Opioid and Marijuana Use Among Older Adults

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Learning Objectives

- Describe current utilization patterns and issues for opioids and cannabinoids in older individuals
- Briefly describe the mechanism of action for cannabinoids when used as a medicinal agent
- Suggest conditions for using cannabidiol (CBD) and tetrahydrocannabinol (THC) that are supported by the medical literature
- List common and potentially dangerous adverse effects associated with cannabinoids and opioid analgesics
- When given a clinical scenario, identify patient characteristics and medications that increase risk when using cannabinoids and opioids in older individuals

Clinical Case

- A 73 year old man has living in an assisted living apartment for the past 2 months due to decreasing ability to ambulate around in his home.
- He has a history hypothyroidism, BPH, hypertension, depression and insomnia. He suffered a cervical fracture in an automobile accident 15 years ago causing quadriplegia. He regained full function after extensive rehab and lived independently for over 12 years.

Clinical Case (continued)

- After a fall approximately 2 years ago, he now has increasing limitations in ambulation following compression fractures in his lower thoracic and lumbar vertebrae.
- He expresses unrelenting pain and muscle cramping in his lower back and now in his shoulders and arms.
- During a recent medical visit, he inquired about the potential benefits of adding oral marijuana to his current pain regimen which includes a combination of an opioid, acetaminophen, muscle relaxants and sedatives.
- His medication list is provided:

Clinical Case (continued)

- Furosemide 40 mg daily
- Levothyroxine 50 mcg daily
- Tamsulosin 0.4 mg BID
- Escitalopram 20 mg daily
- Oxycodone 5 mg every 8 hours
- Acetaminophen 650 mg every 8 hours
- Baclofen 15 mg (5 mg +10 mg) QID
- Pregabalin 75 mg at bedtime
- Melatonin 10 mg daily in the evening
- Temazepam 30 mg at bedtime as needed

Managing Pain in the Older Adult

- Typical issues and questions
  - Choice of medication (class and agent)
  - Dosing (escalating and reducing doses, dependence, deprescribing)
  - Combining therapies
  - Complicating co-therapies
  - Special patient populations
    - Older individuals & pediatrics
    - Renal & liver disease
    - Multiple medical conditions & palliative care
  - Regulatory issues

Opioid and Cannabis Use in Older Individuals

- 1M older individuals with substance use disorder (SUD) (2018 data)
- SUD treatment admissions increasing
- Opioid prescribing in elderly increased by factor of 9X between 1995-2010
- Opioids common in older population
  - 5-10% report regular use for chronic pain
- CDC data (2017) –
  - 17.4% of US population (~57M people) filled at least 1 opioid prescription
  - 26.8% of those > 65 y/o

Source: National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services. 2020

Opioid and Cannabis Use in Older Individuals

- 9% of 50-64 y/o population report marijuana use in 2015-16 vs. 7% in 2012-13
- Evidence suggests 25% of marijuana use in elders recommended by a physician
  - Based on suggested benefit for chronic pain, sleep hygiene, malnutrition, depression, cancer treatment side effects
- Concerns for use in older individuals
  - Marijuana not approved by the FDA as a medicine
  - Potential benefits weighed against risk – multiple concomitant health conditions and use of prescribed medications

Source: National Institute on Drug Abuse; National Institutes of Health; U.S. Department of Health and Human Services. 2020

Cannabis Use and Misuse in Older Adults

- Older adults - fastest growing category of cannabis users
  - 75% relative increase in past-year cannabis use among older Americans
  - 2.7 million engaging in past-year cannabis use
  - 50+ population use 30% of medical and 17% of nonmedical cannabis
  - More lenient perceptions of seniors toward cannabis use contributing to surge
- Evidence of efficacy still lacking for many uses
- Issues in older users:
  - Increased risk (CV, Pulm, GI), drug INX, ADRs (sedation, dizziness, cognitive impairment), neuropsychiatric disorders (depression, anxiety, suicidality, and psychosis)

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AN INTRODUCTION TO CANNABINOIDS

Thanks to:
Jami Johnson, PharmD, DABAT
Assistant Director, Oklahoma Center for Poison & Drug Information

Cannabinoid Primer

- Marijuana
  - Crude drug derived from the Cannabis family (*C. sativa* or *C. indica*)
  - Contains > 400 chemical compounds and over 100 cannabinoids
  - Various marijuana chemotypes
    - Δ-9 tetrahydrocannabinol (THC) predominant
    - Cannabidiol (CBD) predominant
    - Mixed types

Cannabinoid Primer

- Cannabinoids –
  - Active compounds exhibiting drug-like effects
  - Includes THC
    - Main psychoactive component
  - Directly inhibit the release of multiple neurotransmitters
  - Multiple physiological responses:
    - Euphoria, psychosis, impaired memory and cognition, increased appetite, antiemetic properties, neuropathic and nonneuropathic pain relief, and sleep-promoting effects

Characterizing Cannabinoids

Hash

Gathering of trichomes, leading to a highly concentrated resin

Marijuana

Broad word for a plant and its flowers that contain cannabinoids

Cannabis

Plant genus including: *C. sativa* & *C. indica,* typically refers to biologically active substances

Tetrahydrocannabinol (THC)

Most recognized cannabinoid

well-described psychoactive effects

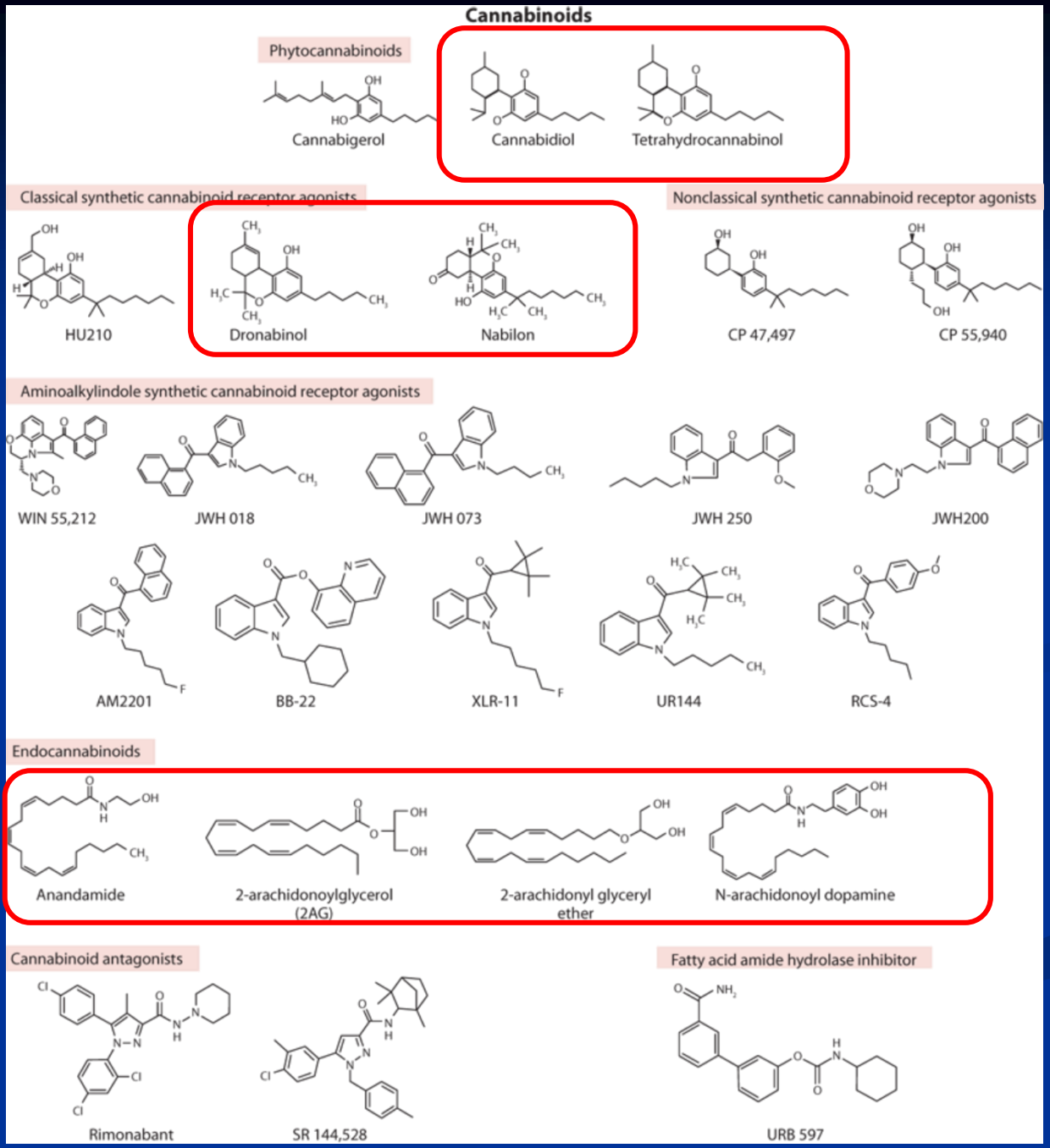
Cannabidiol (CBD)

No psychoactive properties

Cannabinoids

1. Chemical compounds found in the *Cannabis* plant
2. Structures known to act upon CB receptors

Cannabinoid Chemistry



Hoffman RS, et al. *Goldfrank's Toxicologic Emergencies, 10e;* 2015.

Reasons We Don't Know More

- Poor understanding of the endocannabinoid system
- Terpenes chemistry
  - Difficult to isolate compared to alkaloids (opioids and cocaine)
- Cannabis (marijuana) contains > 70 different cannabinoids (including THC)

DuPont MC et al. *Forensic Sci Int.* 1995; 70: 63-76.
Breivogel CS, et al. *Neurobio Dis*. 1998; 5: 417-431.

Endocannabinoid System

Cannabinoid: binds to and agonizes the cannabinoid receptor	Natural, synthetic, or endogenous (neuromodulators)

Receptors

G-protein linked neuromodulators	Inhibit adenylate cyclase

Receptor Types

CB1	CB2

Breivogel CS, et al. *Neurobio Dis*. 1998; 5: 417-431.
Lapoint JM, Cannabinoids. In: Goldfrank's Toxicologic Emergencies, 10e.

CB Receptors

- CB1 = CNS >>> periphery
  - Most numerous G-protein coupled receptors in CNS
  - Behavior, learning, mood, movement, cognition (not brainstem)
  - Exist on both pre- and post-synaptic neurons
  - Also present in GI tract
- CB2 = periphery >>> CNS
  - Proposed modulation of immune response

Breivogel CS, et al. *Neurobio Dis*. 1998; 5: 417-431.
Lapoint JM, Cannabinoids. In: Goldfrank's Toxicologic Emergencies, 10e.

Effect of Route of Administration

SMOKED	VAPORIZED	EATEN/DRUNK
Smoked in a pipe, bowl, cigarette	Inhaled through machine that converts active compounds into inhalable form	Consumed as ingredient in baked goods, candies, sodas
Rapid effects	Rapid effects	Takes time to reach brain, so effects are delayed
Burning marijuana releases toxins that can cause pulmonary problems	Does not release toxins that cause pulmonary problems	Does not release toxins that cause pulmonary problems

Goodwin RS et al. *Ther Drug Monit.* 2006; 28: 545-551.
Busto U et al. *Clin Pharmacokinet*. 1989; 16: 1-26.

Acute Effects of Cannabinoids

Altered Mood	Reduced Anxiety
Cognitive Impairment (Attention, Judgment)	Sedation/Drowsiness
Altered Perception	Sensory Intensification
Impaired coordination/balance	Increased heart rate
Hunger	Hallucinations (in large doses)

Lapoint JM, Cannabinoids. In: Goldfrank's Toxicologic Emergencies, 10e.
Hirst RA. *Br J Anaesth*. 1998; 81: 77-84.

Additional Clinical Effects

- Postural Hypotension
- Lethargy & Obtunded Cognition
- Slurred Speech
- Reported Toxicity in Children
- Systemic Effects Tachycardia, Apnea, Cyanosis, Bradycardia, Hypotonia

Iversen L et al. *Brain*. 2003; 126: 1252-1270.
Jones RT. *J Clin Pharmacol*. 2002; 42: 58S-63S.
Macnab A, et al. *Pediatr Emerg Care*. 1989; 5: 238-239.

The Cannabinoid Conundrum

Positive Effects

- Euphoric
- Calming
- Anxiolytic
- Sleep-inducing
- Generally positive affect on mood

Negative Effects

- Paranoia
- Irritation
- Dysphoria
- Depression
- Depersonalization
- Demotivation

Graczyk M, Łukowicz M and Dzierzanowski T (2021) Prospects for the Use of Cannabinoids in Psychiatric Disorders. Front. Psychiatry 12:620073. doi: 10.3389/fpsyt.2021.620073

Adverse Effects

Cannabis Hyperemesis Syndrome

- Chronic use can cause cyclic nausea, vomiting, abdominal pain, sweating, and weight loss

Refractory to standard measures

- Serotonin antagonists (e.g., ondansetron) usually ineffective for treatment
- Dopamine antagonists (e.g., phenothiazines, butyrophenones) somewhat more effective

Potential therapies

- Hot showers
- Topical capsaicin

Allen JH, et al. *Gut.* 2004; 53:1566-1570.
Lapoint et al. *West J Emerg. Med*. 2018; 19(2): 380-386.

Drug Interactions

Sedatives & Hypnotics

- Additive or synergistic sedation

Anticholinergics & Sympathomimetics

- Additive or synergistic tachycardia

Disulfiram & Fluoxetine

- Hypomania

Warfarin

- Increased effect can increase effect (↑ INR)

Antiepileptics

- ↑ levels of topiramate, zonisamide

Gaston TE et al. *Curr Neurol Neurosci Rep.* 2018; 18(11): 73-82.

CYP_{1A2} Induction: [↓ Activity]

- theophylline
- aminophylline
- caffeine
- clozapine
- duloxetine
- estradiol
- estrogens
- flutamide
- fluvoxamine
- lidocaine
- melatonin
- mexiletine
- mirtazapine
- olanzapine
- propranolol
- ramelteon
- rasagiline
- ropinirole
- tizanidine
- triamterene
- zolmitriptan

Gaston TE et al. *Curr Neurol Neurosci Rep.* 2018; 18(11): 73-82.

Strong CYP_{3A4} Inhibition: [↑] Activity of Cannabinoid

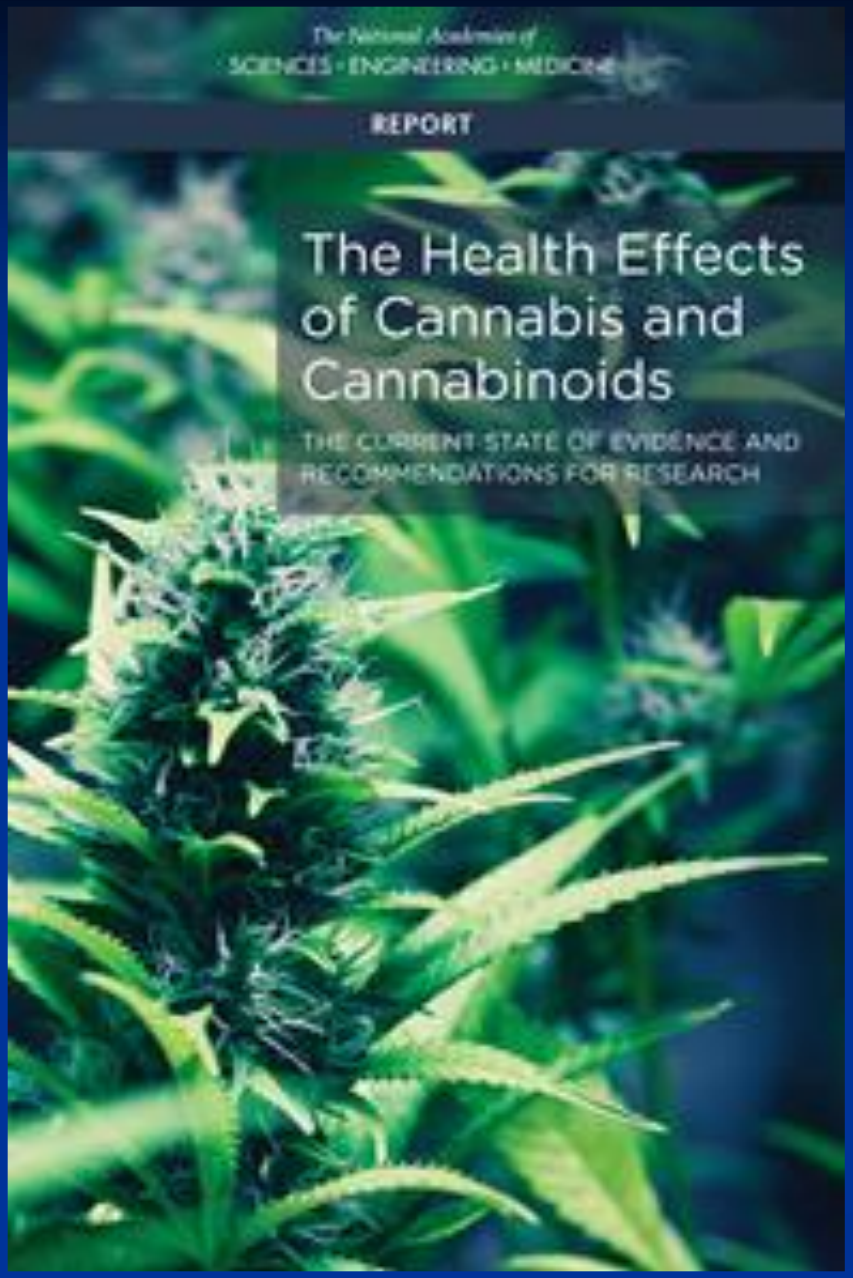
clarithromycin	darunavir	grapefruit juice
itraconazole	ketoconazole	lopinavir
mifepristone	nefazodone	nelfinavir
ombitasvir	paritaprevir	ritonavir
posaconazole	saquinavir	telaprevir
telithromycin	verapamil	voriconazole

Gaston TE et al. *Curr Neurol Neurosci Rep.* 2018; 18(11): 73-82.

Strong CYP_{3A4} Induction: [↓] Activity of Cannabinoids

carbamazepine	**enzalutamide**	**fosphenytoin**	**phenobarbital**	**phenytoin**
primidone	**rifabutin**	**rifampin**	**rifapentine**	**St. John's wort**

Gaston TE et al. *Curr Neurol Neurosci Rep.* 2018; 18(11): 73-82.



Committee on the Health Effects of Marijuana:

- 16 experts
  - Wide areas of expertise
  - 486 page review
  - Published Jan 2017

Conclusive or substantial evidence of cannabis or cannabinoids efficacy for:

Treatment of chronic pain in adults (cannabis)	As antiemetics in the treatment of CINV (oral)	Patient-reported multiple sclerosis spasticity symptoms (oral)

‘Recent’ Systematic Reviews ‘Good - to Fair - Quality’

Whiting PF, Wolff RF, Deshpande S, Di Nisio M, et al. *JAMA*. 2015; 313(24): 2456-2473.

- Most comprehensive
- Non specific formulations

Snedecor SJ, Sudharshan L, Cappeleri JC, Sadosky A, et al. *Journal of Pain Research*. 2013; 6: 539-547.

- Spinal cord injury (dronabinol)

Fitzcharles MA, Ste-Marie PA, Hauser W, Clauw DJ, et al. *Arthritis Care and Research*. 2016; 68(5): 681-688.

- Rheumatoid arthritis

Richards BL, Whittle SL, Van Der Heijde DM, Buchbinder R. *Journal of Rheumatology*. 2012; 39(Suppl 90): 28-33.

- Rheumatoid arthritis
- Cochrane review (neuromodulators)

Andreae MH, Carter GM, Shaparin N, Suslov K, et al. *Journal of Pain*. 2015; 16(12): 1121-1232.

- Peripheral neuropathy
- Inhaled cannabis

Opioid “Sparing” with Marijuana

- Co-administration of opioids and cannabinoids ‘may’ reduce needed opioid doses
- Systematic review of 17 of 19 pre-clinical studies in animal models showed synergistic effects
  - Median morphine effective dose (ED_{50}) 3.6 times lower with delta-9-THC than with morphine alone
- Only 1of 9 clinical studies provided very-low-quality evidence of opioid sparing effect

Neuropsychopharmacology (2017) 42, 1752–1765;
doi:10.1038/npp.2017.51; published online 5 April 2017

Moderate Evidence of Efficacy in:

- Short-term sleep impairment secondary to
  - Seep apnea
  - Fibromyalgia
  - Chronic pain
  - Multiple sclerosis

Limited Evidence of Efficacy in:

- Appetite and weight loss with HIV/AIDS
- Clinician measured outcomes in multiple sclerosis spasticity
- Symptoms of Tourette Syndrome
- Anxiety symptoms (public speaking, test anxiety, social anxiety disorders)
- Symptoms of post-traumatic stress disorder
- Improved outcomes (lower mortality, disability) after traumatic brain injury or intracranial hemorrhage

Limited Evidence showing NO EFFECT on:

- Dementia symptoms
- Intraocular pressure in glaucoma
- Depression symptoms in chronic pain or multiple sclerosis

Insufficient or No evidence of Efficacy in:

- Cancer-associated anorexia or cachexia
- Chorea and neuropsychiatric symptoms in Huntington's disease
- Psychiatric outcomes in schizophrenia
- Motor symptoms in Parkinson’s or drug induced dyspinesia
- Spinal chord injury associated spasticity
- Amylotrophic lateral scherosis (ALS) symptoms
- Improving abstinence in addiction
- Cancers (glioma)
- Epilepsy
- Dystonia
- IBS

Cannabinoid Use for Psychiatric Disorders

- Response to cannabinoids depends on:
  - Endocannabinoid system activity
  - Proportion of phytocannabinoids
  - Terpenoid composition
  - Dose used
- THC and CBD may demonstrate opposing effects on anxiety
- THC may worsen anxiety or mood disorders
- May decrease anxiety or depression symptoms and offer sedative and anxiolytic effects caused by severe chronic diseases

Graczyk M, Łukowicz M and Dzierzanowski T (2021) Prospects for the Use of Cannabinoids in Psychiatric Disorders. Frontiers Psychiatry 12:620073. doi: 10.3389/fpsyt.2021.620073

Cannabinoid Use for Psychiatric Disorders

- Effectiveness possibly influenced by individual genetic factors
- THC may increase the risk of psychosis in younger patients due to incomplete maturation of CNS
- Limited clinical evidence in sleep disorders
- Some evidence for role as substitute alcohol and drugs in opioid addiction
- Evidence lacking or low quality for many clinical conditions
- Some disorders worsened by cannabis use

Graczyk M, Łukowicz M and Dzierzanowski T (2021) Prospects for the Use of Cannabinoids in Psychiatric Disorders. Front. Psychiatry 12:620073. doi: 10.3389/fpsyt.2021.620073

Available Commercial Products

Generic Name	Brand Name(s)	Indications
dronabinol (synthetic THC)	Marinol, Syndros	• Anorexia in patients with AIDS • Chemotherapy induced nausea & vomiting
nabilone (synthetic THC mimic)	Cesamet (not available in US)	• Chemotherapy induced nausea & vomiting refractory to conventional therapy
cannabidiol (cannabidiol)	Epidiolex	• Lennox-Gaustaut syndrome • Dravet Syndrome
Delta-9-THC & cannabidiol	Sativex	• Adjunctive treatment for symptomatic relief of spasticity in adult patients with multiple sclerosis following failure of initial therapy

https://www.bayer.ca/omr/online/sativex-pm-en.pdf

Cannabinoid Legislation

- Medical marijuana as legal agent
  - In 2018 - 29 states (Wheeler and Hagemann 2018)
  - February 2022: 37 states, four territories and the District of Columbia allow medical use of cannabis products (NCSL data)
  - November 2021: 18 states, two territories and the District of Columbia enacted measures to regulate cannabis for adult non medical use (NCSL data)
- CBD oil legal in 30 states where medicinal and/or recreational marijuana is legal (*Governing* magazine)
- 11 states allow use of "low THC, high cannabidiol (CBD)" products for medical reasons
- CBD regulated as ‘nutritional supplement’ by FDA

https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx

State vs. Federal Perspective

- Federal Level: cannabis classified as a Schedule I substance under the Controlled Substances Act
  - Schedule I substances are considered to have a high potential for dependency and no accepted medical use, making distribution of cannabis a federal offense.
- October of 2009 - federal prosecutors encouraged to not prosecute cannabis distributers if approved for medical purposes by state law
- August 2013 – USDOJ statement that while cannabis remains illegal federally, the USDOJ expects states to create "strong, state-based enforcement efforts.... and defers right to challenge their legalization laws at this time
- January 2018 - Marijuana Enforcement Memorandum allows federal prosecutors to “weigh all relevant considerations, including federal law enforcement priorities set by the Attorney General, the seriousness of the crime, the deterrent effect of criminal prosecution, and the cumulative impact of particular crimes on the community.” https://www.justice.gov/opa/pr/justice-department-issues-memo-marijuana-enforcement

https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx

Clinical Case **(revisited)**

- A 73 year old man has living in an assisted living apartment for the past 2 months due to decreasing ability to ambulate around in his home.
- After a fall approximately 2 years ago, he now has increasing limitations in ambulation following compression fractures in his lower thoracic and lumbar vertebrae.
- He has complaints of unrelenting pain and muscle cramping in his lower back and now in his shoulders & arms.
- During a recent medical visit, he inquired about the potential benefits of adding oral marijuana to his current pain regimen which includes a combination of an opioid, acetaminophen, muscle relaxants and sedatives.

Clinical Case (revisited)

- Furosemide 40 mg daily
- Levothyroxine 50 mcg daily
- Tamsulosin 0.4 mg BID
- Escitalopram 20 mg daily
- Oxycodone 5 mg every 8 hours
- Acetaminophen 650 mg every 8 hours
- Baclofen 15 mg (5 mg +10 mg) QID
- Pregabalin 75 mg at bedtime
- Melatonin 10 mg daily in the evening
- Temazepam 30 mg at bedtime as needed

Clinical Case (revisited)

- Cannabinoids (marijuana) will improve which medical conditions exhibited by this individual?
  - Chronic Pain?
  - Depression?
  - Insomnia?

Clinical Case (revisited)

- What risks associated with cannabinoid use are potentially dangerous?
- What other issues complicate use of cannabinoids and opioids in long term care settings?
- What are your thoughts?

Clinical Case (revisited)

- Cannabinoid use will interact with which current medications?
  - Furosemide
  - Levothyroxine
  - Tamsulosin
  - Escitalopram
  - Oxycodone
  - Acetaminophen
  - Baclofen
  - Pregabalin
  - Melatonin
  - Temazepam

Pharmacodynamic Interactions

Pharmacokinetic Interactions

Conclusions and Pearls

- Opioid use has been on the increase – recent focus on negative outcomes hopefully 'turning the tide'
- Public and medical profession looking for alternatives to opioids for chronic conditions
- Proven efficacy of cannabinoids documented for limited select conditions
- Evidence is 'soft' or lacking for many conditions
- Cannabinoid use is not without risk
  - Significant adverse effects
  - Significant drug interactions
- Practitioners have little or no current experience with cannabinoid use in combination with existing therapies
- Cannabinoid use must be documented along with prescription and nonprescription medications, nutritional supplements (including herbals) and other alternative therapies

Questions?

Question 1

Efficacy of cannabinoid use has been conclusively demonstrated for which of the following conditions?

A. Dementia
B. Depression
C. Chronic pain
D. Anxiety

Question 2

What adverse effect associated with cannabinoid use could be enhanced in older adults?

A. Increased blood pressure
B. Altered cognition
C. Nervousness/anxiety
D. Slowed heart rate

Question 3

Use of cannabinoids is advantageous over prescription medications due to the lack of significant drug interactions?

A. True
B. False

CANNABIDIOL (CBD) USE IN COMMUNITY PRACTICE:

HYPE vs. HEALTH

Keith Swanson, Pharm.D.
University of Oklahoma College of Pharmacy

Cannabidiol (CBD) Primer

- Non-intoxicating marijuana extract
- Used for multiple conditions
  - Everything from epileptic seizures to anxiety to inflammation and sleeplessness
- Produced with limited regulation; products vary widely in content and quality
- Regulated by FDA as nutritional supplement

CBD Pharmacology

- Cannabidiol extracted from flowers and buds of marijuana or hemp plants
- No CNS stimulation/intoxication
- Not the same as marijuana
  - CNS effects caused by tetrahydrocannabinol (THC)

Harvesting Hemp and buds for cannabidiol extraction
https://www.youtube.com/watch?v=_AKUCvqppy8

Cannabidiol (CBD) Use in Community Practice

- HYPE vs. HEALTH
  - What suppliers say:
    - https://medium.com/cbd-origin/7-life-changing-health-benefits-of-cbd-for-seniors-958f0818bc9d
  - What clinicians say:
    - https://www.webmd.com/pain-management/news/20180507/cbd-oil-all-the-rage-but-is-it-safe-effective#1

CBD HYPE

- The CBD boom is way ahead of the science
  - https://www.sciencenews.org/article/cbd-product-boom-science-research-hemp-marijuana
- Athletes: 6 Things to Know About Cannabidiol
  - https://www.usada.org/six-things-know-about-cannabidiol/

Cannabidiol (CBD) – Information Limited

- Many indications under study (mainly animal models)
  - Respiratory: asthma, lung cancer
  - Psych: schizophrenia and acute psychosis, depression, autism, anxiety, chronic pain
  - Neurology: seizures, multiple sclerosis, dementia, restless leg syndrome, stroke, neuropathy
  - Cardiac: rhythm disturbances, tachycardia
  - Endocrine: diabetes
  - GI: IBD, hepatic disorders

CBD Pharmaceutics

- 84 products tested for CBD content
  - Accurately labeled (n = 26) 30.95% (95% CI, 22.08%-41.49%)
  - Under labeled (n = 36) 42.85% (95% CI, 32.82%-53.53%)
  - Over labeled (n = 22) 26.19% (95%CI, 17.98%-36.48%)
  - THC was detected (n=18) 21.43% (95% CI, 14.01%-31.35%)

Bonn-Miller MO, et al. Labeling Accuracy of Cannabidiol Extracts Sold Online. JAMA; 2017;318(17) 1708-9.

CBD Pharmacotherapy

- Limited evidence for cannabidiol to treat epilepsy led to FDA approval of highly purified CBD extract
  - June 2018: FDA advisory panel unanimously recommended approval of the CBD medication Epidiolex® to treat two rare forms of childhood epilepsy
- "That's really the only area where the evidence has risen to the point where the FDA has said this is acceptable to approve a new drug," (Welty)

Timothy Welty, Chair Department of Clinical Sciences, Drake University College of Pharmacy and Health Sciences

CBD Pharmacotherapy

- Limited clinical evidence of CBD in other potential uses
  - “preponderance of anecdotal evidence”
- Suggestive evidence of efficacy in treating symptoms of anxiety (esp. social anxiety)
- Information developing for use as an anti-inflammatory medication
  - Most information from animal studies

CBD Pharmacotherapy

- Other potential uses -- antipsychotic, antidepressant or sleep aid, etc.
  - Predominantly animal studies with few studies in human subjects
- “Studies that have featured humans for these other CBD uses have either been case reports or studies that did not compare results against a control group that did not use the oil. (Welty)
- "There's no control, so it's basically how do you know if we're dealing with the true effect of the drug or just simply a placebo effect because somebody thinks they've been given a drug that will be beneficial?“ (Welty)

Timothy Welty, Chair Department of Clinical Sciences, Drake University College of Pharmacy and Health Sciences