CANNABIS LAWS IN THE U.S.

States with MML vary on:
- Allowable conditions and routes of administration.
- Dispensaries/home growth and registries.
- Testing, regulatory requirements.

States with Recreational Laws vary on:
- Marketing, product labeling, distribution (home growth).
- Taxation.
CANNABIS CONTAINS ~100 CANNABINOIDS PLUS OTHER CHEMICALS IN VARYING CONCENTRATIONS

- Plant with long history of use worldwide
- Illegal under Federal law (Schedule I substance—not FDA approved)
- Legal for medical use in 29 States + D.C.
- High CBD variety (or extracts) legal in 16 states for medical use
- Versions of active ingredients approved (or in clinical trials) for medical indications in U.S. and other countries
  - Synthetic - Marinol, Syndros, Cesamet
  - Plant Derived - Sativex (THC/CBD)
  - Plant Derived - Epidiolex (CBD: Phase III trials)
CANNABIS RESEARCH BARRIERS

ADMINISTRATIVE
- Schedule I: Complex and lengthy registration process.
- Single Source: NIDA supply has diversified, but costly and time consuming to grow new products, doesn’t represent diversity of products/formulation currently available.
- Schedule I status of non-intoxicating components of cannabis (e.g. CBD).

SCIENTIFIC
- Complexity of plant (100 cannabinoids + other components), entourage effect?
- Route of administration.
- Need proper controls, sufficient study duration (blinding, driving...)
- Should be taking advantage of what is already happening in the states (patient registries).
ADVERSE EFFECTS:
WHAT DO WE KNOW?
CANNABINOID RECEPTORS ARE LOCATED THROUGHOUT THE BRAIN

Regulation of:

• Brain Development
• Memory and Cognition
• Movement Coordination
• Pain Regulation & Analgesia
• Immunological Function
• Appetite
• Motivational Systems & Reward

Source: Canadian Consortium for the Investigation of Cannabinoids, http://www.ccic.net/
PAST MONTH MARIJUANA USE

Youth Ages 12 to 17 Years Old

College Age 1

Adults Age ≥ 26 Years Old

SOURCE: SAMHSA.gov, National Survey on Drug Use and Health 2014 and 2015

Rocky Mountain HIDTA Report www.rmhidta.org
CHANGING LANDSCAPE: INCREASING POTENCY & NEW ROUTES OF ADMINISTRATION

12th grade Past Year Users

SOURCE: University of Mississippi; University of Michigan, 2014 Monitoring the Future Study
ENDOCANNABINOID SYSTEM INVOLVED IN BRAIN DEVELOPMENT: MOST VULNERABLE POPULATIONS?

Prenatal

Adolescent
PREGNANT TEENS REPORT HIGH PAST MONTH USE OF MARIJUANA HIGHEST RATES OF USE IN FIRST TRIMESTER

2002 to 2015 National Survey on Drug Use and Health (NSDUH)

ADDITION: ABOUT 9% OF USERS BECOME DEPENDENT, 1 IN 6 WHO START USE IN ADOLESCENCE, 25-50% OF DAILY USERS

Estimated Prevalence of Dependence Among Users

* Nonmedical Use

Source: Anthony JC et al., 1994
MULTIPLE STUDIES SHOW ALTERED BRAIN STRUCTURE AND FUNCTION IN YOUTH WHO REGULARLY USE CANNABIS

Early (<18y) Cannabis Use Decreases Axonal Fiber Connectivity

Axonal paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33).

Zalesky et al Brain 2012
Cognition: Persistent Cannabis Use Disorder Linked to Significant IQ Drop Between Childhood and Midlife

- Followed 1,037 individuals from birth to age 38.
- Tested marijuana use and disorders at 18, 21, 26, 32 and 38.
- Tested for IQ at ages 13 and 38

Source: Meier MH et al., PNAS Early Edition 2012
FREQUENCY OF CANNABIS USE BEFORE AGE 17 YEARS AND ADVERSE OUTCOMES (30 YEARS AGE) (N=2500-3700)

Consistent and dose-response association were found between frequency of adolescent cannabis use and adverse outcomes.

Source: Silins E et al., The Lancet September 2014
POLICY CHALLENGES: HOW DO WE MINIMIZE HARM IN AN ENVIRONMENT WHERE POLICY DECISIONS ARE OUTPACING RESEARCH AND KNOWLEDGE?

• Identify what we know and what we don’t

• Prioritize Research Needs
  • Health: brain, heart, lungs, reproductive system, medical use, others
  • Policy: different implementation models, regulations, taxation, marketing

• Communication: Develop credible, persuasive, simple messages for the public, the medical community, policymakers

• Consider the context: many uncertainties regarding State Legalization policies and Federal enforcement priorities
WHAT WE KNOW ABOUT ADOLESCENT CANNABIS EXPOSURE

• Adversely influences learning
• Effects on memory and attention outlast intoxication
• Appear worse with earlier age of onset, more chronic use
• Some neuroimaging data support these effects
• Increased risk of addiction (compared to adults)
• Worse educational outcomes, career achievement, life satisfaction
• Linked with suicidal ideation or behavior
• Earlier onset/worse course of psychotic illness in vulnerable individuals
WHAT WE NEED TO KNOW ABOUT CANNABIS AND NEURODEVELOPMENT

The precise nature of the association between cannabis use and neurodevelopment including who is at risk.

- What are the factors that moderate the impact of cannabis exposure?
- How should we quantify cannabis use: frequency, strain, potency, route of administration?
- Are there permanent effects; compensatory developmental responses; or reversible changes in structure/function?
- How much do other variables contribute to cannabis effects (alcohol, tobacco, prenatal care, BMI, physical activity...)?
- What are the effects of second- or third-hand smoke exposure from cannabis?
Learn from the past: don’t want to re-create a “crack baby” scenario; or a reefer madness approach that will backfire.

Recognize the complexities and nuances: effects may be modest, selective (individual differences), confounded with other drug use, or delayed in onset.

Need concise, accurate health messages for diverse populations, especially teens and pregnant women (Warning labels).

States with medical marijuana laws should recommend against cannabis for pregnant (or breastfeeding) women.

Physicians who are recommending cannabis need better training on risks.
Cannabis-Associated Psychosis

Study of Swedish Conscripts (n=45570)


Regular Cannabis Use Increases Schizophrenia Risk in those with AKT1 rs2494732 genotype

Di Forti et al., Biological Psychiatry, 2012.

Prospective Dunedin study (n=1037)

Risk of schizophrenia-like psychosis at age 26 years

Arseneault et al. BMJ 2002

Effect of High Potency Cannabis on Risk of Psychosis

Di Forti M et al., The Lancet, 2015.
# LEVEL OF CONFIDENCE IN THE EVIDENCE FOR ADVERSE EFFECTS OF CHRONIC MARIJUANA USE ON HEALTH AND WELL-BEING

<table>
<thead>
<tr>
<th>Effect</th>
<th>Overall Level of Confidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addiction to marijuana and other substances</td>
<td>High</td>
</tr>
<tr>
<td>Abnormal brain development</td>
<td>Medium</td>
</tr>
<tr>
<td>Progression to use of other drugs</td>
<td>Medium</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Medium</td>
</tr>
<tr>
<td>Depression or anxiety</td>
<td>Low</td>
</tr>
<tr>
<td>Diminished lifetime achievement</td>
<td>High</td>
</tr>
<tr>
<td>Motor vehicle accidents</td>
<td>High</td>
</tr>
<tr>
<td>Symptoms of chronic bronchitis</td>
<td>High</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Low</td>
</tr>
</tbody>
</table>

Endocannabinoids are produced \textit{on demand}. They travel back to the transmitting neuron to dampen further activity.

THE ENDOCANNABINOID SYSTEM: THERAPEUTIC POTENTIAL OF CANNABIS

- **Exogenous compounds**
  - Phytocannabinoids
    - THC, CBD, combinations
  - Synthetic cannabinoids
    - Dronabinol
- **Endogenous manipulation**
  - FAAH inhibitors
  - MAGL inhibitors
  - Allosteric modulators
- **Receptor targets**
  - CB1, CB2, TRPV1, PPAR, 5-HT, peripheral, others…

Source: Canadian Consortium for the Investigation of Cannabinoids, http://www.ccic.net/
ANNABIS: MOST COMMONLY USED “ILLICIT” DRUG IN THE U.S.

• Over 22 million Americans 12 and older were past month marijuana users.

• Approximately 4.0 million Americans met criteria for cannabis use disorders in 2015.

• An estimated 2.6 million Americans used it for the first time; 1.2 million were between the ages of 12 and 17.

Source: 2016 National Survey on Drug Use and Health, SAMHSA
TRENDS AMONG CURRENT CANNABIS USERS: TWO IN FIVE ARE DAILY OR ALMOST DAILY USERS

Number of Days Used Cannabis in the Past Month

2002

2014

1 to 2 Days, 23%

3 to 5 Days, 16%

6 to 19 Days, 20%

20 or More Days, 42%

22.2 Million Past Month Users of Cannabis in 2014
14.6 Million Past Month Users of Cannabis in 2002

PATTERNS AND TRENDS

What We Know:

• Use among youth (12-17) has not increased in recent years despite decreased perception of risk
• Current users use more often (daily, nearly daily) than in 2002
• Potency is increasing; plant components are changing
• Cannabis is being administered through different routes

What We Need to Know:

• Need improved measures of frequency, dosage, patterns of use
• Persuasive Messaging (especially for youth) to counter the trend of decreasing harm perception
• Greater knowledge of the impact of changing potency (user titration?), constituents, and alternative routes of administration
• Regional differences based on changing laws, policies, and social norms
• Use of other substances: complementarity vs. substitution
CANNABIS USE DURING PREGNANCY IS INCREASING


Source: Brown et al., 2017
# Strength of the Evidence For Marijuana/Cannabinoid Medical Applications

<table>
<thead>
<tr>
<th>Strongest Evidence</th>
<th>Modest Evidence</th>
<th>Weakest Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Nausea (Cancer chemotherapy)</td>
<td>• Anticonvulsant (CBD)</td>
<td>• PTSD</td>
</tr>
<tr>
<td>• Spasticity and Pain (MS)</td>
<td>• Anti-inflammatory (CBD)</td>
<td>• ADHD</td>
</tr>
<tr>
<td>• Appetite Stimulant (AIDS-associated wasting)</td>
<td>• Antitumor (THC/CBD) (animal models/cell cultures: glioblastoma; breast cancer cells; others (mechanisms: apoptosis; inhibition of tumor angiogenesis)</td>
<td>• Alzheimer’s</td>
</tr>
<tr>
<td><strong>Pain esp. neuropathic</strong></td>
<td></td>
<td>• Depression</td>
</tr>
<tr>
<td>• Glaucoma (decreases intraocular pressure; no evidence it slows disease progression; and short acting)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity.
- P.F. Whiting et al; JAMA 2015

“There is evidence for the use of low-dose medical marijuana in refractory neuropathic pain in conjunction with traditional analgesics.”
- A. Deshpande et al; CFP 2015

“currently available cannabinoids are safe, modestly effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain.”
- M.E. Lynch & M.A. Ware; J Neuroimmune Pharmacology 2015