Medical Marijuana: Clinical Implications

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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[1-6]

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

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

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[4]

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

Opioids	Cross-tolerance & potentiation of CNS effects
Alcohol **Benzodiazepines** **Muscle relaxants**	Excess CNS depression
Protease inhibitors **Theophylline**	Decreased effectiveness of the agents by marihuana (due to increased drug clearance)
Fluoxetine	Manic episodes
Sildenafil	Myocardial infarction
Tricyclic antidepressants	Tachycardia, delirium
Anticholinergic agents **α-agonists**	Tachycardia, hypertension
Naltrexone	Increased euphoric effects
Lithium	Increased lithium concentrations

Neuroleptic antipsychotics	Decreased effectiveness, increased risk of extrapyramidal effects
Corticosteroids	Increased risk of immunosuppression
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 combination[6]

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 treatment[11]
      ii. Others

III. Risks Associated with Cannabis Use[7]
   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[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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