ADVENTURES IN PHARMACOTHERAPY DEVELOPMENT FOR CANNABIS USE DISORDER
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
- Cannabinoids and the endocannabinoid system
- Federal and state policies
- Should we worry about cannabis use?
- Psychosocial treatments
- Pharmacotherapy trials
  - Identifying candidate medications
  - Trial design considerations
  - Recent trials of N-acetylcysteine
Polarization, False Equivalency, and 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
Polarization, False Equivalency, and Duality

- Cannabis can
  - Be potentially safe and benign
  - Contain potentially medicinal components
  - Be potentially risky and harmful
- These can all be simultaneously true
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 smoked cannabis, 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 contains more than 500 active chemicals and more than 80 unique cannabinoids
  - Many cannabinoids have dose-dependent effects
  - Cannabis is not consistently standardized in dose, potency, or chemical constituency
  - Recent study of cannabis edibles revealed poor labeled dose accuracy (Vandrey et al., 2015)
Cannabis and cannabinoids

- Some cannabinoids have been isolated and studied as oral compounds for potential medical applications
  - Dronabinol (Marinol) – Oral delta-9-tetrahydrocannabinol (THC)
  - Nabilone (Cesamet) – Oral synthetic cannabinoid (similar to THC)
  - Cannabidiol (CBD) – Non-“high”-inducing cannabinoid with possible anticonvulsant, anxiolytic, and antipsychotic properties
  - Nabiximols (Sativex) – 1:1 THC:CBD standard-dose oral spray derived from cannabis plant
Cannabinoid concentrations

- Average concentration of delta-9-tetrahydrocannabinol (THC) in seized cannabis increased from 4% in 1995 to 12% in 2014 (ElSohly et al., 2016)
- Over the same time, average cannabidiol (CBD) concentration decreased from 0.28% to 0.15%
- The ratio of THC to CBD concentration increased from about 14 to about 80
- The increase in THC concentration coincided with an increase in treatment admissions for cannabis use disorder
Cannabis formulations
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

- 29 states and the District of Columbia have legalized “medical marijuana”
- 8 states have legalized recreational cannabis use
Should we be worried? Is cannabis addictive?

- While most users have occasional and relatively benign experiences with cannabis, some develop a maladaptive pattern of use.
- The term addiction is not used in DSM nomenclature.
  - DSM-IV included Cannabis Abuse and Cannabis Dependence as separate diagnoses.
  - DSM-5 collapsed these into Cannabis Use Disorder (CUD) — combining criteria and adding a craving criterion.
DSM-5 CUD Criteria

- Using in larger amounts or for longer than intended
- Wanting to cut down or quit but not being able to
- Spending lots of time obtaining cannabis
- Craving or strong desire to use cannabis
- Interference with work, school, or home obligations
- Continued use despite resultant social or interpersonal problems
- Stopping or reducing important social, occupational, or recreational activities due to use
- Recurrent use in physically hazardous situations
- Consistent use despite associated physical or psychological problems
- Tolerance
- Withdrawal
DSM-5 CUD

- DSM-5 CUD has three levels
  - Mild (meets 2-3 of 11 criteria)
  - Moderate (meets 4-5 of 11 criteria)
  - Severe (meets ≥6 of 11 criteria)

- Earlier age of onset predicts higher likelihood of developing CUD

- Per DSM-IV criteria
  - 1/11 adults who try cannabis become dependent
  - 1/6 adolescents who try cannabis become dependent (Hall, 2009)
Any other reasons to be worried?

- In a dose-dependent manner, 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), 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 (Hayatbakhsh et al., 2007; Moore et al., 2007; Gage et al., 2016).

- Serious cannabis-associated risks are well recognized, and are particularly striking in adolescents (Volkow et al., 2014).
Evidence-based treatments

- Psychosocial approaches supported by evidence in youth (largely paralleling the evidence in adults)
  - Motivational Enhancement Therapy (Walker et al., 2011)
  - Cognitive Behavioral Therapy (Hendriks et al., 2011)
  - Family Therapy (a variety of modalities) (Rigter et al., 2012)

- While these treatments are effective for cannabis reduction, long-term abstinence outcomes are generally poor (Compton & Pringle, 2004; Dennis et al., 2004; Waldron & Turner, 2008; Hogue et al., 2014)

- Contingency Management can be used to reinforce abstinence and improve outcomes (Stanger et al., 2009; Stanger et al., 2015)
Research pathways to improve treatment outcomes

- Testing new treatment modalities
- Testing modifications to existing treatment modalities
- Testing combinations of existing treatment modalities
- Might there be a role for medication to augment psychosocial treatment?
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)

If we had a good candidate medication, how would we go about designing and executing a trial for CUD?
Conceptualization/Design

- Target CUD or other cannabis use-related condition
- Choice of pharmacotherapy (& dose, frequency, etc.)
- Embedded psychosocial treatment, if any
- Efficacy and safety outcomes
- Participant age range
- Frequency of visits/assessments/interventions
- Length of treatment
- Length of post-treatment follow-up
- Participant compensation/incentives
Conceptualization/Design

- **Target CUD or other cannabis use-related condition**
  - DSM-IV abuse and/or dependence
  - DSM-5 mild, moderate, and/or severe use disorder
  - Hazardous use or other non-diagnostic level of use
  - Require recent minimum frequency/amount of use, in addition to diagnostic requirements?
  - Require positive urine drug test at screening?
  - Allow other substance use disorder comorbidity?
  - Allow psychiatric comorbidity?
  - Require “treatment-seeking” status?
  - Allow legally-involved/treatment-mandated participants?
Conceptualization/Design

- **Choice of pharmacotherapy (& dose, frequency, etc.)**
  - Translation from animal models
  - Progression from human laboratory work
  - Evaluation of medications already deemed efficacious in another age group
  - Balancing potential efficacy, tolerability, and adherence in devising dose schedule
- **Embedded psychosocial treatment, if any**
  - May get maximum drug versus placebo difference with none (avoiding a potential “ceiling effect” of psychosocial treatment)
  - Ethical obligation to provide some established form of care to treatment-seeking participants who may receive placebo
  - May potentially choose a low-intensity but ethically acceptable psychosocial intervention
  - Individual versus group interventions
  - Consider that there may be synergy between particular pharmacotherapies and psychosocial treatments (need for 2×2 designs?)
Efficacy and safety outcomes

- Biological outcome (e.g., urine drug testing) versus self-report outcome (Timeline Follow-Back) versus a combination of the two
- Seek out standards (if they exist) from trials literature, and consider necessary adaptations for developmental stage
- End-of-treatment abstinence (how long?), versus cumulative findings over the course of treatment (e.g., “days abstinent” or “proportion of negative urine drug tests”)
- Full abstinence outcome or reduction in use outcome?
- Functional outcomes beyond abstinence/reduction?
- Passive versus active/focused/specific Adverse Events evaluations (Frequency? Power on safety outcomes?)
Conceptualization/Design

- **Participant age range**
  - *Cannabis use onset* peaks in adolescence but *CUD* peaks in young adulthood and is present in later adulthood.
  - Varying definitions of adolescence (e.g., <18, <21, ≤25, etc.)
  - Young adults are often underrepresented in adult studies.
  - Must consider age range that might benefit most from evidence yielded from the trial, and must consider issues of safety, etc.
  - Might also consider practical issues, such as informed consent, which is different between ≥18 and <18.
Conceptualization/Design

- **Frequency of visits/assessments/interventions**
  - Often VERY difficult to get participants/families to comply with frequent office visits
  - However, frequent visits may be crucial for a number of reasons (e.g., short window of urine drug test accuracy, need for frequency of embedded psychosocial treatment)
  - Must balance participant burden with desired intensity of intervention and adequacy of measures to evaluate outcomes
  - Potential role for data collection via mobile technology?
Conceptualization/Design

- **Length of treatment**
  - How long might it take for the pharmacotherapy to work?
  - How long is it feasible to retain participants in a trial?
  - If using embedded manualized psychosocial treatment, how long is that course of treatment?
  - How long a course of treatment can you fit into the budget (pharmacy costs, participant compensation for visits, etc.)?
  - Do standards exist (e.g., 12 weeks for smoking cessation pharmacotherapies)?
Length of post-treatment follow-up

- Need to evaluate post-treatment efficacy
- Need to evaluate safety with discontinuation of pharmacotherapy
- One month? Six months? One year?
- Difficult to power on post-treatment outcomes, though these are of significant clinical interest
Conceptualization/Design

- **Participant compensation/incentives**
  - Cash versus gift cards/vouchers? Directly compensate participants or parents/guardians or both?
  - Visit-by-visit or lump sum later in study?
  - Maximize to improve attendance/retention?
  - Minimize to reduce concerns about coercion (or about translating to real-world practice)?
  - Consider escalating schedule of reinforcement to encourage steady attendance over time?
Management/Execution

- clinicaltrials.gov registration
- Institutional Review Board
- Data and Safety Monitoring Plan
- FDA Investigational New Drug (IND) application
- Medication blinding and dispensing

RECRUITMENT & RETENTION

- Assessing substance use, safety, and other outcomes
- Assessing and optimizing medication adherence
- Ensuring fidelity of embedded psychosocial treatment
- Addressing unanticipated developments
Management/Execution

- **clinicaltrials.gov registration**
  - Requirement for all clinical trials – must register before beginning enrollment
  - Must provide details of interventions, aims, and outcome measures
  - Must provide periodic updates on status of the trial (i.e., pre-enrollment, actively enrolling, concluded enrollment)
  - Must provide main findings upon conclusion of the trial
Management/Execution

- Institutional Review Board
  - Many IRBs may be anxious about substance use focused pharmacotherapy trials, especially with adolescents
  - Concerns about confidentiality
  - Concerns about medication safety
  - Concerns about adverse event risks with active substance using minors
  - Possible unfamiliarity with limited current evidence base for SUD treatment, and need for investigation of pharmacotherapy
Data and Safety Monitoring Plan

- Data and Safety Monitoring Board (DSMB) needed
- Composition of DSMB, frequency of meetings, etc.
- Plans for documentation of enrollment/retention and adverse events/safety for presentation at DSMB meetings
Management/Execution

- FDA Investigational New Drug (IND) application
  - Even with a medication already FDA-approved in adults for the same SUD, an IND is likely needed for a trial in youth <18
  - Even with a medication already FDA-approved for treatment of another condition, an IND is likely needed for investigation of a new/different indication
Management/Execution

- **Medication blinding and dispensing**
  - Randomized, controlled trials are the gold standard
  - Selection of medication and matching placebo is key
  - Direct supply of medication and placebo from manufacturer?
  - “Over-encapsulation” of active medication and placebo, with filler?
  - Establishment and execution of randomization scheme
  - Methods to ensure ongoing investigator/team blinding
  - “Penetration of the blind” assessments to evaluate whether the blind is effective in the trial
RECRUITMENT & RETENTION

Most studies sink or swim on these critical issues

Must recruit and retain enough participants to collect primary outcome measures for a sufficiently powered analysis

There are countless potential barriers, particularly in adolescent trials

- Adolescents not recognizing a substance-related problem
- Parent/guardian not aware of the problem
- Preference for standard care over research protocol
- Concern about potential adverse events with medication
- Transportation difficulties
- Ambivalence about need to address substance-related problem, even over the course of trial participation
Assessing substance use, safety, and other outcomes

- Method and frequency of biospecimen assessment (e.g., urine or saliva drug testing, carbon monoxide or alcohol breathalyzer)
- Method of self-report assessment (most commonly Timeline Follow-Back)
- Level of detail in self-report (e.g., use versus non-use days, quantity of use within a day, frequency of use within a day)
- Passive versus active/focused adverse event assessment
- Suicidality assessment is generally required (most established measure is the Columbia-Suicide Severity Rating Scale [CSSRS])
Assessing and optimizing medication adherence

- Non-adherence to medication may very likely compromise your ability to detect a between-group effect
- Blister packs, reminders, in-office dosing, pill counts, MEMS caps
- Biomarkers (e.g., riboflavin)
- Video capture of medication-taking (Tomko et al., in press)
- Medication management with motivational approach
- Encouraging honesty about adherence, while praising success and being constructive about addressing non-adherence
Ensuring fidelity of embedded psychosocial treatment

- Varies across psychosocial approaches and designs
- Typically involves consistent training across providers, shared supervision, review of session recordings for fidelity (with feedback)
- Formalized methods of fidelity measurement are available for some manualized interventions
Management/Execution

- **Addressing unanticipated developments**
  - Serious adverse events
  - Unexpected medical events (e.g., pregnancy)
    - Potential importance of conducting urine pregnancy testing BEFORE urine drug testing
  - New FDA “black box warning” or other caution regarding medication safety
  - Approaches to participant drop-out or lost-to-follow up – what to do for intent-to-treat analysis?
So what has been done so far with CUD pharmacotherapy trials?

- Human Laboratory
- Pilot Clinical Trial
- Fully-Powered Clinical Trial
## Published placebo-controlled pharmacotherapy trials for CUD

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<th>Human Laboratory</th>
<th>Pilot Controlled Trials</th>
<th>Fully Powered Controlled Trials</th>
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<td>Discouraging</td>
<td>Encouraging</td>
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<tr>
<td>Bupropion SR</td>
<td>Rimonabant (Haney et al., 2001)</td>
<td>Divalproex (Levin et al., 2004)</td>
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<td>Nefazodone</td>
<td>Oral THC (Haney et al., 2003)</td>
<td>Divalproex (Lofexidine + Oral THC (Haney et al., 2008))</td>
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<tr>
<td>Divalproex</td>
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<td>Bupropion SR (N=156) (McRae-Clark et al., 2009)</td>
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<td>Lithium</td>
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<td>Mirtazapine</td>
<td>Naltrexone (Haney et al., 2015)</td>
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<td>Naltrexone</td>
<td>Nabiximols (1:1 THC/cannabidiol) (Wachtel &amp; de Wit, 2000; Haney et al., 2003; Cooper &amp; Haney, 2010)</td>
<td>Topiramate (N=66 adolescents) (Miranda et al., 2016)</td>
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<tr>
<td>Quetiapine</td>
<td>Zolpidem + Nabilone</td>
<td>Nabiximols (N=51) (Allsop et al., 2014)</td>
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<tr>
<td>Cannabidiol</td>
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<td>Nabilone (McRae-Clark et al., 2016)</td>
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Encouraging

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<tr>
<th>Negative/Null</th>
<th>Positive</th>
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<tr>
<td>Oral THC (N=156) (Levin et al., 2011)</td>
<td>N-acetylcysteine (N=116 adolescents) (Gray et al., 2012)</td>
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<tr>
<td>Venlafaxine XR (N=103) (Levin et al., 2013)</td>
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<tr>
<td>Buspirone (N=175) (McRae-Clark et al., 2016)</td>
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<tr>
<td>Lofexidine + Oral THC (N=156) (Levin et al., 2016)</td>
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<tr>
<td>N-acetylcysteine (N=302 adults) (Gray et al., 2017)</td>
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Background on *N*-Acetylcysteine (NAC)

- 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

- Axon Terminal
- Dendritic Spine
- Glia
- Glutamate Transporter
- From Prefrontal Cortex
- NAC
- GSH
- AMPA
- NMDA (2B)
- mGluR5
- GLT-1
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 (Gray et al., 2012)

- DSM-IV 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)
Adolescent NAC trial

Primary outcome

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

Odds ratio = 2.4, $p = 0.029$
Adolescent NAC trial
Secondary outcomes

- Cognitive task performance improved with cannabis abstinence (Roten et al., 2015)
- Low impulsivity and high medication adherence predicted abstinence; adherence optimization is particularly critical in high-impulsivity individuals (Bentzley et al., 2016)
- NAC was more effective in adolescents with elevated depressive symptoms (Tomko et al., under review)
- Tobacco use and alcohol use did not increase with cannabis use reduction (McClure et al., 2014; Squeglia et al., 2016)
- In the NAC group, but not the placebo group, reductions in cannabis use were associated with reductions in alcohol use (Squeglia et al., 2016)
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)
- DSM-IV 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**

**Primary Outcome**

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

![Graph showing percentage of negative urine cannabinoid tests over weeks. The graph compares NAC+CM (n=153) and Placebo+CM (n=149). The odds ratio is 1.00, p = 0.985.](image-url)
Intent-to-treat (all randomized participants) with participants assumed to be non-abstinent at any missed visit
Adult Trial
Secondary Outcomes

- There was a trend-level ($p=0.083$) race-by-treatment interaction: while racial minority participants had overall lower abstinence rates, they differentially responded more favorably to NAC than placebo (Gray et al., 2017)

- Reductions in cannabis use were associated with improvements in anxiety, depression, and sleep quality (Hser et al., 2017)

- NAC participants, compared to placebo participants, had reductions in alcohol use and had higher rates of alcohol abstinence (Squeglia et al., 2018)
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.
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)
Where are we with NAC?

- NAC remains the only pharmacotherapy with positive published intent-to-treat clinical trial abstinence findings for CUD in adolescents; efficacy may not extend to adults.
- 1200 mg BID (without need for initial titration) is the dose studied to date, and tolerability was good in both trials.
  - NAC is typically available in 600 mg capsules, and titration may be used if there are issues with tolerability (e.g., gastrointestinal upset).
Where are we with NAC?

- **NAC appears to target compulsive drug-seeking**
  - Best used as an adjunct to psychosocial treatments that target other core features of CUD, particularly when compulsive seeking/using continues even with significant motivation to reduce/quit
  - Pharmacological effect tends to be subtle and gradual
    - No “eureka moment,” but rather a reduced compulsion to seek out and use cannabis, often only realized in retrospect
    - Patients may continue using amid easy access/availability or in social situations, but reduce or cease significant efforts to obtain cannabis for use
    - Duration of treatment may vary, but generally ≥2 months is recommended

- **Positive adolescent findings must be replicated, but the necessary behavioral treatment platform must be clarified**
  - R01 DA042114 (N-Acetylcysteine for Youth Cannabis Use Disorder)
Where are we with other candidate pharmacotherapies?

- As we are learning more about the neuropathology and phenomenology of CUD, we are able to identify more candidate pharmacotherapies.
- We are still honing methods to optimally test candidate pharmacotherapies for CUD:
  - Need to have consistency across trials in terms of methods and overall primary outcomes.
  - Need to additionally consider outcomes that may be relevant to specifically-targeted pharmacotherapies.
- Lots of exciting work is ahead!
Questions?

- This work is a team effort, and is supported by the National Institute on Drug Abuse (DA013727, DA026777, DA031779, DA041093, DA042114)