Medical Marijuana and Transplant: What Do We Know?

Celebrating a Second Chance at Life Survivorship Symposium

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At the conclusion of this workshop attendees should have a clear understanding of the following:

- The probable mechanism by which cannabis products affect mood and physical symptoms
- How quality and potency of cannabis varies, depending on source
- Potential benefit, if any, for HCT survivors to use medical cannabis
- Potential adverse effects and drug interactions associated with the use of medical cannabis
Listed in U.S Pharmacopeia 1850-1941

- Marijuana and hashish extracts were the 1st, 2nd, or 3rd most prescribed meds in the U.S. from 1842-1890s
- Labor pain, nausea, rheumatism
- Criminalized in 1914, 1937, 1951, schedule I in 1970
- 2018: first non-synthetic cannabis product approved

Marijuana

Cannabis sativa – flowering herbal plant

- Also refers to indica and ruderalis species
- Originated in Asia, now grown nearly worldwide
- Currently >30 states + D.C. have programs authorizing cannabis use for specific medical conditions
- Additional 14 states allow Low delta 9 tetrahydrocannabinol (THC), High cannabidiol (CBD) products for qualifying medical reasons
Cannabis Compounds

• (Phyto) Cannabinoids
  – Highest concentration found in female flowers
  – Bind to cannabinoid receptors and change body response

• Terpenes (Terpenoids)
  – Aromatic chemicals also found in pine trees, citrus flora, and other odoriferous plants
  – Produce the unique aroma and flavor of cannabis

• Flavonoids
  – Chemicals common to most plant life
  – Many considered to have anti-inflammatory and antioxidant properties

Common Cannabinoids in Use

• Delta-9-tetrahydrocannabinol (THC)
  – Major psychoactive component in cannabis
  – Naturally occurs in concentrations anywhere from 0.5 – 20% depending on cannabis cultivar and how processed

• Cannabidiol (CBD)
  – Lacks any noticeable psychoactive affects - may decrease anxiety
  – Does not interact with cannabinoid receptors
  – Modulates the action of/exposure to THC

• Over 140 different cannabinoids found in cannabis
Dosing Notes

• Generally, 2-3 mg smoked for average “high”

• Oral dose must be 3-5 times the inhaled dose due to stomach acid effects and liver first-pass metabolism.
  – Delayed and unpredictable onset times

• Smoked onset occurs in minutes while oral can take an hour or longer

• Varies by state but often see 5 mg increments in a “dose”
Drug Interactions

- Interactions with prescription medications common
  - Interacts with body metabolism systems
- Dynamic interactions
  - Additive effects to sedating agents
    - Sleeping pills, antihistamines, antianxiety agents and others
  - Opposing effects to stimulants
  - Antidepressants and psychiatric drugs – variable

Cannabis Pharmaceuticals

Dronabinol (Marinol®)
- Synthetic Δ9-THC in sesame oil
- Activates cannabinoid receptors CB₁ and CB₂; has approximately equal affinity for each, but efficacy is less at CB₂ receptors

Nabilone (Cesamet®)
- Synthetic THC that binds both CB₁ and CB₂ receptors

Cannabidiol (Epidiolex®)
- Purified cannabidiol from cannabis plants as a 100 mg/mL oral solution
- Does not bind to the CB₁ or CB₂ receptor
Cannabidiol (CBD)

- Hemp-derived (maximum 0.3% THC)
- Marijuana-derived (5-30% THC common)
- Pharmaceutical-derived
  - Epidiolex: FDA Approved, plant derived, available nationally, < 0.1% THC
- All from Cannabis sativa, but cultivar predicts for CBD vs THC content

Common Cannabis Preparations

- **Marijuana** – dried leaves, stems, flowers
- **Hashish** – concentrated resin, may come as a cake
- **Tincture** – liquid infused with cannabinoid
- **Oil** – extracted from the plant with a variety of solvents (butane, CO₂, ethanol, propane, etc.), different names
- **Infusion** – cannabis plant material mixed with nonvolatile solvent (butter, cooking oil, etc.)
- **Edibles** – Wide variety of choices in solid and liquid form
- **Hemp products** – primarily provide CBD, may have variable THC.
### Natural Product Issues

- **Purity** – (herbicides, pesticides)
  - Some states testing for these
- **Potency** (THC content, other cannabinoid content)
  - All studies thus far show >50% of products are mislabeled
- Each batch, even of the same cultivar, will have different contents
- Appropriate medical dose per condition is unknown

### Synthetic Cannabinoids

- Emerged in the early 2000’s
- Group of compounds that interact with the endocannabinoid system
- 7 major chemical/structural groups
  - Spice, K2, Fake Pot, etc.
- Now schedule I - **NO acceptable medical use**
- Multiple cases of kidney injury and heart attacks with use, ongoing contamination and mislabeling issues
- Variable and unknown toxicity profile
Medical Use of Cannabis

Cannabinoid Effects

Activation of cannabinoid system causes four groups of psychological effects

- **Behavior**: euphoria and easy laughter
- **Sensory**: time and space perception altered and disorientation common
- **Function**: drowsiness, dizziness, and poor motor coordination
- **Thinking**: confusion, memory lapses, and difficulty concentrating
Potential Uses for Medical Marijuana

- Pain
- Nausea
- Cancer
- Anorexia/cachexia
- Neuropathy
- Glaucoma
- Seizures
- Depression and anxiety
- Insomnia
- Muscle spasms
- Migraines
- Post traumatic stress disorder
- Agitation related to Alzheimer's disease
- Anti-mania/bipolar disorder

Pain Management Guideline 2021 (Canada)

- Who might be helped
  - Moderate to severe cancer and non-cancer pain
  - Neuropathic pain and some other types of pain
- Who may not be helped
  - Children
  - Veterans
  - People with mental illness
  - People with disability benefits or involved in litigation
- Does not apply to
  - Inhaled cannabis
  - Recreational cannabis
  - People in end of life care
Pain Management Guidelines 2021 (Canada)

• Potential Benefits
  • Reduced pain: 1 in 5 people (moderate quality evidence)
  • Improved physical function: 1 in 7 people (high quality evidence)
  • Improved emotional function: not different than placebo (high quality evidence)
  • Improved role function: not different than placebo (high quality evidence)
  • Improved social function: not different from placebo (high quality evidence)
  • Improved sleep quality: 1 in 6 people (high quality evidence)

Potential Harms

• Impaired attention: 1 in 3 people (moderate quality evidence)
• Drowsiness: 4 out of 5 people (moderate quality evidence)
• Cognitive Impairment: 1 in 2 people (moderate quality evidence)
Pain Management Guidelines 2021 (Canada)

- Recommendation (due to weak quality evidence for benefit)
  - Only try cannabis if standard treatments are not working
  - If using, try a non-inhaled form of medical cannabis/cannabinoids
  - Add cannabis/cannabinoids to standard therapy

Key Recommendations

- Cannabis should be started at a low dose of non-inhaled cannabidiol products and gradually increased in dose and THC depending on response and tolerability
- Prior cannabis experience should be considered, and side effects should be monitored
- Young and adolescent patients: cannabidiol is preferred as THC effects on neurocognitive development are uncertain
- Avoid driving or operating machinery while starting or changing dose of medical cannabis
- Pregnant women, those considering pregnancy or breast feeding should discontinue the use of cannabis
Is There Harm from Cannabis?

Hard Drugs vs. Soft Drugs

Soft drugs

• Less addictive

• Less dangerous - either side effects or lethality

• Overdose risk of marijuana is very small in comparison to other recreational medications
Cannabis Side Effects*

<table>
<thead>
<tr>
<th>Product</th>
<th>Dronabinol</th>
<th>Nabilone</th>
<th>Cannabidiol</th>
<th>Marijuana</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal thinking</td>
<td>3-10%</td>
<td>2%</td>
<td>NR</td>
<td>Common</td>
</tr>
<tr>
<td>Appetite Increase</td>
<td>FDA use</td>
<td>2%</td>
<td>-13-28%</td>
<td>Common</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>19-31%</td>
<td>NR (constipating)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3-10%</td>
<td>59%</td>
<td>NR</td>
<td>Common</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3-10%</td>
<td>&lt;1%</td>
<td>10-15%</td>
<td>NR</td>
</tr>
<tr>
<td>Euphoria</td>
<td>8-24%</td>
<td>11-38%</td>
<td>NR</td>
<td>Common</td>
</tr>
<tr>
<td>Fatigue</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>20%</td>
<td>NR</td>
</tr>
<tr>
<td>Low blood pressure</td>
<td>&lt;1%</td>
<td>8%</td>
<td>NR</td>
<td>Common inc. orthostatic</td>
</tr>
<tr>
<td>Infection</td>
<td>NR</td>
<td>&lt;1%</td>
<td>11% (URI)</td>
<td>Reported</td>
</tr>
<tr>
<td>Nausea</td>
<td>3-10%</td>
<td>4%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>3-10%</td>
<td>3-66%</td>
<td>15-36%</td>
<td>Drowsiness</td>
</tr>
<tr>
<td>Visual changes</td>
<td>&lt;1%</td>
<td>13%</td>
<td>NR</td>
<td>Common</td>
</tr>
</tbody>
</table>

* Side effects dose related, NR=not reported

Smoke or Vape?

- Cannabis is usually smoked without a filter
  - Particulates delivered to the respiratory tract are about 4 times greater when smoking marijuana than when smoking the same amount of tobacco
- Smoked:
  - Combustion at 600-900°C produces toxic biproducts:
    - tar, hydrocarbons, carbon monoxide and ammonia
- Vaporized:
  - Combustion at 160-230°C
  - reduces carbon monoxide but some hydrocarbons remain
- Vaping is theoretically superior to smoking
  - less harmful byproducts and decreased pulmonary symptoms
Effects on Lungs/Breathing

- Wheezing, sputum production and chronic cough but not COPD
- Inhalation of smoke or vaporized cannabis increases risk of pulmonary infections
  - Most common bacteria = Enterobacteriaceae
  - Most common mold = Aspergillus
- Danger is primarily in patients who are immunocompromised
  - Dry buds more dangerous than oil
- Many medical case reports; a fatal outcome in some
- Sterilization techniques exist, but are not routine in the USA

Is There a Relationship Between Smoking Cannabis and Lung Cancer?

- Retrospective case-control study in New Zealand assessed the risk of lung cancer as it relates to joint-years and other variables
- Risk of lung cancer increased:
  - 8% for each joint-year of cannabis smoking
  - 7% for each pack-year of cigarette smoking
- True risk unclear since most persons also smoked cigarettes
- Joint year = 1 joint/day/year
Effects on Heart and Blood Flow to the Brain

- Many medical reports of different kinds
  - Primarily seen with inhaled cannabis
  - Acute use associated with
    - Increased heart rate
    - Increased cardiac output
    - Increased blood pressure
- Case reports of sudden cardiac death or stroke in young people (men) with no/few risk factors
- Risky in people with angina, arrhythmia or other cardiac or stroke risks, particularly risky with concentrated products to cause heart attacks or strokes

Cannabis in Adolescents

- Endocannabinoid system critical in brain development and maturation processes
- Adolescent exposure causes long-lasting alterations in the endocannabinoid system and other neurotransmitter systems
  - Linked to behavioral and cognitive patterns, and neurochemical consequences lasting into adulthood
- Brain development continues until age 25 years
  - Legal sales to persons aged 21 years or older
Potential Reproductive Harms

- Animal studies show growth retardation and fetal malformations
- Most human studies confounded by concomitant tobacco, alcohol, or other illicit drug use
  - Appears to result in lower birth weight in most infants
- Delayed visual system development, increased tremors
- Lower scores in memory and verbal outcomes seen along with increased rates of delinquency and problem behaviors at age >10
- Prenatal exposure is a risk factor for adolescent mental health issues

Dependence

- Dependence develops in 9-10% of cannabis users
- Risk lower than nicotine (32%), heroin (23%), and alcohol (15%), and equivalent to anxiolytics (sedatives) and cocaine (11%)
- Risk is greater for cannabis smoked versus eaten????
- Physiologic withdrawal after long-term use is common
Driving

• Doubles rate of auto accidents in multiple studies

• Dose related effects to coordination and judgment with more marked effects on automated functions of driving vs. those with cognitive control (oral and inhaled products)
  – Tendency to overestimate impairment and many appear to be able to compensate to some regard

• 12% increase in fatal car crashes on 4/20 vs 1 week before or after

Fungal Infections

• Multiple cases of pulmonary aspergillus infections in oncology patients (inhaled products)
  – Solid tumor, hematologic malignancy, and BMT

• Case reports in non-oncology patients
  – Tends to be associated with longer use and only with smoking marijuana thus far

• Smoking marijuana deposits spores in about 50% of individuals

• Medical sterilization processes successful but no commercial delivery device sterilizes cannabis
Cannabis and the Immune Compromised

• Inhalation of smoke or vaporized product results in direct inhalation of bacteria and molds from plant surfaces.
• Cannabis and tobacco commonly contaminated
  • Aspergillus most concerning
• Cannabis products can be sterilized via autoclave, plasma $H_2O_2$, and ethylene oxide with some loss of THC.
• Home baking 300 degrees F x 50 minutes generally effective with unclear amount of THC loss
• Reduce response rates to immune therapy for cancer

Cannabis is currently framed as 3rd line for medical use or later, not 1st line

• An appropriate candidate should have a debilitating medical condition that trial data suggest would respond to medical marijuana, e.g.:
  • nausea or vomiting associated with cancer chemotherapy
  • anorexia from wasting illnesses like AIDS
  • chronic pain, neuropathic pain
  • spasticity associated with multiple sclerosis
  • multiple trials of first- and second-line therapies for these conditions have failed
Appropriate Candidates for 3\textsuperscript{rd} line therapy, cont'd

- A failed trial of using a US FDA approved cannabinoid (dronabinol or nabilone) if clinically appropriate
- No active substance use disorder or psychotic disorder or no unstable mood disorder or anxiety disorder. Warn about anxiety.
- Residence in a state with medical provider practice act and medical marijuana laws and meets requirement of these laws

Take Home Points - Risk

- Unclear risk for lung cancer
  - Vaping \textit{may} confer lower risks than smoking
- Multiple published case studies regarding heart and stroke risk, but no serious adverse events in controlled trials
- Use in psychiatric disorders is concerning
  - No clear benefit in any psychiatric disorder, harm likely in schizophrenia and bipolar
  - Dose dependent relationship between cannabis and psychosis and schizophrenia, particularly with adolescent/young adult exposure
Take Home Points – Risk cont’d

• Less habit forming than nicotine and ‘hard drugs’ but dependence risk is real (~9%), particularly in adolescents

• Prenatal exposure is concerning

• Need studies in higher risk subgroups (older adults with chronic illnesses)

Take Home Points – Potential Benefits

• True medical benefits unclear

• Areas of Promise
  – Pain relief, especially neuropathic pain
  – Muscle disorders
  – Seizure disorders
  – Appetite and nausea
  – “Mood”

  – Currently cannot “recommend” for any use
Questions?

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