

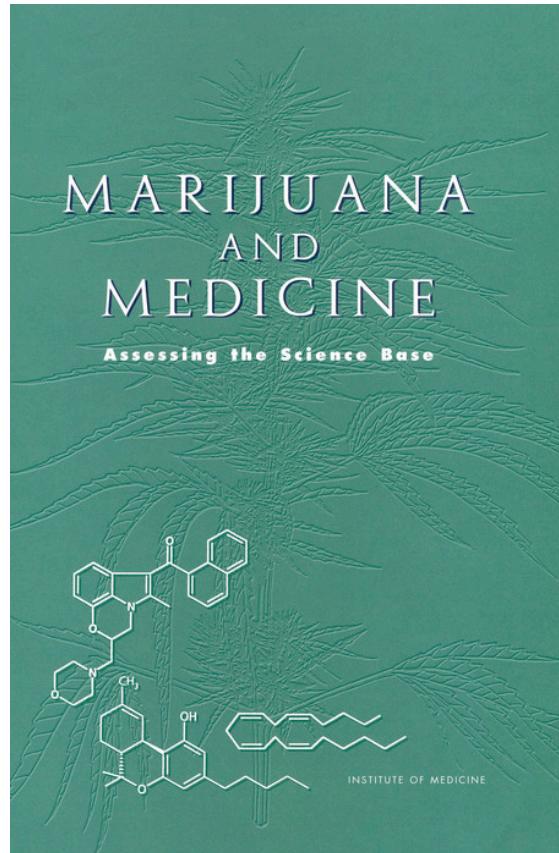
Cannabis and Health

Module 3

Lecture 2: End Result of Barriers to Research

What impact did barriers have?

- National Academy of Sciences produced a report on cannabis in 1999 (see <https://www.nap.edu/read/6376/chapter/2#3>)



Conclusions from 1999 Report (verbatim)

- At this point, our knowledge about the biology of marijuana and cannabinoids allows us to make some general conclusions:
 - Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
 - The natural role of cannabinoids in immune systems is likely multi-faceted and remains unclear.
 - The brain develops tolerance to cannabinoids.
 - Animal research demonstrates the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.
 - Withdrawal symptoms can be observed in animals but appear to be mild compared to opiates or benzodiazepines, such as diazepam (Valium).

Conclusions

CONCLUSION: Scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily THC, for pain relief, control of nausea and vomiting, and appetite stimulation; smoked marijuana, however, is a crude THC delivery system that also delivers harmful substances.

RECOMMENDATION 2: Clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid-on-set, reliable, and safe delivery systems.

Conclusions

CONCLUSION: The psychological effects of cannabinoids, such as anxiety reduction, sedation, and euphoria can influence their potential therapeutic value. Those effects are potentially undesirable for certain patients and situations and beneficial for others. In addition, psychological effects can complicate the interpretation of other aspects of the drug's effect.

RECOMMENDATION 3: Psychological effects of cannabinoids such as anxiety reduction and sedation, which can influence medical benefits, should be evaluated in clinical trials.

Conclusions

A second concern associated with chronic marijuana use is dependence on the psychoactive effects of THC. Although few marijuana users develop dependence, some do. Risk factors for marijuana dependence are similar to those for other forms of substance abuse. In particular, antisocial personality and conduct disorders are closely associated with substance abuse.

CONCLUSION: A distinctive marijuana withdrawal syndrome has been identified, but it is mild and short lived. The syndrome includes restlessness, irritability, mild agitation, insomnia, sleep disturbance, nausea, and cramping.

Result of Barriers

- In 1999, the committee recommended that the nation should engage in clinical trials and more research with cannabis
- What actually happened – very little!!!
- Second National Academy/ IOM report in 2017 (the one you are reading)
- And yet the barriers are still preventing research

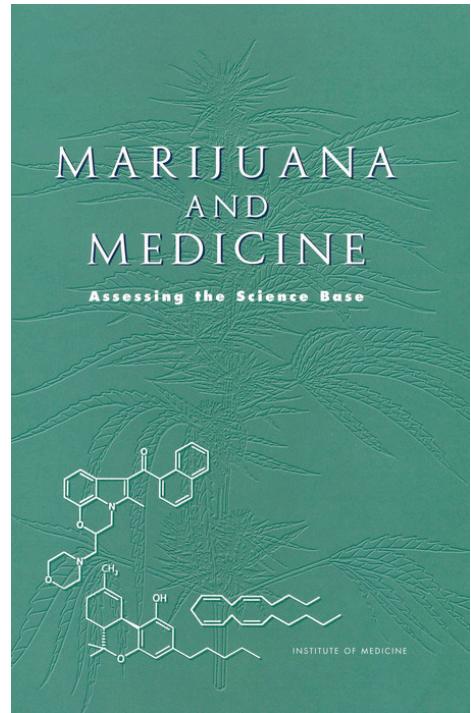
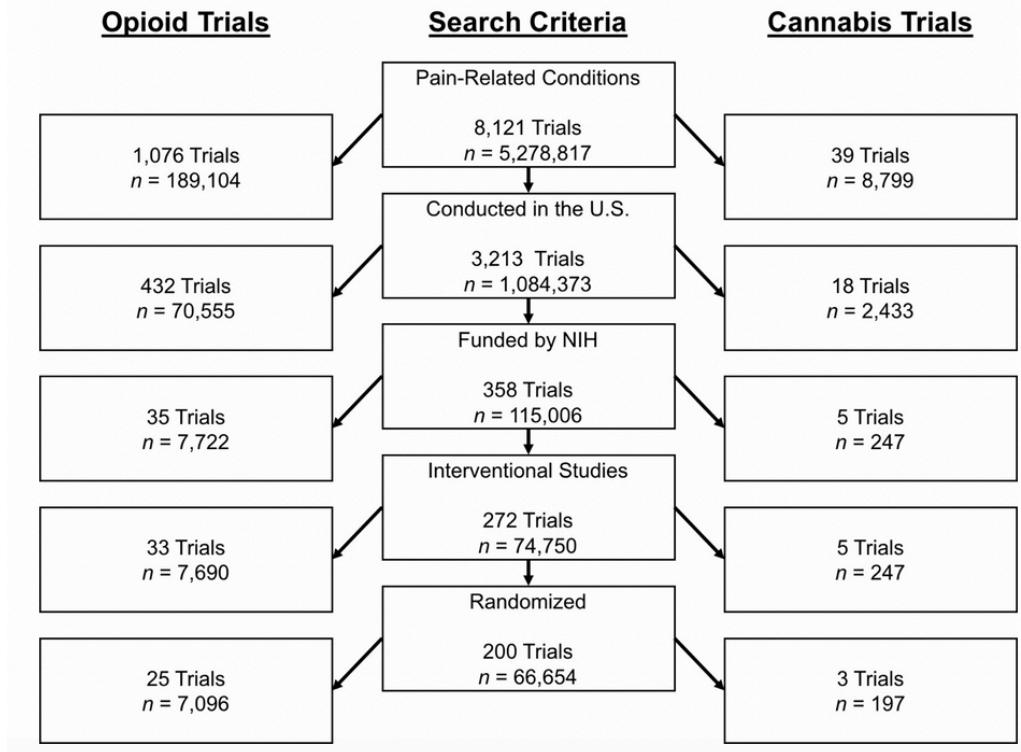


Figure 1. A comparison of individuals enrolled in registered clinical trials (clinicaltrials.gov) on pain using opioid- and cannabis-based interventions.

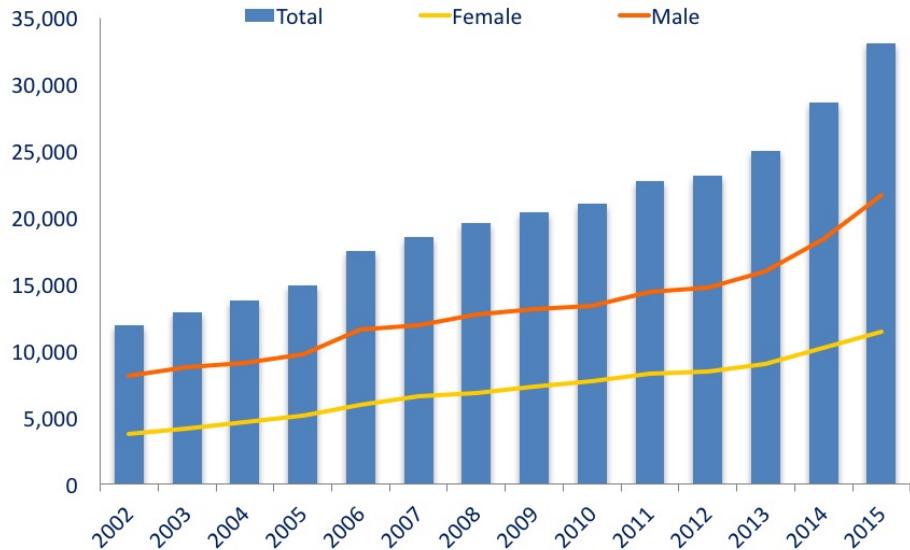


What might have happened?



National Overdose Deaths

Number of Deaths from Opioid Drugs



Source: National Center for Health Statistics, CDC Wonder

Result of Barriers

- Despite widespread acceptance, very little research has been conducted in the U.S.
- Consequently, medical use and state regulated markets are far, far ahead of research on efficacy/safety of products
- Medical marijuana cart is in front of the research efficacy and safety horse



Result of barriers – people uninformed and stereotypes persist

Former New York City Mayor Michael Bloomberg on Tuesday said that attempting to legalize recreational marijuana "is perhaps the stupidest thing anybody has ever done."

January 23, 2019

"Last year, in 2017, 72,000 Americans OD'd [overdosed] on drugs. In 2018, more people than that are OD-ing on drugs, have OD'd on drugs, and today, incidentally, we are trying to legalize another addictive narcotic, which is perhaps the stupidest thing anybody has ever done," he said, according to [WBNG.com](#).

The world scientists live in...

- Each month:
 - 992,870 plants cultivated
 - 34,568 lbs of flower sold
 - 960,831 edible units sold
- State law allows school districts to permit medical cannabis on school grounds



Mission impossible?

- Universities must choose
 - Be compliant with federal law and abdicate their role in providing the public with information critical to safety and health
 - Or serve the public and risk losing federal funds



Our Approach

- Worked very carefully with legal counsel to find a way to do the research without violating laws
- We cannot physically interact with any cannabis material (despite that many of our students are carrying it around campus in their backpack!!)
- We cannot allow people to use it on campus
 - Thought about having them use it just off campus but illegal to use in public
 - Cannot rent space off campus because anywhere we go it becomes federal work place

Mobile Cannabis Pharmacology Lab



- We cannot bring people to the lab – but we can bring the lab to the people
 - Funded by NIDA

Observational Study Design



Time 1

- Regular users
- Baseline Assessment
- Blood Draw
- *Randomly assigned to product that they purchase themselves*

Purchase of Assigned Product
(A or B)
Followed by 5 day period of
ad libitum use

Time 2

- Pre-arranged time
- Assessed in Mobile Pharmacology Lab before and after self-admin
- Blood Draw
- Subjective Effects
- Cognitive Battery
- Motor Control Battery
- Driving Ability

← Flower/Strains: 24% vs 16% THC
(Phase 2 involves varying THC:CBD)

Dabbing/concentrates: 70% vs 90% THC →
concentrated hash oil



1g
Kushberry
PHO
THC:74.1%
CBD:0.20%
Green Leaf Labs
T:S 108044

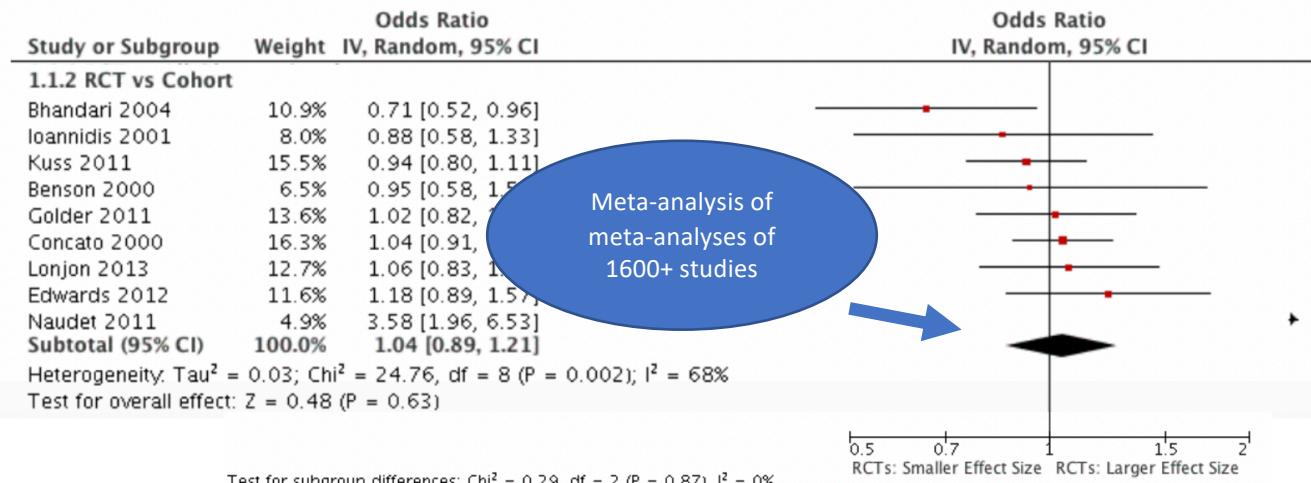
With reboot, what can we do with this approach?

- Most previous research has failed to factor in the following:
 - Potency and dose
 - Cannabinoid and terpene profiles
 - Type of product
 - Risks and benefits may differ between medical vs. recreational user
- Need new approaches to study cannabis products available in state-regulated markets



“Observational” is not a four letter word

Figure 4. Forest plot of comparison: I RCT vs Observational, outcome: I.2 Pooled Ratio of Odds Ratios-- Study Design.



Anglemyer A, Horvath HT, Bero L.

Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials.

Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: MR000034.

DOI: 10.1002/14651858.MR000034.pub2.

What does it mean?

- Probably means that including a “placebo” condition does not necessarily mean that a trial was “controlled”
- When people know that they are getting the active treatment, expectancies can still influence the effect
- People often know that they are getting real cannabis (100% correctly guessed 3.5% THC condition on the second session; Wilsey et al., 2013)
- A well designed study that does not meet the strict definition of an RCT can deliver trustworthy results equivalent to an RCT

Conclusions

- Recommendations from the Institute of Medicine in 1999 went unheeded
- Conclusions suggested potential for harm was not high and potential benefits were substantial (though unproven)
- And then nothing
- Barriers have proven to be incredibly effective at reducing research
- However, we have ways around the barriers and those barriers may be removed soon

Discussion

- What were (are) the not so obvious unintended consequences of the lack of research due to barriers at the federal level? (Hint: How much information can you find on the internet about CBD and health versus how much research has actually been done?)