HASHing It Out:
Medical Uses for Cannabis

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Associate Dean and Professor
Strauss Lecture Series
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The Story...
Disclosures

Dr. Borgelt has no relevant financial disclosures.
Dr. Borgelt will be discussing unapproved drugs and uses.
Dr. Borgelt has served as a member of six working groups:

- Colorado Department of Public Health and Environment (CDPHE): 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
- CDPHE Retail Marijuana Public Health Advisory Committee
- CDPHE Pregnancy and Breastfeeding Guidelines Committee
Objectives

- Describe the pharmacology of cannabis.
- Evaluate and discuss clinical studies using medical cannabis that have been performed in patients with neuropathic pain.
- Compare and contrast clinical studies that have evaluated medical cannabis use in patients with pediatric epilepsy and other neurologic disorders.
- Review clinical studies that have evaluated medical cannabis use in patients with gastrointestinal disorders.
Audience Question

I know someone who consumes marijuana for medical or recreational purposes.

1. Yes, medical purposes only
2. No, recreational purposes only
3. Yes, both
4. No
I believe the most common reason people seek out marijuana is to...

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

- Plant-derived cannabinoids
  - $\Delta^9$-tetrahydrocannabinol - THC
  - $\Delta^8$-tetrahydrocannabinol - THC
  - Cannabidiol – CBD
  - Cannabinol - CBN
  - Cannabigerol - CBG
  - Cannabichromene - CBC
  - Cannabicyclol - CBL
  - Cannabielsoin - CBE
  - Cannabitriol - CBT
  - Miscellaneous
  - Cannabinodiol (air-oxidation)

- Terpenes
- Flavinoids
- And much more…
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 😊
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)

## Functional Effects of Anandamide at CB1 & CB2 Receptors

<table>
<thead>
<tr>
<th>Structure</th>
<th>Anandamide regulates</th>
<th>Resultant effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord</td>
<td>Inhibit GLU &amp; info transfer between body &amp; brain</td>
<td>Decreased pain sensitivity</td>
</tr>
<tr>
<td>Parasympathetic</td>
<td>Inhibit Ach release, HR regulation, urination regulation</td>
<td>HR stimulation, sometimes inhibits urination</td>
</tr>
<tr>
<td>system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sympathetic system</td>
<td>Inhibit NE release, HR regulation, blood vessel constriction</td>
<td>Delayed reduction in HR and blood pressure</td>
</tr>
<tr>
<td>Neuronal cells</td>
<td>Inhibition GLU-induced excitotoxicity</td>
<td>Neuroprotective effect to prevent cell injury</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>Stimulates lipogenesis</td>
<td>Increased adiposity, insulin resistance</td>
</tr>
<tr>
<td>Reproductive tissue</td>
<td>Reduces testosterone, luteinizing hormone</td>
<td>Reduced fertility, altered menstrual cycle</td>
</tr>
<tr>
<td>Skin</td>
<td>Reduces histamine</td>
<td>Anti-pruritic effect</td>
</tr>
<tr>
<td>General</td>
<td>Role in relaxing, eating, sleeping, forgetting protecting</td>
<td>Provide relief from stress, reduction of injury</td>
</tr>
<tr>
<td>General</td>
<td>Inhibits immune B lymphocytes, natural killer cells</td>
<td>Anti-inflammatory activity</td>
</tr>
</tbody>
</table>

http://headsup.scholastic.com/students/more-facts-about-how-drug-abuse-puts-your-whole-body-at-risk
What happens when there is potential endocannabinoid deficiency, dysregulation, destabilization, or decreased binding?

Endocannabinoid System

Endogenous Cannabinoid System
Interfacing with Exogenous Cannabis
Cannabis Pharmacology

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

Another Kid on the Block…Cannabidiol (CBD)

Cannabidiol

- Little binding affinity to CB1/CB2
- Suppresses enzyme fatty acid amide hydroxylase (“FAAH”) – enzyme that breaks down anandamide

Opportunities

- Opposes THC at CB1 receptor
- Stimulates release of 2-AG
- TRPV-1 receptor agonist
- 5-HT1A receptor activation
- GPR55 antagonist

## Cannabis Activity at CB1 Receptors

<table>
<thead>
<tr>
<th>Structure</th>
<th>THC effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neocortex</td>
<td>Altered thinking, judgement</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>Slowed reaction time</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>↑ appetite</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Panic, paranoia</td>
</tr>
<tr>
<td>Nucleus accumbens</td>
<td>Euphoria</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Impaired memory</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Impaired coordination</td>
</tr>
<tr>
<td>Brain stem</td>
<td>Anti-nausea effects</td>
</tr>
<tr>
<td>Hippocampus, forebrain</td>
<td>Anti-epileptic effects ?</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Altered pain sensitivity</td>
</tr>
</tbody>
</table>

**Notes:**
- 1985: Anti-nausea effects
- 1992: ↑ appetite
- 1996: Altered pain sensitivity
3 Routes of Administration

**LUNGS**
- Vaporized or Smoked
  - Onset: sec-min
  - Duration: 2-3 hrs

**GUT**
- Oral Ingestion
  - Onset: 0.5-2+ hrs
  - Duration: 5-8 hrs

**SKIN**
- Topical Application
  - Onset: 15-40 min
  - Duration: 0.75-2 hrs
Considerations for medical use of marijuana are different than considerations for recreational use of marijuana.

Medical use: benefit – risk

Recreational use: risk - risk
Summary: Endocannabinoid System and THC
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Patient Experience with MMJ

- VIDEO: Teri Robnett

https://www.youtube.com/watch?v=eyw1utFTaug
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 HIGHEST” level of evidence

“How LOWEST” level of evidence
# Cannabinoids for Medical Use: Systematic Review and Meta-Analysis

<table>
<thead>
<tr>
<th>CONDITION</th>
<th># TRIALS*</th>
<th>Result vs. placebo</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting due to chemotherapy</td>
<td>3</td>
<td>Complete response</td>
<td>Low-quality evidence suggesting improvements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR 3.82 (95% CI 1.55-9.42)</td>
<td>47% vs 20%</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>8</td>
<td>Reduction of 30% or more in pain</td>
<td>Moderate-quality evidence to support use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR 1.41 (95% CI 0.99-2.00)</td>
<td>37% vs 31%</td>
</tr>
<tr>
<td>Spasticity related to MS or paraplegia</td>
<td>8</td>
<td>Ashworth spasticity scale</td>
<td>Moderate-quality evidence to support use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WMD** -0.12 (95% CI -0.24 to 0.01)</td>
<td></td>
</tr>
</tbody>
</table>

*Variety of cannabinoid products evaluated

**WMD: weighted mean difference

**Common AEs of cannabinoids included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

Inhaled Cannabis for Neuropathic Pain: Meta-Analysis of Individual Data

- Synthesizes the individual participants' original data obtained from the studies' principal investigators
- Five randomized controlled trials evaluating inhaled cannabis
- Compared proportion of patients experiencing >30% clinical improvement in chronic neuropathic pain assessed with a continuous patient-reported instrument (e.g., visual analog scale) at baseline and after inhaled cannabis

**RESULTS**

- 178 patients with 405 observed responses
- Estimated OR (CRI) for >30% ↓ in pain score: 3.22 (1.59-7.24)
- Number needed to treat (CRI): 5.55 (3.35-13.7)

Note: gabapentin NNT 5.9 (4.6-8.3) for diabetic neuropathy
Adverse Effects

- **Serious Adverse Effects (SAEs)**
  - Placebo: 1 (psychosis)
  - Cannabis: 2 (hypertension, increased pain)

- **Mild adverse effects**
  - Anxiety, disorientation, difficulty concentrating, headache, dry eyes, burning sensation, dizziness, and numbness
  - Psychoactive effects (such as feeling “high”) were statistically significantly associated with treatment allocation in 2 studies and increased in frequency with increasing dose
Limitations and Conclusions

- Ineffective participant blinding
- Placebo effects likely
- Different causes of neuropathy
- Small number of studies and participants
- Difficult to estimate bioavailable cannabis
- Short-term data only (up to two weeks)

Inhaled cannabis results in short-term reductions in chronic neuropathic pain for 1 in every 5 to 6 patients treated.

Objective: evaluate analgesic efficacy in patients with neuropathic pain despite traditional treatments

Visual analog scale (0-100)

39 patients with previous cannabis exposure
  » 28 male/11 female
  » Avg age 50 years

Vaporized cannabis
  » Medium-dose (3.53%)
  » Low-dose (1.29%)
  » Placebo

### INHALED CANNABIS

<table>
<thead>
<tr>
<th>Number of episodes</th>
<th>111</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30% ↓ in VAS</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>10/38 [26% (15-42%)]</td>
</tr>
<tr>
<td>Low-dose</td>
<td>21/37 [57% (41-71%)]</td>
</tr>
<tr>
<td>Med-dose</td>
<td>22/36 [61% 45-75%])</td>
</tr>
</tbody>
</table>

Statistical significance
P vs Low: p=0.0069
P vs Med: p=0.0023
Low vs Med: p=0.7

NNT: Low 3.2
NNT: Med 2.9

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)
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>SMOKE CANNABIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of episodes</td>
</tr>
<tr>
<td>≥30% improvement in VAS</td>
</tr>
<tr>
<td>≥50% improvement in VAS</td>
</tr>
<tr>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>NNT (95% CI)</td>
</tr>
</tbody>
</table>

*NNT for capsaicin 8% = 6.46 (3.86-19.69)*
Medical Cannabis and Opioid Use
States with medical cannabis laws had a 24.8% lower mean annual opioid overdose mortality rate (95% CI, −37.5% to −9.5%; P = .003) compared with states without medical cannabis laws.

This association strengthened over time

- Year 1 (−19.9%; 95% CI, −30.6% to −7.7%; P = .002)
- Year 2 (−25.2%; 95% CI, −40.6% to −5.9%; P = .01)
- Year 3 (−23.6%; 95% CI, −41.1% to −1.0%; P = .04)
- Year 4 (−20.2%; 95% CI, −33.6% to −4.0%; P = .02)
- Year 5 (−33.7%; 95% CI, −50.9% to −10.4%; P = .008)
- Year 6 (−33.3%; 95% CI, −44.7% to −19.6%; P < .001)
Medical Cannabis and Opioid Use

- 244 medical cannabis patients with chronic pain in Michigan
- Survey of 46 questions
  - Medical condition(s) for which cannabis was used
  - Method/frequency of cannabis use
  - Changes in noncannabis medication use
  - Changes in medication side effects
  - Quality of life changes since starting cannabis use
  - Demographic information
  - 2011 Fibromyalgia Survey Criteria (0-31 score)
<table>
<thead>
<tr>
<th>Outcome of Interest</th>
<th>Patient Responses (n=244) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibromyalgia score (0-31)</td>
<td>9.23 (5.52)</td>
</tr>
<tr>
<td>Opioid use change</td>
<td>-63% (46%)</td>
</tr>
<tr>
<td>Degree to which side effects of medication affect daily function (before using medical cannabis); scale from 1 to 10</td>
<td>6.44 (2.91)</td>
</tr>
<tr>
<td>Degree to which side effects of medication affect daily function (after using medical cannabis); scale from 1 to 10</td>
<td>2.77 (2.35)</td>
</tr>
<tr>
<td>Number of medication classes used (before cannabis use)</td>
<td>2.35 (1.43)</td>
</tr>
<tr>
<td>Number of medication classes used (after cannabis use)</td>
<td>1.82 (.94)</td>
</tr>
<tr>
<td>Quality of life change</td>
<td>45% (28%)</td>
</tr>
</tbody>
</table>

Summary

Cannabis may have a role in chronic pain, especially neuropathic pain when patients have failed other treatments. Mortality from and use of opioids appears to decrease with cannabis use. Adverse effects do occur so benefits and risks should be weighed for individual patients while considering patient safety and public health concerns.
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Pediatric Epilepsy: AES Annual Meeting 2015

- 261 children (average age 11 years)
- Severe epilepsy not responding to other treatments
- Epidiolex given in increasing doses with other AEDs (avg=3)
- After 3 months of treatment
  - 45% lower frequency of seizures
  - 47% experienced ≥50% reduction in seizures
  - 9% seizure-free
  - Dravet syndrome patients: 62% reduction in seizures, 13% seizure free
  - Lennox-Gastaut patients: 71% reduction in atonic seizures
- Adverse effects (>10%)
  - Sleepiness, diarrhea, fatigue (4% discontinued treatment)
- Serious adverse effects: 5% treatment-related
  - Altered liver enzymes, status epilepticus, diarrhea and others
- Lack of efficacy caused 12% withdrawal

Pediatric Epilepsy: Israeli Experience

- Retrospective review of 74 patients (1-18 years) with intractable epilepsy using CBD-enriched medical cannabis
- Resistant to >7 antiepileptic drugs
- Treated with CBD-enriched product for at least 3 months
  - CBD:THC – 20:1
  - CBD dose ranged from 1-20 mg/kg/day
- Seizure frequency assessed by parental report

Results (n=74 patients)

Seizure Reduction with Cannabis Use

Adverse Effects

- Reported in 34/74 patients
  - Seizure aggravation: 13 (18%)
  - Somnolence/fatigue: 16 (22%)
  - Gastrointestinal problems and irritability: 5 (7%)

Note: side effects led to withdrawal in 5 patients
Limitations and Conclusions

- Lack of a control group
- No consistent rate of dosage elevation
- Reliance upon parental report on seizure frequency
- Short duration of the study
- Lack of long-term outcome
- No EEG results and no measurement of other drug levels

Results of this multicenter study on CBD treatment for intractable epilepsy in a population of children and adolescents are highly promising.
**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.”
Indications for Whole Plant Extracts

Nabiximols (Sativex®)
- Spasticity (muscle stiffness/spasm) due to MS
- Neuropathic pain in MS
- Adjunctive analgesic treatment in patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain

Cannabidiol (Epidiolex®)
- Pediatric epilepsy
  - Lennox-Gastaut Syndrome
  - Dravet Syndrome
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Irritable Bowel Syndrome & Crohn’s Disease

- 313 patients with irritable bowel disease surveyed at University of Calgary
- Comparison of patients that used cannabis and those that did not

- 17.6% of respondents used cannabis to relieve IBD symptoms
- Most chose inhalation route of administration (96.4%)
- Improved symptoms of IBD (next slide)
- Cannabis use >6 months at any time for IBD symptoms was a strong predictor of requiring surgery in patients with Crohn's disease (OR = 5.03, 95% CI = 1.45–17.46)
Symptom Improvement in IBD Patients

Symptom improvement (%)

- Abdominal pain: 83.9%
- Abdominal cramping: 76.8%
- Joint pain: 48.2%
- Diarrhea: 28.6%

Other IBD Studies

- Prospective cohort survey study of 292 patients
  - Among current and past users (51.3%), 16.4% of patients used marijuana for disease symptoms
  - Majority felt marijuana was "very helpful" for relief of abdominal pain, nausea, and diarrhea

- Observational study of 30 patients with Crohn's disease (CD),
  - Medical cannabis associated with improvement in disease activity
  - Reduction in the use of other medications

- Placebo-controlled study in 21 chronic CD patients
  - Decrease in CD activity index >100 in 10 of 11 subjects on cannabis compared to 4 of 10 on placebo
  - Complete remission was achieved in 5 of 11 subjects on cannabis group and 1 of 10 on placebo

- Observational study (number of participants not provided)
  - Low-dose cannabidiol did not have an effect on CD activity.
Other Interesting Clinical Findings

- **Migraine**
  - Pharmacotherapy. 2016;36(5):505-10

- **Pediatric treatment-resistant epilepsy: parental reports**
  - Epilepsy Behav 2015;47:138-41
  - Epilepsy Behav 2015;45:49-52
  - Epilepsy Behav 2013;29:574-7

- **PTSD: cannabis used more frequently for sleep and coping**
  - Drug and Alcohol Dependence 2014;136:162–5
  - J Psychoactive Drugs 2014;46:73-7

- **Alzheimer’s Disease**

- **Bladder Cancer**
  - Urology. 2015 Feb;85(2):388-92
Summary

Cannabis may have a role in a variety of conditions when patients have failed other FDA-approved treatments. Adverse effects do occur so benefits and risks should be weighed for individual patients while considering patient safety and public health concerns.
Marijuana adverse effects:
- Cardiovascular:
  - Tachycardia
  - Palpitations
  - Hypertension

- Respiratory:
  - Coughing
  - Wheezing
  - Sputum production

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

EUPHORIA
Conclusions

- Marijuana and its active components impact the endocannabinoid system to provide various effects.
- Many dosage formulations of marijuana available to patients.
- Clinical studies performed in children and adults demonstrate some effectiveness for certain conditions including neuropathic pain, epilepsy, and gastrointestinal conditions.
- Adverse effects are reported in all studies so benefits and risks must be carefully weighed.
QUESTIONS?
Laura.Borgelt@ucdenver.edu