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OBJECTIVES

- Discuss the good, the bad, and the ugly of the following
  - Opioids
  - Marijuana
    - THC
    - CBD
  - Combination of opioids and marijuana
OPIOIDS
HISTORICAL SIGNIFICANCE OF OPIOIDS

Natural narcotics

Semisynthetic narcotics

Totally synthetic narcotics

Endogenous opioids

Opium

Morphine  Codeine  Thebaine

Heroin  Hydromorphone  Oxycodone  Etorphine

Pentazocine  Meperidine  Fentanyl  Methadone

Nalbuphine  Buprenorphine

Enkephalins  Endorphins  Dynorphins
Opioids and endogenous opioids activate the different opioid receptors on the presynaptic receptor.

This inhibits release of GABA to allow dopaminergic neurons to fire more vigorously.

The extra dopamine is responsible for the pleasure sensation.

OPIOID EFFECTIVENESS ON PAIN

- Meta-analysis of 22 articles (Eisenberg et al.)
  - Intermediate studies demonstrated significant efficacy of opioids over placebo for neuropathic pain

- Meta-analysis of 41 randomized trials involving 6019 patients (Furlan et al.)
  - Opioids were more effective than placebo for both pain and functional outcomes in patients with neuropathic pain or fibromyalgia
  - Opioids were significantly superior to naproxen and nortriptyline for pain relief


OPIOID SIDE EFFECTS

- Nausea and vomiting
- Pruritus
- Sedation
- Respiratory depression
- Urinary Retention
- Constipation

MISUSE, ABUSE, AND ADDICTION

- Patients will take sporadically
  - No medications taken on “good” days, doubling up on “bad” days
- Tolerance develops resulting in needing higher doses
  - The only side effect that tolerance does not develop is constipation
- Chemical coping (taking opioids to manage stress or improve mood)
- Taking opioids just to get “high”

From 1999 to 2016, more than 200,000 people died of prescription opioid overdoses
  - Deaths in 2016 were five times higher than in 1999

According to the National Institute on Drug Abuse, in 2015 Oklahoma providers wrote 101.7 opioid prescriptions per 100 persons
  - 2015 US average was 70

Oklahoma had 88 total opioid prescriptions per 100 people in 2017, according to Statista

Most common drugs involved
  - US: Methadone, oxycodone, hydrocodone
  - Oklahoma: Hydrocodone, fentanyl, oxycodone

U.S. OPIOID PRESCRIBING TRENDS

Trends in Annual Opioid Prescribing Rates by Overall and High-Dosage Prescriptions

Year

Prescribing rate per 100 persons


OKLAHOMA DATA

Substances Involved in Unintentional Poisoning Deaths, Oklahoma, 2012-2016

Opioid Analgesics (Painkillers) 64%
Benzodiazepines (Anti-anxiety) 18%
Antidepressants 8%
Muscle Relaxants 5%
Other 5%

What type of prescription drugs?

Source: OSDH, Injury Prevention Service, Fatal Unintentional Poisoning Surveillance System (Abstracted from Medical Examiner reports)

Nguyen, Claire. Fatal Unintentional Poisoning Surveillance system: data update. Oklahoma State Department of Health
OKLAHOMA PRESCRIPTION DRUG DEATHS

Deaths Involving Most Common Prescription Drug Categories by Year of Death, Unintentional Poisoning, Oklahoma, 2007-2016

Source: OSDH, Injury Prevention Service, Fatal Unintentional Poisoning Surveillance System (Abstracted from Medical Examiner reports)

Nguyen, Claire. Fatal Unintentional Poisoning Surveillance system: data update. Oklahoma State Department of Health
Patient-provider agreement prior to starting opioid therapy
- Risks, benefits, rights of patient, course of therapy parameters

Initial prescription
- Patient has not had an opioid prescription within the past year
- NO more than 7 days of therapy for acute pain

Acute pain
- May result from disease, accidental or intentional trauma that is expected to last only a short period of time
- NOT chronic pain, cancer pain, hospice or palliative pain

Effective November 1st, 2018
Walmart's Opioid Stewardship

- Walmart recently initiated a opioid stewardship program
- Opioid prescriptions for initial therapy of an acute condition is limited to 7 days and up to 50 milli-equivalents of morphine a day
- “DisposeRx” is a packet of powder designed to deactivate the active ingredient
  - Provided free to patients
MEDICAL MARIJUANA (MM)
HISTORICAL SIGNIFICANCE

- 400 AD- first time cannabis was used medicinally (China)
- 1800s-1900s widely used as a patent medicine
- 1851- *USP* classified as legitimate medical compound
- 1937- Marihuana Tax Act restricted use and sales of cannabis
- 1942- *USP* dropped it
- 1970- Prohibition under the Controlled Substances Act
- 1996- California was the first state to permit legal access
- 2017- 21 states with DC decriminalized marijuana and 8 have legalized it for recreational use

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) names
  - Domesticated plants through breeding and genetic stabilization
  - “Skunk #1”, “Haze”, “Northern Lights”,
    “AK47”, “Bubblegum”, “White Widow

3 MAIN CULTIVARS

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

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

3) *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
CB1 Receptors Beyond the CNS

CB1 Activation

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

CARDIOVASCULAR SYSTEM
- Heart rate ↓
- Blood pressure ↓
- Myocardial contractility ↓
- Coronary dilation ↑

LIVER
- Lipogenesis Cerebral ↑
- Adiponectin ↓
- Plasma triglyceride ↑
- HDL cholesterol ↓

ADIPOSE TISSUE
- Insulin and leptin resistance ↑
- Glucose tolerance ↓
- Thermogenesis ↓

SKELETAL MUSCLE

(Pacher et al. 2008)

CB2 Receptors

- CB₂
  - Mainly expressed in the immune system and hematopoietic cells
  - Immunomodulation effects

**ENDOGENOUS CANNABINOID AGONISTS**

- Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are the most understood
  - They come from larger phospholipids in cell membranes
    - Not stored in synaptic vesicles like most neurotransmitters
  - They are cleaved into arachidonic acid and ethanolamine (AEA) or glycerol (2-AG)
  - Arachidonic acid links the endocannabinoid and prostaglandin systems

Department of Health
CB₁ >>> CB₂ partial agonist
- Increases appetite, cerebral dilation
- Decreases core body temperature, heart rate and myocardial contractility

Psychoactive
- Metabolite 11-OH-THC is 4 times more psychoactive

Lipophilic
- Anti-inflammatory, neuro-protective
- Anti-nausea, analgesia

CBD

- Non-psychoactive
- Inhibits formation of 11-OH-THC, the metabolite of THC
  - Mitigates side effects of THC: anxiety, dysphoria, panic reactions, and paranoia
  - Enhances therapeutic side effects of THC
- Inhibits adenosine uptake and release of pro-inflammatory cytokines
- Potent CYP2D6 and CYP3A1 inhibitor
- Meta-analysis suggests clinical improvement in seizure frequency for certain seizure disorders

**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)

Dronabinol (Marinol) – THC (2.5, 5, or 10mg) - May 1985; $200
  - Indicated for chemo related nausea/vomiting, and AIDS-associated anorexia

Nabilone (Cesamet) – THC (1mg) – December 1985; $2,000
  - Indicated for chemo related nausea/vomiting

Cannabidiol (Epidiolex) – CBD – June 2018
  - Indicated for Lennox-Gestault Syndrome or Dravet Syndrome in patients
PRODUCTS OUTSIDE THE U.S.

- Nabiximols (Sativex) – THC/CBD
  - Oromucosal spray for multiple sclerosis and cancer pain
  - Not available in the United States

- Ophthalmic drops (Canasol)- available in Jamaica
DISADVANTAGES OF THC ONLY PRODUCTS

- Lack other constituents in cannabis that mitigate the side effects of THC
- Harmful effects in the elderly and frail more likely with dronabinol
  - Frequent lethargy and dizziness
  - Anxiety and paranoia
  - Seizure risk
  - Depersonalization
- Nabilone adverse effects include lethargy, vertigo, and dry mouth
**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

- **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)

“high”

[THC] active

[THCCOOH] Non-active

Time, min.
QUALITY CONTROL CONCERNS

- Growers may sell herbal cannabis contaminated with harmful fungi and bacteria (McPartland et al)
- Dangerous pesticides may be used to spray the crops allowing residues to left on the product (Sullivan et al)
- Quality control standards for cultivation, drying, and packaging as well as analytical testing
  - Should be more strictly enforced

CHEMICAL EXTRACTION CONCERNS

- Extraction processes may leave behind residual solvents
- E-cigarette formulations often contain propylene glycol
  - When vaporized, carbonyls like formaldehyde may form
- These processes often removes terpenoids that have medical benefits

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
Metabolic and pharmacodynamics 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 increases THC concentrations

- CYP2C19 and 3A4 are responsible for CBD metabolism

- Drugs that utilize these isozymes have potential to create major interactions
ADVERSE EFFECTS

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

RISK FACTORS FOR MM USE PROBLEMS

- Substantial evidence
  - Using MM at earlier ages poses a risk for the development of problem MM use
  - Increases in use of frequency will increase risk of developing problems
  - Males and smoking cigarettes also increases the risk
  - Stimulant treatment of ADHD is NOT a risk factor for developing problems

**SUBSTANTIAL EVIDENCE FOR...**

- MM are effective for
  - Treatment of chronic pain in adults
  - Chemotherapy-induced nausea and vomiting
  - Improving *patient-reported* spasticity symptoms in multiple sclerosis
CBD DECREASES INFLAMMATION IN MULTIPLE SCLEROSIS

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

NEUROPATHIC PAIN

- A RCT study of a single inhalation of smoked cannabis of 25 mg three times daily for 5 days
  - Reduced pain intensity
  - Improved sleep
  - Well tolerated

- Also showed a neuropathic pain reduction that was modest compared to gabapentin and pregabalin

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 of RCTs revealed a superiority of cannabinoids when compared to conventional drugs

- Chemotherapy-induced nausea and vomiting
  - Dronabinol was statistically and clinically more effective as an anti-emetic than neuroleptics
  - Nabilone was clinically more effective without statistical significance

THC/CBD DECREASES INFLAMMATION

THC/CBD DECREASES INFLAMMATION

Other conclusions

- Possible role as gateway drug
- Motor vehicle accidents increase by a factor of 2 when driving after marijuana use
- Number of Emergency Department visits have been increasing every year due to marijuana use
MM AS POSSIBLE GATEWAY DRUG

- There is moderate evidence suggesting MM use and development of other substance disorders
  - Alcohol
  - Tobacco
  - Other illicit drugs
COMBINATION THERAPY
Both receptor types are found in the same region of the brain

- **Periaqueductal gray**, raphe nuclei and central-medial thalamic nuclei
- Mu opioid receptors (MOR) and CB₁ are found in the same neuron within the superficial **dorsal horn** of the spinal cord

Activation of opioid or cannabinoid receptors produce similar effects in

- Anti-nociception, hypothermia, sedation, hypotension, inhibition of intestinal motility and motor depression
SIMILARITIES IN PATHWAYS BETWEEN BOTH

- Both receptors share similar signal transduction
  - Both are GPCRs that couple to $G_{\alpha_i}$ to block cAMP production

- Both activate MAP kinases

- Both inhibit calcium channels and activation of potassium channels

Bushlin I, Rozenfeld R, and Devi LA. Cannabinoid-opioid interactions during neuropathic pain and analgesia. *Current Opinion in Pharmacology.* 2010;10-80-86
IV FENTANYL AND ORAL CANNABIDIOL

- Double-blind, placebo-controlled cross over study

- Results
  - Co-administration did NOT produce respiratory depression or cardiovascular complications
  - CBD did not potentiate fentanyl effects

Results

- Patients on opioids had the highest prevalence of diagnosis of depression and anxiety.
- Patients only on medical marijuana had lower prevalence rates than patients on both opioids and MM and opioids alone.

SYNERGY WITH OPIATE USE

- Cannabinoids act synergistically with opioids and act as opioid sparing agents allowing for lower doses and fewer side effects from chronic opioid therapy for certain conditions (Elikottil J. et al)

- Medical cannabis use was associated with a 64% decrease in opioid use (n=118), decreased number and side effects of medications, and improved quality of life (45%) (Boehnke, et al)

Results

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

- Opioids are effective for pain treatment

- Unintentional deaths due to prescriptions are highest with the opioid class

- New opioid legislature for prescribers will take into effect on November 1st, 2018

- Balancing between pain management, palliative care, and addiction
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
CB1 receptors are found mainly in the CNS while CB2 is in the periphery of the immune system.

There are many routes of administration and dosage forms with different pharmacokinetic parameters.

MM is effective for chemotherapy-induced nausea and vomiting, chronic pain and spasticity symptoms in multiple sclerosis based upon scientific studies and literature.
Some studies state that combination therapy does not enhance the unwanted opioid side effects.

Other studies indicate a potential of combination therapy to lower the dose of the opioid therapy.

However, other studies showed that there is an increase in the risk of opioid use disorder.

Further studies to fill the research gaps is necessary to provide significance evidence for positive clinical outcomes.
Questions?

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