Objectives

• Review therapy goals
• Discuss cannabis history and current use
• Making a decision to integrate cannabis with standard therapies?
Goals of Cancer Therapy

• Cancer Prevention
  – Can we detect pre-cancerous or very early cancer states and reverse them?

• Cancer Cure
  – Significant surgical component to GIST management

• Cancer Control

• Controlling the Effects of Cancer
Why Add Cannabis?

- Control Chemotherapy side effects
- Improve feeling of well being (Quality of Life)
- Prior/ongoing recreational use
- Exasperated with traditional treatments
- “Natural” Alternative
- Increased independence and personal control
- Less expensive?
- Improve response to traditional therapy
- Cure Cancer
• Listed in U.S Pharmacopeia 1850-1941
  – marijuana & hashish extracts were the 1\textsuperscript{st}, 2\textsuperscript{nd}, or 3\textsuperscript{rd} 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
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 alter neurotransmitter release
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 be anxiolytic
- Has low affinity for endogenous cannabinoid receptors
- Modulates the action of/exposure to THC
- Over 140 different cannabinoids and 300-400 different compounds found in cannabis
The Human Endocannabinoid System

THC and CBN are known to “fit” like lock and key into network of existing receptors. The Endocannabinoid System exists to receive cannabinoids produced inside the body called “Anandamide” and “2-Arachidonyl-glycerol”. Stimulating the ECS with plant-based cannabinoids restores balance and helps maintain symptoms.

CB1 receptors are concentrated in the brain and central nervous system but also sparsely populates other parts of the human body. Receptors are found on cell surfaces.

THC
Tetrahydrocannabinol

CBD
Cannabidiol
CBD does not directly “fit” CB1 or CB2 receptors but has powerful indirect effects still being studied.

CBN
Cannabinol

CB2 receptors are mostly in the peripheral organs especially cells associated with the immune system.
Dosing and Absorption

- Generally 2-3 mg THC 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 will oral can take an hour or longer

  - Oregon has 5 mg increments in a “dose”
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”
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®)

- Mimics THC; synthetic cannabinoid receptor agonist 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
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.

Hill KP et al NEJM 2015;313(24):2474-2483
Natural Product Issues

• Purity – (herbicides, pesticides)
  – Oregon testing mandated to start 10/1/16 (modified)

• Potency (THC content, other cannabinoid content)
  – All studies thus far show >50% of products are mislabeled

• Appropriate medical dose per condition is unknown

• Topical preparations are absorbed but it is unclear to what extent
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%)

Bonn-Miller M et al. JAMA 2017;318(17)1708-1709
Drug Interactions

• Dynamic interactions
  • THC inhibits effects of CBD and CBD modulates some of THC psychoactive effects
  • Additive effects to sedating agents
    • Sleeping pills, antihistamines, antianxiety agents and others
  • Opposing effects to stimulants
  • Antidepressants and psychiatric drugs – variable
  • Lithium - Variable
Pharmacokinetic potential to Increase Effects/Side Effects of GIST TKI Drugs

• Dasatinib
• Imatinib
• Nilotinib
• Pazopanib
• Sorafenib
• Sunitinib
• Regorafenib
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 legal medical use
• Multiple cases of organ failure (kidney and liver injury mainly), 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**: temporal and spatial perception alterations and disorientation
- **Somatic**: drowsiness, dizziness, and motor incoordination
- **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

What Uses are you interested in?
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

Wilkinson ST JAMA 2014;311:2377-2378
# Cannabis Side Effects

<table>
<thead>
<tr>
<th>Most Common</th>
<th>Common</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Blurred Vision</td>
<td>Balance problems</td>
</tr>
<tr>
<td>Cognitive - confusion</td>
<td>Headache</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Cough</td>
<td>Intoxication</td>
<td>Heart Rhythm changes</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td>Hyperemesis</td>
</tr>
<tr>
<td>Drowsiness</td>
<td></td>
<td>Low Blood pressure</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>Psychosis</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## 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 reported

---

Drug Information Handbook 14th ed. LexiComp
Take Home Points – Risk

- Unclear risk for lung cancer; vaping *may* confer lower risks than smoking
- Multiple published case studies regarding Cardiac risk, risk likely increases with age, especially > 60 years old
- Should not use if you have a psychiatric disorders
  - No clear benefit in any psychiatric disorder, harm likely in schizophrenia and bipolar disease
  - Dose dependent relationship between cannabis and psychosis and schizophrenia, particularly with adolescent/young adult exposure
  - Do not use if younger than 25 years old
- Less habit forming than nicotine and ‘hard drugs’ but dependence risk is real (~9%), particularly in adolescents
- Prenatal exposure is worrisome, do not use if pregnancy possible
- Need studies in higher risk subgroups (older adults with chronic illnesses)
- Factual medical information: Unclear and hard to find
- Current products: Unregulated for planned medical uses
Take Home Points - Benefits

- True medical benefits unclear
- Areas of Promise
  - Pain relief
  - Muscle disorders
  - Seizure disorders
  - Appetite and nausea
  - “Mood”
Questions?