Medical Marijuana in Geriatrics: Weeding Out the Myths
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Disclosures
Dr. Borgelt reports no relevant financial relationships.
Dr. Borgelt will be discussing unapproved drugs and unapproved uses for drugs.
Dr. Borgelt has served as a member of five working groups:
- Colorado Department of Public Health and Environment: Amendment 64 (Marijuana Legalization) Task Force Working Group: Consumer Safety and Social Issues
- State Licensing Authority Labeling, Packaging, Product Safety and Marketing
- State Licensing Authority Medical and Retail Marijuana Mandatory Testing and Random Sampling
- State Licensing Authority Serving Size and Product Potency
- Colorado Department of Public Health and Environment Public Health Advisory

Objectives
- Describe the clinical pharmacology of marijuana and its active components.
- Explain the various dosage forms of marijuana and their pharmacodynamic impact.
- Evaluate the potential therapeutic and adverse effects of marijuana.

OVERALL goal for this presentation is...
...to help providers better understand the characteristics of marijuana and its effects so you can confidently talk with your patients about the potential benefits and risks of using marijuana.

POLL QUESTION
I believe the most common reason people seek out marijuana is to...
1. relieve pain
2. improve symptoms of nausea and vomiting
3. improve Alzheimer’s or Parkinson’s disease
4. relieve muscle spasms associated with multiple sclerosis
5. get high

Patient Case in Colorado
- 47 yo male
- PMH of HTN, diabetes, peripheral neuropathy, and chronic pain
- Pain Treatment Regimen
  - Extended release morphine 30mg po BID and immediate release morphine 15 mg po as needed for breakthrough pain
  - His pain medications have not changed in over one year
  - Today, he admits that he has also been smoking medical marijuana twice daily for the past two years to help his pain (decreased from 8/10 to 4/10).
  - He has been afraid to tell the healthcare team about this because he believes they will not “approve” of this treatment. He states he saw a different physician to get his card and recommendation for medical marijuana.
A Few Questions to Consider

- Are there other ways for him to consume MMJ to avoid the risks of smoking?
- Is MMJ effective for the treatment of pain?
- What adverse effects might this patient experience with chronic use of inhaled MMJ?
- Are there any drug interactions with MMJ?
- How might MMJ impact his opioid use?
- What other issues might this patient need to consider?
- How can I create an environment where patients feel safe to talk with me about any/all treatments they use?

Marijuana

- Single molecule pharmaceuticals
  - Dronabinol (Schedule III)
  - Nabilone (Schedule II)
- Liquid extract: nabiximols (Sativex®)
  - Approved in 27 countries; U.S. - Phase III trials
- Liquid extract: cannabidiol (Epidiolex®)
  - FDA: orphan drug status for Dravet and Lennox-Gastaut syndromes
  - Expanded access INDs to several independent investigators

- Phytocannabinoid-dense botanicals
  - Cannabis sativa – medicinal plant (Schedule I)

Key Opinion

Considerations for medical use of marijuana are different than considerations for recreational use of marijuana.

Medical use: benefit - risk
Recreational use: risk - risk

Cannabis

- Plant-derived cannabinoids
  - $\Delta^2$-tetrahydrocannabinol - THC
  - $\Delta^8$-tetrahydrocannabinol - THD
  - Cannabidiol – CBD
  - Cannabinol - CBN
  - Cannabigerol - CBG
  - Cannabichromene - CBC
  - Cannabicyclol
  - Cannabiol
  - Cannbitriol
  - Miscellaneous
  - Cannabinodiol (air-oxidation)

POLL QUESTION

The psychoactive component of marijuana is:

1. Cannabidiol (CBD)
2. Cannabinol (CBN)
3. Tetrahydrocannabinol (THC)
4. Cannabigerol (CBG)
Endocannabinoid System

- Endocannabinoids and their receptors found throughout body: brain, organs, connective tissues, glands, and immune cells.
- In each tissue, the cannabinoid system performs different tasks; goal is always homeostasis.
- When cannabinoid receptors are stimulated, a variety of physiologic processes occur:
  - CB1 receptors: nervous system, connective tissues, gonads, glands, organs
  - CB2 receptors: immune system and associated structures
- Endocannabinoids are substances our bodies make naturally to stimulate CB1 and CB2
  - Anandamide
  - 2-arachidonoylglycerol (2-AG)
- Endocannabinoid signaling modulates pathological processes occurring during the silent period of the neurodegenerative process:
  - Protein misfolding, neuron inflammation, excitotoxicity, mitochondrial dysfunction, and oxidative stress.

Cannabis Pharmacology

Endogenous Cannabinoid System

POLL QUESTION
Which of the following receptors is a key target for THC?

1. Cannabinoid-1 receptor (CB1)
2. Cannabinoid-7 receptor (CB7)
3. Peroxisome Proliferator-Activated Receptors (PPAR)
4. G-protein receptor 55 (GPR55)
5. I have no idea

Targets of Marijuana

**CB1 Receptors**
- Basal ganglia
- Motor activity
- Cerebellum
- Motor coordination
- Hippocampus
- Short-term memory
- Neocortex
- Thinking
- Hypothalamus & limbic
- Appetite, sedation
- Peraqueductal gray dorsal horn
- Pain
- Connective tissues
- Heart
- GI tract

**CB2 Receptors**
- Immunologic cells
- B lymphocytes
- Natural killer cells
- Microglial cells
- Brain/CNS
- Role not established

Brit J Clin Pharm 2009;67(1):5-21
J Psychopharmacol 2008;22:707–16
Cannabinoids in Alzheimer’s Disease

- Endocannabinoid system (ECS) in AD brain
  - Alteration of ECS composition and signaling
  - Increase in CB2 receptors on microglia surrounding senile plaques and correlates with Aβ levels and plaque disposition
  - CB1 and CB2 receptors nitrosylated – impaired signaling
  - Lower anandamide levels and increased anandamide degradation

- Cannabinoid effects in AD (anandamide, 2-AG, CBD, THC, etc.)
  - Neuroprotection against Aβ
  - Reduction/inhibition of tau hyper-phosphorylation
  - Anti-inflammatory (activation of CB2 receptors reduced the neuroinflammatory response to Aβ insults)
  - Anti-oxidant (role of CB2 receptors in reducing oxidative stress)
  - THC competitively inhibits acetylcholine esterase, thus increasing Ach

- Therapeutic properties of cannabinoids
  - Analogs of THC show positive behavioral results
  - Volicer 2007; Walther 2006; Walther 2011; Passmore 2008
  - Cochrane Dementia and Cognitive Impairment Group: no evidence of effectiveness (Krishnan 2009)

Non-Cannabinoid Targets Linked to Cannabis

- Other G-protein receptors: GPR55, GPR55940, etc.
- G-protein-coupled receptors: noncompetitive inhibitor at μ- and δ-opioid receptors, NE, DA, 5-HT
- Ligand-gated ion channels: allosteric antagonism at 5-HT3, nicotinic, and enhance activation of glycine receptors
- Transient receptor potential channels (TRPVs): bind and activate TRPV1 similar to capsaicin, also CB1 receptors are located near TRPV1
- Ion channels: inhibition of Ca, K, Na channels by non-competitive antagonism
- Peroxisome Proliferator-Activated Receptors: PPARα and PPARγ are activated

Another Kid on the Block...

Other cannabinoids found in the plant are also providing effects. The cannabinoid that has sparked the most interest is a non-psychoactive component called cannabidiol (CBD).

Little binding affinity to CB1 and CB2

- Suppresses enzyme fatty acid amide hydroxylase ("FAAH") – the enzyme that breaks down anandamide

Suppressed at CB1 receptor

Little suppression of THC release of 2-AG

TRPV1 receptor agonist

5-HT1A receptor activation

GPR55 antagonist
### Potential Physiologic Responses to Cannabis

- Improves sleep
- Anti-seizure effects and neuroprotection
- Reduces anxiety and psychotic symptoms/PTSD
- Prevents nausea and stimulates appetite
- Reduces intravascular pressure
- Bronchodilator
- Relaxes muscles and reduces muscle spasms
- Relieves pain (especially neuropathic)
- Anti-inflammatory
- Anti-proliferative
- Anti-viral

### Adverse Effects of Marijuana

#### Effects of Short-term Use
- Impaired short-term memory
- Impaired motor coordination
- Altered judgment
- Motor vehicle accidents (2x)
- Paranoia and psychosis (high doses)

#### Effects of Long-term or Heavy Use
- Addiction (9% overall)
- Cognitive impairment (with lower IQ)*
- Diminished life satisfaction and achievement*
- Poor educational outcome
- Symptoms of chronic bronchitis
- Increased risk of chronic psychosis disorders

*Effect is strongly associated with initial marijuana use early in adolescence

### Summary of Cannabis Pharmacology

- Cannabinoids may have a role for the treatment of many conditions involving the endocannabinoid system
- Although several possibilities, most well-studied target receptors are CB1 and CB2 found throughout the body
- Adverse effects include central nervous system, cardiovascular, and respiratory effects
- Benefit and risk of cannabis should be evaluated for individual patients
- More research is needed

### Poll Question

Which of the following is/are common adverse effects of marijuana?

1. Slowed reaction time
2. Decreased heart rate
3. Insomnia
4. All of the above
Back to the Patient Case...

Our patient should be asked about adverse effects he may be experiencing and determine if a different dosage form would be more appropriate or safer to use.

POLL QUESTION

Which of the following forms of marijuana has the slowest onset of action?

1. Intravenous
2. Inhaled
3. Oral
4. Buccal

Pharmacokinetics vs. Pharmacodynamics

CONSIDERATIONS IN THE ELDERLY:
* Decreased hepatic drug clearance
* Pharmacodynamic changes in cardiovascular and nervous systems

Medical Marijuana: Strains and Formulations

3 Routes of Administration

- **LUNGS**
  - Vaporized or Smoked
  - Organic material, hash, hash oil

- **GUT**
  - Oral Ingestion
  - Lipophilic, alcoholic, supercritical fluidic extracts of plant material

- **SKIN**
  - Topical Application
  - Creams, buccal tinctures, and patches made from plant extracts

Marijuana Through the Lungs

- Similar to IV bolus
- Passive diffusion into alveolar capillaries
- Bioavailability: 2-56%
- Fraction absorbed: 10-20%
- Rapid onset (sec-min)
- Maximal onset 30 minutes and lasting 2-3 hours
- Metabolism in liver, lung, and brain
- Elimination t½ = 20 hrs (2-13 days)
- Elimination primarily via feces (65%) and urine (20%)
- Can easily titrate to desired effect

http://www.bestvaporizers.com/marijuana-vaporizers.html
http://www.health.harvard.edu/blog/teens-who-smoke-pot-at-risk-for-later-schizophrenia-psychosis-201103071676
http://www.themednote.com/2011/07/10/pharmacodynamics—vs—pharmacokinetics/#.U8yB fldXpU
Accessed 7/20/14

Curr Med Chem 2010;17:571–584
Marijuana Through the Gut

- Variable absorption
- Bioavailability ranges 4-20%
- Onset: 30 minutes-2 hours
- Duration: 5-8 hours
- Metabolized primarily in the liver
  - 11-hydroxy-THC
- Elimination $t_{1/2} = 20-30$ hrs
- High inter- and intra-patient variability

Pharmacodynamics in Action: Oral Formulations

- 225 mg THC
- 200 mg THC
- 100 mg THC
- 85 mg THC
- 300 mg THC
- 225 mg THC
- 175 mg THC
- 10 mg/unit

Marijuana Through the Oral Mucosa

- Onset: 15-40 minutes
- Duration: 45 minutes-2 hours
- May have inter- and intra-patient variability
- Plasma levels of THC and other cannabinoids are lower compared with the levels achieved following inhalation of cannabinoids at a similar dose (nabiximols)
- Metabolized in the liver
- Elimination via feces (65%) and urine (35%)

Key Point

Given the wide variety of formulations available, it is important to consider various pharmacokinetic and pharmacodynamic parameters for individual patients.

A patient-determined, self-titrated dosing model should be used. The most effective and tolerable formulation and dose will vary based on body type, weight, and condition.

Providers need to step into a shared decision making model with patients.

Therapeutic Effectiveness of MMJ

What is the Most Common Reason for MMJ Use in the U.S.?

1. Cancer
2. Epilepsy
3. Glaucoma
4. Muscle spasms
5. Nausea
6. Pain
Concluded moderate harms: number of adverse events avoided or decreased. Synthetic derivatives included.

Efficacy outcome: intensity of pain by VAS (visual analog scale).

Harms: number of adverse events decreased.

Concluded moderate efficacy, but risks may be greater than benefit.

Cannabis Treatment for Chronic Pain

Systematic Review and Meta-Analysis

- 18 double-blind RCTs
- Synthetic derivatives included
- Efficacy outcome: "intensity of pain" by VAS
- Harms: number of adverse events avoided or decreased
- Concluded moderate efficacy, but risks may be greater than benefit

MMJ Registrants in CO and AZ: Qualifying Conditions

CO: current cardholders (n=115,210)
- Severe pain: 19%
- Muscle spasms: 10%
- Severe nausea: 20%
- Cancer: 2%
- Glaucoma: 9%
- HIV/AIDS: 9%
- Muscular disorders: 3%
- Motor disorders: 7%
- Fibromyalgia: 11%
- Depression: 3%
- Anxiety: 2%
- Post-traumatic stress disorder: 2%
- Other: 1%

AZ: current cardholders (n=54,558)
- Severe pain: 19%
- Muscle spasms: 10%
- Severe nausea: 20%
- Cancer: 2%
- Glaucoma: 9%
- HIV/AIDS: 9%
- Muscular disorders: 3%
- Motor disorders: 7%
- Fibromyalgia: 11%
- Depression: 3%
- Anxiety: 2%
- Post-traumatic stress disorder: 2%
- Other: 1%

Treatment of Chronic Non-Cancer Pain: Systematic Review of Randomized Trials

Cannabinoid | Overall result
---|---
Smoked cannabis | All trials found positive effect by improving neuropathic pain vs placebo with no serious adverse effects.
Dronabinol extracts | 6/7 trials demonstrated positive analgesic effects for neuropathic pain, RA, mixed chronic pain. In one trial evaluating RA, significant decrease in disease activity (28 joint disease activity score).
Nabilone | Three showed significant analgesic effect in spinal pain, fibromyalgia, and spasticity related pain vs placebo. One showed similar effect in neuropathic pain vs difenprofen.
Dronabinol | Significant reduction in central pain (MS) vs placebo. Significantly greater analgesia vs placebo for mixed chronic pain on opioids.
THC-11-0ic acid analogue - CT-3 or ajulemic acid | Apomorphine led to significant improvement in neuropathic pain intensity at 3 hours, but no difference at 8 hours compared with placebo.

Cannabinoids may have a role for the treatment of refractory seizures and pain, especially neuropathic pain.

Appropriate and consistent dosing/concentrations difficult.

Study limitations: short duration, small numbers enrolled, varying THC content of plant material, difficult to blind pts.

Unfavorable side effect profile.

More research is needed.

Other Interesting Clinical Findings

- PTSD: cannabis used more frequently for sleep and coping
  - Drug and Alcohol Dependence. 2014;136:162–5
  - Research and Practice. 2014;5:75–80

  - IBD: improved pain and diarrheal symptoms
  - Inflamm Bowel Dis 2013;19:2809–14
  - Multiple Sclerosis (spasms): American Academy of Neurology systematic review - efficacy with oral cannabis extracts
  - Neurology 2014 Apr 29;82(17):1556-63
  - Parkinson’s disease: improved sleep, pain, quality of life

Summary of Clinical Trials

- Cannabinoids may have a role for the treatment of refractory seizures and pain, especially neuropathic pain
- Appropriate and consistent dosing/concentrations difficult
- Study limitations: short duration, small numbers enrolled, varying THC content of plant material, difficult to blind pts
- Unfavorable side effect profile
- More research is needed.
**Impact of MMJ on Opioid Use**

- When used in conjunction with opioids, cannabinoids can lead to greater cumulative relief of pain and potential reduction of opiate use.
- Comparisons in analgesia:
  - 10 mg THC less effective than 60 mg codeine
  - 20 mg THC more effective than 120 mg codeine
- Prevent development of tolerance to and withdrawal from opiates and potentially rekindle opiate analgesia after a prior dosage has become ineffective.
- Potentially less dangerous than opiates (no direct death).

**What about our Patient in Colorado?**

Hash
- Hash oil
- Buds
Edibles
- Tinctures
- Chews
Sodas/Teas
- Topicals

Back to the Patient Case

**Therapeutic Effectiveness**

Patient experienced pain reduction similar to what has been shown in clinical studies (8/10 to 4/10)

**Remaining Questions**

Drug interaction?
- Effect on opioid use?
- Patient safety issues?
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- Literature review on marijuana use and health effects
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  - Unintentional exposures in children
  - Adolescents and young adults
  - Dose and drug interactions
  - Neurological, cognitive, and mental health effects
    - Respiratory effects
    - Extrapolmonary effects
  - Injury
- Monitoring possible marijuana-related health effects
- Glossary

Health Effects: Evidence Statements

- Substantial evidence: robust scientific findings that support the outcome and no credible opposing scientific evidence.
- Moderate evidence: scientific findings support the outcome, but these findings have some limitations.
- Limited evidence: modest scientific findings that support the outcome, but these findings have significant limitations.
- Mixed evidence: both supporting and opposing scientific findings for the outcome with neither direction dominating.
- Insufficient evidence: outcome has not been sufficiently studied.

Respiratory Effects

- Substantial evidence that marijuana smoke contains many of the same carcinogens found in tobacco smoke.
- Substantial evidence that acute use – (within the past hour) – results in immediate, short–term improvement in lung airflow. This finding includes use of both smoked and edible marijuana products. However, we found moderate evidence that heavy marijuana smoking is associated with mild airflow obstruction.
- Substantial evidence: heavy marijuana smoking is associated with chronic bronchitis, including chronic cough, sputum production, and wheezing.
- Substantial evidence: heavy marijuana smoking is associated with pre-malignant lesions in the airway, but mixed evidence for whether or not marijuana smoking is associated with lung cancer.

Extrapulmonary Effects

- Relatively few literature reports of marijuana use related to myocardial infarction (heart attacks), ischemic stroke, male infertility, testicular cancer, prostate cancer and bladder cancer.
- Limited evidence that marijuana use may increase risk for both heart attack and some forms of stroke. These findings were most closely associated with recent, and in some cases heavy, marijuana use.
- Limited evidence also suggests an increased risk in both testicular (nonseminoma) and prostate cancers with marijuana use.
- Mixed evidence for whether or not marijuana use increased the risk of male infertility.

Recommendations

1. Ask about the use of marijuana and consider screening in high-risk patients
2. Check for drug interactions
3. Discuss potential benefits and adverse effects
4. Counsel about patient safety issues including keeping out of the reach of children and using proper packaging and labeling of marijuana
5. Follow clinic/hospital/pharmacy policies and procedures

Conclusions

- Psychoactive effects of marijuana related to THC, but other cannabinoids involved with therapeutic effects.
- Many different formulations and potential dosages available. How to best determine appropriate dose should be individualized.
- Clinical studies indicate MMJ may have a role in patients with pain and Alzheimer’s disease.
- Risk for potential adverse events may or may not outweigh benefit provided.
- Providers should be aware of potential drug interactions and psychiatric implications.
- Resources available to provide insight about health concerns.
THANK YOU!

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