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Does D-Cycloserine Augmentation of CBT Improve Therapeutic Homework Compliance for Pediatric Obsessive Compulsive Disorder?

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by

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Abstract

D-cycloserine (DCS), a partial agonist that acts on the *N*-methyl-D-aspartate (NMDA) receptor of the glutamatergic receptor complex, may enhance fear extinction learning during exposure-based therapy. Clinical studies in adults with obsessive-compulsive disorder (OCD) and non-OCD anxiety disorders - and a recent trial in pediatric OCD - have shown that DCS can improve treatment response to exposure therapy relative to placebo and exposure therapy. Some have hypothesized that improved treatment response is a function of increased compliance and engagement in therapeutic homework tasks, a core component of behavioral treatment. The present study examined the relationship between DCS and homework compliance in a 10-week, double-blind, placebo controlled DCS+CBT treatment trial with 30 children and adolescents with a primary diagnosis of OCD. D-cycloserine was dosed 25 or 50mg (depending on weight) one hour before therapy sessions 4-10. Group status (DCS or placebo) did not predict improved homework compliance over the course of treatment. However, significant group differences in homework compliance were found at the first exposure session. Additionally, homework compliance mediated the relationship between DCS and treatment outcome. When groups were collapsed, homework compliance was directly

associated with treatment outcome. These findings suggest that outside the context of DCS, homework compliance is an integral part of OCD treatment.

Introduction

Obsessive-compulsive disorder (OCD) is a chronic and disabling neuropsychiatric disorder that is characterized by the presence of recurrent obsessions and compulsions (American Psychiatric Association, 2000). Obsessions are persistent thoughts and images that are intrusive, unwanted, and distress-provoking. Compulsions are repetitive behaviors or rituals that serve to either relieve or prevent the distress caused by the obsessions. Obsessive-compulsive disorder tends to have its onset during childhood or adolescence (Berg et al., 1989), has a lifetime prevalence of 1-2% (Douglass, Moffitt, Dar, McGee, & Silva, 1995; Zohar, 1999), and is associated with marked impairments in psychosocial, academic, and family functioning (Lack et al., 2009; Piacentini, Bergman, Keller, & McCracken, 2003). Additionally, childhood OCD is often accompanied by comorbid disorders including tic, anxiety, mood and behavioral disorders, which may further complicate course of illness and treatment (Geller et al., 2000; Geller et al., 1998; Storch et al., 2008).

OCD Treatment

Currently there are two empirically supported methods of treatment for childhood OCD: cognitive behavioral therapy with exposure and response prevention (CBT) and pharmacotherapy using serotonin reuptake inhibitors (SRIs). Studies of pharmacological approaches in childhood OCD have consistently produced modest but positive results relative to placebo controls. For example, Liebowitz et al. (2002), in a 16-week, placebo-

controlled trial (*n* = 43; ages 6-18 years), found that fluoxetine was significantly more efficacious in reducing OCD symptoms than placebo. Similarly, Geller et al. (2001) found in a 13-week, double-blind, placebo controlled trial (*n* = 103; ages 7-17 years) that fluoxetine was associated with significantly greater improvements in OCD than placebo. Paroxetine was also demonstrated superior to placebo in a 10-week randomized, placebo-controlled trial (*n* = 203; ages 7-17 years; Geller et al., 2004). Across studies, medications were generally well-tolerated and there were relatively few treatment discontinuations due to adverse events (Geller et al., 2001; Geller et al., 2004; Liebowitz et al., 2002). Aggregating the extant findings, meta-analytic findings have demonstrated a medium effect size of 0.46 for selective serotonin reuptake inhibitors (SSRIs) relative to placebo in the treatment of childhood OCD (Geller et al., 2003).

Cognitive behavioral therapy has produced high treatment response rates at both post-treatment and follow-up time points in a number of studies (e.g., Barrett, Healy-Farrell, & March, 2004; Storch, Geffken, et al., 2007; POTS, 2004). A current meta-analysis of randomized controlled trials (RCTs) of SSRIs and CBT for childhood OCD found that both treatment modalities were efficacious (Watson & Rees, 2008) with the effect size for CBT (*d* = 1.45) substantially larger than for SSRIs (*d* = 0.48), noting that CBT alone is more efficacious than medication alone in the treatment of childhood OCD. Among specific studies, in a 14-week, randomized, wait-list controlled trial (*n* = 77; ages 7-17 years), Barrett et al. (2004) found that both individual and group CBT were superior to a wait-list control. Treatment gains were maintained at a 7-year follow up (O'Leary, Barrett, & Fjermestad, 2009). Combination therapy with CBT and SSRIs has also shown efficacy in the treatment of OCD. In a 12-week, multi-center, randomized, placebo-

controlled treatment study looking at the efficacy of individual CBT, sertraline, and their combination in children with OCD (n = 112; ages 7-17 years), all three treatments had significantly greater decreases in symptoms relative to the placebo group. The combined treatment and CBT alone arms demonstrated higher remission rates relative to sertraline and placebo (POTS, 2004). Indeed, practice parameters suggest the use of CBT alone for mild and moderate cases, and multimodal cases for severe cases only (POTS, 2004).

Cognitive behavioral therapy incorporates psychoeducation, cognitive training and exposure and response prevention (E/RP). Exposure and response prevention is a critical component to the treatment method whereby individuals are systematically exposed to feared stimuli gradually moving from low-anxiety exposures to high-anxiety exposures without engaging in the ritual. The exposure component is based on the idea that anxiety should eventually abate after an individual is exposed to the feared stimuli for a sufficient amount of time (Dar & Greist, 1992). During exposures, individuals are prevented from engaging in compulsions to relieve their distress. Fear extinction is facilitated through this process where systematic and repeated exposures to the feared stimuli occur in the absence of compulsions. Successful exposures result in habituation, where individuals begin with high anxiety at the beginning of the exposure and experience a substantial decrease in anxiety by the end of the exposure. These exposures are practiced both during therapy and at home in between sessions. Since exposure exercises can be anxiety provoking and time intensive, some patients consider E/RP to be aversive and are not willing to participate in these treatment methods (Franklin & Foa, 1998; McDonald & Blizard, 1988). Therefore, the success of the therapy relies heavily on the individual's willingness to engage in the exposures both in and out of sessions.

Although CBT and CBT and SSRI combination therapy boast high rates of treatment response, remission rates are not robust. In the aforementioned POTS (2004) study, remission rates for children receiving CBT alone, SSRI alone, and CBT and SSRI combination were 39%, 21%, and 53.6% (POTS, 2004), indicating that a substantial number of patients relapsed and remained symptomatic at follow-up. Maintenance of treatment gains is a common concern in OCD treatment, particularly since CBT therapists are not readily available, and a substantial number of patients need to travel long distances to obtain appropriate treatment. Although CBT and SSRI combination therapy has higher remission rates relative to CBT or SSRI monotherapy, some parents are reluctant for their child to take psychotropic medications (Stevens, Wang, Fan, Edwards, Campo, & Gardner, 2009). Additionally, due to the time consuming and modestly aversive nature of E/RP, some patients refuse to participate in therapy and/or eventually drop out of treatment (Schruers, Koning, Luermans, Haack, & Griez, 2005; Storch, Geffken, et al., 2007). Due to these commonly encountered issues, innovative research has begun to focus on methods of augmenting CBT by utilizing d-cycloserine (DCS) as an adjunctive medication to facilitate fear extinction during exposures (Chasson et al., 2010; Kushner et al., 2007; Storch Murphy, et al., 2010; Wilhelm et al., 2008)

D-cycloserine augmentation of CBT

D-cycloserine is a partial agonist that acts on the strychnine-insensitive glycine-recognition site of the *N*-methyl-D-aspartate (NMDA) glutamatergic receptor complex. NMDA antagonists are known to block fear extinction and learning; conversely, NMDA agonists have recently been shown to enhance fear extinction learning (e.g., Ledgerwood, Richardson, & Cranney, 2003; Walker, Ressler, Lu, & Davis, 2002). Extinction does not

refer to the unlearning of associations; instead it involves the formation of new associations that compete with the original aversive associations (e.g., Davis, Falls, & Gewirtz, 2000; Falls & Davis, 1995). Historically used as a second-line antibiotic for tuberculosis, DCS is relatively benign with infrequent side affects. Among the eight human studies utilizing DCS as an adjunct to psychotherapy, there have been few to no serious adverse events (e.g., Kushner et al., 2007; Ressler et al., 2004; Storch, Murphy, et al., 2010; Wilhelm et al., 2008).

Several studies have shown the potential for DCS to facilitate fear extinction in both animals and humans (Davis, Ressler, Rothbaum, & Richardson, 2006; Hofmann, Pollack, & Otto, 2006; Norberg, Krystal, & Tolin, 2008). Animal studies have demonstrated the potential for enhanced fear extinction learning when fear extinction training is augmented with DCS. Walker et al. (2002) first showed that acute doses of DCS prior to extinction training facilitated extinction of learned fear in rats with extinction training, but not in rats without extinction training, suggesting that results were due to enhanced fear extinction learning caused by the DCS, not by any anxiety-reducing properties of DCS. Using a similar paradigm, Ledgerwood et al. (2003) found that DCS enhanced fear extinction in rats when administered either soon before or after extinction training, indicating that DCS may facilitate both the acquisition and consolidation of memories. Furthermore, Ledgerwood et al. (2004) demonstrated that rats that were previously administered DCS during the extinction training did not exhibit a reinstatement effect when re-exposed to the original aversive association, while the rats that were not administered DCS during extinction training, did exhibit a reinstatement effect. Collectively, these results have important clinical implications. In the context of

OCD treatment, administration of DCS may be able to decrease relapse of symptoms after the completion of treatment, thereby increasing remission rates.

The adult anxiety literature has shown promising evidence regarding the potential for DCS to facilitate fear extinction during exposure sessions (Guastella et al., 2008; Hofmann, Meuret, et al., 2006; Otto et al., 2010; Ressler et al., 2004). Exposure therapy is a form of extinction learning where repeated exposures to the feared stimuli eventually lead to the habituation of the feared stimuli. Ressler et al. (2004) found in a double-blinded, placebo-controlled study with 27 adults with acrophobia that DCS (50 or 500 mg) administered 2-4 hours prior to exposure therapy significantly decreased acrophobia symptoms after the first exposure session relative to those that receive placebo. Those in the DCS group maintained their treatment gains at 3-month follow up. In a randomized, double blind, placebo-controlled study, Hofmann et al. (2006) examined the use of DCS as an adjunct to exposure therapy in a group of 27 adults with social phobia. Those who received DCS (50mg) 1 hour prior to exposure therapy experienced greater improvements at post-treatment and 1-month follow up relative to the placebo and exposure therapy group. Similarly, Guastella et al. (2008) found in a randomized, double-blind placebo-controlled study with 56 adults with social anxiety disorder that those who received DCS (50mg) 1 hour prior to exposure therapy had significantly reduced social anxiety symptoms at post-treatment relative to placebo. Progress of the patients was tracked on a weekly basis and significantly greater reductions in social anxiety symptoms were identified on the 3rd administration of DCS during an exposure session. Otto et al. (2010) found positive results in a randomized, double-blind, placebo-controlled, 5-session CBT trial with 31 adults with panic disorder with or without

agoraphobia. Those who received DCS (50mg) 1 hour before sessions 3-5 had significantly greater reductions in panic symptoms at post-treatment relative to those who received placebo. Treatment gains of the DCS group were maintained at 1-month follow up.

There are three published studies regarding DCS and E/RP $^{\Omega}$ for adult OCD (Kushner et al., 2007; Storch, Merlo, et al., 2007; Wilhelm et al., 2008) and one in pediatric OCD (Storch, Murphy, et al., 2010). All studies were randomized, double-blind, and placebo-controlled. Kushner et al. (2007) found that those who received 125 mg of DCS 2 hours before E/RP had significantly lower levels of obsession-related distress after 4 E/RP sessions relative to those who received placebo. The DCS+E/RP group reached a decrease of more than 50% reduction of subjective units of distress scale (SUDS) two sessions more quickly than those in the placebo group. Wilhelm et al. (2008) conducted a study with 23 patients with a primary diagnosis of OCD and found that after 5 exposure sessions, those who received 100 mg of DCS one hour prior to each E/RP session had significantly lower OCD severity scores than the placebo group (Cohen's d = 0.63), indicating that DCS enhanced fear extinction and significantly increased the pace of symptom reduction in those with OCD (Chasson et al., 2010). Storch et al. (2007) (n = 24) did not find significant differences at post-treatment or follow up between the DCS+E/RP and placebo+E/RP group. Both groups improved significantly from pre- to post-treatment. Null findings are likely due to methodological differences as patients were administered 250 mg of DCS four hours prior to the E/RP sessions (versus 1-2 hours) and prior studies with positive findings generally used lower doses.

Currently, there is only one published study on the effect of DCS as an adjunct to CBT in children with OCD. Storch et al. (2010) conducted a randomized, double-blind, placebo-controlled DCS+E/RP treatment trial on 30 children and adolescents (ages 8-17 years) with a primary diagnosis of OCD. Both the placebo+E/RP and DCS+E/RP groups improved significantly from pre- to post-treatment. At post-treatment, significant differences and large effect sizes were found on the Clinical Global Impressions-Severity (CGI-Severity) scale (National Institute of Mental Health, 1985), which is a measure of global functioning severity, between the DCS+E/RP and placebo+E/RP groups ($p < .05$, Cohen's $d = .91$). Additionally, at post-treatment, differences between the two groups approached significance ($p = .08$) and produced moderate effect sizes (Cohen's $d = .67$) on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS; Scahill et al., 1997), a measure of OCD severity, favoring the DCS+ERP group. Group by time interactions produced small to moderate effect sizes in favor of the DCS+E/RP group on the CY-BOCS (Cohen's $d = .31$) and CGI-Severity (Cohen's $d = .47$), indicating that DCS+E/RP may positively enhance E/RP in children with OCD.

Increasing evidence shows the potential benefits of utilizing DCS as an adjunct for exposure sessions in CBT. Improved treatment response may be hypothesized to be a function of increased compliance and engagement in therapeutic homework tasks. This may be because as DCS facilitates fear extinction during exposure sessions, the enhanced association learning makes practicing exposures independently less aversive and easier to complete. To date, there is no information regarding the relationship between DCS and homework compliance. Homework assignments are an integral component of CBT regardless of diagnosis to achieve a meaningful outcome (e.g., Shelton & Levy, 1979).

Given this, E/RP sessions typically end with assigning the patient homework based on session content that lasts up to 60 minutes per day. Between sessions, individuals are instructed to practice E/RP tasks and cognitive strategies used during therapy to enhance generalization.

Cognitive-behavioral models of OCD suggest that faulty interpretations of intrusive thoughts, images, and doubts actuate ritualistic behaviors (Salkovskis, 1985, 1999). Rituals are then maintained through negative reinforcement as the behaviors serve to temporally reduce anxiety and distress induced by the obsessions. Therefore, clinical improvement requires the individual to habituate to the anxiety caused by the obsessions. As previously mentioned, E/RP serves as fear extinction training by exposing the individual to the feared stimuli and removing the reinforcement effect of compulsions. By repeatedly exposing the individual to the anxiety trigger and preventing the corresponding rituals, the relationship between the previously feared stimuli eventually becomes non-anxiety provoking and the conditioned response to the stimuli (compulsions and rituals) is extinguished. For these reasons, homework is a crucial component to CBT as it directs the individual to continuously engage in behaviors that will weaken the behavioral relationship between the feared stimuli and associated compulsions.

The relationship between homework compliance and CBT

To date, a number of studies have examined the role of psychotherapeutic homework compliance among varied adult psychiatric disorders, outside the context of DCS augmentation. Adult depression studies have consistently shown that homework compliance is predictive of enhanced treatment outcome (e.g., Addis & Jacobson, 2000; Coon & Thompson, 2003; Kazantzis, Deane, & Ronan, 2000; Neimeyer, Kazantzis,

Kassler, Baker, & Fletcher, 2008). For example, in a CBT trial for 20 adults with depression, mid-treatment homework compliance significantly contributed to the prediction of mid-treatment change. When combined with ratings of acceptance of treatment rationale, the two variables accounted for 8% of the variance in change (Addis & Jacobson, 2000). Burns and Spangler (2000) have suggested a direct causal effect between greater homework compliance and better treatment outcome. In 521 depressed adults who had completed CBT, a causal effect of homework compliance on post-treatment depressive symptoms was -4.32 (CR=-2.89, $p < .01$), indicating a strong association between increased homework compliance and decreased depressive symptoms.

The adult anxiety literature on the association between homework compliance and treatment outcome has produced inconsistent results (Abramowitz, Franklin, Zoellner, & DiBernardo, 2002; Edelman & Chambless, 1993; Leung & Heimberg, 1996; Schmidt & Woolaway-Bickel, 2000; Woods, Chambless, & Steketee, 2002; Woody & Adessky, 2002). A meta-analysis examining the relationship between homework compliance and treatment outcome in adult depression and anxiety CBT trials found a medium effect size of 0.36 (Kazantzis et al., 2000). However, when analyses separated the effects by diagnostic class, the association between homework compliance and treatment outcome was substantially weaker for anxiety trials than for depression trials. This is reflective of the adult anxiety literature as some trials show strong associations between homework compliance and treatment outcome (Edelman & Chambless, 1993; Schmidt & Woolaway-Bickel, 2000) while others show no relationship (Leung & Heimberg, 1996; Woody & Adessky, 2002).

Very little is known about homework compliance and treatment outcome in children and adolescents. Hughes and Kendall (2007) conducted the only published study examining this association in children 9-13 years old diagnosed with overanxious disorder, separation anxiety disorder, or avoidant disorder. Therapists rated homework compliance on a 1-7 Likert scale based off of the patient's report. Investigators found no significant relationship between homework compliance and treatment outcome.

There is little empirical research specifically examining homework compliance and treatment outcome in the OCD literature (De Araujo, Ito, & Marks, 1996; Lax, Basoglu, & Marks, 1992; O'Sullivan, Noshirvani, Marks, Monteiro, & Lelliott, 1991; Simpson et al., 2011). O'Sullivan et al. (1991) found in 34 adults with OCD (ages 18-60 years) that treatment compliance significantly predicted treatment outcome at 6-year follow up. Abramowitz et al. (2002) found similar results in 28 adults with OCD (ages 18-65 years) after 18 CBT sessions; general CBT compliance was associated with OCD treatment response. Treatment compliance comprised of understanding of the treatment rationale, compliance within sessions and homework compliance. Homework compliance was rated by the clinicians and determined based off of collected homework forms and verbal reports from the patient. Better understanding of the rationale was associated with increased compliance within sessions; greater compliance within sessions was associated with greater homework compliance. When pre-treatment severity scores were controlled for, treatment compliance accounted for 64% of the variance of the post-treatment OCD severity scores ($p < .01$). De Araujo et al. (1996) identified homework compliance during the first week of treatment to be the best predictor of treatment outcome in 46 adult OCD outpatients. Homework adherence was calculated as the

percentage of completed homework (as determined by the clinician) versus agreed upon homework. Most recently, Simpson et al. (2011) found in 30 adults with OCD that homework compliance, as well as early homework adherence (sessions 5-9) significantly predicted lower OCD severity after 18 CBT sessions. Homework compliance was measured by the Patient EX/RP Adherence Scale (PEAS), which took into account quantity of homework (percentage of assigned exposures attempted), quality of homework (how well the exposures were completed), and degree of ritual prevention (how successful was the patient in resisting compulsions).

In contrast to the above positive relationships, Lax et al. (1992) examined E/RP treatment compliance as a predictor of CBT outcome in 49 adults with OCD (ages 18-60 years) but found no relationship between compliance and treatment outcome; however, these results may be due to lack of variance within the sample, as the group had generally high rates of compliance throughout the study. Woods et al. (2002) also found that higher homework compliance throughout treatment was associated with higher post-treatment anxiety symptoms in 82 individuals with OCD or panic disorder with agoraphobia. On balance, this effect was small and although there was a considerable amount of variance in the homework compliance, in general homework compliance was low. Thus, it is possible that if overall homework compliance in the sample were higher, the effect may not have been produced.

The discrepancies in findings in the OCD and anxiety literature may be because each study used different methods of determining homework compliance. Some trials rated homework adherence based on the quantity of homework completed (how much time was spent practicing the exposure), others on the quality of homework (the amount

of distress/anxiety reached and whether habituation was achieved), and a few considered both quantity and quality. Additionally, trials differed as to whether the ratings were self-report or clinician-administered. Unfortunately, no universal measure of homework compliance in CBT exists given differences in treatment approach as a function of disorder; therefore, other than the study conducted by Simpson and colleagues (2011), the validity and the reliability of the homework compliance measures used in the studies have not been determined.

Thus, whether the underlying constructs between homework compliance and treatment outcome are associated is still unclear. In the context of CBT augmented with DCS, DCS may indirectly cause homework adherence to become easier due to the enhanced facilitation of extinction learning during the therapy sessions. Previously mentioned studies have shown that DCS administration is associated with improved treatment outcomes (e.g., Storch, Murphy, et al., 2010; Wilhelm et al., 2008), which theoretically may make individuals more likely to engage in CBT homework between sessions. Should this relationship exist, it may provide a mechanism through which DCS impacts treatment outcome. Outside the context of DCS, the anxiety homework compliance literature has provided discrepant findings regarding the impact of homework adherence on treatment; therefore, the question about the relative contribution of homework to treatment outcome remains unclear.

With this in mind, the primary aim of this study is to examine whether DCS combined with E/RP would be related to improved homework compliance relative to placebo augmentation of E/RP in pediatric OCD and if homework compliance mediated the relationship between group assignment and treatment outcome. It is hypothesized

that the DCS combined with E/RP group will be associated with greater homework compliance ratings and homework compliance will be a mediator between group assignment and treatment outcome. Two exploratory aims were also examined. First, would DCS combined with E/RP be related to improved homework compliance relative to placebo combined with E/RP during the first half of the treatment trial (sessions 4-6) or the second half (sessions 7-10)? Second, will baseline clinical variables, such as OCD severity, internalizing symptoms, externalizing symptoms, and depressive symptoms, predict homework compliance?

Method

Participants

Youth participated in an NIH-funded study examining DCS augmentation of CBT in children and adolescents with OCD (Storch, Murphy, et al., 2010). Data were collected at two study sites: the outpatient psychiatric clinics at University of Florida and Massachusetts General Hospital. The pre-existing treatment dataset consists of 30 children and adolescent outpatients (34.4% female) diagnosed with primary OCD. Fifteen participants (50%) were randomized into the DCS condition, while the remaining 15 received placebo. Twenty-five participants (78%) completed all ten therapy sessions. Five participants (17%) made substantial improvements earlier in the trial and were able to complete the treatment program after session 8. Ages of participants ranged from 8-17 years (M = 12.2, SD = 2.8 years). In terms of race and ethnicity, 97% were Caucasian (N=29), 3% were Hispanic (N=1). Twenty-two participants (73%) had one or more comorbid disorder and 15 participants (50%) were on concomitant psychotropic medication. Participants were included in the study if they had a primary diagnosis of OCD, a Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) $\geq$ 16 (Scahill et al., 1997), no comorbid bipolar disorder, psychotic disorder, mental retardation, autism spectrum disorder, or substance abuse/dependence. Participants were also included if they were English speaking and stable on psychotropic medication for at least 12 weeks (if applicable). Participants with only hoarding symptoms were excluded. Epilepsy,

renal insufficiency, pregnancy or generally poor physical health was exclusionary as well.

Procedures

All research procedures were reviewed and approved by the corresponding institutional review boards, and all parents and children provided written informed consent and assent prior to involvement in the respective treatment protocol. An OCD diagnosis was ascertained before treatment through a clinical evaluation with an experienced psychiatrist or psychologist and confirmed through the Anxiety Disorders Interview Schedule for DSM-IV for Children: Child and Parent Version (ADIS-C/P; Silverman & Albano, 1996) by a trained independent evaluator. The same independent evaluator administered the baseline, mid- and post-treatment CY-BOCS ratings thereafter. The Child Behavior Checklist and Child Depression Inventory were completed at baseline and post-treatment. Parent reports were collected from the primary caretaking parent; information regarding the primary caretaker (mother-report vs. father-report) was not collected. Patients received up to ten 60-minute treatment sessions. At the beginning of each session, therapists reviewed homework from the past week with the patient and completed the homework compliance rating scale.

Physical examinations and laboratory tests (e.g., urine pregnancy and toxicology tests, blood count) were administered. Participants were then randomized via computer, and clinicians, raters, and patients were blinded to medication status. D-cycloserine/placebo administrations were given one hour prior to sessions 4 through 10. Dosing was based according to weight; children who weighed between 25-45kg were given 25mg of DCS or placebo and children weighing ≥ 45 were given 50mg of DCS or

placebo (2 capsules were administered). Dosages used were derived from findings from previous adult studies that indicated that approximately 0.7mg/kg was the most effective (Hofmann, Meuret, et al., 2006; Otto et al., 2010; Ressler et al., 2004; Wilhelm et al., 2008).

Measures

Anxiety Disorders Interview Schedule for DSM-IV– Child and Parent Version (ADIS-C/P; Appendix A): The ADIS-C/P (Silverman & Albano, 1996) assesses current episodes of Axis I disorders and provides differential diagnosis based on DSM-IV-TR criteria (American Psychiatric Association, 2000). The ADIS-C/P has consistently demonstrated strong psychometric properties, including test-retest reliability, inter-rater reliability, and concurrent validity (Silverman & Albano, 1996; Silverman, Saavedra, & Pina, 2001; Wood, Piacentini, Bergman, McCracken, & Barrios, 2002). This measure was completed at screening, before baseline.

Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS; Appendix B(Scahill et al., 1997): The CY-BOCS (Scahill et al., 1997) is a 10-item semi-structured clinician-administered measure of current obsession and compulsion severity. The CY-BOCS has demonstrated good psychometric properties (e.g. inter-rater reliability, internal consistency, test-retest reliability, discriminant validity, convergent validity) and is considered the gold-standard measure for OCD severity in youth (Scahill et al., 1997; Storch et al., 2004). This was completed at screening, baseline, mid-treatment, and post-treatment.

Child Behavior Checklist (CBCL; Appendix C): The CBCL (Achenbach, 1994) is a widely used parent-rated questionnaire that assesses the intensity and frequency of

behavioral and emotional problems exhibited by children within the past 6 months. Composite scores for externalizing (e.g., inattentiveness, aggression) and internalizing (e.g. anxiety, depression) symptoms are provided by this measure. The CBCL has exhibited good reliability, internal consistency and discriminant validity.

Child Depression Inventory (CDI; Appendix D): The CDI (Kovacs, 1985) is a 21-item self-report form that assesses the presence of depressive symptoms within the past two weeks. Responses range from not present (0) to severe (3). The CDI has demonstrated good test retest reliability, internal consistency, construct validity, and concurrent validity (Kovacs, 1985).

Clinical Global Impressions – Severity (CGI-Severity; Appendix E): The CGI-Severity (National Institute of Mental Health, 1985) is a clinician-rated scale of global OCD severity rated on a 7-point Likert scale from 0 (no illness) to 6 (extremely severe). The CGI-Severity has been widely used in treatment studies and has demonstrated sound psychometric properties including convergent validity with the CY-BOCS and treatment sensitivity (Storch, Geffken, et al., 2007; Storch, Lewin, De Nadai, & Murphy, 2010).

Homework Compliance Rating (HCR; Appendix F): HCR was completed by therapists at sessions 2-10 to measure the quantity and quality of homework adherence. Clinicians asked general prompts regarding homework compliance (i.e., how did your homework go this week?) at the beginning of each session. Ratings were determined based on the difficulty of exposures completed, amount of habituation experienced during the exposure, and the deliberateness of the exposure (accidental exposures to feared stimuli was not considered when completing the HCR). The rating scale was based on a 7-point Likert scale ranging from 0 (“did not complete any assigned homework”) to 6

("completed all homework and made efforts above and beyond assignments"). The HCR ratings are modeled off the CGI-Severity scores; ratings for the HCR have similar anchors and scoring processes as the CGI-Severity, providing face validity for the HCR. Additionally, the HCR is moderately and significantly correlated with the post-treatment CGI-Severity (r = -.67) and the post-treatment CY-BOCS total score (r = -.65). The significant negative correlations indicate the strong relationship between the HCR and the CY-BOCS and the CGI-Severity post-treatment scores (greater homework compliance is associated with decreased OCD symptoms and global severity), providing evidence for the construct validity of the HCR. Additionally, the HCR was not significantly correlated with measures of delinquent behaviors and attention problems at post-treatment, providing evidence for discriminant validity for the HCR. See Table 1 for data collection time points.

Analytic Plan

Specific Aim 1. To examine whether group assignment (DCS or placebo) would be related to homework compliance, a random effects model will be employed. The random effects model will be fit with random intercept and slopes. The model will incorporate treatment group, patient level random intercept and a random group by time interaction term. The model will be used to test whether the slopes between the two treatment groups were significantly different over the 7 sessions. A significant interaction will indicate that group assignment predicts homework compliance over time. The previously published Storch et al. (2010) study, given its preliminary nature, lacked sufficient power to detect small to medium post-treatment differences; however, the multiple measurement points utilized in the random effects model for the present analyses will substantially increase power. Power analyses demonstrated that given a sample of $N = 30$, we will have a power of .80 to detect 'medium' sized ($f = .18$) interaction effects.

To examine the relationship between group assignment, homework compliance, and treatment outcome (post-treatment CY-BOCS), a mediation analysis will be conducted. Bootstrapping methods will be utilized to determine if homework compliance is a mediator of group assignment and treatment outcome, with group assignment predicting treatment outcome. A 95% confidence interval will be determined by resampling the provided sample k=5,000 times. The exclusion of zero between the lower and upper bounds of the confidence interval will indicate that the indirect effect of the mediator on the outcome is not zero with 95% confidence (Hayes 2009).

Exploratory Aim 1. To examine whether group assignment (DCS or placebo) would be related to homework compliance during the first half or second half of treatment sessions, a random effects model will be employed. Sessions will be categorized into two groups: sessions 4-6 (first half) and sessions 7-10 (second half). Again, the random effects model will be fit with random intercept and slopes. The model will incorporate treatment group, patient level random intercept and a random group by time interaction term. The model will be used to test whether the slopes between the two treatment groups were significantly different in the first half or the second half of the treatment trial. Power analyses demonstrated that given a sample of $N = 30$, we will have a power of .80 to detect 'medium' sized ($f = .24$ for earlier sessions, $f = .22$ for latter sessions) interaction effects.

Exploratory Aim 2: To examine whether internalizing symptoms (CBCL), externalizing symptoms (CBCL), depressive symptoms (CDI-SF) and baseline OCD symptom severity (CY-BOCS) are predictors of homework compliance, four linear regression analyses will be conducted. Homework compliance will be measured by utilizing the average of homework compliance scores for each individual. Significant relationships will be determined by setting R^2 significance at $p < .05$ level for each predictor.

Results

Relationship between group assignment and homework compliance over time

A mixed model analysis examining the relationship between group assignment (DCS or placebo) and homework compliance was conducted. The mean homework compliance score at the first exposure session (session 4) was 4.26. Relative to the no growth model, the unconditional growth model did not provide a better fit (see Table 2); time parameters for the unconditional growth model were not significant, indicating that there was no change in homework compliance over time. A random effects model was employed and revealed no significant group x time interaction; however, there was a significant effect for group (Table 2). Results indicate that the placebo group scored 1.02 points less on homework compliance ratings at the first exposure session than the DCS group.

Mixed model analyses examining the relationship between group assignment (DCS or placebo) and homework compliance during the first half (sessions 4-6) and second half of treatment sessions (sessions 7-10) were conducted. The mean homework compliance score at the first exposure session (sessions 4 and 7, respectively) was 4.27 for sessions 4-6 and 4.31 for sessions 7-10. However, the unconditional growth model did not provide a better fit than the no growth model for both the first half of sessions (Table 3) and the second half of sessions (Table 4); time parameters were not significant for either.

The relationship between overall homework compliance scores across groups (DCS and placebo combined) and treatment outcome was further examined via mixed model analyses. The mean CY-BOCS score at baseline was 35.07. The random effects model revealed a significant homework compliance-by-time interaction ($F(2, 30) = 9.22$, $p < .01$; Table 5). Results indicate that as mean homework compliance increases by one point, CY-BOCS scores decrease 1.54 points for each assessed time point.

Mediational analysis

Bootstrapping meditational analysis revealed that homework compliance was a mediator of group assignment and treatment outcome (CI = .60-6.76; Table 6). The direct effect between group assignment and treatment outcome approached significance ($p = .08$). After including the impact of homework compliance into the meditational model, the indirect effect between group assignment and treatment outcome no longer approached significance ($p = .53$), which indicates that the influence of the group assignment on treatment outcome goes through homework compliance.

Predictors of homework compliance

Externalizing symptoms significantly predicted homework compliance ($b = -.36$, $t(29) = -2.05$, $p \leq .05$), while baseline OCD severity approached significance ($b = -.35$, $t(29) = -1.99$, $p = .06$; see Table 7). Internalizing and depressive symptoms did not predict homework compliance ($b = -.07$, $t(29) = -.36$, $p = .72$; ($b = -.14$, $t(29) = -.75$, $p = .46$).

Discussion

The present study examined the relationship between DCS group status and homework compliance. Results revealed that DCS group status was not associated with improved homework compliance over the course of treatment. Rather, as the data was not a better fit with the unconditional growth model (relative to the no growth model), the results indicated that homework compliance may be a stable variable that does not change over time. In other words, individuals with initial high homework compliance ratings continued to have high ratings throughout treatment, while those with low homework compliance ratings continued to have low ratings throughout treatment. Levels of motivation may also be associated with homework compliance ratings; those who were more motivated during therapy may have been more engaged and compliant during exposure sessions and while completing homework tasks, while those who were less motivated may have exerted substantially less effort throughout treatment. As motivation is a predictor of treatment response (Vogel, Hansen, Stiles, & Gotestam, 2006), assessing the patient's motivation during the first few session can provide important information regarding the patient's treatment prognosis.

Although DCS group status was not associated with change in homework compliance, homework compliance mediated the relationship between DCS group status and treatment outcome. Because the group x time interaction within the random effects model was not significant, these results indicate that increased homework compliance,

regardless of time, may be related to better treatment outcome. However, bootstrapping results revealed a significant relationship between group status and homework compliance (p=.04), indicating that group status differentiated homework compliance in some manner. Additionally, at the first exposure session (session 4), the DCS group had significantly greater homework compliance scores relative to the placebo group. This indicates that from the first exposure session, there were differences between the two groups and these differences in homework compliance continued throughout treatment. These findings may perhaps be because the DCS group had slightly less severe pre-treatment OCD severity than the placebo group. Additionally, the lack of significant findings in the group x time interaction may be due to insufficient power to detect these effects, the psychometric constraints of the homework compliance measure, the fact that error is compounded by multiplication of variables, or a non-linear interaction between the variables.

Consistent with previous adult OCD research (Abramowitz et al., 2002; De Araujo et al., 1996; Simpson et al., 2011), homework compliance inversely predicted post-treatment OCD severity when the sample was collapsed. That is, the more the child engaged in homework exposures (e.g., exposures that lead to habituation), the more the child was rated to have improved at both mid- and post-treatment time points. Taken together, these findings suggest that good homework compliance is essential for success in treatment. However, as quality and quantity of homework compliance does not tend to change over time, it is important that patients and their families exhibit good homework adherence from the beginning of treatment. Clinicians should emphasize the importance of homework compliance early on, discuss the nature of homework (e.g., what homework

will consist of), agree upon homework exposures and goals, explain implementation of exposures, and stress the necessity of frequent exposure exercises between sessions. Since treatment compliance is unlikely to change over time (i.e., those who are noncompliant at early sessions, are likely to be non compliant at later sessions), compliance should be assessed at every session. Clinicians should then intervene and address issues regarding compliance as soon as it is identified. Motivational interviewing strategies such as decisional balancing (weighing out the good and less good aspects of their behavior to promote change) and eliciting change talk (having the patient come up with ways their lives will change if the behavior changes) can be included in sessions where individuals show low motivation or poor homework compliance at treatment onset, so as to address these issues directly and early on.

Regarding clinical predictors of homework compliance, externalizing symptoms and increased baseline OCD severity were negatively associated with homework compliance but depressive and internalizing symptoms were not. Children with increased externalizing symptoms may be more oppositional when asked to complete exposures for homework by refusing to practice exposures or not completing exposures to habituation. Additionally, parents with children exhibiting externalizing symptoms may engage in more family accommodation (i.e., modify activities due to child's obsessive-compulsive symptoms, do things for the child, participate in child's rituals), so to avoid temper tantrums or arguments. Alternatively, children with externalizing symptoms may purposefully throw temper tantrums so that family members will accommodate their obsessive-compulsive symptoms. Those with more severe obsessive-compulsive symptoms may find exposures to be too aversive and thus may not be able to

complete homework exposures properly. Their symptoms may also be too impairing and cause too much distress and anxiety, making it substantially more difficult for the individual to be able to engage in homework exposures.

This study is the first to examine the relationship between DCS and homework compliance and also adds to the literature on homework compliance in pediatric anxiety disorders. This study has several limitations. First, the sample size is modest and may not be generalizable to the pediatric OCD population; therefore, replication of this study in a larger sample. Second, although therapists carefully assessed homework compliance at the beginning of each session, a one-item measure of homework compliance may not have captured all the nuances of homework compliance. Therefore, ratings may have been constrained by the nature in which the questions were asked, making homework compliance ratings susceptible to floor and ceiling effects and difficult to measure any potential for change. Third, there was no independent verification of homework compliance. A clinical synthesis of all available information was utilized to determine the level of homework adherence; however, parent and/or child may have presented a more favorable representation of homework completion. Additionally, because the initial treatment study was not designed to specifically focus to on homework compliance ratings, homework compliance ratings were not checked for inter-rater reliability. Thus, it may be possible that therapists did not rate homework compliance in a standardized manner. Finally, other salient variables that may have affected the levels of homework compliance and/or improvements in OCD severity throughout treatment, such as motivation or insight, were not assessed in the present study.

Overall, this study provides important information for both the DCS and anxiety

homework compliance literature. First, homework compliance is an important component of E/RP for children and adolescents with OCD. Increased homework compliance not only significantly predicted better treatment outcome, but also mediated the effects of DCS on treatment outcome. Although the exact effect of DCS on homework compliance is unknown, it is clear that increased homework compliance is a good prognostic indicator. Second, obtaining homework compliance early on in treatment is essential as homework adherence may be unlikely to change over time. Therefore, homework compliance should be thoroughly assessed and obstacles that may interfere with homework compliance should be readily addressed. Finally, due to the importance of early homework compliance in treatment outcome, future research should examine possible predictors of decreased homework compliance and investigate methods of increasing homework compliance prior to the start of treatment. Comorbidity, motivation, insight, developmental age, family functioning, and socioeconomic status are all possible variables that may in some way affect homework compliance.

Footnote

[Ω] In this text, exposure and response prevention (E/RP) and cognitive behavioral therapy (CBT) are the same and utilized interchangeably.

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Appendix 1

Tables

Table 1.

Assessment Schedule

Measures	Screening	Baseline	Sessions 2-4	Mid-Treatment (Session 5)	Sessions 6-9	Post Treatment (Session 10)
ADIS-C/P	X					X
CY-BOCS	X	X		X		X
CBCL		X				X
CDI		X				X
CGI-S		X		X		X
HCR			X	X	X	X

Table 2.

Random effects model for homework compliance scores with DCS group assignment (with and without time effects)

	No Growth	Unconditional Growth	Conditional Growth
-2loglikelihood	642.804	642.745	634.915
Δ-2loglikelihood		.059	7.83
Parameters	3	4	5
Δ Parameters		1	1
		χ^2 (1, N=30) =3.84)	χ^2 (1, N=30) =3.84)
Fixed Effects			
Intercept	4.29 (.17) p<.001**	4.26 (.2), p<.001**	5.79 (.59), p<.001**
Time		.01(.04), p=.81	-.07(.13), p=.57
Group			-1.02(.37), p=.008*
Time x Group			.06(.08), p=.49

Note. *p<.01, **p<.001

Table 3.

Random effects model for homework compliance scores with DCS group assignment (with and without time effects) for sessions 4-6

	No Growth	Unconditional Growth
-2loglikelihood	304.901	304.867
Δ-2loglikelihood		.034
Parameters	3	4
Δ Parameters		1
		χ^2 (1, *N*=30) =3.84).
Fixed Effects		
Intercept	4.27 (.17), *p*<.001**	4.25 (.26), *p*<.001**
Time		.03(.14), *p*=.85

Note. **p<.001

Table 4.

Random effects model for homework compliance scores with DCS group assignment (with and without time effects) for sessions 7-10

	No Growth	Unconditional Growth
-2loglikelihood	342.106	342.104
Δ-2loglikelihood		.002
Parameters	3	4
Δ Parameters		1
		χ^2 (1, *N*=30) =3.84).
Fixed Effects		
Intercept	4.31(.17), *p*<.001**	4.29 (.42), *p*<.001**
Time		.01(.04), *p*=.96

Note. **p<.001

Table 5.

Random effects model for CY-BOCS scores with homework compliance and time effects

Parameters	CY-BOCS	*p*
Effects		
Intercept	35.07(5.55)	.00**
Time	-1.38(2.39)	.57
Homework Compliance	-.46(1.25)	.72
Time x Homework Compliance	-1.54(.54)	.006**

Note. ***p*<.001

Table 6.

Results of analyses examining homework compliance as a mediator between group status and treatment outcome

	B	SE	*p*
a	-.66	.31	.04*
b	-4.43	1.12	.0005**
c	4.2	2.31	.08
c’	1.27	2.01	.53
	Estimate	SE	95% CI
Indirect effect	2.85	1.51	.60-6.76

Note. c = direct effect, c’ = indirect effect; *$p < .05$, **$p < .001$

Table 7.

Predictors of average homework compliance

Predictor	B	SE(B)	*b*	*t*	*p*
CDI	-.04	.06	-.14	-.75	.46
CBCL-Internalizing	-.007	.02	-.07	-.36	.72
CBCL-Externalizing	-.05	.02	-.36	-2.05	.05
Baseline CY-BOCS	-.08	.04	-.35	-1.99	.06

Note. CDI = Children's Depression Inventory; CBCL-Internalizing = Child Behavior Checklist – Internalizing symptoms; CBCL-Externalizing = Child Behavior Checklist – Externalizing symptoms; CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale.