THE HIGHS AND LOWS OF MEDICAL MARIJUANA
Outline

**Part I:** Nick Jikomes
- The cannabis plant
- Cannabinoids & psychoactivity

**Part II:** John Hatch
- Marijuana and human health

**Part III:** Kayla Davis
- Public policy and medical marijuana
The cannabis plant: history

Historical uses:
- Fiber
- Food
- Medicine
- Religious/ritual
- Recreation
- Ancient China: surgical anesthetic
- Ancient Egypt: pain relief
- Ancient India: anxiety
- Roman Empire: labor pains
The cannabis plant: basics
The cannabis plant: buds & trichomes

- **Bud**: trimmed portion of female flower; cultivated by humans.
- **Trichomes**: hair-like outgrowths that secrete **terpenes** and **cannabinoids**.
- **Cannabinoids**: a diverse class of chemical compounds that act on **cannabinoid receptors**.
The cannabis plant: why does it contain psychoactive compounds?

Common functions of trichomes:
• Defend against insect herbivores *
• Defend against frost in colder habitats
• Minimize water loss in windy habitats *
• Prevent overheating in dry, open habitats *
• Attract pollinators or prey

Ecological role of psychoactive plant compounds:
• Defense: many used as insecticides
• Caffeine, nicotine
The cannabis plant: break for questions
Cannabinoids: plant cannabinoids

Δ⁹-Tetrahydrocannabinol (THC)

Major psychoactive molecule in marijuana

Cannabidiol (CBD)

Non-psychoactive cannabinoid with many medically useful properties

- Antiemetic (reduced nausea/vomiting)
- Anticonvulsant (suppresses seizure activity)
- Anti-inflammatory
- Anti-oxidant
- Anxiolytic
- Anti-tumoral
- Anti-psychotic

* Based mostly on animal studies, not human clinical trials

British Journal of Clinical Pharmacology
Cannabinoids: plant cannabinoid variability
Cannabinoids: the human endocannabinoid system

Receptors are found on cell surfaces

- **CB1 receptor**: found on neurons throughout the central and peripheral nervous system.
- **CB2 receptor**: found largely outside the nervous system, including the immune and gastrointestinal systems.
- **Psychoactive effects** of marijuana are largely due to **CB1 activation** by THC.
Cannabinoids: endogenous cannabinoids

**Plant cannabinoids (phytocannabinoids)**

- **Δ⁹-Tetrahydrocannabinol (THC)**

  ![Δ⁹-Tetrahydrocannabinol (THC) structure]

- **Cannabidiol (CBD)**

  ![Cannabidiol (CBD) structure]

**Endogenous cannabinoids (endocannabinoids)**

- **2-Arachidonylglycerol (2-AG)**

  ![2-Arachidonylglycerol (2-AG) structure]

- **Anandamide**

  ![Anandamide structure]
Cannabinoids: effects on mammalian nervous system

- **CB1** is one of the most **widely expressed** receptors in the mammalian brain.
- Cannabinoids act as **retrograde signals** sent from “receiver” to “sender” neuron.
Cannabinoids: variability in psychoactive properties

Psychoactive properties (user reported)

- “Euphoric” “uplifting”
- Increases energy, creativity; induces a “mental high”
- “Relaxing,” “sedating”
- Promotes relaxation; induces a “body high”

Medicinal uses (claimed)

- Depression/mood disorders
- ADHD
- Fatigue
- Anxiety
- Insomnia
- Chronic pain
- Muscle spasms
- Nausea
- Inflammation
- Low appetite

Cannabinoids: break for questions
Part II: Marijuana and Human Health
Two Distinct Concepts

- Risks associated with recreational use
- Benefits associated with therapeutic use
Recreational Use: Risks

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Respiratory Damage

- Cannabis smoke contains many harmful chemicals also found in tobacco smoke:
  - Tar
  - Carbon monoxide
  - Ammonia
  - Hydrogen Cyanide
  - Arsenic
  - Formaldehyde
  - Carcinogens
    - Polyaromatic hydrocarbons
Respiratory Damage

- Bronchitis
- Coughing
- Phlegm
- Breathing Difficulty
- Wheezing

Relative Risk

- Nonsmokers
- Tobacco Smokers
- Marijuana Smokers

BA Moore et al. JGIM 2004
S Sidney et al. Cancer Causes & Control 1997
### Verdict

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Two Key Risk Factors

**Age**
- Brain *development* continues through adolescence.

**Frequency of use**
- *Plasticity* means that the brain changes itself in response to experiences.
Cognitive Decline

- Significant changes in IQ only for heavy users who begin use during adolescence.

IQ Change from Age 18-38: Frequent Marijuana Users

Began before Age 18

MH Meier et al. PNAS 2012
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Schizophrenia

- Early data suggested that cannabis use may cause schizophrenia

S Andreasson et al. The Lancet 1987
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Dependency

Addictive drugs often cause long-term changes to the brain's "reward pathway." Marijuana does not satisfy this definition of "addictive." A clinical definition of dependency is based on common-sense criteria:

- How difficult is it to stop using?
- Do you experience withdrawal symptoms?

C Lopez-Quintero et al. Drug Alcohol Depend. 2011
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Questions?

- Next up: therapeutic applications of marijuana and cannabinoids.
Reminder: the endocannabinoid system

- **CB1 receptor**: found on neurons throughout the central and peripheral nervous system.

- **CB2 receptor**: found largely outside the nervous system, including the immune and gastrointestinal systems.
## Potential Therapeutic Uses

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Chronic Pain

- Oldest documented medicinal use of marijuana.
- Best for long-term pain issues, like nerve damage after surgery.
- Functions differently than most (or all) prescription painkillers.
- Not all strains are created equal!

[Image of pain scale from 0 to 10]

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Wikimedia Commons
MC Lee et al. *Pain* 2013
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Glaucoma

- Cannabinoids reduce pressure- may be effective due to:
  - Less secretion of fluid.
  - Better drainage of fluid.
  - Fewer damaging cellular reactions in the nerve.
- CB1 and CB2 receptors are present in the eye- new treatments possible!

Increased Pressure → Damage to Optic Nerve

Wikimedia Commons
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Nausea & Appetite

- “The munchies” have therapeutic benefits for people suffering from cachexia.
  - Chemotherapy
  - HIV/AIDs

Activates CB1 (like THC)
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Seizures & Epilepsy

- Result from excessive neural transmission.
- **CBD** in particular may protect against these disorders.

Devinsky et al. American Epilepsy Society Annual Meeting, April 2015
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**Cancer**

- **Cancer:** Uncontrolled cell division leads to tumor growth.

- Cannabis and related compounds have been shown to inhibit tumor growth *in vitro*.

- THC and cannabinoids may be:
  - Anti-mitogenic (reduce cell division)
  - Anti-angiogenic (reduce blood vessel growth)
  - Pro-apoptotic (induce controlled cell death)

- But we don’t understand the mechanisms!
## Can marijuana treat:

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**Verdict**

Science Says… Needs More Research!
Questions?

- Next up: Marijuana and public policy.
How does policy control marijuana research?

Kayla Davis
History of Drug laws in USA

1611  Jamestown settlers bring Hemp to North America

1850  Marijuana listed in US pharmacopeia

1906  Pure Food and Drugs Act requires labeling of Medicines

1911  Massachusetts outlaws cannabis

1930  Pharmaceutical companies sell cannabis extract and cannabis cigarettes

Marijuana becomes criminal

1937 The Marijuana Tax Act is passed
1937 First marijuana seller convicted under federal law
1942 Marijuana is removed from US pharmacopeia
1951 Boggs Act sets 2-5 year minimum penalty
1956 Minimum penalty extended 2-10 years and maximum $20,000 fine
Research Regulation

1964

http://gallery.marihemp.com/public_domain_free/miss1
Break for questions
Schedule 1 controlled substance

- LSD
- MDMA
- Mescaline
- Peyote
- Marijuana
- Heroin

Schedule 2 controlled substance

- Cocaine
- Vicodin
- Methamphetamine
- Oxycodone
War on Drugs

1972 🌿 National Commission on Marijuana and Drug Abuse recommends decriminalizing marijuana

1973 ☠ DEA established

1978 🌿 Investigational New Drug Compassionate Use Program
Investigational New Drug Compassionate Use Program

- Provides FDA-approved medical marijuana to patients

- Thirty patients enrolled at peak

- Shut down in 1992 as response to Bush administration’s “get tough on drugs” initiative

- Four patients are still enrolled
Decriminalization ends.. for awhile

1980 🍀 Ronald Reagan is elected President

1990

and 🌿 Endocannabinoids and cannabinoid receptors

1992 are discovered

http://www.reagan.utexas.edu/archives/photographs/photo.html
State Marijuana Laws

- Twenty-three states and Washington, DC, allow the use of marijuana to treat certain medical conditions.
Marijuana in Massachusetts

2008  🍀 Massachusetts votes to decriminalize marijuana

2012  🍀 63% of voters approved legalization of medical marijuana

2015  🍀 First dispensary opens

2015  🍀 Ballot question to end marijuana prohibition cleared
Break for questions
Marijuana use statistics

• 7% of Americans reported using marijuana within the past month.

• 7,100 new marijuana users every day in 2011

• 42% of Americans have reported trying marijuana

• 4.2 million people met the criteria for abuse of or dependence on this drug
Marijuana Research

- From 2008-2014 the NIH budget was approximately $120.6 billion.
- $1.4 billion was spent on marijuana research

**Distribution of NIH research funding spent on marijuana research from 2008-2014**

- abuse and addiction
- medical research
Medical Marijuana Research

2014  28 active grants funded by NIH

- Autoimmune disease  1
- Inflammation         2
- Pain                6
- Psychiatric Disorder 2
- Seizures            1
- Withdrawal, Dependence 13

2015  49 new grants funded by NIH

- 115 clinical trials
- 72 marijuana abuse
The future of Marijuana research

Rescheduling
Thank you!

_SITN would like to acknowledge the following organizations for their generous support._

**Harvard Medical School**
Office of Communications and External Relations
Division of Medical Sciences

The Harvard Graduate School of Arts and Sciences (GSAS)

The Harvard Graduate Student Council (GSC)

The Harvard/MIT COOP
NIDA process

- NIH funded projects
  - Demonstrate scientific validity and ethical soundness through NIH review
  - Active-status Investigational New Drug application
  - A DEA registration for marijuana

- Non- NIH funded Human research projects
  - Demonstrate scientific validity and ethical soundness through FDA Investigational New Drug process
  - A DEA registration for marijuana

- Contact NIDA to place an order
Drug Possession Offenders in State Prisons

Percent of State Prisoners, 2004

- Drug possession offenders: 6.0%
- Drug offenders, no prior sentences: 4.4%
- Drug offenders held for crimes involving marijuana: 2.7%
- Drug offenders held for crimes involving only marijuana: 1.4%
- Marijuana only drug offenders: 0.4%
- Marijuana only possession offenders: 0.3%
- Marijuana only possession offenders, no prior sentences: 0.1%