ADOLESCENT MARIJUANA USE

WHAT DO WE KNOW AND WHAT SHOULD WE DO?

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Disclosures

- Research discussed during this presentation was supported by the National Institutes of Health
- I do intend to discuss investigational/off-label use of medication

Overview

- Navigating mixed messages
- A little history/background on marijuana
- The endocannabinoid system and marijuana
- Policy developments and implications
- Specific considerations for adolescents
- Psychosocial treatments
- Pharmacotherapy trials
- Findings from recent trials of *N*-acetylcysteine

Polarization, False Equivalency, and Duality

Polarization, False Equivalency, and Duality

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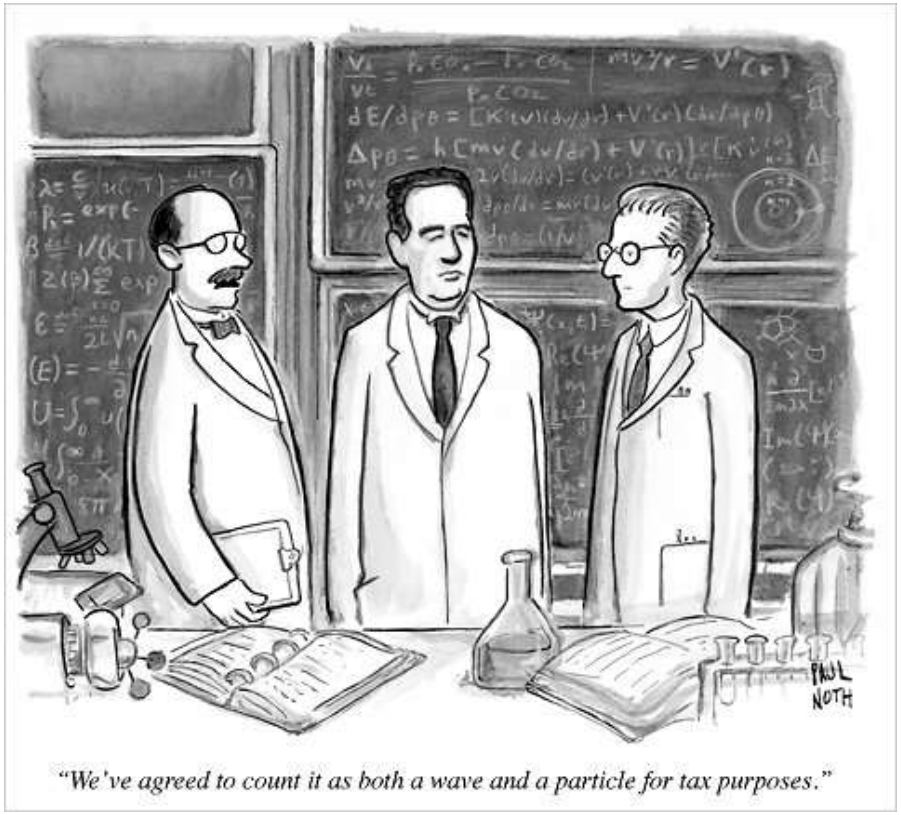
- "*It seems as though we must use sometimes the one theory and sometimes the other, while at times we may use either. We are faced with a new kind of difficulty. We have two contradictory pictures of reality; separately neither of them fully explains the phenomena of light, but together they do.*" –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



"We've agreed to count it as both a wave and a particle for tax purposes."

Polarization, False Equivalency, and Duality

"About your cat, Mr. Schrödinger—I have good news and bad news."

Polarization, False Equivalency, and Duality

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- Marijuana can
  - Be potentially safe and benign
  - Contain potentially medicinal components
  - Be potentially risky and harmful
- These can all be simultaneously true

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); wide variety of edibles now used
- Newer formulations: concentrates (dabs, wax, butane hash oil), vape pen delivery

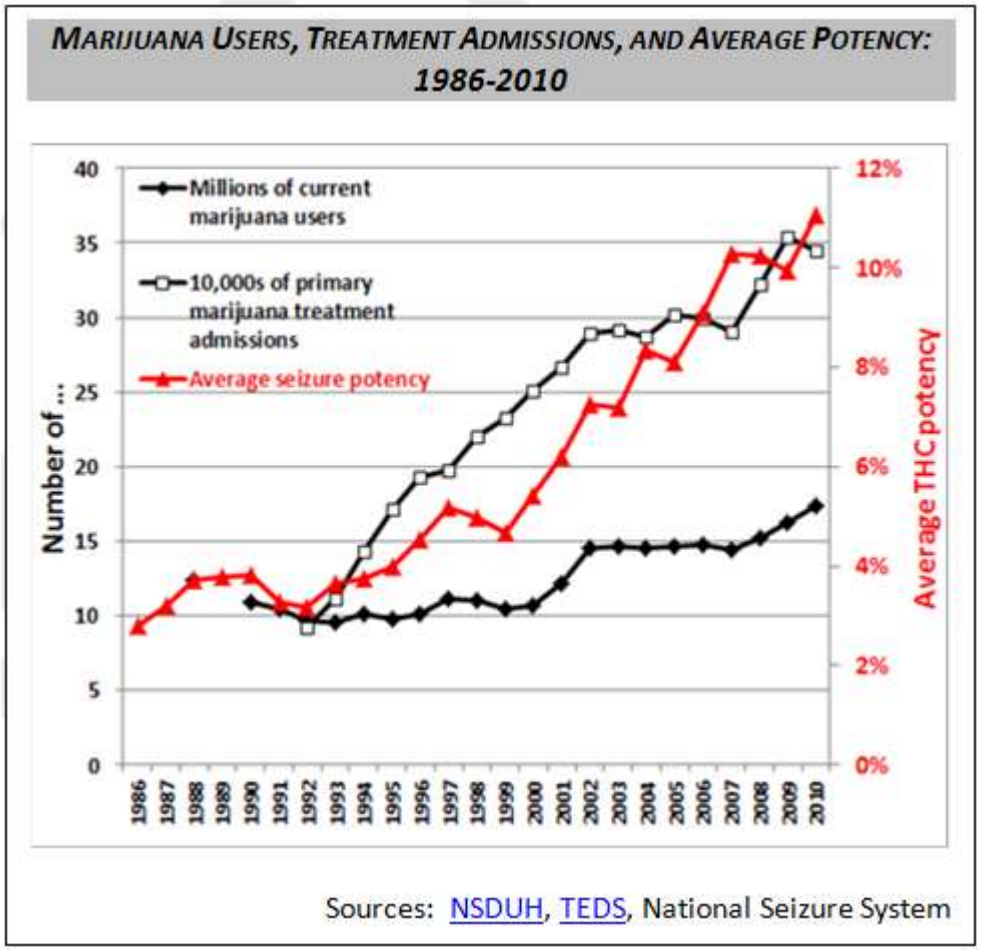
Marijuana use

Marijuana use and addiction

- 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, some users become addicted
- Earlier age of onset predicts higher likelihood of developing addiction
  - 1/11 adults who try marijuana become dependent
  - 1/6 adolescents who try marijuana become dependent (Hall, 2009)

Marijuana potency

- Average potency of delta-9-tetrahydrocannabinol (THC) in seized marijuana increased from 3% in 1992 to 11% in 2010
- This increase in potency coincides with an increase in treatment admissions for cannabis use disorder
- Marijuana concentrates (e.g., butane hash oil) may contain >90% THC



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

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- 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 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
- 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
  - Recent study of cannabis edibles revealed poor labeled dose accuracy (Vandrey et al., 2015)
- 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

- Recent key review/meta-analysis on randomized controlled trials (RCTs)
  - Whiting, P. F., et al. (2015). Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA, 313*, 2456-2473.
- Review of 151 reports, comprising 79 RCTs (6462 participants—all adults) across various target conditions
  - Most trials (70%) deemed to have "high risk of bias"
    - Only 57% with appropriate participant blinding and only 24% with appropriate blinding of outcome assessors
  - Large majority involved oral cannabinoid compounds; *only two involved marijuana (smoked in one study, vaporized in another)*

Cannabinoid therapeutics

- Whiting et al. conclusions
  - Moderate-quality evidence for treatment of chronic pain and spasticity
  - Low-quality evidence for treatment of nausea/vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome
  - Cannabinoids associated with an increased risk of short-term adverse events
- Dronabinol has FDA indication in adults for
  - Loss of appetite in HIV/AIDS
  - Chemotherapy-induced nausea and vomiting
- Nabilone has FDA indication in adults for
  - Chemotherapy-induced nausea and vomiting (refractory to other treatments)
- Ongoing trials evaluating cannabidiol (isolated in oral dosing form) for epilepsy
  - Positive RCT findings recently published in Dravet syndrome (Devinsky et al., 2017)
- *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 misuse and addiction
  - Specific issues with 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

- 28 states and the District of Columbia have legalized "medical marijuana"
- 8 states 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”

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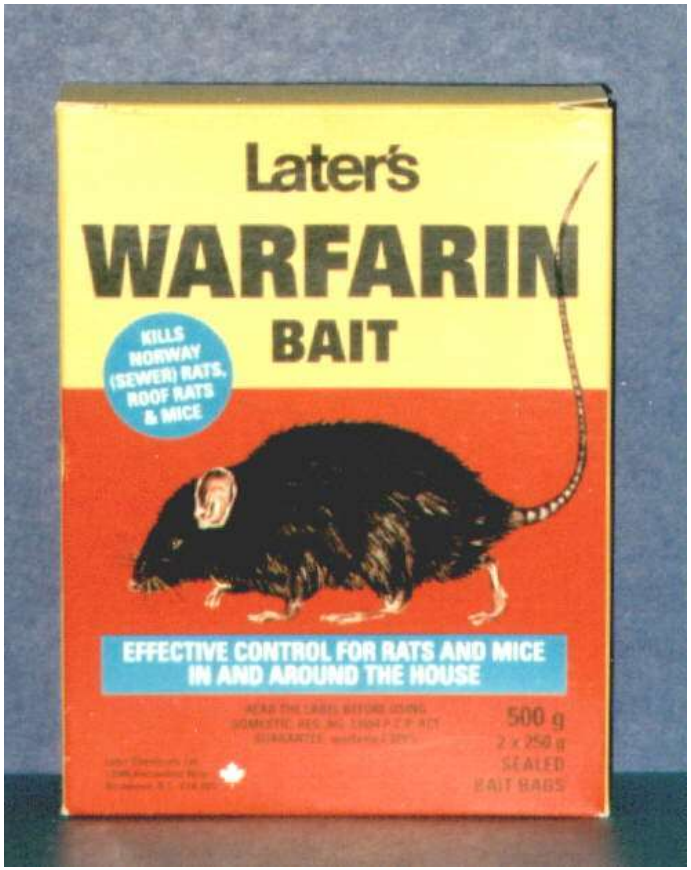
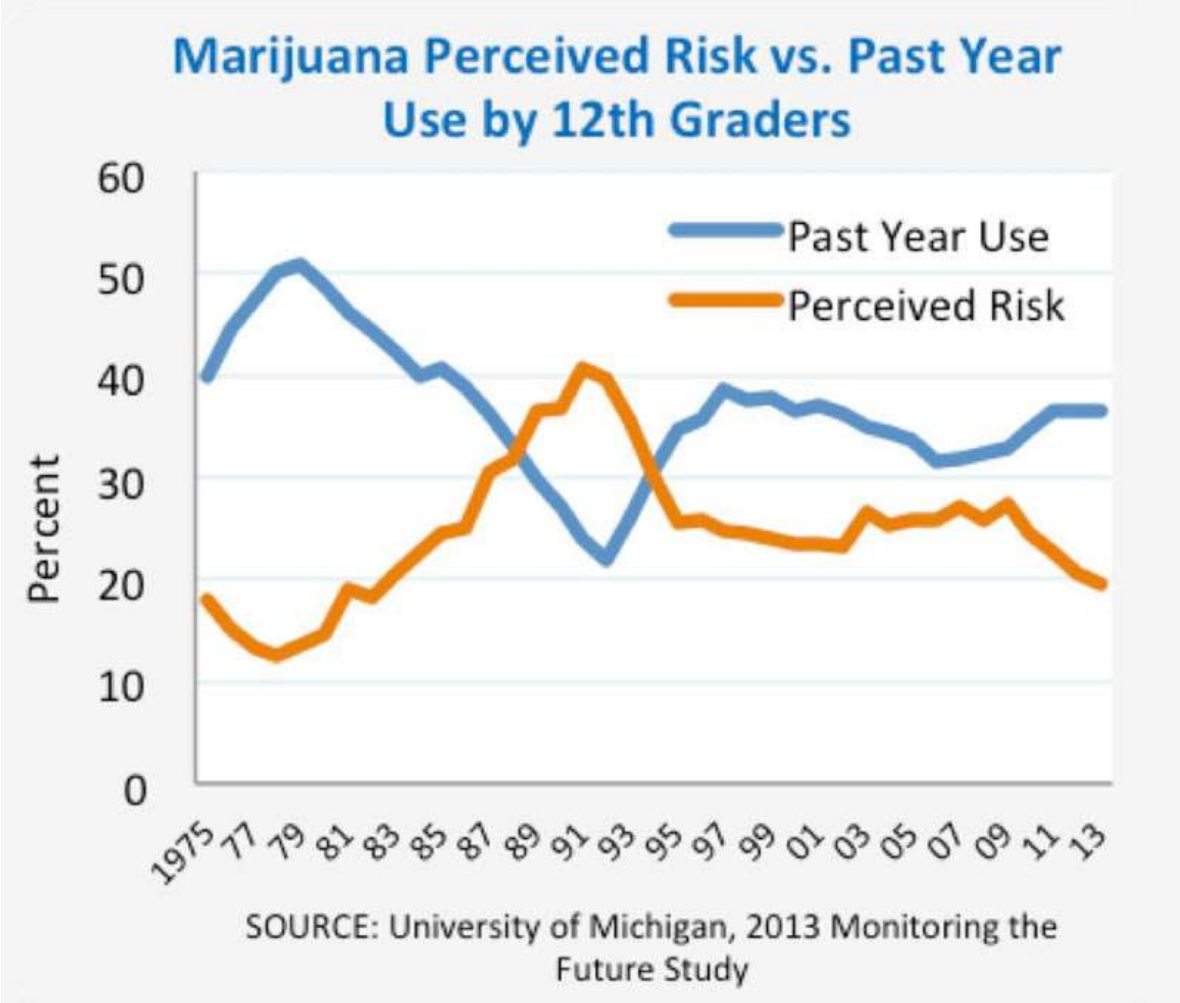
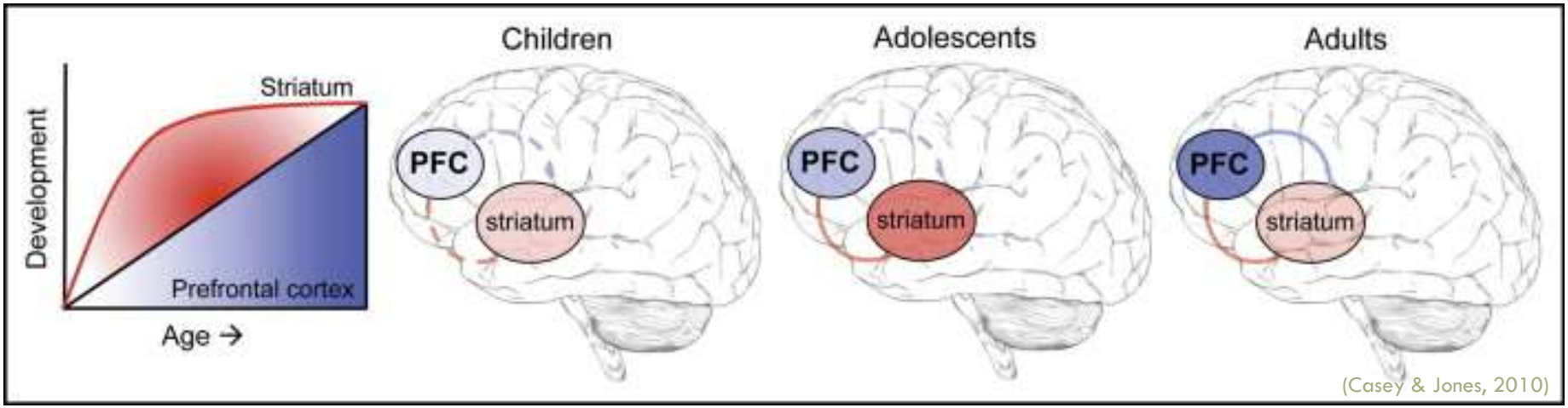
“It’s medicine”



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
- 45% of U.S. high school seniors have used marijuana, 23% use currently, and 6% use daily (Johnston et al., 2016)
- Young users are particularly prone to dependence symptoms and inability to cut down their use (Chen & Anthony, 2003)
- The odds of meeting criteria for cannabis use disorder are substantially greater in adolescent users, compared to adults, regardless of time frame or intensity of use (Richter et al., 2016)
- 9% of cannabis-exposed adults versus 17% cannabis-exposed adolescents develop cannabis dependence (Hall, 2009; Volkow et al., 2014)

Adolescent marijuana use

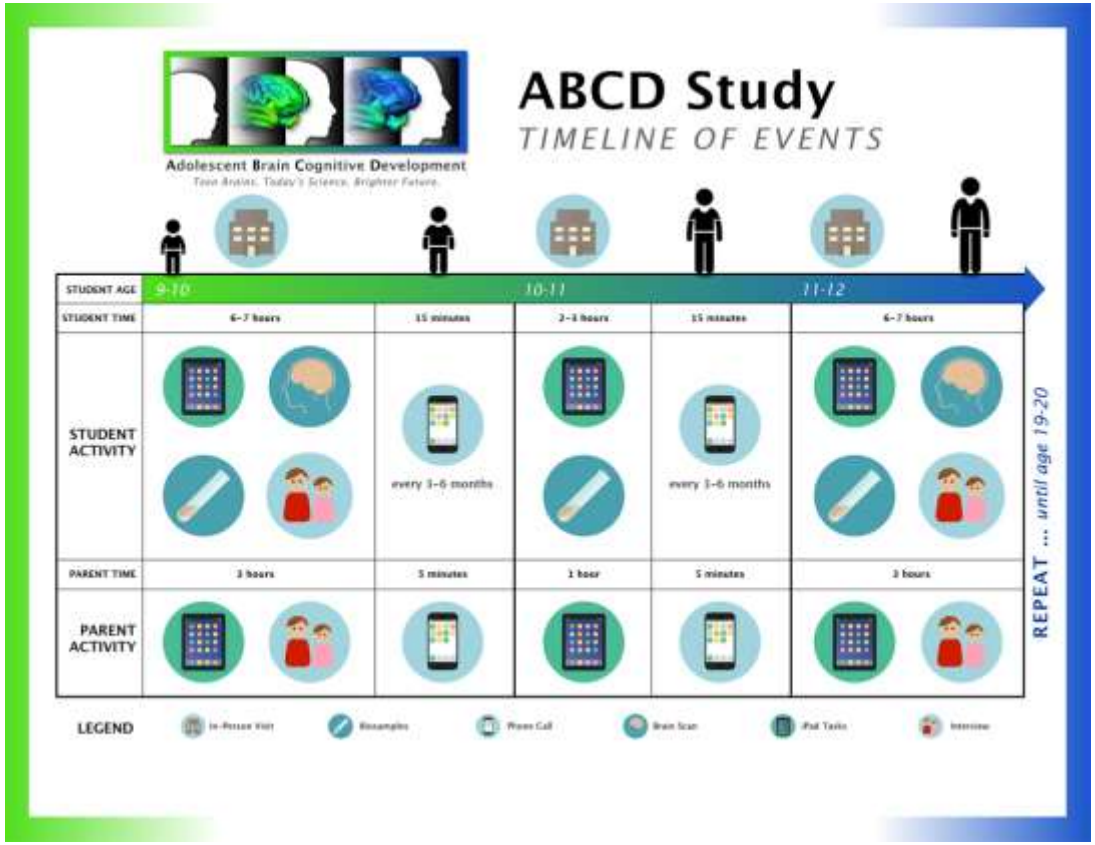
- In a dose-dependent manner, adolescent marijuana use is associated with adverse academic (Pope et al., 2003; Fergusson et al., 2015), occupational (Fergusson et al., 2015), cognitive (Jager & Ramsey, 2008; Meier et al., 2012; Randolph et al., 2013; Camchong et al., 2016), psychiatric (Fergusson et al., 2002; Patton et al., 2002; Moore et al., 2007), and substance use (Patton et al., 2007) outcomes (for review, Volkow et al., 2014, 2016; Levine et al., 2017)
- 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; Gage 2016)
- Serious marijuana-associated risks are well recognized, and are particularly striking in adolescents (Volkow et al., 2014)
- Adult-onset marijuana users may experience fewer adverse effects (Fergusson et al., 2015)

Adolescent marijuana use

- Levine et al. *J Am Acad Child Adolesc Psychiatry* 2017;56(3):214–225.
  - "Based on the data in the current literature, a strong association is found between early, frequent, and heavy adolescent cannabis exposure and poor cognitive and psychiatric outcomes in adulthood, yet definite conclusions cannot yet be made as to whether cannabis use alone has a negative impact on the human adolescent brain. Future research will require animal models and longitudinal studies to be carefully designed with a focus on integrating assessments of molecular, structural, and behavioral outcomes in order to elucidate the full range of potential adverse and long-term consequences of cannabinoid exposure in adolescence."

The need for further observational research

- Animal models
- Prospective, longitudinal human studies (e.g., ABCD)



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; Hogue et al., 2014)
- Cannabis use disorder (in particular)
  - Largest study to date was the Cannabis Youth Treatment (CYT) study (Dennis et al., 2005)
    - Similarly modest effect across interventions
    - Days abstinent per 90-day quarter increased from 52 to 65

Evidence-based treatments

- Psychosocial approaches supported by evidence
  - Motivational Enhancement Therapy (Walker et al., 2011)
  - Cognitive Behavioral Therapy (Hendriks et al., 2011)
  - Family Therapy (Rigter et al., 2012)
  - Contingency Management (Stanger et al., 2009; Stanger et al., 2015)

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; Hogue et al., 2014)

Might there be a role for medication?

- Medications are used in adult substance use disorder 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?

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- 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)

Medication for cannabis use disorder?

- Little progress has been made in medication development specifically targeting cannabis use disorder
- Almost all of this work has focused on adult patients, yielding mixed results

Published CUD placebo-controlled medication trials

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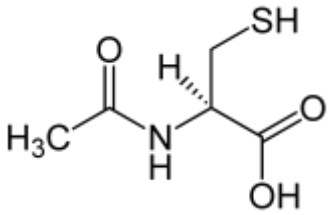
Human Laboratory		Pilot Controlled Trials		Fully Powered Controlled Trials	
Discouraging	Encouraging	Discouraging	Encouraging	Negative/Null	Positive
Bupropion SR (Haney et al., 2001)	Rimonabant (Huestis et al., 2001; Huestis et al., 2007)	Divalproex (Levin et al., 2004)	Buspirone (*N*=50) (McRae-Clark et al., 2009)	Oral THC (*N*=156) (Levin et al., 2011)	*N*-acetylcysteine (*N*=116 **adolescents**) (Gray et al., 2012)
Nefazodone (Haney et al., 2003)	Oral THC (Haney et al., 2004; Budney et al., 2007)	Bupropion SR (Carpenter et al., 2009)	Gabapentin (*N*=50) (Mason et al., 2012)	Venlafaxine XR (*N*=103) (Levin et al., 2013)	
Divalproex (Haney et al., 2004)	Lofexidine + Oral THC (Haney et al., 2008)	Nefazodone (Tirado et al., 2008)	Nabiximols (*N*=51) (Allsop et al., 2014)	Buspirone (*N*=175) (McRae-Clark et al., 2016)	
Lithium (Winstock et al., 2009)	Zolpidem CR (Vandrey et al., 2011)	Atomoxetine (McRae-Clark et al., 2010)		Lofexidine + Oral THC (*N*=156) (Levin et al., 2016)	
Baclofen (Haney et al., 2010)	Nabilone (Haney et al., 2013)	Lithium (Johnston et al., 2014)		*N*-acetylcysteine (*N*=302 **adults**) (Gray et al., 2017)	
Mirtazapine (Haney et al., 2010)	Naltrexone (Haney et al., 2015)	Vilazodone (McRae-Clark et al., 2016)			
Naltrexone (Wachtel & de Wit, 2000; Haney et al., 2003; Cooper & Haney, 2010)	Nabiximols (1:1 THC/cannabidiol) (Trigo et al., 2016)	Topiramate (*N*=66 **adolescents**) (Miranda et al., 2016)			
	Zolpidem + Nabilone (Herrmann et al., 2016)				

Background on *N*-Acetylcysteine (NAC)



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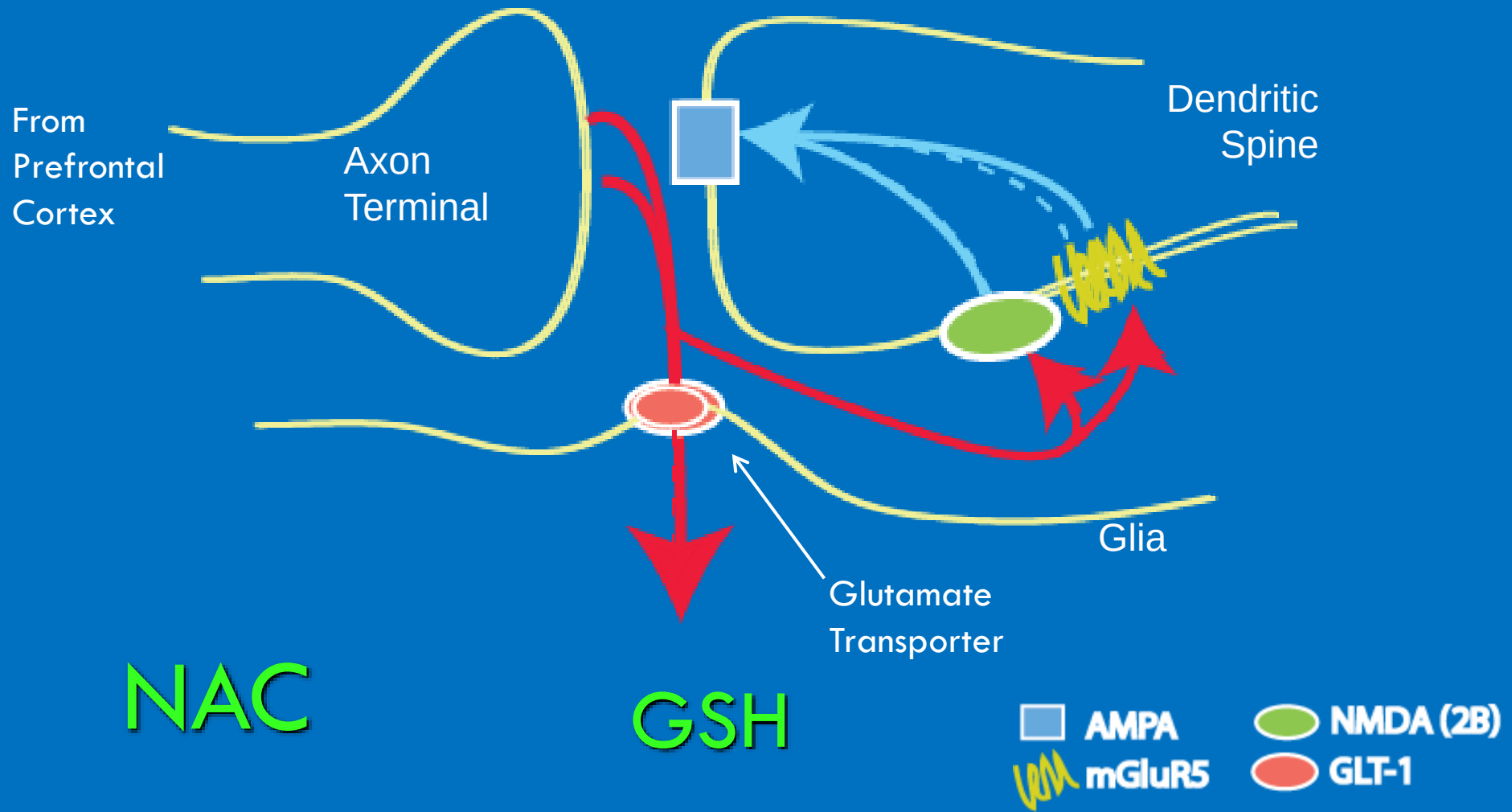
- Glutamate plays an important role in addictive processes across multiple substances, including cannabis (Gass & Olive, 2008)
- Glutamate dysregulation in the nucleus accumbens underlies drug seeking (LaLumiere & Kalivas, 2008; McFarland et al., 2003, 2004)
- NAC administration activates the cystine/glutamate exchanger and upregulates the GLT-1 receptor, leading to reduction in reinstatement of drug seeking in animal models (Baker et al., 2003; Madayag et al., 2007; Moran et al., 2005; Reissner et al., 2015)
- NAC administration directly normalizes a drug-induced pathology (Kalivas et al., 2008)

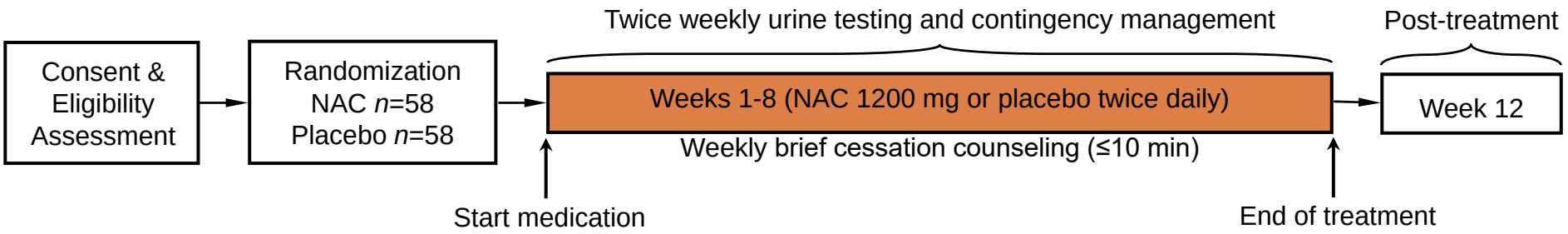
The Tripartite Glutamate Synapse And Addictive Drugs – Target of NAC



Background on NAC

- Unlike many other potential candidate medications for cannabis use disorder 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 cannabis users supported feasibility and tolerability for further study (Gray et al., 2010)

Adolescent NAC trial



- Cannabis-dependent adolescents (*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)

Sample characteristics

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

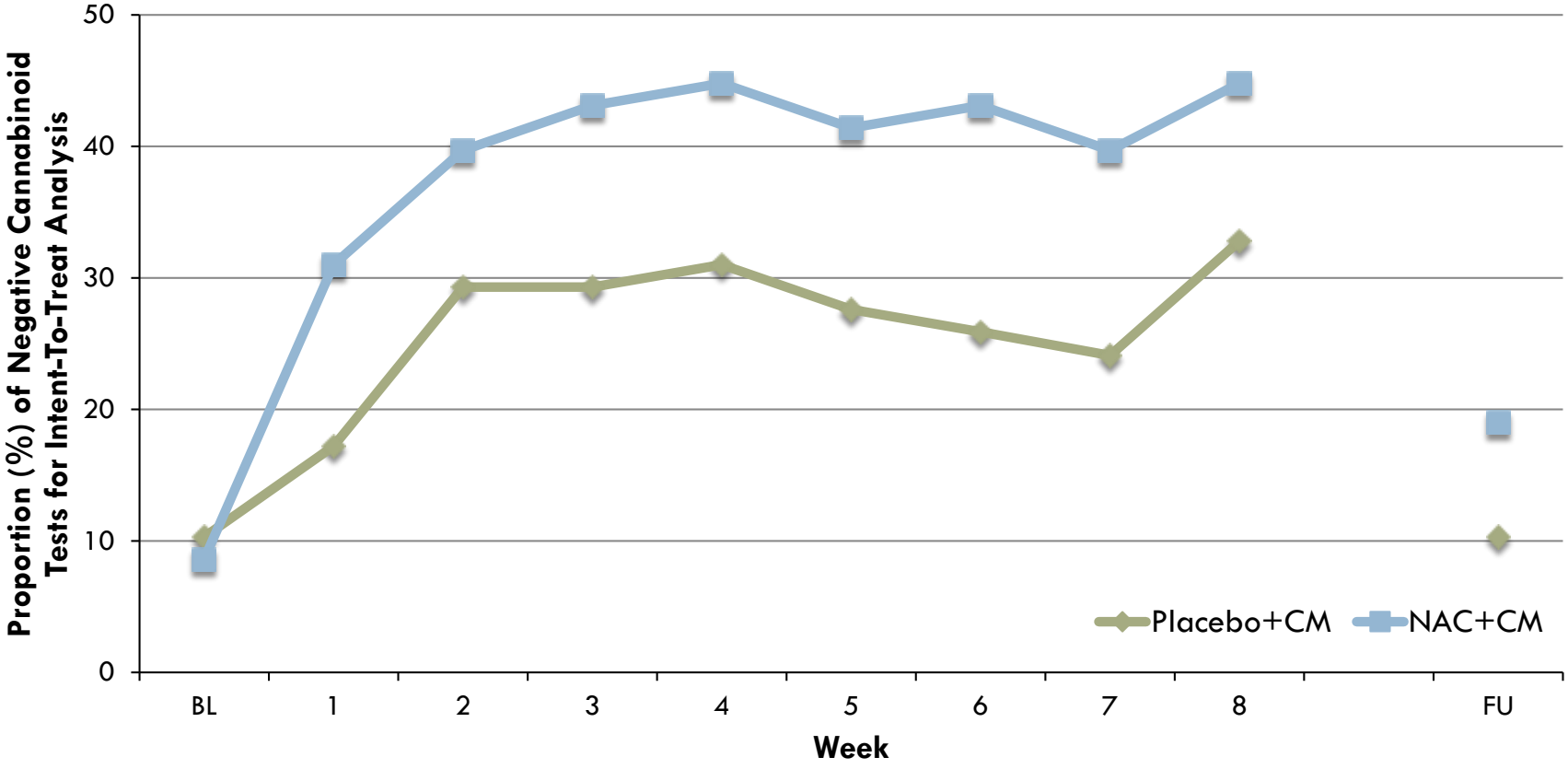
	Overall	NAC	Placebo
Age (range 15-21)	18.9 ± 1.5	18.9 ± 1.5	18.8 ± 1.5
Gender (% male)	73.0%	68.4%	77.6%
Race (% white)	83.5%	79.0%	87.9%
Enrolled in school (%)	73.9%	75.4%	72.4%
Smoke cigarettes (%)	57.0%	58.9%	55.2%
Baseline days using (out of 30)	23.2 ± 6.7	23.3 ± 7.2	23.1 ± 6.1
Years of use	4.2 ± 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)

Treatment response

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



Main outcome analysis

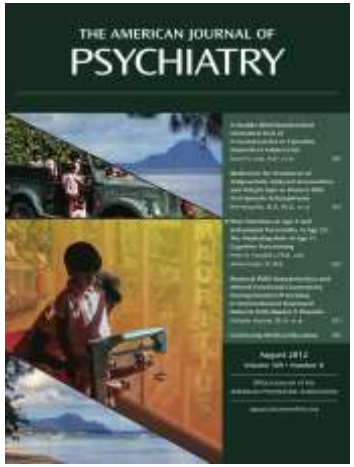
- Repeated measures intent-to-treat (ITT) analysis of weekly urine cannabinoid testing (Generalized Estimating Equations), by treatment group (NAC+CM versus placebo+CM)
  - Odds ratio = 2.4 (i.e., NAC participants had more than twice the odds of submitting a clean urine specimen during treatment, compared 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)

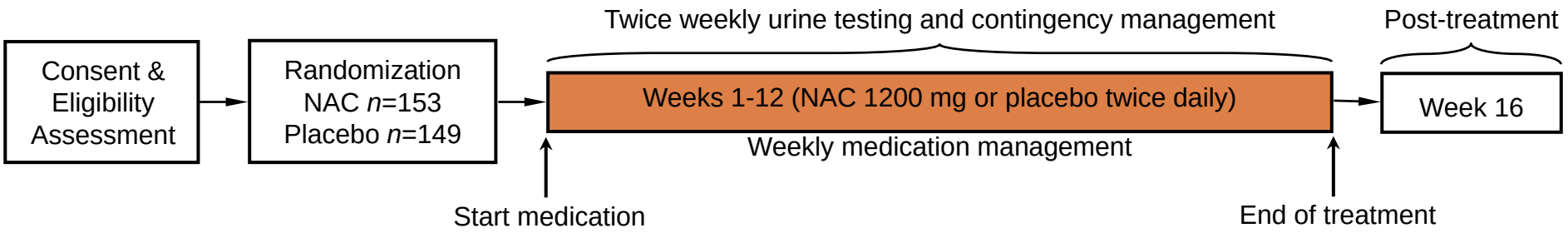
Study conclusions

- 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

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)
- Cannabis-dependent adults (*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

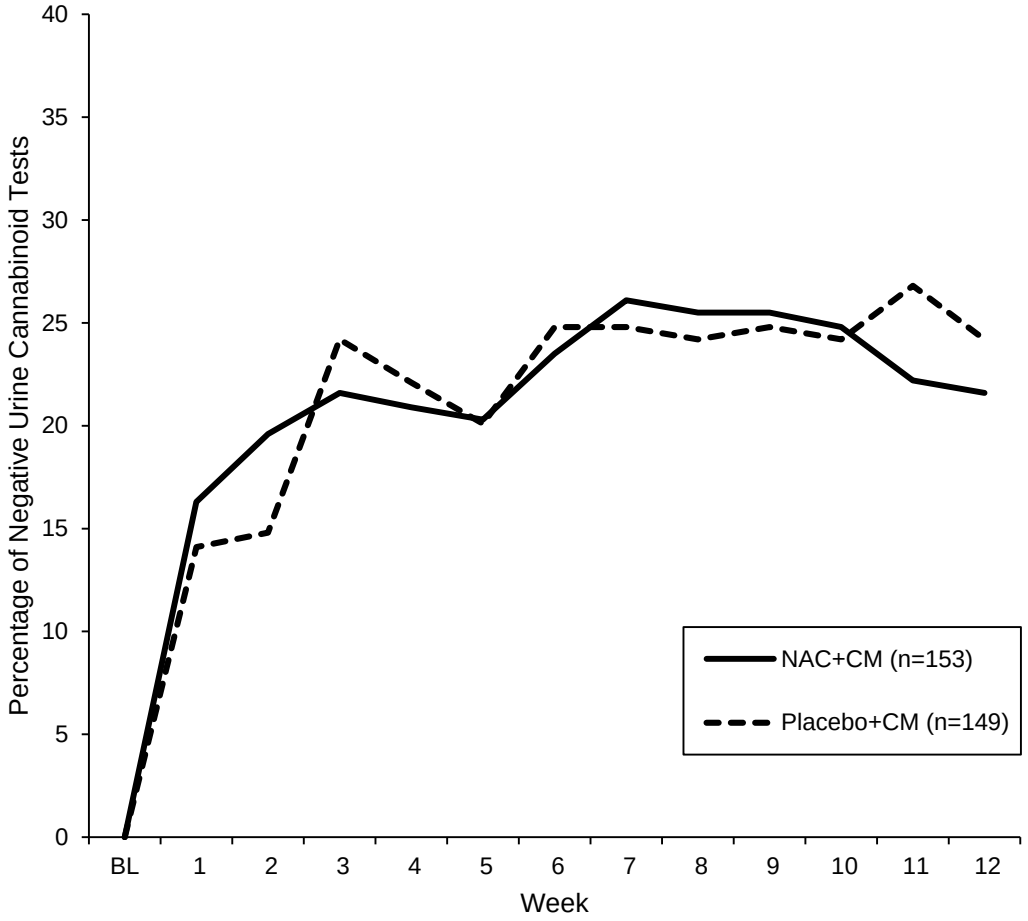
Retention and adherence

- 71.9% of NAC and 68.5% of placebo participants were retained through the end of active treatment
- Only 31 NAC and 26 placebo participants met strict criteria for medication adherence
  - Taking ≥80% of dispensed study medication per study week, confirmed by urine riboflavin level >1500 ng/mL, after subtracting pre-treatment riboflavin level
    - Reflective of poor adherence, overly strict criteria, and/or limitations of riboflavin as an adherence biomarker?
- 73% of dispensed NAC doses and 72% of dispensed placebo doses were taken, compared to 95% and 93% in the prior adolescent trial

Adult Trial

Primary Outcome

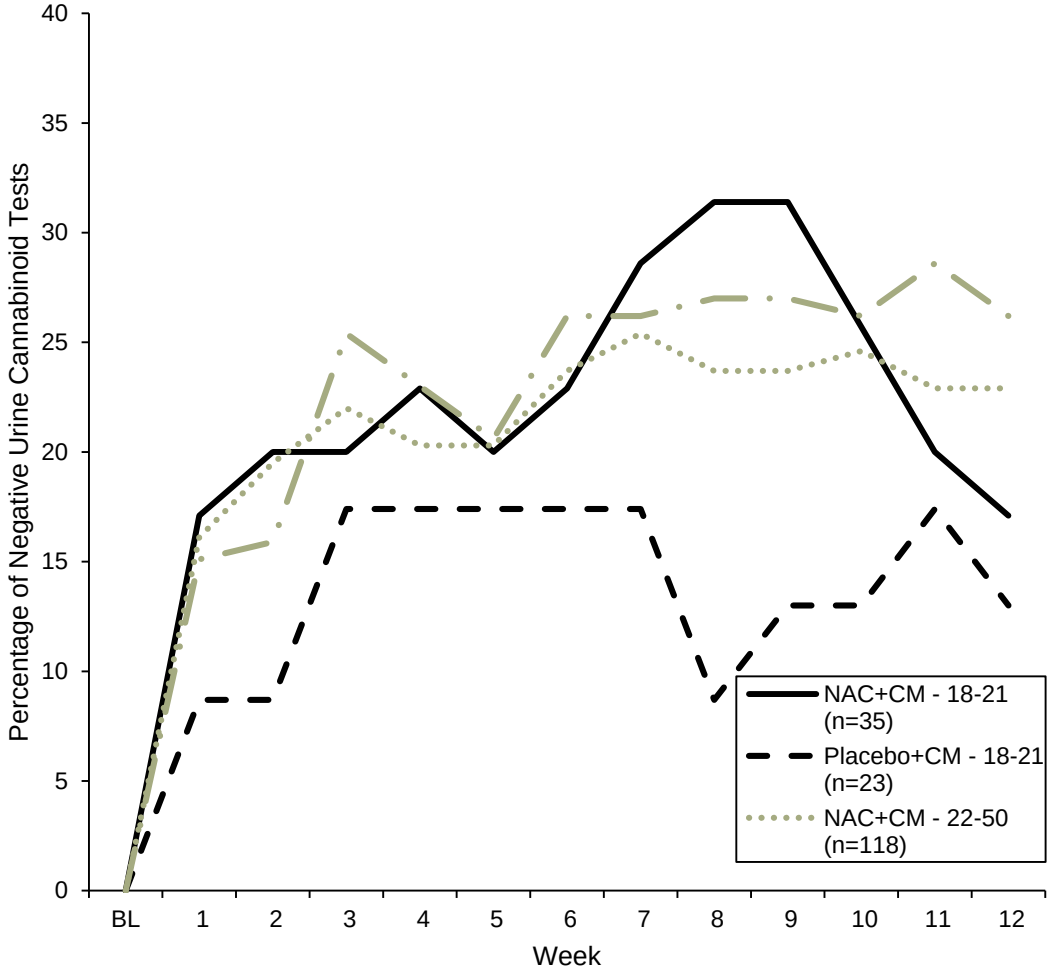
- While there was a significant effect of time on abstinence (p=0.001), there was no difference between the NAC and placebo arms with respect to cannabis abstinence over time (OR=1.00, 95% CI: 0.63-1.59, p=0.985)
  - End-of-treatment and post-treatment analyses similarly yielded no NAC versus placebo effects on abstinence
- Sensitivity analyses revealed that, regardless of the statistical model used, or the method of imputation, there was no statistically significant evidence of a treatment effect for NAC



Adult Trial

Ages 18-21 versus 22-50

- The study's primary outcome measure was examined within participants ages 18-21 (n=58). The small sample size notably limited statistical power, but NAC participants had numerically (but not statistically significantly) superior odds of abstinence than the placebo participants (OR=2.03, 95% CI: 0.70-5.86, *p*=0.187), a magnitude of difference consistent with that observed in the prior adolescent trial.



Adult vs Adolescent Trial

Age and urine cannabinoid levels

- Baseline urine cannabinoid level
  - Adolescent study mean 417.0 ng/mL
  - Adult study mean 1078.0 ng/mL
    - $p<0.0001$
  - Both study ages 18-21 570.7 ng/mL
  - Adult study ages >21 mean 1140.6 ng/mL
    - $p<0.0001$
- Younger (≤21) participants presenting with lower levels of cannabis use (though across studies baseline frequency in days of use is similar – 23/30 versus 26/30)

Adult vs Adolescent Trial

Interpreting discrepant findings

- Adult trial main findings paper currently in press with *Drug and Alcohol Dependence* (Gray et al., 2017)
- Main findings differ between the adolescent and adult NAC trials for CUD
  - Response to NAC for CUD may be age-dependent, with adolescents up to age 21 benefiting, and adults above age 21 not yielding benefit at the 1200 mg twice daily dose.
  - Whether this may be due to developmental differences in the course and phenomenology of CUD, differential effects of NAC based on stage of brain development, potential need for dose adjustment based on age, differences in medication adherence, and/or other factors remains unclear, and is deserving of further examination.

Role of CM

- These studies included contingency management (CM), a potentially powerful behavioral treatment platform.
  - This may have obscured potential medication versus placebo effects
  - However, our prior work has shown synergy between medication and CM in adolescents (bupropion SR + CM for youth tobacco use disorder) (Gray et al., 2011)

So what do we know?

- One trial of NAC, added to CM, supported efficacy in adolescents with CUD
- A similarly designed adult trial indicated that adolescent findings do not translate to adults
- NAC remains the only pharmacotherapy with positive published intent-to-treat clinical trial abstinence findings for CUD in adolescents
- Positive adolescent findings must be replicated, but the necessary behavioral treatment platform must be clarified to translate successfully to real-world practice
  - *R01 DA042114 (N-Acetylcysteine for Youth Cannabis Use Disorder)*

Questions?

- This work is a team effort, and is supported by the National Institute on Drug Abuse (DA026777, DA031779, DA013727, DA042114)