How Cannabis Affects the Body & the Brain

Karen M. Lounsbury, PhD
Peter R. Jackson, MD

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Outline:

Part I: Cannabis Effects on Pain and Pleasure Pathways
  Dr. Karen Lounsbury

Part II: Cannabis and the Developing Brain
  Dr. Peter Jackson
Disclaimer

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Conflict of Interest: Pharmaceuticals will be presented according to their FDA approvals. We have no financial interests to disclose.
Cannabis Effects on Pain and Pleasure Pathways

Karen M. Lounsbury, PhD
Professor of Pharmacology
Larner College of Medicine, University of Vermont

https://www.youtube.com/watch?v=O5RdMvgk8b0
Cannabis: Medicine or Drug of Abuse?
Cannabis and Phytocannabinoids

- *Cannabis* sativa produces many compounds that are secreted by trichromes in the flowers and leaves
- Different strains of *Cannabis* can produce different levels of biologically active components
  - Hemp
  - Charlotte’s Web
  - Sativa/Indica
Biologically Active Cannabinoids

_Cannabis_ produces over 100 cannabinoids

- **Delta-9-tetrahydrocannabinol (THC)**
  - Partial Agonist CB1/CB2 receptors
  - Psychoactive
  - Anti-pain, anti-nausea
  - Anti-spasm, anti-inflammatory

- **Cannabidiol (CBD)**
  - Weak antagonist CB1/CB2 receptors
  - TRP channels or 5-HT receptors?
  - Not psychoactive, moderates THC
  - Anti-seizure activity, anti-pain activity
  - Possible non-receptor activities

- Activated by heating the plant (smoking, vaping, baking, heat extraction)
Cannabis as a Medicine

• Proven effectiveness (THC):
  • Chronic Pain
  • Chemotherapy-induced Nausea
  • Seizures
  • Spasticity (MS and Cerebral Palsy)
  • Cachexia (wasting disorder)

• Likely effective and in clinical trials (THC):
  • Eating Disorders
  • Glaucoma
  • Anxiety Disorders (OCD, PTSD)

• Possibly effective, but needs more research (THC)
  • Addiction
  • Parkinson’s/Alzheimer’s
  • Inflammatory Diseases
  • Cancer

Proven effectiveness is through randomized clinical trials using THC. Whole plant cannabis has been found effective for Pain, Nausea and Seizures, but these trials are sparse and nonexistent for other conditions.

CBD has only been found effective against seizures, other trials have not shown significant effectiveness, but more are needed.


Your body makes its own cannabinoids

Nature Reviews Cancer 12, 436-444 (June 2012)
Cannabinoid Receptors reduce neuronal activity in response to pain, nausea, and anxiety

- Both endocannabinoids and cannabis reduce both pain signal and interpretation of pain
- Similar to the action of opioids
  - Not as effective
  - Produce less tolerance
  - Less risk of addiction
  - Low risk of overdose

Inhibiting the breakdown of endogenous opioids and cannabinoids to alleviate pain, 2012
http://www.nature.com/nrd/journal/v11/n4/full/nrd3673.html
Cannabis Intoxication:

- **Attributed to THC action in the brain**
- Head rush and euphoria (Reward Pathway)
- Appetite increase (Hypothalamus)
- Decreased attention, sedation (Hippocampus-Prefrontal cortex)
- Altered Perceptions (Pre-frontal cortex inhibition)
  - Awareness of the senses and of music may be increased
  - Distorted sense of time
  - Preoccupation with distractions
  - Giggles
Pre-frontal Cortex is primarily active in response to new experiences.
“Executive” functions of the Pre-frontal Cortex

- Planning, organization and execution of complex behavioral sequences (Working Memory)
- Flexible responses to changing environmental contingencies
- Selective attention, noticing change
- Persistence in a task despite distraction
- Creative problem solving
Perception is a combination of sensory input and pre-frontal cortex executive function
Through learning, we are able to distinguish errors in the environment.
Activities that can Reduce the Activity of Pre-Frontal Cortex

• Meditation

• Intense Exercise
  • Runner’s High
  • reduction of pain sensations
  • widespread activation of motor and sensory systems during exercise shunts activity from the higher cognitive centers of the prefrontal cortex.

• Daydreaming
  • Frontal cortex is disengaged
  • Activities are controlled by automatic functions
  • Can perform complex automatic activities (like driving a normal route)

• Some Drugs of Abuse
  • Cannabis, Opioids
Cannabis Effects on Attention: Impaired ability to drive

- Peripheral attention reduced
  - A person who is high may become absorbed in an object, event, or process to the exclusion of everything else
- Memory
  - Both short-term and long-term memory impairment
- Color/Image Perception
  - Hallucinogenic effects
- Motor Coordination
  - Impaired, but much less than alcohol or opioids

States with legalized recreational use have seen increased car accidents in the population that has combined alcohol and cannabis, but there is no significant difference in fatal car accidents in states with legalized cannabis.
Frontal Cortex Impairment: The Problem with Distractors

Stroop task: Identify the color of the words
Again: Identify the color of the words

GREEN
BLUE
RED
BLUE
GREEN
RED
GREEN
BLUE

Subjects intoxicated by THC have a much longer delay in completing the Stroop Test
Cannabis Addiction in Perspective

- 30 million drugs are currently known
- Approximately 100 are addicting
- Many are natural products

- What properties make drugs addicting?
Common Properties of Addicting Drugs

• Stimulate Dopamine signaling in the Reward Pathway
• Rapid acting, can get into the brain
• Withdrawal of drug inhibits the Reward Pathway
• Voluntarily administered (specifically to the reward center in animal models)
• Trigger relapse to drug-seeking behavior
The Reward Pathway:

- Connects limbic regions of the brain
  - Ventral tegmental area
  - Nucleus accumbens
  - Pre-frontal cortex
- Dopamine receptor signaling tracts
- Overactivity is linked to psychologic addiction

Effects of Addicting Drugs on DA signaling: Highjacking reward
Cannabis Addiction Potential

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent of General Population</th>
<th>Of Those Users, Percent Who Ever Became Dependent on the Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco</td>
<td>76%</td>
<td>32%</td>
</tr>
<tr>
<td>Heroin</td>
<td>2%</td>
<td>23%</td>
</tr>
<tr>
<td>Cocaine</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>92%</td>
<td>15%</td>
</tr>
<tr>
<td>Anti-anxiety drugs</td>
<td>13%</td>
<td>9%</td>
</tr>
<tr>
<td>Marijuana</td>
<td>46%</td>
<td>9%</td>
</tr>
</tbody>
</table>

**Marijuana in comparison to Alcohol and Tobacco**

Young People are Particularly Vulnerable

• Substantially higher risk for Substance use disorder when an addicting drug is started before the age of 18, even higher risk with younger patients

• Chronic adverse effects of cannabis are more likely to develop in younger patients

• Dr. Jackson will now provide the viewpoint of a child psychiatrist
Cannabis and the Developing Brain

Peter R Jackson, MD

Community Medical School

October 2, 2019
Outline: Cannabis use and the teenage brain

- What’s the trend?
- What’s great (different) about the adolescent brain and why it matters
- Potential therapeutic benefits vs. well known risks
- A word to the parents in behalf of the kids
- Seeking solid ground
National trends

*Last two decades of alcohol, cigarette, and illicit drug use*

*Past-month use

<table>
<thead>
<tr>
<th>Year</th>
<th>Alcohol</th>
<th>Cigarettes</th>
<th>Illicit drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>50%</td>
<td>10%</td>
<td>30%</td>
</tr>
<tr>
<td>2015</td>
<td>35.3%</td>
<td>6.3%</td>
<td>23.6%</td>
</tr>
<tr>
<td>2016</td>
<td>30%</td>
<td>5%</td>
<td>20%</td>
</tr>
</tbody>
</table>

- **2015**
  - Alcohol: 35.3% of 12th graders, 21.5% of 10th graders, 9.7% of 8th graders
  - Cigarettes: 11.4% of 12th graders, 6.3% of 10th graders, 3.0% of 8th graders
  - Illicit drugs: 23.6% of 12th graders, 16.5% of 10th graders, 8.1% of 8th graders
Past 30 Day Alcohol, Marijuana, and Cigarette Use

- **Alcohol**: 42%, 30%, 33%
- **Marijuana**: 24%, 22%, 24%
- **Cigarettes**: 18%, 11%, 9%

May 2018

VERMONT DEPARTMENT OF HEALTH
Primary Methods Used to Consume Marijuana, Among Current Users

- Smoked (91%)
- Ate/drank (5%)
- Vaped (2%)
- Other (2%)

May 2018

VERMONT DEPARTMENT OF HEALTH
Vermont trends: Middle school

Middle school students believing their parents would think it was wrong to:

- Use alcohol: 85% (down from 91% in 2015)
- Use marijuana: 92% (down from 94% in 2015)

Current middle school student marijuana use: 4% (unchanged)
Vermont Trends: High School

High School students believing their parents would think it was wrong to:

- Use alcohol: 66% (down from 72% in 2015)
- Use marijuana: 76% (down from 80% in 2015)

Current high school student marijuana use: 24% (up from 22%)
Vermont Trends: High School

High School students believing there is a great risk of harm from:

- Binge drinking regularly: 36%
- Smoking a pack or more of cigarettes: 68%
- Using marijuana regularly: 24%
Perception of harm and rates of use
High school graduation isn’t the finish line

What’s happening where recreational use is legal?

Those states have higher than average rates of adolescent use (they were already near the top).

Adolescent use trend is increasing in some states where legalized compared to holding steady for most states. (NSDUH) Conflicting studies abound.

The rate of college age use, which is increasing nationally is increasing faster than the national average.

Adolescent use rates correlate with availability (density of dispensaries: Colorado data).

Marketing targets all audiences, including young people.
Marketing
Brain development: Efficiency and connectivity
Staggered development: Gas before brakes
Substance Use Disorders Among Persons 12 and Older, by Age of First Use

Source: CASA analysis of the National Household Survey on Drug Use and Health (NSDUH), 2009.
Higher risk for earlier use

4 to 7 times more likely to develop a use disorder if you use cannabis prior to age 18 compared to in adulthood. (Winters et al)

1 in 6 adolescents who use will develop a use disorder
What’s the upside… What’s the downside?
Adverse effects of early use

Negative impact on synaptic pruning and myelination

Cognitive effects:

- Verbal learning, recall, attention most impacted
- Some studies showing measurable IQ decrease later in life (Meier et al)
- Some studies showing deficits improve after abstinence

Association with increased incidence of psychosis

Increase likelihood of anxiety disorders (Degenhardt et al)

Increased likelihood of depression (Rubino et al)

Amotivation, related to blunting of the dopaminergic system with chronic use (Bloomfield et al)
Adverse effects of use: short term

Inattention

Impaired reaction time: doubled risk of car accident

Short term memory impairment
Adverse effect of adolescent use: long term

Decreased white matter integrity: poorer connectivity

Poorer attention, processing speed, working memory

Impaired memory: decreased hippocampus volume
Effect on the brain: Hot topics

Cognition

Potential neuropsychological decline into the late 30s for adolescent users compared to adult onset use

Some studies show that this can recover with abstinence

Motivation

Long term heavy use particularly associated with educational underachievement and impaired motivation

Psychosis

Consistent association between adolescent cannabis use and psychosis. Could come from direct causality, gene-environment interaction, shared etiology.
Medical Use of Cannabinoids in Children or Adolescents

Marijuana not FDA approved for the prevention or treatment of any disease process in kids

Evidence for cannabinoids

- Rare and severe forms of epilepsy: Recent FDA approval: Epidiolex (highly purified CBD) approved June 2018 for pediatrics seizures (Lennox Gastaut, Dravet Syndrome)
- Stronger signal: Chemotherapy induced nausea and vomiting (THC)
- Weaker signal/anecdotal: Tourette Syndrome, Spasticity, neuropathic pain, PTSD

“What should I tell parents about the medical benefits for adolescents or children?”

- Benefits have been primarily in case reports, risks are well established
- We will likely learn more as research continues

Note the process of prescribing any medication

- medication, dose, route, frequency
American Academy of Pediatrics

- Opposes medical marijuana outside FDA process
- Opposes legalization for recreational use
- Supports research (move from schedule I to schedule II)
- Strict enforcement of rules against marketing and sale to children (age 21 minimum)
- Supports decriminalization for both adults and youth
- Opposes smoking in any form
- Strongly Discourages any use in the presence of children
AMA position statement: Cannabinoid research

1. Study proposed/promising areas for benefit, see if we can expand the evidence from anecdotal to controlled trials
   1. Reconsider the schedule I status
   2. Put more funding towards it

2. Study the consequences of long term use, particularly in high risk groups

3. Don’t legalize recreational use until we know more about the public health, medical, social and economic consequences of use
AMA position statement: Legalization for medical use

1. Any treatment should be studied to assure safety
2. Should not be done through state legislative, referendum or ballot initiatives
3. Anything not approved labeled “marijuana has a high potential for abuse.”
4. Protect physicians working within state laws
5. Don’t legalize recreational use until we know more about the public health, medical, social and economic consequences of use
What aspects convey the highest risks?

Age of onset of use?
Frequency of use?
Duration of use?
Quantity used?
Strength/potency?
Composition (THC vs. CBD vs. other cannabinoids)?
Teaching, Nurturing, Protecting
Importance of Family
Importance of Family

Community

Peers

Family

Adolescent
Parenting Style

Responsive

Authoritative

Permissive

Unresponsive

Authoritarian

Neglectful
Parental Influence

Shakya, Christakis and Fowler, 2012
Positive Parenting

Communication: calm and clear

Encouragement: of positive behaviors

Negotiation: working towards solution when conflict arises

Setting Limits: calmly and in proportion to behaviors

Supervision: know friends and schedule

Dishion T et al 2003
How do I talk about this with my kids?

Talk early, talk often

Talk with them when calm, not when angry or “high”

Stay calm but serious, not angry

Tell them what you’re worried about, then listen

ParentupVT.org (parent monitoring checklist, “Free marijuana talk kit”)
Warning signs:

Mood and behavior changes: restlessness, paranoia, loss of interest

Rapid peer change and reluctance to introduce new peers

Notable drop in grades, declining participation in school

Significant change in concentration, memory lapses
Genes and addiction

The diagram illustrates the heritability ($h^2$ ± Range) of various addictive agents. The number of twin pairs for each agent is indicated next to the agent's name:

- Hallucinogens: 4,570 (2,212)
- Stimulants: 7,659 (4,758)
- Cannabis: 3,359 (10,820)
- Gambling: 9,897 (6,997)
- Smoking: 3,494 (2,206)
- Alcohol: 2,206

The mean heritability values for each addictive agent are shown with error bars representing the range.
For Parents

Actions speak louder than words

Words speak louder than no words

If substance use disorders have been a problem in the family, give good consideration to educating younger generations early on.

There ARE “sober kids” at school.
Seeking Solid Ground
How have we gotten here?

Grassroots activism

Pharmacological ingenuity

Private Profiteering

Policy moving ahead of science, with gaps in knowledge, underestimation of unintended consequences.

Volkow et. al, JAMA Psychiatry 2016
Seeking Solid Ground
Thank You
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References cont.


References cont.


References cont.

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Peter R Jackson, MD | Assistant Professor of Psychiatry | peter.jackson@uvmhealth.org