MARIJUANA DEPENDENCE

POLICY IMPLICATIONS AND ADVANCES IN TREATMENT

Kevin M. Gray, M.D.

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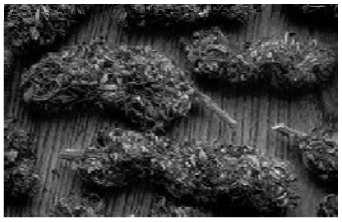
Overview

- A little history/background on marijuana
- The endocannabinoid system and marijuana
- Policy developments and implications
- Specific considerations for adolescents
- Existing treatments
- Findings from a recent trial of *N*-acetylcysteine

Marijuana history

- Use dates back to at least 2700 B.C.
- Plant source is *Cannabis sativa*
- Mixture of dried seeds, stems, leaves, and flowering top
- Usually smoked in rolled form (joint, blunt), in a pipe (bowl), or in a bong
- May also be eaten (brownies)

Marijuana use



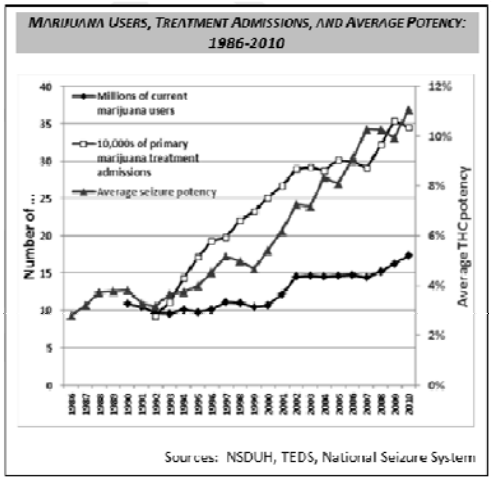



Marijuana use and dependence

- Marijuana is the most commonly used illicit substance in the United States and worldwide
- While most users have occasional and relatively benign experiences with marijuana, about one in ten users become dependent
- Earlier age of onset predicts higher likelihood of developing dependence

Marijuana potency

- Average potency of delta-9-tetrahydrocannabinol (THC) in seized marijuana has increased from 3% in 1992 to 11% in 2010
- This increase in potency coincides with an increase in treatment admissions for marijuana use disorders



Why do people use marijuana?

- To get "high"
  - Acute effects occur almost immediately upon smoking and last 1-3 hours
- For therapeutic/medicinal purposes?
  - May be worthwhile to consider the endocannabinoid system and the potential for cannabinoid therapeutics

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 (main psychoactive ingredient in smoked marijuana) binds to CB_1 receptors to produce its psychoactive effects, though it binds to both CB_1 and CB_2 with equal affinity

Cannabis and cannabinoids

- The terms are not interchangeable
- Smoked cannabis (marijuana) contains more than 460 active chemicals and more than 60 unique cannabinoids
  - Many cannabinoids have dose-dependent effects
  - Cannabis (including "medical marijuana" in dispensaries) is not standardized in dose, potency, or chemical constituency
- Some cannabinoids have been isolated and studied as oral compounds
  - Dronabinol (Marinol) – Oral delta-9-tetrahydrocannabinol (THC)
  - Nabilone (Cesamet) – Oral synthetic cannabinoid (similar to THC)
  - Cannabidiol (CBD) – Non-psychoactive cannabinoid
  - Nabiximols (Sativex) – 1:1 THC:CBD standard-dose oral spray derived from cannabis plant

Cannabinoid therapeutics

- Two key review articles on randomized controlled trials (RCTs)
  - Ben Amar, M. (2006). Cannabinoids in medicine: A review of their therapeutic potential. *Journal of Ethnopharmacology, 105*, 1-25.
  - Hazekamp, A., & Grotenhermen, F. (2010). Review on clinical studies with cannabis and cannabinoids 2005-2009. *Cannabinoids, 5*, 1-21.
- Review 110 RCTs (~6100 participants—all adults) across various target conditions
  - Large majority involved oral cannabinoid compounds; few involved smoked marijuana

Cannabinoid therapeutics

- Results mixed, but areas of therapeutic potential include:
  - Analgesia in chronic neuropathic pain
  - Appetite stimulation in debilitating diseases (e.g., cancer & AIDS)
  - Spasticity in multiple sclerosis
- Dronabinol has FDA indication in adults for
  - Loss of appetite in AIDS
  - Chemotherapy-induced nausea and vomiting
- Nabilone has FDA indication in adults for
  - Chemotherapy-induced nausea and vomiting (refractory to other treatments)
- Smoked marijuana has no FDA indications

Cannabinoid therapeutics

- Potential benefits must be weighed against risks
  - Evidence is limited to short-term use in adults with severe conditions
  - Adverse effects
  - Risk for abuse and dependence
  - Specific issues with smoked marijuana
    - Non-standardized dosing
    - Varying ingredients
    - Smoked delivery

Marijuana policy

- How has the evidence for cannabinoid therapeutics and risks been interpreted to influence policy?

Marijuana policy: Federal

- Marijuana 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")

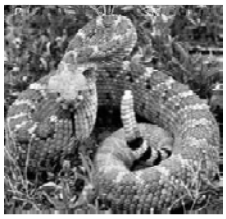
Marijuana policy: States

- 20 states and the District of Columbia have legalized "Medical Marijuana"
- 2 states (Colorado and Washington) have legalized recreational marijuana use

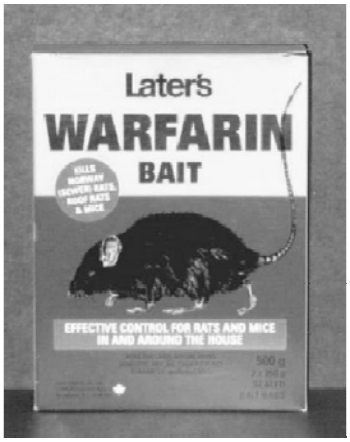
Adolescent considerations

- As practitioners, we are aware of the delicate balance between risk and benefit, even among FDA-approved medications
- However, teens and families may struggle with these nuances, especially in light of the term "Medical Marijuana"
  - Many assume that "medical" implies "beneficial"
  - Many equate "marijuana" with "natural", which they may in turn equate with "harmless"
- Perception is critically important

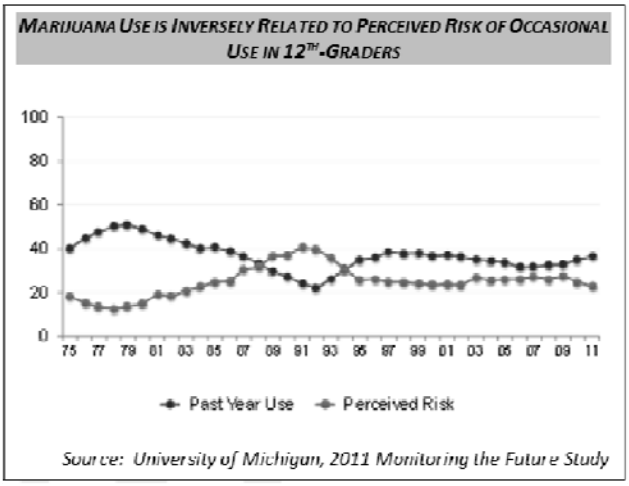
"It's natural"



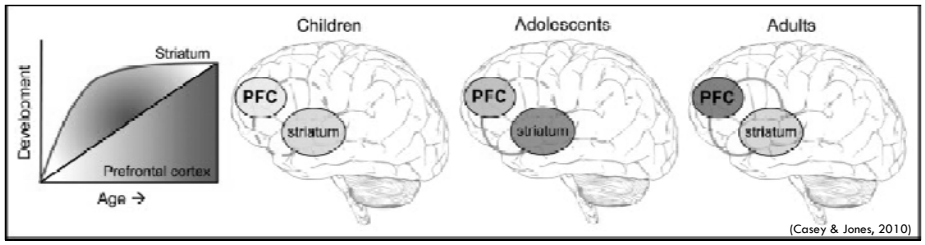
"It's medicine"



Adolescent considerations



Adolescent considerations



- Striatal development (associated with reactivity to motivational stimuli) occurs in curvilinear fashion, while prefrontal development (associated with cognitive control) occurs in linear fashion over the course of adolescence
- Amid a developmental window in which motivational reactivity outpaces cognitive control, adolescents may be particularly prone to making high-risk choices, valuing immediate reward over long-term considerations. (Casey & Jones, 2010)

Adolescent marijuana use

- Marijuana initiation typically occurs during adolescence, and rates of initiation and use are increasing
- 23% of high school seniors are current marijuana users, and 7% use marijuana daily (Johnston et al., 2012)
- Young users are particularly prone to dependence symptoms and inability to cut down their use (Chen & Anthony, 2003)
- Marijuana use disorders (abuse and dependence) are present in 4% of adolescents and 6% of young adults, compared with less than 1% of adults over age 25 (SAMHSA, 2007)

Adolescent marijuana use

- In a dose-dependent manner, adolescent marijuana use is associated with adverse academic (Pope et al., 2003), cognitive (Jager & Ramsey, 2008; Meier et al., 2012), behavioral (Rob et al., 1990), psychiatric (Fergusson et al., 2002; Moore et al., 2007; Patton et al., 2002), and substance use (Patton et al., 2007) outcomes
- Of particular interest to our field, marijuana use in adolescence is associated with increased incidence and worsened course of psychotic, mood, and anxiety disorders (Hayatbakhsh et al., 2007; Moore et al., 2007)

Evidence-based treatments

- Adolescent substance use disorders (in general)
  - Recent meta-analysis of 46 psychosocial treatment approaches revealed that no particular intervention was clearly superior to others (Waldron & Turner, 2008)

Evidence-based treatments

- Marijuana use disorders (in particular)
  - Largest study to date was the Cannabis Youth Treatment (CYT) study (Dennis et al., 2002)
    - Compared 5-session MET/CBT, 12-session MET/CBT, Multidimensional Family Therapy, and Community Reinforcement
    - Similarly modest effect across interventions
    - Days abstinent per 90-day quarter increased from 52 to 65
  - Some emerging evidence that Contingency Management may enhance treatment outcomes (Kamen et al., 2005; Stanger et al., 2009)

Evidence-based treatments

- Long-term abstinence outcomes are remarkably poor with evidence-based adolescent marijuana cessation treatments (Compton & Pringle, 2004; Dennis et al., 2004; Waldron & Turner, 2008)

What should we do clinically?

- Amid a limited evidence base, clinicians may incorporate a variety of treatment elements to help optimize outcomes
  - Functional behavioral analysis
  - Motivational enhancement techniques
  - Cognitive-behavioral approaches
  - Family therapy
  - Contingency management interventions

What should we do in research?

- Testing new treatment modalities
- Testing modifications to existing treatment modalities
- Testing combinations of existing treatment modalities

Might there be a role for medication?

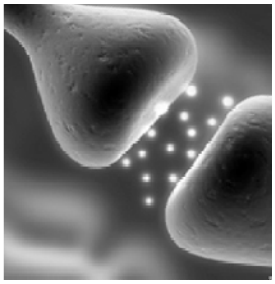
- Medications are used in adult substance dependence treatment *to augment psychosocial interventions and enhance outcomes*
- There is not, and likely never will be, a "magic pill" for any addiction

Might there be a role for medication?

- Potential behavioral targets of pharmacotherapies for substance use disorders
  - Reducing withdrawal
  - Reducing craving/seeking
  - Causing negative effects with drug use (aversion)
  - Reducing positive effects with drug use (decreased reward)
  - Reducing symptoms that may lead to drug use (e.g., anxiety, insomnia)

Might there be a role for medication?

- Potential neurotransmitter targets of pharmacotherapies for substance use disorders
  - Dopamine
  - Norepinephrine
  - Serotonin
  - Glutamate
  - GABA
  - Nicotine
  - Cannabinoid
  - Etc., etc., etc.



FDA-approved medications in adults

- Nicotine dependence pharmacotherapies
  - Nicotine Replacement Therapy
    - FDA "smoking cessation assistance"
    - Agonist therapy (binds to nicotine receptors)
    - Decreases withdrawal and craving
  - Bupropion SR
    - FDA "smoking cessation assistance"
    - Norepinephrine & dopamine reuptake inhibitor and nicotinic antagonist
    - Decreases withdrawal and craving
  - Varenicline
    - FDA "smoking cessation assistance"
    - Nicotinic receptor partial agonist
    - Reduces cravings and reduces pleasurable effects of smoking

FDA-approved medications in adults

- Alcohol dependence pharmacotherapies
  - Benzodiazepines
    - Chlorazepate, oxazepam, diazepam, chlordiazepoxide
    - FDA "alcohol withdrawal syndrome"
    - Enhances GABA-A effects
    - Agonist treatment used for acute detoxification
  - Disulfiram
    - FDA "alcoholism"
    - Blocks metabolism of alcohol via blockade of acetaldehyde dehydrogenase
    - Causes an unpleasant reaction when drinking (aversive treatment)
  - Naltrexone
    - FDA "alcohol dependence, maintenance of abstinence"
    - Opioid receptor antagonist
    - Reduces acute and long-term craving
  - Acamprosate
    - FDA "alcoholism, maintenance of abstinence"
    - NMDA antagonist and GABA-A agonist, with downstream glutamatergic effects

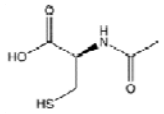
FDA-approved medications in adults

- Opioid dependence pharmacotherapies
  - Methadone
    - FDA "drug detoxification – opioid abuse", "opioid abuse, maintenance therapy"
    - Long-acting opioid
    - Agonist treatment
  - Buprenorphine/Naloxone
    - FDA "opioid dependence"
    - Mixed opioid agonist/antagonist
  - Naltrexone
    - FDA "relapse, following detoxification; prophylaxis"
    - Opioid antagonist
    - Blocks the euphoric effects of opioids

Medication for marijuana dependence?

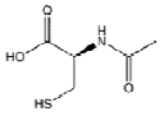
- Little progress has been made in medication development specifically for marijuana dependence
  - Negative/discouraging/mixed studies
    - Bupropion (Carpenter et al., 2009), divalproex (Levin et al., 2004), dronabinol (oral THC) (Levin et al., 2011), mirtazapine (Haney et al., 2010), nefazodone (Carpenter et al., 2009)
  - Encouraging preliminary studies
    - Buspirone (pilot RCT; McRae-Clark et al., 2009)
    - Dronabinol + lofexidine (human lab study; Haney et al., 2008)
    - Gabapentin (pilot RCT; Mason et al., 2012)
  - None of these studies focused on young marijuana users, and none have yielded a significant primary intent-to-treat effect on marijuana use

The argument for *N*-acetylcysteine (NAC)



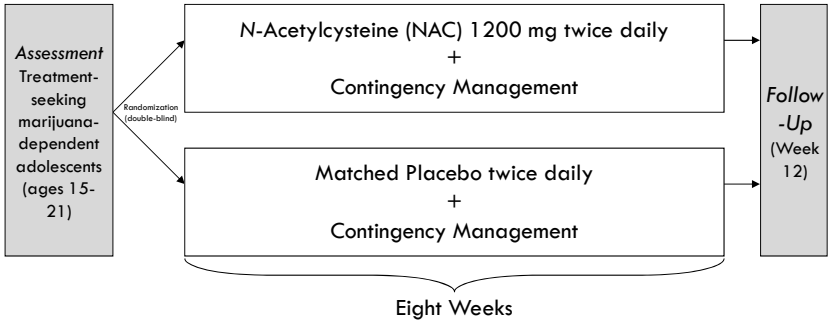
- Glutamate plays an important role in addictive processes across multiple substances of abuse, including cannabis (Gass & Olive, 2008)
- Glutamate dysregulation in the core of the nucleus accumbens underlies drug seeking (LaLumiere & Kalivas, 2008; McFarland et al., 2003, 2004)
- NAC administration activates the cystine/glutamate exchanger, leading to reduction in reinstatement of drug seeking in animal models (Baker et al., 2003; Madayag et al., 2007; Moran et al., 2005)
- Since drug administration down-regulates the cystine-glutamate exchanger (Kau et al., 2008), up-regulation of the exchanger via NAC administration directly normalizes a drug-induced pathology (Kalivas et al., 2008)

The argument for *N*-acetylcysteine (NAC)



- Unlike many other potential candidate medications for cannabis dependence treatment (see Hart, 2005, for review), NAC has a long-established safety record in adults and children, with FDA approval since 1963
- NAC is well tolerated, inexpensive, and readily available over-the-counter at supplement stores
- These factors offer significant appeal in light of escalating FDA, healthcare provider, patient, and family concerns about potential adverse effects of psychoactive medications in children and adolescents (Cheung et al., 2008; Nemeroff et al., 2007)
- Our open-label pilot study in young marijuana users supported feasibility and tolerability for further study (Gray et al., 2010)

Study design



- All participants received a contingency management (CM) intervention reinforcing compliance & abstinence (Carroll et al., 2006) and weekly brief (≤10 min) physician-delivered cessation counseling
- Main outcome measure was weekly urine cannabinoid test

Sample characteristics

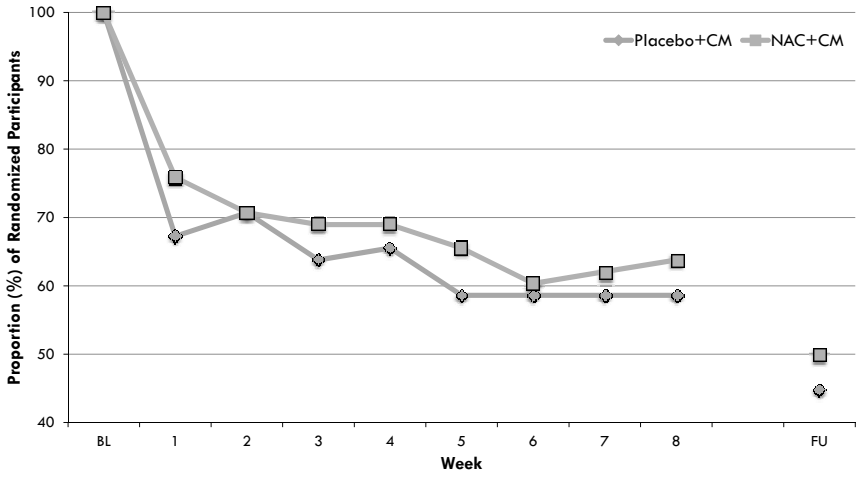
- Enrolled 116 participants over 16 months (no significant between-group differences)

	Overall	NAC	Placebo
Age (range 15-21)	18.9 ± 1.5	18.9 ± 1.5	18.8 ± 1.5
Gender (% male)	73.0%	68.4%	77.6%
Race (% white)	83.5%	79.0%	87.9%
Enrolled in school (%)	73.9%	75.4%	72.4%
Smoke cigarettes (%)	57.0%	58.9%	55.2%
Baseline days using (out of 30)	23.2 ± 6.7	23.3 ± 7.2	23.1 ± 6.1
Baseline "puffs/day"	11.5 ± 16.5	12.1 ± 17.2	11.4 ± 16.8
% positive UDS at BL	90.5%	91.4%	89.7%
Years of use	4.2 ± 1.8	4.1 ± 1.7	4.3 ± 2.0
Prior quit attempts	3.3 ± 9.8	3.9 ± 13.5	2.7± 3.6

Adherence/tolerability

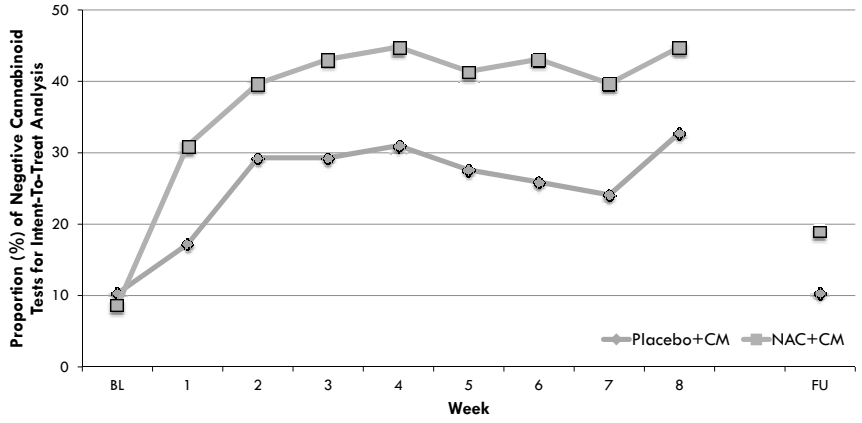
- Adherence (by self-report medication diaries and blister pack pill counts)
  - 95% of dispensed NAC doses were taken
  - 93% of dispensed placebo doses were taken
- Tolerability
  - One participant in NAC group discontinued medication due to severe heartburn
  - No other participants discontinued treatment due to AEs
  - AEs deemed at least possibly treatment-related and occurring in ≥2 participants
    - NAC: Vivid Dreams (3)
    - Placebo: Insomnia (3), Irritability (2)

Retention



Treatment response

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



Main outcome analysis

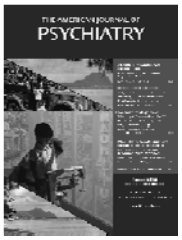
- Repeated measures intent-to-treat (ITT) analysis of weekly urine cannabinoid testing (Generalized Estimating Equations), by treatment group (NAC+CM versus placebo+CM)
  - Odds ratio = 2.4 (i.e., NAC participants had more than twice the odds of submitting a clean urine specimen during treatment, compared to placebo participants)
  - $p = 0.029$
- Results similar for modified ITT (all participants receiving ≥1 dose of study medication) (OR=2.1, p=0.047) and per-protocol (all participants submitting urine sample on a given week) (OR=2.4, p=0.036) analyses

Additional abstinence outcomes

- End-of-treatment abstinence (self-reported abstinence confirmed by negative urine testing throughout the last 2 weeks of treatment) OR=2.3 (p=0.054)
- Statistically significant positive findings remained even when excluding participants with negative baseline urine cannabinoid tests

Study conclusions

- NAC, compared to placebo, significantly improved treatment outcome among cannabis dependent adolescents participating in a psychosocial cannabis cessation program (CM + brief weekly counseling)



Gray, K. M., Carpenter, M. J., Baker, N. L., DeSantis, S. M., Kryway, E., Hartwell, K. J., McRae-Clark, A. L., & Brady, K. T. (2012). A double-blind randomized controlled trial of *N*-acetylcysteine in cannabis-dependent adolescents. *American Journal of Psychiatry, 169*, 805-812. PMCID: PMC3410961

Future directions

- Remaining questions that may be addressed with future studies:
  - Would marijuana-dependent adults respond to NAC?
    - *CTN 0053: ACCENT (Achieving Cannabis Cessation—Evaluating N-Acetylcysteine Treatment)* 
  - Does NAC require a CM (or other psychosocial) treatment platform?
  - Might there be benefit in dose adjustment?
  - Might these effects be seen across other substance use disorders in adolescents or adults?

Questions?

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