BEHIND THE CANNABIS: DRUG INTERACTIONS WITH PSYCHIATRIC MEDICATIONS
Learning Objectives

• Discuss the most appropriate and effective way to communicate with patients about the use of cannabis

• Examine interactions between cannabis and psychiatric medications

• Address the role of pharmacokinetic testing for patients who use cannabis concurrently with psychiatric medications
Behind the Smoke Screen: Cannabis
Components of Cannabis

• Δ9-tetrahydrocannabinol THC (THC); most psychoactive & has most known medical benefits

• Cannabidiol—CBD; now approved drug for intractable seizures & touted for most medical “promise”
Statistics of Marijuana Use

• Marijuana is the most commonly used psychotropic drug in the United States, after alcohol

• In 2018, more than 11.8 million young adults reported marijuana use in the past year

• Its use is more prevalent among men than women

• Following recreational marijuana legalization (RML), the greatest increase in marijuana use has been observed in ages 12–17, and over age 26

What Does Cannabis Do?
The Endocannabinoid (EC) System Regulates:

- Memory
- Cognition
- Reward
- Neurodevelopment
- Coordination
- Stress
- Appetite
- Intraocular pressure
- Heart rate
- GI motility
- Emetic reflex
- Immune function
- Female reproductive function
- CB1 in Brain:
  - Cortex
  - Nucleus accumbens
  - Basal ganglia
  - Hypothalamus
  - Cerebellum
  - Hippocampus
  - Amygdala
  - Spinal cord
  - Brainstem
- CB2 in Brain:
  - Glial cells
  - Brainstem

http://www.fundacion-canna.es/en/endocannabinoid-system;
The Endocannabinoid (EC) System: Retrograde Neurotransmission (NT)

1. EC precursors in lipid membranes
2. NT binding (or depolarization) triggers enzymatic reaction to form and release EC
3. Released EC binds to presynaptic CB1 or CB2 receptors
4. Inhibits release of inhibitory and excitatory NTs
The Endocannabinoid (EC) System: Receptors and Ligands

Central and peripheral neuron terminals

Immune cells

2-AG: 2-arachidonoyl glycerol is an endogenous agonist of the CB1 receptor.

2-AG: high-efficacy agonist

anandamide: low-efficacy agonist

2-AG: high-efficacy agonist

anandamide: very low-efficacy agonist

CB1

CB1

CB2

CB2
Smoking is the principal route of administration

THC is rapidly absorbed in the lungs before crossing the BBB

Peak THC levels ~2–10 min
Bioavailability of THC after inhalation is 10–25%

Average concentrations of THC up to 20% in dried plant preparations

Peak THC levels ~1–2 hours.
Slower and lower bioavailability (2–20%)
Enzymes in the liver turn the original delta-9-THC from the cannabis plant into the metabolite 11-OH-THC which is further metabolized into 11-COOH-THC.

Average concentration of THC and metabolites after smoking one joint of 15.8mg of THC.

Cytochrome P450 (CYP) is a family of isoenzymes that regulate drug phase-1 metabolism.

Due to their high lipophilicity, cannabinoids are potent substrates for the CYP system in the liver.

The phase-1 metabolic pathway is the principal biotransformation pathway for most psychiatric medications.

CYP enzymes are significant contributors to the primary metabolism of cannabinoids, especially 3A4 and 2C9.
CYP Inducers and Inhibitors

Inducers put the enzyme to work speeding up the metabolism of the drug!!

Inhibitors slow down the metabolism of the drug, increasing the half-life.
### Effects of THC/ CBD Activity on Human Cytochromes

<table>
<thead>
<tr>
<th>Compound</th>
<th>CYP Involved</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC (Non-inhalation)</td>
<td>CYP2C9, CYP3A4</td>
<td>Inhibition</td>
</tr>
<tr>
<td>CBD (Non-inhalation)</td>
<td>CYP2C19, CYP3A4</td>
<td>Inhibition</td>
</tr>
<tr>
<td>Marijuana Inhalation</td>
<td>CYP1A1, CYP1A2</td>
<td>Induction</td>
</tr>
</tbody>
</table>

Examples of Cannabinoid Drug Interactions: SSRIs, SNRIs, and Mood Stabilizers/Anticonvulsants

<table>
<thead>
<tr>
<th>Medication</th>
<th>Enzyme Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine (SSRI Antidepressant)</td>
<td>CYP2D6, CYP2C9</td>
</tr>
<tr>
<td>Fluvoxamine (SSRI Antidepressant)</td>
<td>CYP2D6, CYP1A2, P-gp</td>
</tr>
<tr>
<td>Sertraline (SSRI Antidepressant)</td>
<td>CYP2C19, 2B6</td>
</tr>
<tr>
<td>Levomilnacipran (SNRI)</td>
<td>CYP3A4/5</td>
</tr>
<tr>
<td>Venlafaxine (SNRI)</td>
<td>2D6, CYP2C19, CYP3A4/5, P-gp</td>
</tr>
<tr>
<td>Doxepin (TCA)</td>
<td>CYP2D6, CYP2C19</td>
</tr>
<tr>
<td>Imipramine (TCA)</td>
<td>CYP2D6, CYP2C19</td>
</tr>
<tr>
<td>Trimipramine (TCA)</td>
<td>CYP2D6, CYP2C19, P-gp</td>
</tr>
<tr>
<td>Carbamazepine (Mood stabilizer/anticonvulsant)</td>
<td>CYP3A4/5</td>
</tr>
<tr>
<td>Valproate (Mood stabilizer/anticonvulsant)</td>
<td>CYP2C9</td>
</tr>
</tbody>
</table>

Examples of Cannabinoid Drug Interactions: Antipsychotics

<table>
<thead>
<tr>
<th>Medication (Antipsychotics)</th>
<th>Enzyme Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>CYP2D6, CYP3A4/5, P-gp</td>
</tr>
<tr>
<td>Asenapine</td>
<td>CYP1A2, UGT1A4</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>CYP2D6, CYP 3A4/5</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>CYP3A4/5</td>
</tr>
<tr>
<td>Clozapine</td>
<td>CYP1A2, CYP2D6, CYP3A4/5, P-gp</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>CYP2D6, CYP3A4/5</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>CYP3A4/5</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>CYP1A2, P-gp</td>
</tr>
<tr>
<td>Pimavanserin</td>
<td>CYP3A4/5</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>CYP3A4/5</td>
</tr>
<tr>
<td>Risperidone</td>
<td>CYP2D6, CYP3A4/5, P-gp</td>
</tr>
</tbody>
</table>

Cannabinoids and the CYP450 System

Cannabinoids
- Endocannabinoids
- Phytocannabinoids
- Synthetic Cannabinoids
- Cannabinoid-like Substances

Metabolites

Brain
- Neurotransmitters
- Hypothalamus/Pituitary

Cytochrome P450

Increased/Decreased CYP Metabolic Activity

Hormones (Endocrine Disruptors)

• The particular preparations of Δ⁹-THC and/or CBD-based products, and the utilization method (i.e., inhalation, ingestion) are predicted to result in clinically specific drug-drug interactions (DDIs).

• Interpreting the available evidence is limited, particularly by methodological deficiencies (e.g., lack of consistency in the level of exposure to Δ⁹-THC and/or CBD).

• Wide variability in cannabinoid product content and dosing (whether recreational or medicinal) makes it difficult to assess the data.

• “Poor Metabolizers” may be more susceptible to DDIs when consuming cannabinoids, however more research is needed.

• Differential effects of cannabinoids on cytochrome activity due to formulation, route of administration, concentration, and derivation (plant-based versus synthetic).
The Bad Boys: Illicit Substances

Class 1 Drugs:

• Marijuana (Cannabis)
• Heroin
• Lysergic acid diethylamide (LSD)
• 3,4-methylenedioxymethamphetamine (Ecstasy)
• Methaqualone
• Peyote
Case Study: Adverse Effects of Smoking Marijuana While Receiving Tricyclic Antidepressants

- A case study conducted a long time ago (1997) included four male adolescents (age 15–18) being treated with tricyclic antidepressants (TCAs) for ADHD.
- Smoking marijuana resulted in transient cognitive changes, delirium, and tachycardia.

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 16</td>
<td>Age 18</td>
<td>Age 15</td>
<td>Age 16</td>
</tr>
<tr>
<td>Treated with 75mg/day nortriptyline</td>
<td>Treated with desipramine at 200mg/day</td>
<td>Treated with 150 mg desipramine and 50 mg of sertraline/day</td>
<td>Treated with desipramine and clonidine (dose not noted)</td>
</tr>
<tr>
<td>30 minutes after smoking one marijuana cigarette he was taken to the emergency room for delirium, and the ECG indicated sinus tachycardia.</td>
<td>Reported experiencing “severe confusion, light-headedness, spaciness, and feeling ill” after smoking marijuana. MMSE resulted in significant confusion and short-term memory impairment.</td>
<td>A severe “confusional state” developed after he smoked two marijuana cigarettes. He also experience mood lability, irritability, and a “racing heart,” but did not seek medical attention.</td>
<td>He smoked marijuana on weekends. Noted that since he started desipramine he experienced hallucinations, depersonalization, and confusion. He also experienced shortness of breath and elevated heart rate.</td>
</tr>
<tr>
<td>Symptoms resolved in 24 hours</td>
<td>Symptoms resolved in 48 hours</td>
<td>Symptoms resolved in 16 hours</td>
<td></td>
</tr>
</tbody>
</table>

Cannabis Formulations and Doses
# THC Levels in Allowable Dosage Forms

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Bioavail.</th>
<th>Tmax</th>
<th>Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>F: 10–25%</td>
<td>minutes</td>
<td>Formation of noxious compounds</td>
</tr>
<tr>
<td>Vaping</td>
<td>F: 10–25%</td>
<td>minutes</td>
<td>Unfamiliar method</td>
</tr>
<tr>
<td>Oral</td>
<td>F: 5–20%</td>
<td>1–3 hrs</td>
<td>Wide inter-/intra-user PK variability, ↑ risk overdose</td>
</tr>
<tr>
<td>Oromucosal</td>
<td>F: 5–25%</td>
<td>1.4–4 hrs</td>
<td>No evidence different PK from oral</td>
</tr>
<tr>
<td>Topical</td>
<td>unknown</td>
<td>Unknown</td>
<td>No evidence of topical absorption, consistent with most products claim of no psychoactive effects</td>
</tr>
<tr>
<td>Pharm. capsule</td>
<td>F: 5–25%</td>
<td>1–1.5 hrs</td>
<td>Wide inter-/intra user, Tmax seems more reliable</td>
</tr>
</tbody>
</table>
Smoking Cannabis Plant

• Burns 500–2000°F, cannabis combusts at > 392°F

• Benzo[a]pyrene is formed by partial combustion, when cannabis is burned, then binds to DNA, potentially resulting in mutations and drug interactions (CYP 1A2)

• Inhalation provides immediate psychotropic effects

Vaporizing Cannabis Plant or Concentrate

• Same immediate effects and benefits as smoking
• Heats 285–392°F vaporizing cannabinoids → no carcinogens
• Conductive vs. convective heating

Images from: www.cannastick.com; https://spendabit.co/go?q=vape&offset=0; www.procon.org
Cannabis Concentrates: “Dabbing”

• Cannabinoids are extracted by solvents

• Street names: ‘Butane hash oil (BHO), dabs, earwax, butter, or shatter’

• >90% of Cannabinoids

• Users quickly develop tolerance

Edible Baked Goods, Candies, Tinctures

- Edibles have cannabinoids added, or are infused with cannabinoid butter, oil, or alcohol
- 5–10mg serving size and 50–100mg max/product
- Must exit dispensary in child-resistant packaging
- Now also prohibit edibles that resemble animals, people, or fruit

Cannabis-Infused Creams, Lotions, and Oils

- THC not charged, but lipophilic properties limit it getting to site of action
- Most products claim no psychoactive effects, so THC not getting absorbed
- Patch with occlusion and vehicle to enhance absorption

THC Medium dose = 7–18 mg

There is a known tolerance to THC

↑ probability of tolerance with chronic use, and ↓ with intermittent

Chronic = daily for a week, intermittent = weekly

CBD (Epidiolex) Oral solution 100 mg/mL

For Dravet syndrome 2.5–10 mg/kg twice daily

Cancer case studies 2.5–100mg daily

Effective Communication With Patients About Cannabis
Before You Talk to Your Patients About Cannabis...

• Understand that cannabis crosses all ages, cultures, socioeconomics, and genders
• It’s not a “rich man’s drug” or a “poor man’s drug,” and to many it’s not a drug at all, it’s just a plant
• Consider changing the terminology in psychiatric intake forms: instead of “substance use” specifically ask about “marijuana use” or “cannabis use”
• Be comfortable about openly communicating with your patients
• Be prepared to be compassionate and refrain from judgement
• Many patients have convinced themselves (whether the evidence is there or not), that cannabis relieves symptoms for a variety of medical ailments
• Be prepared to discuss the evidence openly but to also offer support
Communicating Effectively With Your Patients About Cannabis Use

• Encourage honesty and open communication

• Encourage them to provide accurate information about their use of cannabis

• Ask them to share how cannabis affects both their physical and mental health on a regular basis

• Obtain a detailed list of the medications they’re currently taking, and any side effects associated with them

• Discuss the current evidence-based research for medical marijuana if it pertains to them
Discussing Side Effects

• It is very important to discuss potential side effects due to interactions of cannabinoids with many psychiatric medications

• Understand and *fully explain* the pharmacokinetics of cannabinoids on the cytochrome p450 system

• You may want to discuss pharmacokinetic and pharmacodynamic testing, for your patient to see if they may be at higher risk for drug-drug interactions

• Ask your patient if they are using recreationally, or if they are trying to treat a medical condition

• Remain educated on the evidence for and against medical marijuana for the treatment of medical conditions, as well as the legality that pertains to your state
Ask About Their Consumption Method

- Each consumption method alters the pharmacokinetics and can influence interactions with psychiatric medications.
- Ask your patient at each visit what method they have been using and if it has changed.
- Methods of administration include:
  - Smoking
  - Vaporization
  - Drinking infused beverages
  - Edibles
  - Transdermal patches
  - Lotions
  - Tinctures
  - Cannabis pills
General Principles for Treating Patients Who Use Marijuana

• Incorporate marijuana-related inquiries into each patient encounter

• Work from a disease model—the drug can take over reward and motivation increasing apathy, depression, paradoxical anxiety/insomnia

• Moral criticism and shaming may elicit defensiveness

• Evaluate the need for psychoeducation: many patients know the risks

• Include family members for evaluation and monitoring

• Use motivational, cognitive-behavioral, and contingency management techniques to discontinue use, if psychiatric drug interactions occur/persist

Summary

• The use of marijuana both recreationally and medicinally is on the rise

• $\Delta 9$-THC is an inhibitor of CYP2C9 and CYP3A4

• CBD is an inhibitor of CYP2C19 and CYP3A4

• Smoking marijuana results in induction of CYP1A1 and CYP1A2

• While there is evidence for potential drug-drug interactions between cannabis and many psychotropic drugs, systematic studies are lacking

• Due to potential DDIs, it is important to have consistent, open communication with patients who use cannabis, and to monitor the use closely
Cannabidiol (CBD) is a non-psychoactive compound found in cannabis and is metabolized via the CYP450 system. As a result, it inhibits:

1. CYP2C9
2. CYP2C19
3. CYP3A4
4. CYP1A2
5. 2 & 3
6. 1 & 2
Posttest Question 2

The route of administration of cannabis affects the degree of drug exposure, and the bioavailability of Δ⁹-THC. Bioavailability of THC is ______, when smoked/vaped versus ______ when ingested orally.

1. 3–5%; 5–10%
2. 5–10%; 5–15%
3. 10–25%; 2–20%
4. 20–25%; 5–35%
When talking to patients about cannabis use with concurrent psychiatric medications, it is important to:

1. Encourage an open, honest discussion
2. Tell them to stop taking cannabis immediately
3. Discuss the pharmacokinetics with them, and explain potential drug-drug interactions
4. Ask about the consumption method of cannabis
5. 1, 3, and 4
6. None of the above