WEB SEMINAR SERIES 2016

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PHARMACOTHERAPY TRIALS
FROM CONCEPT TO EXECUTION

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## Disclosures

<table>
<thead>
<tr>
<th>Source</th>
<th>Research Funding</th>
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<td>National Institutes of Health</td>
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Learning Objectives

At the conclusion of this continuing education activity, the participant will be able to:

- Identify key issues in the conceptualization/design of pharmacotherapy trials for adolescent Substance Use Disorders (SUD).
- Identify methods to optimize the management/execution of pharmacotherapy trials for adolescent SUD.
- Consider strategies to standardize design methods across adolescent SUD pharmacotherapy trials.
Overview

- Conceptualization/Design
  - Choices, choices

- Management/Execution
  - Challenges, challenges

- Toward standardization?
  - Heterogeneity, heterogeneity
Overview

- Slides will focus on common design and execution challenges and variables
- The list is extensive but not exhaustive, and is intended to generate discussion
- I will verbally share challenges encountered and decisions made in three adolescent SUD pharmacotherapy trials
  - Combined Pharmaco-Behavioral Therapy in Adolescent Smokers (R01DA17460)
    - Will refer to it as “Bupropion/Contingency Management (CM) Tobacco Trial”
  - A Controlled Trial of N-Acetylcysteine (NAC) in Cannabis-Dependent Adolescents (R01DA026777)
    - Will refer to it as “NAC Marijuana Trial”
  - A Randomized Controlled Trial of Varenicline for Adolescent Smoking Cessation (U01DA031779)
    - Will refer to it as “Varenicline Tobacco Trial”
Conceptualization/Design

- Target SUD or other substance-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 SUD or other substance-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?
  - Specific substance versus polysubstance
  - Common substance versus rarer but highly impairing substance
  - 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 adults
  - Balancing potential efficacy, tolerability, and adherence in devising dose schedule
Conceptualization/Design

- **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 2x2 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 the adult trials literature, and consider any 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?
- Passive versus active/focused/specific Adverse Events evaluations (Frequency? Power on safety outcomes?)
Conceptualization/Design

- **Participant age range**
  - *Substance use onset* peaks in adolescence but *Substance Use Disorder* peaks in young adulthood
  - Varying definitions of adolescence (e.g., <18, <21, ≤25, etc.) [NIH definition of children is <21]
  - Young adults are generally 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
Conceptualization/Design

- **Length of treatment**
  - How long might it take for the pharmacotherapy to work?
  - How long is it feasible to retain adolescents 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
Management/Execution

- Institutional Review Board (IRB)
- 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

- Institutional Review Board (IRB)
  - Many IRBs may be anxious about adolescent substance use focused pharmacotherapy trials
  - Concerns about confidentiality
  - Concerns about medication safety in minors
  - Concerns about adverse event risks with active substance using minors
  - Possible unfamiliarity with limited current evidence base for adolescent 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
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 in youth, 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

- 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
- Adolescent ambivalence about need to address substance-related problem, even over the course of trial participation
Management/Execution

- 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
- Biomarkers (e.g., riboflavin)
- 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?
Standardization
Standardization

- Is this a reasonable goal?

- Need sufficiently consistent methods across studies to compare efficacy

- Need to balance feasibility and practical issues/challenges with the goal of optimizing contributions to the evidence base and real-world practice
The design and implementation of pharmacotherapy trials targeting adolescent SUD involves several challenges.

With careful planning and consideration, these challenges can be addressed.

Standardization of methods may help streamline these processes and allow for improved contributions to the evidence base and real-world practice.
Discussion/Questions

Contact: graykm@musc.edu
A recording of this presentation will be available electronically.
THANK YOU FOR YOUR PARTICIPATION