Learning Objectives
1. Describe the pharmacological properties of marijuana
2. Discuss the potential risks associated with marijuana use
3. Summarize the clinical evidence surrounding benefits and efficacy

I. Pharmacological Properties of Marihuana
   a. Pharmacology
      i. Preparations of marihuana come from the dried leaves & flowers of the Cannabis sativa plant
      ii. Plant contains > 460 active chemicals and > 60 cannabinoids
      iii. Major active ingredient of marihuana is δ-9-tetrahydrocannabinol (THC) → “therapeutic” and psychoactive effects. Amount of THC in marihuana varies.
      iv. Two types of cannabinoid receptors – Table 1

Table 1: Cannabinoid Receptors

<table>
<thead>
<tr>
<th>Cannabinoid-1</th>
<th>Cannabinoid-2</th>
</tr>
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<tbody>
<tr>
<td>• Present primarily in central nervous system (CNS); some in peripheral tissue</td>
<td>• Present primarily on peripheral tissues and central immune cells</td>
</tr>
<tr>
<td>• Heterogeneous distribution in brain → effects on pleasure, memory, thought, concentration, and coordinated movement</td>
<td>• Activation → immunosuppression, anti-inflammatory effects, anti-nociceptive effects</td>
</tr>
<tr>
<td>• Effects are neuromodulatory and affect other neurotransmitters (acetylcholine, norepinephrine, dopamine, serotonin, δ-aminobutyric acid, glutamate, and D-aspartate)</td>
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</tr>
</tbody>
</table>

   v. Pharmacological effects vary with dose, administration, user, & sensitivity to psychoactive effects
   vi. Intoxication → changes in mood, perception, motivation, cognitive function, reaction time, memory and learning. “High” and “mellowing out” effects. Other behavioral changes include giddiness. Increased hunger also noted.
   vii. Withdrawal → restlessness, irritability, agitation, insomnia, sleep disturbances, nausea, cramping

b. Routes of Administration / Pharmacokinetics
   i. Smoking (hand-rolled cigarettes, cigars, or water pipes)
      1. Onset of effects – immediately
      2. Duration of effects – one to three hours
      3. Highest blood concentration of THC achieved via this route
      4. Metabolites – THC first metabolized by lungs & then liver
         a. 9-carboxy-THC – no psychoactive properties
         b. 11-hydroxy-THC – crosses the blood brain barrier → psychoactive effects. More potent than THC.
c. Highly lipophilic – remain in fat tissues

ii. Oral ingestion (brewed tea or food)
   1. Onset of effects – 30 minutes to one hour
   2. Duration of effects – 4 hours

c. Safety – Table 2

**Table 2:** Adverse Effects Associated with Marihuana Use

| Cardiovascular System | • Tachycardia, hypertension, syncope, palpitations, orthostatic hypotension, atrial fibrillation  
|                        | • Acute myocardial infarction  
|                        | • Transient ischemia attacks, stroke |
| Respiratory System     | • Increased symptoms of chronic bronchitis  
|                        | • Cancers of the aerodigestive tract & lung reported (see carcinogenic effects) |
| Nervous System / CNS   | • Drowsiness, numbness, dizziness, difficulty sleeping, nightmares  
|                        | • Seizures  
|                        | • Visual disturbances, blurred vision, dry eyes, reddening of conjunctiva, mydriasis, photophobia  
|                        | • Psychological dysfunction – inability to form memories, recall events, and focus  
|                        | • Addiction |
| Carcinogenic effects   | • Marihuana contains 50-70 % potentially more carcinogenic ingredients than cigarettes. Inconsistent & lacking evidence on the association of marihuana smoking & cancer  
|                        | • Lung & head & neck cancers reported  
|                        | • Some data suggest marihuana is not mutagenic or carcinogenic |
| Miscellaneous          | • Dry mouth, flu-like symptoms, nausea  
|                        | • Hyperemesis syndrome |

d. Drug-Drug Interactions – Table 3

**Table 3:** Drug Interactions Reported with Marihuana

<table>
<thead>
<tr>
<th>Opioids</th>
<th>Cross-tolerance &amp; potentiation of CNS effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Alcohol</em></td>
<td>Excess CNS depression</td>
</tr>
<tr>
<td><em>Benzodiazepines</em></td>
<td></td>
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<tr>
<td><em>Muscle relaxants</em></td>
<td></td>
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<tr>
<td><em>Protease inhibitors</em></td>
<td>Decreased effectiveness of the agents by marihuana (due to increased drug clearance)</td>
</tr>
<tr>
<td><em>Theophylline</em></td>
<td></td>
</tr>
<tr>
<td><em>Fluoxetine</em></td>
<td>Manic episodes</td>
</tr>
<tr>
<td><em>Sildenafil</em></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td><em>Tricyclic antidepressants</em></td>
<td>Tachycardia, delirium</td>
</tr>
<tr>
<td><em>Anticholinergic agents</em></td>
<td>Tachycardia, hypertension</td>
</tr>
<tr>
<td><em>α-agonists</em></td>
<td></td>
</tr>
<tr>
<td><em>Naltrexone</em></td>
<td>Increased euphoric effects</td>
</tr>
<tr>
<td><em>Lithium</em></td>
<td>Increased lithium concentrations</td>
</tr>
<tr>
<td><strong>Neuroleptic antipsychotics</strong></td>
<td>Decreased effectiveness, increased risk of extrapyramidal effects</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>Increased risk of immunosuppression</td>
</tr>
</tbody>
</table>
| **Chemotherapeutic agents**   | • Marihuana appears to modulate the activity of cytochrome P450 system, especially CYP3A where ~ 37% of anticancer drugs are metabolized. Clinical effects assessing the pharmacokinetic effects of marihuana and anticancer drugs are absent.  
• One study concluded no impact of marihuana on the pharmacokinetics of irinotecan and docetaxel when given in combination⁶ |

e. Drug-Disease Interactions – Table 4

**Table 4: Disease Interactions Reported with Marihuana**

| **Immunosuppressive disorders** | Due to the immunosuppressive effects of marihuana, the following disease states may be at an increased risk: diabetes, HIV, lupus, rheumatoid arthritis, cancer, organ transplant recipients. |
| **Psychiatric disorders**       | Exacerbation of schizophrenia, psychosis, bipolar disorder, depression, eating disorders, and panic/anxiety disorders. |
| **Cardiovascular disease**      | Patients at risk of cardiovascular disease, stroke, or myocardial infarction may be at risk of cardiovascular events. |
| **Respiratory disease**         | Long term use of marihuana may worsen chronic obstructive pulmonary disease, asthma, and tuberculosis. |
| **Diabetes / Obesity**          | Undesirable weight gain |
| **Pregnancy**                   | Impairment of intrauterine growth, neurobehavioral effects on fetus, increased risk of childhood leukemia |

II. Therapeutic Effects / Clinical Efficacy (Cannabis & Cannabinoids)⁷

a. Conclusive / substantial evidence
   i. Chronic pain (adults)⁸  
   ii. Chemotherapy induced nausea & vomiting (CINV)⁹,¹⁰  
   iii. Multiple sclerosis (MS) spasticity symptoms

b. Moderate evidence
   i. Sleep disturbances  
   ii. Associated with sleep apnea, fibromyalgia, chronic pain, MS

c. Limited evidence
   i. Improvements in the following symptoms
      1. Appetite, weight loss (HIV/AIDS)  
      2. MS spasticity symptoms  
      3. Tourette’s
   ii. Anxiety  
   iii. Posttraumatic stress disorder (PTSD)

d. No or insufficient evidence
   i. Cancer treatment¹¹  
   ii. Others

III. Risks Associated with Cannabis Use⁷

a. Cancer: non-seminoma testicular germ cell tumors  
b. Cardiometabolic effects
c. Respiratory disease
d. Immunity
e. Motor vehicle accidents
f. Overdose injury
g. Cognitive impairment
h. Mental health issues
i. Abuse, misuse, addiction
j. Cannabinoid hyperemesis syndrome\textsuperscript{12,13}

IV. Summary & Conclusions
a. Very few controlled studies published for clinical indications
b. Side effects & drug interactions can be significant
c. Cannabinoid receptors – possibly a promising pathway
d. Risks > benefits?

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References

3. Doering Paul L, Boothby Lisa A, "Chapter 68. Substance-Related Disorders: Overview and Depressants, Stimulants, and Hallucinogens" (Chapter).