Pain and Palliative Care PRN—Clinical Controversies of Cannabinoids for Pain Management: Evidence and Political Implications for Pharmacists
Activity No. 0217-0000-14-109-L01, 2.0 contact hours; Knowledge-based activity.

Monday, October 13
1:30 p.m.—3:30 p.m.
Convention Center:
Meeting Room 19

Moderator: Amanda R. McFee Winans, Pharm.D., BCPS
Clinical Pharmacy Specialist, Bassett Medical Center, Cooperstown, New York

Agenda

1:30 p.m.  Medical Use of Cannabinoids: Where’s the Evidence?
Laura B. Borgelt, Pharm.D., FCCP, BCPS
Professor, University of Colorado Anschutz Medical Campus, Skaggs School of Pharmacy & Pharmaceutical Sciences, Aurora, Colorado

2:10 p.m.  Medical Use of Cannabinoids: Clinical Pearls
James B. Ray, Pharm.D.
Pharmacy Clinical Coordinator – Pain/Palliative Care, UVA Health System, Charlottesville, Virginia

2:50 p.m.  “My Doctor Gave Me Marijuana … What’s the Big Deal?”
Jennifer M. Strickland, Pharm.D., BCPS
Vice President, PGT Business Leader, Millennium Labs, San Diego, California

Conflict of Interest Disclosures

Laura B. Borgelt: no conflicts to disclose.
James B. Ray: no conflicts to disclose.
Jennifer M. Strickland: no conflicts to disclose.
Amanda R. McFee Winans: no conflicts to disclose.

Learning Objectives

1. Explain pharmacological principles for the use of cannabinoids for pain or symptom management.
2. Identify appropriate indications for clinical uses of cannabinoids.
3. Apply evidence-based practices in the approach to managing pain or other symptoms for a patient requesting cannabinoids.
4. Describe the mechanism of action and dosing of the cannabinoid agents utilized in pain and symptom management.
5. Explain pharmacokinetics and pharmacodynamics of the various cannabinoids utilized for pain and symptom management.
6. Recognize common or serious drug interactions and adverse effects associated with medical use of cannabinoids.
7. Relate the use of medical marijuana to possible effects on the associated provider-healthcare professional relationship.
8. Explore the psychosocial and societal aspects of medical use of cannabinoids.
9. Differentiate between medical and non-medical uses of cannabinoids in patients with pain or other distressing symptoms.

**Self-Assessment Questions**

Self-assessment questions are available online at www.accp.com/am
Objectives

- Explain pharmacological principles for the use of cannabinoids for pain or symptom management
- Identify appropriate indications for clinical uses of cannabinoids
- Apply evidence-based practices in the approach to managing pain or other symptoms for a patient requesting cannabinoids

Poll Question

I live in a state where medical marijuana (MMJ) laws are enacted.

1. True
2. False

Poll Question

I believe the most common reason people seek out medical marijuana is to...

1. relieve pain
2. improve symptoms of nausea and vomiting
3. improve epilepsy
4. relieve muscle spasms associated with multiple sclerosis
5. get high

Overall goal for this presentation is...

...to help pharmacists better describe the characteristics of marijuana and its effects 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
- Phytocannabinoids
  - Cannabis sativa (Schedule I)

Cannabis

- Plant-derived cannabinoids*
  - Δ9-tetrahydrocannabinol - THC
  - Δ8-tetrahydrocannabinol - THC
  - Cannabidiol – CBD
  - Cannabigerol - CBG
  - Cannabichromene - CBC
  - Cannabicyclol
  - Cannabinol
  - Cannabitriol
  - Miscellaneous
  - Cannabinodiol (air-oxidation)

*Present in varying relative proportions depending on the strain

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)
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, 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)
- Exogenous cannabinoids stimulate CB1, CB2 and others

Cannabis Pharmacology

- Targets of Marijuana
  - CB1 Receptors
    - Basal ganglia: Motor activity
    - Cerebellum: Motor coordination
    - Hippocampus: Short-term memory
    - Neocortex: Thinking
    - Hypothalamus & limbic system: Appetite, sedation
    - Periaqueductal gray: Pain
  - CB2 Receptors
    - Immunologic cells
      - B lymphocytes
      - Natural killer cells
    - Brain: Role not established

Endocannabinoid System

- THC

Marijuana’s Effects on the Brain

- Basal ganglia
- Cerebellum
- Hippocampus
- Neocortex
- Hypothalamus & limbic system
- Periaqueductal gray

Non-Cannabinoid Targets Linked to Cannabis

- Other G-protein receptors: GPR55, GPR55940, etc.
- G-protein-coupled receptor: 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).

Potential Physiologic Responses to Cannabis

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

POLL QUESTION

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

1. Low blood pressure
2. Slowed reaction time
3. Decreased heart rate
4. Insomnia
5. All of the above
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

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

Therapeutic Effectiveness of MMJ

What Should Be Studied?

Muscle Spasms
Asthma
Appetite Loss
Sleep
PTSD
GERD
PAIN
ADHD
Anxiety
CANCER
Nausea
IBS
Seizures
Tourrette’s Syndrome
Vomiting

How Should MMJ Be Studied?

A. Blog
B. Case control study
C. Case report
D. Case series
E. Cohort study
F. Meta-analysis
G. My opinion
H. Randomized controlled trial
I. Review article

How Should MMJ Be Studied?

CO: current cardholders (n=115,210)
AZ: current cardholders (n=54,558)

MMJ Registrants in CO and AZ: Qualifying Conditions

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Pain and Palliative Care PRN—Clinical Controversies of Cannabinoids for Pain Management: Evidence and Political Implications for Pharmacists

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

<table>
<thead>
<tr>
<th>Cannabinoid</th>
<th>Overall result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoked cannabis (n=6)</td>
<td>All trials found positive effect by improving neuropathic pain vs placebo with no serious adverse effects.</td>
</tr>
<tr>
<td>Oromucosal extracts (n=7)</td>
<td>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).</td>
</tr>
<tr>
<td>Nabilone (n=4)</td>
<td>Three showed significant analgesic effect in spinal pain, fibromyalgia, and spasticity-related pain vs placebo. One showed similar effect in neuropathic pain vs dihydrocodeine.</td>
</tr>
<tr>
<td>Dronabinol (n=2)</td>
<td>Significant reduction in central pain (M1) vs placebo. Significantly greater analgesia vs placebo for mixed chronic pain on opioids.</td>
</tr>
<tr>
<td>THC-11-ox acid analogue - CT-3 or ajulemic acid (n=1)</td>
<td>Adequate led to significant improvement in neuropathic pain intensity at 3 hours, but no difference at 8 hours compared with placebo.</td>
</tr>
</tbody>
</table>

*Br J Clin Pharmacol 2011;72(5):735-44*

### 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>
</thead>
<tbody>
<tr>
<td>Intensity of pain</td>
<td>0.61 (0.34, 0.97)</td>
</tr>
<tr>
<td>Euphoria</td>
<td>4.11 (1.33, 12.72)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>2.56 (0.66, 9.93)</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>Dizziness</td>
<td>3.18 (0.89, 11.33)</td>
</tr>
<tr>
<td>Acute psychosis</td>
<td></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>
</tbody>
</table>

*Evidence-Based Med 2009; 33(11):1313-88*

### MMJ in Painful HIV-Associated Sensory Neuropathy: Systematic Review and Meta-Analysis

- Objective: evaluate clinical effectiveness of various analgesics
- Total of 14 trials evaluated
- Smoked cannabis 1-8% and capsaicin 8% found to be effective

<table>
<thead>
<tr>
<th>SMOKED CANNABIS</th>
<th>Number of episodes</th>
<th>230% improvement in VAS</th>
<th>250% improvement in VAS</th>
<th>RR (95% CI)</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>122</td>
<td>32/61</td>
<td>15/61</td>
<td>2.38 (1.38 to 4.10)</td>
<td>3.38 (2.19 to 7.50)</td>
</tr>
</tbody>
</table>

*NNT for capsaicin 8% = 8.46 (3.86-19.69)*


### Smoked Cannabis for Chronic Neuropathic Pain

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

<table>
<thead>
<tr>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain intensity</td>
</tr>
<tr>
<td>9.4% score = 5.4</td>
</tr>
<tr>
<td>0% score = 0</td>
</tr>
<tr>
<td>(p=0.06; difference 0.4, 95% CI 0.02-1.5)</td>
</tr>
<tr>
<td>Sleep (more drowsiness, getting to sleep more easily, faster, and with less wakefulness)</td>
</tr>
<tr>
<td>9.4% vs 0%: p&lt;0.06</td>
</tr>
<tr>
<td>Anxiety and depression improved (EQ5D)</td>
</tr>
<tr>
<td>9.4% vs 0%: p&lt;0.05</td>
</tr>
<tr>
<td>Adverse events</td>
</tr>
<tr>
<td>248 mild, 6 moderate (fall, pain, numbness, drowsiness, pneumonia)</td>
</tr>
</tbody>
</table>

*MMJ 2010;182:E694-701*

### High Concentration Cannabidiol in Highly Refractory Pediatric Epilepsies

- Charlotte’s Web (CW Realm Oil, Realm Oil)
- CBD at a ratio =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
  - 2 stiopathtic 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

<table>
<thead>
<tr>
<th># Patients</th>
<th>Seizure Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50%</td>
</tr>
<tr>
<td>1</td>
<td>66%</td>
</tr>
<tr>
<td>2</td>
<td>74%</td>
</tr>
<tr>
<td>3</td>
<td>82%</td>
</tr>
<tr>
<td>4</td>
<td>90%</td>
</tr>
<tr>
<td>5</td>
<td>96%</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>16/19 (84%) reported a reduction in child’s seizure frequency</td>
</tr>
<tr>
<td>2/19 (11%) ≥ complete seizure freedom</td>
</tr>
<tr>
<td>8/19 (42%) ≥80% reduction in seizure frequency</td>
</tr>
<tr>
<td>6/19 (32%) ≥ 50-60% reduction in seizure frequency</td>
</tr>
<tr>
<td>12/19 parents weaned their child from another AED</td>
</tr>
<tr>
<td>Other benefits: better mood (79%), increased alertness (74%), improved sleep (68%), decreased self-stimulation (32%)</td>
</tr>
<tr>
<td>Side effects: drowsiness (37%) and fatigue (10%)</td>
</tr>
</tbody>
</table>

*Epilepsy Behav. 2013;29(1):514-7*

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Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders

Neurology. 2014 Apr 29;82(17):1556-63

<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>Nabiximols</td>
<td>THC, OCE</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>THC, OCE, nabiximols</td>
<td></td>
<td></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."

Other Interesting Clinical Findings

- PTSD: cannabis used more frequently for sleep and coping
  - Drug and Alcohol Dependence. 2014;136:162–5
- IBD: improved pain and diarrheal symptoms
  - Inflamm Bowel Dis 2014;20:472–80
  - Inflamm Bowel Dis 2013;19:2809–14
- Pediatric treatment-resistant epilepsy: parents giving CBD-enriched cannabis shows decreased seizure frequency
  - Epilepsy Behav. 2013;29(3):574-7

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

What about our Patient?

Hash
Hash oil
Buds
Edibles
Tinctures
Chews
Sodas/Teas
Topicals

Recommendations for Pharmacists

1. Ask about the use of marijuana
2. Discuss potential benefits and adverse effects
3. Check for drug interactions
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 and/or hospital policies and procedures

Conclusions

- The endocannabinoid system, including CB1 and CB2 receptors, is the key target for exogenous cannabinoids.
- Psychoactive effects of marijuana related to THC, but other cannabinoids also involved with physiologic effects.
- 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.
- Patient-provider relationship is an critical component of approaching the management of pain with cannabinoids.

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Medical Use of Cannabinoids: Clinical Pearls

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PHARMACY CLINICAL COORDINATOR — PAIN AND PALLIATIVE CARE
UNIVERSITY OF VIRGINIA HEALTH-SYSTEM
AMERICAN COLLEGE OF CLINICAL PHARMACY
OCTOBER 2004

Objectives

- Describe the mechanism of action and dosing of cannabinoid agents utilized in pain and symptom management
- Explain pharmacokinetics and pharmacodynamics of the various cannabinoids utilized for pain and symptom management
- Recognized common or serious drug interactions and adverse effects associated with medical use of cannabinoids

THC: CBD

- Recreational marijuana vs "medical marijuana"
  - THC levels increased from 4.56% to 11.75% and CBD levels decreased from 0.24% to 0.08%
  - Genetic engineering
  - THC is responsible for the "high" of cannabis
    - Amnesia – lower doses reduce, higher doses increase – in most individuals
    - Common SEs – dizziness, unsteadiness, disorientation, inability to focus thoughts, confusion, mood changes, delusions, and hallucinations
    - Same issues with synthetic THC
  - Memory – STM, LTM?
  - Psychedelic, Addiction
- CBD attenuates the euphoric effects of THC
  - Research needs to focus on CBD for "medical marijuana" to have value

Disclosures

- Dr. Ray reports the following relevant financial relationships:
  - Speakers Bureau
    - Millennium Health
    - Cadence Pharmaceuticals
    - Pan Weekend
  - Consultant
    - Mallinckrodt Pharmaceuticals
  - Other
    - Personal consulting company – Alchemy Consulting, PC.

M.O.A. in Pain Relief

- Antinociceptive effects mediated through mechanisms distinct from those responsible for other behavioral effects
  - Endogenous & exogenous cannabinoids exert influence on the following:
    - Opioid, 5HT1, NMDA and α3 glycine receptors
    - Homeostatic pain modulation
    - Activation of central noradrenergic pathway & peripheral adrenoreceptors
    - CB receptors in DRG, spinal cord, microglia & brain
    - CB agonists trigger release of β endorphin
  - Differential effects
    - Sensory (intensity; quality)
    - Affective (unpleasantness; suffering)

Cannabinol

- Anxiolysis - ↑ 5-HT transmission
- Attenuates memory impairing effect of THC
- Inhibits THC-elevated paranoia
- Anti-emetic
- Reduces/blocks CINP (animal data)
- Antiproliferative effects
  - Cytotoxic to leukemia cells
  - Inhibits lung cell invasion
  - Induces apoptosis
  - Synergistic with chemotherapy

**References**

Cannabidiol Safety Profile

- Not associated with:
  - O Catatopy
  - O Changes in physiological parameters (HR, BP, Temperature)
  - O GI transit changes
  - O Psychomotor function
- Safe in:
  - O Schizophrenic and Parkinson’s patients

Medical marijuana in neurologic disorders

<table>
<thead>
<tr>
<th>Neurologic Condition</th>
<th>Cannabinoid type</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Sclerosis</td>
<td>Cannabis extract &amp; THC</td>
<td>OCS effective for spasticity symptoms &amp; pain reduction, nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td>Oromedoral Spray</td>
<td>OCS effective for improving spasticity symptoms, pain &amp; urinary frequency</td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td>Data inadequate regarding safety or efficacy for spasticity or pain relief</td>
</tr>
<tr>
<td>Huntington Disease</td>
<td>Nabilone</td>
<td>Ineffective for bradykines induced dystonia</td>
</tr>
<tr>
<td>Parkinson’s Disease</td>
<td>Cannabis</td>
<td>Data insufficient to support or refute efficacy for THC for tic severity</td>
</tr>
<tr>
<td>Tourette Syndrome</td>
<td>Cannabis</td>
<td>Data insufficient to support or refute efficacy for THC for tic severity</td>
</tr>
<tr>
<td>Cervical Dystonia</td>
<td>Cannabis</td>
<td>Data insufficient to support or refute efficacy for THC for tic severity</td>
</tr>
</tbody>
</table>

Cannabidiol and NP Pain

<table>
<thead>
<tr>
<th>NP Type</th>
<th># Subjects</th>
<th>Cannabinoid type</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>50</td>
<td>5-56% THC, smoked</td>
<td>5 days</td>
</tr>
<tr>
<td>Chronic NP</td>
<td>34</td>
<td>THC+CBD 1:1, SL</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Chronic NP</td>
<td>23</td>
<td>CT-3 (THC analog)</td>
<td>7 days</td>
</tr>
<tr>
<td>MS</td>
<td>630</td>
<td>THC extract – oral</td>
<td>15 wk with up to 52 wks</td>
</tr>
<tr>
<td>MS</td>
<td>24</td>
<td>Dronabinol</td>
<td>3 wk</td>
</tr>
<tr>
<td>MS</td>
<td>137</td>
<td>THC+CBD (Sativex)</td>
<td>10 wk with up to 52 wks</td>
</tr>
<tr>
<td>MS</td>
<td>66</td>
<td>Sativex</td>
<td>4 week</td>
</tr>
<tr>
<td>Chronic NP</td>
<td>24</td>
<td>THC+CBD</td>
<td>2 week</td>
</tr>
<tr>
<td>Essential phlebitis 48</td>
<td>Sativex vs THC vs P</td>
<td>Three 2 wk periods</td>
<td></td>
</tr>
<tr>
<td>Peripheral NP 125</td>
<td>Sativex</td>
<td>5 wk with up to 52 wks</td>
<td></td>
</tr>
</tbody>
</table>

Synthetic THC

- **Delta-9-tetrahydrocannabinol (THC)**
  - THC 1.0mg/kilogram
  - Usually male
  - THC and CBD appear in the plasma within 30 minutes after single oral administration.

Nabiximols (Sativex™)

- **Delta-9-tetrahydrocannabinol 2.7mg and cannabidiol (CBD) 2.5mg/100 microlitre**
  - THC and CBD appear in the plasma within 30 minutes after single oral administration.
  - Cmax of about 60min, 45-120 minutes after a single dose administration of a 5.25mg THC dose.
  - With food the mean Cmax and AUC for THC were 1.6- and 2.8-fold higher compared with fasting conditions.

PK parameters for Sativex, vaporized THC extract and smoked cannabis

- **Drug Interactions**
  - O Inhibition of the CYP2C19 inhibitor ketocapno produces an increase in Cmax and AUC of THC (1.2- and 1.8-fold, respectively), its primary metabolite and CBD (1.8- and 2.2-fold, respectively).
  - O Concomitant treatment with the CYP2C19 inhibitor ketoconazole can be used to reduce the effects of THC, CBD, and their metabolites.
  - O Rifampicin can reduce the effectiveness of THC and AUC of THC (40% and 20% reduction, respectively), its primary metabolite (50% and 35% reduction, respectively) & CBD (50% and 60% reduction, respectively).
  - O Concomitant with photosensitization should be recommended, usually within the two weeks following use of the inhibitor.

- **Pharmacodynamic Interactions**
  - O Sedatives, anti-spasticity agents, DOH
### Sativex

**Clinical Efficacy**
- MS Spasticity
- Neuropathic pain
- Cancer pain

**Adverse Effects**
- No evidence of withdrawal or habituation
- Dizziness, diarrhea, fatigue, nausea – (mild-moderate)
- Low abuse potential

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### Oral edibles have high first pass, 11-hydroxy-THC

- More psychotropic and long lasting
- Many products almost pure THC
- Many doses of THC contained within one product


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### Palmitoylethanolamide (PEA)

- Congener of the endocannabinoid anadamide
- Inhibits release of pro-inflammatory mediators
- Inhibits microglia activation
- Dietary food, nutraceutical
- (Normast®, PeaPure®)
- Most research done in Europe
  - Chronic pelvic pain
  - Neuropathic pain

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### Conclusions

- Commercially available cannabinoids have poor efficacy and tolerability for treating pain
- Nabiximols appear promising – studies just getting underway
- Medical marijuana based on current science appears to have little value for pain, especially with high concentration of THC
- Palmitoylethanolamide deserves further investigation in well designed RTC for prevention and as an adjunct for pain management

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My doctor gave me marijuana… what’s the big deal?

Jennifer M. Strickland, PharmD, BCPS
October 13, 2014

Learning Objectives

1. Relate the use of medical marijuana to possible effects on the associated provider-healthcare professional relationship.
2. Explore the psychosocial and societal aspects of medical use of cannabinoids.
3. Differentiate between medical and non-medical uses of cannabinoids in patients with pain or other distressing symptoms.

Why Do People Use Marijuana?

Among people who used marijuana in the past year:

23% For Fun
47% For Medical Reasons
30% For Fun and for Medical Reasons

Cannabis / Marijuana

Complex alkaloid mixture
- more than 400 compounds derived from the Cannabis sativa plant
- Up to 80 cannabinoids (Radwan 2009)

Most abundant and active:
- Delta-9 tetrahydrocannabinol (THC- most psychoactive)
- Cannabidiol
- Cannabinol
- Cannabichromene CBC (second most abundant)

Marijuana

Dry, shredded mix of leaves, flowers, stems, and seeds, usually from Cannabis sativa or Cannabis indica plant

Hundreds of variants of plants
- North American plant bred to exhibit high concentrations of THC
- Common names: grass, weed, pot, reefer, Mary Jane, ganja
- Smoked, inhaled, ingested

Conflict of Interests

- None relevant
Available “Preparations”

- Dried flowering tops/leaves of plant
  - THC concentration 0.5-5% in past, now 20-25%
- Hashish
  - Dried cannabis resin and flowers
  - THC concentration 2-8% or higher
- Hash Oil (“Wax”)
  - Extraction of THC from hashish with an organic solvent
  - THC concentration 15-50%
- Synthetic Marijuana (“Spice”, “K2”)


Delivery Systems

- Variable delivery systems
  - Joints
    - ~500 mg of marijuana inside of rolled papers
    - 0.5-1 gram cannabis typically
    - THC concentration: 5-150 mg (only need 2-3 mg for effect)
    - 20-70% of THC delivered in smoke
  - Blunts
    - 20% THC absorption
  - Pipes
    - 50% absorption
  - Water pipes
    - 90% absorption (“Bongs”)
  - Ingestion

Delivery System: Smoked

- No rate control for dosing or potency
- No standardization
  - Variable strains
- Unpredictable
- Absorption dependent on
  - Technique
  - Delivery method
  - Time to exhale

“It’s not your father’s ‘pot’ anymore”

- Increased potency over time
- 1960s-70s average THC concentrations: 1-2%
- Today: Concentrations up to 20%

Medical Marijuana vs. THC Medications

- Medical Marijuana is not FDA approved
  - FDA approval assures that medications are effective, safe, and properly labeled
  - FDA cannot evaluate medical marijuana as a drug since it is a plant, not a standardized medical formulation
  - Medical marijuana is different everywhere, depending on how it is bred, under what conditions it is grown, etc.
  - No way to know if medical marijuana is pure. Can be contaminated by pesticides, mold, fungus.

SOURCES: Kleber, 2012; TRI, 2012 (reference list).

“Medical” marijuana

- Not homogenous material
  - Varies widely based on strain, cultivation, storage, harvesting and other factors (similar to opium)
  - Various methods of delivery (smoked, vaporized, teas, etc) – no standardized or reproducible way of ensuring a specific reproducible dose
  - No quality control mechanisms (no recalls)
    - Microbe contamination
      - Aflatoxins not destroyed by heat or smoking – may lead to aspergillosis
    - Heavy metal or pesticide contamination
  - Los Angeles dispensary: pesticide levels 170 times permitted for herbal products
  - Unmonitored supply chain, no labeling, advice given by unlicensed and untrained personnel in dispensaries

SOURCES: Kleber, 2012; TRI, 2012 (reference list).
Efficacy

- Numerous claims
  - Pain, including neuropathic pain
  - Nausea/vomiting
  - Cachexia/anorexia
  - MS
  - ALS
  - Glaucoma
  - Alzheimer’s
- Few randomized trials
- Mostly small studies, case reports

State Laws

- Laws legalizing marijuana in some form exist in 23 states and the District of Columbia


Financial Impact

- $9 billion dollars spent annually on fight against marijuana
  - 33,000 state inmates, 10,000 federal inmates due to marijuana use / distribution
  - Estimated cost ~$1 billion / annually

Physician – patient relationship

- May negatively impact patient – physician relationship
  - May be due to inherent conflicts of interest within the healthcare system
  - Patient demands for medical marijuana
  - Patient reliance on single “magic bullet”
  - May be used as replacement for prescription medications by patient
    - Over 50% may be utilizing medical marijuana rather than proven prescription medication
    - ~13% appear to be using to replace alcohol

Physician – Patient Relationship

- Public acceptance rather than clinical data has driven approval of medical marijuana
  - Colorado:
    - 46% believe physicians should NOT recommend medical marijuana
    - 60% believe drug’s risks outweigh benefits
- Federal status may discourage patients from self-reporting
- Risks of drug interactions
- Possible limitations to treatment (e.g., organ transplant)
- Perception of “aiding and abetting” drug use

Marijuana use and Opioid Use

- 25% fewer opioid-related deaths in states allowing medical marijuana
  - 24.8% lower annual opioid overdose mortality rate
  - Relationship stronger over time
    - 20% lower in first year after medical marijuana law enacted
    - 33.7% lower five years after implementation

**Physician-Patient Relationship**

*State Requirements*

- Varies due to state requirements
  - Minnesota – requires physicians who choose to participate to certify the patient has one of 9 eligible conditions, counsel patients appropriately, provide information about outcomes to registry
- Often places clinicians in difficult position
  - White papers and statements suggesting that providers should not advocate for a therapy with limited evidence

**Medical Associations**

- Conflicting positions regarding MM
  - VA – against
  - American Academy of Physicians – against except under medical supervision and for specific indications
  - American College of Physicians – support prescription cannabinoids over MM
- Many Medical Associations have called for further studies of medical marijuana
  - Many are not supportive of legislation that involves physicians certifying, authorizing, or otherwise directing patients in the area of medical marijuana outside of clinical trials (e.g., Minnesota)

**Organizational Viewpoints**

- American Medical Association
- Institute of Medicine
  - Called for further research
- American Society of Addiction Medicine (ASAM)
  - White Paper
    - "All cannabis based therapy should be subjected to the rigorous scrutiny of the FDA regulatory process"
    - "Lacks quality control and standardization"
    - "Physicians should carefully consider their ethical and professional responsibilities... should not advise a patient to seek treatment... about which the physician has inadequate knowledge regarding the composition, dose, side effects or appropriate therapeutic targets..."

**Pharmacist-Patient Relationship**

- Some states have suggested pharmacists should be responsible for dispensing medical marijuana
- Due to federal laws, pharmacists should be careful in recommending specific use, sources of medical marijuana or obtaining the drug for patient’s use.
- ASHP Policy
  - Calls for making “cannabis available as a legal medicine where shown to be safe and effective and to immediately allow access to therapeutic cannabis through investigational new drug program.”

**Gaming the System?**

- 2011 survey of medical cannabis users
  - Critics have suggested that some users “game the system” to obtain medical cannabis “legitimately” for treatment of a condition, but then use it for nonmedical purposes

**Health Impact of Marijuana Use**

- Carcinogenic
  - Possibly more carcinogenic than tobacco smoke
    - due to carcinogenic hydrocarbons
    - Inhaled more deeply and held longer
  - Maertens et al 2009 found marijuana smoke caused more DNA and cellular damage than tobacco smoke
- Respiratory illness
  - One marijuana cigarette = pulmonary problems from 4-10 tobacco cigarettes
  - Increased risk for various pulmonary diseases (bronchitis, emphysema, lung cancer)


Maertens et al. The Genotoxicity of Mainstream and Sidestream Marijuana and Tobacco Smoke Condensates. Chemical Research in Toxicology, Online July 17, 2009
Health Impact (continued)

Cardiovascular illness
- Increases blood pressure & heart rate 20-100%  
- Up to 4.8 times risk of heart attack in hour after use

Cerebrovascular risks
- Frequent use associated with reduced blood flow to posterior cerebellum
  - Impacts memory, attention, overall cognition
  - 50% reduction in information processing speed in MS patients
  - Association with depression and anxiety

Psychosocial and Cognitive Impact

Frequent use associated with altered memory-related brain function
- Decreased blood flow in prefrontal cortex

Neuropsychological decline
- Across numerous domains of functioning
- Increased cognitive difficulty over time
- Discontinuation of cannabis did not fully reverse neuropsychological dysfunction in adolescent-onset cannabis users

Depression / Anxiety

Significant increase in Depression/Anxiety in frequent users
- N=1600
- 7 years
- Frequent users (every day)
  - 5 times more likely to suffer from depression and anxiety compared to non-users
  - Less frequent use (at least once per week)
  - 2X as likely to develop depression than non-users
- Increased risk of schizophrenic symptoms
  - Correlated with early onset prior to age 15

Social Impact: Colorado

Traffic fatalities testing positive for marijuana (2007 – 2012)
- 100%

Marijuana-related emergency room visits (2011-2013)
- 57%

- 268%

Potency of THC (1995-2013)
- ~4%

Other Botanicals

Required FDA approval
- Digitalis purpurea – fox glove - CHF
- Papaver somniferum – opium poppy
- Atropa belladonna – nightshade - IBS
- Ephedra sinica – ephedrine - hypotension
- Salix alba – willow tree - ASA
- Taxis brevifolia – Pacific Yew tree - breast cancer

Summary

- Growing use of medical marijuana
- Potential for significant impact on physician-patient or pharmacist-patient relationship
  - Conflicts of interest
  - State or professional organization point of view
  - Federal laws
- Significant medical, psychosocial, and social impact to patients and communities