Augmentation of Brief Habit Reversal Training with D-Cycloserine or Placebo (DCS+HRT)

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1. Protocol Title:

Augmentation of Brief Habit Reversal Training with D-Cycloserine or Placebo (DCS+HRT)

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3. Abstract:

Habit reversal training (HRT) is a treatment for youth with chronic tic disorders (CTDs). Data from large scale studies suggests that 8-10 sessions of HRT can meaningfully reduce tic severity for many youth. However, not all youth experience a meaningful reduction, with most youth continuing to exhibit tic symptoms after HRT. Emerging research suggests that an antibiotic medication called d-cycloserine (DCS) holds promise to improve therapeutic reductions for psychosocial interventions for anxiety disorders, obsessive-compulsive disorder, and posttraumatic stress disorder. DCS is an antibiotic that has been approved by the United States Food and Drug Administration for the treatment of tuberculosis in high doses. At substantially lower doses, DCS is suggested to strengthen the learning that occurs in psychosocial interventions such as cognitive behavioral therapy and HRT.

This study will evaluate whether a single session of DCS-augmented HRT will lead to better symptom improvements compared to a single session of placebo-augmented HRT in youth with CTDs. Interested participants with a CTD will complete a screening assessment that includes a structured clinical interview and clinical rating scales (Visit 1). Participants who meet eligibility criteria will be invited back a week later to complete the session of HRT. At this visit (Visit 2), participants will be randomly assigned to receive either a 50 mg DCS pill or 50mg placebo pill. Participants, clinicians, and the therapist will be blind to random assignment (DCS or placebo), with only the research pharmacy and research coordinator being aware of medication assignment. At Visit 2, participants will complete rating scales and a computer task. Afterward, the participant will receive a session of HRT. Afterward, participants and clinicians will complete rating scales to assess the participant's mastery of components of HRT within session. The clinician will use a standardized form to evaluate any possible side effects of DCS. Participants will be asked to practice the strategies to control their tics over the next week, and complete a homework monitoring form. Participants will be asked to return 1 week later (Visit 3) to evaluate their overall tic severity and specifically the severity of targeted tics using standardized rating scales. Participants will also be asked about any side effects and evaluate homework

compliance using standardized measures by an independent clinician blind to treatment condition.

4. Background and Significance:

Chronic Tic Disorders and Tourette Disorder (collectively referred to henceforth as CTDs) are characterized by the childhood onset of tics that persist for more than one year (American Psychiatric Association, 2013). Collectively, these conditions are estimated to affect 0.8%-2.0% of youth (Centers for Disease Control and Prevention, 2009; Scharf, Miller, Mathews, & Ben-Shlomo, 2012). For individuals with CTDs, tic symptoms typically emerge in childhood (Bloch & Leckman, 2009), and exhibit a fluctuating course with peaks in symptom severity that stabilize over a period of weeks (Lin et al., 2002). The limited information available suggests that tics reach their greatest severity in adolescence, and subside into early adulthood for some youth (Bloch & Leckman, 2009; Bloch et al., 2006). Youth with CTDs are reported to experience significant impairment (Conelea et al., 2011; Storch et al., 2007) and poor quality of life (Conelea et al., 2011; Storch et al., 2007). Therefore, efficient and effective treatments are imperative for youth with CTDs.

Expert reviews and practice parameter papers recommend behavior therapy as a first-line intervention for youth with CTDs that have mild-to-moderate tic severity (Murphy, Lewin, Storch, Stock, & AACAP Committee on Quality Issues, 2013; Verdellen, Van De Griendt, Hartmann, & Murphy, 2011). Behavioral interventions such as Habit Reversal Training (HRT) and its successor the Comprehensive Behavioral Intervention for Tics (CBIT) are efficacious in reducing tic severity for individuals with CTD (McGuire et al., 2014b; Piacentini et al., 2010; Wilhelm et al., 2012) with long-term improvement observed for up to six months (Piacentini et al., 2010; Wilhelm et al., 2012; Woods et al., 2011). Despite its therapeutic benefit, only about 50% of youth exhibit a positive treatment response, with full tic remission being infrequent. Thus, there is a clear need to delineate the mechanisms of CBIT and identify strategies to improve treatment response to this evidence-based intervention (Scahill et al., 2013).

The behavioral treatment model underlying CBIT (Woods et al., 2008) acknowledges the neurological origin of tics (McNaught & Mink, 2011), but suggests that tics are influenced by internal and external contextual factors (Conelea & Woods, 2008). Prominently, many individuals with CTD experience aversive premonitory urges (internal factors) that are relieved by tic expression (Leckman, Walker, & Cohen, 1993; Woods, Piacentini, Himle, & Chang, 2005) and are associated with greater tic severity (Reese et al., 2014; Woods et al., 2005). It is suggested that the relief from the aversive premonitory urge experienced by tic expression serves to negatively reinforce (i.e., strengthen) tic expression (Woods et al., 2008). The primary component of CBIT is HRT, which employs mechanisms of both extinction and associative learning. In CBIT, patients learn to implement competing responses contingent upon internal triggers such as premonitory urges to prevent tics and the associated urge alleviation. Consequently, the negative reinforcement cycle between tic expression and urge reduction is extinguished. Furthermore, as not all tics have urges and not all urges may be extinguished, CBIT facilitates the formation of new learning associations between tic triggers (i.e., premonitory urges) and competing responses (e.g., not ticcing) that compete with previously developed urge-tic associations (associative learning).

Although previous investigations among youth with CTDs (Lyon et al., 2010) and related disorders (e.g., obsessive-compulsive disorder, Storch et al., 2013; anxiety disorders, Walkup et al., 2008) have explored the use of pharmacological augmentation strategies to improve therapeutic outcomes, findings from these investigations have been mixed. Emerging research from translational neuroscience suggests that cognitive enhancers such as d-cycloserine (DCS)

present a viable option to safely enhance therapeutic outcomes and expedited treatment gains for exposure-based therapies. D-cycloserine is a partial glutamatergic NMDA receptor agonist that is approved by the United States Food and Drug Administration to treat tuberculosis in high does, but works as a cognitive enhancer for psychosocial interventions in much lower doses (e.g., 50 mg). DCS has been found to enhance extinction (Walker, Ressler, Lu, & Davis, 2002) and associative learning (Quartermain, Mower, Rafferty, Herting, & Lanthorn, 1994) across numerous animal and human studies (Davis, 2011; Fitzgerald, Seemann, & Maren, 2014).

Exposure-based psychosocial interventions that utilize these mechanisms have demonstrated greater therapeutic outcomes and/or expedited therapeutic gains when augmented with DCS relative to placebo across a variety of psychiatric disorders (e.g., anxiety disorders, obsessive-compulsive disorder, post traumatic stress disorder, schizophrenia; Gottlieb et al., 2011; McGuire, Lewin, & Storch, 2014a). Moreover, across multiple RCTs of DCS-augmented treatment, few side effects have been reported with no serious adverse events identified (Ori et al. 2015). Although the results from these RCTs have been mixed across disorders (McGuire et al. 2014a), they bear considerable promise. Indeed, DCS-augmentation of HRT may yield greater overall reductions in tic severity and/or expedited therapeutic gains resulting from enhanced extinction and associative learning.

5. Study Aims

Primary Aim#1: To examine whether a single session of HRT+DCS will produce faster reductions in tic severity relative to HRT+placebo for tics targeted in treatment.

Hypothesis#1: We hypothesize that HRT+DCS will produce faster reductions in tic severity relative to HRT+placebo for tics targeted in treatment on the Hopkins Motor/Vocal Tic Scale (HM/VTS).

6. Administrative Organization

This study will only take place at the University of California Los Angeles (UCLA). There are no other participating study sites, laboratories, data management centers, and/or coordinating centers.

7. Study Design

This is a double-blind placebo controlled study that will compare the efficacy of a single session of HRT augmented by either DCS or placebo in youth (age 8-17) who have either Tourette Disorder or a Persistent Tic Disorder. The sample size was determined based on the feasibility of the recruitment period. Participants will complete an initial evaluation to determine eligibility (Visit 1). Afterward, eligible youth will be randomly assigned to receive either DCS or placebo prior to a single session of HRT (Visit 2). During this visit, two tics will be targeted for treatment using HRT. One week after the therapy session, youth will return (Visit 3) to complete a follow-up assessment to determine improvement in tics targeted in treatment. The primary outcome measure will be the improvement in two bothersome on the Hopkins Motor/Vocal Tic scale (HM/VTS) at Visit 3.

8. Study Procedures:

Participants:

Included in this study will be up to 20 children and adolescents between the ages of 8 and 17

years (inclusive), who meet diagnostic criteria for Tourette Disorder or a Persistent Tic Disorder and the inclusion and exclusion criteria.

Recruitment:

Recruitment will occur through the UCLA OCD, Anxiety, and Tic Disorder's Program, as well as the greater Los Angeles Community.

Inclusion/Exclusion Criteria:

Inclusion criteria for this study are as follows: (1) ages 8 years to 17 years (inclusive); (2) meet diagnostic criteria for either Tourette Disorder or a Persistent Tic Disorder; (3) moderate tic severity or greater as evidenced by a Yale Global Tic Severity Scale (Leckman, Riddle, Hardin, & Ort, 1989) total score greater than 13 (>9 for children with motor or vocal tics only); (4) be fluent in English; (5) be medication free or on a stable dose of a non-antipsychotic medication for 6 weeks with no planned changes. Co-occurring psychiatric disorders are permissible for enrollment.

Exclusion criteria for this study are as follows: (1) pregnant or breast feeding; (2) an unstable medical condition (e.g., a seizure disorder, kidney or liver disease); (3) current diagnosis of substance abuse/dependence; (4) lifetime diagnosis of schizophrenia, autism spectrum disorder, bipolar disorder, or psychosis; (5) evidence of a seizure disorder, kidney or liver disease, pregnant and/or breast feeding; (6) four or more previous sessions of HRT; or (7) currently taking an antipsychotic medication.

Procedures:

The study will consist of three visits over 3 weeks. Visit 1 is a baseline visit to determine eligibility, Visit 2 is a single session of HRT with either DCS or placebo, and Visit 3 is a follow-up assessment to measure change in tic symptoms.

Prior to coming in for Visit 1, interested children and families will complete a brief telephone screen to evaluate eligibility criteria conducted by either the principal investigator or research staff. If children and families appear to meet eligibility criteria, they will be scheduled for a baseline assessment to ascertain eligibility for participation.

At Visit 1 (Baseline), children and parents interested to participate will meet with the PI and other research staff to provide a general explanation of the study including eligibility requirements, study aims, and study procedures. The PI will give the consent forms to the families and explain what the forms mean. Written informed consent will be required from parents and written assent from children. After consent and assent are obtained, children and their parents will complete an assessment battery to determine eligibility, evaluate co-occurring psychiatric conditions, and measure tic symptom severity and related constructs that may take up to 3 hours to complete. An experienced clinician will conduct the following semi-structured clinical interviews with parents and children to identify psychiatric diagnoses, tic severity, premonitory urge presence, most bothersome tics, and global tic severity: the Anxiety Disorder Interview Schedule-Parent and Child Version (ADIS-C/P); the Yale Global Tic Severity Scale (YGTSS); the Individualized Premonitory Urge for Tics Scale (I-PUTS); Hopkins Motor and Vocal Tic Scale (HM/VTS) and the Clinical Global Impression of Severity (CGI-S). Children will also be asked to complete a standardized 10 minute video observational protocol to identify the frequency and severity of tics (Himle et al. 2006). Parents will be asked to complete a

demographic questionnaire, a parent-report of the child's tic severity called the Parent Tic Questionnaire (PTQ), and a rating scale of ADHD severity called the Swanson Nolan and Pelham Scale-4th edition (SNAP-IV). After completing the video observation protocol, children will be asked to complete a child-report of tic severity called the Child Tic Questionnaire (CTQ), a self-report Premonitory Urge for Tics Scale (PUTS) to measure the child's global premonitory urge, and a self-reported rating scale of puberty development called the Peterson Puberty Development Scale (PDS). For female participants who have had first menses, a pregnancy screen will be conducted. Interested participants who meet full eligibility criteria will be invited back to complete Visit 2 (HRT session) approximately 1 week later.

At Visit 2, participants will arrive and will be randomly assigned to receive either a 50 mg placebo pill or a 50 mg d-cycloserine pill. Evaluating clinicians, participants, and the therapist will be blind to randomization assignment, with only the study coordinator and research pharmacy having access to randomization assignment. As d-cycolserine typically takes 1 hour to become active in participants' system, children and adult will be re-administered the following rating scales to evaluate the current severity of the participant's tics, most bothersome tics, and premonitory urge: the CTQ; PTQ, HM/VTS and I-PUTS. Children will then be asked to complete a computer task to evaluate habit learning called the Weather Prediction task. Afterwards, children will complete a session of HRT that will target two tics in treatment as identified by the HM/VTS. After the participant has completed the session of HRT, the participant will be asked to practice the skills learned in the session over the next week and to document practices using a homework monitoring form. The therapist will complete a session summary sheet to evaluate the patient's mastery of the skills within session. After the completion of the HRT session, a standard side effect form will also be administered to the participant to assess for any side effects. Participants will be asked to return 1 week later for a follow-up assessment. Visit 2 may take up to 4 hours to complete.

At Visit 3, participants will complete a battery of tic assessment to monitor change in tic severity. These assessments will be administered by a clinician blind to randomization assignment, and will include the YGTSS, I-PUTS, HM/VTS, and the Clinical Global Impression of Improvement that serves as a global rating of improvement of tics. Participants will also be administered a standard side effect form to monitor for any possible side effects of d-cycloserine. Children will complete a standardized 10 minute video observational protocol to identify the frequency and severity of tics (Himle et al. 2006). Parents will be asked to complete the PTQ to assess parent report of tic severity and a homework compliance monitoring form to evaluate the participant's practice of skills learned in HRT over the past week. Children will be asked to complete the CTQ to assess child-reported tic severity and the PUTS to evaluate their premonitory urge globally. Children will also complete a homework compliance form. This visit may take up to 2 hours. Participants and their families will be collectively compensated $30 for each study visit.

Tests/Measures Administered:

The following measures and tasks will be administered this study.

Clinician Administered:

Anxiety Disorder Interview Schedule-Parent and Child Version (ADIS-C/P; Silverman & Albano, 1996). This is a clinician-administered, structured diagnostic interview based on DSM-IV diagnostic criteria. Diagnoses reflect endorsement of symptoms as well as a severity rating (patient impairment/distress) of at least 4 on a 0-8 scale. The tic disorder section, created

by Dr. Piacentini, will be used to confirm tic diagnoses. The ADIS-C/P is widely used in both research and practice.

Yale Global Tic Severity Scale (YGTSS; Leckman et al., 1989). The YGTSS is a semi-structured interview that examines the presence and severity of motor and phonic tics over the previous week across 5 domains: total motor tics, total phonic tics, total tics, overall impairment rating, and a global severity score. The YGTSS has well-supported psychometric properties (Storch et al., 2005; Leckman et al., 1989).

Individualized Premonitory Urge for Tics Scale (I-PUTS). The I-PUTS is a clinician-administered scale that assess the frequency, intensity and body region of premonitory urges that are associated with tics endorsed on the YGTSS.

Clinical Global Impression – Severity (CGI-S; Guy, 1976). The CGI-S is a 7-point clinician rating of illness severity that is anchored by 0 (no illness) and 6 (extremely severe). The CGI-S will be used as an overall measure of tic severity.

Clinical Global Improvement (CGI; Guy, 1976). The CGI is a clinician-rated measure of treatment response on a 7-point scale ranging from 1 ("very much improved") to 7 ("very much worse"). Response status is defined as a rating of "very much improved" or "much improved" and based on the participant's level of overall tic severity relative to baseline (Visit 1).

Hopkins Motor/Vocal Tic Scale (Walkup et al. 1992). Participants nominated up to five motor and five vocal tics they deemed most bothersome. These tics are rated by a clinician on a 5-point scale that ranged as follows: 0 (none), 1 (mild), 2 (moderate), 3 (moderately severe), and 4 (severe). These ratings incorporated frequency, forcefulness, interference, and subject distress. Participants are also asked about whether a premonitory urge is associated with each bothersome tic.

Adverse Event Review Form. A modified version of the Safety Monitoring Uniform Report Form will be completed at Visit 2 and Visit 3 to monitor for any possible adverse events or side effects from the single administration of d-cycloserine or placebo.

Direct Observation Video Recordings:

Direct Observation of Tics (Himle et al., 2006). An observed tic frequency count will be obtained through partial-interval scoring of a 10 minute video recording of participants. After video observation is collected, raters will record the number of 10-second intervals during which participants have at least one tic. Ten-second intervals are most commonly used in tic studies and this method of scoring has been shown to be highly correlated with total tic frequency (Woods et al., 1996, 2003; Himle et al., 2006).

Computer Tasks:

The Weather Prediction Task (Knowlton, Squire & Gluck, 1994). The Weather Prediction task is a measure of procedural or habit learning that requires gradual acquisition of stimulus-response associations. Participants are asked to predict rain or sunshine based on the presentation of a varying combination of a set of four different cards on a computer screen by pressing one of two letters on the keyboard. Each card is independently and probabilistically related to the

outcomes, each of which occurs equally often. Participants receive positive or negative feedback after each prediction via visual feedback on the computer screen. The task consists of 90 trials lasting approximately 15 minutes. Accuracy (% correct) and reaction time scores across six learning blocks were used as the outcome variables.

Parent Report Forms:

Demographic Form. A demographic form will assess information regarding the participant's age, gender, ethnicity, living situation, parental marital status, parental income, and parental occupational status. Additionally, the form will assess the participant's past treatment history and whether they are have taken medications and for what duration of time. Finally, this demographic form also inquires about the participant's health including whether the participant has an unstable medication condition, is pregnant or breast feeding, and/or has a history of a seizure disorder, kidney disease, or liver disease.

Parent Tic Questionnaire (PTQ, Chang et al. 2009). The PTQ is a 28 item measure comprised of 14 commonly experienced motor tics and 14 commonly experienced vocal tics. Parents are asked to identify whether each of these tics have been absent or present over the past week for their child. For tics that are endorsed over the past week, parents are asked to make a separate rating of the frequency and intensity of the tic on a 1-4 scale. Items are summed separately for motor tics and phonic tics, with all items summed for a total parent-reported rating of tic severity over the past week.

Swanson Nolan and Pelham-4th Revision (SNAP-IV, Swanson, 1992). The psychometrically sound, parent-rated SNAP-IV (Swanson, 1992) provides a dimensional scaling of the *DSM* items for inattention, impulsivity, hyperactivity, oppositionality, and related behaviors. Symptoms are scored by assigning a severity estimate for each item on a 4-point scale.

Parent Reported Homework Compliance. The parent-reported homework compliance form consists of 9 questions that ask about the parent's perception of the child's duration of practice over the past week, and the child's mastery over the skills learned in HRT across settings (home and school).

Child Report Forms:

Child Tic Questionnaire (CTQ). The CTQ is the parallel version of the PTQ, but is reported by the child. The CTQ is a 28 item measure comprised of 14 commonly experienced motor tics and 14 commonly experienced vocal tics. Children are asked to identify whether each of these tics have been absent or present over the past week. For tics that are endorsed over the past week, children are asked to make a separate rating of the frequency and intensity of the tic on a 1-4 scale. Items are summed separately for motor tics and phonic tics, with all items summed for a total parent-reported rating of tic severity over the past week.

Premonitory Urge for Tics Scale (PUTS; Woods et al. 2005). This is a 9-item scale that evaluates the presence and strength of premonitory urges on a global scale, with items being rated on a 1 (not at all true) to 4 Likert scale (very much true). The PUTS has been used in several randomized controlled trials of HRT (Piacentini et al. 2010).

Child Reported Homework Compliance. The child-reported homework compliance form consists of 9 questions that ask about the child's perception of their duration of practice over the past

week, and their mastery over the skills learned in HRT across settings (home and school).

Peterson Puberty Development Scale (PDS). The PDS is an 8-item measure of a child's pubertal development reported by the child. The scale consists of three questions for boys and girls about the development of body hair, the occurrence of a growth spurt, and changes in complexion. Two additional items are asked of girls, one about breast development and the other about the onset of menstruation. Boys are asked about changes in voice and growth of facial hair. With the noted exception of menarche (dichotomy), all of the questions are answered on a 4-point scale (1= has not yet begun, 2= has barely started, 3= is definitely under way, and 4= growth or development it complete). The PDS has been used in randomized controlled trials to assess youth's pubertal development (Walkup et al. 2008).

Therapist Form:

Session Summary Sheet. The session summary sheet is a therapist completed form that identifies the tics targeted in session, and monitors the participants habituation to the premonitory urge across trials (if present) and mastery of competing response skills for each of the two targeted tics in the HRT session.

9. Safety Monitoring Plan:

Definition of adverse events, and serious adverse events
For the purposes of this study, an adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

For the purposes of this study, a serious adverse event is characterized as any adverse drug event (experience) occurring at any dose that in the opinion of the study investigator results in any of the following outcomes: (1) death, (2) life-threatening adverse drug experience, (3) inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours), (4) persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, (5) congenital anomaly/birth defect, and (6) important medical event (IME) that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Procedures will be used to monitor subject safety
Adverse events will be systematically assessed at Visits 2 and 3 using a standardized adverse event review form (i.e., modified version of the Safety Monitoring Uniform Report Form). This will allow study investigators to monitor for any possible adverse events or side effects from the single administration of d-cycloserine or placebo.

Who (list names) will identify, document, and report adverse events?
The study PI will identify and document adverse events when they have been identified during the study.

What is the frequency for review of summarized safety information and who will perform the review?
Any serious, unanticipated problems (e.g., serious adverse events) will be reported to the IRB within 3 working days of study investigators' awareness.

What are the stopping rules with regard to efficacy and safety?

In the event of a serious adverse event, the subject will discontinue study participation and the attending psychiatrist (the prescribing physician) will be notified. The research staff will monitor the participant closely until the adverse reaction remits.

10. Potential Risks of Study Participation

The risks of participating in this project include relatively lengthy psychiatric evaluations, participating in a single session of HRT, and the medication (placebo or DCS).

One potential risk of participating in this project includes discomfort associated with the psychiatric evaluation and administration of rating scales – either due to the discussion of subjectively difficult topics, or due to the length of time required for the interviews and questionnaires. In efforts to minimize subject burden, we only chose measures that were central to study questions and did not overlap considerably with other study measures. With regard to potential discomfort, our experience indicates that most people welcome the opportunity to discuss their experiences with a trained clinician; and any information shared by the subject will be kept confidential. Additionally, we have done our best to minimize subject burden while assessing relevant constructs and maintaining the internal validity of the study. Breaks will be given as much as possible to decrease boredom and physical/psychological discomfort. As well, we will compensate families $30 for each study visit. This compensation will be split equally between parent and child participants.

Another possible risk is that participants may feel subjective distress when learning skills to manage their tics as part of habit reversal training (HRT). This effect is usually very transitory and mild, and though to be a result of the participant gradually habituating to a distressing internal sensation referred to as a premonitory urge. This effect of HRT will not be described as an adverse event, unless a subject or parent specifically descries the reaction as an adverse event of participation. However, in general, participants in randomized controlled trials (RCTs) find HRT to be beneficial in learning to manage their tics, with no significant adverse events reported (Piacentini et al. 2010).

Finally, the potential side effects associated with the administration of DCS include drowsiness, headache, prolonged or momentary dizziness, seizures, confusion, hallucinations, weakness, coma, rash, vitamin B_{12} deficiency and/or folate deficiency (both of which may cause weakness and anemia), liver enzymes increases (which could cause weakness or bleeding), and shaking. However, these side effects are most commonly related with doses greater than 500mg/day and when dosed chronically (versus acutely), which is at least ten times greater than what we propose to administer in this study. DCS has been approved by the Food and Drug Administration for the treatment of tuberculosis for over 20 years, and, as discussed by Rothbaum et al. 2008, single-pill administrations have been associated with no adverse effects. Furthermore, a recent meta-analysis of over 20 randomized controlled trials of DCS-augmentation that included multiple doses of DCS within each trial, identified no greater adverse event profile relative to placebo with as many as 8 trials reporting no adverse events at all. In the event of a moderate or severe adverse event related to the medication, the subject will be withdrawn from the study, the attending psychiatrist (Dr. McCracken will be notified), and the research staff will monitor the participant closely until the adverse reaction remits.

Although not a risk directly associated with d-cycloserine, there is always the chance that a participant may report either the perceived risk of suicidality or suicidality itself. In these cases, standard protocol will be followed. If, during an assessment, research staff determines that a

youth endorses a serious mental health program such as suicidal behavior, referral information and telephone numbers to appropriate community services will be provided. The PI will conduct a risk assessment for suicidal ideation and/or behavior. Although unanticipated, if the detected problem is imminent and of crisis status, the PI will take appropriate immediate action including calling emergency services and/or calling UCLA campus police to escort the youth to the emergency department (on-site at UCLA). These situations will be reviewed immediately with the PI's research mentor (Dr. Piacentini), who is a licensed clinical psychologist.

11. Analysis Plan

Descriptive statistics will be used to characterize the entire sample and two conditions (DCS, placebo). Independent sample t-tests and chi-square tests will be used to examine for between-group differences (DCS versus placebo) for continuous and categorical variables respectively. Although no significant differences in conditions are expected due to random assignment, any significant between group differences will be controlled for during data analysis. Given that co-occurring ADHD and alpha-2 agonists have been found to influence tic severity outcomes to HRT, these will interested a covariates at baseline.

The primary outcome in this study will be the reduction in bothersome tic severity on the HM/VTS for the two tics targeted in treatment. The average score for these two bothersome tics will be interested into a repeated measures analysis of variance (ANOVA), with the covariates of ADHD diagnosis and alpha-2 agonist status at baseline. The diagnosis of ADHD will be identified from the structured clinical interview (ADIS), and alpha-2 agnostic will come from demographic information form. This data will be entered across three assessment visits, with a between group factor of treatment condition (DCS+HRT or PLBO+HRT).

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