Disclosures & Disclaimers

No conflicts of interest

This talk does not, intentionally or otherwise, endorse the use of these substances or represent the views of Columbia Pacific CCO
Objectives

Review the history of marijuana in the United States including current legal status and national trends

Discuss mechanism of action and potential role in medicine for cannabinoids

Review marijuana use trends and risks to adolescents and adults

Recognize patterns of use that constitute medical use, recreational use, and cannabis use disorder
“There are thousands of patients who currently use cannabis as medicine... There is no question about its safety. It is one of humanity’s oldest medicines, used for thousands of years by millions of people with very little evidence of significant toxic effects. More is known about its adverse effects than about those of most prescription drugs.”

Dr. Lester Grinspoon, Harvard Medical School
“Deaths Prompt Crackdown on Pot Infused Food”

Newsweek, May 2014

"Since the ... legalization of recreational marijuana sales, Children's Colorado has treated nine children, six of whom became critically ill from edible marijuana," the statement from Colorado Children's Hospital said.

A student from the Republic of Congo who attended college in Wyoming jumped to his death from a hotel balcony in March after ingesting six times the suggested maximum amount of marijuana cookies, according to the Denver medical examiner's office.

In another incident, a Denver man was accused of shooting his wife as she was on the phone with an emergency dispatcher, saying her husband had used pot, was hallucinating and was frightening her and the couple's three children.”
History of Cannabis

Chinese Emperor Shen Nung 2727 BC

Brought to the American continent by Jamestown settlers in 1611

Listed in the US Pharmacopoeia in 1850

1889 Lancet article sites cannabis for treatment of opium withdrawal

First states pass anti-marijuana laws, 1911-1927

“Reefer Madness”, 1936

Marijuana Tax Act, 1937

Cannabis and Medicine: Interesting Intersects

Evidence of abuse potential- early and heavy use among adolescence appears deleterious
  ◦ *We need to protect our youth*

Evidence of cannabis having legitimate medical value for certain indications
  ◦ *We need to provide access to medicine for those suffering*

Evidence that cannabis can be used safely without causing a substance use disorder (SUD) in most adults; little evidence supporting current policy and regulatory stance of federal government
  ◦ *We need sensible laws that align with evidence!*

“*Cannabis legislation is continuing to evolve, the era of prohibition is likely drawing to an end, and clinicians need to be prepared to provide objective and evidence-based information on the risks and benefits of cannabis to a variety of users*”

Benjamin Malcom, PharmD
The Cannabis Plant

Also known as: pot, ganja, weed, 420, reefer, maryjane, flower, bud, marijuana

Two main species or “effect types”
- *Cannabis indica*
- *Cannabis sativa*

Active ingredients
- *Tetrahydrocannabinol (THC)*
- *Cannabidiol (CBD)*
- *Entourage phytocannabinoids*
- *Entourage terpenes*

Psychoactive cannabinoids are produced in glandular trichomes of unfertilized female cannabis plants.
Marijuana Strains

Large growth in diversity of cannabis cultivation since 1960s

Some strains have THC content around 30%; concentrates may be >90% THC

High CBD strains such as “Charlotte’s Web” have 0.3% THC or less

Due to heterogeneity, difficult to determine effects
Cannabis Products and Routes of Administration
FDA Approved Cannabinoid Products

- Dronabinol (Marinol)
  - Synthetic delta-9 THC
  - HIV/AIDS-related loss of appetite
  - Chemotherapy induced N/V

- Nabilone (Cesamet)
  - Synthetic cannabinoid similar to THC
  - Chemotherapy induced N/V

- Sativex (available in the UK)
  - Spasticity related to Multiple Sclerosis
  - Contains THC and CBD extract

Synthetic Cannabis (Spice)

Artificial cannabinoids sprayed onto plant material

Avoids illegality issues

Brands K2 and Spice, sold in head shops

Associated with psychosis, hospitalization, and death

Significantly more health risks than cannabis
Cannabis Pharmacology
Endogenous Cannabinoid System

Neuromodulatory role
- Cannabinoid 1 (CB1) and Cannabinoid 2 (CB2) receptors

CB1 are found mostly in the CNS
- Concentrated in the limbic structures
- Affect the function of many neurotransmitters

CB2 is found in the periphery and in the CNS
- Role in analgesia
- Immunomodulation by suppressing cytokine release and migration of macrophage and neutrophils

Active Ingredient: THC

Δ9-tetrahydrocannabinol

Complex pharmacology- low potency partial agonist at CB1 and CB2

Active ingredient in dronabinol (Marinol)

Effects: variable depending on person, dose, route, and product used

- ↑ hemodynamic parameters; tachycardia
- Euphoria and increased well-being
- Dysphoria, paranoia, anxiety, avolition, psychosis
- Conjuctivitis, drowsiness, xerostomia
- Disrupted learning, memory, problem solving
Active Ingredient: CBD

Cannabidiol (CBD)

Pharmacology

◦ Very low potency partial agonist at CB1 and CB2
◦ Buffers against effects of THC
◦ Considered “non-psychoactive”

Neuroprotectant under investigation for anti-inflammatory, antiepileptic, anticonvulsant, analgesic, neuroregenerative, and antipsychotic indications
The ‘Entourage Effect’ postulates that a combination of compounds working simultaneously can improve upon or modulate the pharmacological action of a single compound.

- Other cannabinoids
- Terpenes and aromatics
- Whole cannabis flower varietals and individual cannabinoids display significantly different effects
Clinical Effects of Cannabis Intoxication

- Sociability and sensitivity to certain stimuli (e.g., colors, music) enhanced
- Perception of time is altered
- Appetite for sweet and fatty foods is heightened
- Relaxation
- Decreased short-term memory
- Dry mouth
- Impaired perception and motor skills
- Panic attacks, paranoid thoughts, and hallucinations
- Impairment of driving abilities during acute intoxication
- Desensitization and tolerance
Regulations and Policy
Cannabis Use and Legality in US

Most commonly used illicit drug
- 13.5% (36 million) in 2015
- 2.6 million new users in 2015, 45% were age 12-17
- Cannabis use disorder prevalence 1.5%

Evolving perspective nationally
- 8 states with recreational marijuana
- 28 states with medical marijuana
- Prohibited federally and in many states
Cannabis in Oregon and Nationally

<table>
<thead>
<tr>
<th></th>
<th>Oregon - Recreational</th>
<th>United States - Illicit</th>
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<tbody>
<tr>
<td>Legislation</td>
<td>Voter initiative- state statute, passed November 2015</td>
<td>Controlled Substances Act of 1970</td>
</tr>
<tr>
<td>Allows/Prohibits</td>
<td>Public possession: 28.5 gm</td>
<td>Cannabis is a C1 substance; possession, use, transfer, or sale considered criminal</td>
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<tr>
<td></td>
<td>Home possession: 228 gm</td>
<td>• Dronabinol (THC) is a CIII substance</td>
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<td></td>
<td>4 plants in flower</td>
<td>• Nabilone is a CII substance</td>
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<td>17% tax on recreational sales, municipalities can enact</td>
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<td></td>
<td>additional 3% tax</td>
<td></td>
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<tr>
<td></td>
<td>Controlled by Oregon Liquor Commission</td>
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Policy Landscape and Public Opinion

Obama administration created guidelines for states reforming cannabis laws- allowing a rules-based cannabis industry guided by state regulations.

In 2015, Gallup Poll showed 58% of Americans favored legalization, third straight year of majority.

Growing public acceptance is advancing state laws and voter initiatives.

Drugged driving enforcement continues to be a legal challenge, many states have zero tolerance on any level of cannabis or its metabolites.

Overall lack of evidence due to research barriers affects ability to develop evidence-based policies.
MEDICAL MARIJUANA

THIS SIMPLE DRIED HERB IS ILLEGAL

HOWEVER, IF A MULTINATIONAL DRUG COMPANY GRINDS UP THAT HERB, EXTRACTS THE CANNABIS SATIVA AND CREATES SYNTHETIC DELTA-9-TETRAHYDROCANNABINOL, COMBINES IT WITH GELATIN, GLYCERIN, IRON OXIDE RED, IRON OXIDE YELLOW, TITANIUM DIOXIDE, MARKETS IT TO DOCTORS AND HOSPITALS UNDER THE NAME MARINOL AND IN THE PROCESS MAKES A BUNCH OF WEALTHY WALL STREET INVESTORS EVEN RICHER, THEN IT'S LEGAL.
Therapeutic Evidence
Previous Barriers to Research

Until August 2016, all cannabis research required approval from DEA, FDA, Health and Human Services, and the National Institute of Drug Abuse (NIDA)

NIDA-contracted monopoly of research-grade cannabis grown at the University of Mississippi

“It is not NIDA’s mission to study medicinal uses of marijuana” Stephen Gust, PhD

Been accused of federal obstruction of research

Lack of NIDA approval and access to research cannabis has significantly limited body of evidence to demonstrate risks, harms, and therapeutic effects
Conclusive or Substantial Evidence of Efficacy

For the treatment of chronic pain in adults

As antiemetics in the treatment of chemotherapy-induced nausea and vomiting (oral cannabinoids)

For improving patient-reported multiple sclerosis spasticity symptoms (oral cannabinoids)
Moderate Evidence of Efficacy

Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis
Limited Evidence of Efficacy

Increasing appetite and decreasing weight loss associated with HIV/AIDS

Improving clinician-measured multiple sclerosis spasticity symptoms (oral cannabinoids)

Improving symptoms of Tourette syndrome

Improving anxiety symptoms, as assessed by a public speaking test, in individuals with social anxiety disorders (CBD)

Improving symptoms of posttraumatic stress disorder (nabilone; a single, small fair-quality trial)

Better outcomes (i.e., mortality, disability) after a traumatic brain injury or intracranial hemorrhage
Limited Evidence of Inefficacy

Improving symptoms associated with dementia

Improving intraocular pressure associated with glaucoma

Reducing depressive symptoms in individuals with chronic pain or multiple sclerosis
Insufficient/No Evidence

Cancers, including glioma
Cancer-associated anorexia cachexia syndrome and anorexia nervosa
Symptoms of irritable bowel syndrome
Epilepsy
Spasticity in patients with paralysis due to spinal cord injury
Symptoms associated with amyotrophic lateral sclerosis
Chorea and certain neuropsychiatric symptoms associated with Huntington’s disease
Motor system symptoms associated with Parkinson’s disease or the levodopa-induced dyskinesia
Dystonia
Achieving abstinence in the use of addictive substances
Mental health outcomes in individuals with schizophrenia or schizophreniform psychosis
Evidence of Risks
Cancer

- **Moderate evidence** of no statistical association between cannabis use and:
  - Incidence of lung cancer (cannabis smoking)
  - Incidence of head and neck cancers

- **Limited evidence** of a statistical association between cannabis smoking and:
  - Non-seminoma-type testicular germ cell tumors (current, frequent, or chronic cannabis smoking)
Cardiometabolic Risk

- **Limited evidence** of a *statistical association* between cannabis use and:
  - The triggering of acute myocardial infarction (cannabis smoking)
  - Ischemic stroke or subarachnoid hemorrhage
  - Decreased risk of metabolic syndrome and diabetes
  - Increased risk of prediabetes

- **No evidence** to support or refute a *statistical association* between *chronic effects* of cannabis use and:
  - The increased risk of acute myocardial infarction
Respiratory Disease

- **Substantial evidence** of a statistical association between cannabis smoking and:
  - Worse respiratory symptoms and more frequent chronic bronchitis episodes (long-term cannabis smoking)
- **Moderate evidence** of a statistical association between cannabis smoking and:
  - Improved airway dynamics with acute use, but not with chronic use
  - Higher forced vital capacity (FVC)
- **Moderate evidence** of a statistical association between the cessation of cannabis smoking and:
  - Improvements in respiratory symptoms
- **Limited evidence** of a statistical association between cannabis smoking and:
  - An increased risk of developing chronic obstructive pulmonary disease (COPD) when controlled for tobacco use (occasional cannabis smoking)
- **No or insufficient evidence** to support or refute a statistical association between cannabis smoking and:
  - Hospital admissions for COPD
  - Asthma development or asthma exacerbation
Injury and Death

- **Substantial evidence** of a statistical association between cannabis use and:
  - Increased risk of motor vehicle crashes

- **Moderate evidence** of a statistical association between cannabis use and:
  - Increased risk of overdose injuries, including respiratory distress, among pediatric populations in U.S. states where cannabis is legal

- **No or insufficient evidence** to support or refute a statistical association between cannabis use and:
  - All-cause mortality
  - Occupational accidents or injuries (general, nonmedical cannabis use)
  - Death due to cannabis overdose
Prenatal, Perinatal, and Neonatal

- **Substantial evidence** of a **statistical association** between maternal cannabis smoking and:
  - Lower birth weight of the offspring

- **Limited evidence** of a **statistical association** between maternal cannabis smoking and:
  - Pregnancy complications for the mother
  - Admission of the infant to the neonatal intensive care unit (NICU)

- **Insufficient evidence** to support or refute a statistical association between maternal cannabis smoking and:
  - Later outcomes in the offspring (e.g., sudden infant death syndrome, cognition/academic achievement, and later substance use)
Psychosocial

- **Moderate evidence** of a statistical association between cannabis use and:
  - The impairment in the cognitive domains of learning, memory, and attention (acute cannabis use)

- **Limited evidence** of a statistical association between cannabis use and:
  - Impaired academic achievement and education outcomes
  - Increased rates of unemployment and/or low income
  - Impaired social functioning or engagement in developmentally appropriate social roles

- **Limited evidence** of a statistical association between sustained abstinence from cannabis use and:
  - Impairments in the cognitive domains of learning, memory, and attention
Mental Health

- **Substantial evidence** of a statistical association between cannabis use and:
  - The development of schizophrenia or other psychoses, with the highest risk among the most frequent users

- **Moderate evidence** of a statistical association between cannabis use and:
  - Better cognitive performance among individuals with psychotic disorders and a history of cannabis use
  - Increased symptoms of mania and hypomania in individuals diagnosed with bipolar disorders (regular cannabis use)
  - A small increased risk for the development of depressive disorders
  - Increased incidence of suicidal ideation and suicide attempts with a higher incidence among heavier users
  - Increased incidence of suicide completion
  - Increased incidence of social anxiety disorder (regular cannabis use)

- **Moderate evidence** of no statistical association between cannabis use and:
  - Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders
Mental Health

- **Limited evidence** of a statistical association between cannabis use and:
  - An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders
  - The likelihood of developing bipolar disorder, particularly among regular or daily users
  - The development of any type of anxiety disorder, except social anxiety disorder
  - Increased symptoms of anxiety (near daily cannabis use)
  - Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder

- **No evidence** to support or refute a statistical association between cannabis use and:
  - Changes in the course or symptoms of depressive disorders
  - The development of posttraumatic stress disorder
Problem Cannabis Use

- **Substantial evidence** that:
  - Stimulant treatment of attention deficit hyperactivity disorder (ADHD) during adolescence is not a risk factor for the development of problem cannabis use
  - Being male and smoking cigarettes are risk factors for the progression of cannabis use to problem cannabis use
  - Initiating cannabis use at an earlier age is a risk factor for the development of problem cannabis use

- **Substantial evidence** of a statistical association between:
  - Increases in cannabis use frequency and the progression to developing problem cannabis use
  - Being male and the severity of problem cannabis use, but the recurrence of problem cannabis use does not differ between males and females
Problem Cannabis Use

- **Moderate evidence** that:
  - Anxiety, personality disorders, and bipolar disorders are not risk factors for the development of problem cannabis use
  - Major depressive disorder is a risk factor for the development of problem cannabis use
  - Adolescent ADHD is not a risk factor for the development of problem cannabis use
  - Being male is a risk factor for the development of problem cannabis
  - Exposure to the combined use of abused drugs is a risk factor for the development of problem cannabis use
  - Neither alcohol nor nicotine dependence alone are risk factors for the progression from cannabis use to problem cannabis use
  - During adolescence the frequency of cannabis use, oppositional behaviors, a younger age of first alcohol use, nicotine use, parental substance use, poor school performance, antisocial behaviors, and childhood sexual abuse are risk factors for the development of problem cannabis use
Cannabis and Other Substances

- **Moderate evidence** of a statistical association between cannabis use and:
  - The development of substance dependence and/or a substance abuse disorder for substances, including alcohol, tobacco, and other illicit drugs

- **Limited evidence** of a statistical association between cannabis use and:
  - The initiation of tobacco use
  - Changes in the rates and use patterns of other licit and illicit substances
    - Some evidence suggesting decreases in opioid use among patients using cannabis
Risks to Adolescents

Dose-dependent outcomes (suggesting causal relationship)

- Adolescents who used marijuana daily were significantly less likely than never users to:
  - Graduate from high school (54% compared to 80% of never users)
  - Attain a college degree (12% compared to 41%)
- And more likely to:
  - Become physically dependent (55% to 4%)
  - Use other illicit substances (31% to 9%)
  - Attempt suicide (4% to 2%)
  - Suffer from depression (14% to 9%)
  - Be dependent on welfare (14% to 7%)

Silins et al. Young adult sequelae of adolescent cannabis use: an integrative analysis. 2014
Conducting Patient Interviews
Interview Tips

Approach patient’s cannabis use with curiosity and openness, rather than judgemental or authoritative tone

Ask about both benefits as well as risks or adverse effects of use

Ask questions that help to inform if a cannabis use disorder (CUD) may be present

Ask about use parameters such as: amount, frequency, route, source, indication, and spending habits

Tailor interview to patient’s situation and education level

Discuss harm-reduction strategies (eg. avoid driving after use)
Case 1: A Mid-Life Crisis

MJ is a 45 y/o male who presents to your outpatient office for management of anxiety and a “mid-life crisis”. He states that he has been smoking cannabis since college and uses after work every day. He relays that he feels cannabis “takes the edge off” and helps him sleep, yet occasionally makes him paranoid. He reports that his wife feels his cannabis use prevents him from being present with his family and is a financial burden. He states he has tried to stop in the past although has strong cravings, anxiety, and disturbed sleep with vivid dreams when he does, which resolves upon resumption of cannabis use.

What additional questions do you have?
Cannabis Use Disorder (CUD)

A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least 2 of the following within a 12 month period:

- Persistent desire or unsuccessful attempts to cut down or control use
- Cannabis used in larger amounts or over a longer period than intended
- Excessive time spent obtaining, using, or recovering from effects
- Craving or strong desire to use
- Use resulting in failure to fulfill obligations at work, school, or home
- Continued use despite recurrent or persistent interpersonal difficulties
- Social, occupational, or recreational activities given up due to cannabis use
- Recurrent cannabis use in situations which are physically dangerous
- Continued use despite physical or psychological problems resulting or exacerbated by cannabis
- Tolerance or Withdrawal present
Cannabis Withdrawal

Usually occurs in the context of heavy and prolonged use

Most signs and symptoms of withdrawal are self-limiting in 1-4 weeks and do not present a physical danger to the patient

Signs & symptoms:
- Irritability, anger, aggression
- Nervousness or anxiety
- Sleep difficulty (disturbing dreams)
- ↓ appetite or weight loss
- Restlessness
- Depressed mood
- Abdominal pain, shakiness/tremors, sweating, fever, chills, or headache
Follow-up Questions

• How do you use cannabis? 2-4 hits of oil concentrates (dabs) after work every day

• How much money do you spend on cannabis? ~200-300$/month

• Do you miss social or family engagements due to cannabis use? Yes, reports falling asleep on couch instead of reading bedtime stories to children and missing kids sporting events due to “forgetting”

• Any other consequences of use? Feel that it has prevented career advancement due to fear of failing a urine drug screen, conflicts with wife

• Any other substances or illicit drugs? (+) coffee 1 cup per day in am, (+) EtOH2 glass wine on weekend (-) tobacco, (-) other illicit drugs
Which of the following best represents MJ’s cannabis use pattern?

A) Recreational (Adult Use)
B) Medical Use
C) Cannabis Use Disorder
Treatment of CUD

Requires further discussion of patient treatment goals as well as assessment of motivation and readiness to quit:

• Referral to substance use support services such as narcotic anonymous

• Work-up and treatment for possible underlying or comorbid anxiety disorder

• Psychosocial intervention (CBT, motivational interviewing)

• Harm-reduction: switching delivery forms/routes, using cannabis with less THC and more CBD, using strains of cannabis with less sedating effects

• No established evidence base for pharmacotherapy intervention

Case 2: Skateboarding Trauma

BB is a 33 y/o male who is admitted to the inpatient setting after crashing on a skateboard. He suffered a moderate concussion although is A & O x4 today, doing well, and likely ready to be discharged soon. He states he was “showing his 6 y/o son how to bomb a hill” when he fell, breaking his L wrist and suffering a TBI. A urine drug screen was performed as part of standard admission labs for trauma patients and found (+) for THC.

What additional questions do you have?
Follow-Up Questions

• *How do you use cannabis?* 1 joint on Friday nights (accident occurred on a Sunday afternoon)

• *How much money do you spend on cannabis?* ~50$/month

• *Do you miss social or family engagements due to cannabis use?* No, reports cannabis helps to unwind from his long and stressful weeks at the law firm and focus on family time during the weekends

• *Any other consequences of use?* Reports heightening of senses with increased appetite and enjoyable intimacy with wife. Denies anxiety or paranoia as consequence of use

• *Any other substances or illicit drugs?* (+) coffee 2-3 cups per day during the week, (+) EtOH1-2 glasses of craft beer on weekends (-) tobacco, (-) other illicit drugs
Which of the following best represents BB’s cannabis use pattern?

A) Recreational (Adult Use)
B) Medical Use
C) Cannabis Use Disorder
AR is a 66 y/o female with a PMH of insomnia due to chronic R shoulder & neck pain after a MVA 4 years ago. She presents for routine follow up at your outpatient office, with a curious smile on her face. She reports she has not used the zolpidem 5mg PO QHS prn insomnia or tramadol 50mg PO BID prn pain medications you furnish to her in the past 6 weeks. She relays her “new secret” is cannabis and has allowed her to “sleep like a baby” recently. Her neck pain can still be bothersome, although with the extra sleep she has “come to terms with the pain”.

What follow-up questions do you have?
Follow-up Questions

• **How do you use cannabis?** 1 bowl of finely ground cannabis, vaporized after dinner, around 7pm in the evening. Reports using an “Indica” (OG Kush) since the budtender recommended it for sleep.

• **Where do you obtain cannabis?** Mary Jane’s Medical Club

• **How much money do you spend on cannabis?** ~60$/month

• **Do you miss social or family engagements due to cannabis use?** No, reports cannabis has helped her sleep so much she has been able to resume playing bridge at the “Ol’ gals club” since she doesn’t nap anymore and is better able to “keep up” with her grandkids.

• **Any other consequences of use (e.g. hangover effect, balance issues, driving ability)?** Reports feeling refreshed in morning, no history of falls, states she doesn’t drive anymore.

• **Any other substances or illicit drugs?** (+) tea 2 cups per day (-) EtOH(-) tobacco; quit 20 years ago, (-) other illicit drugs.
Which of the following best represents AR’s cannabis use pattern?

A) Recreational (Adult Use)
B) Medical Use
C) Cannabis Use Disorder
Summary and Conclusions

The current legal patchwork of cannabis laws and conflicting motivations present challenges for clinicians, researchers, policy-makers and patients.

Cannabis use is here to stay and healthcare practitioners likely need additional training to be effective patient advocates.

Cannabis and cannabis products are incredibly diverse, adding to difficulty in delineating both risks and benefits.

A non-judgmental and comprehensive interview style allows for the best clinical decisions regarding risk/benefit calculus of cannabis use for individual patients.
Questions?