Protocol

1. Project Title:

1/2 D-Cycloserine Augmentation of Cognitive Behavioral Therapy for Pediatric OCD

2. Investigator(s):

Eric A. Storch, Ph.D.
Principal Investigator

Adam Lewin, Ph.D.
Co-Investigator

Jessica Morgan, B.A.
Co-Investigator

Anna Jones, B.A.
Co-Investigator

Megan Toufexis, D.O.
Co-Investigator

Tanya Murphy, M.D.
Co-Investigator

P. Jane Mutch, Ph.D.
Co-Investigator

Omar Rahman, Ph.D.
Co-Investigator

Sponsor:
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Other Site Investigators:

Brent Small, Ph.D.
Daniel Geller, M.D.
Sabine Wilhelm, Ph.D.
Daniel Pine, M.D.

3. Abstract:

Obsessive-compulsive disorder (OCD) affects 1-2% of children, runs a chronic course without treatment, and is associated with considerable functional impairment and poor quality of life.
Although most patients with OCD respond to cognitive-behavioral therapy (CBT) or pharmacotherapy with a serotonin reuptake inhibitor (SRI), a substantial number of youth remain symptomatic after receiving these therapies. Pharmacological interventions with SRIs are only moderately efficacious, rarely produce remission, may be accompanied by side effects, and may not be an acceptable intervention to some parents. Medication augmentation strategies such as atypical antipsychotics are often used in children with partial response but have concerning metabolic effects and no systematic supporting efficacy or safety data. Although CBT is the gold standard treatment for pediatric OCD, not all patients benefit and the availability of skilled therapists is quite limited. Thus, there is a critical need for interventions to optimize treatment outcome in pediatric OCD. The primary mechanism in CBT is repeated and prolonged exposure to feared situations while abstaining from OCD rituals. This treatment is based on animal models of extinction of conditioned fears. Basic research on the neural circuitry underlying fear extinction led to the examination of d-cycloserine (DCS), a partial agonist at the NMDA receptor in the amygdala, as an agent capable of enhancing extinction learning. Following successful validation of this strategy in animals, six trials in adult humans – and our NIH-funded pilot study in youth with OCD – provide support for DCS dosing as facilitating extinction learning that occurs during exposure-based psychotherapy. However, experts and agencies responsible for regulating drug indications in the US, including the FDA, recognize that safety and efficacy findings in adults should not be routinely extrapolated to children. The present study further our pilot work on DCS to augment the effects of CBT in children with OCD. We propose a double-blind randomized controlled trial, conducted at two sites, to examine the relative benefit of 10 psychotherapy sessions of which sessions 4-10 will be augmented with weight-adjusted doses of DCS (25/50mg) compared to CBT augmented with placebo. 150 youth (ages 7-17) with OCD will be randomly and evenly assigned to one of the two treatment conditions. The primary outcome will be change in OCD symptom severity assessed by independent evaluators. The study recruitment sites are the University of South Florida (USF) and Massachusetts General Hospital/Harvard Medical School (MGH). USF will provide data management services while MGH will provide pharmacokinetic assays. Our study extends the first report of DCS augmentation in youth with anxiety disorder/OCD by conclusively investigating an innovative research approach that manipulates glutamatergic pathways to mediate improved outcomes of exposure-based psychotherapy based upon a translational model of the neurobiology of OCD. This study will yield clinically important data, which could ultimately improve the treatment of youth with OCD and reduce exposure to potentially harmful medications.

4. Specific Aims:

Primary Aim 1: To determine whether DCS augments the short-term efficacy of CBT to a greater extent than does placebo.

Hypothesis 1A: Patients in the CBT+DCS condition will report a greater reduction in OCD symptoms relative to the CBT+PBO condition at post-treatment.

Hypothesis 1B: Patients in the CBT+DCS condition will exhibit a more rapid reduction in OCD symptom severity than will patients receiving CBT+PBO.

Secondary Aim 1: To determine whether adding DCS to CBT results in greater treatment efficacy relative to CBT+PBO at six month follow-up.

Secondary Aim 2: To examine whether adding DCS to CBT results in improved responder status, remission rates, reduced depressive and anxiety symptoms, improved quality of life and OCD-related impairment relative to CBT+PBO.

Exploratory Aim 1: To explore whether DCS augments CBT differentially for patients who have
been partial responders to past pharmacotherapy interventions.

**Exploratory Aim 2:** To explore whether DCS is associated with hierarchy progress and CBT adherence.

**Exploratory Aim 3:** To explore moderators of treatment outcome including OCD symptom dimensions, demographic variables, severity and duration of illness, comorbidity, and fear extinction learning.

**Exploratory Aim 4:** To obtain pharmacokinetic data documenting individual variability in systemic exposure to DCS using standardized doses by assaying 2-hour post dose plasma levels at EOW 9.

**Exploratory Aim 5:** To collect blood samples, create cell lines and extract DNA for future genetic research, including functional gene studies and sequencing, using results from the Genome-Wide Association study (GWAS) of OCD (MGH is coordinating site for GWAS) to examine specific loci in glutamatergic genes.

5. **Background and Significance:**

Obsessive-compulsive disorder (OCD) among children and adolescents has a prevalence of approximately 1-2%.8, 9 OCD is a significant public health problem, causes impairment in academic, social and family functioning, and left untreated is frequently unremitting into adulthood.10-12 Currently, two treatment modalities have demonstrated efficacy among pediatric OCD patients, namely pharmacotherapy with serotonin reuptake inhibitors (SRIs) and cognitive-behavioral therapy (CBT) with exposure and response prevention (E/RP; see 13 for a meta-analytic review). Several RCTs examining CBT protocols involving E/RP for pediatric OCD have provided strong empirical support.2, 14, 15 Pooled effects suggest that CBT may have some advantage over SRI treatment alone13 leading to the suggestion that children receive CBT alone or with SRI therapy.2, 16

Why Consider DCS Augmentation of CBT for OCD? The available evidence suggests that CBT is among the most efficacious treatments for adult and childhood OCD.2, 17 However, there are several reasons to augment CBT. First, there is clearly room for improvement. In the largest CBT study to date for pediatric OCD (POTS),2 remission rates for youth receiving CBT alone, CBT+SSRI, and SSRI alone were 39%, 53.6%, and 21%, and up to 25% of patients discontinue treatment before completing a 12 week CBT protocol.2, 14, 18 Thus, between 61-79% of youth receiving CBT or SRI monotherapy and 46% of those receiving combined treatment remain symptomatic. Second, there is a shortage of trained CBT providers. Speeding up the rate and improving the degree of recovery could reduce caseloads and allow more people to receive treatment. Third and most relevant, usual pharmacological interventions involving serotonergic medications are efficacious but rarely produce remission,2 may be accompanied by side effects,3, 19 and may not be an acceptable intervention to some parents.4 Even approved treatments may have potentially serious adverse events, such as agitation or suicidal behavior that show inverse developmental trends with increasing risk at younger ages. Clinical efforts to improve response rates in pediatric OCD have employed various augmentation strategies (e.g., atypical antipsychotics, more intensive CBT20). However, numerous issues preclude successful provision of these therapies, including drug side effects (e.g., weight gain, cardiovascular effects), the scarcity of qualified CBT practitioners, and cost.21 Consequently, there is a clear need for additional interventions that are safe and tolerable, more effective (to enhance quality of immediate response and prevent relapse) and more efficient (to accelerate response and reduce the likelihood of noncompliance and premature termination).
Why Augment CBT with a Novel Compound? The evidence that current pharmacologic strategies enhance CBT efficacy has been mixed. Medications for OCD have traditionally targeted serotonergic pathways. Among adults, some studies have suggested benefit for combined CBT and pharmacotherapy relative to CBT alone while others have not. Among youth with OCD, POTS showed an advantage for combined CBT and SSRI relative to CBT alone. However, significant site differences in CBT efficacy leave doubt if combined CBT-SSRI is superior to CBT alone as the Pennsylvania site reported $d=1.6$ for CBT alone and $d=1.5$ for combined treatment while the Duke site found relative equivalence between CBT and SSRI alone. In addition, some youth experience adverse effects with SRI medications that cause treatment discontinuation. Even combined CBT and SRI therapy leave a large number of children with substantial residual symptoms, leading to the use of unproven and potentially harmful medication augmentation trials with limited efficacy, tolerability, and safety data. Current data suggest that antipsychotics and benzodiazepines are frequently prescribed among pediatric OCD patients without supporting pediatric data and strong concerns of adverse behavioral, metabolic, and cardiovascular effects. Taken together, psychopharmacological augmentation may not be clinically indicated or desired by a family, and be associated with safety risks.

Why Study a Medication That Targets Extinction? The search for a reliable pharmacological adjunct to CBT is best aided by an examination of the mechanisms underlying its efficacy. Behavioral therapy for anxiety incorporates exposure to anxiety-producing stimuli with subsequent response prevention. The putative mechanism of exposure is extinction, whereby repeated presentations of a conditioned stimulus (CS), outside the presence of an unconditioned stimulus (US), leads to reductions in the conditioned response (CR). Importantly, extinction represents the learning of new associations (e.g., CS becomes associated with stimuli other than the US) that compete with the former aversive association. Through repeated benign experiences with the feared stimulus, the person develops an accurate cognitive appraisal of the stimulus’ danger.

Why Target the NMDA Receptor? The N-methyl-D-aspartic acid (NMDA) subtype of glutamate receptor is a tetramer consisting of two NR1 subunits and two NR2 subunits (isoforms NR2A–NR2D) that has binding sites for two glutamate molecules, two glycine molecules, and a variety of other modulatory sites. When glutamate is released onto an activated dendritic spine, NMDA receptors are recruited. NMDA receptors have an established role in the induction of many forms of neuroplasticity. This role is best seen at the molecular level in long-term potentiation (LTP), in which an increase in post-synaptic alpha-amino-3-hydoxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors mediates an increase in post-synaptic glutamate response. In sum, glutamatergic activity at the NMDA receptor seems to be critically involved in the neural mechanisms of learning and memory. At the neural level, learning (including extinction) reflects a synaptic association between two or more neurons. During extinction, the neural association is not broken; rather, new neural associations are formed that eventually predominate. Extinction of fear may be mediated by NMDA receptor-dependent LTP-like plasticity within the baso-lateral amygdala (BLA). The evidence supporting this includes: 1) NMDA and AMPA glutamate receptors are postsynaptic to afferent projections in the BLA, 2) NMDA receptor antagonists injected into the BLA block both the acquisition and extinction of learned fear, 3) extinction is facilitated by the injection of the glycine-B partial agonist d-cycloserine (DCS) into the amygdala.

Animal Models of the Effect of NMDA-Related Compounds on Fear Extinction. NMDA receptor antagonists block the extinction of learned fear associations in rats and in humans. In contrast, NMDA receptor agonists may accentuate extinction effects. Several animal studies...
have demonstrated the potential of DCS to enhance learning extinction learning. Walker et al.\textsuperscript{48} found that DCS facilitated extinction of conditioned fear in rats with extinction training, but had no effect in animals without extinction training. A similar paradigm\textsuperscript{49} found DCS administered before or after extinction training enhanced extinction. Extinction was enhanced up to 3 hours after training suggesting that DCS helped consolidate extinction learning during the post-acquisition period. Longer intervals between DCS administration and extinction training were associated with lower benefits. Ledgerwood et al.\textsuperscript{50} found that re-exposure to an US after extinction training did not elicit fear of a previously extinguished CS (known as reinstatement) for the DCS-treated rats, but did for control rats and that DCS-treated rats were less fearful than controls to a second CS that had not been extinguished.\textsuperscript{51} Clinical implications for OCD treatment of these animal studies\textsuperscript{48-51} and data demonstrating the cognitive enhancing properties of DCS include: (1) enhancing NMDA receptor functioning via acute DCS dosing might facilitate extinction of conditioned fear by enhancing associative learning that takes place in exposure therapy, (2) DCS administration may prevent relapse after re-exposure to a previously extinguished event and maintain treatment gains through consolidation of newly formed associations, and (3) the effects of DCS on associative learning may generalize to other non-extinguished fear-evoking stimuli. Since anxiety disorders are characterized by a reduced ability to extinguish learned fears\textsuperscript{52} and extinction of conditioned fear is central to exposure therapy,\textsuperscript{50, 53, 54} pharmacological agents that enhance associative learning that occurs in psychotherapy have very important clinical benefits in the effectiveness of exposure-based psychotherapies.

**Human Trials using DCS.** Given that extinction of conditioned fear is central to exposure-based CBT\textsuperscript{55}, DCS augmentation of exposure therapy has been tested in several adult anxiety disorders. Ressler et al.\textsuperscript{56} randomized 27 adults with acrophobia to either placebo (n=10), 50mg (n=8), or 500mg (n=9) DCS 2-4 hours before 2 virtual reality exposure sessions separated by 1-2 weeks. There were no outcome differences between the 50mg and 500mg groups, so the groups were combined. Overall, the DCS condition was associated with significantly greater reductions of acrophobia symptoms at post-treatment and 3-month follow-up. Hofmann et al.\textsuperscript{57} randomized 27 adults with social phobia to 50mg DCS or placebo taken 1 hour prior to 4 weekly exposure sessions. The DCS+therapy condition experienced greater improvements relative to placebo+therapy on clinician-rated and self-reported social anxiety at post-treatment (d=0.73-0.98) and 1-month follow-up (d=0.69-1.43). Guastella et al.\textsuperscript{56} replicated Hofmann et al.\textsuperscript{57} in 56 adults with social phobia. Relative to the placebo arm, participants randomized to DCS showed a greater reduction in social anxiety symptoms from pre- to post-treatment; effect sizes were generally moderate to large (d=0.42-0.70). Finally, Otto et al.\textsuperscript{59} randomized 31 adults with panic disorder to 50mg DCS or placebo taken 1 hour prior to 3 exposure sessions. Large effect sizes were shown in favor of DCS at post-treatment (d=1.11) and 1-month follow-up (d=0.88) on measures of symptom severity and clinically significant change status (77% vs. 33%).

Three randomized, double-blind, placebo-controlled trials of DCS versus placebo augmentation of exposure and response prevention (E/RP) therapy in adult OCD samples have been published. Wilhelm et al.\textsuperscript{60} randomized 23 participants to either placebo (n=13) or 100mg DCS (n=10) one hour before each of 10 E/RP sessions. Group differences emerged at mid-treatment in favor of the DCS arm (d=1.17), but were not statistically significant at post-treatment and one-month follow-up. However, non-significant findings at end point were likely due to limited power as between-group effect sizes were large and in favor of DCS (d=0.63 and 0.66 at post-treatment and follow-up). Response to E/RP was more than two times faster in the DCS group, with most effect occurring in the first half of treatment.\textsuperscript{61} At post-treatment, those randomized to
the DCS group evidenced significantly fewer depressive symptoms than did those randomized to placebo ($d=0.99$). In Kushner et al.\textsuperscript{62}, 32 participants received either placebo ($n=17$) or 125mg DCS ($n=15$) 2 hours before each of 10 E/RP sessions. Relative to the placebo arm, the DCS arm had significantly more rapid reductions in obsession-related fear ratings on the Subjective Unit of Distress Scale (SUDS; $d=0.77$). The DCS group required two fewer sessions than did the placebo group to attain a $>50\%$ reduction on all hierarchy items for SUDS ratings, but groups did not differ in SUDS or Y-BOCS scores at post-treatment. Finally, Storch et al.\textsuperscript{63} randomized 24 adults with OCD to either placebo ($n=12$) or 250mg DCS ($n=12$) 4 hours before each of 12 E/RP sessions. No significant group Y-BOCS differences existed at post-treatment ($d=-0.19$), and the two groups did not differ significantly in slope of reductions. However, Storch et al.\textsuperscript{63} dosed DCS in higher doses (250mg) and timed DCS dosing 4 hours before E/RP sessions; these methodological differences likely explain the null findings as the critical period of DCS augmentation is hypothesized to take place not during the exposure session, but afterward during the period of memory consolidation.\textsuperscript{60} In sum, the 6 positive trials used similar methodologies and yielded large effect sizes relative to an exposure-therapy-alone condition.

**DCS Work in Children with OCD.** In a collaborative effort between USF funded by NIMH (PI: Storch; MH076775) and MGH funded by the Pediatric OCD Research Program (PI: Geller; philanthropic), we examined if weight-adjusted DCS (25 or 50mg) enhanced CBT efficacy in 30 youth with OCD (ages 8-17).\textsuperscript{1} The study design was a randomized, double-blinded, placebo-controlled augmentation trial examining CBT+DCS versus CBT+Placebo (15 per group). Patients received 10 CBT sessions; the first 3 were non-E/RP sessions (i.e., psychoeducation) while the last 7 were E/RP sessions paired with DCS or placebo taken 1 hour before. Assessments were conducted at baseline, mid-treatment, and post-treatment, and there were no baseline group differences on outcomes. Compared to the CBT+Placebo group, youth in the CBT+DCS arm showed reduced OCD symptoms at post-treatment on the CGI-Severity rating ($d=0.97$, $p=.02$) and CY-BOCS ($d=0.66$, $p=.09$). Although not statistically significantly different, effect sizes of DCS at mid-treatment were moderate in strength on the CGI-Severity rating ($d=0.53$, $p=.17$) and CY-BOCS ($d=0.41$, $p=.13$). While the trend-level significant group difference on the post-treatment CY-BOCS and non-significant mid-treatment effects were likely due to insufficient power, the effect size is notable when considering that the CBT+DCS arm was compared to an active treatment arm (CBT+Placebo). A $d=0.5$ represents a clinically meaningful effect when comparing two active treatments\textsuperscript{64}, while Kraemer et al.\textsuperscript{65} suggest that an effect size of 0.5 provides an optimal balance between efficacy and clinical significance. The average CY-BOCS reduction for the CBT+DCS arm was 72% versus a 58% symptom reduction for those randomized to CBT+Placebo. No statistically or clinically meaningful differences were found for self-reported depressive or anxiety symptoms. No participant reported adverse effects related to DCS or placebo. No between group differences in assayed lab values (e.g., CBC, metabolic panel) were found at post-treatment. Treatment and assessments were conducted per protocol consistent with the goals of pilot work\textsuperscript{66}, and there were no site differences in findings. This study is the only report of DCS augmentation among a pediatric clinical population to date and has established the clinical trials infrastructure between USF and MGH.\textsuperscript{1} This study was designed to pilot this work and develop the capabilities of the research team, however it was not sufficiently powered to conclusively demonstrate efficacy. While preliminary, these findings and the reasons noted below in Innovation indicate further examination of DCS among pediatric OCD patients in a definitive study.

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6. Research Plan:

Overview. The proposed investigation is a two-site controlled trial of DCS augmentation of CBT in youth with OCD aged 7-17 years. We will randomly assign 200 patients (100 at each site) to CBT+DCS or CBT+PBO in a 1:1 allocation. Assessments will occur at Screening, Baseline, before randomization (before CBT Session 4), Mid-treatment, Post-treatment and 1, 3, and 6-month follow-up.

Initial Evaluation Phase. Patients will be recruited through the normal patient flow at the Rothman Center for Neuropsychiatry and Massachusetts General Hospital. Individuals who meet basic eligibility requirements during a phone interview (Gate A) and remain interested will be invited for a Screening visit (Gate B), where the site PI or Co-I (i.e., Dr. Murphy) in his absence will obtain informed consent from the parent and assent from the child. Families will have the option to decline participation in the genetic testing but still participate in the overall study. Consented youth will have a screening assessment thereafter.

Assessment Timeline. Seven days after the Screening visit (Week 0), patients who remain eligible will be scheduled for a Baseline assessment (end of week [EOW] 1; Gate C). Thereafter, patients will receive 10 CBT (sessions 4-10 involve E/RP) sessions over 8 weeks (EOW 2-9). The CY-BOCS will be administered at every second session, and primary and secondary outcomes will be administered prior to randomization (before CBT Session 4). At the final CBT session (EOW 9), blood will be drawn for PK study and to assess laboratory values (lab values will be reviewed with parents at EOW 10 Post-treatment assessment). At EOW 10, patients will complete the Post-treatment assessment. At EOW 14, 22, and 34, youngsters will complete 1, 3, and 6-month Follow-up assessments. Consistent with other NIH funded multimodal trials, families will be seen every four weeks for booster sessions during the Follow-up period. Those with insufficient treatment response at Post-treatment will be withdrawn and offered best clinical practice treatment.

Inclusion/Exclusion Criteria

Inclusion criteria: 1) Outpatient youth with OCD between the ages 7-17 years and a CY-BOCS≥16 (moderately severe). Only youth who meet OCD diagnostic criteria (assessed via all available information and confirmed by the caseness panel) with 100% consensus will be included. OCD must be determined to be the primary or co-primary diagnosis using the KSADS-PL based on all available information. 2) Child has a Full Scale IQ≥85 as assessed on the WASI (within 90% CI). 3) English speaking. Exclusion criteria: 1) Receiving concurrent psychotherapy or a past adequate trial of CBT for OCD. Families will have the option of discontinuing such services to enroll in the study. 2) New Treatments: Initiation of an antidepressant within 12 weeks before study enrollment or an antipsychotic 6 weeks before study enrollment. No new alternative medications, nutritionals or therapeutic diets within 6 weeks of study enrollment. 3) Established Treatment changes: Any change in established psychotropic medication (e.g., antidepressants, anxiolytics, stimulant, alpha agonist) within 8 weeks.
weeks before study enrollment (6 weeks for antipsychotic). Alternative medications must be stable for 6 weeks prior to baseline. Any medications must remain stable during treatment; downward adjustments due to side effects may be acceptable. For Exploratory Aim 1, we will use the definition of partial response used in the NIH-funded POTS-II trial. Briefly, patients must have had at least three weeks of stable OCD symptoms at a therapeutic SRI dose; or experienced adverse effects related to a dosage adjustment; or had a flat dose-response curve for one dose increment above the minimum expected starting dose. A caseness panel consisting of Drs. Geller (MGH PI) and Murphy will determine if a child has received an adequate dose using procedures delineated in Freeman et al. and Geller et al. (a) Current clinically significant suicidality or (b) individuals who have engaged in suicidal behaviors within 6 months will be excluded and referred for appropriate clinical care. 5) DSM-IV conduct disorder, autism, bipolar, schizophrenia or schizoaffective disorders; or substance abuse in past 6 months using all available information. 6) Youth with hoarding symptoms due to difficulty in implementing E/RP tasks. Hoarding OCD may be conceptually and genetically different from other subtypes, and may be excluded from OCD in the DSM-V. 7) Weight less than 25.0 kg. 8) Epilepsy, renal insufficiency, and current/past history of alcohol abuse (DCS is contraindicated). 9) Pregnant or having unprotected sex [in females] as the effects of DCS on pregnancy are unknown. 10) Presence of a significant and/or unstable medical illness that might lead to hospitalization during the study. 11) Known DCS allergy.

Procedures

Randomization. Subjects will be randomized before CBT Session 4 (before DCS/PBO and E/RP is initiated) to receive DCS or PBO in a 1:1 ratio, and will be randomly assigned to a CBT therapist. Randomization will be computer generated and not revealed to the IEs. Primary and secondary outcomes measures will be assessed prior to randomization before CBT Session 4.

Cognitive-Behavioral Therapy. Consistent with our NIH-funded pilot trial and other studies that have used a relatively truncated treatment course, all patients will receive 10 sessions of therapy over 8 weeks using the evidence-based CBT protocol in POTS. Sessions 1-4 will be held twice weekly; sessions 5-10 will be held on a weekly basis. Sessions 1-3 do not include exposures and are devoted to psychoeducation, cognitive therapy, and hierarchy development. Sessions 4-10 involve E/RP exercises specific to each youth. The manual provides sufficient flexibility to accommodate differing developmental needs as a function of participant age (e.g., simplified cognitive therapy, increased parental involvement) and address maladaptive parent-child interactions (e.g., accommodation). Consistent with others, an abbreviated CBT protocol was chosen over a full protocol because: 1) it derives from our basic hypothesis regarding enhanced fear extinction using DCS; 2) it conforms to our tested pilot protocol which yielded promising initial results; 3) an abbreviated protocol, if effective, will reduce patient, family and therapist burden, optimize current treatment, and improve overall compliance; 4) it would lend itself well to dissemination to naturalistic clinical settings.

D-Cycloserine. The site psychiatrist will provide blinded medication management (DCS or PBO) to patients at 3 sessions (Baseline, EOW 6 [which corresponds to 4 E/RP sessions paired with DCS/PBO and approximate midpoint of active treatment], and Post-Treatment). DCS/PBO will be distributed by the study pharmacy to the research coordinator before CBT Session 4. Study medications will be stored on site (in secure, temperature-controlled cabinets with a daily temperature log [~72 degrees]), and administered by the research coordinator 1 hour prior to sessions 4-10. Time of administration will be logged. Medication management sessions will last

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~30 minutes and focus primarily on medication related issues (e.g., tolerance, side effects), health problems, interval illness, adherence, and concomitant medications (e.g., over-the-counter). Sessions will not include putative CBT ingredients.

**DCS Dosing.** D-cycloserine will be encapsulated by the respective site research pharmacy into 25mg with identical placebo capsules. Youth will take (one or two) DCS or identical PBO capsule one hour before sessions 4-10 only (E/RP exercises are not conducted in sessions 1-3) in the presence of a research coordinator to ensure compliance. Having the coordinator administer DCS/PBO ensures compliance and a more exact post-dose sampling time frame for PK assay. During the one-hour interval, relevant measures (e.g., CY-BOCS, Harm Form, etc.; see 6.2.b.1.) or vitals will be administered or the child will engage in appropriate activities (e.g., snack). To date, the literature on DCS dosing has been in adults, or children with conditions other than OCD/anxiety. For example, Posey et al. administered DCS in ascending dosages of 0.7, 1.4, and 2.8 mg/kg/day in a chronic format to youth with autism, and found minor adverse effects in two children at the highest dosage only. A 0.7mg/kg dosage corresponds with dosages found to be effective in adult studies (50mg/estimated average adult weight of 70kg=71mg/kg). In addition, data in adults indicate a lack of benefit with higher DCS doses, i.e., 250mg or 500mg. Accordingly, doses for the present study will be approximately 0.7mg/kg. Specifically, two dosing levels will be used, based upon weight ranges, to ensure comparable mg/kg levels: children weighing between 25-45kg will be given a dosage of 25mg (~0.56-1.0 mg/kg/day), and children ≥46kg will be given 50mg provided in two 25mg capsules (~0.50-1.08mg/kg/day).

**Timing of administration.** The choice to use DCS in an acute fashion rather than chronically is based on several factors. First, there may be significant compensatory changes in the NMDA receptor complex (i.e. down-regulation) following chronic administration. Some animal data suggest that the NMDA receptor can become desensitized following prolonged DCS exposure. Second, several clinical trials that have given DCS chronically have failed to show efficacy with comparative animal trials suggesting no additional benefit to chronic dosing. Third, while DCS offers a relatively low adverse effect profile at chronic doses, the adverse event profile is almost negligible when dosed acutely.

**Masking.** All treatment received will be double-masked to subjects, their guardians, and the research staff involved in adjusting study treatments or evaluating treatment response. However, the investigational drug service at each site will maintain records of medication assignment that are accessible to authorized staff.

**Safety Monitoring.** Laboratory tests and physical examination will be conducted at Screening (EOW 0) and after the final CBT session (EOW 9). We chose to administer final laboratory safety tests and physical exam with PK assays after the final CBT session to minimize venipunctures. At EOW 6, each site psychiatrist will conduct a physical exam and interview (no labs). Dr. Geller will prescribe medication for the MGH subjects, and will oversee medical and safety aspects of the entire study; Dr. Murphy will prescribe medication and oversee the medical aspects at USF. Vital signs will also be completed at each visit. Adverse effects (AE) will be systematically reviewed at each psychiatrist visit using the Safety Monitoring Uniform Report Form, a semi-structured guide to assess AEs. The physician will also include a general inquiry about health, other medications, and visits to medical providers. The psychiatrist will meet with the patient between scheduled visits in the event of an AE (blind will be broken for
Table 1. Study Visit and Assessment Schedule.

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<th>Procedures</th>
<th>Screening Week 0</th>
<th>Baseline EOW 1</th>
<th>Before CBT Session 4</th>
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* Administered every second session. ** Labs are obtained at EOW 0 and EOW 9. PK assay conducted at EOW 9. This includes a urine drug screen which is obtained at Screening visit.

CBT Therapist Training. Postdoctoral clinical psychology fellows or junior faculty with at least one year of experience in CBT for pediatric OCD, under the direct supervision of Drs. Storch (USF) or Wilhelm (MGH), will provide CBT to participants. Therapist training will include the attendance of a two-day training workshop, advanced guided reading of the protocol, observing standardized videotapes of the PIs conducting treatment according to this protocol, and completing at least two training cases with full integrity checks under supervision.

Psychopharmacologist Training. Training will consist of attendance at a one-day training workshop that details the medical component of the trial. Since the psychiatrist (Drs. Geller and Murphy) will not provide other treatment during the protocol, a more detailed training is not required.

CBT Integrity. Treatment integrity will be standardized and closely monitored through the use of a treatment manual, ongoing cross-site supervision, and regular rating of audiotaped sessions. Specifically, the following steps will be taken. First, CBT will follow the POTS manual with an Adherence and Competence Checklist used in that study and in Storch et al. To increase protocol adherence and verify the adequacy of the treatment delivered, all clinicians will complete routine forms with the content of each session (Session Summary Sheets). Second, supervision and team meetings will be conducted at each site on a weekly basis. Weekly cross-site conference calls under Dr. Storch’s direction will be held with study therapists to ensure high quality CBT. Drs. Storch and Wilhelm will be available for consultation with each other regarding the CBT protocol and as needed supervision. Dr. Wilhelm will provide on-site supervision at MGH. Third, the integrity and quality of CBT sessions will be assessed by rating audiotaped sessions. To avoid the possibility that periodic spot checks may alter the therapists’ behavior, all intervention sessions will be audiotaped (with subject consent) and 20% of tapes will be randomly selected for rating by the USF site under Dr. Storch’s direction. Trained raters will rate each audiotape for adherence to the respective treatment manual. Fourth, the therapist will rate the degree of patient effort and homework compliance on a 5-point scale after each session (Patient adherence to homework, and exposure and ritual prevention will be tracked separately).
Tests/Measures Administered

Questionnaires and tests will consist of clinician-administered measures. The following is a list of the tests that are specific to the current study and will be administered to participants:

An independent evaluator who is not involved in the patient’s treatment will administer the following:

Clinician-Rated Measures.

KSADS-PL. The KSADS-PL\textsuperscript{135} is a clinician-administered diagnostic interview for DSM-IV childhood disorders. This will be administered at EOW0 to both parents and children, and clinical judgment used to determine diagnoses based upon combined reports.

CY-BOCS. The CY-BOCS\textsuperscript{136} is a psychometrically sound \textsuperscript{2, 118, 120, 136, 137} clinician-rated interview assessing OCD symptom severity.

Clinical Global Impression-Severity (CGI-S). The CGI-S\textsuperscript{138} is a widely used 7-point clinician rating of clinical severity.

Clinical Global Impression-Improvement (CGI-I). The CGI-I \textsuperscript{139} is a 7-point rating of treatment response anchored by 1 (very much improved) and 7 (very much worse).

Children’s Depression Rating Scale-Revised (CDRS). The CDRS-R\textsuperscript{140} is a semi-structured child interview to assess depression severity.

Family Accommodation Scale for Obsessive-Compulsive Disorder Interviewer Rated (FAR-IR). The FAR-IR is a semi-structured interview that assesses the extent to which relatives of patients with OCD engage in 12 types of accommodating behaviors.

Parent and Child Measures.

Child Obsessive Compulsive Impact Scale (COIS). The COIS-C/P\textsuperscript{11} are 56-item, child- or parent-report measures, which assess OCD-related impairment.

Columbia Impairment Scale (CIS). The CIS\textsuperscript{142} are 13-item youth- and parent-report scales that assess impairment in several domains of functioning (e.g., social, school).

Pediatric Quality of Life Inventory (PedsQL). The PedsQL consists of parallel child and parent-proxy measures of children’s QoL\textsuperscript{143}

Youth-Rated Measures.

Obsessive-Compulsive Inventory-Child Version (OCI-CV). The OCI-CV\textsuperscript{144} is a 21-item self-report measure designed to assess varied OCD symptom dimensions that are relevant for Exploratory Aim 3.

Multidimensional Anxiety Scale for Children (MASC). The MASC\textsuperscript{145} is a psychometrically sound 39-item self-report questionnaire that assesses symptoms of general, social, and separation anxiety.
Obsessional Belief Questionnaire– Child Version (OBQ): The OBQ is a 44 item scale that assesses the child's thoughts and beliefs.

Metacognitions Questionnaire – C (Metacognitions): The Metacognitions is a 24-item scale that also assesses the child’s thoughts and beliefs.

Parent-Rated Measures.

Child Behavior Checklist (CBCL). The CBCL is a 118-item scale that assesses behavioral and emotional functioning across a variety of domains (e.g., Internalizing, Externalizing).

Demographics Form: This is provides a detail history of the child's development and medical history to date.

PNGU MEDICAL QUESTIONNAIRE – PARENT ON CHILD VERSION (PNGU): The PGNU is a parent questionnaire focusing on the child’s personal and family medical history.

Satisfaction/Adherence/Fidelity Measures.

Client Satisfaction Questionnaire (CSQ-8). The 8-item CSQ-8 is a measure of general satisfaction with services. Parents will complete this at EOW10.

Therapist Alliance Scale–Child/Parent Reports (TAS-C/P). The TAS-C/P are 8-item measures of youth and parent affect toward the therapist.

Expectancy Rating Questionnaire (ERQ). The ERQ will be given to parents to assess treatment expectancy and credibility.

Assessment of Fear Extinction. A novel experimental paradigm of fear conditioning/extinction paradigm will be computer-administered at EOW 1. Three trials are collected over 30-minutes: pre-acquisition, acquisition, and extinction. During the pre-acquisition phase, children are presented with two neutral stimuli for 8 seconds each (i.e., pictures of two adult female faces). Following habituation, participants view these same two faces, but one face is paired with a moderately aversive stimulus (i.e., a brief 95 dB scream, the unconditioned stimulus [UCS]) over 8 trials while the other is not. This is followed by an extinction phase, consisting of 12 presentations of each female face without the UCS. Subjects indicate on a 10-point likert scale the degree to which they feel afraid of the varied stimuli. Dr. Daniel Pine of the NIMH will supervise and instruct the research team in the administration and interpretation of this task.

Pharmacokinetic assay. At EOW 9 coinciding with the venipuncture for final safety assessment, a further 10ml of blood will be drawn into heparinized (green-top) tubes. The samples are centrifuged, and the plasma separated and frozen at -20°C until assay. In younger children, smaller volumes can be used (5ml). Samples will be stored on site at -20°C and shipped quarterly on dry ice for processing following procedures delineated in David et al. using instrumentation at Dr. Greenblatt’s lab to do the plasma analyses.
Safety Monitoring. The physical examination and laboratory tests collected by trained phlebotomists or site physician (CBC, metabolic panel) will be conducted at EOW 0 and EOW 9 (urine toxicology and pregnancy test EOW 0 only). A full discussion of safety monitoring is in Protection Against Risks.

Rater Training. All symptom oriented assessments will be conducted by highly trained blinded raters. Precautions taken to maintain the IE blind include: a) subjects and their families will be provided with both written and verbal reminders before each assessment to not disclose treatment-identifying information to the IE. b) IEs will not attend CBT supervision meetings, and will be trained to avoid any discussion of treatment with families–focusing only on outcome measurement. c) Use of matching DCS and placebo. Under the direction of Dr. Geller, MGH will also serve as the primary quality assurance site for all IE measures. They will hold twice-monthly conference calls with USF and MGH IEs. To ensure cross-site consistency, 20% of IE audiotaped interviews per year will be blindly reviewed by the project coordinator under Dr. Geller’s supervision to assess inter-rater reliability and rater drift.

DNA Collection. Subjects unwilling to provide blood may instead give saliva, which will be sent to the NIMH OCD repository at Rutgers where DNA will be extracted and, from blood samples, lymphoblastoid cell lines established.

Analytic Plan

Specific Analyses for the Individual Study Aims: Aims 1-3: For Primary Aim 1, we will model OCD symptoms continuously using the CY-BOCS as the dependent measure. For Hypothesis 1A, we will employ an ANCOVA with treatment group (CBT+DCS, CBT+PBO) as the between-subject factor and CY-BOCS scores at the post-treatment assessment serving as the outcome and CY-BOCS scores from the pre-randomization assessment (i.e., before CBT Session 4) as covariates to control for differences at the randomization step. For Hypothesis 1B, a mixed effects model with treatment group (CBT+DCS, CBT+PBO) as the between-subject factor, time (EOW5 through EOW10) as the within-subject factor and a group x time interaction will be computed. Scores from the pre-randomization assessment will be included as a covariate to ensure that differences prior to randomization are accounted for in the change scores during active treatment. A significant group x time interaction would indicate that changes in symptoms vary as a function of group status. Linear and quadratic effects of time, and their respective interactions with group, will be included in this analysis and will allow us to draw conclusions regarding the nature of the change in symptoms for both groups. For Secondary Aims 1 and 2, continuous variables will be modeled using the ANCOVA analyses described above and for dichotomous outcomes (e.g., CGI), remission and response, we will use logistic regression. For Secondary Aim 1, scores from the six month follow-up will serve as the outcome, whereas scores from the post-treatment assessment will serve as the outcome in Secondary Aim 2. Scores at the pre-randomization assessment (i.e., before CBT Session 4) will serve as covariates, where appropriate, and group (CBT+DCS, CBT+PBO) will serve as the main predictor. Exploratory Aims 1-5: For Exploratory Aim 1, we will include an additional between subjects variable (treatment history status) to the analyses described above to determine whether previous treatment history status might moderate the CBT-DCS intervention effects. For Exploratory Aim 2, we will evaluate the extent to which differences are present in adherence or hierarchy progression as a function of intervention group using logistic regression analyses. For Exploratory Aim 3, moderation will be modeled by including interactions between treatment group and potential moderator variables discussed in Assessment of Moderators (i.e., OCD symptom dimensions, demographics, illness severity/duration, comorbidity [e.g., tics, ADHD, disruptive behavior, depression], and fear.
extinction) in the models described above for 1A. For Exploratory Aim 4, between group (CBT+DCS, CBT-PBO) differences using ANOVA will be conducted on plasma levels of DCS to confirm that group assignments are accurate. Mediation of treatment response by plasma levels of DCS will be examined using standard mediation analyses in regression with clinical outcome at EOW 10 serving as the dependent variable, treatment group as the predictor, plasma DCS at EOW 9 as the mediator, and the clinical outcome at the pre-randomization assessment (before CBT Session 4) serving as a covariate to control for differences at randomization. Bootstrapping will be employed to estimate the indirect effect of treatment group to clinical outcome through DCS plasma levels. Exploratory Aim 5 involves sample collection only; no analyses are required for this proposal.

Power Analyses and Sample Size Considerations: We will enroll a total of N=150 subjects, randomizing 75 to each of the CBT+DCS and CBT+PBO arms. This sample size achieves sufficient power for the primary and secondary aims outlined above, while conservatively allowing for significant attrition. We anticipate a 15% attrition at the end of the acute phase of treatment resulting in 128 subjects (64 per group) and an additional 15% attrition at the 6-month follow up point (n=54 per group). With this design, a two-sample t-test has 80% power to detect a difference in means between any two groups of $d=.49$ SDs at the end of acute treatment and $d=.54$ at the 6-month follow-up point, just above a standard medium effect size using Cohen. These effect sizes are considerably smaller than those reported previously, indicating that our study is powered sufficiently. Moreover, calculations are conservative as they ignore the added power gained from our repeated measures design. Using conventions outlined by Diggle et al., a final sample size of 54 per group would allow us to detect a 20% difference in the slopes of the repeated measures over a minimum of three measurement occasions. For comparisons that involve more repeated measures, the minimum difference in slopes is even smaller. Thus, this study is well powered to detect these effects. For categorical outcomes, the 6 month follow-up is sufficiently powered to detect differences of 20% between the intervention and control group. Thus, we have adequate power to detect the expected differences at individual time points.

Attrition: Dropout that is differentially associated with outcomes could compromise valid treatment comparisons. We will attempt to identify possible sampling biases by performing multiple logistic regression analyses on dropout using measures of clinical status at the pre-randomization assessment (before Session 4) or prior to dropout as covariates. If warranted, we will use imputation and propensity score approaches to handle bias problems. Every effort will be made to prevent dropouts/missing data using an ASAP, or to complete relevant assessments for patients who drop out.

7. Potential Discomforts and Risks:

The risks of participating in this project include relatively lengthy psychiatric evaluations, participating in psychotherapy, blood draw for lab, pharmacokinetic and genetic assays, and the medications (placebo and DCS). As detailed below in the ‘Protection Against Risk’ section, our adverse events monitoring strategy includes an initial screening of any baseline adverse effects (AEs) by the project coordinator when they provide the DCS for the child at sessions 4-10. In the presence of a significant AE(s), the project coordinator will notify the site psychiatrist if possibly medication related or therapist if related to therapy. The treating clinician reviews the AE report and documents the AE, its severity and association with study treatments, and all
actions taken by the study team. Training in the collection and coding of adverse events will occur at the study start-up meeting to standardize data collection and maintain quality assurance of these procedures for all clinicians.

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. We recognize that child participants must complete a number of measures that were chosen to assess a range of constructs that we believe may be impacted by the intervention or help understand (i.e., moderate) treatment outcome. 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 each for the Screening (EOW 0), Mid-treatment (EOW 6), and Post-treatment (EOW 10) assessments, and $50 each for the three follow-up assessments ($240 total). This compensation will be split equally between parent and child participants.

Drawing blood at the Screening and EOW 9 visits requires venipuncture and is associated with the momentary discomfort of the needle stick; however, a local anesthetic cream will be offered to the subject to minimize this discomfort. The risks of venipuncture include discomfort at the site of puncture; possible bruising and swelling around the puncture site; rarely, an infection; and, uncommonly, faintness.

A computer-administered fear conditioning paradigm will be conducted where children learn to associate an aversive unconditioned stimulus with a paired conditioned stimulus (CS+) but not an unpaired conditioned stimulus (CS-). The methodology associated with this paradigm has been shown to be ecologically-valid and well-tolerated by anxious youth, while avoiding the safety and ethical issues related to more aversive unconditioned stimuli (e.g., electric shocks). At the onset of the task, which takes place at a computer terminal in a private room, youngsters will be told: “You will see pictures of two women on the screen. Please watch the pictures while they are on the computer screen. While you are watching the pictures, you will see a mildly unpleasant picture of a person and an unpleasant sound”. Youth will then be told they may discontinue the study procedures at any point if they desire by simply telling the investigator or informing their parent. In this paradigm, there are three trials over a 30-minute period. In the first phase, children are presented with two neutral stimuli (i.e., pictures of two adult female faces). They view four pictures of each of the two different female faces, totaling 8 presentations. In the next phase (habituation), youth view these same two female faces, but one face is paired with a moderately aversive stimulus (i.e., a loud but brief 95 dB scream, the unconditioned stimulus [UCS]) over 8 trials while the other female is not paired with an aversive cue. In the final phase (extinction), 12 presentations of each female face are given without the loud noise. Subjects indicate on a 10-point likert scale the degree to which they felt afraid of the varied stimuli.

Increased anxiety and subjective distress is commonly acknowledged as an appropriate and expected reaction to psychotherapies such as CBT that are aimed at anxiety reduction. This effect is usually very transitory and mild, and is thought to be a result of the patient gradually stopping his or her avoidance of anxiety provoking situations while simultaneously allowing one’s self to approach and/or think about these situations. If noted or described to the therapist (e.g., on CBT homework forms, during the course of discussion), this effect of treatment will not be described as an adverse event. The exception to this would be cases whereby a subject or
parent specifically describes the reaction as an adverse effect of participation. In such cases, CBT therapists can make certain adjustments to the pace or intensity of therapy (e.g., do a simpler exposure exercise; do guided, therapist-assisted exposures) until the patient is ready to or asks to approach the anxiety-provoking stimuli again.

The potential side effects associated with the administration of DCS include drowsiness, headache, prolonged or momentary dizziness, seizures, confusion, hallucinations, weakness, coma, rash, vitamin B₁₂ 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 Rothbaum¹５⁷, single-pill administrations have been associated with no adverse effects. Our pilot study in youth witnessed no DCS (or placebo) related adverse effects or abnormal laboratory values.¹ As well, no significant DCS-related adverse effects have been reported in any of the adult trials that used doses ranging from 100-250mg.⁵⁶-⁶⁰, ⁶², ⁶³ The use of DCS at isolated doses of 25-50 mg (as in this study) does not appear to be associated with significant emergent adverse effects.

There is a small risk that DCS may make OCD symptoms worse. However, as noted above, the published reports using DCS together with exposure therapy have found few DCS related side effects. Of the side effects reported, none included worsening of symptoms. Within our own work in child and adult OCD patients, worsening of symptoms has not occurred in any patient that was linked to DCS. In extant child trials, DCS has not been associated with increased anxiety symptoms (e.g.,¹, ¹₂⁷). For example, in a trial of children with autism,¹₂⁷ 12 subjects with a mean age of 10.0 years (SD=7.7, range=5.1-27.6) completed an eight-week trial in which each was administered three different DCS doses during three two-week periods (0.7, 1.4, and 2.8 mg/kg/day). Only two subjects experienced adverse side effects (transient motor tic, increased echolalia) at the highest dosage. Further, end-of-study physical examination and laboratory values were not significantly different from pretreatment. Based on this, our pilot work in youth,¹ and other reports,⁵⁷-⁶⁰, ¹⁵⁸ acute dosing DCS at the proposed levels is unlikely to be associated with significant adverse effects and unlikely to be associated with worsening of OCD symptoms.

In the event of a moderate or severe AE related to the medication, the subject will be withdrawn from the study and clinical staff will follow the patient closely until the adverse reaction remits. In the event of minor side effects (e.g., mild headaches), the medication may be maintained at the current dose levels/schedule based upon clinical judgment of the PIs/Co-Is who will be available 24/7 via pager for emergency calls.

During the Follow-up phase, all of those who have responded to their treatment will continue in their study delivered treatment arm for up to an additional 6 months. This is to allow responders to consolidate treatment gains and to be assessed for 6-month outcome.

8. Protection Against Risks

Effective screening and psychiatric evaluation will rule out other psychiatric conditions that may prevent someone from participating in this study. Once the subject enters the study, an experienced cohesive research team will closely follow him or her. The research team has considerable expertise in monitoring the safety of subjects participating in research studies. Drs. Storch or Geller (or a covering clinician, i.e., Drs. Wilhelm or Murphy) will be available for IRB # 11 - 0347

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research subjects 24 hours a day, 7 days a week. If at any point in the procedures symptoms become distressing or dangerous, subjects will be withdrawn from the study and, if necessary, treatment will be instituted. Adverse effects will be monitored very closely throughout the study, through structured assessments including screening and post-treatment lab assays, and clinical interactions. The project coordinator (and the respective clinician if appropriate) will conduct inquiries regarding any health complaints, recent illness or injury, need for medical consultation since the previous visit. This will ensure that we are detecting and appropriately responding to any adverse event experienced by the child while maintaining the blindness of the IE (i.e., although unlikely given the minimal side effect profile of DCS, asking the child about certain side effects may be suggestive of treatment arm). We will use the same coding system as that used in CAMS for reported complaints: reported complaints will be coded as Mild, Moderate, Severe, Serious, or Fatal (see below for definitions of each).

- Mild: AE poses no interference and no intervention is required
- Moderate: AE poses some interference OR requires some intervention.
- Severe: AE poses some interference AND requires intervention.
- Serious AEs are defined as follows:
  - Life threatening
  - Potential for permanent disability
  - Requiring hospitalization (or prolonging hospitalization)
  - Intentional Drug overdose
  - Fatal AE

When the project coordinator/clinician elicits an AE, it will be documented on a case report form, regardless of suspected relationship to the treatment arm. For all AEs, the investigator will obtain sufficient information to determine the onset, course and outcome of the AE. The treating clinician will make a judgment about whether the AE can be attributed to the study treatment. Attribution is classified as:

- Definite: AE is clearly related to study treatment
- Probable: AE is likely to be related to the study treatment
- Possible: AE may be related to study treatment
- Unlikely: AE is doubtfully related to the study treatment
- Unrelated: AE is clearly not related to the study treatment

AE complaints will be relayed to the site PI, psychiatrist (if related to DCS/PBO), or therapist (if related to CBT) who will take appropriate action, which may include monitoring, adjunctive intervention within study protocol (see below), or removal from the study and provision of off-protocol intervention.

The interviews during the course of the study involve no specific risk or discomfort beyond those of a standard clinical interview. All interviews are conducted by experienced clinicians sensitive to the developmental age of the child and experienced in pediatric OCD. If necessary or requested by the child or parent, any interview can be interrupted or terminated. The family (parent and patient) is clearly informed that they are free to terminate participation in the protocol at any point.

At the baseline assessment (EOW 1), the site physician (i.e., Drs. Geller or Murphy) will review results of laboratory assays with families. In the presence of any significant abnormalities, the site physician’s clinical judgment (in conjunction with the other site physician) will be used regarding continued study participation. As well, the physician will review lab values obtained at the EOW 9 venipuncture during the EOW 10 assessment with the family. Coordinating the pharmacokinetic study with end of treatment laboratory assessment will prevent the child from having an additional blood draw. In the event of an intermediate AE visit,
laboratory assays may be taken if clinically indicated. Appropriate treatment and/or consultation recommendations would be conveyed in the presence of significant abnormalities.

As noted, there may be some discomfort related to drawing blood for lab, pharmacokinetic, and genetic assays. If appropriate, numbing EMLA cream will be placed on the area where blood is taken to reduce the pain from the needle stick.

Within the conditioning paradigm, there may be some discomfort related to seeing pictures of fearful women while hearing a moderately loud shrieking noise. These pictures are no more upsetting than those that are routinely presented in prime-time media and were very well tolerated by youth in the Lau et al. study (Pine, personal communication 11/09/10). Subjects will be exposed to loud noises as part of the fear-conditioning paradigm. However, this degree of loudness has been used in many prior studies, and youth regularly are exposed to sounds of similar intensity. Overall, this task, which was funded by the NIMH Intramural Program, was shown to be safe and well tolerated by anxious children. We will make it very clear to the child and parent that they may discontinue this procedure at any time.

Following acute treatment with CBT (with or without DCS), treatment responders (defined as CGI-I=1-2) will enter the Follow-up phase of the study. Responders will be asked to continue to practice skills, but refrain from pursuing additional treatment until after the 6-month Follow-up assessment to provide an un-confounded assessment of treatment durability. Similar to other NIH-funded trials such as CAMS, CBT responders will receive 6 50-minute maintenance CBT sessions (held every 4 weeks). Although no new material will be introduced, the CBT therapist will be permitted to revisit the subject’s hierarchy, and reinforce the necessity of exposure activities. Non-responders to either treatment arm (IE assessment of CGI-I>3) will be offered a consultation with the site PI to discuss alternative treatment options.

All female subjects of child bearing age are required to have a negative urine or serum (depending on local IRB requirements) pregnancy test. New pregnancies, although unlikely given the demographic characteristics of subjects, will be tracked during the study via parent disclosure and require premature termination from the study as the impact of DCS on a developing fetus is unknown. Sexually active girls must agree to use an effective form of birth control, either hormonal (BCP, Depo-Provera or Norplant), spermicide (foam or vaginal suppository) or a barrier method (condoms, diaphragm, cervical cap) or a combination of barrier/spermicide contraception in order to participate in the study.

DCS is free of electrocardiographic impact; hence, there is no requirement for baseline or serial electrocardiographic monitoring.

Our procedures for monitoring side effects, as outlined in the study procedures, will reduce the likelihood of adverse reactions. We closely monitor AEs in all treatment arms and medication-related side effects. During the acute and maintenance (i.e., Follow-up) phases, subjects are monitored closely for evidence of therapeutic progress and relapse. Those who become more symptomatic without resolution or who develop exclusionary criteria during the trial (e.g., bipolar disorder, suicide attempt) will be removed from the trial and offered a treatment consultation.

This project will be conducted in compliance with research statutes outlined in the Health Insurance Portability and Accountability Act. Confidentiality of participants’ research information will be carefully protected by the research team. Research staff will be carefully trained about the importance of confidentiality and, consistent with USF and MGH regulations, will be required to sign confidentiality agreements. To the extent permitted by law, no participant information will be given to anyone without a signed release by the child’s parents. In addition, all paper-generated data will be stored as described above. The routine monitoring, maintenance, and quality control of the databases will be the responsibility of Drs. Storch, Geller, and Small.
9. **Potential Benefits:**

There are several potential benefits to participation in this study: having comprehensive psychiatric and medical assessments and carefully monitored, state of the art treatment, and no burden of financial cost. In addition, there is a likelihood that the patient's OCD will improve with CBT, and as a consequence the subject may experience improvement in their academic, social, and family functioning. Subjects will be compensated for completing assessments ($30 each for the Screening (Week 0), Mid-treatment (EOW 6), and Post-treatment assessments (EOW 10), and $50 each for the Follow-up assessments (EOW 14, 22, and 34; $240 total)).

10. **Conflict of Interest:**

There is no conflict of interest involved with study beyond the professional benefits from academic publication or presentation of the results.

**References**


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