The American Cannabis Experiment:
Extracting data from the largest unregulated clinical trial in the history of medicine

Kalev Freeman, M.D. Ph.D.
Disclosures

Is there anything to disclose?  Yes

Please list the Potential Conflict of Interest:

PhytoScience Management Group (Vermont Patients Alliance, PhytoCare, CASE Institute)

All Potential Conflicts of Interest have been resolved prior to the start of this program.  Yes

All recommendations involving clinical medicine made during this talk were based on evidence that is accepted within the profession of medicine as adequate justification for their indications and contraindications in the care of patients.

This talk includes discussion of drugs not approved for use in the United States.
Outline

- Challenges in clinical studies of cannabis
- Strategies used to obtain IRB approval for research
- Considerations in context of 2018 Agriculture Improvement Act
- Risks of research without regulatory approvals
- Future directions - crowd sourcing

Hemp Farm, Hardwick VT – Courtesy of Green Mountain CBD
Introduction

• Restrictive federal policies and regulations severely limit clinical research on the health effects of cannabis and cannabinoids, limiting the evidence available to physicians.

• Researchers in the USA have increasingly utilized surveys and public health data to understand the impact of our "great cannabis experiment" - the largest unregulated clinical trial in the history of medicine.

• As the cannabis industry adopts pharmaceutical grade CGMPs, randomized controlled trials become possible.

• We will discuss strategies for overcoming barriers to cannabis research and how scientists in the industry can help.
Regulatory paradox in clinical studies of cannabis

Patients report benefit from cannabis-based medicine

Researcher plans RCT

IRB approval requires IND application to FDA

Can’t study what patients are actually taking

Study drug from NIDA or pharmaceutical industry

FDA only permits study of standardized drugs produced under CGMPs
Solutions

Usual practice: NIDA or pharma provides INDs

Alternative 1: Cannabis industry adopts CGMPs

Alternative 2: Observational studies
  - Cohort studies (eg. survey individuals using medical cannabis over time)
  - Case-control studies (eg. cross-sectional survey study)
  - Case series /reports

*Agriculture Improvement Act of 2018 didn’t solve problems for researchers hoping to study hemp-derived CBD
Usual practice: NIDA or pharma provides INDs

- Successful clinical trials have provided rigorous evidence for cannabis-based medicine
- Regulations limit ability to study the actual products used by public
- FDA approval for THC and CBD isolates means they are considered drugs and not dietary supplements

Systematic Review and Meta Analysis of Cannabis Based Medicine, JAMA 2016
Groundbreaking Clinical Trials, 2007 – 2011

• Therapeutic trials of smoked cannabis cigarettes
• Funded by State grants to Center for Medicinal Cannabis Research, UCSD
• INDs obtained from NIDA containing THC versus placebo

Clinical trials funded by “Big Pharma” provided additional evidence supporting medical cannabis

- Compilation of data from randomized clinical trials (RCTs) comparing cannabinoids to placebo
- Identified and reviewed 23,754 abstracts, 505 full-text, 151 reports to yield 79 studies that were included in meta-analysis
- Also provides best available information about potential for adverse events (AEs) with cannabis

Smoked cannabis (NIDA), nabilone and sublingual nabiximols

Table 2. Summary Estimates From Meta-analyses of Parallel-Group Studies and Results for Primary Outcomes With Associated GRADE Ratings

<table>
<thead>
<tr>
<th>Indication*</th>
<th>No. of Studies (No. of Patients)</th>
<th>Cannabinoid (No. of Studies)</th>
<th>Comparator</th>
<th>Outcome*</th>
<th>Summary Estimate</th>
<th>Favors</th>
<th>I², %</th>
<th>GRADE Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pain (neuropathic and cancer pain)</td>
<td>8 (1370)</td>
<td>Smoked THC (1), Nabilimols (7)</td>
<td>Placebo</td>
<td>Pain reduction ≥ 30% NRS or VAS scores follow-up 2-15 weeks</td>
<td>OR (95% CI), 1.41 (0.99 to 2.00)</td>
<td>CBM</td>
<td>48</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>6 (948)</td>
<td>Nabilimols (6)</td>
<td>Placebo</td>
<td>Pain NRS scores (0-10) follow-up 2-14 weeks</td>
<td>WMD (95% CI), -0.46 (-0.80 to -0.11)</td>
<td>CBM</td>
<td>59</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>3 (613)</td>
<td>Nabilimols (3)</td>
<td>Placebo</td>
<td>Pain Brief Pain Inventory-Short Form scale (0 to 10) follow-up 3-15 weeks</td>
<td>WMD (95% CI), -0.17 (-0.50 to 0.16)</td>
<td>CBM</td>
<td>0</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>6 (267)</td>
<td>Nabilimols (5), Nabilone (1)</td>
<td>Placebo</td>
<td>Patient global impression of change follow-up 3-14 weeks</td>
<td>OR (95% CI), 2.08 (1.21 to 3.59)</td>
<td>CBM</td>
<td>68</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>5 (764)</td>
<td>Nabilimols (5)</td>
<td>Placebo</td>
<td>Neuropathic pain Neuropathic Pain Scale (0-100) follow-up 5-15 weeks</td>
<td>WMD (95% CI), -3.89 (-7.32 to -0.47)</td>
<td>CBM</td>
<td>41</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>3 (573)</td>
<td>Nabilimols (3)</td>
<td>Placebo</td>
<td>Quality of life EQ-SD scale (0 to 100) follow-up 12-15 weeks</td>
<td>WMD (95% CI), -0.01 (-0.05 to 0.02)</td>
<td>Placebo</td>
<td>0</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; CBM, cannabis based medicine; EQ-SD, EuroQol Five Dimension Scale; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NA, not applicable; NRS, numerical rating scale; OR, odds ratio; THC, tetrahydrocannabinol; VAS, visual analog scale; WMD, weighted mean difference.

* No studies for glaucoma were included in the study estimate. The authors note that THC and cannabinoid were the interventions used in the reviewed glaucoma studies.

* Outcome includes the specific indication that was assessed, the means by which assessment was made, and follow-up (not shown for all studies).

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Odd ratios show cannabinoids improve pain

Included 28 studies of chronic pain (63 reports, 2454 individual participants)

Summary Estimates of Adverse Events (AEs)

Approximately 3x odds of any AE compared to placebo (n=3714 subjects)

- Dizziness (5x)
- Disorientation (5x)
- Confusion (4x)
- Drowsiness (4x)
- Euphoria (4x)
- Dry Mouth (3x)
- Somnolence (3x)
- Asthenia (2x)
- Anxiety (2x)
- Balance (2x)
- Hallucination (2x)
- Paranoia (2x)
Evidence has led to increasing support by physicians and development of new medical school curricula.
Medical Marijuana Is Legal in Most States, but Physicians Have Little Evidence to Guide Them

Rita Rubin, MA

Five patients have confided to Key West internist John Norris III, MD, that they use marijuana to relieve painful, persistent muscle spasms resulting from strokes or multiple sclerosis.

Norris’s patients have been buying their marijuana illegally. “They can get it from some high school kid or bartender in Key West,” he said. But Floridians voted to legalize medical marijuana this past November by a nearly 3-to-1 margin, spurring Norris to enroll in an 8-hour course required of all physicians in the state who want to be able to recommend the treatment to their patients.

Norris paid $955 for the course, co-sponsored by the Florida Medical Association and the Florida Osteopathic Medicine Association, and traveled to Miami over Thanksgiving weekend to take it. But even though he passed the final exam, he still doesn’t feel prepared to advise patients who’d like to try medical marijuana.

“The course has no dosing data. You go to the smallest amount possible and then work your way up,” Norris explained. “It’s like trying to prescribe St. John’s wort instead of Prozac.” The lack of clear dosing guidelines also makes it difficult to determine whether a patient is misusing medical marijuana.

Further complicating matters, he said, is the fact that “you have no idea of the concentration of the active ingredients,” which vary depending on when and where the plant was grown, and, for edibles and other products containing marijuana, the manufacturing process.

Gaps in Knowledge
Norris’s complaints highlight the knowledge gaps physicians confront when it comes to medical marijuana, now legal in 28 states, the District of Columbia, Puerto Rico, and Guam. They didn’t learn about it in medical school, and, because it is not a US Food and Drug Administration-approved drug backed by randomized controlled trials, they can’t turn to the Physicians’ Desk Reference for information about dosage, indications, and contraindications. The federal Drug Enforcement Administration (DEA) still classifies marijuana as a schedule I drug, along with heroin and ecstasy, that has a high potential

Pot 101
On the other side of the country, a University of Vermont (UVM) Larner College of Medicine pharmacology course, PHRM 296: Medical Cannabis, drew more than twice as many students as expected when it was first offered last spring semester.

The school had to twice change the location of the elective course, as enrollment grew to 99—filling the largest available lecture hall, said Kalev Freeman, MD, PhD, an emergency department physician and assistant professor of surgery at UVM whose wife, a botanist on the medical school faculty, coteaches the class. Thought to be the first of its kind at a US academic institution, it delves into molecular biology, neuroscience, chemistry, and physiology. Students who’ve taken it include undergraduates, medical students, physicians, and a state legislator.

Thanks to the enthusiasm of pharmacology chair Mark Nelson, PhD, Freeman said, he expects that beginning this fall, the subject of cannabis will be woven into the UVM medical school curriculum, instead of offered only as a stand-alone course. In other words, he said, when medical students study psychiatry, neuroscience, cell biology, and chronic pain, cannabis will become part of the discussion.
Alternative 1: Industry adopts CGMPs allowing IND application

Patients report benefit from cannabis-based medicine

Researcher plans RCT

IRB approval

FDA approves IND application for CGMP-compliant cannabis-based medicine
Does the Farm bill open the door for CBD research?

Hemp Farm, Hardwick VT – Courtesy of Green Mountain CBD
“Hemp hemp hooray for cannabis research”

From editorial written by scientists at Tobacco Research and Development Center, University of Kentucky:

• The farm bill’s new definition of hemp will allow researchers to order live seeds without limitation, facilitating biological and agricultural research.

• Scientists can now grow or purchase materials needed for studies involving most cannabinoids (except THC).

• Scientists can investigate properties of the rapidly diversifying Cannabis varieties and products not readily available through the government.

• Agriculture
  • Unlike the seeds of many commercial crops (such as corn and wheat), hemp seeds are attractive to many animals
  • hemp requires limited agricultural inputs in fields, thus allowing greater biodiversity than that supported by a field of conventional crops
  • Hemp can also bioremediate toxins from the environment

• Industrial
  • Hemp fiber is environmentally friendly to produce and has a high strength-to-weight ratio
  • Hempseed oil, fiber, and the inner woody core of the stem may be valuable for developing sustainable construction materials that sequester carbon, such as epoxies, biocomposite plastics, and hempcrete,
  • Hemp fibers may also be a cheap platform for producing carbon nanosheets for electronics applications
  • Fast growth, high yield, and cellulose-rich content of hemp stalks provide a suitable platform for biofuel production

Science. 15 FEBRUARY 2019. VOL 363 ISSUE 6428
FDA Support for the Development of Botanical Drugs

Guidance for Industry
Botanical Drug Products

June 2004

Botanical Drug Development
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of this draft guidance. Submit electronic comments to http://www.fdasite.gov. Submit written comments to the Division of Dissolution Management (HFA-350), Food and Drug Administration, 10900 New Hampshire Ave., Bldg. 8, Room 2104, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes this draft guidance.

For questions regarding this draft document contact the CBER at J.L. Lore or email (http://www.fda.gov, 301-259-2305, or 301-259-2839). As an alternative, contact Dan Shih (http://www.fda.gov, 301-259-1317).

August 2015
Pharmaceutical Quality/CME
Revision 1
FDA authority to regulate drug claims

• Hemp is no longer an illegal substance under federal law
• However, FDA has the authority to regulate drug claims (FD&C Act)
• FDA commissioner:
  • “We continue to be concerned at the number of drug claims being made about products not approved by the FDA that claim to contain CBD or other cannabis-derived compounds.”
  • “Among other things, the FDA requires a cannabis product (hemp-derived or otherwise) that is marketed with a claim of therapeutic benefit, or with any other disease claim, to be approved by the FDA for its intended use before it may be introduced into interstate commerce.”
Research on dietary supplements may be exempt from FDA oversight

- *Dietary supplements* = products taken by mouth that contain a "dietary ingredient" intended to supplement the diet and fall under a special category under the general umbrella of "foods"
- Under DSHEA, the manufacturer is responsible for ensuring safety before marketing
- The FDA is responsible for taking action against any unsafe product *after* it reaches the market.
- Can we apply “Exemption 45 CFR 46.101(b)(6) (for Food Taste and Acceptance Studies)” to study CBD?
Exemption 45 CFR 46.101(b)(6) (for Food Taste and Acceptance Studies)

- Can only investigate “taste and food quality” or “consumer acceptance” *
- The food ingredient must be “generally recognized as safe” (GRAS)

* If studying a dietary supplement with the intent of diagnosis, cure, mitigation, treatment or prevention of disease in humans (e.g., hope of reducing medication with use of the supplement), it would be need to be treated as a drug under FDA oversight requiring Investigational New Drug (IND) application.
Does the FDA consider hemp safe as food?

FDA completed evaluation of Generally Recognized as Safe (GRAS) notices:

1. hulled hemp seeds
2. hemp seed protein
3. hemp seed oil

• These products are considered safe

• Can be legally marketed in human foods provided they comply with all other requirements and do not make disease treatment claims

FDA Statement from Commissioner Scott Gottlieb, M.D., on signing of the Agriculture Improvement Act and the agency’s regulation of products containing cannabis and cannabis-derived compounds (December 20, 2018)
FDA Crackdown on CBD

• Parts of the cannabis plant containing CBD and THC are considered drug ingredients, still require IND application for study, and cannot be added to foods or otherwise used.
  • “It’s unlawful under the FD&C Act to introduce food containing added CBD or THC into interstate commerce, or to market CBD or THC products as, or in, dietary supplements, regardless of whether the substances are hemp-derived.”
  • “This is because both CBD and THC are active ingredients in FDA-approved drugs and were the subject of substantial clinical investigations before they were marketed as foods or dietary supplements.”
Alternative 2: Observational studies

Patients report benefit from cannabis-based medicine

Researcher plans observational study

IRB approval

General types of observational studies:
- Cohort studies (eg. survey individuals using medical cannabis over time)
- Case-control studies (eg. cross-sectional survey study)
- Case series /reports
The Dosing Project:
Logistic Regression with Effect Likelihood Ratio Tests and Profiler Prediction to Determine Optimal Dosing

<table>
<thead>
<tr>
<th>Self-Report Improvement</th>
<th>Categorical Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completely improved</td>
<td>Sleep</td>
</tr>
<tr>
<td>Almost completely</td>
<td></td>
</tr>
<tr>
<td>improved</td>
<td></td>
</tr>
<tr>
<td>Somewhat improved</td>
<td>Pain</td>
</tr>
<tr>
<td>No improvement</td>
<td></td>
</tr>
</tbody>
</table>

Ordinal Logistic Regression Curve:
- Steeper for Sleep
- Different pharmacologic mechanisms?
- Lack of stratification in Pain cohort?

Dose in mg/kg (mpk)

0.5  1.0  5.0
Observational Studies

- Substitution of cannabis for opioids in chronic pain
- Online survey of 244 medical cannabis patients with chronic pain to examine whether medical cannabis changed individual patterns of opioid use; N=184 analyzed
- Found that cannabis was associated with
  - Decrease in opioid use (65%)
  - Decreases in other medications
  - Improved quality of life (45%)

<table>
<thead>
<tr>
<th>Medication type</th>
<th>Use before initiation of cannabis (n/N)</th>
<th>Use after initiation of cannabis (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>119/184 (65%)</td>
<td>33/184 (18%)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>115/184 (62%)</td>
<td>38/184 (21%)</td>
</tr>
<tr>
<td>Disease-modifying antirheumatic drugs (DMARDs)</td>
<td>15/184 (8%)</td>
<td>3/184 (2%)</td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>72/184 (39%)</td>
<td>25/184 (14%)</td>
</tr>
<tr>
<td>Serotonin–norepinephrine reuptake inhibitors (SNRIs)</td>
<td>13/184 (7%)</td>
<td>3/184 (2%)</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs)</td>
<td>34/184 (18%)</td>
<td>8/184 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>69/184 (38%)</td>
<td>40/184 (22%)</td>
</tr>
</tbody>
</table>

NOTE. Study participants reported using fewer medication classes of all categories after initiation of cannabis.
Can research be conducted without regulatory approvals?

Bioethical principals of research protections

- Respect for persons (informed consent, anonymity)
- Beneficence (and non-maleficence) (maximize possible benefits and do no harm)
- Justice (who ought to receive the benefits of research and bear its burdens, in context of historical injustice)

International and US regulations

- Nurenberg Code
- Declaration of Helsinki
- Belmont report/ Common Rule
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins.

- Independent of the researcher, the sponsor and any other undue influence.
- Takes into consideration laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards.
- Must have the right to monitor ongoing studies.
- The researcher must provide monitoring information to the committee, especially information about any serious adverse events.
- No change to the protocol may be made without consideration and approval by the committee.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
Search for “cannabis” on Feb 20, 2019 yielded 775 studies
Legal liability - lack of informed consent

Alabama 1972 – Class action lawsuit
Tuskegee Syphilis Study (1932-1972) – federally funded experiment on course of untreated syphilis, $9M settlement

Alabama 2018 - Looney v. Moore
Courts rejected invitation to provide clinical trial patients recovery for failure of informed consent in the absence of provable injury.

*Clinical trial insurance may cover contingencies that require reimbursement or compensation

https://apnews.com/e9dd07eaa4e74052878a68132cd3803a
Lawsuits challenging adequacy of informed consent

- Failure to disclose potential risks from the research (or their likelihood)
- Failure to inform subjects of the researchers’ financial interest in the new therapy
- Falsification of Institutional Review Board approval

→ In all cases, plaintiffs were injured
Professional liabilities for academic physicians

- Hospital credentials
- State medical license
- DEA license

- University contract
- Federal grants

University of Vermont Medical Center
Freeman Lab, UVM College of Medicine
• University informed her that contract wouldn't be renewed
• Her role as coordinator for a physician-education program on medical marijuana would no longer be supported -- even though the three-year program was in its first year, with two-thirds of its money still in the bank
• She was given 3 months to vacate her office
Pathways for IRB-approved clinical research

- FDA approves IND application for clinical trials
- Observational study
- Patients report benefit from cannabis-based medicine
- IRB specializing in cannabis research?
Crowd-sourcing - new paradigm for industry studies?

The Dosing Project™

Thank you for your interest in participating in our crowd-sourced scientific project. This project is designed to discover accurate cannabis dosing for a wide array of diseases and ailments. We expect many patients will benefit from our efforts in pursuing evidence-based medicine. This brochure will tell you more about who we are, how you can anonymously participate, and what outcomes are expected.

What is the Dosing Project™?
The Dosing Project™ is the flagship program of the CESG, a non-profit organization. The objective of The Dosing Project™ is to capture information from a large number of patients and determine how they respond to specific doses of cannabis products for medical conditions, such as chronic pain and disordered sleep. For a more in depth and technical description of the study design and rationale, CLICK HERE.

Do I qualify?
Your role in this project is actually quite simple. After receiving your medical cannabis recommendation from a MedCann Affiliate doctor or any qualified doctor in your state, you can enroll in the Dosing Project™. We ask that you accurately and truthfully respond to the survey to the best of your ability. Every answer brings us one step closer to determining how cannabis works best as medicine. We thank you in advance for your participation!

How do I join the study?
After you enroll, we will provide you with a way to track your cannabis use and symptoms. Answer a short series of questions through your mobile phone or computer. The questions are regarding what you are using, how you are using and how you feel after medicating. All collected information will be coded to protect your identity. To join the study, CLICK HERE.

Can I see the results?
At the end of each response session, our Dosing Calculator will present information on dosage for the response you just concluded. The Dosing Project™ will collate and analyze your answers. We will determine which dose works best for which ailments. As statistically significant patterns emerge, the CESG will provide HIPAA protected information to patients, physicians, sponsors and the general public using web-based and other media presentations.

Conclusions

• Challenges in clinical studies of cannabis
• Strategies used to obtain IRB approval for research
• Considerations in context of 2018 Agriculture Improvement Act
• Risks of research without regulatory approvals
• Future directions - crowd sourcing as a new paradigm?
Acknowledgements

Cannabis Science and Medicine

Translational Cannabis Science and Medicine at the University of Vermont College of Medicine Department of Pharmacology

Through education we help turn observations in the laboratory, clinic and community into interventions that improve health and bridge scientific discoveries in medical Cannabis with the needs of health care providers, researchers, students, and professionals.

https://learn.uvm.edu/com/program/cannabis-science-and-medicine/
Extra slides
Looney Case (Alabama 2018)

First to hold researchers liable for failure of informed consent in absence of physical injury

• U of Alabama study of premature infants with varying levels of oxygen; consent did not adequately describe risks (blindness, neurological damage, death)

• Suit claimed negligence, negligence per se, breach of duty and products liability, in addition to lack of informed consent.

• All dismissed by US District Court except lack of informed consent

• Eleventh Circuit determined it was not clear under Alabama law whether a plaintiff must “prove that an injury actually resulted from the medical treatment in order to succeed on a claim that his consent to the procedure was not informed.”

• Alabama Supreme Court declined to resolve the issue, without comment.

→ Informed consent claims depend on negligence and thus require an actual injury.
Risks in Publication of Research

Condemned by Declaration of Helsinki

Editors of journals are not legally liable, but they are ethically obligated according to the Declaration of Helsinki to ensure study was reviewed by ethics board

- Rejection Policy
  - Analogous to using illegally obtained evidence
  - Acceptance would encourage further such research

- Acceptance Policy
  - Good may come from evil
  - Forces unethical research “under the table”
  - Information might be unobtainable ethically