CANNABIS AND THE OLDER ADULT: PHARMACOLOGIC CONSIDERATIONS

GRAND RIVER HOSPITAL
Advancing Exceptional Care

Presenter COI Disclosure

Faculty: Dr. Joanne Ho

- **Relationships with financial sponsors:**

  Speaker Honoraria from Not-For-Profit Organizations: North-East Specialized Geriatric Services; Ontario Long Term Care Association

  Other: Employee of McMaster University and Schlegel Research Institute; GeriMedRisk

Disclosure of Financial Support

This program has received financial support from the following organizations in the form of unrestricted educational grants:

Astellas, Bayer, Bayshore Home Health, Boehringer Ingelheim, Eli Lilly, GSK Canada, Merck, Mylan, Novartis, NovoNordisk, Pfizer and Purdue

This program has received financial support from Grand River Hospital Foundation in the form of speaker honoraria. This program has received in-kind support from Grand River Hospital in the form of logistical support.

<u>Potential for conflict(s) of interest</u>:

Dr. Joanne Ho is receiving payment from the Freeport Physicians' Education Fund for this presentation

Mitigating Potential Bias:

- Recommendations for Drug Therapy will be based on peer reviewed journal articles and published guidelines

FACULTY/PRESENTER DISCLOSURE

- **Faculty:** Joanne Ho
- **Relationships with commercial interests:**
  - **Grants/Research Support:** None
  - **Speakers Bureau/Honoraria:** None
  - **Consulting Fees: None**
  - **Other: None**

Relationships with noncommercial interests:

- **McMaster University: Department of Medicine/Division of Geriatric Medicine/Division of Clinical Pharmacology (JH)**
- **Schlegel Research Institute for Aging: Clinical Scientist (JH)**
- **GeriMedRisk: Geriatrician (JH), Clinical Pharmacologist (JH), CMHA WW, WWLHIN, Schlegel RIA, McMaster University, St. Joseph's Health Centre Guelph, Ontario Poison Centre, Ontario Telemedicine Network, CLRI, Grand River Hospital, Regional Geriatric Program Central**

MITIGATING POTENTIAL BIAS

- No potential sources of bias

OBJECTIVES

- Practical approach to cannabinoids in older adults with cognitive impairment
  - Pharmacologic changes with ageing
  - Pharmacology of cannabinoids
  - Drug-drug interactions to consider with cannabinoids

CANADIAN CANNABIS ACT

- October 17, 2018
- https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids.html

- Significant interest:
  - US: National Survey on Drug Use and Health 2006-2013
    - 1.4% >=65 years old; Colorado 15.9% 61-70 years age, 4.1% 70 years of age and older
    - 10 fold increase in cannabis use among older adults over the last decade
  - Canada:2012, 1% of Canadians > 65 years old using cannabis
    - 15% Canadians, 11% female, 19% male; 5.2% age 65 years and older
  - Be prepared for questions from patients and their caregivers

- Be prepared for questions from patients and their caregivers

How Seniors Joined the Cannabis Craze | The New Yorker

THE NEW YORKER

CASE (FICTITIOUS)

- 85 year old F with excellent function, no hospitalizations aside from C-sections for her 3 children
- ADL 6/6 IADL 8/8; still maintains a full garden and social schedule (family, friends, church), regular tai chi and dance classes, hikes
- PMHx: C-section, osteoarthritis
- Her daughter wants to the patient to try cannabis and asks you if there might be differences in her response to cannabis due to her age?

- Does age affect how the body handles the drug?
  - Pharmacokinetics
  - ? Differences in drug levels (old vs young)
- Does age affect how sensitivity body is to the drug?
  - Pharmacodynamics
  - ? Differences in what happens when the drug reaches its target/receptor

OLDER PATIENTS AND ADVERSE DRUG EVENTS

- Increased mortality
- Increased morbidity
  - Increased severity
  - Hospital admission
    - Decrease in function
    - Delirium
    - Cost
      - >$35 million in Canada
      - Delirium US $143-152 billion

Wu et al Drugs and Aging 2009
Budnitz NEJM 2011
Morgan CMAJ Open 2016

OLDER ADULTS AND ADVERSE DRUG EVENTS

- Risk factors:
  - Advanced age
    - 3.5X more likely to be admitted compared to those 65-69 years old
    - **3% increased risk of severe ADR/year increase in age**
  - Polypharmacy (>=5 meds)
  - LTC
  - Multiple prescribers
  - Multiple pharmacies
  - **Multiple medications**
  - Multiple comorbidities
  - **New medications**

Wu et al 2012
Budnitz et al 2011

PHARMACOLOGIC CHANGES WITH AGING

- Pharmacokinetics
- Pharmacodynamics
- Drug interactions

PHARMACOLOGIC CHANGES WITH AGING

- **Pharmacokinetics (what the body does to the drug)**
- Pharmacodynamics
- Drug interactions

PHARMACOLOGIC CHANGES WITH AGING

- **Pharmacokinetics (what the body does to the drug)**
- Absorption
- **Distribution: Greater portion of fat increases the elimination half life of lipophilic drugs, increased CNS penetration of medications that are substrates of P glycoprotein or BRCP**
- **Metabolism: Decreased phase 1 metabolism (CYP450)**
- **Elimination: Decreased renal function and drug clearance**
- Pharmacodynamics
- Drug interactions

PHARMACOLOGIC CHANGES WITH AGING

- Pharmacokinetics
- **Pharmacodynamics (what the drug does to the body)**
- Drug interactions

PHARMACOLOGIC CHANGES WITH AGING

- Pharmacokinetics
- **Pharmacodynamics (what the drug does to the body)**
- **Increased sensitivity to psychotropics (opioids, benzodiazepines, sedative hypnotics, antipsychotics)**
- Drug interactions

PHARMACOLOGIC CHANGES WITH AGING

- Pharmacokinetics
- Pharmacodynamics (what the drug does to the body)
- **Drug interactions**

CANNABIS AND POLYPHARMACY

- “Cannabis could be the treatment for polypharmacy”
  - Pain
  - BPSD

BUT WHAT IS CANNABIS?

WHAT IS IT?

- **Endocannabinoids (what our body makes)**
  - Endogenous cannabinoids act on CB-1 and CB-2 cannabinoid receptors
    - Anandamide, 2-arachidonoylglycerol (2AG); other endogenous molecules with “cannabinoid-like” effects
    - CB1 receptor activation: Decreases release of multiple neurotransmitters (Ach, NE, dopamine, 5HT, GABA, glutamate, D-aspartate, cholecystokinin)
    - Affects multiple ion channels
- **Phytocannabinoids (the plant-Cannabis)**
  - Cannabis sativa, Cannabis indica
- **Cannabinoids (what humans make)**
  - Nabilone (mimic THC)
  - Nabiximols (THC/CBD spray)

THC

- Δ9-Tetrahydrocannabinol (THC)
- Partial agonist at CB-1>CB-2
  - Antispasmodic, appetite, analgesic, anti-emetic, psychoactive
- Decomposes when exposed to air, heat, light (acid)
- Bioavailability:
- **Inhaled 2-56% (variability between individuals)**
  - fast onset (3-10 min), high peak concentrations
- **Ingested 5-20%**
  - Slower onset to peak (4-6hrs; some individuals 0.5 hrs), Lower peak concentrations
  - Chocolate cookie 4-12%

Huestis et al 2007
Health Canada 2013

THC

- Distribution
  - Very lipophilic (fat)
- Extensive metabolism
  - Half life 2 hrs (parent), 35 hrs (active metabolites) (detectable up to 96 days)
  - CYP 2C9, 2C19, 3A4
- Elimination
  - 15-20% renal, 50-65% feces

Huestis 2009
Spiro 2012

THC PHARMACOLOGY **WITH AGE**

- Distribution
  - Very lipophilic (increased fat content->longer elimination half life)
- Extensive metabolism (decrease phase 1 metabolism->longer elimination half life)
  - Half life 2 hrs (parent; (increased to 5 hrs) , 35 hrs (metabolites) CYP 2C9, 2C19, 3A4
  - Enterohepatic circulation
- Elimination (decreased renal function and renal drug clearance)
  - 15% renal, 50% feces

Ahmed 2015

THC DRUG INTERACTIONS

- Substrate: CYP 2C9, 2C19, 3A4
  - May have increased THC levels with trimethoprim/sulfamethoxazole, metronidazole, amiodarone
- Inhibitor: 1A1 1A2 and 1B1 (in vitro 2C8, 2C9, 2C19, 3A4, 3A5 ?Pglycoprotein (chronic))
- Drug Transporter: Pglycoprotein (substrate and inhibitor)
  - May increased THC levels with macrolides, verapamil, quinidine

CANNABIDIOL (CBD)

Non-psychoactive, analgesia, sedating, anti-emetic, anti-inflammatory, antispasmodic, anxiolytic

- Weak activity at CB-1 and CB-2 receptors; 5HT1a and TRPV1-2 vanilloid receptors, antagonist a1 adrenergic and u-opioid receptors, inhibits uptake of noradrenaline, dopamine, 5ht, GABA, anandamide. Also acts on Ca stores, blocks low voltage activate (T-type) Ca channels. Stimulates activity of the inhibitory glycine receptor and inhibits activity of fatty amide hydrolase

Bioavailability:

- Inhaled 13-31% (variability)
- Fast onset
- High peak

Oral

Onset 1.5-3 hrs (oral), 2.8 hr (buccal)

Ohlsson
Huestis 2009

CBD

- Metabolism:
- Half life:
  - Redistribution results in decrease plasma levels with half life 1-2 hrs
  - But terminal half life can be at least 24-36 hr (can be stored for 4 weeks in fat)
- CYP 2c9, 2c19, 2d6, 3a4, 2E1, 3A5

Zhu 2006
Holland 2006

CBD PHARMACOLOGY **WITH AGE**

- Metabolism:
- Half life:
- Redistribution results in decrease plasma levels with half life 1-2 hrs (increased fat content->longer elimination half life)

- But terminal half life can be at least 24-36 hr (can be stored for 4 weeks in fat)
- CYP 2c9, 2c19, 2d6, 3a4, 2E1, 3A5 (decrease phase 1 metabolism->longer elimination half life)

- Drug interactions:
- Inhibits P-glycoprotein (BBB) and BRCP; phase 2?

Zhu 2006
Holland 2006

CBD DRUG INTERACTIONS

- Substrate: CYP 2c9, 2c19, 2d6, 3a4, 2E1, 3A5
- Inhibitor: **2C19 (human)**, 1A1 1A2 and 1B1; 3A4, 2C9 (minor)
  - Increased levels of topiramate, clobazam, eslicarbazepine
  - Increased levels of norclobazam (active metabolite; epidiolex)
  - Increased liver enzymes when coadministered with valproic acid
- ?Inhibits P-glycoprotein (BBB)
  - Potentially increased risk of toxicity with digoxin, verapamil, dabigatran, loperamide

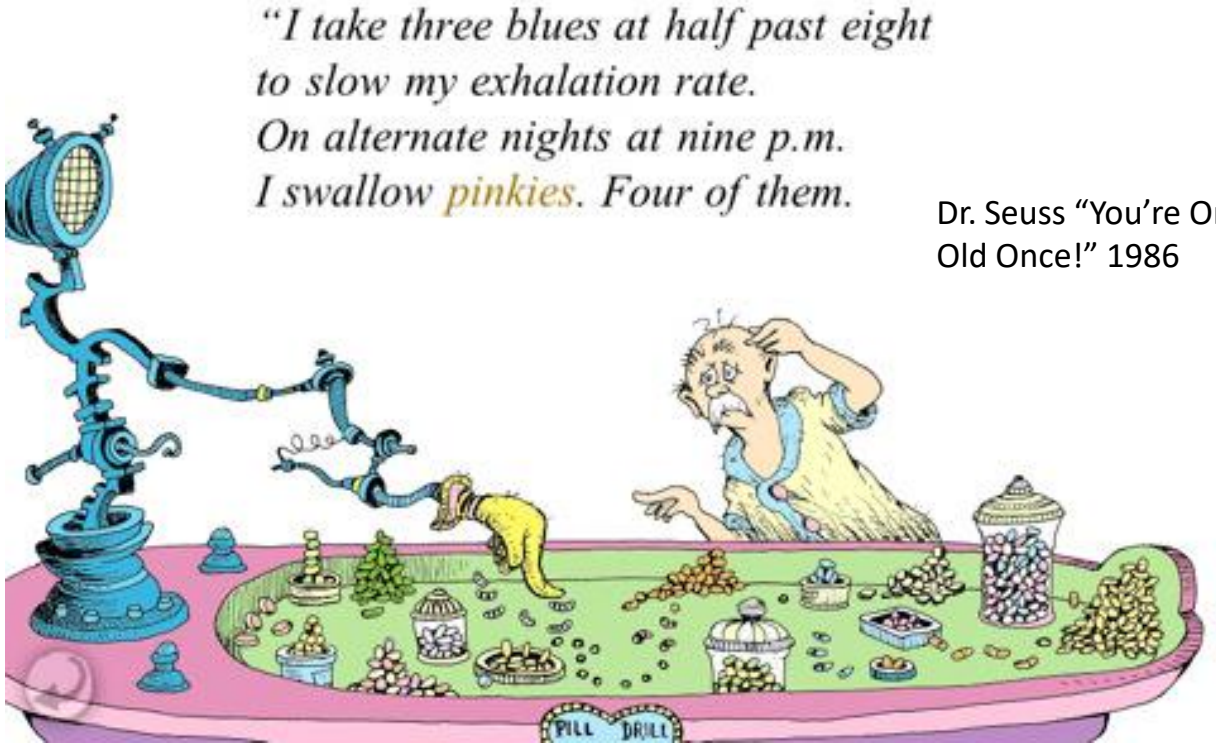
PHYTOCANNABINOIDS

- >100 compounds found in Cannabis plants
- More complex than pure THC or CBD
  - 18 different classes of chemicals
    - Cannabinoids (THC, CBD), nitrogenous compounds, amino acids, hydrocarbons, carbohydrates, terpenes, simple and fatty acids, proteins, enzymes, etc…
- Terpenoids: drug interactions, CNS effects
  - Varies with growing conditions and Cannabis strains
  - More than just the fragrance
- C. sativa
  - >489 compounds
  - >70 cannabinoids
  - THC>CBD
- C. indica
  - CBD>THC
  - terpenoids

PHYTOCANNABINOIDS

- Significant heterogeneity in one product
  - One product has multiple drugs
    - Polypharmacy?

ADVERSE DRUG EVENTS AND THE OLDER PATIENT



Dr. Seuss "You're Only Old Once!" 1986

ADVERSE EFFECTS

Noradrenergic effects

- Acute
  - Tachycardia
  - Postural hypotension/hypertension
- Chronic
  - Volume retention

Cognition

- Cognitive impairment (HIV study using cannabis for anxiety, 93% cited improved anxiety but 47% reported deterioration in memory)
  - Impaired driving performance
- Psychotropic

Tolerance

GI (smoked)

Resp (smoked, vap)

CNS: psychotropic

DRUG INTERACTIONS

- Smoked: induce 1A2
- With other psychoactive medications/substances (ETOH, sedatives, opioids)
  - Cognition (working memory processing speed, executive function, visuospatial perception)
  - Increased sedation
    - Increased driving impairment

TAKE HOME

- Cannabis is heterogeneous
  - Various compounds THC, CBD, terpenes each have CNS effects, drug interactions and their pharmacology changes with aging
- Synthetic cannabinoids
  - Safety has not been established among older patients with comorbidities
    - Cardiac, drug interactions, falls, cognition
- If cannabinoids will be added to a patient's management:
  - Weight the risks and benefits to alternatives
  - Know the product (ingredients: CBD, THC, terpenoids)
  - Medication review
    - Chronic diseases
    - Medications
  - Start low and go slow
  - Monitor:
    - Maintain communication with prescribing clinicians in cannabis clinics

THANK YOU

QUESTIONS