Adverse Effects of Marijuana: What We Know, What We Need to Know, and What Keeps Us Up at Night

THE TRIANGULUM: TOBACCO, MARIJUANA, AND E-CIGARETTES
May 26, 2016
Susan R.B. Weiss, Ph.D.
Director
Division of Extramural Research
Marijuana: Most Commonly Used Illicit Drug In the U.S.

- Over **117 million** Americans 12 and older have tried it at least once; ~13% used it in the past year

- An estimated **2.6 million** Americans used it for the first time in 2014

Tetrahydrocannabinol (THC)
Psychoactive Ingredient in Marijuana

2015 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

University of Michigan, 2015 Monitoring the Future Study.
Changes in Marijuana Laws in the U.S.

Adolescents Marijuana Use Higher in States Where it is Legal

Source: NORML, Drug Policy Alliance, and the Marijuana Policy Project

Source: SAMHSA.gov, National Survey on Drug Use and Health 2012 and 2013
Marijuana contains ~100 cannabinoids plus other chemicals in varying concentrations.
Cannabinoid Receptors Are Located Throughout the Brain and Regulate:

- Brain Development
- Memory & Cognition
- Motivation & Reward
- Appetite
- Immune Function
- Reproduction
- Movement/Coordination
- Pain & Analgesia
Cannabis Effects on the Brain
Marijuana’s *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
Marijuana’s *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)
  - Anxiety – panic attacks
  - Psychosis – paranoia
Long Term Outcomes:

We know less about the long term health impact following chronic marijuana use, particularly with respect to causality.
Long Term Effects of Marijuana

**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**

* Nonmedical Use

Anthony JC et al., 1994
Cannabis-Associated Psychosis

**Study of Swedish Conscripts (n=45570)**

<table>
<thead>
<tr>
<th>No of times cannabis taken</th>
<th>Cases per 1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.5</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>4.5</td>
</tr>
<tr>
<td>&lt;50</td>
<td>4.5</td>
</tr>
<tr>
<td>&gt;50</td>
<td>4.5</td>
</tr>
</tbody>
</table>


**Prospective Dunedin study (n=1037)**

Risk of schizophrenia-like psychosis at age 26 years

<table>
<thead>
<tr>
<th>Cannabis users by age 15 years</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis users by age 18 years</td>
<td>Odds ratio</td>
</tr>
</tbody>
</table>

| Cannabis users by age 15 years | 4.5 |
| Cannabis users by age 18 years | 1.6 |

Arseneault et al BMJ 2002

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

<table>
<thead>
<tr>
<th>AKT1(T/T)</th>
<th>AKT(C/T)</th>
<th>AKT1(C/C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds Ratio</td>
<td>Odds Ratio</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>0.49</td>
<td>0.62</td>
<td>0.91</td>
</tr>
<tr>
<td>1</td>
<td>2.7*</td>
<td>5.4*</td>
</tr>
</tbody>
</table>

Di Forti et al., Biological Psychiatry, 2012.

**Effect of High Potency Cannabis on Risk of Psychosis**

<table>
<thead>
<tr>
<th>Regular Cannabis Use</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never used cannabis</td>
<td>1</td>
</tr>
<tr>
<td>Hash &lt; than weekly</td>
<td>0.49</td>
</tr>
<tr>
<td>Hash at week ends</td>
<td>0.62</td>
</tr>
<tr>
<td>Hash daily</td>
<td>0.91</td>
</tr>
<tr>
<td>Skunk &lt; than weekly</td>
<td>1.9</td>
</tr>
<tr>
<td>Skunk at week ends</td>
<td>2.7*</td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>5.4*</td>
</tr>
</tbody>
</table>

Di Forti M et al., The Lancet published online February 18, 2015.
The Brain Continues to Mature into Early Adulthood.

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

Adjusted Odds Ratios

Less than Monthly
Monthly or More
Weekly or More
Daily

Cannabis Dependence
Other Illicit Drug Use
Suicide Attempt

High School Completion
Degree Attainment
Depression
Welfare Dependence

Silins E et al., The Lancet September 2014.
Persistent Cannabis Users Show Neuropsychological Decline from Childhood to Midlife

Dunedin prospective study of 1037 Ss born 1972/73,

Tested for IQ at age 13 and 38y.

Tested for cannabis dependence ages 18, 21, 26, 32 and 38y

Adolescent Vulnerability

<table>
<thead>
<tr>
<th>Change in Full-Scale IQ (in standard deviation units)</th>
<th>1 Diagnosis</th>
<th>2 Diagnoses</th>
<th>3 Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis Dependent Before Age 18 (n=17)</td>
<td>p=.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Cannabis Dependent Before Age 18 (n=57)</td>
<td></td>
<td>p=.09</td>
<td></td>
</tr>
<tr>
<td>Cannabis Dependent Before Age 18 (n=12)</td>
<td></td>
<td></td>
<td>p=.02</td>
</tr>
<tr>
<td>Not Cannabis Dependent Before Age 18 (n=21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis Dependent Before Age 18 (n=23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not Cannabis Dependent Before Age 18 (n=14)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Brain Structure: Early (<18y) Long-Term 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.
Gateway Effects
Drug Use Outcomes in Twin Pairs (n=234) Discordant for **Cannabis** Use Before Age 17

Gateway Effects: Nicotine Pre-exposure Enhances Cocaine Effects in Mice, but not Vice-Versa

Adapted from Levine et al, 2011
What do we need to know about the Triangulum: cigarettes, e-cigarettes and cannabis?

- **Substance Initiation:** does using one substance increase the likelihood of using others?
  - Epidemiological evidence--Yes
  - Common genetic vulnerabilities--Yes
  - Common environmental vulnerabilities--Yes
  - Neurobiological evidence--Likely

- **Cessation:** does using one interfere with the ability to quit using another?
  - Data are mixed
What do we need to know about the Triangulum?

- Health Effects
  - Addiction
    - Are combined products more addictive than either alone?
  - Cancer
    - Can we disentangle cannabis vs. tobacco effects?
  - Heart Disease
  - Cognitive function, Affect, Motivation
    - Will cannabis and nicotine worsen or counter each other’s effects?
- Let’s not forget the Quadrangulum: Alcohol or even the Pentagulum (?) Mental Illness