In Defense of Our Brains

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McLean Hospital
Our Nation’s Challenges

- Marijuana
- Opioids, overdose deaths
- New Psychoactive Drugs
- Hallucinogens As Medicines

Next...
All Drugs Legal?
Opponents, Supporters: Marijuana Legalization

“Hurts society” vs “It’s a medicine”

**Opponents:** Dangers to Individuals, Society, to Youth, Addictive

- Rec. no, medicinal yes
- Bad for youth
- Gateway drug
- Illegal, should be policed
- Dangerous, addictive
- Hurts society

**Supporters:** Medicinal, Taxation benefits, Harmless, Freedom

- Do what we want to do
- Current enforcement costly
- Benefits of regulation, taxes
- Not as dangerous as other drugs
- Medicinal benefits

Adapted by BK Madras from: PEW RESEARCH CENTER Survey conducted March 25-29, 2015. Open-ended question. Total exceeds 100% because of multiple responses
How Does Marijuana Act?
Marijuana Chemistry

*Cannabis sativa* contains ~ 750 chemicals

\[ \Delta^9\text{-TetraHydroCannabinol} \text{ (THC)} \text{ highest} \]

- ~104 *Phytocannabinoids*, 200-300 terpenoids
- *Synthetic* cannabinoids: 1,000’s made by chemists
- *Endocannabinoids*: Made by brain, body
# Endocannabinoids: Brain, Organs, Blood Cells

## CB1 receptors

- **BRAIN**
  - Heart
  - Pancreas
  - Muscle
  - Testis, ovaries
  - Uterus
  - Prostate
  - Vascular tissue
  - Immune cells

## CB2 receptors

- **BLOOD CELLS**
- **IMMUNE CELLS**
  - Brain
  - Heart
  - Adrenal
  - Intestinal tract
  - Pancreas
  - Bone
  - Smooth muscle
  - Reproductive organs
Marijuana Affects Cannabinoid Signals in Brain

- **NEOCORTEX**: Higher brain functions
- **BASAL GANGLIA**: Motor control, planning
- **VENTRAL STRIATUM**: Predict, feel rev
- **AMYGDALA**: Emotion, anxiety, fear
- **HYPOTHALAMUS**: Hormones, appetite, sex
- **HIPPOCAMPUS**: Memory learning
- **CEREBELLUM**: Motor control coordination
- **BRAIN STEM**: Vomiting, nausea
Is Marijuana Safe?

- Can overdose cause death?
- Cognitive degradation
- Cannabis (Marijuana) Use Disorder
- Motivation
- Psychosis
- Marijuana and other drugs:
  - Alcohol or marijuana?
  - “Opioid priming”?
- Social problems
  - Educational
  - Workplace
  - Parenting
Does Marijuana Kill?
Heroin Overdose Deaths Are Common, not Marijuana... Why?

**Marijuana unlikely to produce an overdose death**
- Marijuana targets (cannabinoid receptors) *scant* in brain stem region that regulates heart rate and breathing.
- Heroin targets (mu opioid receptors) *abundant* in brain stem.

**Intoxication can lead to injuries; injuries can be fatal**
- Marijuana can affect judgment, perception, coordination:
  - driving
  - extreme anxiety with high doses (panic attacks)
  - psychosis in vulnerable people (loss of reality, paranoid)
Cognitive Degradation
Marijuana Intoxication Can Impair Higher Brain Function

- Impairs learning, working memory
- Reduces attention span and concentration
- Reduces ability to plan
- Reduces organizational skills
- Reduces problem solving
- Reduces decision making
- Reduces perception of facts
- Reduces emotional control
- Reduces behavioral control
- Impairs motor coordination
- Increases impulsivity
- Increases hunger
- Distorts perception of time, distance, sounds
- Promotes euphoria, relaxation, sedation
Cognitive Degradation Associated with Short or Long term Marijuana Use

- Impairs learning and memory (short and long term)
  - Verbal IQ, Memory
  - Word associations
  - Processing speed
  - Perseveration

- Impairs decision making
  - Risky sexual behavior
  - Driving
  - Executive function
  - Psychosis

- Impairs motor function
  - Balance, coordination in sports, driving, aviation, workplace

Cognitive Degradation: Early, Persistent Marijuana Use Associated with Reduced I.Q.

<table>
<thead>
<tr>
<th>Age</th>
<th>13 yr</th>
<th>18 yr</th>
<th>21 yr</th>
<th>32 yr</th>
<th>38 yr</th>
</tr>
</thead>
</table>

**IQ drop associated:** with age of onset of use and length of time addicted

**IQ drop most:** if use before age 18, continue, and addicted at 38

**IQ reduced:** if did not quit use at age 38

**IQ still reduced:** if use before 18 and then quit later

Cannabis Use Disorder

- Marijuana: 4.3 million people
- Pain Killers
- Cocaine
- Heroin
- Stimulants
- Tranquilizers
- Hallucinogens
- Inhalants
- Sedatives

Most recent data:
- 6.3% with lifetime cannabis use disorder
- Mild (2.9%) moderate (1.4%) severe (2%)

Blanco et al. JAMA 2016

Prevalence of Addiction to Marijuana is Higher Among Early Users
5-6 Times Higher if Teenager Starts Using at Age 14 or Less

Addiction Higher to Drugs
- Nicotine
- Alcohol
- Marijuana
- Inhalants
- Stimulants
- Cocaine
- Opioids
- Hallucinogens
- Anxiolytics
## Cannabis Use Disorder

<table>
<thead>
<tr>
<th>User</th>
<th>Ratio</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>~1 in 10</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30.5% (recent)</td>
</tr>
<tr>
<td>Mid-teen</td>
<td>1 in 6</td>
<td>16.6%</td>
</tr>
<tr>
<td>Daily use</td>
<td>1 in 2-3</td>
<td>25-50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cannabis Use Disorder and Public Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis use associated: increased prevalence of drug/alcohol use disorders (nicotine)</td>
</tr>
<tr>
<td>Smoking and alcohol: 1\textsuperscript{st} and 3\textsuperscript{rd} leading causes of preventable death</td>
</tr>
<tr>
<td>Illicit drug use associated: $\sim$ $200$ billion/year costs health care, lost productivity, incarceration, drug enforcement</td>
</tr>
<tr>
<td>Caution in implementing legalization of cannabis for recreational use,</td>
</tr>
<tr>
<td>Legalization may lead to:</td>
</tr>
<tr>
<td>more marijuana availability</td>
</tr>
<tr>
<td>more acceptance</td>
</tr>
<tr>
<td>reduced perception of risk</td>
</tr>
<tr>
<td>increased risk of adverse mental health outcomes.</td>
</tr>
<tr>
<td>Public education on consequences of cannabis use may limit expansion of recreational use and inform ongoing debates on legalization.</td>
</tr>
</tbody>
</table>
Motivation

Teen Marijuana Use Affects Adult Motivation

Motivation
More Marijuana Use, Worse Outcomes

Completed high school or college degree

Frequency of Use

Silins et al, Lancet Psychiatry 1: 286–93, 2014; n = 2537-3765; 13-30 years
Psychosis

Strength, Frequency of Marijuana Use Increases Risk

Hash: THC 4%+
Skunk: THC: 16%

Odds ratio

Never used
Hash daily
Skunk <1Xweek
Skunk weekends
Skunk daily

Psychosis

Strength, Frequency of Marijuana Use Lowers Age When Psychosis Appears

Age of Onset of Psychosis Depends on frequency of use and potency of marijuana

Is Marijuana Safe for Children? Adversity Associated With Marijuana Use Higher for Adolescent Initiates...

- Addiction; addiction to other drugs
- Marijuana poisoning
- Brain changes
- IQ loss; cognitive impairment
- Poor grades at school (drop-out)
- Psychosis
<table>
<thead>
<tr>
<th>ISSUE</th>
<th>MARIJUANA</th>
<th>ALCOHOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent, teacher, supervisor relationships</td>
<td>Worse</td>
<td>Better</td>
</tr>
<tr>
<td>Education</td>
<td>Worse (direct link)</td>
<td>Better (No direct link)</td>
</tr>
<tr>
<td>Energy</td>
<td>Worse</td>
<td>Better</td>
</tr>
<tr>
<td>Interest in activities</td>
<td>Worse</td>
<td>Better</td>
</tr>
<tr>
<td>Work, school</td>
<td>Worse</td>
<td>Better</td>
</tr>
<tr>
<td>Adverse psychological</td>
<td>Worse</td>
<td>Better</td>
</tr>
<tr>
<td>Burden of disease</td>
<td>Better</td>
<td>Worse</td>
</tr>
<tr>
<td>Adverse psychosocial</td>
<td>Better</td>
<td>Worse</td>
</tr>
</tbody>
</table>

Marijuana Compared with Alcohol

Emergency Department Mentions: Higher Proportion of Marijuana Users Compared with Alcohol Users

**Numbers of ED Mentions**

- Alcohol ER mentions: 700,000
- Marijuana ER mentions: 400,000

**Ratio of ED Mentions: % of Users**

- Alcohol ED: % Use: 10,000
- Marijuana ED: % Use: 50,000
Marijuana Compared with Alcohol Use Before Age 17 and Academic Achievement

N=2,179-3,678; longitudinal study between 13-25 years

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E. Silins et al. Drug and Alcohol Dependence 156 (2015) 90–96; previous research (Esch et al., 2014; Macleod et al., 2004; Maggs et al., 2015; Silins et al., Lancet Psychiatry, 2014; Townsend et al., 2007).
Marijuana Compared with Alcohol
Marijuana Effects Persist

<table>
<thead>
<tr>
<th>MARIJUANA</th>
<th>ALCOHOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>• THC dissolves in fat; cleared slowly</td>
<td>• Alcohol dissolves in water: quickly cleared</td>
</tr>
<tr>
<td>• IMMEDIATE EFFECTS: up to 6 hours</td>
<td>• IMMEDIATE EFFECTS: no effects or intoxication depends on amount consumed</td>
</tr>
<tr>
<td>• SUB-ACUTE EFFECTS: can last 6 - 20 days</td>
<td>• One drink clears the body within ~3 hours</td>
</tr>
<tr>
<td>• LONG-TERM EFFECTS: more than 20 days</td>
<td>• SUB-ACUTE EFFECTS: do not persist longer than 24 h</td>
</tr>
<tr>
<td>• Even if not using now, learning ability may be compromised for several days</td>
<td>• LONG-TERM EFFECTS: depends on how much, how frequently used</td>
</tr>
</tbody>
</table>

Marijuana and Opioids

Cannabinoid and Opioid Signaling Systems Co-exist in Brain

Marijuana Use Primes Brain to “Like” Opioids: Children at Risk

- Marijuana use during adolescence: *human and rodent research*

- Marijuana use during pregnancy: human research on marijuana consequences (not opioids) and *rodent research*

- Marijuana use before conception: *rodent research*
Humans: Adolescent Marijuana Use and Opioid Addiction...

Twin A started marijuana before age 17
Co-Twin B after age 17: Twin A is 4x risk for opioid addiction

Michael T. Lynskey; Andrew C. Heath; Kathleen K. Bucholz JAMA, January 22/29, 2003—Vol 289, 427-433
Marijuana Exposure During Human Pregnancy: Association with Developmental Problems (causation? Or co-factor?)

**In utero:**
- Infertility
- Placental problems
- Low birth weight

< week- 1 month
- Increased tremor, startle

9 months
- Impaired mental development

3 – 6 years
- Inattention, impulsivity, hyperactivity, impaired memory, behavioral problems

14-21 years
- Increased risk of smoking, marijuana

19-21 years
- Altered brain function during memory task
- Increased incidence of schizophrenia, addiction

THC Exposure in Adolescent Rodents Primes Brain to Seek More Heroin During Adulthood

- Male rats received THC (1.5 mg/kg, i.p.) or vehicle every third day for 21 days.
- Heroin self-administration studied in young adults 10 days after last THC dose until 53 days later

THC-pretreated animals showed:

- Upward shift during heroin self-administration acquisition.
- Heightened opiate sensitivity manifest by higher heroin consumption.
- Changed endogenous opioid system in brain of adults after adolescent exposure

Findings support gateway hypothesis:

- adolescence THC exposure had an enduring impact in adults
- enhanced opiate intake, possibly a consequence of changed opioid neurons in brain.

THC Exposure Prenatally in Rodents
Primes Brain to Greater Response to Heroin in Adulthood

If rodents are exposed to THC daily in utero, adult rodents are more vulnerable to heroin:

- Shorter time to the first active heroin seeking
- Respond more to lower doses of heroin
- Seek heroin more after a mild stress
- Seek heroin more if heroin not available
- Brain opioid system in adults is different than brains of adults never exposed to THC

THC Exposure in Rodents Prior to Conception Primes Offspring for Heroin

Step 1: Adolescent males, females given THC, 1X/every three days, for 3 weeks

Step 2. At 3 weeks, THC stopped

Step 3. Adolescents mature to adults (no THC)

Step 4. Adults mate (no THC in brain or blood)

Step 5. Rate of pregnancy reduced 40% in THC-exposed females

Step 6. Offspring (no THC exposure ever) mature to adults

Adolescent Rodents THC Exposure Long Before Conception Primes Offspring for Heroin

What happens to adult rats, never exposed to THC, whose parents were exposed to THC during adolescence?

Compared with offspring whose parents were never exposed to THC, adult offspring of parents exposed to THC during adolescence:

- Seek heroin more compulsively
- Show greater heroin withdrawal symptoms
- Show changed behavior
- Show brain changes (abnormal receptors) in reward region

Implications

• Some brain changes in offspring may remain dormant
  • *But may interact with environment to change vulnerability to addiction, to psychiatric illness*

• Increased marijuana use among young people who may bear children
  • *Highlights possible impact of drugs not only on the user but also on their future generations.*
<table>
<thead>
<tr>
<th><strong>Legalization?</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colorado 1 year change: 2013-2014</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traffic deaths</td>
<td>increased</td>
</tr>
<tr>
<td>Driving under the influence</td>
<td>increased</td>
</tr>
<tr>
<td>Marijuana-related emergency room visits</td>
<td>increased</td>
</tr>
<tr>
<td>Marijuana-related hospitalizations</td>
<td>increased</td>
</tr>
<tr>
<td>Marijuana-only related poison exposures</td>
<td>increased</td>
</tr>
<tr>
<td>THC production lab explosions</td>
<td>increased</td>
</tr>
</tbody>
</table>

Marijuana Status and Youth Marijuana Use in U.S.

<table>
<thead>
<tr>
<th>12-17 year olds</th>
<th>(past month)</th>
<th>2013/2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-MMJ</td>
<td>5.99%</td>
<td></td>
</tr>
<tr>
<td>MMJ</td>
<td>8.52%</td>
<td>11.31%</td>
</tr>
<tr>
<td>MMJ/Legal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: NSDUH, 2014, Issued 2015
Marijuana Status in Colorado and Youth Marijuana Use in CO and in U.S.

Age 12-17: National vs CO use rates

Source: NSDUH, 2014, Issued 2015
## Predictions of Legalization? Mental Health Care

<table>
<thead>
<tr>
<th>Impact of non-medical marijuana use on health</th>
<th>Improve, no change or worsen?</th>
<th>Evidence strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis, psychotic symptoms</td>
<td>Worse</td>
<td>Very strong</td>
</tr>
<tr>
<td>Brain function</td>
<td>Worse</td>
<td>Strong</td>
</tr>
<tr>
<td>Psychosocial function</td>
<td>Worse</td>
<td>Strong</td>
</tr>
<tr>
<td>Addiction</td>
<td>Worse</td>
<td>Very Strong</td>
</tr>
<tr>
<td>Addiction other drugs</td>
<td>Worse</td>
<td>Strong</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Worse</td>
<td>Fair</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Worse</td>
<td>Fair-weak</td>
</tr>
<tr>
<td>Depression</td>
<td>Worse</td>
<td>Fair-weak</td>
</tr>
</tbody>
</table>

Health Impact Assessment: Marijuana Regulation in Vermont; Vermont Dept. of Health 2016 HealthVermont.gov; BK Madras edits
## Predictions of Legalization?
### General Health Care

<table>
<thead>
<tr>
<th>Impact of non-medical marijuana use on health</th>
<th>Improve, no change or worsen?</th>
<th>Evidence strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor vehicle accidents</td>
<td>Worse</td>
<td>Very strong</td>
</tr>
<tr>
<td>Child poisoning</td>
<td>Worse</td>
<td>Fair [strong]</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>Worse</td>
<td>Strong</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Worse</td>
<td>Strong</td>
</tr>
<tr>
<td>Stroke, heart attack</td>
<td>Worse</td>
<td>Fair</td>
</tr>
<tr>
<td>Cancer</td>
<td>?</td>
<td>Limited</td>
</tr>
</tbody>
</table>

### Predictions of Legalization?
#### Society and Welfare

<table>
<thead>
<tr>
<th>Impact of non-medical marijuana use on health</th>
<th>Does condition improve, no change or worsen?</th>
<th>Evidence strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic performance</td>
<td>Worse</td>
<td>Strong</td>
</tr>
<tr>
<td>Welfare</td>
<td>Worse</td>
<td>Strong</td>
</tr>
<tr>
<td>Life Satisfaction</td>
<td>Worse</td>
<td>Good</td>
</tr>
<tr>
<td>Employment, economic</td>
<td>Worse</td>
<td>Good</td>
</tr>
<tr>
<td>Workplace</td>
<td>Worse</td>
<td>Limited</td>
</tr>
</tbody>
</table>

Health Impact Assessment: Marijuana Regulation in Vermont; Vermont Dept of Health 2016 HealthVermont.gov; BK Madras
The Present and Future

SCIENTIFIC EVIDENCE WILL PREVAIL

FULL ACCESS
- Only a plant
- SAFE
- Pleasure
- No addiction
- Civil right
- Beneficial
- Alcohol worse
- Victimless
- **MMJ:** Patients suffering
- **MMJ:** FDA cumbersome
- **MMJ:** Difficult to patent
- **MMJ:** Cheap alternative

RESTRICT
- Plants produce toxins
- UNSAFE
- Cognitive degradation
- Addiction, Amotivation
- Greater good
- Psychiatric, behavioral
- Marijuana vs alcohol
- Adolescents, children at risk
- Public health, safety
- **MMJ:** No accountability
- **MMJ:** NOFDA approval
- **MMJ:** Circumvents FDA
This is not a war on drugs
It is a Defense of our brains

The brain is the repository of our humanity, wisdom, our ability to love, learn, create, compute, compose, contemplate, think, to remember, to feel empathy for others, to administer justice and compassion. How precious, unique and fortunate we are to be the bearer of unclouded minds. We are united in a passionate desire to defend the minds of our most vulnerable – our youth.
World Health Organization Report

Update of Cannabis
and its medical use

Bertha K. Madras
Professor of Psychobiology
Department of Psychiatry
Harvard Medical School

This update of cannabis and its medical use was commissioned by the Secretariat of the Expert Committee on Drug Dependence, Department of Essential Medicines and Health Products, World Health Organization. This document is not a comprehensive review of the literature on cannabis, but a summary of the current status of the field and a framework to incorporate new information as it arises.