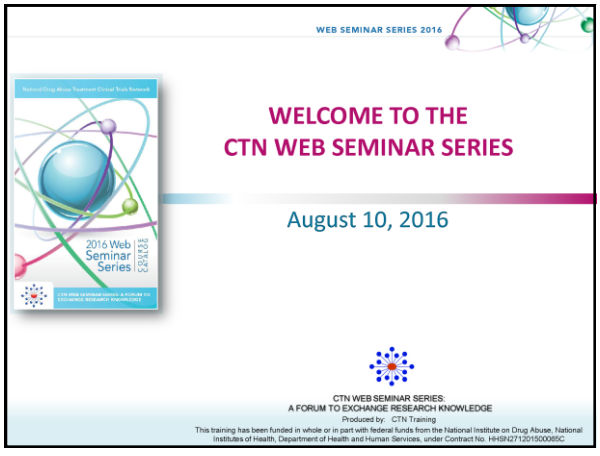
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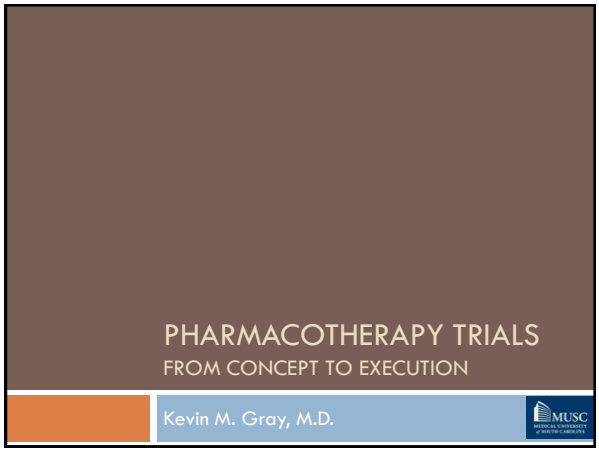
PHARMACOTHERAPY TRIALS
FROM CONCEPT TO EXECUTION
Kevin M. Gray, M.D.
MUSC


Disclosures
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Source
Research Funding
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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

6

- 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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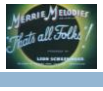
- Is this a reasonable goal?
- Need sufficiently consistent methods across studies to compare efficacy
- Need to balance feasibility and practical issues/challenges with the goal of optimizing contributions to the evidence base and real-world practice

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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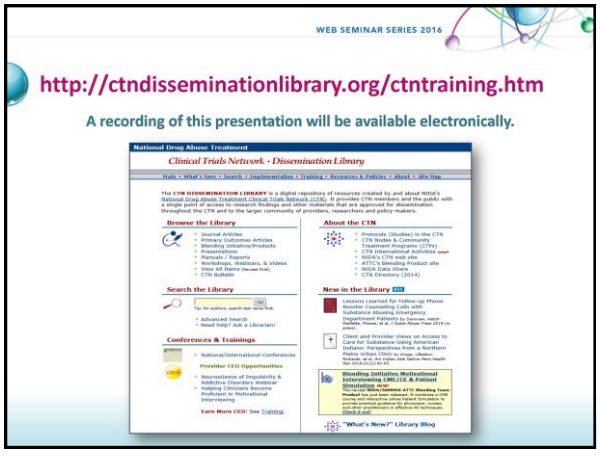

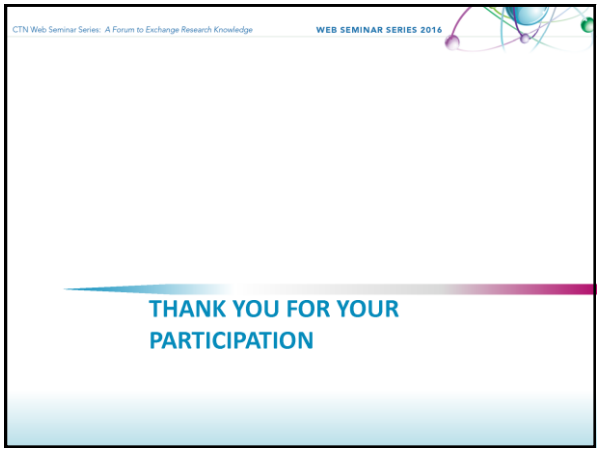
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