YOUTH MARIJUANA USE

WHAT DO WE KNOW AND WHAT SHOULD WE DO?

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Disclosures of Potential Conflicts

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- Dr. Gray, a physician-scientist and board-certified child and adolescent psychiatrist, co-leads the MUSC Youth Collaborative, focused on understanding and addressing substance use, including cannabis use, among adolescents and young adults

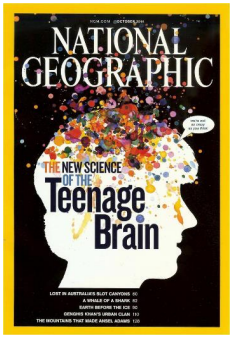
YOUTH COLLABORATIVE

MUSC Medical University of South Carolina

Overview

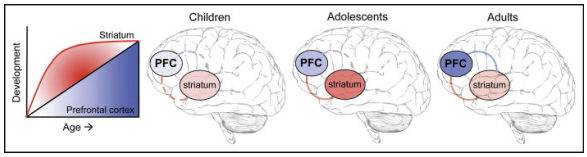
- Adolescents and substance use
- Navigating mixed messages
- What's going on with marijuana/cannabis policy?
- What is the endocannabinoid system?
- What is marijuana/cannabis?
- What are cannabinoids?
- How do we interpret risks and benefits overall?
- How do we apply what we know to help adolescents avoid cannabis-related harms?

Adolescents and Substance Use



- Critical developmental stage with everything in flux
- "They are always different; they are always the same" – John Peel, BBC Radio 1

Adolescents and Substance Use



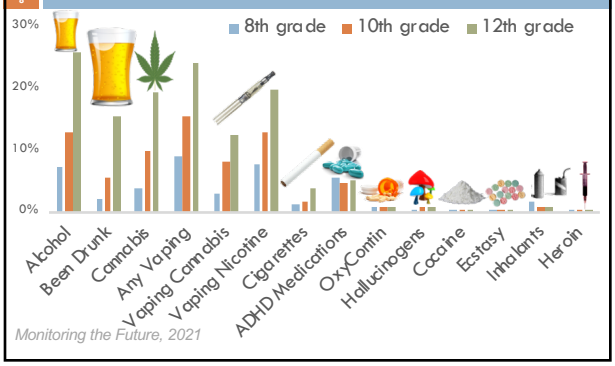
- Why do adolescents make risky decisions?
- Understanding brain development helps us understand adolescent behavior, including risk for substance use (Casey & Jones, 2010)
- Brain development continues into the mid-20s

Adolescents and Substance Use

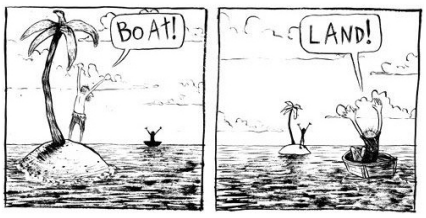
- Substance use almost always starts during adolescence (Miech et al., 2017)
- Adolescent substance users are more prone than adults to developing substance-related problems and difficulty cutting down (Chen & Anthony, 2003)
- While in the past we waited for "rock bottom" before intervening, we now understand that reducing and addressing substance use in adolescence is critically important to public health

Polarization

Past Month Substance Use

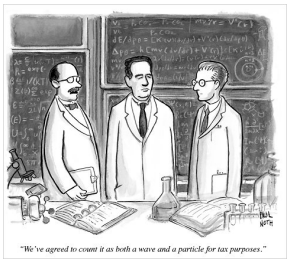


Perspective(s)



Duality

- *"It seems as though we must use sometimes the one theory and sometimes the other, while at times we may use either. We are faced with a new kind of difficulty. We have two contradictory pictures of reality; separately neither of them fully explains the phenomena of light, but together they do."* – Albert Einstein



Misleading messages

("medicine" ≠ good for all)

Misleading messages

("natural" ≠ good for all)

Embrace complexity!

- Cannabis can
  - Be potentially safe and benign
  - Contain potentially medicinal components
  - Be potentially risky and harmful
- These can all be simultaneously true
- And there can still be a lot more to learn

Avoid paralysis!

- This topic is complex, and we're still learning about it, and that's OK
- Let's make the best decisions we can, based on what we know now
- Let's pursue research to address what we don't know now

Cannabis policy

- Not a black and white issue
- There is a full range of options, each with potential risks and benefits
  - Prohibition
  - Decriminalization
  - Medicalization
  - Legalization
  - Commercialization
- Who is at risk? Who benefits? What factors drive policy changes? Are there unintended effects?

Cannabis policy: Federal

- Cannabis is classified as a Schedule I Controlled Substance by the United States Drug Enforcement Agency
- Substances in this schedule have no currently accepted medical use in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse
- Some examples of substances listed in Schedule I are: heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), peyote, methaqualone, and 3,4-methylenedioxymethamphetamine ("Ecstasy")

Cannabis policy: States

- 37 states have legalized "medical marijuana"
- 21 states have legalized recreational cannabis use
  - Age 21 and up

The endocannabinoid system

- Located in central and peripheral nervous system
- Involved in **appetite, pain sensation, mood, memory, immune function**, and **neurodevelopment**
- Two well-described cannabinoid receptor types
  - CB_1 and CB_2
- Two well-described endogenous cannabinoids
  - anandamide and 2-arachidonoylglycerol
- Tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis, binds to CB_1 receptors to produce its psychoactive effects ("high"), though it binds to both CB_1 and CB_2

Marijuana/cannabis

- Use dates back to at least 2700 B.C.
- Plant sources include *Cannabis sativa* and *Cannabis indica*
  - Mixture of dried seeds, stems, leaves, and flowering top
- Traditionally smoked in rolled form (joints, blunts), in a pipe (bowl), or in a water pipe (bong), to produce a characteristic "high"
- Edibles are increasingly popular
- Newer formulations: concentrates (dabs, wax), vape pen delivery, synthetics

Cannabis formulations

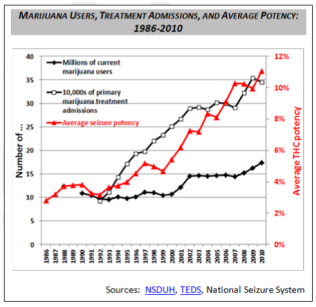
Cannabis & cannabinoids

- The terms are not interchangeable
- Cannabis contains more than 500 active chemicals and more than 100 unique cannabinoids
  - Many cannabinoids have distinct, dose-dependent effects
  - Cannabis is not consistently standardized in dose, potency, or chemical constituency, though in some states regulations require quality control regarding contents in dispensary-sold cannabis preparations
  - Cannabis edibles may have poor labeled dose accuracy; state regulations regarding cannabis product labeling are inconsistent (Vandrey et al., 2015; Kruger et al., 2022)

Cannabinoid concentrations

- Average concentration of delta-9-tetrahydrocannabinol (THC) in seized cannabis increased from 4% in 1995 to 14% in 2019 (ElSohly et al., 2016, 2021)
- The increase in THC concentration coincided with an increase in treatment admissions for cannabis use disorder (CUD)
- Formulations such as dabs/wax may contain 90% or higher THC concentration

Cannabinoid concentrations



What do we know about cannabis-related benefits?

- Many people have occasional, benign, and pleasant experiences with recreational cannabis use
- There is evidence of therapeutic roles of specific, reliably-dosed, orally-administered, pharmaceutical-grade cannabinoids for specific conditions
  - Oral THC (Dronabinol) for loss of appetite in HIV/AIDS and for chemotherapy-induced nausea and vomiting
  - Oral CBD (Epidiolex) for seizures in Lennox-Gastaut syndrome, Dravet syndrome, and tuberous sclerosis

What level of evidence is needed?

- FDA approval of medication typically requires, at minimum, 2 independent randomized controlled trials with positive primary outcomes reflecting efficacy and safety with standardized dosing
- With cannabis we have an unusual situation, with federal DEA Schedule 1 designation in parallel with wide public access and significant potential for commercialization at the state level
  - Rigorous research is difficult to conduct
  - High likelihood of bias in observational/non-rigorous studies
- We must objectively and critically evaluate an imperfect but improving body of research on cannabis and cannabinoid therapeutics

Cannabinoids and mental health treatment

- "There is scarce evidence to suggest that cannabinoids improve depressive disorders and symptoms, anxiety disorders, attention-deficit hyperactivity disorder, Tourette syndrome, post-traumatic stress disorder, or psychosis. There is very low quality evidence that pharmaceutical THC (with or without CBD) leads to a small improvement in symptoms of anxiety among individuals with other medical conditions. There remains insufficient evidence to provide guidance on the use of cannabinoids for treating mental disorders within a regulatory framework. Further high-quality studies directly examining the effect of cannabinoids on treating mental disorders are needed." (Black et al., 2019)

What do we know about cannabis risk/benefit?

- There may be times when benefits are outweighed by risks and/or alternatives
- The balance between risk and benefit depends upon several factors, both at the human level (age, genetic and environmental factors) and at the cannabis/cannabinoid level (strain, constituency, route of administration)
- To date, the established medicinal applications are quite limited and specific to relatively rare conditions

What do we know about cannabis-associated risks?

- Acute/intoxication
  - Driving performance and decision-making
- Chronic/repeated use
  - Adverse effects on airway systems with both smoked and vaporized delivery (Boyd et al., 2021; Murtha et al., 2022)
  - Cannabis use disorder (CUD)
    - More prevalent than previously thought
      - 1/5 lifetime users, of whom 23% are symptomatically severe, of whom 48% are not functioning in any role (e.g., work)
    - Treatment outcomes are limited – room for improvement!
  - Use during pregnancy – effects on neonate/child
  - **Exposure/use during childhood/adolescence**
    - **Higher (~2×) rate of CUD than in adult cannabis users**
    - **Effects on cognition, emotion, and development** (for review, Hasin 2018)

Other reasons for concern about youth cannabis use?

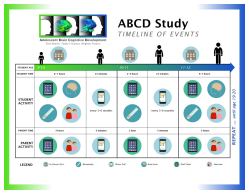
- Adolescent cannabis use is associated with adverse academic (Pope et al., 2003; Fergusson et al., 2015), occupational (Fergusson et al., 2015), cognitive (Jager & Ramsey, 2008; Meier et al., 2012; Randolph et al., 2013; Camchong et al., 2016), psychiatric (Fergusson et al., 2002; Patton et al., 2002; Moore et al., 2007; Gobbi et al., 2019), and substance use (Patton et al., 2007) outcomes (for review, Volkow et al., 2014, 2016; Levine et al., 2017)
- Cannabis use in adolescence is associated with increased incidence and worsened course of psychotic, mood, and anxiety disorders, and increased suicidality (Hayatbakhsh et al., 2007; Moore et al., 2007; Gage et al., 2016; Gobbi et al., 2019)
- "Early, frequent, and heavy adolescent cannabis exposure is associated with poor cognitive and psychiatric outcomes in adulthood" (Levin et al., 2017)

What treatments work for addressing cannabis use disorder in youth?

- Approaches supported by evidence
  - Motivational Interviewing (Walker et al., 2011)
  - Cognitive Behavioral Therapy (Hendriks et al., 2011)
  - Family Therapy (Rigter et al., 2012)
- While these treatments are effective, long-term abstinence outcomes are limited (Compton & Pringle, 2004; Dennis et al., 2004; Waldron & Turner, 2008; Hogue et al., 2014)
- Contingency Management can be used to reinforce abstinence and enhance outcomes (Stanger et al., 2009; Stanger et al., 2015)
- *Room for improvement → researching treatment enhancements*

The need for further research

- Animal models
- Prospective, longitudinal human studies (e.g., ABCD)
- Prevention and treatment studies for youth cannabis use disorder and other substance use disorders



(Volkow et al., 2017)

Cannabis use disorder treatment research

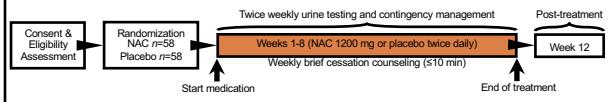
- Studies examining novel treatments in adolescents and adults, spanning behavioral and pharmacological approaches
- Considering a number of outcomes, including changes in cannabis use, withdrawal, craving, cognitive performance, emotions, and quality of life

One example of treatment research: Trials of N-acetylcysteine (NAC)

- NAC has been FDA-approved since the 1960s for other indications and it has a strong safety record even at high doses in children and adults
- NAC is available over-the-counter as a supplement
- NAC, via effects on glutamate in the nucleus accumbens, reduces drug seeking in animal models of addiction

(Kalivas et al., 2008)

Adolescent NAC trial (Gray et al., 2012)

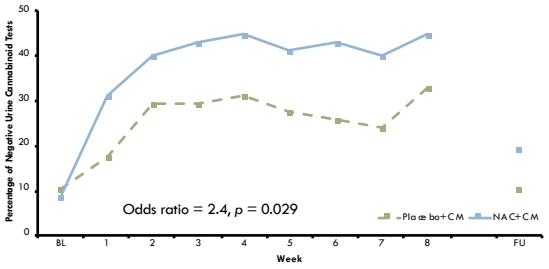


- Adolescents with cannabis use disorder (n=116; ages 15-21)
- Eight weeks of active treatment
  - Double-blind placebo-controlled NAC 1200 mg BID
- All participants received weekly brief cessation counseling and twice-weekly contingency management (CM)
  - Two-tiered escalating reinforcement schedule with resets, rewarding both study retention and cannabis abstinence (Carroll et al., 2006)

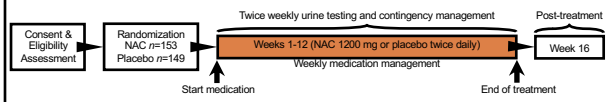
Adolescent NAC trial

Primary outcome

- Intent-to-treat (all randomized participants) with participants assumed to be non-abstinent at any missed visit



Does it work in adults, too?



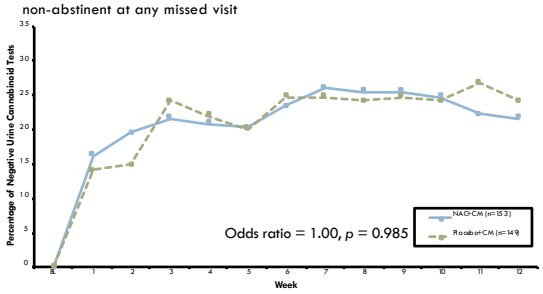
- National Drug Abuse Treatment Clinical Trials Network (CTN) effort to see if positive adolescent findings extend to adults (CTN-0053) (Gray et al., 2017)
- Adults with cannabis use disorder (N=302; ages 18-50; recruited across six CTN sites)

- Twelve weeks of active treatment
  - Double-blind placebo-controlled NAC 1200 mg BID
- All participants received weekly medication management and twice-weekly contingency management
  - Two-tiered escalating reinforcement schedule with resets, rewarding both study retention and cannabis abstinence

Adult Trial

Primary Outcome

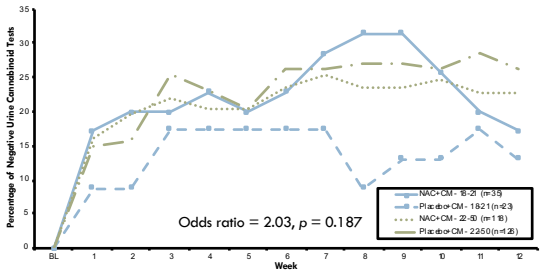
- Intent-to-treat (all randomized participants) with participants assumed to be non-abstinent at any missed visit



Adult Trial

Ages 18-21 versus 22-50 (*post-hoc* comparison)

- Intent-to-treat (all randomized participants) with participants assumed to be non-abstinent at any missed visit



Where are we with NAC?

- NAC is the only medication with positive cessation efficacy findings for CUD in adolescents; efficacy does not extend to adults
- NAC, via its effects on glutamate, appears to target compulsive drug-seeking; in the trials summarized here it was used as an adjunct to Contingency Management
- Positive adolescent trial findings must be replicated and examined further (R01 DA042114 nearing completion!)

Where are we in general?

- Cousijn et al., *Addiction* 2017 doi:10.1111/add.14084
  - "Beneficial and harmful effects of cannabis may differ between and within individuals, and the existence of positive health effects does not make the harmful effects less severe, and vice versa. Given the list of potential harms and benefits, these two aspects of cannabis clearly coexist. Therefore, a shift is called for that goes beyond questions of harms and benefits to that of questions of for whom/what it is harmful and beneficial."

Messaging for our kids

How can we translate a complicated topic into a digestible format for kids?

General themes

- As much as we'd like to be able to make good decisions for our kids, we ultimately want to empower them to make their own good decisions
- Information is key – well-informed kids make better decisions!
- "Planting seeds" in conversations rather than extended lectures
- They are listening (even when their eyes roll), but we have to make the information clear, relevant, and digestible

General themes

- We undermine our messaging when we are too extreme (in either direction!)
  - Minimizing risks may be interpreted as endorsement
  - Exaggerating risks undermines credibility
- "Know your audience and know yourself"
  - We all have our own parenting styles
  - Each kid is unique
  - Each kid is developing
  - Messaging can be matched to all these factors

Things that work

- Keep it simple and digestible
  - "Bite-sized chunks" of information
- Allow for dialogue and discussion
  - Can provide the chance to dispel myths and understand information kids are hearing
    - Despite what many kids perceive, most kids don't use cannabis
- It's OK to say it's a complicated topic, but we must be clear about youth-specific risks
  - Acute impairment
    - Risk for impaired driving and altered judgment
  - Chronic issues
    - Adverse effects on brain development, mental health, and thinking ability

Addressing the general topic of addiction

- Not every substance user becomes addicted, but it is an inherent risk with any repeated substance use
- Some are at higher risk than others (genetic factors, etc. – important to note if addiction runs in the family)
- Addiction is a brain disease that involves hijacking our body's natural reward system (designed to help us survive)
- "Nuggets" is a thoughtful cartoon illustration of the progression from substance use to addiction:
  - https://www.youtube.com/watch?v=HUngLgGRJpo

Additional resources

- NIDA for Teens – resources for teens, teachers, and parents
  - https://teens.drugabuse.gov
- Partnership to End Addiction – resources for parents
  - https://drugfree.org/article/connecting-with-your-teen/
  - https://drugfree.org/article/brain-development-teen-behavior/
  - https://drugfree.org/article/set-limits-monitor-your-teens-behavior/
  - https://drugfree.org/article/healthy-risk-taking/

Summary

- This topic is complex, we're still learning about it, and that's OK
- Avoid exaggeration, deliver digestible information, "plant seeds," and allow for dialogue
  - Cannabis and cannabinoids are neither all good nor all bad
  - However, there are very clear reasons to be particularly concerned about youth cannabis use
    - **Risks to the developing brain, mental health, and the ability to learn and achieve**

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