Medical Marijuana
Delving into the Weeds

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Senior Clinical Pharmacist
Craig Hospital
Englewood Colorado
Disclosure

Dr. Collins has no financial or non-financial conflicts of interest related to this activity.

Non-FDA approved products and indications will be discussed during this presentation.
State Regulated Cannabis Programs

Limited adult possession and growing allowed, no regulated production or sales: DC

May 2022

NCSL 2022
Past-Year Marijuana Use among People Aged 12 and Older

<table>
<thead>
<tr>
<th>Region</th>
<th>14.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>National</td>
<td>16.2%</td>
</tr>
<tr>
<td>Kansas</td>
<td>14.4%</td>
</tr>
</tbody>
</table>

2017-2019
Recreational Versus Medical Use

- Risk vs. Risk
- Risk vs. Benefit

Recreational

Medical
Objectives

- Describe how different types of marijuana products may impact a patient.

- Summarize the available evidence using marijuana for therapeutic purposes.

- List at least three specific safety concerns for the use of marijuana.
Marijuana Basics
Cannabis

- Contains over 400 compounds
- Over 100 cannabinoids
  - $\Delta^9$-tetrahydrocannabinol - THC
  - Cannabidiol – CBD
- Over 200 terpenes
- Sterols
- Thiols
- Flavonoids
- Phenols
- Fibrous material
Comparing THC and CBD

**Source**

**Molecular Formula**

THC  
*Cannabis sativa*  
C$_{21}$H$_{30}$O$_2$

CBD  
*Cannabis sativa*  
C$_{21}$H$_{30}$O$_2$

**Chemical Structure**

THC contains cyclic ring

CBD contains hydroxyl group

THC Activity

- Primarily at CB1 receptors in the brain
- Abundant in parts of brain that regulate movement, coordination, learning and memory, higher cognitive functions such as judgement and pleasure

## CBD Activity

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Action</th>
<th>Possible Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB1</td>
<td>Direct antagonist and negative modulator antagonist</td>
<td>Attenuation of impaired learning, memory, and psychosis effects inducted by THC</td>
</tr>
<tr>
<td>CB2</td>
<td>Antagonist and inverse agonist</td>
<td>Anti-inflammatory effects</td>
</tr>
<tr>
<td>GPR55</td>
<td>Antagonist</td>
<td>Possible vasodilation, anti-inflammatory effects</td>
</tr>
<tr>
<td>5HT-1A</td>
<td>Agonist</td>
<td>May have antidepressant and anxiolytic effects</td>
</tr>
<tr>
<td>TRPV-1</td>
<td>Agonist</td>
<td>May have a role in pain responses and regulation of body temperatures</td>
</tr>
<tr>
<td>Adenosine A2A</td>
<td>Enhanced adenosine concentrations</td>
<td>Pain and anti-inflammatory effects</td>
</tr>
<tr>
<td>FAAH enzyme</td>
<td>Inhibition</td>
<td>Decreased breakdown of anandamide and intracellular transport of THC</td>
</tr>
</tbody>
</table>
Hemp

🌿 Federal legal limit of 0.3% THC
Marijuana Effects
Dependent on Formulation

- THC versus CBD
- Concentration of Cannabinoid
- Plant Strain
Marijuana Formulations
Current FDA Approved Cannabis Products

**THC**
- Dronabinol (Marinol®)
  - Capsules (Schedule III)
  - Oral solution (Schedule II)
- Nabilone (Cesamet®)
  - Capsules (Schedule II)

**CBD**
- Cannabidiol (Epidiolex®)
  - Oral solution (Schedule V)
# Marijuana Testing

## Marijuana Detection Times

<table>
<thead>
<tr>
<th>Test Type</th>
<th>One time use</th>
<th>Regular use</th>
<th>Heavy use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood &amp; Saliva</td>
<td>Up to 13 days</td>
<td>Up to 45 days</td>
<td>Up to 90 days</td>
</tr>
<tr>
<td>Urine</td>
<td>Up to 13 days</td>
<td>Up to 45 days</td>
<td>Up to 90 days</td>
</tr>
<tr>
<td>Hair</td>
<td>Up to 90 days</td>
<td>Up to 90 days</td>
<td>Up to 90 days</td>
</tr>
</tbody>
</table>

- **Blood & Saliva**: A few hours
- **Urine**: Up to 13 days
- **Hair**: Up to 90 days
Marijuana Efficacy
Medical Marijuana Patients by Condition

Chronic or severe pain 61%

PTSD 11%

All other conditions 13%

Epilepsy or seizures 1%

Cachexia 0.4%

Cancer 3%

Muscle spasms 6%

Glaucoma 0.7%

Nausea 3%

HIV/AIDS 0.4%

Note: Similar conditions have been grouped together. Some patients may fall into more than one category.

Source: Arizona, Arkansas, Colorado, Delaware, Illinois, Michigan, Minnesota, Missouri, Montana, Nevada, New Hampshire, New Mexico, Oregon, Rhode Island and Utah state MMJ programs.
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National Academies: Health Effects of Cannabis

**No or insufficient evidence** to support or refute that cannabinoids are effective for...

- cancer-associated anorexia cachexia syndrome and anorexia nervosa
- cancers, including glioma
- irritable bowel syndrome
- epilepsy
- spasticity in patients with paralysis due to spinal cord injury
- chorea and certain neuropsychiatric symptoms - Huntington’s disease
- symptoms associated with amyotrophic lateral sclerosis (ALS)
- Parkinson’s disease or levodopa-induced dyskinesia
- dystonia
- treatment for mental health outcomes in individuals with schizophrenia or schizophreniform psychosis
- achieving abstinence in the use of addictive substances
CONCLUSION 4-1

There is substantial evidence that cannabis is an effective treatment for chronic pain in adults.
Cannabinoids for Medical Use
Chronic Pain

**Results**
- Reduction in pain of at least 30%
  - **37% versus 31% placebo** (OR 1.41 95% CI, 0.99-2.00)
- Reduction in pain on 10 point numerical scale
  - **-0.46** (95% CI, -0.80 to -0.11)

**Limitations**
- Small, short, difficult to blind studies

**Conclusion**
- Cannabis may provide pain relief in the short term

Cannabinoids for Medical Use
Chronic Pain

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Medical Cannabis Effects on Opioid Use

Retrospective study of 77 medical cannabis patients (intractable pain)
- 45% female; avg 54 years

Primary Outcome: amount of opioid use
- Milligram morphine equivalents

<table>
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<tr>
<th></th>
<th>Baseline (mg)</th>
<th>6 months (mg)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine equivalents, median (IQR); n=74</td>
<td>105 (43.75 to 155.63)</td>
<td>65.9 (28.13 to 150)</td>
<td>P = 0.001</td>
</tr>
<tr>
<td>Morphine equivalents, average ± SD; n=74</td>
<td>140.64 ± 184.64</td>
<td>103.1 ± 115.31</td>
<td>P = 0.009</td>
</tr>
</tbody>
</table>

Patients using cannabis for intractable pain may have experienced a significant reduction in opioid use.

CONCLUSION 4-7

4-7(a) There is **substantial evidence** that oral cannabinoids are an effective treatment for improving patient-reported **multiple sclerosis spasticity** symptoms, but limited evidence for an effect on clinician-measured spasticity.
Cannabis for Spasticity Due to MS

Systematic review of cloned THC/CBD product used outside the U.S. (Sativex®)

Results

- Improved Ashworth scale compared to placebo
  - 12% (95% CI -.24 to 0.01)
- Improved spasticity using a numerical scale
  - 0.76 (95% CI -1.38 to -0.14)

Conclusion

Cannabis may provide a modest subjective improvement in spasticity due to MS.

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Conclusion
- Cannabis may provide a modest subjective improvement in spasticity due to MS.

Sleep Abnormalities with Cannabis: A Comprehensive Review

There is an initial improvement in subjective sleep complaints.

Objective measurements have shown both positive and negative effects.

Tolerance to beneficial effects occurs in chronic users.

Prominent negative effects on sleep occur during withdrawal.

Cannabinoids and Post-traumatic Stress Disorder (PTSD)

- High prevalence of cannabis use among PTSD patients.
- Higher levels of PTSD symptoms with increased marijuana use.
- Small studies suggest possible benefit

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>cannabinoid</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elms (2019)</td>
<td>11</td>
<td>CBD</td>
<td>&quot;decreased symptoms at 8 weeks&quot;</td>
</tr>
<tr>
<td>Roitman (2014)</td>
<td>10</td>
<td>THC - nabilone</td>
<td>&quot;improvement in global symptom severity, frequency of nightmares and hyperarousal symptoms&quot;</td>
</tr>
<tr>
<td>Fraser (2009)</td>
<td>47</td>
<td>THC - nabilone</td>
<td>&quot;lessening in nightmare severity&quot;</td>
</tr>
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</table>

Safety Concerns
# Cannabis Adverse Effects

## Short term
- Dizziness
- Euphoria
- Anxiety
- Decreased psychomotor function
- Cognitive impairment
- Memory impairment
- Sedation
- Hallucinations
- Increased heart rate
- Weight gain
- Cardiac arrhythmias/MI
- Decreased pulmonary function
- Vision disturbances
- Decreased blood sugars
- MS relapse
- Increased risk of bleed
- Vomiting
- Urinary tract infections
- Withdrawal

## Long term
- Addiction
- Dependence
- Withdrawal
- Depression
- Memory impairment
- Cognition decline
- Decreased pulmonary function
- Cannabis Hyperemesis Syndrome
- Worsening symptoms of schizophrenia
- MS relapse
- Relationship problems
- Lower life satisfaction
- Less academic success
- Less career success

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Adverse Effects of Medical Cannabinoids: a Systematic Review

- Review of cannabis studies for adverse drug reactions (ADRs)
  - 23 randomized controlled trials
  - 4779 adverse events reviewed

- Majority of ADRs were non-serious (96.6%)

- Rate of the non-serious events was higher with medical use versus controls (RR 1.86 95% CI 1.57-2.21)

Patient Safety

- Focus on patient specific factors
  - Drug interactions
  - Comorbid conditions
  - High risk populations
Patient Safety - Drug Interactions

- Many significant interactions including with high risk medications

- Majority of interactions are additive
  Central Nervous System Depression

- Systemic >>> Topical
- Dose dependent
- Frequency dependent
- Duration dependent

Image: https://illustoon.com/?dl=4281
Patient Safety - Comorbid conditions
Mental Health Conditions

- Acute psychotic symptoms during intoxication
- Decreased memory
  - Worse with increasing years of regular use
- Impaired cognition
  - With regular use impairment lasts up to 2 days after last use

Volkow N et al. NEJM (2014)
Regular marijuana use is associated with increased risk of anxiety and depression

- Weekly or more frequent cannabis use in teenagers predicted an approximately twofold increase in risk for later depression and anxiety (OR 1.9, CI 1.1 to 3.3) after adjustment for potential baseline confounders

Dependence may occur with increased risk with more frequent use

- Dependence - average 9% lifetime dependence
- Heavy users - 50%

Volkow N et al. NEJM (2014)
Patient Safety - Comorbid conditions
Mental Health Conditions

Meta-analysis of the association between the level of cannabis use and risk of psychosis. (Marconi 2016)

- 18 studies
- 66,816 individuals

Higher levels of cannabis use were associated with increased risk for psychosis in all the included studies.

Risk of schizophrenia and other psychosis-related outcomes among the heaviest cannabis users compared to the nonusers OR of 3.90 (95% CI 2.84 to 5.34)
38% of high school students report having used marijuana in their life
23% in the past 30 days
71% of high school seniors do not view regular marijuana smoking as being very harmful

## Safety - Adolescence

### Outcomes with use before age of 17

<table>
<thead>
<tr>
<th></th>
<th>Never</th>
<th>Less than monthly</th>
<th>Monthly or more</th>
<th>Weekly or more</th>
<th>Daily</th>
<th>p value</th>
<th>N</th>
</tr>
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<tbody>
<tr>
<td><strong>Adjusted Odds Ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td><strong>High School completion</strong></td>
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<td><strong>1.67</strong> (1·45–1·92)</td>
<td><strong>2.79</strong> (2·11–3·69)</td>
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<td><strong>Suicide</strong></td>
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<td><strong>1.62</strong> (1·19–2·19)</td>
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Safety - Adolescence

• Impact of cannabis use during adolescence and subsequent cognitive function

  – Dunedin Study
    • Prospective study following 1,037 individuals followed from birth to age 38
    • Interviews at ages 18, 21, 26, and 38 years
    • Neuropsychological testing completed at age 13 and again at age 38 years

Meier et al. Proc Natl Acad Sci USA (2012)
### Persistence of cannabis use

<table>
<thead>
<tr>
<th>Persistence of cannabis use</th>
<th>n</th>
<th>% male</th>
<th>Age 7–13 full-scale IQ (SD)</th>
<th>Age 38 full-scale IQ (SD)</th>
<th>Δ IQ effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never used, never diagnosed</td>
<td>242</td>
<td>38.84</td>
<td>99.84 (14.39)</td>
<td>100.64 (15.25)</td>
<td>0.05</td>
</tr>
<tr>
<td>Used, never diagnosed</td>
<td>479</td>
<td>49.48</td>
<td>102.32 (13.34)</td>
<td>101.25 (14.70)</td>
<td>−0.07</td>
</tr>
<tr>
<td>1 diagnosis</td>
<td>80</td>
<td>70.00</td>
<td>96.40 (14.31)</td>
<td>94.78 (14.54)</td>
<td>−0.11</td>
</tr>
<tr>
<td>2 diagnoses</td>
<td>35</td>
<td>62.86</td>
<td>102.14 (17.08)</td>
<td>99.67 (16.11)</td>
<td>−0.17</td>
</tr>
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<td>3+ diagnoses</td>
<td>38</td>
<td>81.58</td>
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Adapted from: Meier et al. Proc Natl Acad Sci USA (2012)
## Safety - Adolescence

### IQ before and after cannabis use

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Safety - Adolescence

• Or did it?

• Two longitudinal twin studies
  • Risk Factors for Antisocial Behavior (RFAB) study from Southern California (789 children)
  • Minnesota Twin Family Study (MTFS; 2,277 children)

“children’s genes and family environments set them on pathways that lead both to the use of marijuana and to IQ decline.”

Perceptions regarding the harm of marijuana may contribute to risky behaviors

A developing brain may be more vulnerable to marijuana effects

Higher doses, frequencies, and durations pose greater risk
Other safety considerations

- **Labeling**
  - May be absent or inaccurate

- **Driving**
  - Abstain from driving for at least 6 hours after smoking or 8 hours after oral consumption

- **Storage**
  - Keep in a locked box, away from children and pets
Medical Marijuana
Delving into the Weeds

Kathy Collins PharmD, BCPS
Senior Clinical Pharmacist
Craig Hospital
Englewood Colorado
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