Medical Marijuana and Stem Cell Transplant: What Do We Know?

Celebrating a Second Chance at Life Survivorship Symposium

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Medical Marijuana and Stem Cell Transplant…. What Do We Know?

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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 discomfort
- 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 US 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

- 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

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

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 erratic onset times
- Smoked onset occurs in minutes while oral can take an hour or longer
- Oregon has 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 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
- Multiple cases of acute kidney injury 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

• Affective: euphoria and easy laughter
• Sensory: time and space perception altered and disorientation common
• Somatic: drowsiness, dizziness, and poor motor coordination
• Cognitive: 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

Author Conclusion

Meta-analysis including 79 randomized controlled trials of cannabis across a broad range of conditions

- Most evaluated prescription cannabinoids (dronabinol, nabilone, nabiximols)
- moderate-quality evidence to support the use of cannabinoids for the treatment of chronic nerve-caused or cancer pain (smoked THC and nabiximols)
- Limitations: short study length, differing outcome measures, lack of blinding, crossover trials were not included in analysis

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>Emesis</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>Hypotension</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>Somnolence</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
Smoke or Vape?

- Cannabis is usually smoked without a filter, and smoking dynamics studies among habitual marijuana users show that the overall burden of particulates delivered to the respiratory tract is 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 regarding less harmful byproducts and decreased pulmonary symptoms.

Non-Cancer Respiratory Effects

- 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 to the immunocompromised host:
  - 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.
Dose Dependent Relationship Between Cannabis Smoking 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 and 7% for each pack-year of cigarette smoking
- Joint year = 1 joint/day/year

Cardiac and Cerebrovascular Effects

- Many medical reports of different kinds
- Acute dosing associated with
  \[ \uparrow \text{heart rate} \quad \uparrow \text{cardiac output} \quad \uparrow \text{blood pressure} \]
- 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 maturational processes

- Adolescent exposure causes long-lasting alterations in the endocannabinoid system and other neurotransmitter systems
  - Linked to affective, behavioral, cognitive, 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 at the very least

- 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

- Public opinion considers cannabis non-addictive, especially when ingested orally rather than inhaled
  - dependence is common in some as the brain develops a tolerance to cannabinoids
- 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%)
- 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
  - 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
  - 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 result 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$_2$O$_2$, and ethylene oxide with some loss of THC.
- Home baking 300 degrees F x 50 minutes generally effective with unclear amount of THC loss
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 data from trials suggest would respond to medical marijuana (e.g., N/V associated with cancer chemotherapy, anorexia from wasting illnesses like AIDS, chronic pain, neuropathic pain, or spasticity associated with multiple sclerosis)
- Multiple failed trials of first- and second-line therapies for these conditions

Cannabis is currently framed as 3rd line for medical use or later cont’d

- A failed trial of 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 nurse practice act and medical marijuana laws and meets requirement of these laws
Take Home Points - Risk

- Unclear risk for lung cancer
  - vaping *may* confer lower risks than smoking
- Multiple published case studies regarding CVD/CAD risk, but no serious AEs in controlled trials
- Use in psychiatric disorders 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 problematic
- Need studies in higher risk subgroups (older adults with chronic illnesses)
Take Home Points – Benefits?

- True medical benefits unclear
- Areas of Promise
  - Pain relief, especially neuropathic pain
  - Muscle disorders
  - Seizure disorders
  - Appetite and nausea
  - “Mood”

Questions?

- Spell Caster
- Kimbo Kush
- Dream Dog
- Power Nap
- Real McCoy
- Cornbread
- Snow Leopard
- Koala
- Wedding Cake Bud
- OG Kush
- Silver Tip
- POG
- Maui Wauí
- Star Killer
- Nukén
- Moon Puppy
- Strawberry Satori
- Sunset Sherbert
- Life Me Up
- Extreme Cream
- Triangle Dragon
- Zam Skunkband
- Lime Squeeze
- Corazon
- Buzzed Aldrin
Therapeutic Cannabis Dosing

- Start low and go slow
- “U” shaped effect curve
- Oral dosing
  - Initial dose 2.5 mg (THC content)
  - 5 mg moderate
  - 10 mg strong
  - 15 mg increased risk of adverse effects
  - Questionable benefits for doses > 25 mg depending on use
- No current guidance for CBD- “threshold dose”

Edibles (medibles)
75 products analyzed for labeling accuracy with respect to THC and CBD content
- 17% were accurately labeled
- 23% were underlabeled
- 60% were overlabeled
- Median THC:CBD ratio of products with detectable CBD was 36:1
  - 7 had ratios of <10:1
  - 1 had a 1:1 ratio
- Need for child resistant packaging
Cannabidiol Extract Labeling Accuracy

<table>
<thead>
<tr>
<th>Product</th>
<th>Oil (n=40)</th>
<th>Tincture (n=20)</th>
<th>Vaporization Liquid (n=24)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accurate</td>
<td>45% (18)</td>
<td>25% (5)</td>
<td>12.5% (3)</td>
<td>31% (26)</td>
</tr>
<tr>
<td>Under</td>
<td>25% (10)</td>
<td>40% (8)</td>
<td>75% (18)</td>
<td>42.9% (36)</td>
</tr>
<tr>
<td>Over</td>
<td>30% (12)</td>
<td>35% (7)</td>
<td>12.5 (3)</td>
<td>26.2% (22)</td>
</tr>
</tbody>
</table>

Accurate = within 10% of stated amount

- Products purchased from online retailers 9/16-10/16, blinded and sent to an independent lab
- THC up to 6.43 mg/mL found in 18 samples (21.43%)

Product Issues: In the News

- Idaho – Synthetic cannabinoid labeled as CBD\(^1\)
- Illinois – synthetic cannabis (plant matter sprayed with K2) contaminated with rat poison – 3 deaths, 116 severe bleeding
Oral Cannabis Notables

- Not all cooking temperatures sterilize cannabis and the heat stability of the different compounds is unclear.
- All cannabinoids are degraded by heat labile with differing levels of loss during heating
- Lower risk for pathogen contamination overall depending on adherence to food handling rules

Sterilizing Cannabis

- Initial cultures yielded enterobacteriaceae and a mixture of molds, primarily aspergillus.
- Cookies, dried buds, and SubLingual oil were compared pre and post sterilization
  - Cookies – limited contamination risk
- All 3 methods were able to sterilize the product with associated THC loss
  - Plasma 12.6%
  - Ethylene oxide 26.6%
  - Autoclave 22.6%
- Irradiation doesn’t appear to diminish cannabinoids
- Oregon tests for water content as opposed to molds
Questions?

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