Medical Cannabis Across the United States

Laura M. Borgelt, PharmD, FCCP, BCPS
Professor, University of Colorado Anschutz Medical Campus
Departments of Clinical Pharmacy and Family Medicine
Iowa Pharmacists Association
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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

- Review recent regulations to determine status of marijuana across the United States.
- Describe the clinical pharmacology of marijuana and its active components.
- Review various dosage formulations of marijuana available to patients.
- Evaluate and discuss clinical studies performed in patients with various conditions to determine the effectiveness of medical marijuana (MMJ).
- Identify adverse effects, psychiatric implications, potential drug interactions, and other patient safety issues that may occur with the use of MMJ.
OVERALL goal for this presentation is...

...to help pharmacists better understand the characteristics of marijuana and its effects, whether used medicinally or recreationally, so you can confidently talk with your patients about the potential benefits and risks of using marijuana.
Patient Case in Colorado

- 47 yo male
- PMH of HTN, diabetes, peripheral neuropathy, and chronic pain
- Pain Treatment Regimen
  - Oxycontin 30mg po BID and oxycodone 5 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 prescription 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 24 countries; U.S. - Phase III trials

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

1937
- Federal Prohibition
- Prohibited by federal law (Controlled Substances Act 1970)

1996
- Legal Medical Marijuana (22 states and District of Columbia)
- Legal access under a physician’s supervision
- Marijuana may be possessed or grown for personal use

2012
- Legal Recreational Marijuana (CO and WA)
- Eliminates prohibition for possessing small amounts
- Requires legislatures to regulate recreational use

2014
- Pro-Medical Marijuana (10 states)
- Marijuana not necessarily legal for all state residents
- Limits conditions and/or marijuana components
History of Medical Marijuana Use

A BLIP ON THE RADAR?

3000 BC

*Not drawn to scale

1937-1996

Medical use of marijuana
Current Status (as of July 3, 2014)

- States with Legal Medical Marijuana laws
  - Alaska
  - Arizona
  - California
  - Colorado
  - Connecticut
  - Delaware
  - District of Columbia
  - Hawaii
  - Illinois
  - Maine
  - Maryland
  - Massachusetts
  - Michigan
  - Minnesota
  - Montana
  - Nevada
  - New Hampshire
  - New Jersey
  - New Mexico
  - Oregon
  - Rhode Island
  - Vermont
  - Washington

- Pending: FL, NY, OH, PA

Current Status (as of July 3, 2014)

- States with Pro-Medical Marijuana laws
  - Alabama
  - Florida
  - Iowa
  - Kentucky
  - Mississippi
  - North Carolina
  - South Carolina
  - Tennessee
  - Utah
  - Wisconsin

- Pending: MO
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
  - $\Delta^9$-tetrahydrocannabinol - THC
  - $\Delta^8$-tetrahydrocannabinol - THC
  - Cannabidiol – CBD
  - Cannabinol - CBN
  - Cannabigerol - CBG
  - Cannabichromene - CBC
  - Cannabicyclol
  - Cannabielsoin
  - Cannabitriol
  - Miscellaneous
  - Cannabinodiol (air-oxidation)

Br J Pharmacology 2006;147:S163-171
Br J Pharmacology 2011;163:1344-1364
Endogenous Cannabinoid 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 System

- Anandamide
- 2-AG
- NAPE-PLD
- NAPE
- DAGL
- DAG
- TRPV1
- FAAH
- CB₁
- CB₂
- Arachidonate
- Ethanolamine
- Glycerol
- GPR55
- MAGL
- 2-AG
- EMT

Cannabis Pharmacology

Brain's Chemical
Anandamide

Drug
THC

http://www.tokeofthetown.com/2011/03/worth_repeating_bodys_own_cannabinoids_are_the_bli.php
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
The New Kid on the Block...

THC may be the psychoactive component of cannabis effecting CB1 and CB2 receptors, but it is most likely that 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).

Marijuana’s Effects on the Brain

When marijuana is smoked, its active ingredient, THC, travels throughout the body, including the brain, to produce its many effects. THC attaches to sites called cannabinoid receptors on nerve cells in the brain, affecting the way those cells work. Cannabinoid receptors are abundant in parts of the brain that regulate movement, coordination, learning and memory, higher cognitive functions such as judgment, and pleasure.
Endocannabinoid System

Cannabis Pharmacology

http://www.tokeofthetown.com/2011/03/worth_repeating_bodys_own_cannabinoids_are_the bli.php
http://www.herbalmission.org/medical-marijuana/endocannabinoid-system
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

http://www.bestvaporizers.com/marijuana-vaporizers.html
http://www.health.harvard.edu/blog/teens-who-smoke-pot-at-risk-for-later-schizophrenia-psychosis-201103071676
Marijuana Through the Lungs

- Similar to IV bolus
- Passive diffusion into alveolar capillaries
- Rapid onset (sec-min)
- Maximal onset 30 minutes lasting 2-3 hours
- If smoked, ~50% of THC content delivered through smoke
- Some metabolism in lung=10-25%

Marijuana Through the Gut

- Variable absorption
- Bioavailability ranges 5-20%
- Onset: 30 minutes-2 hours
- Duration: 5-8 hours
- High intra-patient variability
- Difficult self-titration for appropriate dosing
Dosing of Oral Marijuana

“So...you leave a Saturday open...”
Choosing a Bud
Dosing for Oral Formulations

200 mg THC
100 mg THC
85 mg THC
300 mg THC
225 mg THC
175 mg THC
10 mg/unit
Examples of Reported CBD-Rich Products

- Charlotte’s Web (Realm Oil) – CBD-rich oil extract (CO)
- Statewide Collective – CBD-rich oil extracts (CA)
- Rimidyia – Whole plant and blended emulsified CBD-rich extracts (CA)
- GOOD-EZ and CBDOOS – CBD-rich lozenges from Jolly Meds (CA)
- Veda Chews – Sugar-free, high CBD chocolate truffles from Avedica Nutraceuticals (CA)
- Veda Balm – CBD-rich topical rub from Avedica Nutraceuticals (CA)
- XXXBody – Rescue Balm from Cannabis Basics (WA)
- Mt. Si Edibles & Topicals - Strain-specific CBD-rich and CBD-dominant capsules (WA)
- Mountains High Suckers – CBD-rich infused edibles (CO)
- Ruby Slippers and Glinda’s Tonic - from Wizard’s Garden (WA)
- Breamworth Elixirs - CBD-rich tinctures (CA)

Given the wide variety of formulations available, a patient-determined, self-titrate dosing model should be used for medical marijuana.

The most effective and tolerable 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 Should Be Studied?

- Muscle Spasms
- PTSD
- Glaucoma
- Nausea
- GERD
- IBS
- ADHD
- Tourette’s Syndrome
- PAIN
- Sleep
- Anxiety
- Seizures
- Vomiting
- Asthma
- Appetite Loss
- Cancer
Summary of Iowa Bill (SF 2360)

Allows the possession or use of cannabidiol that has less than 3% tetrahydrocannabinol [THC] for the treatment of intractable epilepsy with the written recommendation of a neurologist.

The bill states that the cannabidiol must be obtained from an out-of-state source and "recommended for oral or transdermal administration" (non-smoked).
High Concentration Cannabidiol in Highly Refractory Pediatric Epilepsies

- Charlotte’s Web (CW Realm Oil, or Realm Oil)
  - CBD at a ratio of >16:1 relative to other cannabinoids
- 11 patients with severe, medically refractory epilepsy and who had received Realm Oil for at least 3 months
  - 4 Doose syndrome, 2 Dravet syndrome, 1 Lennox-Gastaut syndrome, 1 metachromatic leukodystrophy, 1 cortical dysplasia and 2 idiopathic epilepsy
  - Average of 10 AEDs in their lifetime
  - Average dose was 4 to 12 mg/kg/day, in 2 or 3 divided doses

Side effects:
- Sedation
- Unsteadiness

In Press with the American Epilepsy Society, 67th Annual Meeting, December 6-10, 2013
Parent Survey of Cannabidiol-enriched Cannabis use in Pediatric Treatment-Resistant Epilepsy

- 19 responses from parents belonging to Facebook group
  - Children age 2-16 years with epilepsy and current use of CBD-enriched cannabis (dose ranging from 0.5-28.6 mg/kg/day)
- Avg # of AEDs prior to CBD-enriched cannabis = 12
- Results
  - 16/19 (84%) reported a reduction in child’s seizure frequency
    - 2/19 (11%) = complete seizure freedom
    - 8/19 (42%) = >80% reduction in seizure frequency
    - 6/19 (32%) = 25-60% reduction in seizure frequency
    - 12/19 parents weaned their child from another AED
  - Other benefits: better mood (79%), increased alertness (74%), improved sleep (68%), decreased self-stimulation (32%)
  - Side effects: drowsiness (37%) and fatigue (16%)
MMJ Registrants in CO and AZ: Qualifying Conditions

CO: current cardholders (n=115,208)

- Severe pain: 94%
- Muscle spasms: 10%
- Severe nausea: 13%
- Cancer: 3%
- Cachexia: 1%
- Glaucoma: 1%
- HIV/AIDS: 1%
- Seizures: 2%

AZ: current cardholders (n=50,073)

- Severe pain: 72%
- Muscle spasms: 20%
- Severe nausea: 1%
- Cancer: 1%
- Cachexia: 1%
- Glaucoma: 1%
- HIV/AIDS: 1%
- Seizures: 1%

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

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>OR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Intensity of pain</td>
<td>-0.61 (-0.84, -0.37)</td>
</tr>
<tr>
<td>Euphoria</td>
<td>4.11 (1.33, 12.72)</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>2.56 (0.66, 9.92)</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>8.34 (4.63, 15.03)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>2.18 (0.93, 5.11)</td>
</tr>
<tr>
<td>Disorientation/Confusion</td>
<td>3.24 (1.51, 6.97)</td>
</tr>
<tr>
<td>Dissociation/Acute psychosis</td>
<td>3.18 (0.89, 11.33)</td>
</tr>
<tr>
<td>Speech disorders</td>
<td>4.13 (2.08, 8.20)</td>
</tr>
<tr>
<td>Ataxia, muscle twitching</td>
<td>3.84 (2.49, 5.92)</td>
</tr>
<tr>
<td>Numbness</td>
<td>3.98 (1.87, 8.49)</td>
</tr>
<tr>
<td>Impaired memory</td>
<td>3.45 (1.19, 9.98)</td>
</tr>
<tr>
<td>Attention disturbances</td>
<td>5.12 (2.34, 11.21)</td>
</tr>
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Smoked Cannabis for Chronic Neuropathic Pain

- 21 adults post-traumatic or post-surgical neuropathic pain
- Cannabis 25 mg at 0%, 2.5%, 6%, and 9.4% THC smoked 3x/day
- Four 14-day periods in crossover trial
- Primary outcome: pain intensity (11-item scale)

**RESULTS**

- Pain intensity
  - 9.4%: score = 5.4
  - 0%: score = 6.1
  - (p=0.023; difference 0.7, 95% CI 0.02-1.4)

- Sleep (more drowsiness, getting to sleep more easily, faster, and with less wakefulness)
  - 9.4% vs 0%: p<0.05

- Anxiety and depression improved (EQ5D)
  - 9.4% vs 0%: p<0.05

- Adverse events
  - 248 mild; 6 moderate (fall, ↑pain, numbness, drowsiness, pneumonia)
In Patients with Multiple Sclerosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effective</th>
<th>Possibly effective</th>
<th>Probably or possibly ineffective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasticity</td>
<td>OCE</td>
<td>Nabiximols, THC</td>
<td></td>
</tr>
<tr>
<td>Central pain or painful spasms</td>
<td>OCE</td>
<td>Nabiximols, THC</td>
<td></td>
</tr>
<tr>
<td>Urinary dysfunction</td>
<td></td>
<td>Nabiximols</td>
<td>THC, OCE</td>
</tr>
<tr>
<td>Tremor</td>
<td></td>
<td></td>
<td>THC, OCE, nabiximols</td>
</tr>
</tbody>
</table>

*OCE= oral cannabis extract

“The risks and benefits of medical marijuana should be weighed carefully.”
“Comparative effectiveness of medical marijuana vs other therapies is unknown for these indications.”

Neurology. 2014 Apr 29;82(17):1556-63
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 and CBD content of plant material, difficult to blind pts
- Unfavorable side effect profile
- More research is needed
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**
- Adverse effects?
- Drug interaction?
- Effect on opioid use?
- Patient safety issues?
- Tachycardia
- Palpitations
- Hypertension

Cardiovascular

Marijuana Adverse Effects

Respiratory

- Coughing
- Wheezing
- Sputum production

Nervous Systems

- Lethargy, Sedation, Slowed Reaction Time
- Psychological dysfunction
  - impaired coordination, memory formation, recollection, focus)
- Visual Disturbances

Am J Health-Syst Pharm. 2007; 64:1037-1044
Psychiatric Implications

- **Acute cannabis psychosis**
  - Very large dose of cannabinoid botanical consumed
  - Typically through oral ingestion (concentrated preparation)
  - Agitation, confusion, sedation
  - Self-limiting and generally disappears after metabolism/excretion

- **Acute schizophreniform reaction**
  - Young adults under stress and have other vulnerabilities to schizophreniform illness
  - Early and heavy cannabis exposure may increase the risk of developing a psychotic disorder such as schizophrenia
  - Carefully monitor or avoid in early teens or preteens with preexisting symptoms of mental illness or patients with significant family or personal history of mental illness

J Psychiatr Res 2013 Apr;47(4):438-44
J Clin Psychiatry 2012 Nov;73(11):1463-8
Clin J Pain 2013;29:164-71
Marijuana Exposure in Childhood and Adolescence

- **3Ds**: Dependence – Depression – Dysfunction
- **Dunedin Study (Meier 2012)**
  - Over 1000 individuals followed from birth (‘72/’73) to 38 years
  - Cannabis use ascertained at 18, 21, 26, 32, and 38 years
  - Neuropsychological testing at 13 and 38 years
  - Results for persistent adolescent users:
    - Greater decline in IQ (~6 IQ points)
    - Greater neuropsychological impairment
      - Executive functioning and processing speed
      - Informants reported observing significantly more attention and memory problems
  - Conclusion:
    - Neurotoxic effects of cannabis on the adolescent brain

Proc Natl Acad Sci U S A. 2012;109(40):E2657-64. doi: 10.1073/pnas.1206820109
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.
Other Patient Considerations

- Drug interactions
- Impact of MMJ on opioid use
- Packaging and labeling
- Testing of marijuana
- Patient-provider relationship
Drug Interactions

- THC metabolized by microsomal oxidation to several hydroxylated metabolites (11-hydroxy-THC pharmacologically active) by CYP2C9 and CYP3A4
- May be more critical for oral administration
- CYP2C9-mediated metabolism
  - Tricyclic antidepressants (tachycardia, delirium)
  - Selective serotonin reuptake inhibitors (manic symptoms)
- CYP3A4-mediated metabolism
  - Protease inhibitors (reduction in indinavir and nelfinavir concentrations may or may not be clinically significant)
  - Sildenafil (myocardial infarction or pulmonary hemorrhage)
- Warfarin
  - Increased INR reported with frequent marijuana use
- CNS depressants (additive depressant effects)
  - Barbiturates, alcohol, benzodiazepines, antihistamines, narcotics
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)
Marijuana Packaging

- Container must be designed to ensure contents are secure and are child-resistant
- Concern for pediatric ingestions

<table>
<thead>
<tr>
<th>Ingestion</th>
<th>1/1/05-9/30/09 (n=790)</th>
<th>10/1/09-12/31/11 (n=588)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>90 (11.3%)</td>
<td>48 (8.2%)</td>
</tr>
<tr>
<td>Marijuana exposure</td>
<td>0</td>
<td>14 (2.3%)</td>
</tr>
</tbody>
</table>

**Symptoms:** lethargy (n=9); dizziness (n=1); ataxia (n=1); resp insuff (n=1); fussiness (n=1); asymptomatic (n=1)

**Tests:** total of 74 ancillary tests performed

**Disposition:** admission (n=8); observation (n=5); discharge (n=1)

**Source:** family member (n=8); babysitter (n=1); unknown (n=3); cake (n=1)
Practically Speaking...

...how does all of the required labeling fit on one package of shatter?
What about our Patient in Colorado?

Hash
Hash oil
Buds
Edibles
Tinctures
Chews
Sodas/Teas
Topicals
Recommendations for Pharmacists

1. Ask about the use of marijuana

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 pharmacy, clinic and/or hospital 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 seizures refractory to other treatments.
- Risk for potential adverse events may or may not outweigh benefit provided.
- Providers should be aware of potential drug interactions and psychiatric implications, especially in adolescent population.
- Other patient safety issues need to be considered such as packaging, labeling, testing, laws, and patient-provider relationships.
THANK YOU!

Email: laura.borgelt@ucdenver.edu