Marijuana 101

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Disclosure

In the past 12 months, 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 an unapproved/investigative use of a commercial product/device in my presentation.
Marijuana

• Contains many chemicals called cannabinoids such as...
  – delta-9-tetrahydrocannabinol (THC)
  – delta-8-tetrahydrocannabinol
  – cannabidiol
  – cannabinol
  – cannabichromene
  – cannabigerol
  – Etc.

Endo-cannabinoid (Anandamide)

Marijuana (Tetrahydrocannabinol)
THC vs. Anandamide

• Both **dial down** neuron activity to change neurotransmitter release

• THC has a **MUCH STRONGER, LONGER** effect than anandamide on brain cells

• THC **interferes** with anandamide function hampering the innate homeostatic system in chronic marijuana users
Content of THC has increased over time

Activation of the reward pathway by addictive drugs

- Alcohol
- Cocaine
- Heroin
- Nicotine
- Marijuana
- Heroin
Endocannabinoid System: Regulation

• The neuron’s “volume control”: dials down neuron activity when too strong

• Regulates levels of important neurotransmitters affecting pleasure, mood, pain, appetite, sleep, motivation, focus, memory, attention etc. (dopamine, serotonin, endorphins)

• Helps keep neuron activity in balance, not underactive or overactive
Marijuana and alcohol tilt the balance toward inhibition.

Chronic exposure causes brain to increase excitation to compensate...

Marijuana Withdrawal Symptoms

- Restlessness, anxiety
- Increased irritability, anger, aggression
- Difficulty falling and staying asleep, nightmares/strange dreams
- Decreased appetite
- Weight loss

Endocannabinoid System: Growth

• Shapes **brain development** by...
  – guiding neurons to grow to the right places in the brain for correct function
  – controlling neuron activity, thereby shaping brain wiring
  – supporting myelin growth on neurons

Chronic substance use changes the brain...

• Causes too much excitation of brain cells, leading to “Excitotoxicity,” cell damage and death

• Changes brain’s own chemistry and ability to regulate mood, feel pleasure, etc.

• Dopamine cells and receptors especially sensitive to damage leading to either “Reward deficiency” or “Reward sensitivity”

Source: Bossong MG, Niesink RJM. Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. Progress in Neurobiology. 2010;92:370-385.
Effect on Memory

• THC reduces hippocampal neuron activation, below the level needed to trigger memory formation

• With chronic THC exposure, neuron connections involved in memory are gradually lost due to continual suppression

• Brain imaging studies show regular THC users have smaller hippocampuses, and poorer memory

Persistent cannabis users show neuropsychological decline from childhood to midlife

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The Dunedin Study (New Zealand) (N=1,037)

Assessment ages:

13 yrs (Pre-initiation) 18 yrs 21 yrs 32 yrs 38 yrs

Source: Meier et al. PNAS, 2012
Change in IQ from 13 to 38 yrs old

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
IQ Change by Age when Marijuana Dependence Started

Source: Meier et al. PNAS, 2012
IQ Change by Age when Weekly Use Began, Among Those No Longer Using at age 38

Source: Meier et al. PNAS, 2012
White matter structure differences between marijuana users and non-users

Similar altered white matter structure found in the brains of schizophrenics and teen marijuana users

Marijuana use in adolescence also increases mental illness in adulthood

Regular marijuana use during adolescence found to increase risk 2 to 5 times of developing psychosis, schizophrenia, anxiety, and depression in adulthood.
A large longitudinal study of an all-male cohort (n=45,087), heavy cannabis users (used >50 times by age 18-20) were found more than six times more likely to develop schizoaffective disorder later in life than individuals who had never used.
Anxiety Disorders

- Adolescents who used cannabis daily were 2.5 times more likely to have an anxiety disorder controlling for SES, alcohol and other substance use and depression (OR=2.5, 95% CI 1.2-5.2)

- Heavy cannabis users during adolescence had increased rates of anxiety disorders at age 29 even if they quit in young adulthood.

Depression

• Both early onset (<15 years old) and adult onset (>18 years old) moderate cannabis use (weekly) increases the risk for major depression (OR=1.7).

“Medical Marijuana”

• Cannabinoids have long been noted for their therapeutic potential.
• 1990: IOM noting that fast-acting cannabinoid pharmaceuticals not available posed the idea of “compassionate” use of marijuana to relieve suffering in terminally ill patients.
• 1996: CA passes first “medical marijuana” law, significantly broadening the range of conditions and eligible patients beyond IOM.
• Studies on “medical marijuana” have found limited efficacy for analgesia in chronic neuropathic pain, appetite stimulation and spasticity in multiple sclerosis.
• No studies of “medical marijuana” have included children or adolescents.

# “Medical Marijuana” vs. Cannabinoids

<table>
<thead>
<tr>
<th>“Medical Marijuana”</th>
<th>Cannabinoids</th>
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<tbody>
<tr>
<td>Plant species</td>
<td>Pharmaceutical product</td>
</tr>
<tr>
<td>Decided by popular vote in 18 states</td>
<td>Regulated by the FDA</td>
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<tr>
<td>Efficacy poorly defined</td>
<td>Efficacy carefully studied</td>
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<tr>
<td>Delivered orally or by smoking</td>
<td>Delivered orally or by inhalation</td>
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<tr>
<td>“Recommendation” by physician; patient/parent determines dose</td>
<td>Standard prescribing procedures</td>
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Medical cannabinoids

Marinol (dronabinol) – synthetic delta-9-tetrahydrocannabinol (THC).

• Oral formulation; relatively slow acting

• FDA approved in 1985 to treat anorexia, nausea and vomiting associated with chemotherapy.

• FDA approved in 1992 to treat anorexia and weight loss in patients with AIDS.
Medical cannabinoids

*Cesamet* (*nabilone*) – synthetic cannabinoid.

- FDA approved in 1985 to treat nausea and vomiting associated with chemotherapy.
- Never marketed in the US.
Medical cannabinoids

*Sativex* *(delta-9-tetrahydrocannabinol/cannabidiol formulation)* – combination of cannabis plant extracts.

- Approved in Canada, New Zealand, and 8 EU countries to treat neuropathic pain, spasticity, and overactive bladder in patients with multiple sclerosis.
- FDA approval is expected at the end of 2013.
Summary

• Marijuana use by adolescents is associated with significant mental health risks. Many disorders occur years after use, making it hard to appreciate associations.

• Cannabinoids have therapeutic potential as a pharmaceutical product, but have not been fully developed/explored.

• Further research on cannabinoid pharmaceuticals is critical for understanding the benefits and long term health consequences of cannabinoid exposure for adolescents.