CANNABIS: STATE OF THE SCIENCE

National Cannabis Summit
August 29, 2017
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Division of Extramural Research
PREVALENCE AND TRENDS
CANNABIS: 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.

Tetrahydrocannabinol (THC)
Psychoactive Ingredient in Marijuana

Source: 2016 National Survey on Drug Use and Health, SAMHSA
Past Month Use of Cigarettes, Marijuana, and Alcohol in 12th Graders

nearly 6% report daily use of marijuana

Source: University of Michigan, 2016 Monitoring the Future Study
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
AMONG CURRENT MARIJUANA USERS, MORE THAN TWO IN FIVE ARE DAILY OR ALMOST DAILY USERS

Number of Days Used Marijuana in the Past Month

<table>
<thead>
<tr>
<th>Days Used</th>
<th>2002 Percentage</th>
<th>2015 Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 2 Days</td>
<td>24%</td>
<td>22%</td>
</tr>
<tr>
<td>3 to 5 Days</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>6 to 19 Days</td>
<td>25%</td>
<td>20%</td>
</tr>
<tr>
<td>20 or More Days</td>
<td>33%</td>
<td>42%</td>
</tr>
</tbody>
</table>

22.2 Million Past Month Users of Cannabis in 2015
14.6 Million Past Month Users of Cannabis in 2002

Source: SAMHSA, 2015 National Survey on Drug Use and Health (September 2016).
CHANGING LANDSCAPE: INCREASING POTENCY & NEW ROUTES OF ADMINISTRATION

Δ-9 THC

12th grade Past Year Users

SOURCE: University of Mississippi; University of Michigan, 2014 Monitoring the Future Study
PATTERNS AND GAPS

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
ADVERSE HEALTH AND SOCIAL CONSEQUENCES OF CANNABIS USE
CANNABIS’ ACUTE EFFECTS
(INTOXICATION PHASE)

- Euphoria
- Calmness
- Appetite stimulation
- Altered perception of time
- Heightened sensation
- Impairs coordination and balance
- Increased heart rate: 20 - 100%
  - Some evidence for increased risk of heart attack, may be exacerbated in vulnerable individuals (e.g., baby boomers?)
- Orthostatic (postural) hypotension
- Increased risk of accidents (~2 fold), higher when combined with alcohol
CANNABIS’ ACUTE EFFECTS (INTOXICATION PHASE)

- Cognition
  - Impaired short-term memory
  - Difficulty with complex tasks
  - Difficulty learning
- Executive Function
  - Impaired decision-making
  - Increased risky behavior – STDs, HIV?
- Mood (especially after high doses or Edibles)
  - Anxiety – panic attacks
  - Psychosis – paranoia
LONG TERM OUTCOMES:

WE KNOW LESS ABOUT THE LONG TERM HEALTH IMPACT FOLLOWING CHRONIC CANNABIS USE, PARTICULARLY WITH RESPECT TO CAUSALITY.
CANNABIS AND BRAIN DEVELOPMENT: MOST VULNERABLE POPULATIONS

Prenatal

Adolescent
Compared to those who did not report severe nausea during pregnancy, women who did experience severe nausea were more likely to report marijuana use during pregnancy (3.7% vs 2.3%; $P = .034$).

CANNABIS USE DURING PREGNANCY IS INCREASING


Source: Brown et al., 2017
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)

By Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Pregnant</th>
<th>Nonpregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-17 y</td>
<td>14.02</td>
<td>6.45</td>
</tr>
<tr>
<td>18-25 y</td>
<td>14.11</td>
<td>6.21</td>
</tr>
<tr>
<td>≥ 26 y</td>
<td>1.77</td>
<td>5.17</td>
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</table>


By Trimester

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>6.44</td>
</tr>
<tr>
<td>Second</td>
<td>3.34</td>
</tr>
<tr>
<td>Third</td>
<td>1.82</td>
</tr>
</tbody>
</table>

WHAT WE KNOW ABOUT PRENATAL CANNABIS EXPOSURE

- Cannabinoids → lipid soluble, cross the placenta and accumulate in fetal tissues, especially, the brain.
- Components of the endocannabinoid system are present during embryonic development as early as 16-22 days’ gestation in humans.
  - Time of neural plate and neural tube development, the basic scaffold for the forebrain, midbrain, and hindbrain establishment.
- Several cohort studies have documented modest neurodevelopmental deficits in children, adolescents, and young adults who were prenatally exposed to cannabis (multiple caveats).
- Recent meta-analysis → infants exposed to cannabis in utero have lower birth weight and are more likely to be admitted to the neonatal intensive care unit (NICU) compared to infants without such exposure.
- Preclinical studies show multiple effects of THC exposure on adult drug seeking behavior, reward and other brain systems, and epigenetic mechanisms.
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?
The Brain Continues to Mature into Early Adulthood.

Does Cannabis (and other substances) affect the developing brain and an individual’s trajectory into adulthood?
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).

Source: 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
**ADDICTION**: 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>32</td>
</tr>
<tr>
<td>Alcohol</td>
<td>15</td>
</tr>
<tr>
<td>Cannabis</td>
<td>9</td>
</tr>
<tr>
<td>Cocaine</td>
<td>17</td>
</tr>
<tr>
<td>Stimulant</td>
<td>11</td>
</tr>
<tr>
<td>Analgesics</td>
<td>8</td>
</tr>
<tr>
<td>Psychedelics</td>
<td>5</td>
</tr>
<tr>
<td>Heroin</td>
<td>23</td>
</tr>
</tbody>
</table>

*Nonmedical Use*

Source: Anthony JC et al., 1994
Cannabis-Associated Psychosis

Andréasson et al. Lancet, 1987

Study of Swedish Conscripts (n=45570)

- Cases per 1,000
- # of times cannabis used

<table>
<thead>
<tr>
<th># of times cannabis used</th>
<th>Cases per 1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1.6</td>
</tr>
<tr>
<td>2</td>
<td>4.5</td>
</tr>
<tr>
<td>10</td>
<td>5.4*</td>
</tr>
<tr>
<td>&lt;50</td>
<td>1.9</td>
</tr>
<tr>
<td>&gt;50</td>
<td>2.7*</td>
</tr>
</tbody>
</table>

Arseneault et al. BMJ 2002

Prospective Dunedin study (n=1037)

- Risk of schizophrenia-like psychosis at age 26 years

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

- Di Forti et al., Biological Psychiatry, 2012

- Effect of High Potency Cannabis on Risk of Psychosis

- Di Forti M et al., The Lancet, 2015
When MJ Sales Were Restricted in the Netherlands, University Grades Improved

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
Adolescent Brain Cognitive Development (ABCD) Study

A Federal Collaboration: NIDA, NIAAA, NCI, NIMH, NIMHD, NICHD, NINDS, OBSSR, ORWH, CDC-DASH, DOJ

Ten year longitudinal study of 10,000 children from age 10 to 20 years to assess effects of childhood experiences, including use of cannabis and other substances on individual brain development trajectories.
THERAPEUTICS: PROMISE OF CANNABIS AND THE ENDOCANNABINOID SYSTEM
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)
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/
Cannabinoid Receptors Are Also Located Throughout the Body

Whole Body Distribution of CB1 Receptors (11C-MePPEP)

Distribution of CB2 Receptors [11C]-NE40

Terry et al., Eur J Nucl Med Mol Imaging. 2010

Ahmad et al., Mol Imaging Biol. 2013 A
Endocannabinoids are produced on demand. They travel back to the transmitting neuron to dampen further activity.

What is Cannabidiol (CBD)?

- Schedule 1 controlled substance
- It doesn’t act through CB1 or CB2 receptors
- Potential mechanisms of action: 5HT1a receptors; glycine receptors; orphan G-protein coupled receptors; FAAH inhibition; more...
- Does not have rewarding effects
- May counteract some effects of THC
  - Bred out of “high potency” cannabis
- May have a wide range of medical uses
- Promising effects in childhood epilepsy (Epidiolex)
Epidiolex (Cannabidiol) in Tx Resistant Epilepsy

Devinsky O et al., Poster presented at the 2015 Annual Meeting of the American Epilepsy Society. Funded by GW Pharmaceuticals, the company developing Epidiolex.
Enzyme Inhibitors (e.g., AEA degradation)

Indirect enhancers of CB activity—more selective, less side effects

What have we learned?

- FAAH inhibitors
- Reduce anxiety-like behaviors
- Reduce depression-like behaviors
- Enhance social behavior in ASD models
- Reduce nicotine addiction
- May be effective for cannabis use disorder

Very mild side effect profile in animals and humans

Piomelli, 2016
EXPLOITING THE CANNABINOID SYSTEM FOR THERAPEUTIC PURPOSES

- 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/
POLICY:  
CANNABIS POLICY IS INFLUENCED BY A VARIETY OF FACTORS

Complicated and Moving Fast
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.
51 Medical Conditions For Which Marijuana Is Approved by a State

1. Alzheimer's Disease
2. Anorexia
3. Arnold-Chiari malformation
4. Arthritis
5. Ataxia
6. Cachexia
7. Cancer
8. Cardiopulmonary respiratory syndrome
9. Causalgia
10. Cervical dystonia
11. Crohn's disease
12. Decompensated cirrhosis
13. Dystonia
14. Epilepsy
15. Fibromyalgia
16. Glaucoma
17. Hepatitis C
18. HIV/AIDS
19. Huntington's disease
20. Hydrocephalus
21. Inflammatory autoimmune-mediated arthritis
22. Inflammatory bowel disease (IBS)
23. Inflammatory demyelinating polyneuropathy
24. Interstitial cystitis
25. Lou Gehrig's disease (amyotrophic lateral sclerosis, ALS)
26. Migraines
27. Multiple Sclerosis
28. Muscle spasms
29. Muscular dystrophy
30. Myasthenia gravis
31. Myoclonus
32. Nail-patella syndrome
33. Nausea or vomiting
34. Neurofibromatosis
35. Neuropathy
36. Pain
37. Pancreatitits
38. Parkinson's disease
39. Peripheral neuropathy
40. Post-traumatic stress disorder (PTSD)
41. Reflex sympathetic dystrophy
42. Residual limb pain from amputation
43. Seizure disorders
44. Sjogren's syndrome
45. Spasticity
46. Spinal cord damage with intractable spasticity
47. Syringomyelia
48. Terminal illness
49. Tourette’s syndrome
50. Traumatic brain injury

### 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</strong> esp. neuropathic</td>
<td></td>
<td>• Depression</td>
</tr>
<tr>
<td>• Glaucoma (decreases intraocular pressure; no evidence it slows disease progression; and short acting)</td>
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</tbody>
</table>
RECENT META-ANALYSES SUPPORT THE USE OF CANNABINOIDs FOR CHRONIC NEUROPATHIC NON CANCER PAIN, BUT.....

- Studies generally short, small, with modest effect sizes.

- "Limited evidence suggests that cannabis may alleviate neuropathic pain in some patients, but insufficient evidence exists for other types of chronic pain." - S. Nugent et al; Annals of Internal Medicine 2017

- "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

- "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

- "Limited evidence suggests that cannabis may alleviate neuropathic pain in some patients, but insufficient evidence exists for other types of chronic pain." - S. Nugent et al; Annals of Internal Medicine 2017
Urgent Need for Alternative Pain Management, but
The Medical Cannabis “Store”...

*States with MML/Dispensaries report:*
- Decreasing rates OD deaths
- Fewer opioid treatment admissions
- Fewer opioid Rxs
- Savings in Medicare spending
- Patient – reported decreases in opioid and other pain medication use
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).
POLICY CONUNDRUMS:

- Although some form of cannabis legalization is occurring in most states, uncertainties exist because it remains illegal under Federal law.
- Science is lagging behind policy, and policymakers are looking for data to guide their decisions.
- Health messaging must be nuanced and accurate; discussions about cannabis rarely are.
- Scientists are more conservative in their messaging than advocates.
- Hard to control messaging even if marketing of products is restricted.
OTHER POLICY CONSIDERATIONS:

- Substance use is affected by availability, cost, perception of harm (including risk of criminal penalties).
- Perceptions of harm are decreasing across all age groups.
- The 2 currently legal drugs (tobacco and alcohol) are the most costly to society—*because* they are widely used—*not* because they are the most dangerous.
- Societal norms influence use (tobacco use is dropping).
- Big money has been influencing state legalization efforts. Lobbying will increase if these efforts succeed.
- With no Federal oversight or guidance, state are implementing diverse policies.
CHALLENGE:
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
  • Surveillance: Problematic use, ER visits, Accidents, Academic Achievement
• Communication: Develop credible, persuasive, simple messages for the public, the medical community, policymakers