The Role of Cannabis During the Spectrum of Cancer Treatment

Benjamin S. Kematchik, PharmD, BCACP
benjamins_kematick@dfci.harvard.edu

Objectives

• Comprehend the basic pharmacology of common phytocannabinoids
• Discuss the state of the science regarding the use of cannabis in patients with cancer
• Navigate common counseling and logistical scenarios that will occur when discussing cannabis with patients

History of Medicinal Cannabis

• Cannabis species used for thousands of years
  • China, 2700 BCE – menstrual disorders, gout, malaria, constipation
  • Middle East, 5th to 15th centuries – vomiting, epilepsy, inflammation, pain, fever
  • America, 1800s – common analgesic

• Between 1840 and 1900, scientific journals published articles describing the therapeutic benefits of cannabis
• United States Pharmacopeia initially classified cannabis as a legitimate medical compound in 1851
• Bristol-Myers Squib and Eli Lilly used cannabis in patented medicines to treat insomnia, migraines and rheumatism that were widely sold in pharmacies

Legal History

• Marihuana Tax Act of 1937
  • Made possession or transfer of marijuana illegal
  • Excise tax on all sales of the marijuana plant
  • Declared unconstitutional in 1969
• Controlled Substances Act of 1970 (CSA)
  • Marijuana moved to Schedule I
  • Still listed as Schedule I today (November 2018)

Unclear DOJ positions

• 2013: “Prosecutors should continue to review marijuana cases on a case-by-case basis... including but not limited to, whether the operation is demonstrably in compliance with a strong and effective state regulatory system”
• 2018: “Given the Department's well-established general principles, previous nationwide guidance specific to marijuana enforcement is unnecessary and is rescinded”
Medical Society Position Statements

**American Medical Association**

- Discourages cannabis use, especially by persons vulnerable to the drug’s effects and in high-risk situations.
- Supports the determination of the consequences of long-term cannabis use through concentrated research, especially among youth and adolescents.
- Supports the modification of state and federal laws to emphasize public health based strategies to address and reduce cannabis use.
- The AMA also urges that marijuana’s status as a federal schedule I controlled substance be reviewed with the goal of facilitating the conduct of clinical research.

Source: American Medical Association 2017 Interim Meeting Report of the Council on Science and Health

**American Society of Addiction Medicine**

- Supports the "decriminalization" of marijuana.
- Recommends that jurisdictions that have already legalized marijuana or that may act to legalize it in the future implement public health and safety measures to minimize potential harms to vulnerable populations.
- Supports the use of cannabinoids and cannabis for medicinal purposes only when governed by appropriate safety and monitoring regulations, such as those established by the FDA research and postmarketing surveillance processes.
- ASAM does not support the legalization of marijuana-based products for use in neurologic disorders at this time, as further research is needed to determine the benefits and safety of such products.

Source: ASAM Public Policy Statement on Marijuana, Cannabinoids and Legalization

**American Academy of Neurology**

- Supports all efforts to conduct rigorous research to evaluate the long-term safety and effectiveness of marijuana-based products.
- For research purposes, requests the reclassification of marijuana-based products from their current schedule I status as to improve access for study of marijuana or cannabinoids.
- Does not advocate for the legalization of marijuana-based products for use in neurologic disorders at this time, as further research is needed to determine the benefits and safety of such products.
- Recognizes that there may be potential use for these agents in the treatment of canine neurologic disorders; however, there is not sufficient evidence to make any definitive conclusions regarding the effectiveness of marijuana-based products for canine neurologic conditions.
- Each product and formulation of cannabis should demonstrate safety and effectiveness via scientific study similar to the process required by the US Food and Drug Administration (FDA).

Source: AAN Press Release “AAN Calls for More Research on Medical Marijuana for Brain Diseases” 12/17/2014
Pharmacist Association Position Statements

American Society of Health System Pharmacists

• To oppose state legislation that authorizes the use of medical marijuana until there is sufficient evidence to support its safety and effectiveness and a standardized product that would be subject to the same regulations as a prescription drug product;
• To encourage research to define the therapeutically active components, effectiveness, safety, and clinical use of medical marijuana;
• To advocate for the development of processes that would ensure standardized formulations, potency, and quality of medical marijuana products to facilitate research;
• To encourage the Drug Enforcement Administration to eliminate barriers to medical marijuana research, including review of medical marijuana’s status as a Schedule I controlled substance, and its reclassification, if necessary, to facilitate research;
• To oppose the procurement, storage, preparation, or distribution of medical marijuana by licensed pharmacies or health care facilities for purposes other than research;
• To oppose the smoking of marijuana in settings where smoking is prohibited;
• To encourage continuing education that prepares pharmacists to respond to patient and clinician questions about the therapeutic and legal issues surrounding medical marijuana use.

Source: ASHP Policy Positions, 1982–2017

Endocannabinoid system

Endocannabinoids are rapidly metabolized by fatty acid amidase
• Evidence suggests that NSAIDs may work in part through a cannabinoid mechanism
• Delta-9-tetrahydrocannabinol (THC) is a more potent version of anandamide
• Researchers believe there are likely many other cannabinoid receptors and endocannabinoids

Endocannabinoid System

Anandamide (endogenous) has a similar affinity for TRPV1 as capsaicin, but at a lower potency
• The role of TRPV1 and the ECS is still being investigated
• Capsaicin in hyperemesis?
THC – Pharmacology

- THC and other cannabinoids are extremely fat soluble
- Distribute widely to tissues proportional to blood flow
- Peak concentrations in fatty tissue occur after 4-5 days
- THC is metabolized in the liver to both active and inactive metabolites.
- THC is excreted in both urine and bile
- Complete elimination of a single dose of THC may take up to 7 days due to this sequestration in fatty tissue.
- High concentrations of THC seem to be mostly responsible for the psychoactive effects of smoked marijuana

THC – Drug Interactions

- Substrate of 2C9 and 3A4
- Does not inhibit or induce major enzymes
- When smoked induces CYP1A2
- Undergoes extensive first pass metabolism via microsomal hydroxylation (oral administration)
- Can undergo enterohepatic cycling
- Biphasic elimination – rapid redistribution to fatty tissues, long terminal half life

CBD – Pharmacology

- Does not activate CB1 or CB2; psychoactive effects are mitigated
- Antagonism of CB1 in the CNS
- May play a role in the periphery
- Anti-inflammatory, neuroprotective, anxiolytic, and anti-psychotic properties
- Additional non-endocannabinoid signaling system
- Implications for role in controlling epilepsy
- Some studies have shown that patients taking high CBD:low THC preparations experience less psychotic symptoms, even when consuming more THC, possibly due to antagonism of CB1 in the CNS

CBD – Drug Interactions

- Oral administration: substrate of CYP 2C9 and 3A4, UGT 1A7, 1A9 and 2B7
- Metabolized to active metabolite 7-OH-CBD and inactive metabolite 7-COOH-CBD
- Active ~38% lower AUC than CBD
- Potential to inhibit CYP450 2C8, 2C9, and 2C19
- Inhibits UGT1A9 and 2B7 (phenanthrene opioids)
- Patients with moderate to severe hepatic impairment have greater exposure
- Caused transaminase elevations during clinical trials

A panacea?

Where is the evidence?
Efficacy- Pain

- NASEM: “There is substantial evidence that cannabis is an effective treatment for chronic pain in adults”
- Most studies conducted outside the US, with many studies investigating nabiximols
- Few high quality RCTs, but many systematic reviews available in pubmed
  - 126 systematic reviews in pubmed- half published after 2016
  - 50 systematic reviews for pain - 30 in the last three years

Whiting et al. 2015 JAMA

- Systematic review and meta-analysis
- 28 trials included with 2454 participants (Pain)
  - 13 trials of SL nabiximols, 4 for smoked THC, 5 for PO nabilone, 3 for THC SL spray, 2 for PO dronabinol, 1 for vaporized cannabis, one for PO THC
  - 12 studies of neuropathic pain, 3 for cancer pain, 3 for PDN, 2 for FM, 2 for HIV associated sensory neuropathy, 6 “others”
  - 17 of 28 studies determined to be at high risk of bias
- Moderate-quality evidence to suggest that cannabinoids may be beneficial for the treatment of chronic neuropathic or cancer pain (smoked THC and nabiximols)

Overview of systematic reviews (Hauser et. al 2018)

- 10 SRs identified
  - 4 of high quality, 6 of moderate quality
- For cancer related pain
  - 2 studies of 307 patients, one testing dronabinol, one of nabiximols found that cannabinoids were not superior to placebo for cancer pain (>30% pain relief) (2-3 week duration)
  - No statistical differences for adverse events vs. placebo
- Most RCTs performed and included were of a very short duration

Efficacy- Cancer Related Nausea and cachexia

- NASEM: “conclusive evidence that oral cannabinoids are effective antiemetics in the treatment of chemotherapy induced nausea and vomiting”
- “Insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancer-associated anorexia-cachexia syndrome”
- No RCTs of plant derived cannabis studying with appetite and weight as an endpoint

Evidence (?) for cytotoxic potential

- NASEM: “Insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancers including glioma”
- Overwhelming majority of evidence is in animal models
- Small pilot study of intratumoral THC in glioma- found to be safe, no noted impact on survival (no comparator)
Safety – Common ADE’s

- In a review of the literature, Kalant found that the most frequently reported side effects with medical marijuana consumption were:
  - Dizziness or lightheadedness (30-60%)
  - Dry mouth (10-25%)
  - Fatigue (5-40%)
  - Muscle weakness (10-25%)
  - Myalgia (25%)
  - Palpitations (20%)

- These most common side effects are generally considered mild in nature.

Safety – Driving

- In Scandinavia, 10% of drivers arrested for driving under the influence with blood alcohol levels below the legal limit had positive blood tests for cannabinoids.
- However, a study attempting to elucidate a causal role for cannabis impairing driving ability was not able to establish that relationship for cannabis alone.
- 2016 Meta-Analysis found that presence of THC was associated with 20-30 percent higher odds of MVA, OR=1.36, (1.15-1.61) controlled for EtOH, 1.11 (1.04-1.18).

Safety – Psychiatric

- Cannabis use has been associated with:
  - Higher percentage of active symptoms in schizophrenia
  - More intensive exacerbations
  - In a retrospective study of more than 50,000 Swedish soldiers, those having used cannabis were 20% more likely to develop schizophrenia than those who did not.
  - Frequent users over 600% more likely to develop schizophrenia.

Safety – Cardiovascular

- Cannabis use can also increase heart rate, blood pressure, and cardiac muscle workload requirements.
- Case reports of patients with pre-existing CV risk have shown higher rate of acute myocardial infarction.
- Those with advanced disease experiencing transient ischemic attack at a higher rate.
- NASEM found limited evidence of statistical association between smoking marijuana and triggering of AMI.
Safety – Cardiovascular

- Potential for exacerbations of arrhythmias in patients taking other drugs which can affect heart rhythm and rate
- In adolescent patients receiving tricyclic antidepressants, moderate to severe tachycardia, confusion and delirium were noted
- Use medical cannabis in patients with underlying cardiovascular disease with caution and consider potential drug interactions

Safety – Respiratory

- Respiratory effects have also been noted with long-term smoking of cannabis including increased inflammatory changes in the lungs
- Limited evidence of statistical association between occasional cannabis smoking and increased risk of developing COPD, when controlling for tobacco use
- Substantial evidence of association between long-term cannabis smoking and worse respiratory symptoms
- Resolve on cessation of cannabis smoking

Safety – Cancer

- Moderate evidence to suggest smoking cannabis does not increase the risk for lung and head and neck cancers
- Current, frequent, or chronic smoking of cannabis was associated with a statistical association with non-seminoma-type testicular germ cell cancers
- NASEM recommends further, higher quality studies in regard to cancer

Safety – Interactions

- Most relevant interactions will be pharmacodynamic in nature
  - Additive cognitive impairment
  - Potentially increased cardiotoxicity

Counseling – choosing a preparation

- Most of the data made available on the use of medical cannabis comes from smoked and inhaled preparations
- Data does exist for transmucosal sprays however, positive results are not necessarily applicable to all of the dosage forms due to differences in absorption
  - Tincture, oils, patches?

Medical Marijuana – Vaporized
Pharmacokinetics

Inhaled THC
- When smoked, THC rapidly demonstrates an effect on the order of minutes
- Only slightly lower peaks than IV administration
- Absolute bioavailability varies wildly – 2-56% due to inter and intrapatient variability
  - Number, duration, spacing of puffs and inhalation volume

Inhaled CBD
- Less well studied
- Bioavailability ~13% in 5 human subjects with wide variability
Pharmacokinetics
Oral THC
• Slower absorption when compared to inhaled route
• Readily absorbed due to high lipophilicity
• Extensively metabolized via first-pass metabolism
• Absolute bioavailability varies - 4% to 20%
• Depends on excipients
• Two peaks may occur due to enterohepatic circulation
• Effects may be prolonged when compared to inhaled

Pharmacokinetics
Oral CBD
• Does not demonstrate linear PK of absorption (higher at lower doses)
• Tmax of 2.5-5 Hours
• Greatly affected by high-fat meal administration (Cmax increase by ~ 5X, AUC ~4X)
• >94% protein bound
• Steady state T ½ of 56-61 hrs

Pharmacokinetics
Topical THC and CBD
• Not well studied
• Cannabinoids are highly hydrophobic, making flux across aqueous layers of skin difficult
• In vitro, CBD diffuses across skin at concentrations 10X more than THC
• Polarity: CBD > CBN > THC
• May require development of synthetic cannabinoids with therapeutic potential, amenable for TD administration

Current State of affairs in MA
• Two ways to obtain marijuana today – via certification or via adult use (21+)
• 19 adult use dispensaries open in MA today (August 2019)
• Cost for marijuana certification – $150-400/ year for MD certification, $50 per card per year to MA
• Cost for recreational – 10.75% state excise tax, 6.25% sales tax, up to 3% local tax (20% tax possible, each sale)
Current medical pricing

Medical requirements

- Patients must have qualifying medical condition
  - Cancer, Glaucoma, AIDS, Hepatitis C, ALS, Crohn's disease, Parkinson's disease, Multiple Sclerosis, Other conditions as determined in writing by physician

- Bona fide physician-patient relationship

- Physician or NP must complete 2 credits of CME prior to becoming registered

- Can authorize up to 10 oz of flower in 60 day period
  - Authorizations last up to 1 year in length

Adult use possession limits

- Current limits for adult use (without certification)
  - 1 oz flower on person in public
  - 10 oz flower possession limit at home
  - 5g of concentrates
  - Grow up to 6 plants in home per person, up to 12 plants per household
  - No open containers in vehicles
  - Landlords, cities, and towns may pose their own restrictions


https://mass-cannabis-control.com/cnb-faqs/#toggle-id-7
Conclusions

- Clinicians need to be well equipped to answer questions regarding therapeutic benefits and harms using available evidence
- A variety of preparations and delivery methods may make it difficult for patients to achieve expected results
- Medical and pharmacy associations agree, more research is needed into potential therapeutic benefit of medical marijuana.

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