Medical Effects of Marijuana

Rupal Shah MD

Marijuana

- Cannabis genus of flowering plants
- More than 500 compounds
  - 60 pharmacologically active cannabinoids
- 2 major pharmacologically active compounds
  - Cannabidiol
  - Delta 9 tetrahydrocannabinol (THC)

Mechanism of Action

- Cannabinoid receptors in brain and spinal cord
- CB1 receptors in the nervous system
  - Blocks neurotransmitters such as GABA, DA, glutamate
    - Euphoria, psychosis, impaired memory, increased appetite, anti-emetic
- CB2 receptors primarily in the immune system
  - Pain and anti-inflammatory effects
- Metabolized by the liver

Mechanism of Action

- Therapeutic effects depend on concentration of THC and ratio of THC:cannabidiol
- Cannabidiol does NOT activate CB1/CB2 receptors
  - Can mitigate effects of THC
- THC concentration increasing in potency:
  - Previously 4% in 1980s, now 15% in 2016
Medical Marijuana

• 2 FDA indications:
  – nausea and vomiting associated with chemotherapy
  – wasting associated with AIDS

• Best evidence for use in:
  – Chronic pain
  – HIV associated Nausea
  – Chemotherapy
  – Spasm

• *No evidence to suggest superior efficacy over FDA drugs*

California: Approved Conditions

• Arthritis
• Anorexia
• Cachexia
• Cancer
• Chronic Pain
• HIV or AIDS
• Glaucoma
• Migraine
• Persistent Muscle Spasms
• Severe Nausea
• Seizures
• *Any debilitating illness where the medical use of marijuana has been “deemed appropriate and has been recommended by a physician”*

Forms

<table>
<thead>
<tr>
<th>Table 2. Common Cannabis Preparations</th>
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<tbody>
<tr>
<td><strong>Preparations</strong></td>
</tr>
<tr>
<td>Marijuana</td>
</tr>
<tr>
<td>Hashish</td>
</tr>
<tr>
<td>Tincture</td>
</tr>
<tr>
<td>Hashish Oil</td>
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<tr>
<td>Infusion</td>
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</tbody>
</table>

*These preparations are available from state-approved medical marijuana dispensaries.*

Hill, K. *Medical marijuana for the treatment of chronic pain and other medical and psychiatric problems: a clinical review.* JAMA 2015
The case against medical marijuana in solid organ transplant

Rupal J. Shah, MD
September 30, 2016

Outline

• Pharmacokinetics
• Infectious risk
• Medical Complications
• Ethics

Pharmacokinetics

• Over 500 chemicals in marijuana
• Over 60 different types of cannabinoids
  – Unclear which is the active agent

Ray, O and Ksir, C. Drugs Society and Human Behavior 2004
Interaction

- Cannabinoids are known to inhibit P-glycoprotein and CYP3A
- These proteins are important in metabolism of anti-rejection medications, including tacrolimus

Pharmacokinetics

- At least one case report of supratherapeutic levels from inhaled/edible marijuana
- Narrow therapeutic window for tacrolimus
- Elevated levels can lead to kidney injury, neurologic, hematologic complications

Interaction

- Commonly used medications in transplant can also magnify effects of THC
- 35 adverse events reported in this arm

Lack of Regulation

- No federal oversight as not legal
- However, FDA has identified several companies with discrepancies in marketed concentration of THC and actual concentration
- California: Bureau of Medical Cannabis Regulation
  - Developing regulations by 2018
Conclusion

• Given uncertainty about potency of marijuana and extent of inhibition, would be dangerous to allow use of cannabinoid with rejection medications

Infectious Risk

• There are several fungal species that are ubiquitous in soil, air, and vegetable matter
  – Aspergillus is one of the more common pathogens
• After transplant, we discourage patients from gardening without significant respiratory protection
• As marijuana is harvested from the earth, it has potential to be contaminated with mold

Infectious Risk

• Multiple cases of invasive aspergillus infection related to smoking marijuana
• High mortality (Range from 60-90%)
Infectious Risk

- Aspergillus has been found in the marijuana and in the inhalation device
- In one study 11/12 marijuana cigarettes had aspergillus
- 11/21 had reactivity to aspergillus

Kagen SL. Aspergillus: an inhalable contaminant of marijuana. NEJM 1981

Conclusion

- The infectious risk of inhaled marijuana is high, particularly in immunosuppressed patients
- The role of marijuana in regulating immunity is unknown

CBD and the Immune System

Di Marzo, V. Targeting the endocannabinoid system: to enhance or reduce? Nature 2008
Klein, TW. Cannabinoid-based drugs as anti-inflammatory therapeutics. Nature Reviews Immunology 2005

Cognition

<table>
<thead>
<tr>
<th>Table 1: Adverse Effects of Short-Term use and Long-Term or Heavy Use of Marijuana.</th>
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</thead>
<tbody>
<tr>
<td><strong>Effects of short-term use:</strong></td>
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<tr>
<td>Impaired motor function, making it difficult to learn and retain information.</td>
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<tr>
<td>Impaired motor coordination, interfering with daily tasks and increasing the risk of injury.</td>
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<tr>
<td>Impaired judgment, increasing the risk of risky behaviors that facilitate the transmission of sexually transmitted diseases.</td>
</tr>
<tr>
<td>Impaired memory and psychomotor performance.</td>
</tr>
<tr>
<td><strong>Effects of long-term or heavy use:</strong></td>
</tr>
<tr>
<td>Addiction in about 5% of users overall, 17% of those who began using adolescence, and 25 to 50% of those who regularly use.</td>
</tr>
<tr>
<td>Stunted brain development.</td>
</tr>
<tr>
<td>Poor educational outcomes, with increased likelihood of dropping out of school.</td>
</tr>
<tr>
<td>Increased impulsive behavior, lower IQ among those who were frequent users during adolescence.</td>
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<tr>
<td>Increased likelihood of violent behavior, related to the onset of subjective and objective measures as compared with those ratings in the general population.</td>
</tr>
<tr>
<td>Symptoms of cannabis dependence.</td>
</tr>
<tr>
<td>Increased risk of chronic psychotic disorders, including schizophrenia, with a predisposition to such disorders.</td>
</tr>
</tbody>
</table>

Waskow KD. Adverse Health Effects of Marijuana Use. NEJM 2014
Cognition

- Post transplant medication regimen is quite complex, patients are on between 20 and 30 medications which are time sensitive
- Impaired cognition leading to medication mismanagement can be life threatening

Impact on Sedation

- Post transplant procedures are very common
- Unclear interaction between narcotics/BZ
- How long to hold medical marijuana?

Other Concerns

- Marijuana has a described withdrawal syndrome
- Allowing patients to continue to use may interfere with peri-operative pain and anxiety management
  - Precedent with requirement to wean off narcotic and benzodiazepenes

Cognition
Respiratory Complications

- Risk of pneumothorax given long breath hold
- Case of hypersensitivity pneumonitis from vape pen

**Table 1.** Effects of regular use of marijuana alone on chronic respiratory symptoms and lung function in comparison with non-smoking control subjects.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Regular Use of Marijuana Alone</th>
<th>Non-Smoking Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Increase 1</td>
<td>25%</td>
<td>30%</td>
</tr>
<tr>
<td>Increase 2</td>
<td>20%</td>
<td>15%</td>
</tr>
</tbody>
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Pneumothorax, pneumomediastinum and pneumopericardium following Valsalvas maneuver during marijuana smoking NYSJMed

Legal Policy

- Assembly Bill 258, the Medical Cannabis Organ Transplant Act, prohibits transplant centers from denying transplantation to medical marijuana users *solely* based on their use of the drug.
- There is precedent for requiring abstinence from certain substances prior to transplant
  - Cigarettes
  - Alcohol
  - Narcotics and Benzodiazepenes

Other Concerns

- Majority of practitioners still favor abstinence prior to transplant

**Jonathan Neyer et al.** Circ Heart Fail. 2016;9:e002851

Limited Resource

- Solid organ transplant is a limited resource with many people dying prior to receiving a transplant
- In this situation, it is justifiable to select for patients who will have the best possible outcome
- Currently, marijuana provides an unnecessary risk for poor outcomes
Need for more research

- “Caring without science is well-intentioned kindness, but not medicine.”
  
  *Bernard Lown*

- Need more research to better understand the pharmacology, infectious risk, side effects, and dosing profile prior to being acceptable in transplant.