



## D-Cycloserine Augmented Treatment of Anxiety Disorders in Children and Adolescents: A Review of Preliminary Research

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### Abstract

This paper reviews evidence for using the “cognitive enhancer” D-Cycloserine (DCS) to treat anxious young people. Adult studies indicate DCS consolidates fear extinction learning into memory during exposure therapy, thereby increasing the speed of remission. This paper examines basic research indicating both fear extinction and DCS may work differently in younger animals compared to adults. It reviews trials using DCS to enhance treatment of obsessive compulsive disorder in youths. Given there is often ambivalence about using medication to treat young people, this paper also reviews current research examining parental attitudes to DCS. It considers specific challenges facing DCS research, particularly with regard to maintaining experimental control and managing negative perceptions associated with using medication. Finally, this paper considers current research underway, particularly with regard to using DCS to treat young people with specific phobias. Overall, findings indicate that DCS shows promise for enhancing the treatment of anxiety in young people, but further investigation is needed to determine whether it provides significant benefits over and above current therapies.

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**Keywords:** Cognitive Enhancer, D-Cycloserine, Exposure Therapy, Anxiety, Specific Phobia, Obsessive Compulsive Disorder

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## Introduction

Anxiety disorders represent one of the most common and burdensome forms of pathology amongst children and adolescents. Estimates indicate that up to 5% of young people experience clinically severe anxiety at any one time (e.g., Rapee, Schniering, & Hudson, 2009) and these disorders have a moderate to high impact on a child's functioning (Ezpeleta, Granero, de la Osa, & Guillamon, 2000). Fortunately, this burden of illness has been met with some effective interventions. Skills-based Cognitive Behaviour Therapies (CBT) have demonstrated approximately 60% of young people are diagnosis free following treatment (James, Soler, & Weatherall, 2006). Selective serotonin reuptake inhibitors (SSRIs) have also shown efficacy compared to a placebo (58% responsive versus 32%: Ipser, Stein, Hawkrigge, & Hoppe, 2009). While these outcome figures are encouraging, they also imply that the "gold standard" treatments for child anxiety are far from representing a "silver bullet": many young people do not respond to treatment, those who do report greater symptoms than the normal population and some require extensive therapy prior to remission (e.g., Rapee, et al., 2009). Brief and effective early intervention has the potential to alter trajectories for anxious youth and reduce cost to the community. There is clear value in developing treatments which are tailored to this vulnerable population (e.g., Pine, Helfinstein, Bar-Haim, Nelson, & Fox, 2009; Rapee, 2011).

Combining psychotherapy and pharmacotherapy would seem an intuitive means to improve outcomes: the combination of different treatments working through different processes may yield better outcomes than either therapy in isolation. A single study with children by Walkup et al. (2008) reported that the combination of CBT and SSRIs was more efficacious than either therapy component. Unfortunately, combination therapies have shown less promise in adults, where they have been more rigorously studied (Otto, Smits, & Reese, 2005). SSRIs have also been associated with serious adverse events in young people (e.g., Hammad, Laughren, & Racoosin, 2006) and parents may be uncomfortable with their child's prolonged usage of these medications. Furthermore, unlike psychotherapy, the therapeutic effects of antidepressants are only maintained while they are being taken. While combining pharmacotherapy and psychotherapy may have additive benefits, an alternative strategy to improve outcomes may be to enhance components of existing psychological treatments (e.g., Rapee, 2011). In view of this, researchers have begun to examine whether the chemical substrate D-Cycloserine (DCS) can augment exposure for young people experiencing clinically severe anxiety (e.g., Byrne, Farrell, & Rapee, 2011).

## D-Cycloserine as a Cognitive Enhancer for Exposure Therapy

During exposure therapy, the anxious client is encouraged to calmly and gradually "face their fears". Fear extinction through exposure therapy represents the single most powerful process for treating clinically severe anxiety in both adults and children (e.g., Abramowitz, Deacon, & Whiteside, 2012). Despite the efficacy of exposure for treating anxiety, there is the potential for relapse, as the original fear association may remain intact (e.g., Bouton, 2002). For example, fear extinction learning may not generalize to different exemplars of the feared stimulus or to different contexts in which it is encountered. Furthermore, young clients may prematurely drop-out of exposure therapy as it

is inherently anxiety-provoking, highlighting the need for early treatment success. In view of how fundamental exposure is for treating anxiety, any improvements in this process could yield significant treatment gains.

During successful exposure, the client is believed to learn new non-fearful associations with a previously feared stimulus. Scientists have implicated N-Methyl-D-Aspartate (NMDA) glutamate receptors in the basal lateral amygdala in the associative learning that takes place during fear extinction (e.g., D'Souza, Charney, & Krystal, 1995). DCS is believed to stimulate (or partially agonise) NMDA receptors at this site, such that synaptic changes made during extinction are strengthened (e.g., Walker, Ressler, Lu, & Davis, 2002). DCS was originally approved for treating tuberculosis in 1965 ("Cycloserine"), where it would typically be taken in high doses over a period of months. When used to enhance extinction, low doses of DCS ingested around the time of a successful exposure session can "consolidate" the new non-fearful learning into memory (e.g., Davis, Ressler, Rothbaum, & Richardson, 2006). Therapeutically, this means if the feared stimulus is encountered at a later time, there should be less return of fear. Put simply, DCS helps maintain the neurophysiological changes that take place during fear extinction. This can help the client to remember not to be fearful after exposure therapy.

In this sense, DCS is considered "cognitive enhancing" rather than "psychotropic": it improves learning during therapy rather than directly and independently reducing symptoms. Hence, there are significant differences between DCS and psychotropic medications traditionally used to treat anxiety (e.g., Byrne et al., 2011). Firstly, DCS is not an anxiolytic, so the young person will not notice any change in their mental state from ingesting DCS alone (Norberg, Krystal, & Tolin, 2008). Secondly, DCS must be used in conjunction with exposure therapy, as it has little value if there is no fear extinction (Norberg et al., 2008). Thirdly, unlike psychotropic medications, DCS is most effective when it is administered briefly (or acutely: Norberg et al., 2008). Finally, the potential for adverse events or side-effects associated with DCS is minimal, being described by Storch, McKay, et al. (2010) as "...almost negligible". All of these factors may make DCS a more attractive treatment option for concerned parents.

## What Can Be Learnt From Adult D-Cycloserine Studies

The first successful clinical trial using acute DCS dosing was conducted with a group of  $N = 28$  patients experiencing fear of heights (Ressler et al., 2004). In a randomised placebo-controlled trial (RCT), patients who received a single session of "virtual elevator" exposure combined with DCS demonstrated significantly greater improvement in the same follow-up task. Since this time there have been a number of adult studies reporting DCS effects, including clinical trials for social anxiety disorder (Guastella et al., 2008; Hofmann, Pollack, & Otto, 2006), obsessive compulsive disorder (Wilhelm et al., 2008; Kushner et al., 2007) and panic disorder (Otto et al., 2010). Despite these promising results, not all studies have demonstrated DCS augmentation. Null effects were reported for spider fear by Guastella, Dadds, Lovibond, Mitchell, and Richardson (2007) and OCD (Storch et al., 2007). To summarise these mixed results, Norberg et al. (2008) conducted a meta-analysis of studies and showed that DCS had a small augmenting effect in adult humans ( $d = .42$ ).

Since Norberg et al.'s (2008) review, two studies found DCS did not augment imaginal exposure for post-traumatic stress disorder (de Kleine, Hendriks, Kusters, Broekman, & van Minnen, 2012; Litz et al., 2012), however, post-hoc analysis of de Kleine et al.'s (2012) study found it did increase treatment response for patients with more severe symptoms over a full course of therapy. Similarly, Tart et al. (2013) did not detect DCS augmentation when it was administered after virtual reality exposure for height phobia, however, Smits et al.'s (2013) re-analysis of this data revealed patients with successful extinction did receive added benefit. Most recently, the largest study to date ( $N = 125$ ) found DCS did not augment overall treatment for social anxiety disorder, however, it did speed remission by 24-33% (Hofmann et al., 2013).

Results from clinical trials of DCS in adults are clearly mixed, however, they may not reflect the true potential of DCS as an augmenting agent. For example, variation in treatments and study designs differences in DCS dosing and regimens may have resulted in DCS being used sub-optimally. However, these studies and post-hoc analyses do provide some insight into treatment parameters for DCS augmentation. Results suggest DCS can enhance the efficacy of individual exposure sessions (Norberg et al., 2008). It is most effective when administered acutely (Norberg et al., 2008) and for clinically severe anxiety (e.g., de Kleine et al., 2012; Norberg et al., 2008). More recent analyses suggest that DCS should be delivered following effective fear extinction (Tart et al., 2013).

Research also suggests the effects of exposure alone may be commensurate to DCS augmentation by treatment endpoint, however, DCS can improve the speed of remission (e.g., Chasson et al., 2010; Hofmann et al., 2013). Hence, DCS augmentation should be most evident early in treatment.

## Will D-Cycloserine Work in Children? Evidence from Fear Extinction in Younger Animals

The formative DCS fear extinction research was conducted with adult rats (see Richardson, Ledgerwood, & Cranney, 2004 for review). The basic finding was that after fear conditioning (where a noise was paired with a shock), rats would typically elicit a fear response such as freezing upon later hearing the noise. Rats administered DCS prior to extinction (where the noise was repeatedly presented alone until freezing dissipated) were less prone to recovery of fear (they froze less in response to the noise). The suppression of fear with DCS was reported as a large and robust effect in animals ( $d = 1.19$ ; Norberg et al., 2008). More recently, research has focussed on whether these same effects are observed in younger animals with developing brains. This could have implications as to how effectively DCS can be used to treat children and adolescents.

There is now a significant body of research to suggest that fear extinction in developing animals is a qualitatively different process to fear extinction in adults (e.g., Kim & Richardson, 2010a). Furthermore, there are changes in extinction and its related neurophysiology over the course of early development. For example, pre-weanling rats (17 days old approximating human infants) do not demonstrate return of fear after extinction that is typical of adults (Kim & Richardson, 2010b). For example, they do not exhibit reinstatement (freezing in response to the shock being presented again) or contextual renewal (freezing when the noise is presented in different context). This suggests extinction at this young age may be more effective and less vulnerable to relapse (Kim & Richardson, 2010a). Furthermore, the NMDA antagonist MK-801 does not improve fear retention in preweanlings, suggesting fear extinction at this age is NMDA independent (Langton, Kim, Nicholas, & Richardson, 2007). Research now indicates preweanling rats rely on opioid receptors rather than NMDA receptors to facilitate extinction (Kim & Richardson, 2010a). It now appears NMDA receptors do not mediate extinction in infancy, however, they do start to play a role in childhood, suggesting DCS may still be of value in children. For example, Gupta et al. (2013) recently reported evidence that DCS's neural action in juvenile rats (18-24 days old) may be caused by increasing activity in the medial prefrontal cortex and amygdala subnuclei.

As rats approach adolescence, there are further changes in their neurophysiology and fear extinction process. For example, Kim, Li, & Richardson (2011) found adolescent rats are less efficient at using their prefrontal areas (having less neuronal activity in their infralimbic medial prefrontal cortex), which may lead to reduced extinction retention. Pattwell et al. (2012) found that reduced synaptic plasticity in the prefrontal regions during adolescence was associated with reduced regulation of fear extinction. McCallum, Kim, & Richardson (2010) similarly observed that the reduction in the synaptic density at the prefrontal cortex (a "natural lesion") was associated with impaired retention of extinction learning. They also found that DCS was able to increase extinction retention despite this deficit. These results suggest exposure therapy in adolescence may be less efficacious than at other life stages, however, DCS may partially overcome this impairment. In addition to changes in fear extinction, early development is associated with greater plasticity, possibly providing more opportunity to reduce long term fear trajectories (e.g., Pine et al., 2009). While it is difficult to know the extent to which these factors will influence treatment, there seems sufficient evidence to suggest there may be differences in how DCS and fear extinction take place for young people compared to adults. Depending on age, some factors may facilitate the effects of DCS and exposure, whereas others may inhibit it.

## D-Cycloserine Augmentation for Childhood Obsessive Compulsive Disorder

Research in developing humans has initially focussed on whether DCS can augment treatment for obsessive compulsive disorder (OCD). OCD has shown to be one of the more severe and interfering anxiety disorders in both children and adults (Shaffer et al., 1996; Zohar, 1999). Hence, there may be a particular role for using DCS to treat this disabling anxiety disorder. In adults, two studies have demonstrated DCS improved the effects of Exposure/Response Prevention (E/RP) for OCD (Wilhelm et al., 2008; Kushner et al., 2007). Storch et al.'s (2007)

was unable to replicate these significant findings, possibly due to administering DCS in higher doses and too far in advance of extinction (Norberg et al., 2008). Researchers have more recently begun to examine whether DCS can enhance early intervention for OCD.

In the first DCS trial for anxious young people, Storch, Murphy, et al. (2010) examined whether DCS (25 or 50mg depending on weight) enhanced E/RP efficacy in 30 young people with OCD (aged 8-17 years). The study design was a randomized, double-blinded, placebo-controlled augmentation trial examining E/RP+DCS versus E/RP+placebo (PBO). Patients received ten CBT sessions: the first three were non-E/RP sessions (i.e., psychoeducation, hierarchy development, cognitive therapy) while the last seven were E/RP sessions paired with DCS or PBO taken one hour beforehand. Compared to the E/RP+PBO group, youth in the E/RP+DCS arm showed reduced obsessive-compulsive symptom severity at post-treatment on the Clinical Global Impressions Rating – Severity (CGI-S; Guy, 2000) with large effect sizes ( $d = 0.97$ ,  $p = .02$ ). Compared to the E/RP+PBO group, youth in the E/RP+DCS arm also showed a (non-significant) reduction in Yale-Brown Obsessive Compulsive Scale (CY-BOCS; McKay et al., 2008) scores with moderate effect sizes ( $d = 0.66$ ,  $p = .09$ ). The average CY-BOCS reduction for the E/RP+DCS arm was 72% versus 58% for those randomized to E/RP+PBO over the course of treatment. In a further analysis of this data set, Park et al. (2013) examined whether DCS predicted the extent to which children practiced self-exposure between sessions. Although homework compliance predicted better overall treatment outcome, DCS did not improve homework compliance. The researchers concluded that any DCS memory consolidation must have occurred during within-session exposure, rather than during extraneous self-exposures.

More recently, Farrell, Waters, Boschen, et al. (2013) examined the efficacy of DCS augmentation (25 or 50mg depending on weight) of CBT relative to PBO in  $N = 17$  difficult-to-treat youth with OCD. This sample was composed of youths aged 8-18 years who had not responded to at least five sessions of CBT. These researchers hypothesized DCS may have a particular role in augmenting therapy of treatment-resistant anxiety. Youths were randomized to nine sessions of CBT in which the last five sessions involved E/RP augmented by DCS or PBO [E/RP+DCS versus E/RP+PBO] taken one hour before E/RP sessions. Impressively, the E/RP+DCS arm demonstrated greater rates of improvement on a number of outcomes (i.e., obsession symptom severity, diagnostic severity, parent-reports of the youths OCD symptoms;  $\eta^2$  ranging from .18 to .33) relative to the E/RP+PBO arm at one-month follow-up (but not at three-month follow-up). Across the Farrell, Waters, Boschen, et al. (2013) and Storch, Murphy, et al. (2010) studies, DCS was very well tolerated and associated with no treatment related adverse effects or changes in post-treatment laboratory assays.

## Will Parents Allow their Children to Take D-Cycloserine?

While DCS has shown some promise for augmenting exposure for children, parents' perceptions regarding the acceptability of this treatment are yet to be determined. Regardless how effective or well indicated DCS is as an intervention, it will be parents who decide whether the treatment is appropriate or not. Equally effective treatments may vary in terms of their acceptability to potential clients. For example, stimulant medication and behavioural parent training are both empirically supported treatments for attention deficit hyperactivity disorder in youth (Gage & Wilson, 2000), however, behavioural parent training is consistently found to be more acceptable to parents. Treatment acceptability may be a strong predictor of parent and child engagement in therapy, treatment adherence, as well as ultimately predicting treatment success (Cross-Calvert & Johnson, 1990).

Roberts, Farrell, Waters, and Ollendick, (in review) examined attitudes to treatments from parents with children enrolled in exposure therapy augmented with either DCS or Attention Bias Modification (ABM:  $n = 55$  parents of anxious children and  $n = 38$  parents from the community). Parents' perceptions of acceptability, believability and effectiveness of established treatments (CBT and SSRIs) were examined relative to their beliefs about novel treatments (DCS and ABM). Parents of children with a specific phobia perceived CBT more favorably than SSRIs and either novel treatment. Parents of phobic children also perceived psychological treatments (CBT and ABM) more favorably than pharmacological treatments (SSRIs and DCS), suggesting less acceptability for medical treatments more generally. Interestingly, parents of children enrolled in the DCS trial perceived it more favorably than parents of children receiving ABM or the community parent sample. This suggests parents generally do not view DCS as a favorable intervention relative to psychological treatments, however, once they have been informed of the potential risks and benefits, there is a significant increase in perceptions of acceptability. Results indicate the

importance of socializing parents to novel treatments like DCS: once parents are given information regarding DCS they may find the treatment more acceptable.

Parents often have a number of concerns regarding the use of medication to treat children with mental disorders (e.g., Lazaratou, Anagnostopoulos, Alevizos, Haviara, & Ploumpidis, 2007). Byrne and Rapee (2013) examined parent willingness to allow their children to take DCS for an anxiety disorder, as well as any specific concerns about the medicine. The researchers gave a community sample of  $N = 176$  parents information about how DCS could be used to treat anxiety, describing it as being “very safe” and “like taking a few doses of antibiotic” (as it was originally used as an antibiotic). They asked parents to imagine their first child was ten years old and to rate their willingness to allow this child to take medication on an 11-point scale (0 = definitely not; 5 = maybe; 10 = definitely) for three types of disorder: 1. severe/interfering anxiety (two year duration panic disorder), 2. mild/non-interfering anxiety (three month duration spider phobia), or 3. a two week duration infection. Parents were more willing to allow their child to take DCS for severe anxiety to take medication for an infection ( $M = 9.5/10$ ,  $SD = 2.1$ ) rather than a severe anxiety disorder ( $p < .001$ ), however, they were also more willing to allow their child to take medication for an infection ( $M = 9.5/10$ ,  $SD = 2.1$ ) rather than a severe anxiety disorder ( $p < .001$ ). This suggests greater severity may be associated with increased willingness to use DCS, however, similar to the findings of Rappaport and Chubinsky (2000), parents were more comfortable allowing their child to take medication for a physical ailment.

Despite being informed DCS is safe, parents had a number of reservations about its use. On the same rating scale they reported they would be concerned about side-effects ( $M = 7.7$ ,  $SD = 2.7$ ), DCS controlling their child's thoughts ( $M = 5.9$ ,  $SD = 3.2$ ) and that the medication would not work ( $M = 4.2$ ,  $SD = 2.3$ ). Willingness to try DCS for mild anxiety was most strongly predicted by the belief it would not work ( $r = -.59$ ,  $p < .001$ ), followed by the belief it would control their child's thoughts ( $r = -.36$ ,  $p < .001$ ) and that it would have Side-effects ( $r = -.24$ ,  $p < .001$ ). This suggests it is important that parents feel confident DCS can help their child before they will consent to its use. Overall, these preliminary results suggest there is parental ambivalence about using DCS, even when they are made aware it is safe and has the potential to help. The concerns regarding this low risk intervention may reflect a general sensitivity regarding the use of medication to treat childhood mental disorders.

## Issues when Conducting D-Cycloserine Research in Children: Maintaining Control Whilst Managing Perception

Research attempting to demonstrate drug augmentation of psychological therapy in children faces a number of unique challenges. One such challenge is the need to maintain sufficient experimental control to detect effects. While large DCS effects can be demonstrated within the tight control of an animal laboratory, much smaller effects are evident in the real world (Norberg et al., 2008). Demonstrating DCS augmentation in young people may be compromised by a variety of factors, including the heterogeneity of anxiety presentations, variation in fear extinction (both within session and extraneous exposures), facilitation or hindrance of treatment by parents and potentially dubious self-report from younger children. Internal validity may also be compromised by limited knowledge regarding treatment parameters for DCS in children. For example, there are no firm guidelines regarding dosing, the duration of augmentation effects or the optimal timing of medication delivery. Finally, DCS effects may be elusive as they are relatively small compared to the effect of exposure alone (the “ceiling effect”). In many ways it is promising that researchers have demonstrated effects despite these constraints.

Experimental control can obviously be increased by standardizing treatment as much as possible. Greater control can also be gained by taking multiple forms of measurement, including BATs, diaries, video/audio record of exposure and having multiple informants. For example, the seminal study by Ressler et al. (2004) was able to dose and control acrophobia exposure using virtual reality, whilst taking behavioural, physiological and self-report measures. Post-hoc analysis of clinical trial data has also shown to be valuable to determine treatment parameters (e.g., Chasson et al., 2010; Smits et al., 2013). While a number of clinical trials to date have shown DCS does work, there now seems a particular need for research focussing on how it can most effectively be used. This is pertinent for younger clients, considering basic research suggests there may be differences in fear extinction for children, adolescents and adults (e.g., Kim & Richardson, 2010a). Experimental designs examining treatment

parameters and the development of clinical assays to test DCS effects would be of value at this stage (e.g., Rodebaugh & Lenze, 2013). As research clarifies how DCS can be used optimally, studies should produce larger and more consistent effects.

Another important issue involves being aware of and managing any negative perceptions associated with the use of medication to treat mentally ill children (e.g., Byrne et al., 2011). As discussed, parents and the community at large are often wary of the use of medication for treating children with mental disorders. Therefore, psychologists using medication may also be viewed negatively. Furthermore, psychologists have traditionally been associated with non-medical treatments, so the use of DCS could be confusing to clients. For example, parents may be less willing to take their child to a psychologist if they think their child will be medicated. When Byrne and Rapee (2013) asked parents if they thought psychologists should use cognitive enhancers to improve their therapies on an 11-point scale (0 = definitely not; 5 = maybe; 10 = definitely), they reported a high level of ambivalence ( $M = 5.7/11$ ,  $SD = 2.7$ ).

If DCS does prove to be a valuable treatment adjunct for children, parents will need to be made aware it is very different from taking psychotropic medications. The authors have found providing clear and open information regarding risks and benefits of DCS to parents and other stakeholders is important when conducting this research. As Roberts et al. (in review) report, the more parents know about DCS the less concerning they find it. There seems a particular need to conduct this research in a sensitive and open manner, with an awareness of both parent and community sentiment. Collaboration and oversight from medical doctors is also important to mitigate any (remote) risk associated with the medication. While the benefits of using DCS may be considerable and the risks minimal, researchers and clinicians should remember that individual concerns regarding DCS, whether they are imagined or real, can have implications for the development of this field.

## Current Trends and Future Directions

Research is currently examining the potential for DCS to augment treatment of specific phobias in young people. One-Session Treatment (OST) involves a single massed session of *in vivo* exposure to the feared object or situation and has shown to be a fast and effective treatment (Ollendick, et al., 2009; Ost, Svensson, Hellstrom, & Lindwall, 2001). Unfortunately 20-50% of young people still meet criteria for specific phobias following OST (Ollendick, et al., 2009), highlighting the need for augmentation strategies. Farrell, Waters, Milliner, et al. (2013) recently presented outcomes of a preliminary double-blind RCT of DCS augmented OST for youths (aged 7-17 years) with a range of specific phobias. The fears included animal phobia (mostly fear of dogs) and natural/environment phobias (mostly fear of the dark), as well as other types of phobias, such as fear of costumed characters and food neophobia. Thirty-five youths were randomly administered either DCS ( $n = 17$ ) or PBO ( $n = 18$ ) immediately before a three and a half hour OST session targeting their primary specific phobia. Youths received a weight-dependent DCS dose of either 35mg (weight  $\leq 44$ kg) or 70mg (weight  $\geq 45$ kg).

Preliminary results demonstrated a significant time by treatment interaction on clinical global severity ratings, with youths in the DCS condition demonstrating significantly greater improvements from post-treatment to one-month follow-up relative to PBO. The researchers then examined the effects of DCS on "successful exposure therapy", which was defined as at least a 40% mean reduction in Subjective Units of Distress (SUDS) during exposure session. These researchers found a significant time by treatment condition interaction across clinical global severity, clinical global improvement ratings and child rated coping beliefs at three months after therapy. In this reanalysis, there were moderate to large between group effect sizes in favour of DCS ( $n = 11$ ) relative to PBO ( $n = 9$ ;  $d = .51-.71$ ).

In another double-blind placebo controlled trial, Byrne, Rapee, Malhi, Richardson, and Hudson (2013) presented research where they treated  $N = 35$  children (aged 6-14 years) experiencing dog or spider fears with a single session of exposure in combination with 50mg of DCS ( $n = 18$ ) or a PBO ( $n = 17$ ). The parents of the children were seeking treatment for their child's fears. The fears were assessed as causing significant interference by the therapist. Improvement was measured with standardized Behavioural Approach Tests (BATs), where successive steps increased proximity/contact to the feared stimulus and anxiety ratings (SUDS) were reported at each step. BATs were conducted at Pre-Treatment and Post-Treatment to gain a baseline measurement of avoidance and

then one week later, first in the clinic (Follow-Up 1) and then outdoors to change context (Follow-Up 2). Follow-Up BATs were conducted with a different stimulus (a different dog or spider) to examine whether there was generalization of the fear extinction learning. The same stimulus was used for both Follow-Up BATs. Across all participants, there was improvement in BAT steps completed from Pre-treatment to Post-Treatment, as well as significant return of fear from Post-Treatment to Follow-Ups. The researchers were primarily interested in the extent to which fear extinction learning was retained at Follow-Up for children who took DCS versus PBO. There was no significant difference between DCS and PBO when the new stimulus was presented in the treatment context. However, when the stimulus was then presented outdoors, the DCS group demonstrated less avoidance and less increase in anxiety during the BAT. Preliminary results suggest that DCS did augment exposure therapy in these children. They also suggest this new learning generalized across different stimuli and contexts.

The promising results from preliminary DCS augmented OCD studies has led to funding for larger clinical trials. Eric Storch (the third author) recently received a grant from the USA's National Institute of Health in which  $N = 150$  youth with OCD will be randomized to receive E/RP either with DCS or placebo augmentation (McGuire et al., 2012). Primary questions include establishing if there are group differences in post-treatment outcome, the rate of response, and the degree to which gains are maintained.

## Conclusions

Research into using DCS for treating childhood anxiety is still in its infancy. Preliminary results suggest DCS can enhance exposure in young people, at least to some extent. This augmentation takes place in spite of possible developmental differences in children and adolescents (e.g., Kim & Richardson, 2010a). DCS may achieve its effects by enhancing early exposures, making subsequent exposures more successful, thereby increasing the overall speed of remission. While research suggests DCS can assist in making early gains, it also indicates that the effects of exposure alone may be commensurate by treatment endpoint (e.g., Chasson et al., 2010; Hofmann et al., 2013). Therefore, a pertinent question at this stage is whether DCS has clinical value over and above current treatments. It is important to remember that both exposure therapy and CBT are effective treatments for young people in their own right. Hence, parents, clinicians and researchers will need to weigh up the potential costs and benefits associated with DCS as an intervention for an anxious child.

Fortunately, the direct risks associated with DCS appear fairly minor, as the potential for side-effects or adverse events is very small. There have been some concerns raised about the possibility DCS may reconsolidate fearful learning should extinction be unsuccessful (e.g., Kalisch et al., 2009). While there is no evidence this represents a significant risk at this stage, clinicians and researchers should be mindful of this possibility. When considering costs, researchers and clinicians should also be aware of broader perceptual issues associated with using medication to treat children. Overall, the risks associated with DCS appear relatively small, however, it is also possible the benefits are only modest compared to the effects of first-line treatments. Yet even a small augmentation effect could be important. For example, a faster remission could reduce treatment duration and cost and prevent premature client drop-out. The cost-benefit analysis would logically shift more towards the use of DCS for treatment-resistant cases (e.g., Farrell, Waters, Boschen, et al., 2013). For example, if fear extinction failed to generalize outside of therapy, DCS augmentation may be indicated.

While RCTs in both children and adults have demonstrated effects, it would now seem valuable to understand how DCS can most effectively be used. Javitt (2013) argues there is a particular need to examine biomarkers to compliment behavioural measures, as this would help with the interpretation of negative results. There is also a need for well controlled and powered studies examining treatment parameters for using DCS in children. Some key questions include assessing optimal dosage, timing of medication delivery and determining the core mechanisms underlying DCS's therapeutic effects. Perhaps most importantly, research needs to examine if there are any age differences for DCS response.

While it is difficult to gauge the clinical value of DCS at this stage, it is clear that the theoretical implications of research into "cognitive enhancers" as adjuncts to therapy may be far reaching in the future. Researchers are continuing to gain a better understanding of the neurophysiological basis of anxiety and fear extinction (e.g., Kim & Richardson, 2010a). Neurotransmitters and receptor sites are being identified as targets for intervention. More

effective and less tolerance-prone chemical substrates may also be considered as cognitive enhancers (e.g., Javitt, 2013). As basic research develops, it will hopefully guide and translate into better clinical practice.

At this early stage, it is difficult to predict the extent to which DCS will have a role in the treatment of anxiety disorders in children and adolescents. Preliminary results indicate DCS shows some promise for enhancing exposure therapy in young people. Yet it must be acknowledged that effects in both adults and children are small and inconsistent thus far. Results from clinical trials are mixed, however, they also indicate this area should not be dismissed: research into DCS and cognitive enhancers has the potential to change how we treat and think about anxiety disorders. Young people needing fast and effective treatment for anxiety may benefit from this research in the future. As further investigation into DCS contributes to our existing knowledge, there would seem a particular need for cautious optimism, continued rigour, as well as some perspective regarding the potential benefit.

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## References

- Abramowitz, J. S., Deacon, B. J., & Whiteside, S. P. (2012). *Exposure therapy for anxiety: Principles and practice*. Guilford Press.
- Bouton, M. E. (2002). Context, ambiguity, and unlearning: sources of relapse after behavioral extinction. *Society of Biological Psychiatry*, 52, 976-986. [http://dx.doi.org/10.1016/S0006-3223\(02\)01546-9](http://dx.doi.org/10.1016/S0006-3223(02)01546-9)
- Byrne, S., & Rapee, R. (2013). [Parent Attitudes to D-Cycloserine]. Unpublished raw data.
- Byrne, S., Rapee, R., Malh, G., Richardson, R., & Hudson, J. (2013, July). D-Cycloserine Augmented Exposure Therapy for Children with Animal Phobia. In E. Milliner & L. Farrell (co-chairs), *Current Advances in Treatment for Paediatric Specific Phobia*. Symposium conducted at the 7th World Congress of Behavioural and Cognitive Therapies, Lima.
- Byrne, S. P., Farrell, L. J., & Rapee, R. M. (2011). Using cognitive enhancers to improve the treatment of anxiety disorders in young people: Examining the potential for D-Cycloserine to augment exposure for child anxiety. *Clinical Psychologist*, 15, 1-9. <http://dx.doi.org/10.1111/j.1742-9552.2011.00005.x>
- Chasson, G. S., Buhlman, U., Tolin, D., Sowmya, R. R., Hannah, E. R., Rowley, T.,... Wilhelm, S. (2010). Need for speed: Evaluating slopes of OCD recovery in behavior therapy enhanced with D-Cycloserine. *Behaviour and Research Therapy*, 48, 675-679. <http://dx.doi.org/10.1016/j.brat.2010.03.007>
- Cross-Clavert, S., & Johnston, C. (1990). Acceptability of treatments for child behavior problems: Issues and implications for future research. *Journal of Clinical Child Psychology*, 19, 61-74. [http://dx.doi.org/10.1207/s15374424jccp1901\\_8](http://dx.doi.org/10.1207/s15374424jccp1901_8)
- D'Souza, D. C., Charney, D. S., & Krystal, J. H. (1995). Glycine site agonists of the NMDA receptor: A review. *CNS Drug Reviews*, 1, 227-260. <http://dx.doi.org/10.1111/j.1527-3458.1995.tb00285.x>
- Davis, M., Ressler, K., Rothbaum, B. O., & Richardson, R. (2006). Effects of D-Cycloserine on extinction: Translation from preclinical to clinical work. *Biological Psychiatry*, 60(4), 369-375. <http://dx.doi.org/10.1016/j.biopsych.2006.03.084>
- de Kleine, R., Hendriks, G., Kusters, W., Broekman, T., & van Minnen, A. (2012). A Randomized Placebo-Controlled Trial of D-Cycloserine to Enhance Exposure Therapy for Posttraumatic Stress Disorder. *Biological Psychiatry*, 71, 962-968. <http://dx.doi.org/10.1016/j.biopsych.2012.02.033>
- Ezpeleta, L., Granero, R., de la Osa, N., & Guillamon, N. (2000). Predictors of functional impairment in children and adolescents. *Journal of Child Psychology & Psychiatry*, 41(6), 793-801. <http://dx.doi.org/10.1111/1469-7610.00666>
- Farrell, L. J., Waters, A. M., Boschen, M. J., Hattingh, L., McConnell, H., Milliner, E. L.,... Storch, E. A. (2013). Difficult-to-treat pediatric obsessive compulsive disorder: feasibility and preliminary results of a randomized pilot trial of D-Cycloserine-augmented behaviour therapy. *Depression and Anxiety*, 30, 723-731. <http://dx.doi.org/10.1002/da.22132>

- Farrell, L. J., Waters, A. M., Milliner, E., Tiralongo, E., McConnell, H., Zimmer-Gembeck, M.,... Ollendick, T. H. (2013, July). One-session treatment for childhood specific phobias: Preliminary outcomes of D-Cycloserine augmented intensive behaviour therapy. In E. Milliner & L. Farrell (co-chairs), *Current Advances in Treatments for Paediatric Specific Phobia*. Symposium conducted at the meeting of the World Congress of Cognitive and Behavioural Therapies, Lima.
- Gage & Wilson (2000). Acceptability of Attention Deficit Hyperactivity Disorder: A comparison of parents. *Journal of Attention Disorders*, 4, 178-182.
- Guastella, A. J., Dadds, M. R., Lovibond, P., Mitchell, P., & Richardson, R. (2007). A randomized controlled trial of the effect of D-Cycloserine on exposure therapy for spider fear. *Journal of Psychiatric Research*, 41, 446-471. <http://dx.doi.org/10.1016/j.jpsychires.2006.05.006>
- Guastella, A. J., Richardson, R., Lovibond, P. F., Rapee, R. M., Gaston, J. E., Mitchell, P., & Dadds, M. R. (2008). A randomised controlled trial of D-Cycloserine enhancement of exposure therapy for social phobia. *Biological Psychiatry*, 63, 544–549. <http://dx.doi.org/10.1016/j.biopsych.2007.11.011>
- Gupta, S. C., Hillman, B. G., Prakash, A., Ugale, R. R., Stairs, D. J., & Dravid, S. M. (2013). Effect of D-Cycloserine in conjunction with fear extinction training on extracellular signal-regulated kinase activation in the medial prefrontal cortex and amygdala in rat. *European Journal of Neuroscience*, 37, 1811-1822. <http://dx.doi.org/10.1111/ejn.12197>
- Guy, W. (2000). *Clinical Global Impressions Scale*. Washington DC: APA.
- Hammad, T. A., Laughren, T., & Racoosin, J. (2006). Suicidality in pediatric patients treated with antidepressant drugs. *Archives of General Psychiatry*. 63, 332-339. <http://dx.doi.org/10.1001/archpsyc.63.3.332>
- Hofmann, S., Smits, J., Rosenfield, D., Simon, N., Otto, M., Meuret, A.,... Pollack, M. (2013). D-Cycloserine as an Augmentation Strategy With Cognitive-Behavioural Therapy for Social Anxiety Disorder. *American Journal of Psychiatry*, 170, 751-758. <http://dx.doi.org/10.1176/appi.ajp.2013.12070974>
- Hofmann, S. G., Pollack, M. H., & Otto, M. W. (2006). Augmentation treatment of psychotherapy for anxiety disorders with D-Cycloserine. *CNS Drug Reviews*, 12(3-4), 208-217. <http://dx.doi.org/10.1111/j.1527-3458.2006.00208.x>
- Ipser, J. C., Stein, D. J., Hawkrigge, S., & Hoppe, L. (2009). Pharmacotherapy for anxiety disorders in children and adolescents. *Cochrane Database of Systematic Reviews* (Issue 3. ), Art. No.: CD005170.
- James, A., Soler, A., & Weatherall, R. (2006). Cognitive behavioural therapy for anxiety disorders in children and adolescents. *The Cochrane Library*, 1, 1-25.
- Javitt, D. (2013). Harnessing N-Methyl-D-Aspartate Receptors for New Treatment Development in Psychiatry: Positive Lessons from Negative Studies. *American Journal of Psychiatry*, 170(7), 699-702. <http://dx.doi.org/10.1176/appi.ajp.2013.13040503>
- Kalisch, R., Holt, B., Petrovic, P., De Martino, B., Klöppel, S., Büchel, C., & Dolan, R. The NMDA Agonist D-Cycloserine Facilitates Fear Memory Consolidation in Humans (2009). *Cerebral Cortex*, 19(1), 187-196. <http://dx.doi.org/10.1093/cercor/bhn076>
- Kim, J. H., Li, S., & Richardson, R. (2011). Immunohistochemical analyses of long-term extinction of conditioned fear in adolescent rats. *Cerebral Cortex*, 21, 530-538. <http://dx.doi.org/10.1093/cercor/bhq116>
- Kim, J., H. & Richardson, R. (2010a). New Findings on Extinction of Conditioned Fear Early in Development: Theoretical and Clinical Implications. *Biological Psychiatry*, 67, 297-303. <http://dx.doi.org/10.1016/j.biopsych.2009.09.003>
- Kim, J. H., & Richardson, R. (2010b). Extinction in preweanling rats does not involve NMDA receptors. *Neurobiology of Learning and Memory*, 94, 176-182. <http://dx.doi.org/10.1016/j.nlm.2010.05.004>
- Kushner, M. G., Kim, S. W., Donahue, C., Thuras, P., Adson, D., Kotlyar, M., et al. (2007). D-Cycloserine augmented exposure therapy for obsessive-compulsive disorder. *Biological Psychiatry*, 62(8), 835-838. <http://dx.doi.org/10.1016/j.biopsych.2006.12.020>
- Langton, J. M., Kim, J. H., Nicholas, J., & Richardson, R. (2007). The effect of the NMDA receptor antagonist MK on acquisition and extinction of learned fear. *Learning and Memory*, 14(10), 665-668. <http://dx.doi.org/10.1101/lm.692407>

- Lazaratou H., Anagnostopoulos D. C., Alevizos E. V., Haviara, F., & Ploumpidis, D. N. (2007). Parental attitudes and opinions on the use of psychotropic medication in mental disorders of childhood. *Annals of General Psychiatry*, 6, 32. doi: 10.1186/1744-859X-6-32. <http://dx.doi.org/10.1186/1744-859X-6-32>
- Litz, B. T., Salters-Pedneault, K., Steenkamp, M., Hermos, J., Bryant, R., Otto, M., & Hofmann, S. G. (2012). A randomized placebo-controlled trial of D-Cycloserine for posttraumatic stress disorder. *Journal of Psychiatric Research*, 46, 1184-1190. <http://dx.doi.org/10.1016/j.jpsychires.2012.05.006>
- McCallum, J., Kim, J., & Richardson, R. (2010). Impaired Extinction Retention of Extinguished Fear in Adolescent Rats: Effects of D-Cycloserine. *Neuropsychopharmacology*, 35, 2134-42. <http://dx.doi.org/10.1038/npp.2010.92>
- McGuire, J. F., Lewin, A. B., Geller, D. A., Brown, A., Ramsey, K., Mutch, J.,... Storch, E. A. (2012). Advances in the Treatment of Pediatric OCD: Rationale and Design for the Evaluation of D-Cycloserine with Exposure and Response Prevention. *Neuropsychiatry*, 2, 291-300. <http://dx.doi.org/10.2217/npv.12.38>
- McKay, D., Piacentini, J., Greisberg, S., Graae, F., Jaffer, M., Miller, J.,... Yaryua, T. (2003). The Children's Yale-Brown Obsessive-Compulsive Scale: Item Structure in an Outpatient Setting. *Psychological Assessment*, 578-581. <http://dx.doi.org/10.2217/npv.12.38>
- Norberg, M., Krystal, J. H., & Tolin, D. F. (2008). A meta-analysis of D-Cycloserine and the facilitation of fear extinction and exposure therapy. *Biological Psychiatry*, 63, 1118-1126. <http://dx.doi.org/10.1016/j.biopsych.2008.01.012>
- Ollendick, T. H., Ost, L.-G., Reuterskiöld, L., Costa, N., Cederlund, R., Sirbu, C.,... Jarrett, M. A. (2009). One-session treatment of specific phobias in youth: A randomized clinical trial in the United States and Sweden. *Journal of Consulting & Clinical Psychology*, 77(3), 504-516. <http://dx.doi.org/10.1037/a0015158>
- Öst, L. G., Svensson, L., Hellstrom, K., & Lindwall, R. (2001). One-session treatment of specific phobias in youths: A randomized clinical trial. *Journal of Consulting & Clinical Psychology*, 69(5), 814-824. <http://dx.doi.org/10.1037/0022-006X.69.5.814>
- Otto, M. W., Smits, J. A., & Reese, H. (2005). Combined psychotherapy and pharmacotherapy for mood and anxiety disorders in adults: Review and analysis. *Clinical Psychologist*, 12, 72-86.
- Otto, M. W., Tolin, D. F., Simon, N. M., Pearson, G. D., Basden, S., Meunier, S. A.,... Pollack, M. H. (2010). Efficacy of D-Cycloserine for enhancing response to cognitive-behavior therapy for panic disorder. *Biological Psychiatry*, 67(4), 365-370. <http://dx.doi.org/10.1016/j.biopsych.2009.07.036>
- Park, J., Small, B., Geller, D., Murphy, T., Lewin, A., & Storch, E. (2013). Does D-Cycloserine Augmentation of CBT Improve Therapeutic Homework Compliance for Pediatric Obsessive Compulsive Disorder? *Journal of Child and Family Studies*. <http://dx.doi.org/10.1007/s10826-013-9742-1>
- Pattwell, S. S., Duhoux S., Hartley, C. A., Johnson, D. C., Jing, D., Elliott, M. D.,... Lee, F. S. (2012). Altered fear learning across development in both mouse and human. *Proceedings of the National Academy of Sciences USA*, 109(40), 16318-23. <http://dx.doi.org/10.1073/pnas.1206834109>
- Pine, D. S., Helfinstein, S., Bar-Haim, Y., Nelson, E. & Fox, N. (2009). Challenges in Developing Novel Treatments for Childhood Disorders: Lessons from Research on Anxiety. *Neuropsychopharmacology*, 34, 213-228. <http://dx.doi.org/10.1038/npp.2008.113>
- Rapee, R. M. (2011). Treatments for childhood anxiety disorders: integrating physiological and psychosocial interventions. *Expert Reviews in Neurotherapeutics*, 11(8), 1095-1097. <http://dx.doi.org/10.1586/ern.11.85>
- Rapee, R. M., Schniering, C. A., & Hudson, J. L. (2009). Anxiety disorders during childhood and adolescence: Origins and treatment. *Annual Review of Clinical Psychology*, 5, 311-341. <http://dx.doi.org/10.1146/annurev.clinpsy.032408.153628>
- Rappaport, N., & Chubinsky, P. (2000). The meaning of psychotropic medication for children, adolescents and their families. *Journal of American Academy of Child and Adolescent Psychiatry*, 39, 1198-1200. <http://dx.doi.org/10.1097/00004583-200009000-00021>
- Ressler, K. J., Rothbaum, B. O., Tannenbaum, L., Anderson, P., Graap, K., Zimand, E.,... Davis, M. (2004). Cognitive enhancers as adjuncts to psychotherapy: Use of D-Cycloserine in phobics to facilitate extinction of fear. *Archives of General Psychiatry*, 61, 1136-1144. <http://dx.doi.org/10.1001/archpsyc.61.11.1136>
- Richardson, R., Ledgerwood, L., & Cranney, J. (2004). Facilitation of Fear Extinction by D-Cycloserine: Theoretical and Clinical Implications. *Learning and Memory*, 11, 510-516. <http://dx.doi.org/10.1101/lm.78204>
- Roberts, C., Farrell, L. J., Waters, A. M., & Ollendick, T. H. (in review). Parents' Perceptions of Novel Treatments for Child and Adolescent Specific Phobia and Anxiety Disorders. *Child Psychiatry and Human Development*.

- Rodebaugh, T., & Lenze, E. (2013). Lessons Learned from D-Cycloserine: The Promise and Limits of Drug Facilitation of Exposure Therapy. *Journal of Clinical Psychiatry*, 74(4), 415-416. <http://dx.doi.org/10.4088/JCP.13ac08464>
- Shaffer, D., Gould, M. S., Fisher, P., Trautman, P., Moreau, D., Kleinman, M., & Flory, M. (1996). Psychiatric diagnosis in child and adolescent suicide. *Archives of General Psychiatry*, 53(4), 339-348. <http://dx.doi.org/10.1001/archpsyc.1996.01830040075012>
- Smits, J., Rosenfield, D., Otto, M., Powers, M., Hofmann, S., Telch, M.,... Tart, C. D. (2013). D-Cycloserine Enhancement of Fear Extinction is Specific to Successful Exposure Sessions: Evidence of Treatment of Height Phobia. *Biological Psychiatry*, 73, 1054-1058. <http://dx.doi.org/10.1016/j.biopsych.2012.12.009>
- Storch, E. A., McKay, D., Reid, J. B., Geller, D. A., Goodman, C., Lewin, A. B., & Murphy, T. K. (2010). D-Cycloserine Augmentation of Cognitive-Behavioral Therapy: Directions for Pilot Research in Pediatric Obsessive-Compulsive Disorder. *Child Youth Care Forum*, 39, 101-112. <http://dx.doi.org/10.1007/s10566-010-9094-6>
- Storch, E. A., Merlo, L. J., Bengtson, M., Murphy, T. K., Lewis, M. H., Yang, M. C.,... Goodman, W. K. (2007). D-Cycloserine does not enhance exposure-response prevention therapy in obsessive-compulsive disorder. *International Clinical Psychopharmacology*, 22(4), 230-237. <http://dx.doi.org/10.1097/YIC.0b013e32819f8480>
- Storch, E. A., Murphy, T. K., Goodman, W. K., Geffken, G. R., Lewin, A. B., Henin, A.,... Geller, D. A. (2010). A Preliminary Study of D-Cycloserine Augmentation of Cognitive-Behavioural Therapy in Paediatric Obsessive-Compulsive Disorder. *Biological Psychiatry*, 68(11), 1073-76. <http://dx.doi.org/10.1016/j.biopsych.2010.07.015>
- Tart, C., Handlesman, P., Deboer, L., Rosenfield, D., Pollack, M., & Hofmann, S.,... Smits, J. A. (2013). Augmentation of Exposure Therapy with Post Session Administration of D-Cycloserine. *Journal of Psychiatric Research*, 47, 168-174. <http://dx.doi.org/10.1016/j.jpsychires.2012.09.024>
- Wilhelm S., Buhlmann U., Tolin D. F., Meunier, S. A., Pearlson G. D., Reese H. E.,... Rauch, S. L. (2008). Augmentation of behavior therapy with D-Cycloserine for obsessive-compulsive disorder. *American Journal of Psychiatry*, 165, 335-41. <http://dx.doi.org/10.1176/appi.ajp.2007.07050776>
- Walker, D. L., Ressler, K. J., Lu, K.T., & Davis, M. (2002). Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-Cycloserine as assessed with fear-potentiated startle in rats. *Journal of Neuroscience* 22(6), 2343-2351.
- Walkup, J. T., Albano, A. M., Piacentini, J., Birmaher, B., Compton, S. N., Sherrill, J. T.,... Kendall, P. C. (2008). Cognitive behavioral therapy, sertraline, or a combination in childhood anxiety. *The New England Journal of Medicine*, 359(26), 2753-2766. <http://dx.doi.org/10.1056/NEJMoa0804633>
- Zohar, A. H. (1999). The epidemiology of obsessive-compulsive disorder in children and adolescents. *Child and Adolescent Psychiatric Clinics of North America*, 8(3), 445-460.