Pharmacognosy at its Finest: Marijuana Strains, Pains, and Potential Gains

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Science in Action: October 2013

Disclosures

Drs. Wempe and Borgelt report no relevant financial relationships.

Drs. Wempe and Borgelt will be discussing unapproved drugs and unapproved uses for drugs.

Dr. Wempe is conducting research involving stability of THC and will be working on a working group through the State Licensing Authority for Mandatory Testing and Random Sampling (November 2013)

Dr. Borgelt has served as a member of two 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 stakeholder working group

And will be serving on a third working group (November 2013):
- State Licensing Authority Mandatory Testing and Random Sampling Working Group
Objectives

- Describe the biosynthesis of marijuana and its active components.
- Compare and contrast various analytical techniques for testing marijuana.
- Explain the pharmacology of various marijuana dosage formulations.
- Identify potential drug interactions that may occur with the use of marijuana.
- Evaluate the therapeutic effectiveness of marijuana.

Marijuana

- Single molecule pharmaceuticals
  - Dronabinol (Schedule III)
  - Nabilone (Schedule II)
- Liquid extract: nabiximols (Sativex®)
  - Approved in 8 countries; U.S. - Phase III trials
- 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
  - Cannabichromene
  - Cannabicyclol
  - Cannabielsoin
  - Cannabitriol
  - Miscellaneous
  - Cannabinodiol (air-oxidation)

Different strains of Cannabis have different and unique smells and are believed to work with or against the cannabinoids (i.e. THC, CBD, CBGA) to afford unique physiological effects.

Many of these cannabis aromatic smells come from small molecules known as terpenes (terpenoids) …. A better understanding of terpene composition and their interactions with the endo-cannabinoid system may help to explain why certain strains make one feel “up and alert” versus “groggy and sedated”. 
Various Cannabis strains have been shown to have as many as > 120 different terpenes (terpenoids)
n-hexanoyl-CoA → Malonyl-CoA → C12 Polyketide → Geranyl Pyrophosphate → Olivetolic acid → Cannabigerol Acid (CBGA)
Compare and contrast various analytical techniques for testing marijuana.

1) Testing marijuana plant material
2) Testing biological samples

<table>
<thead>
<tr>
<th>Non-destructive</th>
<th>Destructive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin Layer Chromatography</td>
<td></td>
</tr>
<tr>
<td>HPLC / UV-VIS (High-Performance liquid chromatography)</td>
<td>HPLC/MS-MS</td>
</tr>
<tr>
<td>GC (Gas Chromatography)</td>
<td>LC/MS-MS</td>
</tr>
<tr>
<td>NMR (Nuclear Magnetic resonance spectroscopy)</td>
<td>GC/MS</td>
</tr>
<tr>
<td>IR (Infrared Spectrometry)</td>
<td></td>
</tr>
</tbody>
</table>

Qualitative

TLC of Inks #1 to #3

![TLC Image](image_url)
Quantitative


LC/MS-MS

An illustration of Coulomb fission of the charged droplets and ion formation in ESI source

The tip of ESI needle (capillary)

Duration Coulomb fission solution instable

To MS

RF-only multiple

Ionen CID capillary

To the atmosphere

Turbo Pump

Rough Pump
THC - MAJOR IN VIVO METABOLISM

SELECTION OF RESEARCH ARTICLES

Forensic Science International 1986, 32, 259-266
Bioorg. & Med. Chem. 1995, 3 (7), 899-906
Forensic Science International 2000, 113, 381-387
Forensic Science International 2001, 123, 159-164
Forensic Science International 2002, 128, 66-78
J. Chromatography B 2002, 772, 239-248
J. Chromatography B 2003, 798, 145-154
J. Pharmaceutical and Biomedical Analysis 2005, 38, 112-118
Forensic Science International 2005, 149, 3-10
Forensic Science International 2007, 170, 148-155
J. Chromatography B 2008, 875, 465-470
J. Chromatography B 2009, 877, 4115-4124
Clinical Biochemistry 2012, 45, 605-609
Forensic Science International 2012, 223, 266-272
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)

Cannabis Pharmacology

http://www.tokeofthetown.com/2011/03/worth_repeating_bodys_own_cannabinoids_are_the bli.php

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

Marijuana Formulations

- Typically 3 routes of administration
  - Lungs
    - Vaporized or smoked
    - Organic material, hash, hash oil
  - Gut
    - Oral ingestion (edibles, drinks)
    - Lipophilic, alcoholic, supercritical fluidic extracts of plant material
  - Skin
    - Topical application of plant extracts (e.g., creams)
    - Buccal absorption of plant extracts (tinctures)

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 Considerations

- Variations in strain and phenotype of cannabis
  - Wide variation in THC or CBD dose needed to produce effects
  - Patient dependent
- Route of administration
  - Pharmacokinetics
  - Differing concentrations and ratios of cannabinoids based on route (e.g., potency, vaporized vs. smoked)
- Many different debilitating or terminal conditions
- Amount of marijuana needed
  - Review of 165 studies attempted to normalize THC dose
    - Low <7 mg; medium 7-18 mg; high >18 mg
  - Estimated 3–5 times greater quantity of marijuana required for oral products (assuming equal efficiency and loss in both processes)

References:
- Pharmacotherapy 2013;33:195-209
- Brit J Clin Pharm 2009;67(1):5-21
Dosing of Marijuana

“So...you leave a Saturday open...”

Key Point

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

Questions about how to best determine the most effective and tolerable dose and how to best involve health care providers into shared decision making with patients are not yet answered.

Therapeutic Effectiveness of MMJ

What Should Be Studied?

- Muscle Spasms
- Asthma
- Appetite Loss
- Sleep
- PAIN
- Anxiety
- CANCER
- PTSD
- GERD
- ADHD
- Nausea
- IBS
- Seizures
- Vomiting
- Tourette’s Syndrome
What is the Most Common Reason for MMJ Use in the U.S.?

1. Cancer
2. Glaucoma
3. Muscle spasms
4. Nausea
5. Pain

MMJ Registrants in CO and AZ: Qualifying Conditions

CO: current cardholders (n=106,817)  AZ: current cardholders (n=37,343)

Severe pain
Muscle spasms
Severe nausea
Cachexia
Cancer
Glaucoma
HIV/AIDS
Seizures

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

“HIGHEST” level of evidence

“LOWEST” level of evidence

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=4)</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 (MS) vs placebo. Significantly greater analgesia vs placebo for mixed chronic pain on opioids.</td>
</tr>
<tr>
<td>THC-11-oic acid analogue - CT-3 or ajulemic acid (n=1)</td>
<td>Ajulemic acid 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
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></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of episodes</td>
<td>122</td>
</tr>
<tr>
<td>≥30% improvement in VAS</td>
<td>31/61</td>
</tr>
<tr>
<td>≥50% improvement in VAS</td>
<td>15/61</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>2.38 (1.38 to 4.10)</td>
</tr>
<tr>
<td>NNT (95% CI)</td>
<td>3.38 (2.19 to 7.50)</td>
</tr>
</tbody>
</table>

*NNT for capsaicin 8% = 6.46 (3.86-19.69)

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 (-0.84, -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>
</tbody>
</table>
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)

Smoked Cannabis for Neuropathic Pain in HIV

- Phase II, single group, double-blind, placebo-controlled, crossover trial of smoked cannabis (1-8%) for the short-term treatment of neuropathic pain associated with HIV infection
- 1 wk washout (baseline) → 5 days cannabis or placebo → 2 wks washout → 5 days cannabis or placebo → 2 wks washout

Median difference in DDS pain severity change was 3.3 points (p = 0.016)
Adverse Effects of MMJ

- Important to consider studies that have included botanicals
- Systematic review of chronic non-cancer pain
  - 766 patients
  - No serious adverse events reported
  - Adverse effects were well tolerated, transient or mild to moderate
  - Most common
    - Sedation
    - Dizziness
    - Dry mouth
    - Nausea
    - Disturbances in concentration
  - Adverse effects did not lead to withdrawal from study (compared with opioid studies with abandonment approximately 33%)

Br J Clin Pharmacol 2011;72(5):735-44
Clin J Pain 2013;29:164-71

Summary of Clinical Trials: Pain

- Cannabinoids may have a role for the treatment of refractory 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 Considerations

- Psychiatric implications
- Drug interactions
- Impact of MMJ on opioid use
- Packaging
- Labeling
- Testing of marijuana
- Patient-provider relationship

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
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)
  - Barbituates, 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 (Medical)

- 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)

Marijuana Labeling (Medical)

- May not make any false or misleading statements regarding health or physical benefits to the consumer
- Must be no smaller than 1/16 of an inch
- Clearly written or printed and in English
- Must be unobstructed and conspicuous
- List all ingredients, including all chemical additives, including but not limited to nonorganic pesticides, herbicides, and fertilizers that were used in its cultivation and production
- Batch Number
- Complete list of solvents and chemicals used in the creation of any medical marijuana concentrate
- License number of the cultivation facility, if different than the MMJ center’s license number
- License number of the MMJ center that sold product
- Date of sale


Marijuana Labeling (Medical), con’t

- Patient registry number of the purchaser
- The following statement:
  - “This product contains medical marijuana and was produced without regulatory oversight for health, safety or efficacy and there may be health risks associated with the consumption of the product.”
- For MMJ-infused products, product identity and net weight statements must appear on the portion of the label displayed to the patient
- List of ingredients and company name must be conspicuously listed on the MMJ-infused product package (may include a list of any potential allergens contained within, or used in manufacture)
- Nutrition facts panel may be required for nutritional claims
- Statement that MMJ-infused product, if perishable, must be refrigerated
- Product expiration date

Selected Retail Marijuana Labeling

- Permissive statements when testing for cannabinoid potency profile, and/or contaminants; labeling required if potency or contaminant testing not performed
- Universal symbol indicating container holds marijuana
- Warning statements
  - “There may be health risks associated with the consumption of this product.”
  - “This product is intended for use by adults 21 years and older. Keep out of the reach of children.”
  - “This product is unlawful outside the State of Colorado.”
  - “There may be additional health risks associated with the consumption of this product for women who are pregnant, breastfeeding, or planning on becoming pregnant.”
  - “Do not drive or operate heavy machinery while using marijuana.”
Practically Speaking…

…how does all of this labeling fit on one package of shatter?

Testing of Marijuana (Retail)

- License privileges
- General limitations or prohibited acts
- Certification requirements
- Personnel
- Standard operating procedure manual
- Analytical process
- Proficiency testing
- Quality assurance and quality control
- Chain of custody
- Records retention
- Reporting

The Patient Experience

BUDS
_HASH/HASH OIL_

Tinctures
Chews
Sodas/Teas
Topicals

EDIBLES

Knowledge Gaps

- Full potential of plant
- Proper and validated methods for testing
- Safety and efficacy of marijuana for many different uses
- Drug interactions, especially in liver and kidney

Conclusions

- It is important to understand the biosynthesis of marijuana and its active components to appreciate the full potential of the plants’ effects.
- Several different analytical techniques are needed to most appropriate test plant and biologic samples involving marijuana.
- THC is the best studied cannabinoid and is known to have psychoactive effects by targeting CB1 receptors in the brain.
- Many different formulations and potential dosages available to patients. How to best determine appropriate dose should be individualized.
- Clinical studies indicate MMJ may have a role in patients with pain and other disorders refractory to other treatments.
- 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, and patient-provider relationships.

THANK YOU!

QUESTIONS?