; $\Delta^8$-THCV, $\Delta$-tetrahydrocannabivarin; CBC, cannabichromene; CBG, cannabigerol; $\Delta^8$-THCA, $\Delta$-tetrahydrocannabinolic acid; CBDA, cannabidiolic acid; TRPV1, transient receptor potential vanilloid type 1; PPAR, peroxisome proliferator-activated receptor $\gamma$; ROS, reactive oxygen species; 5-HT$_{1A}$, 5-hydroxytryptamine receptor subtype 1A; FAAH, fatty acid amide hydrolase. (+), direct or indirect activation; ↑, increase; ↓, decrease.


Article: Literature Review in Trends in Pharmacological Sciences 30(10):515-27 · October 2009 with 283 Reads

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Disease States Cannabis has Efficacy

- Alzheimer’s Disease
- Anxiety Disorders
- Arthritis
- Asthma
- Autoimmune Disorders
- Cachexia/Appetite Disorders
- Cancer
- Chronic Fatigue Syndrome
- Fibromyalgia
- GI Disorders
- Glaucoma
- HIV/AIDS
- Insomnia Sleep Disorders

- Migraine and Headaches
- Multiple Sclerosis
- Nausea and Vomiting (CINV)
- Neuropathy
- Pain
- Parkinson’s Disease
- PTSD
- Schizophrenia
- Seizure Disorders
- Skin Conditions
- Stress
- Diabetes
References

- “Gil Bar-Sela, M. Vorobiehik, S. Drawsheh, A. Omer, V. Goldberg, E. Muller, “The Medical Necessity for Medicinal Cannabis: Prospective, Observational Study Evaluating the Treatment in Cancer Patients on Supportive or Palliative Care,” Evidence-Based Complementary and Alternative Medicine (2013).”
References

Cannabis and Cancer Pain

- Pain was the primary symptom for which the evidence supporting the use of cannabis medicines was rated as strong in the 2017 National Academies report.
- Pain is the most common condition for which patients report using cannabis.
- Finding the optimal dose for pain relief has been shown to be very important.
- A University of California San Diego study showed that low doses provided little relief while moderate doses produced good pain relief.
- This same study showed that larger doses actually increased pain levels.
- Perhaps confirming the results of the UC San Diego study a study of Sativex® cannabinoid spray for intractable cancer pain showed that cannabis was most effective at lower and medium doses, which would seem to support the hypothesis that higher doses of cannabinoids do not necessarily provide increased pain relief.

Cannabis and Cachexia

- Cannabis medicines have shown effective in treating AIDS associated cachexia. An early trial with oral THC using a dose or 2.5mg did show success in maintaining patients appetite over the 7 months of the study.
- Research studies looking at cancer-related cachexia has shown conflicting results
- The Cannabis in Cachexia Study Group was discontinued when cannabis showed little advantages over placebo.
- This study is often cited and was a randomized double-blind study of cancer patients
- It found that low doses of THC-CBD extract or THC were no better than placebo for appetite and produced more side effects.


Cannabis Cancer Treatment

- Of many studies worldwide using cannabis as a treatment for GBM, I found this one most interesting
- A pilot study published in 2006 (referenced below) involved nine patients with glioblastoma multiforme that showed disease progression after all other conventional treatments were exhausted.
- A catheter was inserted in the tumor and a THC solution was injected daily in increasing doses for 10 days.
- The starting dose was small 20-40mg and was titrated up to 80-180mcg.
- Three of the nine patients improved clinically and two lived approximately one year.
Cannabis use in Cancer - Summary

- The treatment of the major symptoms of cancer by cannabis in various forms is not controversial. In fact a medical review of the uses of cannabis show strong scientific evidence to support use in pain, CINV, appetite stimulation and sleep.

- There are randomized controlled clinical trials of good quality to support the treatment of pain, and controlled trials of weaker quality that support the treatment of CINV, insomnia, and appetite stimulation with weight loss. (one conflicting study cited and National Academies Report states insufficient evidence to support or refute.

- Medical cannabis is also effective for reducing, preventing, relieving, or distracting from both neuropathic and visceral pain.
References

Pharmacy Implications

- Smoked/Vaped Cannabis show peak concentrations in 10 minutes-decreased to 60% of peak in 15 minutes and 20% in 20 minutes. Allows patient to titrate dose
- Ingested Cannabis- lower plasma levels due to first-pass effect and highly variable with peaks 1-6 hours later
- Sublingual admin levels similar to smoked/NO first pass
- 11-OH metabolite of ingested THC contribute greatly to psychotropic effects
- More than 55% of THC is excreted in the feces and ~20% in the urine
- Synthetic THC Marinol (Dronabinol) and Synthetic analog of THC Cesamet (Nabilone) Bioavailability 5-20%, Peak 1-6 hours, 10% of that achieved with smoking
- Side Effects of Medical Cannabis both inhaled and orally (THC)
  - Euphoria
  - Dry mouth
  - Reddening of the eyes
  - Increased appetite
  - Blurred vision
  - Dizziness and headache
  - Sedation
  - Anxiety
Pharmacy Implications (Cont)

- Currently very little data regarding potential drug interactions with cannabis. We can make some predictions based on the known pharmacology of the compounds
- THC and CBD extensively metabolized by CYP3A4/5 and CYP2C9/19
- Patients who are poor metabolizers of CYP2C9 have been shown to have THC concentrations 3 times higher than extensive metabolizers
- Inhibitors of CYP2C9 could be expected to increase plasma concentration of THC
- Amiodarone, cimetidine, cotrimoxazole, metronidazole, fluconazole, voriconazole
- Ketoconazole is an inhibitor of CYP3A4 and has been reported to increase the AUC time curve of THC 1.2-1.8 fold
Pharmacy Implications (Cont)

• Other CYP3A4 inhibitors could be expected to produce similar increases

• Rifampin is a CYP3A4 inducer and has been reported to reduce THC levels by 20-40%. One study has shown a reduction CBD levels of 50-60%

• In vitro studies have shown THC and CBD to have limited ability to inhibit CPY450 enzymes

• Smoking itself (e.g. tobacco or cannabis) induces CYP1A2 which may increase clearance of some antipsychotics and antidepressants
History of Cannabis

- 10,000 Years ago Cannabis found in clay jars in Japan
- 4700 Years ago Cannabis was an important herbal remedy in China
- 1500–200 BC Cannabis used as a medicine in India
- 500 BC Cannabis was the most important of all known medicinal plants in Persia
- 200 BC Cannabis used as a medicine in Egypt and Greece
- 1800’s Cannabis Indica brought to the US from India
- 1850–1941 Cannabis Tincture USP
The Federal Prohibition

Cannabis remains a Schedule I drug on a Federal Level
The Federal Prohibition

- Marijuana Tax Act of 1937
- AMA and Pharmacist fought this act but succumb and Cannabis removed from USP in 1942
- Controlled Substance Act is a statute under the Comprehensive Drug Abuse Prevention and Control Act of 1970 signed by President Nixon
- Medical Cannabis is now legal in 33 States and D.C.
- NIDA controls supply of Cannabis legal for Medical Research. University of Mississippi
- DEA and NIDA have recently relaxed rules allowing researcher to obtain cannabis from other sources for research
- Until Rescheduled at a Federal level has no place in any licensed Pharmacy. Would be putting DEA license at risk
- If legal at a State level, Pharmacist should be able to counsel patients on potential SE and drug interactions
- In some States Medical Professional cannot obtain a Medical Cannabis Card
- Why is most psychoactive component of Cannabis Schedule III and the raw plant Schedule I?
Question?