Title: Intervention for Teen with ADHD and Substance Use
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FLORIDA INTERNATIONAL UNIVERSITY

RESEARCH SUBJECT INFORMATION AND CONSENT FORM
(Parent Consent for Minor Child)

TITLE: Intervention for Teens with ADHD and Substance Use

PROTOCOL NO.: DA034731
WIRB® Protocol #20141988

SPONSOR: National Institute on Drug Abuse

INVESTIGATOR: William E. Pelham Jr., PhD
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Miami, FL 33199
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STUDY-RELATED PHONE NUMBER(S): William E. Pelham Jr., PhD
305-348-0477

Janellie Azaret, MD
305-348-0477
786-361-7151 (24 hours)

SUMMARY

You are being asked to allow your teen to be in a research study. The purpose of this consent form is to help you decide if you want your teen to be in the research study. This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

You should not join this research study until all of your questions are answered.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help teens with ADHD in the future.

- The decision to join or not join the research study will not cause you or your teen to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat your teen.
- Parts of this study may involve standard medical care. Standard care is the treatment normally given for a certain condition or illness.
- After reading the consent form and having a discussion with the research staff, you should know which parts of the study are experimental and which are standard medical care.

If your teen takes part in this research study, you will be given a copy of this signed and dated consent form.

PURPOSE OF THE STUDY

Adolescents who are diagnosed with Attention Deficit-Hyperactivity Disorder (ADHD) are at higher risk for problems with alcohol and other drugs. Adolescents with ADHD are particularly at risk for problems with substances when they also have begun to experience other risk factors for substance use (e.g., problems with grades, difficulty getting along with parents and other adults, trying alcohol and other drugs). The purpose of this study is to test a brief, early intervention specifically designed for adolescents with ADHD who have also started to face some of these tough situations. The goal is to see whether this program helps prevent problems with alcohol and other drugs by helping adolescents develop skills to make healthy choices when dealing with these situations. Importantly, this intervention will be used with adolescents who have some of these risk factors but do not yet have a problem with using substances.

Depending on progress toward treatment goals, some of the adolescents and their parents may be assigned to receive more intensive treatment to prevent the development of substance use problems. This may include sessions for parents focused on parenting and communicating with teens as well as sessions for teens focused on healthy problem solving and coping skills. Some teens may also receive stimulant medication. The goal is to determine which treatment works best to help adolescents meet treatment goals and avoid problems with drugs and alcohol.

PROCEDURES

Your teen is being asked to participate in this research study because he or she has ADHD and started to experience some of the other difficulties described above. A total of 300 adolescents between the ages of 12 and 16 and their parents will participate in the study. The study will last for 24 - 36 months, depending on the treatment condition your teen receives.

First, you, your teen, and your teen's teachers will be asked to complete some questions about your teen's behavior to make sure he or she will be eligible for the study. We will also monitor your teen's academic progress through the grade portal while you and your teen are participating in the study. Your teen will be asked some questions about his or her use of alcohol and other substances, and he/she will be

asked to give a urine sample for drug testing. You will also answer some questions about yourself (including questions about using alcohol and other drugs) and your relationship with your teen. This assessment will occur during a 3-4 hour visit.

If you and your teen decide to participate, you and your teen will receive the Brief Early Intervention program that has been expanded to specifically address the needs of teens with ADHD and their parents. Your teen will receive 5 counseling sessions conducted at the Center for Children and Families. You will join your teen during portions of some sessions. Your teen will learn about things like setting goals, decision-making skills, reducing risky behavior (e.g., drug use) and addressing barriers to reaching goals. You will discuss things like monitoring, rule setting, and other ways you might support your teen in reaching these goals.

After 6 months, you and your teen will come back to the CCF for your first follow-up visit. You will have additional follow-up visits every three months. During these visits, your teen will answer questions about progress towards treatment goals and questions about substance use. Your teen also will take a urine test. During some visits, you will answer questions about your teen's behavior and your parent/teen relationship. During some visits, we will obtain your teen's GPA from your teen's school. Depending on progress at these follow-up visits, your teen may be randomly assigned (by chance) to one of three conditions, as listed below:

- Continued monitoring and assessment
- Intensive parent counseling and teen counseling sessions
- Intensive parent counseling and teen counseling sessions + stimulant medication

Your child will have an equal chance of being assigned to one of these three groups. Once your teen is assigned to one of the three conditions, you and your teen will participate in the study for an additional 18 months. During this time, teens are asked ***not*** to use any additional medication for ADHD or other mental health problems (like anxiety or depression) besides the treatment they receive as part of this study.

The more intensive cognitive/behavioral treatment focuses on preventing adolescent problems with alcohol and other drug use. It will consist of 12 additional sessions with you and 12 sessions with your teen, including family contracting, parent training in behavior modification, and adolescent training in decision-making skills. Some sessions will include you and your teen together.

The medication condition will include once-a-day stimulant medication (e.g., Concerta), taken 7 days a week. In general, teens will start on the lowest available dose of the medication; however, the study doctor may start teens at a higher dose if they were already taking a higher dose of stimulant medication prior to entering this phase of the study. If teens are already taking other medications for ADHD at the time they enter the medication condition, the study doctor will meet with teens and their parents to evaluate whether the teens can safely continue to take the medications in addition to study medications or whether changes are needed (e.g., safely withdrawing the other

medications, reducing dose, etc.). The doctors will ask you and your teen how well the medication is working after 1 week.
If your teen does not show a favorable response to the dose of medication, then the study doctor can increase the dose, as long as there are no bad side-effects of the medication. Your teen will stay on the medication for 18-months.

You and your teen will return to the CCF for a follow-up interview 6 months after treatment begins and again 12 months after the follow-up.

If, based on progress toward treatment goals, your teen is never randomly assigned to one of the additional conditions, your participation in the study will be complete approximately 24 months after you enroll.

You will **not** have access to information provided by your teen, including the results of your teen's drug tests. Your teen will **not** have access to information provided by you.

RISKS AND DISCOMFORTS

You or your teen may have discomfort from completing some of the research questions including reporting on drug use and other antisocial or illegal behaviors. The investigators have obtained a Certificate of Confidentiality (see below) to protect the privacy of all information collected during the project. You may refuse to answer questions that are uncomfortable.

You or your teen may also experience discomfort during the intervention that focuses on changing your behaviors or attitudes. The study doctors will work with you and your teen to address any concerns you have. Your teen may decide not to participate in sessions that are uncomfortable.

For teens who receive the secondary treatment involving medication, there are risks associated with side effects from stimulant medication. The most common side effects with stimulant medication include feelings of nervousness, loss of appetite, and insomnia (hard time falling asleep).

Other reactions that can occur in varying frequency include nausea, dizziness, stomachaches, headaches, tachycardia (rapid heartbeat), increases in blood pressure, skin rashes, drowsiness, motor movements (particularly of the mouth, jaw and tongue called motor or verbal tics), and social withdrawal.

In children with preexisting motor tics, heart problems (high blood pressure, irregular heart rhythms) or seizures, stimulants may worsen these problems.

There is a potential for mild growth suppression (1/2 inch to an inch in final adult height) with the continued use of daily stimulant medications. Studies have found evidence of growth rebound after stopping medication.

Stimulant medication can also be associated with circulation problems in the fingers and toes (called peripheral vasculopathy or Raynaud's phenomenon).
If your child has any of these issues, please tell the study doctors before starting medication. After starting medication, please tell the study doctors if your child complains of numbness, pain, a change in color or an odd or cold feeling in their finger or toes.

Methylphenidate based medications for ADHD like Concerta® have been associated in rare instances with priapism in males, which is a prolonged and painful erection. If your son is experiencing a sustained, painful erection lasting for more than an hour, you should contact the study nurse and your child's pediatrician immediately.

Teens who have not previously taken the study medication will be started at the lowest available dose of the study medication to minimize the chance of side effects. If your child does not react well to one stimulant study medication, it may be changed for an alternate stimulant study medication. There may be side effects that are not known at this time. Doses will not exceed the U.S. Food and Drug Administration (FDA) maximum recommended doses for their age.

It has not been established that Concerta® and other ADHD medications are safe during pregnancy. Therefore, pregnant females will not be enrolled. If you or your daughter suspects that she has become pregnant while participating in the study, you or she must contact the study doctor immediately. If your teen becomes pregnant during the study, all study medication will be stopped. The teen may continue to receive the behavioral treatments or discontinue from the study.

If your child has significant side effects related to the study medication, you can contact a study doctor, 24 hours a day, 7 days a week. Monday through Friday from 9 am to 5 pm, you can contact our research center at 305-348-0477 to speak to the study nurse or one of the study doctors. If you have a medical emergency relating to the study treatments and need to reach a study doctor outside of these hours or on the weekend, you must call the Center for Children and Families at 786-361-7151 to reach the doctor on call.

Additional risks include the time and effort it takes to complete the rating forms and attend the study visits. Some of the study doctors' visits may be audiotaped while some of the behavior therapy sessions may be audiotaped or videotaped. Before each study visit, you will be informed if any audio or video recording is being done. All collected recordings will be stored in a secured area at our center and reviewed only by people working on this study.

The password provided for the grade portal log-in may also be a personal password that you use for other electronic or computer log-ins. Research staff will see this password. You are free to change the password at any time.

Other Risks

Your teen's condition may not get better or may get worse during this study.

Only your teen should take the study medication. It must be kept out of the reach of children or anyone else who may not be able to read or understand the label.

NEW INFORMATION

You will be told about any new information that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS

Your teen will receive monitoring of ADHD symptoms and other behaviors (e.g., conduct problems and substance use) during the entire study period, and all participants will receive the brief intervention, which has been shown to be effective in scientific studies. The two follow-up treatments have also been shown to be effective treatments for ADHD and other problematic behaviors in scientific studies, and your teen's behavior may improve; however, this cannot be promised. You may learn new ways to communicate with your teen. The results of this study may help people with ADHD in the future.

PAYMENT

Parents and teens will each receive a gift card for $25 at each of the major assessment points (baseline, 6-month, 12-month/post-treatment, 24-month/1-year follow-up), and your teen will receive $25 at each of the shorter screening assessments (9 month, 15 month, and 18 month). If you do not complete the study, you will be paid for the visits you have completed. You will receive the gift cards at the end of the study visits. Your child's teacher will receive a $10 gift card after completing questionnaires.

COSTS

All study interventions, including medication, will be provided to you and your son or daughter at no charge during this study. Tests and procedures that are done only for the study will not be billed to you or your insurance company.

You might have unexpected expenses from being in this study. Ask your study doctor to discuss the costs that will or will not be covered. This discussion should include who will pay the costs of treating possible side effects.

ALTERNATIVE TREATMENT

You may elect not to have your teen participate. Instead of participating in this study, your son or daughter may continue on his or her usual treatments for ADHD with your doctor, seek out new treatment, or receive no treatment. Counseling treatments for

ADHD and teen substance use are available from clinics and practitioners in Miami-Dade County.

CONFIDENTIALITY:

Your identity and your child's identity will be coded and will not be associated with any published results. Your code number and your identity will be kept in a locked file room of the Center for Children and Families. All study data will be stored in a secured area at our center and reviewed only by individuals working on this study. Log-in information for the grade portal will be kept in a password protected database on a secured server that will only be accessible to research staff. Study information collected about your children may be provided to the study sponsor (The National Institute on Drug Abuse or NIDA which is a branch of the government) as well as the U.S. Food and Drug Administration if requested. In order to monitor this research study, representatives from Florida International University, and other federal agencies such as NIDA and OHRP (Office of Human Research Protection) as well as the Western Institutional Review Board® (WIRB®) may inspect the research records, which may reveal your identity and your child's identity. Total confidentiality cannot be guaranteed because of the need to give information to these parties.

The results of this research study will be presented at meetings and the results will be published in professional journals. Your identity and that of your teen will not be given out during those presentations or in these publications.

INFORMATION ABOUT A CERTIFICATE OF CONFIDENTIALITY FOR THIS RESEARCH:

To help us protect your privacy and your teen's privacy, the investigators have obtained a Certificate of Confidentiality from the National Institutes of Health. The researchers can use this Certificate to legally refuse to disclose information that may identify you and your teen in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you or your teen, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). The Certificate of Confidentiality will not be used to prevent disclosure to local authorities of child abuse and neglect, or harm to self or others.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your teen or your family's involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may

not use the Certificate to withhold that information. This means that you and your family must also actively protect your own privacy.

REIMBURSEMENT FOR MEDICAL TREATMENT:

Routinely, Florida International University (FIU), its agents, or its employees do not compensate for or provide free care for human subjects in the event that any injury results from participation in a research study. If your child becomes ill or injured as a direct result of participating in this study, you should contact their regular medical provider. If you have insurance, your insurance company may or may not pay for these costs. If you do not have insurance, or if your insurance company refuses to pay, you will be billed. Funds to compensate for pain, expenses, lost wages and other damages caused by injury are not routinely available. By signing this consent form, you do not give up any legal rights you or your teen would otherwise have.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide not to participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any of the following reasons:

- if it is in your best interest;
- you do not consent to continue in the study after being told of changes in the research that may affect you; or
- for any other reason.

If you leave the study before the planned final visit, you may be asked by the study doctor to have some tests or procedures done so that you leave the study safely.

SOURCE OF FUNDING FOR THE STUDY

The sponsor, the National Institute on Drug Abuse will pay for this research study.

QUESTIONS

Contact Dr. William E. Pelham, the Principal Investigator of the study and the Director of the Center for Children and Families or any of the research study staff at 305-348-0477 or Janellie Azaret, MD at 786-361-7151 (24 hours) for any of the following reasons:

- if you have any questions about your participation in this study,
- if you feel you have had a research-related injury or a reaction to the study drug, or
- if you have questions, concerns or complaints about the research

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who independently review research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have gotten satisfactory answers.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

VOLUNTARY CONSENT

I have read the information in this consent form (or it has been read to me). All of the above has been explained to me and all of my current questions have been answered. I am encouraged to ask questions about any aspects of this research study and future questions will be answered by the researchers listed on the front page of this consent from.

By signing this consent form, I agree to freely allow my child to participate in this research study. By signing this consent form, I have not given up any of my child's legal rights.

I can ask the study Principal Investigator, William Pelham, or the Western Institutional Review Board® (WIRB®) any questions I have about my child's rights as a research subject.

I agree to release my log-in information for my child's school grade portal to the Center for Children and Families in order to monitor my child's academic progress during the school year. I understand that this authorization is in effect until my child's participation in this study is complete or my child withdraws from the study.

I understand that I have the right to revoke this authorization at any time by changing my password or by sending a written request to the investigator.

☐ Yes, I agree to release my log-in information.

☐ No, I do not agree to release my log-in information.

Consent and Assent Instructions:

Consent: For subjects under 18, consent is provided by the parents or guardian.

Assent: Written assent is required for all subjects using the Assent section below and the Information Sheet for Adolescents.

Minor's Name (type or print):_____

CONSENT SIGNATURE:

Parent's Name:_____

Parent's Signature:_____ Date:_____

OR *if other than Parents are consenting:*

Guardian's Name:_____

Guardian's Signature:_____ Date:_____

You must provide a description of the guardian's authority to act for the individual:

_____

Person Conducting Informed Consent Discussion Name:

_____

Person Conducting Informed Consent

Discussion Signature:_____ Date:_____

ASSENT SECTION:

Statement of person conducting assent discussion:

1. I have explained all aspects of the research to the subject to the best of his or her ability to understand.
2. I have answered all the questions of the subject relating to this research.
3. The subject agrees to be in the research.
4. I believe the subject's decision to enroll is voluntary.
5. The study doctor and study staff agree to respect the subject's physical or emotional dissent at any time during this research when that dissent pertains to anything being done solely for the purpose of this research.

_____ _____
Signature of Person Conducting Assent Discussion Date

Signature of subjects:

This research study has been explained to me and I agree to be in this study.

_____ _____ _____
Subject's Signature for Assent Date

Statement of Parent or Guardian:

My child appears to understand the research to the best of his or her ability and has agreed to participate.

_____ _____
Signature of Parent or Guardian Date

---------- Use this witness section only if applicable ----------

If this consent form is read to the subject's parent or guardian because the parent or guardian is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject's parent or guardian. The subject's parent or guardian freely consented to allow the subject to be in the research study.

Signature of Impartial Witness	Date

TITLE: **Intervention for Teens with ADHD and Substance Use**

PROTOCOL NO.: DA034731

SPONSOR: National Institute on Drug Abuse

INVESTIGATOR: William E. Pelham, Jr., Ph.D.

SITE(S): Florida International University

DATE: June 4, 2019

ABSTRACT

Individuals with ADHD are at markedly high risk for increased substance use and Substance Use Disorder (SUD; Barkley et al., 2004; Charach et al, 2011; Derefinko & Pelham, in press; Lee et al., 2011; Molina & Pelham, 2003; Sibley et al., 2011). They have high rates of substance use across a wide range of substances, including illicit drugs, alcohol, and cigarettes (Arias et al., 2008; Molina & Pelham, 2003; Szobot et al., 2007), and are at risk for early onset of substance use behaviors and disorders (Arias et al., 2008; Milberger et al.,1997; Molina & Pelham, 2003). Importantly, these substance use problems do not abate over time; among individuals with adult ADHD, rates of substance use disorders approach 40% (Kalbag & Levin, 2005; Biederman et al., 1995), suggesting the need for early intervention. However, treatment of ADHD and substance use concurrently presents a number of problems for clinicians, including poor treatment adherence, lack of treatment progress, and impaired achievement of treatment goals, (Carroll & Rounsaville, 1993; Levin et al., 2004; Wise et al., 2001). Given these barriers, it is clear that future prevention and intervention development should follow the guidelines provided by the current literature on both ADHD and substance use treatment. Several psychosocial interventions for teens with SUD are well-established (Waldron & Turner, 2008; Winters & Leitten, 2007). However, typical studies that have examined efficacy of substance use interventions have conducted only secondary analyses to see if comorbid psychiatric diagnoses moderate outcome. There have been no controlled evaluations of how comorbid ADHD affects the efficacy of early intervention for early substance use. Given the strong evidence for the negative trajectory for individuals with co-occurring ADHD and substance use initiation, our goal is to conduct a controlled examination of a brief, early intervention for substance use (BEI; Teen Intervene, Winters & Leitten, 2007) modified for adolescents with ADHD by using the evidence from both treatment literatures. Importantly, this intervention will address individuals who are at risk for problems with substance use, but do not yet meet criteria for severe SUD. Although brief interventions have been found to be effective in other populations, their efficacy in an ADHD population with emerging substance use remains uninvestigated. We expect BEI to be effective for some but not all ADHD teens, with lower rates of response than have been obtained with nonADHD populations. To better understand why some adolescents with ADHD and elevated risk for substance use problems respond to BEI and others do not, we investigate the contributions of several cognitive, proximal and situational factors to treatment response. Finally, we will randomize non-responders to the BEI to three secondary treatment conditions (monitor only, parent training/adolescent cognitive behavioral therapy, and medication plus parent training/adolescent cognitive behavioral therapy) to determine the relative efficacy of these more intensive interventions for insufficient responders to brief treatment.

INNOVATION

Given the barriers to treatment known to surround adolescents with ADHD and comorbid substance use, it is clear that future intervention development should follow the guidelines provided by the current literature on both ADHD and substance use treatment. By combining multiple previously validated treatment strategies for ADHD and substance abuse, it is likely that treatment will be maximally effective. Early adolescence is the most effective period to deliver prevention and early intervention efforts. Early intervention offers the benefits of (1) directly addressing substance use at initiation, (2) intervening prior to escalation into more serious substance use disorders (Winters et al., 2007), and (3) capitalizing on the nature of adolescence: caregivers still possess the ability to monitor and influence adolescent behavior. Even within the substance use literature, little work examines critical periods for intervention, such as the window between initiation and escalation of substance use. Our goal is to examine whether tailoring a BEI strategy to address substance use patterns in adolescents with ADHD is an effective first line approach to intervention. Further, we subsequently examine the most likely options for effective intervention when brief intervention has failed, providing a tailored intervention for a high risk population at a relatively low cost.

In addition to exploring the efficacy of brief and more intensive interventions, we will examine potential mechanisms of treatment response. We will measure the contribution to substance use and response to intervention of ADHD symptom severity, situational factors (parental monitoring, academic functioning, peer relations), proximal deviancy outcomes (deviant peer affiliations and substance use, delinquency, family conflict, and teen attitudes/beliefs (motivation to change, self-efficacy) and the relationships among these factors in order to understand the mechanisms through which the proposed treatment model may disrupt escalations in substance use. Since participants in the current study will be young adolescents who do not yet demonstrate escalated substance use, initial measures of and changes in situational and proximal correlates of

substance use may be the best indicators of use and explanation of prevention in escalation.

APPROACH

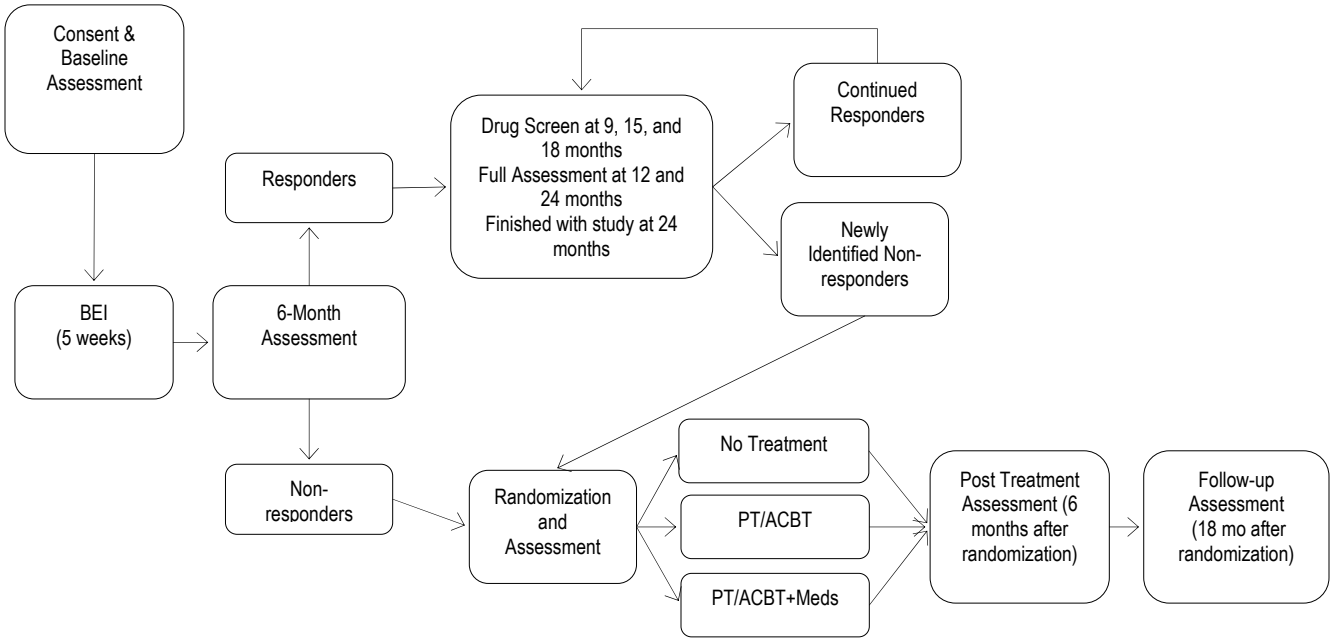
Research Design and Methods

The goal of this study is to evaluate the efficacy of a Brief Early Intervention (BEI) for reducing early alcohol and marijuana use in a group of adolescents (age 12-16) with ADHD who are at elevated risk for substance use problems. All adolescents will receive the BEI (based upon Teen Intervene). The Brief Early Intervention (BEI; 5 individual sessions with adolescent with some parent involvement during 3 of these sessions) will consist of a modification of a brief early intervention program designed by Winters (Winters & Leitten, 2007) with the addition of enhanced decision making skills. Due to the existing support for the intervention, the criterion for eligibility (elevated risk factors for early initiation of substance use), and concern for randomizing families with adolescents at risk for worsening substance use outcomes into a control (no treatment) condition for one to two years, no control condition is used in the current design at the first level of intervention. Similarly, due to the time required to see a potential effect of the treatment (6 months post-brief intervention), a wait-list control condition was not considered.

Adolescents will be evaluated for treatment non-response to the BEI at 6, 9, 12, 15, and 18 months post-treatment. Non-response is defined as non-normative use of alcohol, marijuana, or other drugs in the past 90 days. Alcohol and marijuana are the outcomes of interest in this study; however, non-normative use of any psychoactive substance will be considered non-response. **Alcohol use norms by age are presented in Table 4 and any marijuana use in adolescence is considered non-normative (NHSDAH, 2007).** Tobacco and caffeine products are excluded from consideration. For alcohol, marijuana, and other drugs, frequency and quantity of substance use will be collected for the past 90-days using the Substance Use Questionnaire (SUQ). Adolescents who do not demonstrate a response to the BEI **at the 6, 9, 12, 15, or 18 month assessment** (i.e., use substances at non-normative levels) will be randomized to either (1) **No Additional Treatment Monitoring Group**, (2) **Parent Training/Adolescent CBT** (PT/ACBT; e.g., 12 weeks of parent training and adolescent CBT) (3) **PT/ACBT plus concurrent stimulant medication** (PT/ACBT+MED). Adolescents who demonstrate immediate initial response will be released from treatment and assigned to a monitoring condition in which they are reassessed at 9, 12, 15, and 18 months. Any adolescent who demonstrates non-normative use at any of the follow-up assessments as defined above will be immediately eligible for randomization to further treatment (as detailed above). Adolescents and parents will complete an assessment battery at the randomization point as outlined in Table 5 unless randomization occurs immediately following the 6 or 12 month assessment (in which case the measures will not need to be repeated).

It is important for adolescents to be able to participate in research and substance use problems prevention programs without being required to disclose substance use to parents. Without this guarantee of confidentiality, adolescents have a disincentive to participate in this study and to provide honest disclosure of substance use. Therefore, participants will not be informed that the specific reason for randomization is the presence of adolescent substance use. Rather, parents and youth will be provided with a more general description of the reason for randomization: youth who demonstrate a lack of progress toward the treatment goals of the initial brief intervention will be assigned to the second arm of the study for randomization to an additional condition. This more general description still accurately describes the reason for randomization. Further, parents and adolescents will be informed of the purpose of interventions included in the secondary arm of the study (i.e., preventing the escalation of substance use problems among adolescents) and will provide consent/assent to participate in the treatment.

Based on prior research with Teen Intervene, and correcting for the likelihood that the ADHD sample in the proposed study represents a more intervention resistant group than was the case in the Winters et al. studies, we conservatively expect that the **6**-month *non-response* rate will be over 50%. *Thereafter, adolescents who demonstrate non-response post-BEI and are randomized will be assessed at post-treatment (6 months following randomization), and one year follow-up (12 months after post-treatment assessment).*



The Parent Training and Adolescent CBT (PT/ACBT) will be longer in duration than the BEI (12-family sessions with individual adolescent, parent, and joint adolescent and parent time), and will include additional parent training in behavioral modification, adolescent and parent contracting, and adolescent decision making skills. The PT/ACBT and Medication (PT/ACBT+MED) condition will be identical to the PT/ACBT condition but will include concurrent stimulant medication administration. Recruitment will continue on a rolling basis over the course of the year. The primary outcome measure will be alcohol and marijuana use. Secondary outcome measures include adolescent ADHD symptom severity, situational impairment (e.g., academic and social impairments, parental monitoring), proximal deviancy measures (e.g., delinquency, deviant peer affiliations, risky sexual behavior, family conflict), and teen attitudes and beliefs (motivation to use, self-efficacy). (see Table 5).

Participants. Three-hundred adolescents with ADHD between the ages of 12-16 who displayed elevated risk for substance use problems (but not severe abuse of alcohol, marijuana, or other drugs) will be recruited beginning in YR01 of the project on a rolling basis. Elevated risk is defined as the presence of at least risk factor from each of the following two categories of risk:

1. General Risk Factors
    a. Elevated symptoms of ODD or CD (Elevated parent or teacher scores on relevant subscales of the CBCL, TRF, or the DBD-RS).
    b. Elevated conflict with parents (Elevated parent-reported conflict on the CBQ)
    c. Low parental monitoring (Parents are aware of teen activities or teens disclose activities to parents only some of the time or less often.)
    d. Academic failure (Teens have previously failed a grade in school or earned Ds or Fs on most recent report card.)
2. Substance Use Specific Risk Factors
    a. Adolescent non-normative use of alcohol or other drugs indicated either by a positive urine drug screen or by adolescent self-report on the Substance Use Questionnaire.
    b. Adolescent use of cigarettes or e-cigarettes indicated by self-report on the SUQ or the E-Cigarette Questionnaire.
    c. Elevated parental use of alcohol or other drugs indicated by AUDIT score of 8 or higher or parent self-report of any use of other drugs for non-medical reasons.

d. Family history of substance use problems indicated by adolescent report of parent substance use problems or parent report on the Mann Family Tree indicates at least one parent or other family member is either a possible problem drinker/user or a definite problem drinker/user.
e. Other child in home using drugs or alcohol indicated by parent or adolescent report that at least one other child in the home uses alcohol or other drugs on the Mann Family Tree.
f. Perceived peer substance use indicated by adolescent report that at least one peer uses alcohol or other drugs.

Attempts will be made to recruit at a rate of approximately 100 participants per year during YR01 through YR03. All participants will receive the brief early intervention. The participants will be approximately 20% female and 80% male as these gender rates are representative of epidemiological prevalence estimates of ADHD (American Psychiatric Association, 2000). The combined population of Broward and Miami Dade Counties is approximately 57% Hispanic, 25% Caucasian, and 18% African American. We expect to reach a goal of at least 75% minority enrollees (see targeted enrollment chart), surpassing the percentage in the MTA (MTA, 1999). The diversity of our sample will allow us to examine the moderating effects of race/ethnicity on the impact of the proposed adherence intervention.

Recruitment. Participants will be recruited from a variety of potential sources, including psychiatric centers, pediatric offices, schools, parent support groups, and through advertisements placed in community locations and in local media outlets, and through direct mailings. Our center has an extensive history of running large scale ADHD clinical trials. Between 2002 and 2008, our center recruited 600 families with ADHD children for 6 clinical trials, and recruitment targets for all studies were met. Currently, our Center has a waitlist of over 300 adolescents between the ages of 12-16 whose parents are interested in participating in treatment studies for ADHD In addition, in the past year, our Center has provided medication or psychosocial treatment to approximately 150 adolescents with ADHD. Among these adolescents, the majority, (53.8%) were not actively taking ADHD medication upon referral to our clinic. During the past year, our Center also enrolled children and adolescents with ADHD for one foundation funded, one industry funded, and four federally funded clinical trials (two focused exclusively on adolescents), with all projects meeting or exceeding annual recruitment goals. Hence, we expect to meet the projected recruitment goals in a timely fashion. Families who previously have expressed interest in receiving information about studies, will be contacted via mail, email, and/or phone depending on the contact information they have provided. Information distributed to families will invite the parents to call the FIU Center for Children and Families (CCF) to receive additional information or to register to participate in the project.

Inclusion/Exclusion. Participants will be screened over the phone to ensure that only eligible participants are brought in for intake. Inclusion criteria will include a DSM-5 diagnosis of ADHD, a Full Scale IQ above 80, and elevated risk for the development of substance use problems as outlined above. ADHD diagnoses will be established based on information gathered from parent, teacher, and adolescent self-report as well as records of previous evaluations and school history provided by parents. The Full Scale IQ criterion will be considered met if upper bound of the 95% confidence interval for any composite score on the WASI is equal to or greater than 80. Following recommendations by Sibley et al. (2012), adolescents with fewer than 6 symptoms of either hyperactivity/impulsivity or inattention may still receive ADHD diagnoses for the purposes of this study when there is evidence of significant impairment. This decision is based on the finding that severity of impairment may be a better indicator than symptom counts of the presence of ADHD among adolescents (Sibley et al., 2012). Exclusionary criteria will include: (1) current substance use disorder meeting DSM-V criteria for the severe qualifier; (2) active medical conditions that could be worsened by stimulants (seizures, pregnancy, arrhythmias, hypertension, Tourette's Disorder, etc.) unless approved for participation by the treating physician; (3) a formal diagnosis of Bipolar Disorder, schizophrenia, and/or other psychotic disorders (4) a formal diagnosis of autism spectrum disorder (ASD) with a severity level of 2 or 3 or significant intellectual or language impairment. Youth with a documented intolerance to amphetamine or methylphenidate will not be enrolled as this would eliminate the possibility for randomization to the medication arm of the study. Youth with a mood or anxiety disorder not

Table 4. *NHSDAH Age-based norms for frequency of alcohol use (days per month)*

Age	Alcohol days per month
12	0
13	0
14	0
15	1
16	2
17	2
18	3

requiring psychotropic medication will be allowed to enroll as long as they do not need emergent treatment (mania, active suicidal ideation).

Consent and Intake. At an initial visit, informed parental consent and youth assent will be obtained via IRB-approved consent forms. Substance use (e.g., ever used, age first use, lifetime use), substance use disorders, adolescent demographics, family history of substance abuse, prior mental health treatment, psychosocial stressors (e.g., self-image, interpersonal life, mental health disorders), and level of functioning will be assessed using the Adolescent Diagnostic Interview (ADI; Winters & Henley, 1993), a structured interview with the adolescent. Parent report of adolescent substance use problems will also be obtained using a questionnaire; however, adolescent report is expected to be the best measure given parents appear to under report teen substance use (Weissman et al., 1987; Winters et al., 1996). Detailed assessment of substance use quantity and frequency will be conducted using teen self-report on the Substance Use Questionnaire (SUQ; Molina & Pelham, 2003). Urine drug screens will also be obtained from participants at intake. Diagnosis of ADHD will be assessed through a combination of parent semi-structured interview (NIMH Diagnostic Interview Schedule for Children IV, computerized version: Shaffer et al., 2000) and parent and teacher rating scales of Disruptive Behavior Disorders (Pelham et al, 1992), as is the standard and recommended practice in the field, including for adolescents (Pelham et al., 2005; Wolraich et al., 2005). Information will be independently reviewed by two doctoral-level clinical psychologists and when diagnostic disagreement occurs, a third clinician will be consulted and the majority will prevail. Functional Impairment will be assessed via parent and teacher ratings (Fabiano et al., 2006). Additionally, the clinician will administer to the adolescent the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence – 2nd Edition (WASI-II; Wechsler, 2011). Adolescent academic achievement will be assessed using subscales from the Wechsler Individual Achievement Test – 3rd Edition (WIAT-3; Wechsler, 2002). Parents and adolescents will also complete an intake battery as detailed in Figure 5. If the adolescent meets full criteria for the study after intake, he/she will be assigned to participate in the early intervention. Parents will also complete self-report measures of substance use and will provide information about substance use problems among adolescents' family members.

Follow-up Assessment and Interventions. The schedule of assessment and interventions will depend upon participants' progress following the initial brief intervention. Participants meeting study criteria will participate in the activities as outlined below. Table 5 details the schedule of assessment for responders (i.e., teens engaging in no more than normative substance use following the brief intervention) and non-responders (i.e., teen engaging in more than normative substance use following the brief intervention). Participants who are initially identified as responders, may be subsequently identified as non-responders should there be evidence of non-normative use at any of the assessment points from 6 to 18 months. Once identified as a non-responder, participants are randomized to one of the three previously described treatment conditions. The post-treatment assessment point will occur 6 months after the start date for the treatment. The 1-year follow-up will occur 1 year after the post-treatment assessment.

Parents and teens will each receive $25 in gift cards upon completing each assessment point with the exception of the 9, 15, and 18-month screens. For the 9-month, 15-month, and 18-month screens, each teen who completes the assessment will receive $25 in gift cards. Teachers will receive a $10 gift card each time they return completed measures.

Table 5. Assessment measures Study 1

Baseline Diagnostic Measures	All Participants		Responders					Non-Responders		
	Intake	6-Month	9-Month Screen	12-Month	15-Month Screen	18-Month Screen	24-Month	Random-ization Visit[1]	Post-Tx	1-Year Follow-Up
Telephone Screening	P									
Diagnostic Interview Schedule for Children (DISC-IV; Shaffer et al., 2000)										
ADHD Module	P									
ODD Module	P									
CD Module	P									
Parent Report of Son/Daughter Substance Abuse (PRASU) Baseline Version	P									
Parent Report of Son/Daughter Substance Abuse (PRASU) Past 3 month Version		P		P			P	P	P	P
Family Information Form	P									
Clinical Intake Interview	P									
Adolescent Diagnostic Interview - Baseline Version (ADI ITAS Baseline)	A									
Adolescent Diagnostic Interview - Past 3 Month Version (ADI ITAS Past 3 Month)		A		A			A	A	A	A
Wechsler Abbreviated Scale of Intelligence - 2nd Ed (WASI-II; Wechsler, 2011)										
Vocabulary	A									
Matrix Reasoning	A									
Wechsler Individual Achievement Test - 3rd Ed. (WIAT-3; Wechsler, 2002)										
Word Reading	A									
Spelling	A									
Numerical Operations	A									
DBD - RS (Pelham et al., 1991) - DSM-V Version										
DBD-RS Parent Report	P	P		P			P	P	P	P
DBD-RS Adolescent Report	A	A		A			A	A	A	A
DBD-RS Teacher Report	T									
Impairment Rating Scale (Fabiano et al., 2006)										
IRS Parent Report	P	P		P			P	P	P	P
IRS Adolescent Report	A	A		A			A	A	A	A
IRS Teacher Report Short	T									
CBCL/YSR (Achenbach, 2009)										
CBCL	P	P		P			P	P	P	P
YSR	A	A		A			A	A	A	A
Treatment History Form	P	P		P			P	P	P	P
Primary Outcome Measures										
Substance Use Questionnaire Baseline Version (Molina & Pelham, 2003)	A									
Substance Use Questionnaire Past 3 Month Version (Molina & Pelham, 2003)		A	A	A	A	A	A		A	A
E-Cigarette Questionnaire ITAS Baseline Version	A									
E-Cigarette Questionnaire ITAS Past 3 Months Version		A	A	A	A	A	A		A	A
Current Substance Use (urine screen)	A	A	A	A	A	A	A		A	A
Secondary Outcome Measures & Potential										

Moderators										
Peer Substance Use and Peer Tolerance of Substance Use (Johnston et al., 1988)	A	A		A			A	A	A	A
Academic Functioning (GPA) - Grade Portal Log	School	School		School			School	School	School	School
Conflict Behavior Questionnaire (CBQ; Robin & Foster, 1989)										
CBQ Parent	P	P		P			P	P	P	P
CBQ Teen	A	A		A			A	A	A	A
Parent Monitoring Scale (Steinberg et al., 2001)	A	A		A			A	A	A	A
Child Disclosure Scale (Stattin & Kerr, 2000)	A	A		A			A	A	A	A
Deviant Behavior Subscale - Teen Version Baseline (PEI; Winters)	A									
Deviant Behavior Subscale - Teen Version Past 3 Months (PEI; Winters)		A		A			A	A	A	A
Deviant Behavior Subscale - Parent Version Baseline (PEI; Winters)	P									
Deviant Behavior Subscale - Parent Version Past 3 Months (PEI; Winters)		P		P			P	P	P	P
Brief Situational Confidence Questionnaire (Sobell, 1996)	A	A		A			A	A	A	A
Problem Recognition Questionnaire (Cady et al., 1996)	A	A		A			A	A	A	A
Expectancies Questionnaire	A	A		A			A	A	A	A
Likelihood of Future Use	A	A	A	A	A	A	A	A	A	A
Mann Family Tree Brothers and Sisters (PALS)	A									
Motives for Drinking (Cooper; PALS) - Baseline	A									
Motives for Drinking (Cooper; PALS)		A		A			A	A	A	A
Marijuana Motives Measure (Comeau) - Baseline	A									
Marijuana Motives Measure (Comeau)		A		A			A	A	A	A
Fagerstrom Test for Nicotine Dependence (1-7 on PALS NDS)	PA	A		A			A	A	A	A
Mann Family Tree (PALS)	P									
Marijuana Use Questionnaire	P									
AUDIT	P									
Abuse Columns (PALS)	P									
Alcohol Use Questionnaire	P									
Cigarette Use Questionnaire (PALS)	P									
Bidimensional Acculturation Scale	PA									
Treatment History Form	**P**	**P**	**P**	**P**	**P**	**P**	**P**	**P**	**P**	**P**
Readiness to Change Ruler (Miller)	**A**	**A**		**A**				**A**	**A**	**A**
IGIC-R (Trucco)	A									

Note. P=Parent. A=Adolescent. T=Teacher.

[1] These measures will only be completed by families who are randomized following the 9, 15, or 18-month screening point.

Interventions. The Brief Intervention will be a brief early intervention program based upon Teen Intervene, an early intervention designed by Winters (Winters & Leitten, 2007). Due to the known executive functioning

deficits associated with ADHD, this program will be modified to be longer in duration (5 sessions). Primarily the teen will meet individually with the clinician for the sessions; however, the parent will join the teen for portions of some sessions. These sessions will have additional focus on decision making skills, as these are believed to have a direct impact on the characteristic impulsivity of ADHD. The standard Teen Intervene (Winters & Leitten, 2007) is a brief, outpatient intervention geared at reducing alcohol and drug use in adolescents and youth at risk for developing substance use problems. The standard program consists of three 60-minute, one-on-one therapy sessions that employ motivation and self-change techniques. The first session elicits information about the individual's substance use and its related consequences, evaluates the student's willingness to change, and helps the individual set goals that he or she would like to pursue. The second session reviews the patient's progress toward reaching goals, discusses high-risk situations that have caused difficulty in reaching the goals, discusses strategies to overcome these barriers, and negotiates the continuation of goals. A third session is conducted with the adolescent's parent. This session also uses motivational goal setting and addresses the following topics: a) The adolescent's substance use problem, b) the parent's attitudes or behaviors towards the substance use problem, c) parental monitoring and supervision, and d) healthy substance use behaviors and attitudes by the parent. The proposed modification of the Teen Intervene builds on this content with additional emphasis on problem-solving skills, management of emotion triggers of substance use, and skills for resisting peer pressure to use substances. Evaluation of treatment response will include the following outcome measures based upon the Substance Use Questionnaire for the past 90 days: Number of alcohol use and marijuana use days will be examined as a combined variable and will be examined separately. For alcohol, separate analyses will also be conducted for number of drinks per drinking day. Age will be employed as a covariate in these analyses to account for developmental differences between early and late adolescence.

The Parent Training and Adolescent CBT (PT/ACBT) (e.g., individual family sessions of parent training and adolescent CBT) will be longer in duration (12 sessions total, with parent and adolescent receiving individual services, one after the other, then joint contracting time at the end of session). Content will follow standard practice in the externalizing disorder field (Barkley, Edwards, & Robin, 1999; McGillicuddy, Rychtarik, Duquette, & Morsheimer, 2001; Waldron, Slesnick, Brody, Turner, & Peterson, 2001), and will include adolescent CBT (12 sessions of cognitive behavioral strategies for decreasing substance use, including negative mood management and coping, problem solving, motivation and goal-setting, and peer refusal skills), parent skills training (12 sessions of coping, A-B-C model of behavior, problem-solving, use of positive and negative consequences, rule-setting, psychoeducation about substance use, and how to seek additional help and services), and parent-adolescent contracting at the end of each session.

Concerta was chosen as the stimulant medication to remain consistent with Riggs and colleagues' (2011) major medication trial in adolescents with combined ADHD and established substance use disorder. Optimal dose will be defined as one enabling adolescents to reach a level of home/school functioning considered good with no further room for improvement that represents a meaningful change from baseline with a tolerable level of side effects. A similar definition has been employed in the MTA and other large ADHD trials (Vitiello et al., 2001, Palumbo et al., 2008, Collins et al., 2006). All adolescents in this arm will start the protocol taking medication seven days a week (no drug holidays). Adolescents who have not previously taken stimulant medication for ADHD will be started on the lowest available dose of Concerta (18mg which approximates 5mg TID of MPH). Adolescents who are already taking medication for ADHD at the time of randomization will have a consultation with the study doctor to determine whether their current medication can be safely continued with the study medication or whether changes are needed (e.g., safely withdrawing the other medications, reducing dose, etc.) prior to initiating the study medication. After one week, parents and teens will rate efficacy and tolerability using parent symptom rating scales, the parent and teen versions of the Impairment Rating Scale (IRS) and the Clinical Global Impression Scales for ADHD (CGI; Rapoport et al.,1985). The Pittsburgh Side Effects Rating Scale (PSERS) will be used to assess drug tolerability. At each medication assessment visit, a study physician will meet with the family to review the efficacy and tolerability ratings and complete the ADHD CGI-I/S (Improvement and Severity Scales) to determine the need for a dose change. The assessing clinician will be instructed to increase the dose (to 36mg, 54mg, then 72mg, respectively) unless the physician believes the subject's functioning has been optimized (CGI-S <3) or the teen cannot tolerate a higher dose. This threshold has been found to be a valid definition of optimal dose (Gao et al., 2006). This process will be repeated in one-week intervals until the lowest effective dose that is well-tolerated has been identified. We chose a one week duration for each dose to allow for a thorough assessment of the therapeutic effects of that dose and timely collection of ratings from home. These one-week follow-up appointments may take place in

person or over the phone; however, the initial medication visit and the 3-month follow-up medication visits will take place in person to allow a brief medical exam (i.e., height, weight, blood pressure, temperature, heart rate, etc). Once the lowest effective dose is identified, families will continue to have follow-up medication visits at least once every three months throughout the duration of their participation in the study.

Measures of treatment satisfaction will be administered to parents and teens after the final session of both the BEI and the PT/ACBT session.

Hypotheses and Data Analysis

Aim 1: We will investigate response to a brief early intervention (BEI) for substance use among adolescents with ADHD. We hypothesize that approximately 50% of adolescents will show meaningful response to the BEI, as evidenced by no more than normative substance use assessed at 6-months following treatment. **Aim 2:** We will also test whether key variables associated with ADHD (ADHD symptoms) and with the development of substance use (parental monitoring, social impairment, academic functioning, family conflict, deviant peer affiliation and peer drug use, risky sexual behavior, delinquency, teen motivation and self-efficacy) predict response to the BEI. It is expected that poor response to treatment will be associated with high ADHD symptomatology, concurrent delinquency, risky sexual behavior, deviant peer affiliations, academic impairment, family conflict, lack of parent monitoring, poor self-efficacy and high motivation to use substances. **Aim 3:** We will also examine relative efficacy between the randomized second level interventions for BEI non-responders (i.e., no treatment control, augmented psychosocial treatment (PT/ACBT) and combined medication and PT/ACBT) for non-responders to the BEI treatment. Adolescents who do not respond to the BEI and are randomized to the intervention arms of (PT/ACBT) or combined intervention (PT/ACBT+MED) will show differential improvements in primary and secondary outcomes (see Table 5). We hypothesize that relative to the no treatment control group, both groups will show improvements, with the largest effects for those who receive PT/ACBT+MED. Secondary analyses will be conducted for the one-year follow-up assessment for all groups. It is expected that therapeutic gains will extend through the follow-up period. Secondary analyses of treatment-related changes in the associated variables listed above will examine whether these changes mediate improvements in substance use.

Analyses

The initial part of the study design is to evaluate the effectiveness of the brief early intervention for substance use. Analyses will be based upon measures of substance use and ADHD symptoms, measured at baseline and 6 month assessments. The analytical plan addresses the multiple measurements on the same participant, with a cautious eye toward any concerning missing data issues. We expect drop out to be minimal as has been the case in our decade of experience with treatment studies of ADHD teens. To date, our collective dropout rate is below 5% per year. *Studies conducted in Miami-Dade County with Hispanic adolescents who display behavior problems and emergent substance use report slightly lower retention, with 16-19% attrition (Pantin et al., 2009; Prado et al., 2007). In our studies, data loss has also been relatively low;* should there be a missing data issue, we suspect that the last observation carried forward method (LOCF) will be a satisfactory strategy to use. However, we are well aware of other methods and would also use the Mixed-Effects Model Repeated Measures (MMRM) which is more robust to biases and provides better control on type I and II error.

A careful assessment of data quality will be undertaken as data are being collected and entered, with the usual set of appropriate value, range and logic checks. Data will be collected and handled in a manner that satisfies all local and national requirements for personal privacy, specifically PHI, and data security. Prior to analyzing outcome, comprehensive assessments of data quality, including examination of requirements for the assumptions underlying outcome analyses (i.e., normality, linearity, independence, homogeneity of variance) will be undertaken. Should these assumptions not be met, we will adjust the analytical approach or use transformations as appropriate. We will also apply standard methods for outlier detection (e.g., analysis of leverage statistics, residuals, and df Betas), and use robust statistical significance tests if variance is heterogeneous or re-specify model terms if assumptions of linearity are violated.

Aim 1: The first aim is to test whether individuals' substance use outcomes decrease significantly from baseline to 6-month assessment. We will calculate days of alcohol and marijuana use during the past 90-days using data from the Substance Use Questionnaire. We will also examine quantity of alcohol use gathered from the SUQ. Repeated measures GLM techniques as implemented by SAS PROC GLM will be used. Several control variables (age, ethnicity, family SES, gender, and functional impairment associated with ADHD) will be entered into the model as covariates. As a secondary analysis, we will also examine % of participants at each

randomization point (6-months, 9 months, 12 months, 15 months, 18 months) who continue to maintain normative use in a time until they stop context. For these analyses, we expect to use Cox Proportional Hazards Regression techniques.

Aim 2: The second aim of this study is to test whether situational, proximal, and cognitive variables listed above predict response to the BEI. At this stage of the study, we will investigate whether each secondary outcome (see Table 5) is a significant predictor of treatment response. Using the GLM as described above, we will investigate the impact of the covariates on substance use variables over time. Predictors will be entered in to the model simultaneously, so long as our sample size adequately supports such inclusion. Should the Cox Regression model, which measures timing, provide a more sensitive measure of substance use trajectories, we will include moderator terms in this model as well.

Aim 3: The third aim is to determine if, given nonresponse to the BEI, it is preferable to augment treatment with enhanced psychosocial intervention or multimodal treatment. As previously stated, we expect less than 50% of the sample to respond to the BEI, leaving at least 150 treatment-resistant adolescents to be randomized into one of the three treatment arms: (1) No treatment, (2) PT/ACBT, (3) PT/ACBT + MED. Using the general linear modeling techniques as implemented by SAS PROC GLM, we will examine differences between the treatment arms over post-treatment and one year follow-up measurement points with fixed effects of treatment arm. Analyzing each time period will address separate questions about the effect of intervention immediately post-treatment and at one-year follow-up. For these analyses, mixed linear models and/or GEE strategies will be used (Hedeker et al., 2006). Primary and secondary outcome measures will be evaluated separately (see Table 5). As our sample size permits, as a secondary analysis, we will also examine whether changes in the secondary outcomes listed above following treatment mediate response to treatment and substance use during the follow up phase.

Power Analysis: For Aim 1, previous evaluations of BEI report a large effect of treatment on days of alcohol use (d=2.67; Winters et al., 2007). A sample size of 300 (G*Power 3.1.2 software), with alpha of 0.05 for a two-tailed test, will provide power = 0.96 to detect a small treatment effect size of 0.25 if there are no drop outs. Assuming a maximum dropout rate of 15%, as shown in previous studies with Hispanic adolescents with behavior problems (Pantin et al., 2009; Prado et al., 2007), the power drops slightly to 0.90. We also plan to measure the impact of concurrent medication use on treatment effect. For this analysis there are now two groups of participants, those currently using stimulant medication and those not using stimulant medication. The sample size of 300 with a maximum drop-out rate of 15% will provide .90 power to detect an interaction effect of medication, assuming a small pre-test to post-test correlation among measures (r = .25). For Aim 3, a sample size of 150 with a maximum drop-out rate of 15% will provide .90 power for a treatment effect size of .40, which is adequate considering that most ES for similar treatments range between .40 and .80 (Waldron & Turner, 2008). Thus, the sample should be sufficient to detect significant effects of treatment as well possible prediction models.

c. Potential Risks

Risk: Participants may experience mild and transitory psychological discomfort from completing research measures that deal with emotionally laden material, including reporting on illicit drug use and other antisocial or illegal behaviors, which may be uncomfortable for some participants. **Procedure:** We will inform participants of the NIH Confidentiality Certificate prior to collecting any data for the study, which will shield the research data from a subpoena or court order. In addition, participants and their parents will be advised to ask questions of study personnel if confidentiality is of a concern, and to refrain from answering questions that cause them personal distress.

Risk: Participants may face risk as they may experience mild and transitory psychological discomfort from changing their behaviors and attitudes as part of the goals of the brief intervention procedures, or from the material or exercises included in the brief intervention sessions. **Procedure:** We recognize that by targeting a substance using population, initial motivation to participate may be low. However, the psychosocial intervention is designed to address motivational deficits through a combination of motivational interviewing techniques, contingency management, and parent- adolescent negotiation sessions. It is expected that the majority of adolescents will be willing to participate in these activities as attendance will be a means of obtaining additional privileges and freedoms at home. Our Center is experienced at running psychosocial interventions for ADHD adolescents and only therapists who have prior experience working with this population will be employed in the study. We experience very low attrition rates (under 5%) from our clinical and research programs for adolescents. None the less, adolescents can refuse to participate in any session they so choose, and families

may discontinue the study at any time. Efforts will be made to reengage adolescents refusing to attend specific sessions.

Risk: Randomization to the augmented treatment arms for non-responders. **Procedure:** This risk will be addressed through the informed consent/assent process, where parents and children will agree to be assigned to treatment groups. Parents and children are free to withdraw from the study at any time and are not obligated to participate in the treatment group they are assigned to. Withdrawing from this study will not affect any future interactions or their participation in any future clinical services or studies at the CCF.

Risk: Participants may experience adverse events related to medication. **Procedure:** While ADHD medication will not occur for all participants, all participants must be able to tolerate stimulant medication to participate in the study. Therefore, the side effect profile of ADHD medications will be reviewed with families during the consent process. Participants with a documented history of intolerance to all approved ADHD medications will be excluded from the study. All participants will undergo structured assessments of psychiatric comorbidity at baseline as well as medication tolerability which should further reduce the rate of serious adverse events For individuals randomized to the psychosocial treatment and medication arm of the study, height, weight, resting blood pressure and pulse will be collected at each following assessment. All of these procedures should minimize the risk of serious adverse events. Each personal care physician's office has their own procedures for handling emergencies, including a 24 hour on call system. To ensure the safety of all participants, Dr. Humphery (the study psychiatrist and a board certified child psychiatrist) will be available by pager 24 hours a day during medication phases of the study.

Confidentiality Assurances

In virtually all instances, research data collected in the study will be kept strictly confidential and will not be shared with anyone outside of the research team, including referring schools and care providers. The only exceptions to confidentiality, which will be clearly specified in the consent form, will be for information related to medical emergencies, current child abuse or neglect, or imminent risk of death or serious injury to the participant or others. All research materials will be encoded by a research number and will contain no other identifying information. Written materials will be maintained in locked filing cabinets or storage boxes and computer spreadsheets will be saved in protected files requiring a password for access.

Potential Benefits

There may be considerable potential social, emotional, and behavioral benefits to adolescents who all receive the brief intervention, who may learn new skills to help them reduce or stop their substance use and improve their family and peer relationships. Long term benefits may include a reduced risk for later developing a substance use disorder, or becoming part of the legal system. The relatively small risks to the participants described above are reasonable in light of these potential benefits. The information gained from the study may also help clinicians working with adolescents with ADHD who have comorbid substance use.

Importance of the Knowledge to be Gained

Adolescents with ADHD are a population that is greatly impaired and on track to develop a number of negative outcomes, including substance use and Substance Use Disorder (SUD; Barkley et al., 2004; Charach et al, 2011; Derefinko & Pelham, in press; Lee et al., 2011; Molina, in press; Molina & Pelham, 2003; Sibley et al., 2011). Individuals with ADHD have high rates of substance use across a wide range of substances, including illicit drugs, alcohol, and cigarettes (Arias et al., 2008; Molina & Pelham, 2003; Szobot et al., 2007), and are at risk for early onset of substance use behaviors and disorders (Arias et al., 2008; Milberger et al., 1997; Molina & Pelham, 2003). This proposal represents the first randomized study of brief, early substance use intervention designed specifically for ADHD youth within a sample of clinic-referred adolescents with co-occurring ADHD and emerging substance use. If the proposed treatment is found to be efficacious, it may enhance the long term functioning of the millions of ADHD youth in this country. Information gained from this study concerning behaviors that place adolescents with ADHD at risk for drug use, and how best to intervene with adolescents with these kinds of problems, can assist with developing services for this group, for whom no targeted services are currently available. Given the minimal risk to participants that is incurred by this study, it seems clear that the propensity to gain the above knowledge far outweighs the risks.

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