Health Effects of Cannabis Use

David C. Rettew, M.D.  PediPsych
Associate Professor of Psychiatry and Pediatrics
Director, Pediatric Psychiatry Clinic
Program Director, Child Psychiatry Fellowship
University of Vermont, College of Medicine
### Disclosures of Potential Conflicts

<table>
<thead>
<tr>
<th>Source</th>
<th>Research Funding</th>
<th>Advisor/Consultant</th>
<th>Employee</th>
<th>Speakers’ Bureau</th>
<th>Books, Intellectual Property</th>
<th>In-kind Services (example: travel)</th>
<th>Stock or Equity</th>
<th>Honorarium or expenses for this presentation or meeting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norton &amp; Norton</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIMH</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychology Today</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Blogs**

- [http://blog.uvm.edu/drettew](http://blog.uvm.edu/drettew)
- [http://www.psychologytoday.com/blog/abcs-child-psychiatry](http://www.psychologytoday.com/blog/abcs-child-psychiatry)
Outline

• Review current trends in cannabis use
• Outline medical evidence regarding links between cannabis use and psychiatric/cognitive problems
• Discuss cannabis dependence
Marijuana/Cannabis / Cannabinoids
Over 100 compounds; over 70 phytocannabinoids

Delta-9 THC prominent psychoactive constituent

Dose related effects:
- High, euphoria, relaxation
- Cognitive impairment (memory, learning, attention, time perspective)
- Anxiety, Panic, Hallucinations, Psychosis?
- Abuse/Dependence
Increased THC Content of Cannabis

Figure 1. Average Δ^3-tetrahydrocannabinol (THC) concentration of Drug Enforcement Administration specimens by year, 1995-2014.

With increased potency, decreased ratio of THC/cannabadiol
• Key Findings from Oct 2015 report
• Face to face interviews with 80,000 adults
• Past year use up from 4.1% (2001) to 9.5% (2013)
• Use disorder rose from 1.5% to 2.9%, mainly from new users
• 1 in 3 users have problematic use
National Cannabis Use Past 40 Years
Monitoring the Future Study

Use
% who used in last 12 months

YEAR
PERCENT

8th Grade
10th Grade
12th Grade

Vermont Center for Children Youth & Families
Vermont Family Based Approach
Prevalence of Current Use of and Dependence on Cannabis

- 1995: 0.5% Use, 1.5% Dependence
- 2001: 2.0% Use, 1.5% Dependence
- 2012: 4.0% Use, 3.0% Dependence, 10.0% Use, 3.0% Dependence

Vermont Center for Children Youth & Families
Vermont Family Based Approach
National Cannabis Use Trends

Teen marijuana use holds steady
Past-month marijuana use by age group, 2002 to 2014

Source: 2014 National Survey on Drug Use and Health

Vermont Center for Children Youth & Families
Vermont Family Based Approach
Cannabis Use Among Youth

Figure 1. Marijuana use in the past month among youths aged 12 to 17, by state: percentages, annual averages, 2013–2014

Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Surveys on Drug Use and Health (NSDUHs), 2013 and 2014.
Marijuana Use in the Past 30 Days

- Just over one in five students (22%) used marijuana at least one time during the past 30 days.
- Males were significantly more likely to use marijuana than females.
- Current marijuana use increased significantly from ninth through eleventh grade.
- Current marijuana use was similar in 2013 and 2015. Current marijuana use remains above the Healthy Vermonters 2020 goal of 20%.

Substances Except Cannabis Dropping

Use of Alcohol and Cigarettes Steadily Drops While Marijuana Use Holds Steady

Between 2010 and 2015, alcohol use and cigarette use, respectively, decreased 20% and 47% among 8th, 10th, and 12th graders, while marijuana use remained unchanged.

Source: 2015 Monitoring the Future Survey, National Institute on Drug Abuse
Use Goes Up As Perceived Risk Falls

In VT, perception of harm 21.06% 2012-2013 to 18.89% in 2013-2014 (not significant)
Adult Cannabis Use by Sales

Recreational use Up 88%

Where will it plateau?

Sales stats for Colorado weed
A month-by-month look comparing sales of recreational and medical marijuana

Washington's Cash Crop: State Reaps Marijuana Tax Windfall
As pot sales climb, so does state's share of the revenue

Source: Washington Economic & Revenue Forecast Council

Bloomberg

Source: Colorado Dept. of Revenue, graphic by Kevin Hamm, The Denver Post

2015 Recreational total $587,834,219
2015 Medical total $408,350,569

2015: $996,184,788

2014 Recreational total $313,226,353
2014 Medical total $385,972,452

2014: $699,198,805
Teen Cannabis In 3 Highest Use States

Colorado 2011-2012 rate: 10.47%
What is the effect of commercialization?
Murray: *think we should wait and see what happens in the US. I say doing research on monkey and rats is very expensive, you have to look after them, keep them in cages. Americans are doing it for free. So we just wait and see what happens in Colorado, more psychosis, and more road traffic accidents. We should be cautious.*

Host: *Lab rats. Human lab rats.*

Murray: *American lab rats for free.*
Brain Cannabinoid System

- Brain has cannabinoid receptors in brain
- Anandamine is brain endocannabinoid
- Involved in
  - Brain growth
  - Myelin growth on neurons
  - Neuronal activity
  - Regulates other neurotransmitters
- Plant THC stronger and longer lasting effect than anandamine
Circuits Involved In Drug Abuse and Addiction

All of these brain regions must be considered in developing strategies to effectively treat addiction
cannabinoid CB1 receptor

endogenous ligands:
anandamine, 2-arachidonoylglycerol, palmitoylethanolamide

post-synaptic membrane

cytoplasm

inhibitory G-protein
Cannabis Changes the Brain, Especially Young Ones

Long-term effects of marijuana use on the brain

Francesca M. Filbey\textsuperscript{a,1}, Sina Aslan\textsuperscript{a,b}, Vince D. Calhoun\textsuperscript{c,d}, Jeffrey S. Spence\textsuperscript{a}, Eswar Damaraju\textsuperscript{e}, Arvind Caprihan\textsuperscript{c}, and Judith Segall\textsuperscript{c}

Neurobiology of Disease

Cannabis Use Is Quantitatively Associated with Nucleus Accumbens and Amygdala Abnormalities in Young Adult Recreational Users

Fig. 1. Group comparison of the gray matter volume by SPM8 plus DARTEL analysis demonstrates significant reduction of gray matter volume in bilateral orbitofrontal gyri (AAL atlas) in marijuana users compared with controls. Right side of the image represents the right hemisphere in axial view.

Effect of high-potency cannabis on corpus callosum microstructure
Brain Changes with Cannabis Use

• Adolescence period of intense brain changes
  – Lower grey/white
  – Lower to higher areas
• Review of 31 studies
• Changes found in areas with high CB receptors (hippocampus, cerebellum, prefrontal cortex, amygdala)
• Magnitude related to dose and earlier age of use

(Lorenzetti et al., 2016)
Animal Model Studies
(Rubino & Parolaro, 2016)

- Cannabinoid exposure in adolescent animals
  - Decreased social behavior
  - Decreased motivation
  - Mixed results with anxiety
  - Impairment in working memory and decision making

**Figure 1.** Diagram representing the most important events altered by adolescent cannabinoid exposure leading to impaired behavior in adulthood. ECS, endocannabinoid system; GABA, gamma-aminobutyric acid; THC, delta9-tetrahydrocannabinol.
Medical Marijuana

• Started as “compassionate use” in terminally ill patients
• Medical evidence quite limited, strongest for
  – Chemotherapy induced nausea and vomiting
  – Muscle spasticity in MS
  – Increasing appetite in wasting due to AIDS
  – Intractable epilepsy
• Studies often use isolated compounds not smoking plant
  – Analogy with penicillin and mold
• Some products already on market: Marinol and Sativex
Link to Psychiatric Disorders

- Psychosis and Schizophrenia
- Depression
- Anxiety and PTSD
- Other Substance Use Disorders
- Cognition and IQ
Cannabis Use Doubles the Risk for Psychosis

Table 1: General population studies of the effect of cannabis use on the risk of psychosis

<table>
<thead>
<tr>
<th>Country in which the study was conducted</th>
<th>Number of participants</th>
<th>Follow up</th>
<th>Odds ratio (95% confidence interval)</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>4,494</td>
<td>NA</td>
<td>2.4 (1.2, 7.1)</td>
<td>Population based</td>
</tr>
<tr>
<td>Sweden</td>
<td>50,053</td>
<td>25 years</td>
<td>2.1 (1.2, 3.7)</td>
<td>Conscript cohort</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>4,045</td>
<td>3 years</td>
<td>2.8 (1.2, 6.5)</td>
<td>Population based</td>
</tr>
<tr>
<td>Israel</td>
<td>9,724</td>
<td>4–15 years</td>
<td>2.0 (1.3, 3.1)</td>
<td>Population based</td>
</tr>
<tr>
<td>New Zealand (Christchurch)</td>
<td>1,265</td>
<td>3 years</td>
<td>1.8 (1.2, 2.6)</td>
<td>Birth cohort</td>
</tr>
<tr>
<td>New Zealand (Dunedin)</td>
<td>1,253</td>
<td>15 years</td>
<td>3.1 (0.7, 13.3)</td>
<td>Birth cohort</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>1,580</td>
<td>14 years</td>
<td>2.8 (1.79, 4.43)</td>
<td>Population based</td>
</tr>
<tr>
<td>Germany</td>
<td>2,436</td>
<td>4 years</td>
<td>1.7 (1.1, 1.5)</td>
<td>Population based</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>8,580</td>
<td>18 months</td>
<td>1.5 (0.55, 3.94)</td>
<td>Population based</td>
</tr>
</tbody>
</table>

NA, not applicable.

2–fold increase

Morrison, Murray et al., Nature Neuroscience, 2008

Alan Budney PHD  Giesel School Of Medicine, Dartmouth
Is Cannabis Causal in Psychosis?

- Overall risk 1.46 or ever-users and 2.1 for heavier users
- Factors leading to overestimation of risk
  - Residual confounding (e.g. shared genetics): possible
  - Bias of labeling intoxication as psychosis: unlikely
  - Reverse causation: unlikely
- Factor leading to underestimation of risk
  - Misclassification of use
  - Attrition in follow-up
  - Lower THC content of earlier studies
- Other factors indicating causation
  - Dose dependence
  - Potency differences
  - Acute intoxication effects
  - Increased risk in with certain genes

Gage et al., Bio Psychiatry, 2015
Teen Cannabis and Subclinical Psychosis

- Increased subclinical psychosis among regular cannabis users
  - Persisted after 1 year of abstinence
  - Analyses controlled for many other factors including other types of psychopathology
- Study analyses change in cannabis use and change in psychosis

Bechtold et al., AJP, 2016
BMJ Open  Association of cannabis use with hospital admission and antipsychotic treatment failure in first episode psychosis: an observational study

Rashmi Patel,1 Robin Wilson,1 Richard Jackson,2 Michael Ball,2 Hitesh Shetty,3 Matthew Broadbent,3 Robert Stewart,2 Philip McGuire,1 Sagnik Bhattacharyya1

- Published March 2016
- Up to 5 year clinical outcomes studied from electronic records
- Cannabis use among first-episode psychosis associated with
  - More and longer hospital admissions
  - More antipsychotics needing to be tried
- Possible mediation of link through poorer medication response
A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population - a meta-analysis of 31 studies

- From Kedzior & Laeber, BMC Psychiatry, 2014
- Overall increase with cannabis use (OR 1.24) and cannabis use disorder (OR 1.68)

<table>
<thead>
<tr>
<th>Study name</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crum et al. 1993 [38]</td>
<td>1.54</td>
<td>0.78</td>
<td>3.04</td>
<td>0.218</td>
</tr>
<tr>
<td>Fergusson et al. 1996 [42]</td>
<td>1.20</td>
<td>0.51</td>
<td>2.84</td>
<td>0.678</td>
</tr>
<tr>
<td>Brook et al. 1998 [28]</td>
<td>1.16</td>
<td>1.00</td>
<td>1.35</td>
<td>0.063</td>
</tr>
<tr>
<td>Brook et al. 2001 [29] combined</td>
<td>1.18</td>
<td>0.94</td>
<td>1.48</td>
<td>0.153</td>
</tr>
<tr>
<td>Degenhardt et al. 2001 [39]</td>
<td>0.89</td>
<td>0.62</td>
<td>1.28</td>
<td>0.528</td>
</tr>
<tr>
<td>Chabrol et al. 2005 [34]</td>
<td>1.36</td>
<td>0.83</td>
<td>2.22</td>
<td>0.222</td>
</tr>
<tr>
<td>Lamers et al. 2006 [44]</td>
<td>0.55</td>
<td>0.15</td>
<td>2.03</td>
<td>0.368</td>
</tr>
<tr>
<td>Zvolensky et al. 2006 [54]</td>
<td>0.89</td>
<td>0.62</td>
<td>1.28</td>
<td>0.528</td>
</tr>
<tr>
<td>van Laar et al. 2007 [52]</td>
<td>1.18</td>
<td>0.71</td>
<td>1.97</td>
<td>0.525</td>
</tr>
<tr>
<td>Wittchen et al. 2007 [53]</td>
<td>1.50</td>
<td>1.09</td>
<td>2.07</td>
<td>0.014</td>
</tr>
<tr>
<td>Buckner &amp; Schmidt 2008 [31]</td>
<td>0.81</td>
<td>0.50</td>
<td>1.33</td>
<td>0.409</td>
</tr>
<tr>
<td>Chabrol et al. 2008 [35]</td>
<td>1.94</td>
<td>1.14</td>
<td>3.30</td>
<td>0.015</td>
</tr>
<tr>
<td>NCS-R 2010 [37,55] combined</td>
<td>2.04</td>
<td>1.50</td>
<td>2.78</td>
<td>0.000</td>
</tr>
<tr>
<td>Buckner et al. 2012 [32]</td>
<td>1.05</td>
<td>0.62</td>
<td>1.80</td>
<td>0.853</td>
</tr>
<tr>
<td>Degenhardt et al. 2013 [41]</td>
<td>3.20</td>
<td>1.11</td>
<td>9.25</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>1.24</td>
<td>1.06</td>
<td>1.45</td>
<td>0.006</td>
</tr>
</tbody>
</table>

- association + association
Cannabis Associated with Worse PTSD

- Recent study of over 2,000 veterans
- Cannabis use associated with the following
  - Worse PTSD symptoms
  - Higher aggression
  - More alcohol and drug use

**Conclusions:** In this observational study, initiating marijuana use after treatment was associated with worse PTSD symptoms, more violent behavior, and alcohol use. Marijuana may actually worsen PTSD symptoms or nullify the benefits of specialized, intensive treatment. Cessation or prevention of use may be an important goal of treatment.

Wilkinson et al., J Clin Psychiatry, 2015
Cannabis and Psychiatric Disorders
(Blanco et al., JAMA Psychiatry, 2016)

- From the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)
- Nationally representative sample of >30,000; Mean age 27, follow up 3 years
- Increased rate of alcohol and drug use at time 2 but not mood and anxiety*
- Note: main analysis divided group by any usage at time 1 and did not focus on heavy use

*Significant connection with Social Anxiety Disorder Found with propensity score analysis
Gateway Hypothesis

- Hypothesis that cannabis use increases likelihood of using even more dangerous drugs
- Studies that have attempted to control for potential confounds and genetic diathesis (discordant twin designs) continue to support this pathway (Lynskey et al., 2003, 2006)
- New evidence of “reverse gateway” with regard to tobacco smoking (Patton et al., 2005)
Cognitive Function

• Strong evidence of impairment in attention, memory, learning when intoxicated (Volkow et al., 2016)

• 2 Meta-analyses show evidence of poorer neuropsychological test performance (executive function, verbal ability, attention, memory) related to longer term use (Grant et al., 2003; Schreiner et al., 2012)
  – Related to age on onset, frequency, length of abstinence
  – BUT restricting studies to those with longer abstinence shows no differences in performance
Cannabis and IQ

• Dunedin study found IQ drop of 8 points from adolescence to adulthood among heavy users who started in adolescence

• Deficits related to frequency and duration of use and age of initiation (adolescence)

• Other studies do not show as sharp of a drop when controlling for other factors (Jackson et al., 2016)

Meier et al., PNAS, 2012
## Cannabis and Cognitive Function
(Broyd et al., Bio Psych, 2016)

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Acute</th>
<th>Chronic</th>
<th>Abstinence</th>
<th>Pertinent Cannabis Use Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal learning and memory</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>Frequency; lifetime use; duration; age of onset; sex</td>
</tr>
<tr>
<td>Working memory</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Frequency; lifetime use; recency; sex</td>
</tr>
<tr>
<td>Other memory function</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Age of onset; frequency; recency</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>Dose; age of onset; length of abstinence; withdrawal effects</td>
</tr>
<tr>
<td>Attentional bias</td>
<td>+</td>
<td>+++</td>
<td>NA</td>
<td>Craving; dependence; frequency; CBD</td>
</tr>
<tr>
<td><strong>Psychomotor Function</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Executive Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planning, reasoning, interference control, and problem solving</td>
<td>+ -</td>
<td>+ -</td>
<td>+ +</td>
<td>Neurodevelopmental stage; age of onset; frequency</td>
</tr>
<tr>
<td>Inhibition</td>
<td>+</td>
<td>-</td>
<td>NA</td>
<td>Frequency; task complexity</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Time estimation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Decision Making</td>
<td>+ -</td>
<td>+ -</td>
<td>-</td>
<td>Age of onset; lifetime exposure; frequency; cannabis use disorder</td>
</tr>
</tbody>
</table>

CBD, cannabidiol; NA, not available (not investigated).

*a* The prevalence of studies focused on acute vs. chronic effects is unequal, as is the literature, subjectively weighed on greater or lesser evidence for impairment across the p size, reached by consensus between the authors of this review.

*b* +++ strong and largely consistent evidence for impairment; ++, moderate evidence; + - , mixed evidence; -, little or no evidence for impairment.
• Longitudinal study of over 50,000 Swedish male soldiers
• Outcome documented to age 60
• Early and “heavy” use (> 50 times) linked to increased risk of death (Adjusted OR 1.4, Raw OR 3.0)
• Controlled for early smoking, alcohol and other factors
Cannabis Use in Pregnancy

• Recent meta-analysis of 24 studies (Gunn et al., 2016)
• Use associated with increased odds of
  – Anemia (OR 1.36)
  – Low birth weight (OR 1.77)
  – Need for intensive care treatment (OR 2.02)
• Dutch studies show negative effect of intrauterine cannabis and fetal growth (Marroun et al., 2009) as well as increase aggression and poorer attention in 18-month old girls (Marroun et al., 2011)
Cannabis Dependence

- Overall risk estimated to be around 9% among ever-users (Hall 2014)
- If use begins in adolescence: rises to 16% (Anthony, 2006)
- If daily use: up to 50% (van der Pol et al., 2013)
Cannabis and Alcohol

The Real Dangers of Marijuana

Jonathan P. Caulkins

Author from RAND

- Cannabis “may generate 62% more abuse and dependence per current user than alcohol does.”

<table>
<thead>
<tr>
<th>Question (Abbreviated)</th>
<th>Relative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needed to use more to get desired effect</td>
<td>3.3</td>
</tr>
<tr>
<td>Spent a lot of time getting or using the drug</td>
<td>3.2</td>
</tr>
<tr>
<td>Drug caused serious problems at home, work, or school</td>
<td>2.8</td>
</tr>
<tr>
<td>Took time from work/school/other important activities</td>
<td>2.6</td>
</tr>
<tr>
<td>Tried to limit use but failed</td>
<td>1.7</td>
</tr>
<tr>
<td>Tried to cut down but failed</td>
<td>1.6</td>
</tr>
<tr>
<td>Caused problems with emotions, nerves, or mental health</td>
<td>1.5</td>
</tr>
<tr>
<td>Continued use despite those problems</td>
<td>1.6</td>
</tr>
<tr>
<td>Drug caused problems with family or friends</td>
<td>1.5</td>
</tr>
<tr>
<td>Continued use despite those problems</td>
<td>1.7</td>
</tr>
<tr>
<td>Using same amount had less effect</td>
<td>1.2</td>
</tr>
<tr>
<td>Drug put you in physical danger</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Source: Author’s analysis of National Household Survey data.
Cannabis Withdrawal Symptoms

1) irritability, anger, or increased aggression
2) nervousness or anxiety
3) sleep difficulty (insomnia)
4) decreased appetite or weight loss
5) restlessness
6) depressed mood
7) at least 1 physical symptom causing significant discomfort (stomach pain, shakiness/tremors, sweating, fever, chills, headache)
Primary Substance of Abuse (Other Than Alcohol) at Admission to U.S. State Licensed or Certified Substance Abuse Treatment Facilities, Ages 12 and Older, 1992 to 2010

- Marijuana
- Heroin
- Other Opiates
- Cocaine
- Methamphetamine

Percentage of All Admissions

Year:
- 1992
- 1994
- 1996
- 1998
- 2000
- 2002
- 2004
- 2006
- 2008
- 2010
Reasons for Quitting

Alcohol/Cocaine/Opioids: In trouble with social, legal, health, work, financial problems

Tobacco: Health concerns, embarrassment

Cannabis: Unfulfilled potential, amotivation, loss of control
Summary Points

• Bulk of scientific evidence supports links between cannabis use and impaired mental functioning, particularly with regard to psychosis and cognition
• Effect sizes, especially when confounds well controlled, often small for non-dependent users
• Risk varies according to genetic diathesis, age and intensity of use, and other factors
• Research is flawed, particularly in ability to completely rule out confounding factors
  • But no more so than many other accepted health risks
Thank you!

QUESTIONS?