MARIJUANA & THE EFFECTS ON THE BRAIN
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DISCLOSURES

• I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

• I do not intend to discuss any unapproved or investigative use of a commercial product in my presentation.
OBJECTIVES

• Provide brief background on biology of marijuana and the endocannabinoid system

• Describe the adverse short- and long-term health and developmental effects of marijuana on children and adolescents, focusing on brain development
### RATES OF MARIJUANA AND TOBACCO USE

<table>
<thead>
<tr>
<th>NSDUH Stats</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past month all tobacco products use aged 12 or older</td>
<td>23.9%</td>
<td>23.5%</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>19.4%</td>
<td>19.1%</td>
</tr>
<tr>
<td>Smokeless tobacco</td>
<td>3.4%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Cigars</td>
<td>4.7%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Pipe tobacco</td>
<td>0.8%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Marijuana Use in past month aged 12 or older</td>
<td>8.3%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Past month all tobacco products use aged 12-17</td>
<td>6.0%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>4.2%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Smokeless tobacco</td>
<td>1.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Cigars</td>
<td>2.1%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Pipe tobacco</td>
<td>0.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Marijuana Use in past month aged 12-17</td>
<td>7%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

### MARIJUANA BIOLOGY

- The cannabis plant: contains more than 400 biologically active substances
- More than 100 types of cannabinoids
- Numerous species and subspecies
  - Cannabis sativa and indica the two most common.
  - Cause a variety of psychotropic effects
- Both species have been hybridized repeatedly
MARIJUANA BIOLOGY

• Delta 9 –Tetrahydrocannabinol - THC
  • The primary psychoactive cannabinoid in the marijuana plant.
• Selective breeding of marijuana species has resulted in higher concentrations of THC in plant products
• From 1995 to 2013 - ~4% to 17% THC
  • Now > 20%
• New ways of using (dabbing, volatilizing oils) create even higher concentrations
  • More potent psychotropic effects as well as increased risk of adverse effects

CANNABIDIOL (CBD)

• CBD is a non-psychoactive cannabinoid.
  • Low affinity for CB receptors
  • Can interfere with endocannabinoid degradation;
    • Agonist of serotonin 5HT1A receptors → neuroprotection?
• Focus on CBD for medical effects:
  • Improved control of certain chronic neurological conditions, including intractable seizures: Epidiolex
  • Immune enhancement.
  • Cancer treatment.
• Little is known about dose-response relationships of CBD; too little may be ineffective and too much may cause adverse effects.
THE ENDOCANNABINOID SYSTEM: ECS

- Humans produce “endocannabinoids”
  - Anandamide and 2-AG (2-arachidonoylglycerol).
  - Biologically active molecules that serve a number of regulatory functions.
- Two endocannabinoid receptors: CB1 and CB2.
  - CB1 - in the brain and nervous system
  - CB2 - in immune system cells, wide range of somatic cells.
  - Can be detected as early as 5 weeks gestation
- THC from marijuana binds to CB receptors
  - Partial agonist with biologic activity

Cannabinoid Receptors Are Located Throughout the Brain and Regulate:

- Brain Development
- Memory and Cognition
- Motivational Systems & Reward
- Appetite
- Immunological Function
- Reproduction
- Movement Coordination
- Pain Regulation & Analgesia

Volkow NIDA 2014
ENDOCANNABINOID SYSTEM (ECS)

• Critical for early neonatal brain development
  • Role in microtubule function → axonal growth
  • Involved in orderly fetal development of neural systems
• THC crosses placental readily
  • Binds to CB receptors in brain
  • Concern that THC “highjacks” or disrupts this highly sequenced pattern of normal neuronal development
• Is this why we are seeing neurodevelopmental deficits in infants and children whose mothers used marijuana during pregnancy?

ECS – IMPORTANCE IN ADOLESCENCE

• ECS has dynamic role in brain development during adolescence
• Brain development characterized by increase in white matter, decrease in gray matter – pruning, efficiency
  • Especially in areas associated with reward, motivation and cognition
• CB1 receptor density increases in these areas during adolescence compared with adult brain
  • THC found to affect density of CB receptors, and activity of neurotransmitters
• Concern that THC disrupts “perfectly orchestrated” maturation
  • Unclear how brain maturation may be affected, trajectory of effects
  • Mostly animal studies - Unclear whether results in animal studies apply to humans
CANNABINOID MECHANISMS OF ACTION

- Cardiovascular: BP, HR, vasodilation
- Liver: lipogenesis
- GI Tract: Motility, Satiety
- Immune system: Alter IL synthesis, Neutrophil recruitment
- Pancreas: Insulin sensitivity and secretion
- Adipose Tissue: Lipid metabolism, FFA oxidation

ADVERSE EFFECTS OF CANNABINOIDS
DEVELOPMENTAL EFFECTS OF PRENATAL EXPOSURE

Neurocognitive and Behavioural Effects

<table>
<thead>
<tr>
<th>18 months</th>
<th>3–6 years</th>
<th>9–10 years</th>
<th>14–16 years</th>
<th>17–22 years</th>
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<tbody>
<tr>
<td>Increased aggressive behaviour*</td>
<td>Deficits in:</td>
<td>Deficits in:</td>
<td>Deficits in:</td>
<td>Deficits in:</td>
</tr>
<tr>
<td>Attention deficits (females)*</td>
<td>• Verbal and perceptual skills†</td>
<td>• Visual reasoning†</td>
<td>• Visual-cognitive functioning†</td>
<td>• Executive functioning†</td>
</tr>
<tr>
<td></td>
<td>• Verbal reasoning†</td>
<td>• Reading*</td>
<td>• Academic achievement*</td>
<td>• Response inhibition†</td>
</tr>
<tr>
<td></td>
<td>• Visual reasoning†</td>
<td>• Spelling*</td>
<td>• Information processing speed*</td>
<td>• Visual motor coordination*</td>
</tr>
<tr>
<td></td>
<td>• Verbal and quantitative reasoning†</td>
<td>• Hyperactivity*</td>
<td>• Substance use*</td>
<td>• Smoking*</td>
</tr>
<tr>
<td></td>
<td>• Short-term memory*</td>
<td></td>
<td>• Early initiation of substance use*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperactivity*</td>
<td>Attention deficits‡</td>
<td></td>
<td>Delinquency*</td>
</tr>
<tr>
<td></td>
<td>Attention deficits‡</td>
<td>Impulsivity*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Impulsivity*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Impaired vigilance*</td>
<td></td>
<td></td>
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</tbody>
</table>

*OPPS  †MHPCD  ‡Generation R

From: Canadian Centre on Substance Abuse: Clearing the Smoke on Cannabis
ASSOCIATED BRAIN CHANGES: ADOLESCENTS

• Effects from Prenatal Exposure
  • Increased neural activity in PFC during inhibitory control tasks (fMRI)
  • Altered neuronal functioning during visuo-spatial memory tasks
  • Disruption of dopamine and opioid neurotransmitter systems
  • Concerns about alterations in epigenetic gene regulation mechanisms
    • May explain in part why prenatal drug exposure causes long-lasting changes in behavior

• Current focus of research and concern

EFFECTS DURING ADOLESCENCE
EFFECTS WITH REGULAR USE

- Dependence in 1 in 6 teens who use regularly
  - Craving, Tolerance, Withdrawal
  - DSM V Diagnosis – Marijuana use disorder
- Chronic bronchitis and impaired respiratory function
- Increased risk of MVAs when used alone
  - 50-90% more car accidents when also used with alcohol
- Higher rates of use of alcohol, tobacco and other drugs
- Higher rates of anxiety
- Hyperemesis syndrome

LONG TERM EFFECTS – CHRONIC, HEAVY USE

- Short-term memory impairment - long lasting
- Likely permanent cognitive impairment and loss of IQ in adolescents
  - Especially when use begins at an early age and heavy use continues
- Poorer psychosocial development
- Impaired academic achievement/educational outcomes
  - Increased unemployment, lower income
- Impaired social functioning
- Unclear association with chronic respiratory diseases
- Higher rates of schizophrenia, anxiety and mood disorders, PTSD
  - Increased rates of suicidal ideation/attempts
LONG TERM EFFECTS – CHRONIC, HEAVY USE

• Short-term memory impairment that is long lasting
• Likely permanent cognitive impairment and loss of IQ in adolescents who begin use at an early age and continue heavy use into late adolescence
• Poorer psychosocial development
• Impaired academic achievement/educational outcomes
  • Increased unemployment, lower income
• Impaired social functioning
• Unclear association with chronic respiratory diseases
• Higher rates of schizophrenia, anxiety and mood disorders, PTSD
  • Increased rates of suicidal ideation/attempts


Persistent cannabis users show neuropsychological decline from childhood to midlife

Madeline H. Meier\textsuperscript{ah}, Avshalom Caspi\textsuperscript{abced}, Antony Ambler\textsuperscript{a}, Honalee Harrington\textsuperscript{bced}, Renate Houbs\textsuperscript{bced}, Richard S. E. Keefe\textsuperscript{a}, Kay McDonald\textsuperscript{d}, Aimee Ward\textsuperscript{d}, Richie Poulton\textsuperscript{d}, and Terrie E. Moffitt\textsuperscript{abced}

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Average IQ change:

- “Never used”  
  - 99.8 to 100.6
- “Mj dependent 3+ yrs”  
  - 99.7 to 93.9

Source: Meier et al. PNAS, 2012

<table>
<thead>
<tr>
<th>Exposure</th>
<th># Cases</th>
<th>HR Crude</th>
<th>HR adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never used cannabis</td>
<td>47</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ever used cannabis</td>
<td>12</td>
<td>2.1 (1.1-3.8)</td>
<td>0.8 (2.2-2.9)</td>
</tr>
<tr>
<td>&gt;50 times</td>
<td>7</td>
<td>7.4 (1.0 – 54.3)</td>
<td></td>
</tr>
</tbody>
</table>

* Adjustments for: prior personality disorders at conscription, IQ, disturbed behavior in childhood, social adjustment, risky use of alcohol, smoking, early adulthood socioeconomic position, use of other drugs, brought up in a city. The category “Ever used cannabis” includes all individuals who reported cannabis use, including those who reported “>50 times”.

Griffith-Lendering. Addiction. 108(4), 733-74D.
Manrique-Garcia. BMC Psychiatry. 12, 112.
Poorer communication across different parts of the brain

Source: Arnone D, Barrick TR, Chengappa S et al. Corpus callosum damage in heavy marijuana use: Preliminary evidence from diffusion tensor tractography and tract-based spatial statistics. Neuroimage, 2008; 41:1067-1074

NEUROIMAGING STUDIES WITH ADOLESCENTS

• fMRI Studies
  • Differences in levels of activation of hippocampus (memory) compared with controls*
  • Functional connectivity studies of frontoparietal areas of brain - disrupted neuro-circuitry during task demands**
  • Inhibitory processing studies - marijuana users had exaggerated responses to both inhibitory and non-inhibitory trials – in prefrontal and parietal regions***

• DTI (diffusion tensor imaging) studies
  • no effects on white matter integrity

• Overall – evidence of altered neural response patterns in marijuana using teens that is consistent with neurocognitive studies.
  
CONTINUING CHALLENGES:

• Getting the message out that marijuana is NOT benign for our adolescents and young adult populations!
• Making marijuana smoking as undesirable as cigarette smoking
• Enforcing “underage recreational marijuana use” for <21 year olds
  • Avoiding similar marketing experience of “big tobacco”
• Counseling parents about their own legal or medical use
• Supporting the need for research on adverse effects as well as efficacy of medical marijuana

TAKE-AWAY MESSAGES

• There is accumulating scientific data about the adverse effects of marijuana use for both the developing fetus, and adolescents
• These are specifically concerning about brain development, behavior and mental health disorders
• Despite this, there are high rates of use among adolescents and young adults and the perception that marijuana use is harmful is at an “all-time low”.
• The challenge of the health care providers is to counter arguments that marijuana is benign and that the benefits of legalization outweigh the risks to society.
THANK YOU!

RESOURCES

- American Academy of Pediatrics: www.aap.org/marijuana
- National Institute on Drug Abuse: www.drugabuse.gov
- Office of National Drug Control Policy: www.whitehouse.gov/ondcp
- Smart Approaches to Marijuana: http://learnaboutsam.com
- Substance Abuse and Mental Health Services Administration: www.samhsa.gov