MEDICAL CANNABIS: WHAT YOU NEED TO KNOW

Kelay Trentham, MS, RDN, CSO, FAND
Oncology Dietitian
MultiCare Regional Cancer Center
Tacoma, WA
What we’ll talk about today

• Brief history of medical cannabis use
• Does it work? If so, for what?
• Pros and cons of forms of use
• Reasons not to use it & adverse effects
What *Cannabis* is…

- A plant From the *Cannabaceae* family:
  - Hops
  - Hackberry

- *Cannabis* by any other name:

Is still *Cannabis*!
Cannabis History “Tour”

- Medicinal use = before *written* history
- Early written history:
  - >3500 yrs ago in Egypt
  - 1st-2nd century China
  - Intro to modern Western medicine: 1840’s

- US ban via taxation: 1937
- Schedule 1 classification (US): 1970
  “high risk for abuse, … no accepted medical use”

(Russo 2007; NIH-NCI; Backes 2014)
Our Endocannabinoid System

• Receptors: CB1 (nervous system) & CB2 (immune cells)
• Endocannabinoids
• Enzymes

Schicho, R. & Storr, M. (2013) Patients with IBD find symptom relief in the Cannabis field

(Battista 2012, Vemuri & Makriyannis 2015)
What’s so special about Cannabis?

- **Phytocannabinoids:**
  - “…any plant-derived natural product capable of either directly interacting with cannabinoid receptors or sharing chemical similarity with cannabinoids, or both.”
  - 110+ in cannabis

- **Properties:**
  - Pain-relieving
  - Anti-anxiety
  - Anti-seizure
  - Anti-nausea
  - Anti-inflammatory
  - Anti-oxidant
  - Anti-tumor
  - Neuroprotective

*And the list goes on!*

(Pacher et al. 2006; Gertsch et al. 2010; Russo 2011; Ahmed et al. 2015)
# The “Most Studied” Cannabinoids

<table>
<thead>
<tr>
<th>Cannabinoid:</th>
<th>Receptor Activity:</th>
<th>Major Effects:</th>
<th>Associated Rx drug:</th>
</tr>
</thead>
</table>
| **THC:**    | CB1: nervous system (strong)  
CB2: immune cells (weak) | Psychoactive  
Anti-nausea  
Pain relief  
Anti-spasmodic  
Anti-inflammatory | Marinol (dronabinol)  
Cesamet (nabilone)  
Sativex (nabiximols)  
Levonantradol |
| **CBD:**    | CB1: nervous system (weak)  
CB2: immune cells (weak) | Pain relief  
Neuroprotective  
Anti-seizure  
Anti-anxiety  
Anti-nausea | Sativex (nabiximols)  
Epidiolex (cannabidiol) |
Terpenoids in Cannabis

- Essential oil components
- Characteristic aroma
- Pharma effects

- Limonene
- Myrcene
- Pinene
- Linalool
- Caryophyllene(s)
- Nerolidol
- Phytol

(Russo 2011)
Some Terpenoid Activities

<table>
<thead>
<tr>
<th>Terpenoid</th>
<th>Noted Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limonene</td>
<td>anti-anxiety, anti-depressant</td>
</tr>
<tr>
<td>Myrcene</td>
<td>anti-inflammatory, sedative</td>
</tr>
<tr>
<td>Pinene</td>
<td>anti-inflammatory, bronchodilator</td>
</tr>
<tr>
<td>Linalool</td>
<td>anti-anxiety, anti-convulsant</td>
</tr>
<tr>
<td>Caryophyllenes</td>
<td>anti-inflammatory, anti-fungal</td>
</tr>
<tr>
<td>Nerodilol</td>
<td>sedative, anti/protozoal</td>
</tr>
</tbody>
</table>

(Russo 2011)
The “Entourage Effect”

Cannabinoids

Terpenoids
Noted “entourage” effects

• When THC:CBD @ ~ 1:1
  • ↓ anxiety, memory issues
  • May ↑ pain control

• Terpenoids
  • Caryophyllene: ↓ pain, inflammation
  • Linalool, limonene: ↓ anxiety
  • Myrcene: sedating, ↓ pain
  • Pinene: ↓ memory issues

(Russo & Guy 2006; Morgan et al. 2010; Russo 2011, Nielsen et al. 2017)
• Indica? Sativa? Strains?

• “New speak” = Chemovars
  • Type I: THC predominant
  • Type II: THC & CBD
  • Type III: CBD predominant

• Additional distinctions: terpenoid profile

(Lewis et al. 2018)
Terpenoid Analysis

PhytoPrint™

- terpinolene: 0.01%
- α-phellandrene: 0.22%
- β-octimene: 0.09%
- carene: 0.13%
- limonene: 0.02%
- γ-terpinene: 0.10%
- α-pinene: 0.10%
- α-terpinene: 0.02%
- β-pinene: 0.10%
- fenchol: 0.10%
- camphene: 0.10%
- α-terpineol: 0.27%
- α-humulene: 0.73%
- β-caryophyllene: 0.73%
- linalool: 0.24%
- caryophyllene oxide: 0.03%
- myrcene: 0.44%

Note: Variations may occur with individuals, climate, and location.
Reviewing the Evidence

- Available studies will include:
  - Synthetic THC (dronabinol, nabilone)
  - Extracted THC +/- CBD
  - Less often: “whole cannabis”
# Nausea/Vomiting

<table>
<thead>
<tr>
<th>Cannabinoid</th>
<th>Control</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dronabinol</td>
<td>Anti-nausea meds &amp; Placebo</td>
<td>➢ More effective</td>
<td>Tramer et al. 2001</td>
</tr>
<tr>
<td>Levonantradol</td>
<td></td>
<td>➢ Preferred</td>
<td></td>
</tr>
<tr>
<td>Nabilone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dronabinol</td>
<td>Anti-nausea meds</td>
<td>Dronabinol: decreased nausea, was preferred</td>
<td>Rocha et al. 2008</td>
</tr>
<tr>
<td>Nabilone</td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Levonantradol</td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Nabilone</td>
<td>Anti-nausea meds</td>
<td>80%: ↓ nausea</td>
<td>Ware et al. 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>78%: people: preferred</td>
<td></td>
</tr>
<tr>
<td>Dronabinol</td>
<td>Ondansetron &amp; Placebo</td>
<td>Dronabinol: 71%</td>
<td>Parker et al. 2011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ondansetron: 64%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo: 15%</td>
<td></td>
</tr>
</tbody>
</table>
Appetite

• **Dronabinol vs. Megestrol acetate** (Jatoi et al. 2002)
  • Improved appetite:
    Megace 75% vs. Dronabinol 49%

• Advanced cancer patients
Appetite

• **THC+CBD vs. THC vs. Placebo** (Strasser et al. 2006)
  - No Difference

*Very low dose studied (2.5 mg THC)*
Taste and Smell

- **THC vs. placebo** (Brisbois et al. 2011)
  - Chemosensory response:
    - Significant improvement: 36% THC vs. 15% placebo

- “Food tastes better”:
  - 55% THC, 10% placebo (p = 0.04)

- Pre-meal Appetite score:
  - THC > placebo

- Pilot study: n= 11 (THC), 10 placebo
## Pain/neuropathy

<table>
<thead>
<tr>
<th>Cannabinoid</th>
<th>Pain</th>
<th>Results</th>
<th>Notes</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed</td>
<td>CA, other</td>
<td>Canna &gt; Effective than placebo</td>
<td>Significant Adverse effects</td>
<td>1</td>
</tr>
<tr>
<td>Mixed</td>
<td>Neuro, other</td>
<td>15/18 trials: sig, modest effect</td>
<td>No severe AEs, no dropouts; placebo or active control</td>
<td>2</td>
</tr>
<tr>
<td>Mixed</td>
<td>CA, other</td>
<td>27/38 RCTs: sig relief</td>
<td>Placebo or active control</td>
<td>3</td>
</tr>
<tr>
<td>Cannabis</td>
<td>Neuro</td>
<td>6 RCTs: All = sig relief</td>
<td>3 studies: clinically meaningful relief</td>
<td>4</td>
</tr>
</tbody>
</table>

Cannabis (smoked)

Prospective, observational study: n = 131

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Grade</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>None</td>
<td>+37%</td>
</tr>
<tr>
<td></td>
<td>Mod</td>
<td>-38%</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>+1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>None</td>
<td>+23%</td>
</tr>
<tr>
<td></td>
<td>Mod</td>
<td>-23%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>None</td>
<td>+36%</td>
</tr>
<tr>
<td></td>
<td>Mod</td>
<td>-38%</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>+2%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>None</td>
<td>+35%</td>
</tr>
<tr>
<td></td>
<td>Mod</td>
<td>-32%</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>-5%</td>
</tr>
</tbody>
</table>

- P>0.001 for trend (after 6-8 wks)

(Bar-Sela et al. 2013)
Cannabis (smoked)

Prospective, observational study: $n = 131$

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<thead>
<tr>
<th>Symptom</th>
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<th>Change</th>
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<tbody>
<tr>
<td>Pain</td>
<td>None</td>
<td>+23%</td>
</tr>
<tr>
<td></td>
<td>Mod</td>
<td>+3%</td>
</tr>
<tr>
<td></td>
<td>Sev</td>
<td>-26%</td>
</tr>
</tbody>
</table>

- $P > 0.001$ for trend (after 6-8 wks)

(Bar-Sela et al. 2013)
Cannabis a “Cancer Cure”? 

- Limited Preclinical Evidence:
  - *In vitro, In vivo*
  - 1 small human study: GBM

- Potential? *maybe*

- Certainty? *No*

- Needs more research!!
Cannabis Administration Routes
Inhalation (Smoking & Vaping)

- Onset: 5 – 10 minutes
- Duration: 2-4 hours
- Bioavailability: 10-35%

- Vaping: less toxic byproduct (than smoking)

(Grotenhermen 2003; Huestis 2007; MacCallum & Russo 2018)
Caution…

• What is a “dab”?
  • Volatile “concentrate”
  • Extracted via solvents, liquid gas, CO2

• Safety concerns:
  • Residual solvents: >80% samples
  • Pesticides: 33% samples
    • Paclobutrazol: not listed with EPA for use on food crops
  • Increased in adverse effects*

• Best avoided as medicine

(Raber et al. 2015, MacCallum & Russo 2018)
Caution…

- Risk to the severely immunocompromised patient…
  - Bacteria, molds on green bud
  - Few case reports: aspergillus via inhaled cannabis
    *can be fatal

- Testing?
- Sterilization?

(Ruchlemer 2015)
Oral Ingestion: Edibles, Capsules

- Onset: 1 - 3 hours
- Duration: 6 - 8 hours
- Bioavailability: variable, 4-20%

*First-pass metabolism: 11-OH-THC
  - Potent psychoactive
  - Reduces bioavailability THC

- More difficult to determine dose

(Grotenhermen 2003; Huestis 2007; MacCallum & Russo 2018)
Caution…

- Labeling inaccuracies…

- Content analysis:
  - 17% accurately labeled
  - 23% **under-labeled** (had >THC content!)
  - 60% over-labeled

- Contributes to:
  - Overdosing
  - Difficulty dosing

(Vandrey et al. 2015)
Oromucosal: Sprays, Tinctures

- Onset: ~15 – 45 minutes (average)
- Duration: 6 - 8 hours
- Bioavailability:
  - Highly variable
  - Inhaled > OM >/= oral
  - Increases with food
  - *Less first-pass metabolism

(Guy & Robson 2003, MacCallum & Russo 2018)
Rectal

• **Suppositories**
  - Favored for absorption, no first-pass metabolism
  - Peak concentration: 1-8 hours
  - Bioavailability: ~2 X that of oral
  - Availability?
  - *Best to avoid during chemo

(Huestis 2007; Grotenhermen 2003)
Skin

- **Creams, Ointments**
  - Few Studies
  - Local effect only

- **Transdermal Patch**
  
  *Preclinical research*
  - Animal model → plasma for 48 hrs

- **More research needed**

(www.hc-sc.gc.ca/dhp-mps/marihuana)
Contraindications

• Allergy
• Pregnancy & breastfeeding
• Heart, Respiratory
• Hepatic, Renal
• Mental health hx
  • schizophrenia, bipolar d/o, depression

(Kahan 2014, Sachs 2015, Health Canada)
Use with Caution

- History of: Heart, Angina
- High Blood Pressure
- Asthma, COPD (inhaled)

(Kahan 2014, Sachs 2015, Health Canada)
Adverse Effects

**Most Common:**
- Drowsiness/fatigue
- Dizziness
- Anxiety
- Nausea
- Cognitive effects (confusion, disorientation, hallucination, impaired memory)
- Cough/phlegm/bronchitis (with smoking)

**Common:**
- Euphoria (adverse?)
- Blurred vision
- Headache

**Rare:**
- Hypotension
- Psychosis/paranoia
- Rapid heart rate
- Hyperemesis
- Diarrhea
- Loss of coordination

(MacCallum & Russo 2018)
Cannabis-Drug Interactions

Drug effects increased by cannabis:

- **THC:**
  - Alcohol
  - Benzodiazepines (Ativan, Valium, Xanax, Restoril, etc.)
  - Opiates: codeine, fentanyl, morphine

- **CBD (high dose):**
  - Clobazapam – will need dose reduction

(MacCallum & Russo 2018)
About Dosing…

• “Start low, go slow, stay low”
  - Helps limit fatigue, high heart rate, dizziness
  - Aids tolerance to psychoactive effects

• Consider Type II (THC + CBD) or Type III (CBD)
  - CBD tempers unwanted THC effects

• Chronic issues: oral product* = “mainstay”
  *If tolerated

• Acute/breakthrough symptoms: vaporization useful

(MacCallum & Russo 2018, Ware et al. 2015)
About dosing…

- Starting and increasing (*per* MacCallum & Russo 2018):
  - At bed time:
    - Day 1-2: 1.25 – 2.5 mg THC (lower if >65 yrs old)
    - If tolerating: may ↑ by 1.25 – 2.5 mg every 2 days til desired effect
  - If day time use:
    - Day 1-2: 2.5 mg THC
    - Day 3-4: 2.5 mg THC 3x/day
    - May increase (slowly!) as tolerated towards 5 mg 3x/day
    - Include CBD @ equal amount to ↓ THC side effects

- Amounts > 20-30 mg THC/day = ↑ side effects, don’t improve effects
About dosing… CBD

• CBD = fewer side effects (not psychoactive)

• No well-established dose guidelines

• Possible benefit:
  • 5-20 mg /day
  • Divide into 2x/day or 3x/day
  • Example: if taking 10 mg total, take 3 mg 3x/day or 5 mg 2x/day

• Possible interaction:
  • May increase sedation of benzodiazepines at high dose (>400 mg)

(MacCallum & Russo 2018)
Don’t Drive!!!

I couldn't help noticing, you were driving exceptionally well.

Hide the dope.

Frank, he's onto us.
In Summary

- Cannabis
  - has a long history of medical use
  - may be effective for some conditions

- Pros/cons include:
  - Mode of use: difference in effects, contaminants, variability
  - Individual medical history

- Best dose: lowest for relief, good tolerance
Resources

• International Association for Cannabis as Medicine
  • cannabis-med.org – database of studies

• Americans for Safe Access
  • Safeaccessnow.org

• “Cannabis Pharmacy” by Michael Backes

• “Chronic Relief” by Nishi Whitely

• MacCallum & Russo, “Practical considerations in medical cannabis administration and dosing”, European Journal of Internal Medicine, 2018, 49:12-19.