Medical Cannabis
Help and Hype

Nicholas Butowski MD
Professor | Neurological Surgery
Director, Translational Research | Neuro-Oncology
Director, UCNS Fellowship | Neuro-Oncology
Chair, CNS Tumors Site Committee | UCSF Helen Diller Family Comprehensive Cancer Center

American Brain Tumor Association® 2019 NATIONAL CONFERENCE
DISCLOSURES & SUPPORT

• I have no stocks, patent rights or employment with any related company

• I have consulting/advisory board agreements with:
  • VBL, Bayer, Amgen, Del Mar

• I have pre-clinical laboratory and/or clinical trial support from the following companies:
  • Novartis, VBL, Bayer, BMS, Medicenna, Ipsen, Deciphera, Epicentrix, Orbus, Amgen, Istari, Oncoceutics,
Disclaimer

- This presentation involves the discussion of a Schedule I controlled substance and is meant to serve as an informational review.

- Cannabis is an unregulated product with rapidly changing genetics
  - we don't know what we are buying and we're only starting to understand the health consequences

- Federal Level – illegal

- State level
  - Regulation varies from state to state as to how much medical cannabis patients may possess and how it can be obtained (e.g., personally grown vs. obtained from a dispensary).

- Not prescribed --> certified condition, which varies by state

### Drug Scheduling Guide
#### United States

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Schedule I</strong></td>
<td>Most potential for abuse and dependence</td>
</tr>
<tr>
<td></td>
<td>No medicinal qualities</td>
</tr>
<tr>
<td></td>
<td>Heroin, LSD, Marijuana Ecstasy, Peyote</td>
</tr>
<tr>
<td><strong>Schedule II</strong></td>
<td>High potential for abuse and dependence</td>
</tr>
<tr>
<td></td>
<td>Some medicinal qualities</td>
</tr>
<tr>
<td></td>
<td>Vicodin, Cocaine, Meth, OxyContin, Adderall</td>
</tr>
<tr>
<td><strong>Schedule III</strong></td>
<td>Moderate potential for abuse/dependence</td>
</tr>
<tr>
<td></td>
<td>Acceptable medicinal qualities</td>
</tr>
<tr>
<td></td>
<td>Doctor's prescription required</td>
</tr>
<tr>
<td></td>
<td>Tylenol with Codeine, Ketamine, Steroids, Testosterone</td>
</tr>
<tr>
<td><strong>Schedule IV</strong></td>
<td>Low potential for abuse and dependence</td>
</tr>
<tr>
<td></td>
<td>Acceptable medicinal qualities</td>
</tr>
<tr>
<td></td>
<td>Prescription required - fewer refill regulations</td>
</tr>
<tr>
<td></td>
<td>Xanax, Darvon, Valium, Ativan, Ambien, Tramadol</td>
</tr>
<tr>
<td><strong>Schedule V</strong></td>
<td>Lowest potential for abuse/dependence</td>
</tr>
<tr>
<td></td>
<td>Acceptable medicinal qualities</td>
</tr>
<tr>
<td></td>
<td>Prescription required - fewest refill regulations</td>
</tr>
<tr>
<td></td>
<td>Robitussin AC, Lomotil, Motofen, Lyrica</td>
</tr>
</tbody>
</table>

Source: United States Drug Enforcement Agency
National Academy of Science Recommendations

- Address Research Gaps
  - Funding for health, public safety, etc.
  - HHS should convene a workgroup to improve research quality (measures, tools, etc.)
- Improve surveillance capacity (public health outcomes, etc.)
- Address research barriers (legal prohibitions, infrastructure, etc.) with an expert committee including industry
Outline

<table>
<thead>
<tr>
<th>History &amp; Properties</th>
<th>Use in Oncology Patients</th>
<th>Drug Interactions</th>
<th>Real-World Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Forms</td>
<td>• Nausea/vomiting</td>
<td>• Types of</td>
<td>• Regulations in</td>
</tr>
<tr>
<td>• Pharmacology</td>
<td>• Pain/neuropathy</td>
<td>interactions</td>
<td>California</td>
</tr>
<tr>
<td>• Pharmacokinetics</td>
<td>• Appetite/anorexia</td>
<td>• Management</td>
<td>• Step-wise approach</td>
</tr>
<tr>
<td>• Adverse effects</td>
<td>• Other uses</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
History
History

- 1753 Linnaeus names cannabis sativa
  - Tall and thin leaves
  - Energetic high
- Indica from India
  - Darker and thicker leaves; cold resistant
  - Lethargic stoned high
- Ruderalis
  - From Russia – smaller, shorter, sprout faster
- Reality – can’t really visually inspect due to cross breeding
- Linnaeus
  - noticed some plants only produced seeds (female) and other pollen (male)
  - Female plants get you high - produce high THC, CBD reduces anxiety
  - More than 100 canninbinoids that affects us; 400 chemical compounds (Terpenes =aroma; Flavinoids =flavor)
History: introduction

- Forms ---> THC Tetrahydrocannabinol CBD Cannabidiol
  - the more THC in the plant the less CBD

- Endocannabinoid systems are present in every animal but insects
  - Evolutionary role in appetite regulation, help us to forget, reduce stress, exercise euphoria

- Routes of admin: smoking, vaporization, eating, tinctures, salves
  - Each affects onset of action, intensity, and duration
A Deep-Rooted History

~8000 BC: cultivation of hemp as grain and fiber

~800 BC: hemp used in wound dressings

~1840's: medical cannabis research published

~1910: pharmaceutical companies with medical marijuana in catalogs

~2700 BC: earliest known use of cannabis as medicine

~2000 BC: cannabis as a sacred plant with “release from anxiety”
**Bad Reputation**

1937: Marihuana Tax Act
- “Violence-causing drug”
- Opposed by American Medical Association

1942: Cannabis removed from U.S. Pharmacopoeia

1970: Controlled Substances Act
- Marijuana classified as Schedule I

1985: Dronabinol approved for chemotherapy-induced nausea/vomiting

1992: Dronabinol approved for AIDS-associated cachexia

1996: Compassionate Use Act
- Medical cannabis for cancer, HIV/AIDS, painful diseases

2006: Nabilone approved for refractory chemotherapy-induced nausea/vomiting

2018: Cannabidiol approved for Lennox-Gastaut syndrome and Dravet syndrome

**Marijuana-Derived Epilepsy Drug in Clinical Trial for Children with Uncontrolled Seizures**

A new international, multi-center study led by researchers from UCSF Benioff Children’s Hospital is the first to evaluate whether purified cannabinoid is effective in treating severe forms of childhood epilepsy that do not respond to standard antiepileptic drugs.
Properties
Forms of Cannabis: Plant Products

**Cannabis sativa**

- **Inhaled**
  - Vaporized
  - Cigarettes
  - Smoked via water pipes

- **Oral**
  - Edibles
  - Tinctures
  - Lozenges
  - Tea

- **Topical**
  - Balm
  - Oil
  - Transdermal patch

- **Rectal**
  - Suppository

- **441 non-cannabinoids**

- **104 cannabinoids**
### Forms of Cannabis: Pharmaceuticals

<table>
<thead>
<tr>
<th>Cannabis sativa</th>
<th>441 non-cannabinoids</th>
<th>104 cannabinoids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nabiximols</strong></td>
<td><strong>Dronabinol</strong></td>
<td><strong>Nabilone</strong></td>
</tr>
<tr>
<td><em>(Sativex®)</em></td>
<td><em>(Marinol®)</em></td>
<td><em>(Cesamet®)</em></td>
</tr>
<tr>
<td>Extract with THC:CBD 1:1</td>
<td>THC trans isomer</td>
<td>THC analog</td>
</tr>
<tr>
<td>Mucosal spray</td>
<td>Capsule, oral solution</td>
<td>Capsule</td>
</tr>
<tr>
<td>Approved in Canada, UK</td>
<td>Schedule III</td>
<td>Schedule II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Schedule V</td>
</tr>
<tr>
<td><strong>Cannabidiol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(Epidiolex®)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highly purified, plant-derived CBD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capsule, oral solution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral solution</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Forms of Cannabis:**
- **Nabiximols (Sativex®):** Extract with THC:CBD 1:1, Mucosal spray, Approved in Canada, UK, Schedule III.
- **Dronabinol (Marinol®):** THC trans isomer, Capsule, oral solution, Schedule III.
- **Nabilone (Cesamet®):** THC analog, Capsule, Schedule II.
- **Cannabidiol (Epidiolex®):** Highly purified, plant-derived CBD, Oral solution, Schedule V.
Cannabinoid Pharmacology

The Endocannabinoid System

Fatty acid precursors

Ca²⁺

Phosphodiesterase enzymes

Endocannabinoids (anandamide, 2-arachidonoyl glycerol)

Agonism

Degradation

Cannabinoid receptors

Secondary messengers

Transporter

Arachidonic acid, ethanolamine, etc.

Hydrolytic enzymes
Cannabinoid Receptors

<table>
<thead>
<tr>
<th>CB1</th>
<th>CB2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS neurons</td>
<td>Immune cells</td>
</tr>
<tr>
<td>Peripheral neurons and tissues</td>
<td>Peripheral tissues</td>
</tr>
<tr>
<td>Modulates acetylcholine, norepinephrine, dopamine, serotonin, GABA, glutamate, aspartate</td>
<td>Suppresses immune cell migration and cytokine production</td>
</tr>
<tr>
<td></td>
<td>Modulates immune cell proliferation and apoptosis</td>
</tr>
<tr>
<td>Effects on pleasure, pain, appetite, concentration, sensory and time perception, movement coordination</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td></td>
<td>Immunomodulatory</td>
</tr>
</tbody>
</table>
Cannabinoid Pharmacology

CBD is a negative regulator of THC
- can balance out AE’s (important when dispensaries titrating CBD vs THC based on patients’ AE’s

Many different compounds and interactions:
- 5-HT1A is target for many drugs: agonists (buspirone) or modulators (SSRI) relieve anxiety and depression. 5-HT2A involved in emotions and memory. CBD of interest in psych d/t anxiolytic and antipsychotic effects
- 5-HT3 antagonists for antiemetics, 5-HT3 also involved in pain transmission
- TRP involved in pain and sensation,
- PPARs are nuclear receptors in which activation has anti-inflammatory and analgesic effects,
- GPR (atypical cannabinoid R’s) have effects on BP and inflammation
- Glycine R’s inhibit nerve activation, regulate pain and inflammation:
- GABA-A: mediates effects of BZD, barbiturates. CBD interactions contribute to anti-SZR effects.
Molecular Properties

First-pass metabolism
- Major metabolite: 11-OH-THC
- Biphasic elimination

Elimination
- 65-80% in feces
- 20-35% in urine

Typical dosing
- Herbal cannabis: 1-3 g/day
- THC
  - >20-30 mg/day had more adverse effects without benefit
- CBD (may require higher dosing)
  - Start 5-20mg/day
  - Max 800 mg (psychosis), 2500 mg or 25-50 mg/kg (seizure)
- Inhalation
  - 15-30 min intervals
  - Nabiximols: 6-8 sprays/day (>12 had more adverse effects without benefit)
  - Consider titrating every few days

Varieties
- Type I cannabis: THC-predominant
- Type II cannabis: mixed THC:CBD
- Type III cannabis: CBD-predominant
Pharmacokinetics

Inhaled
- Onset within seconds
- Peak 15-30 min
- Duration 2-3 hr

Ingested
- Onset 30-90 min
- Peak 2-4 hr
- Duration 4-12 hr

Oromucosal
- Onset 15-45 min
- Duration 6-8 hr

Topical
- Variable pharmacokinetics
- Fewer systemic effects

Suppositories
- Variable absorption

“PRN” usage for symptom exacerbation
- Variable bioavailability
- Prefer vaporizer (harmful byproducts, pulmonary symptoms with smoking)

“Basal” usage for chronic symptoms
- Oils, capsules improve dosing accuracy
- Tinctures, lozenges have faster onset
Adverse Effects

Psychotropic effects
- Affective
- Sensory
- Somatic
- Cognitive

Withdrawal (usually mild)
- Irritability, tremor
- Insomnia
- Heart rate changes

Risk of dependence
- Risk factors: anxiety, cigarette smoking

Acute toxicity
- Hallucinations
- Paranoia
- Ataxia
- Increased heart rate
- Blood pressure changes

Dizziness, drowsiness
Cognitive impairment
Impaired motor control
Reduced reaction time
Headache
Anxiety

Dry eyes
Blurred vision

Dry mouth
Tachycardia
Orthostatic hypotension
- Caution falls risk

Cough, sputum production
Wheezing, dyspnea
- Not associated with decreased FEV1

Risk of pneumonia
- Aspergillus exposure
- Impaired immune defenses

Pregnancy/lactation
- Crosses placenta
- Small amount secreted in breast milk

Risk of dependence
- Risk factors: anxiety, cigarette smoking

# Evidence of Harm?

<table>
<thead>
<tr>
<th>Overall Health</th>
<th>Cancer Risk</th>
<th>Psychiatric</th>
<th>Brain Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of Harm</td>
<td>Impaired driving Drug interactions Reduced memory Pulmonary function Stroke Birth complications</td>
<td>Testicular</td>
<td>Dependence Psychosis Schizophrenia relapse</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>Atrial fibrillation Bone loss All-cause mortality</td>
<td>Bladder Prostate Cervical</td>
<td>Depression Anxiety Suicide</td>
</tr>
<tr>
<td>No Evidence of Harm</td>
<td>Lung Head &amp; neck</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Synthesis of 68 reviews**
  - Most low- or moderate-quality evidence
  - Based on association (unknown causation)
Considerations in Elderly Patients

Comorbidities

Drug interactions

Pharmacokinetic changes
- Reduced hepatic, renal function → prolonged THC, CBD half-life
- Increased relative body fat → increased distribution

Risk of adverse effects

Gait and stability
- Falls risk

Cognition
- Short-term memory
- Emotional processing
- Psychotic episodes

Cardiac comorbidities
- Association with risk of MI, stroke/TIA, arrhythmias

Patient-specific assessment and pragmatic approach
- Trial of other non-pharmacologic and pharmacologic treatment
- Start at low doses, give at night
- Consider standardized pharmaceutical preparations, or plant-based preparations with lower THC and more CBD

Counseling Points

- Expected pharmacokinetics
  - Inhaled vs ingested

- Adverse effects
  - Avoid driving, especially during initiation and dose increases
  - Monitor tolerability, especially in elderly patients
  - Theoretical infection risks in immunocompromised
  - Avoid during pregnancy and breastfeeding
Use in Oncology
Use of Medical Cannabis in Cancer Patients

- 2970 cancer patients treated with medical cannabis 2015-2017
  - Average age 60 yo

- Prior cannabis use:
  - Female
  - Male
  - No prior cannabis use

- Stages I-III
  - Stages IV

- Breast
  - Lung
  - Pancreatic
  - Colorectal
  - Other

- Symptom Relief:
  - Sleep problems
  - Pain
  - Weakness
  - Nausea
  - Lack of appetite

Chemotherapy-Induced Nausea/Vomiting

- Cannabinoids prevent CINV by blocking pro-emetic effects of endogenous neurotransmitters (negative allosteric inhibitor of 5-HT3 receptors)

  Different mechanism
  Potential use for refractory CINV

- Cannabinoid-induced hyperemesis syndrome
  - Associated with long-term cannabis use

- Cannabinoid pharmaceutical preparations primarily studied in 1970-1980’s
  - Standard of care at the time: phenothiazines, metoclopramide
  - Today: 5-HT3 antagonists, corticosteroids, NK1 antagonists, olanzapine

- Anxiolytic, sedative effects
  Potential use for anticipatory CINV
Cannabinoids for CINV

Guideline Recommendations

NCCN 2018

- Recommend adding an agent of a different drug class for breakthrough CINV.

ASCO 2017

- Recommend adding an agent of a different drug class for breakthrough CINV (recommend dronabinol or nabilone if choose cannabinoid).
- Insufficient evidence for medical marijuana to prevent nausea or vomiting with chemotherapy or radiation therapy.

- Atypical antipsychotic
  - Olanzapine (category 1)
  - Benzodiazepine
    - Lorazepam
- Cannabinoid
  - Dronabinol
  - Nabilone
- Phenothiazine
  - Prochlorperazine
  - Promethazine
- 5-HT3 antagonist
  - Dolasetron
  - Granisetron
  - Ondansetron
- Steroids
  - Dexamethasone
- Other
  - Haloperidol
  - Metoclopramide
  - Scopolamine
Cannabinoids for CINV

**Place in Therapy**

- Consider dronabinol or nabilone as an alternative agent for refractory CINV
  - Risk of adverse effects (dizziness, dysphoria, euphoria, sedation) consistent across studies, and different from other antiemetics
  - Limited evidence for medical marijuana

**Dronabinol**
- Capsules: 5-10 mg PO 3-4 times daily
  - Consider 2.5 mg if adverse effects
  - Max 15 mg/m² per day
  - 2.1 mg oral solution = 2.5 mg capsule

**Nabilone**
- Capsules: 1-2 mg PO BID
  - Consider 1 mg for adverse effects
  - Max 6 mg per day (divided in 3 doses)
Cancer-Related Pain

Background

- Endocannabinoid system involved in pain transmission, modulation, perception
  - NSAIDs, opioids, acetaminophen, antidepressants increase activity of endocannabinoid system
  - CB1 is highly prevalent in central and peripheral neurons
  - CB2 involved in inflammation
  - CB1, CB2 receptors implicated in modulation of chemotherapy-induced neuropathy
- Potential synergy with opioids
  - Cannabinoids may increase synthesis and release of endogenous opioids
Cancer-Related Pain

- Endocannabinoid system involved in pain transmission, modulation, and perception

- Most studies with nabiximols
  - May need combination of THC and CBD for analgesic effect

- Large RCT’s with mixed results
  - Statistically significant improvements in pain found in subgroup of <65 yo from US, but not rest of the world
    - ≤150 morphine equivalents per day in US subgroup
  - Cochrane review: limited evidence of efficacy in chronic neuropathic pain
Cannabinoids for Cancer-Related Pain

Guideline Recommendations

NCCN 2018

- Dronabinol as alternative agent to treat opioid-induced nausea

ASCO 2016

- Insufficient evidence to recommend medical cannabis for first-line chronic pain in cancer survivors
- Evidence suggests considering as adjuvant analgesic or in refractory pain
- Insufficient evidence to recommend specific cannabis preparation
Cannabinoids for Cancer-Related Pain

Place in Therapy

- May consider as an adjunct or in refractory cases
  - May have more benefit in combination with lower doses of opioids
  - Relatively low abuse potential

- Potential efficacy in neuropathic pain

- Caution adverse effects
  - Consider overlapping adverse effects

- Limited evidence for optimal dosing of oral cannabinoid pharmaceuticals
  - Dronabinol
    - 10 mg per day shown to have analgesic effect
  - Nabilone
    - Start at 0.5 mg HS, may increase to 1 mg BID

- Nabiximols
  - Target dose 10 actuations per day
    - Equivalent to THC 27 mg, CBD 25 mg
    - Start at 4-6 actuations per day
    - Titrate over 2 weeks
Cancer-Associated Cachexia and Cannabinoids

Background

Cancer-associated cachexia

- Metabolic imbalance
  - Tumor products
  - Endocrine impairment
  - Liver metastasis

- Inflammatory response
  - Proinflammatory cytokines

- Treatment effects
  - Nausea, vomiting, diarrhea
  - Impaired taste, smell
  - Pain, depression

Cannabinoids

- "Wanting"
  - Cravings
  - Improved pre-meal appetite

- "Liking"
  - Enhanced chemosensory perception
  - Intensified reward properties of food

Limitation
- THC reduces gut motility
Dronabinol for Cancer-Associated Cachexia

Randomized, double-blind, parallel group study (n=496)
- Advanced malignancies

- Megestrol 800 mg daily
- Dronabinol 2.5 mg PO BID
- Combination

Median 10 wk on study

Appetite improvement
- 75% megestrol
- 49% dronabinol

≥10% baseline weight gain
- 11% megestrol
- 3% dronabinol

No additional benefit with combination

Potential under-dosing: previous phase II showed dronabinol 2.5 mg PO TID improved appetite, but adverse effects in 20% of patients

Randomized, double-blind randomized controlled trial in lung cancer (n=65)
- Nabilone (0.5 mg PO daily for 2 weeks, then 1 mg daily for 6 weeks) vs placebo

Benefits of nabilone
- Increased caloric intake by 342 kcal vs placebo
- Improved pain, insomnia

No significant difference vs placebo
- Appetite, weight
- Fatigue
- Nausea/vomiting

American Brain Tumor Association
2019 NATIONAL CONFERENCE
Cannabinoids for Cancer-Associated Cachexia

Pharmacokinetic Considerations

Absorption
- Altered intestinal permeability and fat absorption

Distribution
- Reduced body fat, altered protein binding

Metabolism
- Altered expression and function of liver metabolizing enzymes

Excretion
- Hepatobiliary transport may be altered

- Pharmacokinetic study in HIV-associated cachexia showed variability in AUC
Cannabinoids and Cancer-Associated Cachexia

**Guideline Recommendations**

- **NCCN 2018**
  - Anorexia/cachexia with life expectancy of months to weeks: may consider cannabinoid

- **ASCO**
  - Nutrition and cachexia guidelines in development

**Life expectancy years to months**
- Low appetite: megestrol
- Depression: mirtazapine
- Gastroparesis: metoclopramide

**Life expectancy months to weeks**
- Megestrol, dexamethasone, olanzapine
- Depression: mirtazapine
- **Consider cannabinoid**
Cannabinoids and Cancer-Associated Cachexia

Place in Therapy

- May consider as a treatment option if refractory to or intolerant of other treatments
  - Appears less effective than megestrol, but possibly more favorable adverse effect profile
  - Combination with megestrol does not appear to add benefit
  - Theoretical benefit for nausea, mood, pain
  - Caution pharmacokinetic changes in cachexia

- Dronabinol
  - 2.5 mg PO BID is best studied
    - May consider higher dose (2.5 mg PO TID), but increased risk of adverse effects
    - Max in HIV/AIDS-related cachexia is 20 mg per day

- Nabilone
  - Consider 0.5 mg PO daily for 2 weeks, then 1 mg PO daily as studied
Other Roles in Symptom Management

Properties of Cannabinoids

Sleep
- Generally improvement in sleep onset insomnia
- Fatigue, somnolence most frequent adverse effect in survey of cancer patients using medical cannabis

Mood
- Early studies in healthy volunteers found anxiety-reducing and anxiety-provoking properties
- Better coping
- Improved existential and spiritual well-being
  - Mild euphoria
  - Enhanced senses
  - Awareness

Spasticity
- Meta-analysis showed trend towards efficacy in reducing spasticity severity and frequency

GI effects
- Cannabinoids reduce intestinal transit
Correlation of Cannabinoids and Cancer Risk

• Association between marijuana smoking and cancer
  • Most are case-control studies
    • Retrospective → risk of recall bias
    • Tobacco smoking as a confounder
  • No conclusive evidence of causation of head and neck, lung cancer
  • Lack of evidence for cancer risk with oral or vaporized marijuana

• Testicular cancer risk
  • Epidemiology study in 50,000 men
    • No relationship with “ever” lifetime cannabis use
    • Heavy cannabis users associated with higher incidence of testicular cancer
Mechanisms of Action
1) Cytotoxic
2) Cytostatic
3) Anti-angiogenic
4) Anti-invasion
5) Anti-Stem Cell

Activity in Brain tumors: CB1 CB2, ?
Neuro Oncology: seizure management and anti-tumor

- **Seizures:** the FDA recently approved Epidiolex oral solution in the management of seizures in those children with Dravet syndrome or Lennox–Gastaut syndrome at doses as high as 25–50 mg/kg per day.
  - The initial dose is 2.5 mg/kg twice daily by mouth and increased to a maintenance dose of 10 mg/kg twice daily.

- **Anit-glioma?**
  - GBM expresses CB1 and CB2
  - Cannabinoids reduce glioma tumor growth either *in vitro* or in animal models
  - Cannabinoids appear to be selective antitumoral agents as they kill glioma cells without affecting the viability of nontransformed counterparts.

- **Clinical trials**
  - GW clinical trial on patients with glioblastoma multiforme demonstrated their good safety profile together and interesting antitumor effects, and may set the basis for further studies aimed at better evaluating the potential anticancer activity of cannabinoids.
  - Ongoing NIDA sponsored tolerability trial at Columbia for nGBM NCT03246113
Drug Interactions
Pharmacokinetic Interactions

**CYP Enzymes**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>THC</th>
<th>CBD</th>
<th>CBN</th>
<th>Dronabinol (Marinol®)</th>
<th>Nabilone (Cesamet®)</th>
<th>Cannabidiol (Epidiolex®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td>No sig inhibition</td>
<td>Inhibitor/inducer</td>
<td></td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td></td>
<td>Inhibitor/inducer</td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Substrate (minor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td>Inhibitor (moderate)</td>
<td>Inhibitor</td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Substrate</td>
<td></td>
<td>Substrate (minor)</td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Unknown</td>
<td>Inhibitor</td>
<td>Unknown</td>
<td>No sig inhibition</td>
<td>Inhibitor (moderate)</td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Substrate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td>No sig inhibition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Substrate (minor)</td>
<td>Substrate (minor)</td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td></td>
<td>Inhibitor (weak)</td>
<td></td>
</tr>
</tbody>
</table>

Smoking cannabis induces CYP1A2
### Pharmacokinetic Interactions

**Glucuronidation and Transporters**

<table>
<thead>
<tr>
<th></th>
<th>THC</th>
<th>CBD</th>
<th>CBN</th>
<th>Cannabidiol (Epidiolex®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-glycoprotein</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Substrate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td></td>
</tr>
<tr>
<td>BCRP</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Substrate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>MRP1</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Substrate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td></td>
</tr>
<tr>
<td>UGT1A7</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Substrate</td>
</tr>
<tr>
<td>UGT1A9</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Substrate</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
<td>Inhibitor</td>
<td>Inhibitor</td>
<td></td>
</tr>
<tr>
<td>UGT2B7</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Substrate</td>
<td>Substrate</td>
</tr>
</tbody>
</table>
Cannabinoid-Drug Interactions in Oncology

Potential Drug Interactions with Common Medications

- Calcineurin inhibitors
- Azole antifungals
- Tamoxifen
- Small molecule inhibitors (some)
- Antidepressants
- DOACs
## Cannabinoid-Drug Interactions in Oncology

### Examples of Potential Interactions with Chemotherapy

<table>
<thead>
<tr>
<th>P-glycoprotein/BCRP substrates</th>
<th>CYP3A4 substrates</th>
<th>CYP2C9 substrates</th>
<th>CYP2C19 substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Cyclophosphamide, ifosfamide</td>
<td>Cyclophosphamide, ifosfamide</td>
<td>Cyclophosphamide, ifosfamide</td>
</tr>
<tr>
<td>Docetaxel, paclitaxel</td>
<td>Docetaxel, paclitaxel</td>
<td>Imatinib</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Vincristine, vinblastine, vinorelbine</td>
<td>Vincristine, vinblastine, vinorelbine</td>
<td>Tamoxifen</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Etoposide, irinotecan, topotecan</td>
<td>Etoposide, irinotecan, topotecan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daunorubicin, doxorubicin, idarubicine, mitoxantrone</td>
<td>Daunorubicin, doxorubicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib, dasatinib, ponatinib</td>
<td>Imatinib, dasatinib, ponatinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib, osimertinib</td>
<td>Gefitinib, osimertinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Crizotinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Sorafenib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pazopanib</td>
<td>Lapatinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Pazopanib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venetoclax</td>
<td>Vemurafenib</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tamoxifen, letrozole</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Venetoclax</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cannabinoid-Drug Interactions in Oncology

Applicability

- Characteristics of inhibition and induction
  - Systemic concentrations of cannabinoids with approved use are generally lower than CYP inhibitory concentrations of THC, CBD, and CBN for in vivo studies
  - Limited clinical studies
  - Clinical significance varies widely
    - Variability in product content, doses, routes

- Always screen for drug interactions
  - Caution variability in drug interaction studies
  - Prefer pharmaceutical preparations
  - Potentially greater extent of interactions with CBD than THC

- Consider empiric dose reduction if risk of interaction
  - Cannabidiol (Epidiolex®) package insert
    - Moderate or strong CYP3A4 or 2C19 inhibitors: consider Epidiolex® dose reduction
    - Strong CYP3A4 or 2C19 inducers: consider Epidiolex® dose increase
    - Consider dose reduction of CYP2C8, 2C9, 2C19, UGT1A9, 2B7 substrates
    - CYP1A2, 2B6 may require dose adjustment

- Systemic concentrations of THC, CBD, and CBN for in vivo studies
- Limited clinical studies
- Clinical significance varies widely
- Variability in product content, doses, routes
- Always screen for drug interactions
- Caution variability in drug interaction studies
- Prefer pharmaceutical preparations
- Potentially greater extent of interactions with CBD than THC
- Consider empiric dose reduction if risk of interaction
- Cannabidiol (Epidiolex®) package insert
  - Moderate or strong CYP3A4 or 2C19 inhibitors: consider Epidiolex® dose reduction
  - Strong CYP3A4 or 2C19 inducers: consider Epidiolex® dose increase
  - Consider dose reduction of CYP2C8, 2C9, 2C19, UGT1A9, 2B7 substrates
  - CYP1A2, 2B6 may require dose adjustment
Real-World Considerations
So... what about medical marijuana?

The case for medical marijuana vs pharmaceutical preparations

- Less consistency, standardization, purity
- Lack of high-quality evidence (mainly small observational studies)
- Potentially more drug interactions

Cost and access?
- Quick onset ideal for PRN symptom relief for vaporized, inhaled
- Possible benefit of CBD and synergy from other pharmacologically active compounds

Patient preferences and beliefs?

RCT’s on pharmaceutical preparations

Efficacy and safety of medical marijuana?
Step-wise Approach
Evaluating Use of Medical Marijuana and Cannabinoids

Indication
- Refractory or intolerant to standard treatment
  - Yes
  - No

Risk of adverse effects
- Significant cardiac or psychiatric condition
- Avoid inhaled route if pulmonary condition
  - Yes
  - No

Consider trial other treatment options

Potential drug interactions
- Yes
- No

Elderly
- Yes
- No

Hepatic and/or renal dysfunction
- Yes
- No

Counseling
- Administration
- Adverse effects
- Drug interactions
- Expectations

Discuss treatment plan
- Prefer pharmaceutical preparations
- Recommend dispensary with tested products
- Higher doses may be more efficacious if tolerated

Follow-up and monitoring

Consider trial of cannabinoids

Discuss treatment plan
- Higher doses may be more efficacious if tolerated
- Consider empiric dose reduction and monitoring

Assess risk and clinical significance
- Discuss risks and benefits with providers and patient

Recommend dispensary with tested products
- Higher doses may be more efficacious if tolerated

Prefer pharmaceutical preparations
- Consider empiric dose reduction and monitoring

Higher doses may be more efficacious if tolerated
- Consider empiric dose reduction and monitoring
## Cannabis Product Testing

**ALL CANNABIS HARVESTED ON OR AFTER 1/1/2018 AND ALL CANNABIS PRODUCTS MANUFACTURED ON OR AFTER 1/1/2018, SHALL BE TESTED ACCORDING TO TITLE 16 OF THE CALIFORNIA CODE OF REGULATIONS, SECTION 5715, AND THE REGULATIONS THAT FOLLOW.**

<table>
<thead>
<tr>
<th>Phase-In of Required Laboratory Testing</th>
<th>Inhalable Cannabis</th>
<th>Inhalable Cannabis Products</th>
<th>Other Cannabis &amp; Cannabis Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>January 1, 2018</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cannabinoids Testing</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moisture Content Testing</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category II Residual Solvents and Processing Chemicals Testing</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Category I Residual Pesticides Testing</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbial Impurities Testing (A. fumigatus, A. flavus, A. niger, A. terreus)</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Microbial Impurities Testing (Escherichia coli and Salmonella spp.)</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Homogeneity Testing of Edible Cannabis Products</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>July 1, 2018</strong></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Category I Residual Solvents and Processing Chemicals Testing</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Category II Residual Pesticides Testing</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foreign Material Testing</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>December 31, 2018</strong></td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Terpenoids Testing</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycotoxins Testing</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy Metals Testing</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water Activity Testing of Solid or Semi-Solid Edibles</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**For the latest updates, follow the Bureau on social media**
UCSF Medical Center Medical Marijuana Policy

- Pharmacy is NOT allowed to store marijuana as patient’s own medication.
  - Medical marijuana may be returned to a patient representation so long as it is removed from UCSF Medical Center.
  - If there is no patient representative available to remove the marijuana, then it will be disposed of.
- Illicit drugs shall not be used or possessed on UCSF Medical Center premises by patients or visitors.
  - Any illicit drugs found will be coordinated by UCSF Medical Center Security Services and given to UCPD for disposal, with the exception of medical marijuana; it will be given to a family member or friend, for safekeeping if possible, prior to disposal.
  - Marijuana, in whatever form (oral, smoked or vaporized) shall not be used or possessed on UCSF Medical Center premises by patients or visitors.
Primary challenge for cannabis research

- How do we support faculty research that addresses important health and societal issues related to cannabis while at the same time protecting the interests of both faculty and the University?

- The legalization of cannabis in California and other states raises a number of important social and public welfare questions, including, for example:
  - Potential adverse effects of the drug in vulnerable populations
  - Potential health benefits of cannabis and cannabinoids
  - Many plant science related challenges

- Research expertise should be brought to bear on these issues.

- The complexities of the legal status of cannabis (legal under the state; illegal under the federal government) provide unique challenges to the research entities in developing a well-articulated approach to supporting research involving cannabis and its products.
Resources

- Americans for Safe Access
  - [https://www.safeaccessnow.org/](https://www.safeaccessnow.org/)
  - Information on obtaining medical cannabis ID card
- ReLeaf
  - [https://releafapp.com/](https://releafapp.com/)
  - Application for patients to guide marijuana use
- Society of Cannabis Clinicians
  - Library, continuing education, practitioners
- Lecture series for health care providers
  - Thomas Jefferson University
    - [https://cme.jefferson.edu/lambert](https://cme.jefferson.edu/lambert)
  - University of Vermont
    - [https://learn.uvm.edu/program/cannabis-science-and-medicine](https://learn.uvm.edu/program/cannabis-science-and-medicine)
Questions?

Thank you for going on this “trip” through the literature with me!

The Role of Medical Marijuana in Oncology Patients

Weeding the Evidence
Supplemental Slides
Preview of a Dispensary
Thank you for joining us for our presentation on “Insert Presentation Name”). We hope the information that you received was beneficial. This Presentation was offered by the American Brain Tumor Association, an Illinois not for profit corporation (the “Company”), at no charge to users of the World Wide Web, with the express condition that the Presentation’s attendees agree to be bound by the terms and conditions set forth herein.

The information provided from this Presentation was for informational purposes only. This Presentation: (i) was not intended as medical advice, diagnosis or treatment; (ii) was not a substitute for medical advice, diagnosis or treatment; and (iii) does not provide advice on diagnoses, treatments or conditions for individual patients. All health and treatment decisions must be made with your physician(s), utilizing your specific, confidential and individual medical information.

This Presentation may have contained sponsorships. Sponsors are solely responsible for ensuring that material submitted for inclusion in this Presentation on the Company’s website is accurate and complies with applicable laws.

A sponsor’s inclusion in this Presentation is not an endorsement or recommendation of any product, treatment, physician, hospital, test, procedure, opinion or other information that may be mentioned during this Presentation. Reliance on any information in this Presentation is solely at your own risk.

The Company, its affiliates, assigns and agents are not responsible, and expressly disclaim any liability, for errors or omissions in information provided in this Presentation or any actions resulting from the use of such information.

In addition, the references set out in this Presentation are provided for your convenience only. The Company does not endorse the information contained on linked websites or individual(s), companies or institutions operating such websites.

Please do not hesitate to contact us if you have any further questions. Thank you for being an exceptional audience.