Cannabis is a Gateway Drug for Opioids

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Disclosures

• Conflicts of Interest
  • I have NIH funding to study opioid outcomes among medical cannabis users

• Current Funding
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The Gateway Hypothesis

• A drug “that lowers the threshold for addiction” to other substances

• The use of X, in and of itself, creates risk de novo for Y that otherwise would not exist

• Use of cannabis introduces additional likelihood of opioid initiation (or dose escalation or addiction...) that otherwise would be less likely to occur
Where we agree

- People who do something are more likely to do it
- People who use drugs are more likely to use other drugs
- People who use cannabis are more likely to use opioids
Where we also agree

- Causes of (opioid) addiction
  - Genetic predisposition
  - Environmental risk factors
  - Trauma
  - Psychiatric comorbidity
  - Individual factors, impulsivity, thrill-seeking

Addiction, neural circuits

(Volkow Koob 2016)

The debate

- Cannabis causes opioid initiation
- Cannabis causes increased amount/frequency of opioid use
- Cannabis causes opioid use disorder
Snails and memory (Kandel and Kandel 2014)

Mice and memory (Kandel and Kandel 2014)

• “Nicotine is a gateway drug that exerts a priming effect on cocaine through increased global acetylation in the striatum”

Mice and nicotine (Kandel and Kandel 2014)

Locomotor sensitization
• Nicotine for 7 days, followed by 4 days of nicotine and cocaine
• Exposed mice were significantly (~2x) more active than control mice
• Not observed if reversed (i.e. cocaine for 7 days first)

Conditioned Place Preference
• Nicotine pre-treated mice had 78% greater preference for cocaine
Mice and nicotine (Kandel and Kandel 2014)

• "Priming with nicotine has been shown to lead to enhanced cocaine-induced locomotor activity and increased initial self-administration of cocaine among adolescent, but not adult, rats."

• Effects more pronounced among adolescents?

Myelination continues through age ~25
Risk of Cannabis Use Disorder

- Higher with earlier age of initiation
- Adults: 9%
  - Adolescents: 16-25%

Cannabis impacts adolescent neurodevelopment

(Hurd 2014)

- Adolescent brain constant state of “pruning” and “remodeling”
- Pruning of excitatory synapses key to executive function, inhibition
- Endocannabinoids regulate synapse plasticity
- Cannabis use affects adolescent emotion and cognition circuits
- Adolescents with intermittent cannabis use have higher opioid use and tolerance

Cannabis impacts adolescent neurodevelopment

- Loss of whole dendrites including synapses (Miller 2018)
- Reduction in post-synaptic glutamate A2 AMPA receptors (Szutorisz et al 2016)
- Disruption of stathmin signaling and impaired neurogenesis, spinogenesis and NMDA-receptor mediated memory formation.
- Cyclic-AMP Response Element Binding protein (CREB) is known to be a key target of addictive drugs including cannabinoids and directly regulates the sirtuin group of histone deacetylases
Cannabis may interfere with pruning (Orr 2019)

Cannabis changes adolescent gene expression (Hurd 2014)
Genes predict cannabis impact on heroin

For those at risk, cannabis worsens course?

(Hurd 2014)

Cannabis and Opioids : Systems Interaction

Findings across settings
• High rates cannabis use among methadone patients
• Intermittent cannabis associated with less opioid withdrawal
• Medical cannabis participants reduce prescribed opioid use
• Cannabis now proposed as adjunct treatment for OUD
• Cannabis and opioids combined provide superior analgesia
Cannabis and Opioids: Systems Interaction

Medical Cannabis Laws and OD rates (Bachhuber 2014)

Cannabis Use Predicts OUD (Olfson et al 2017)
Marijuana and Mental Health (Compton ed. 2015)

- Cannabis use can worsen symptoms of
  - Anxiety
  - Depression
  - PTSD
  - Psychosis

- Cannabis withdrawal includes
  - Anxiety
  - Irritability
  - Insomnia
  - Pain
Where we also agree

- Causes of (opioid) addiction
  - Genetic predisposition
  - Environmental risk factors
  - Trauma
  - Psychiatric comorbidity
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Conclusion

- Whether gateway exists at population level is a distraction
- How best identify which adolescents at risk
- Focus on trauma, mental health, and protective environments

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