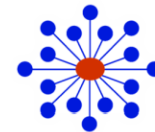




WELCOME TO THE CTN WEB SEMINAR SERIES

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CTN WEB SEMINAR SERIES:
A FORUM TO EXCHANGE RESEARCH KNOWLEDGE

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PHARMACOTHERAPY TRIALS

FROM CONCEPT TO EXECUTION

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Disclosures



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Source	Research Funding
National Institutes of Health	X

Learning Objectives



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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



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- Conceptualization/Design
 - ▣ Choices, choices
- Management/Execution
 - ▣ Challenges, challenges
- Toward standardization?
 - ▣ Heterogeneity, heterogeneity

Overview



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- 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



Conceptualization/Design



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- ❑ 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



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- **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



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- **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



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- **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?)

Conceptualization/Design



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□ 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



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□ 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



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- **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



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□ 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)?

Conceptualization/Design



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- **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



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- **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



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- 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



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□ 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

Management/Execution



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□ **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



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- **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



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- **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

Management/Execution



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□ 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



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- **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])

Management/Execution



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- **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

Management/Execution



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- **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



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- **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



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- 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

Summary



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- 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



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
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