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Enhancing Exposure Therapy for Anxiety Disorders, Obsessive Compulsive Disorder, and Posttraumatic Stress Disorder

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Abstract

Translating findings from basic science, several compounds have been identified that may enhance therapeutic outcomes and/or expedite treatment gains when administered alongside exposure-based treatments. Four of these compounds (referred to as cognitive enhancers) have been evaluated in the context of randomized controlled trials for anxiety disorders (e.g., specific phobias, panic disorder, social anxiety disorder), obsessive compulsive disorder (OCD), and posttraumatic stress disorder (PTSD). These cognitive enhancers include D-cycloserine, yohimbine hydrochloride, glucocorticoids and cortisol, and brain derived neurotrophic factor. There is consistent evidence that cognitive enhancers can enhance therapeutic outcomes and/or expedite treatment gains across anxiety disorders, OCD, and PTSD. Emerging evidence has highlighted the importance of within-session fear habituation and between-session fear learning, which can either enhance fear extinction or reconsolidate of fear responses. Although findings from these trials are promising, there are several considerations that warrant further evaluation prior to wide-spread use of cognitive enhancers in exposure-based treatments. Consistent trial design and large sample sizes are important in future studies of cognitive enhancers.

Keywords

cognitive behavioral therapy; exposure therapy; D-cycloserine; yohimbine; glucocorticoids; cortisol; brain-derived neurotrophic factor

INTRODUCTION

Psychiatric conditions classified as anxiety disorders in the Diagnostic and Statistical Manual (DSM)-Fourth Edition (Text Revision) include specific phobia (SP), panic disorder (PD), social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), and

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posttraumatic stress disorder (PTSD) [1]. Although SP, PD, and SAD remained classified as anxiety disorders in the updated DSM-Fifth Edition, OCD and PTSD were reclassified separately due to their distinctive features [2]. These psychiatric conditions (formerly classified as anxiety disorders) affect between 2% and 29% of individuals [3,4], and are characterized by clinically significant fear, anxiety, and distress that occurs in response to stimuli and/or situational cues. Although the etiology of these conditions may be multi-factorial, the mechanisms of fear learning (i.e., fear conditioning) play an important role in symptom acquisition and maintenance. Anxiety develops when a previously neutral stimulus becomes paired with an aversive stimulus via classical conditioning. Examples of fear learning exist across all formerly classified anxiety disorders: SP (e.g., seeing a spider--worries about being harmed by the spider); PD (e.g., panic attack outside of the house--worries about panic attack whenever leaving home); SAD (e.g., public speaking--worries about negative social evaluation); OCD (e.g., touching a door handle--worries about being contaminated by a virus); and PTSD (e.g., driving a car--worries about being in a car accident again). Thus, a relative neutral stimulus generates a conditioned fear response associated with the original aversive stimulus, which in turn elicits anxiety and distress. In response to the acquired fear and anxiety, the individual engages in avoidance and/or compulsive behaviors to alleviate the experienced distress. The reduction in anxiety and distress associated with avoidance or compulsive behaviors negatively reinforces these actions, and contributes to its maintenance (and enhancement) via negative reinforcement [5,6]. As avoidance and compulsive behaviors temporarily alleviate distress, these behaviors persist and prohibit new learning opportunities taking place that could potentially extinguish the conditioned fear response.

Cognitive behavioral therapy (CBT) is an efficacious treatment for anxiety disorders (SP, PD, SAD), OCD, and PTSD [7]; with the core therapeutic component being exposure with response prevention. While fear learning plays a pivotal role in symptom acquisition and maintenance, fear extinction plays a central role in its treatment. In exposure-based CBT, patients are repeatedly exposed to situational (e.g., separation from parents, public speaking, touching a “contaminated” object) and/or internal triggers (e.g., increased heart rate, shortness of breath) via imagined or i*n vivo* exposures that elicit anxiety and trigger compulsive behaviors (e.g., seeking reassurance, hand washing) or avoidance. While completing these exposures, patients are instructed to resist engaging in compulsive behaviors and avoidance and learn to habituate to the associated anxiety and distress. As habituation to feared stimuli is achieved without engagement in avoidance or compulsive behaviors, patients learn that these behaviors are not required to reduce anxiety and recognize their inaccurate appraisal of feared outcomes. Thus, the associations between previously acquired fear and worrisome consequences are diminished via extinction of the negative reinforcement paradigm. Moreover, new fear learning occurs that develops and strengthens new associations between the feared stimuli and non-feared outcomes. Through repeated and graduated exposures, severity of symptoms decrease.

Randomized controlled trials (RCTs) have found positive treatment outcomes for exposure-based therapies relative to control conditions for adults with anxiety disorders, OCD, and PTSD [7,8], with parallel findings among youth with anxiety disorders [9,10], OCD [11,12],

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and PTSD [13]. Despite its noted efficacy, several challenges exist when implementing exposure-based treatments for these psychiatric conditions. First, a considerable percentage of youth and adults do not adequately respond to exposure-based therapies (40–60%), with a limited number of participants achieving symptom remission (15%–46%) [9,11,14]. Second, treatment discontinuation poses a challenge for exposure-based therapies, with attrition rates among RCTs ranging between 13%–27% [15–17]. Treatment discontinuation may occur for several reasons including difficulty engaging in exposures, a perceived lack of immediate therapeutic benefit, or treatment burden. Third, there are a limited number of trained treatment providers that conduct exposure-based therapies, which prohibits many patients from either receiving exposure-based treatment or experiencing long-waiting periods prior to treatment. Across these challenges, a common theme emerges for the need to enhance therapeutic outcomes and expedite treatment gains of exposure-based therapies. 'Enhanced' or 'improved' therapeutic outcome refers to: (a) greater reductions in symptom severity or (b) greater treatment response rates at post-treatment or follow-up assessments. Meanwhile, 'expedited' treatment gains describes the phenomena of patients: (a) exhibiting significant therapeutic benefit earlier in treatment or (b) obtaining treatment goals in a shorter duration. If the therapeutic benefits of exposure-based treatments were improved, a greater number of patients could potentially achieve symptom remission. Moreover, if therapeutic gains were expedited, barriers to treatment attrition (e.g., a perceived lack of immediate therapeutic benefit) could be diminished, and treatment duration periods could be potentially shortened. Collectively, this could allow trained practitioners to provide more patients with evidence-based care.

When considering options to enhance therapeutic outcomes and expedite treatment gains for exposure-based therapies, there exists some support for the augmentation of exposure-based treatments with serotonin reuptake inhibitors (SRIs)[9]. Although commonly used in clinical practice, this therapeutic approach does not consistently yield greater therapeutic outcomes [12,15] and may be accompanied by adverse side effects [18]. Cognitive enhancers present an alternative option to safely enhance therapeutic outcomes and expedite treatment gains for exposure-based therapies. Broadly stated, cognitive enhancers are compounds that influence signaling pathways involved in synaptic plasticity of brain regions (e.g., amygdala, hippocampus, prefrontal cortex) associated with fear learning to enhance the neurological circuitry of fear extinction. Several cognitive enhancers have been examined in both animal and human studies (see Fitzgerald, Seemann & Marin [19] for an extensive review). Although prior reviews have examined the efficacy of cognitive enhancing compounds either by themselves [20] or for specific disorders [21], this review synthesizes and extends prior reports by evaluating the evidence for multiple cognitive enhancers across psychiatric conditions formerly classified as anxiety disorders. A comprehensive literature search of cognitive enhancers was conducted using PubMed and PsycInfo, and was circumscribed to human RCTs. Four cognitive enhancers were identified that have been evaluated in the context of RCTs for youth and adults. This paper reviews the support for D-cycloserine (DCS), yohimbine hydrocholoride (YHCL), glucocorticoids and cortisol (G-CORT), and brain-derived neurotrophic factor (BDNF), and examines the ability of these cognitive enhancers improve therapeutic outcomes and expedite treatment gains of exposure-based treatments.

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D-cycloserine (DCS)

Animal studies have revealed that the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor found in the amygdala and prefrontal cortex plays a critical role in fear extinction (see Davis [22] for a detailed review). Recognizing the implications of these findings, several clinical researchers have explored the use of D-cycloserine (DCS) to enhance and expedite extinction learning. D-cycloserine is a partial NMDA agonist that has been approved by the United States Food and Drug Administration (FDA) for the treatment of tuberculosis. As evidence suggests that fear learning is dependent upon neural activity in the amygdala and involves the neural transmission of glutamate through NMDA receptors [23], it is believed that acute DCS administration stimulates NMDA glutamate synapses involved in emotional learning and strengthens extinction learning that takes place in the context of exposure-based treatments [24,25]. Although different neural mechanisms may be utilized depending on the temporal delay of fear extinction relative to fear learning [26], multiple studies indicate that the neural associations between feared stimuli and conditioned responses are not “forgotten” and instead new associations are developed that eventually predominate over the prior associations [22]. Beyond promoting the extinction of conditioned fear [27,28], there is some evidence to suggest that DCS also facilitates the consolidation of fear learning associated with extinction training [29]. Indeed, memory consolidation is an important mechanism in fear learning, as emerging research has found that extinction training during periods of memory reconsolidation has the potential to either enhance or diminish previously learned fear [30,31]. Translated into a therapeutic context, these findings suggest that learned fear memories can be updated with new information during specific time periods that can allow practitioners to maximize the therapeutic effects of exposure-based treatments. Randomized controlled trials have examined the benefit of DCS-augmented exposure-based treatment across specific phobias (e.g., acrophobia [32,33], arachnophobia [34,35], ophidiophobia [36]), PD [37,38], SAD [39–42], OCD [43–48], and PTSD [49–52]. Table 1 presents the characteristics and findings from RCTs that have evaluated DCS in the context of exposure-based interventions.

Specific Phobias (SP)—Several RCTs have evaluated the benefit of exposure enhanced DCS for SP. In the first RCT evaluation of DCS-augmented exposures, Ressler et al. [32] compared exposure therapy conducted using virtual reality for acrophobia (fear of heights) that was augmented with either 50mg, 500mg, or a placebo. Although Ressler et al. [32] found no significant difference between participants receiving different DCS dosages, Ressler et al. [32] identified improved therapeutic outcomes at post-treatment and the follow-up assessment for participants receiving DCS-augmented exposures relative to placebo. Moreover, participants receiving DCS-augmented exposures also exhibited expedited treatment gains relative to placebo [32]. Similar findings for an expedited therapeutic benefit were observed among DCS-enhanced exposures for ophidiophobia (fear of snakes) as evidenced by shorter time to complete a 13-step exposure hierarchy [36], as well as enhanced therapeutic outcome after DCS-augmented subliminal exposures for sub-threshold arachnophobia (fear of spiders) as evidenced by a significantly lower rating of disgust [35]. Countering these findings, Guastella et al. [34] found no enhanced benefit of DCS-augmented exposures among individuals with sub-threshold arachnophobia. Similarly, Tart et al. [33] found no enhanced therapeutic benefit of DCS-augmented virtual reality

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exposure therapy for acrophobia. However, the DCS administration timing for those RCTs with null findings varied from the previous studies. When DCS was administered approximately one hour prior to exposure sessions, a positive effect was found. However, Guastella et al. [34] administered DCS between two to three hours prior to a single session exposure and Tart et al. [33] administered DCS immediately after exposure sessions. While the findings from Guastella et al. [34] suggest that dose timing and level of fear may influence DCS-augmented exposure outcomes in specific phobias, post-hoc analyses of Tart et al. [33] reveal a more nuanced relationship. D-cycloserine administered after exposure sessions appeared to enhance the benefits of successful exposure therapy sessions (as defined by a low fear level at the end of a session), but had adverse consequences when administered after inadequate exposure session (as defined by a high fear level at the end of a session) [53]. Collectively, these findings suggest exposure-based therapy augmented with DCS can significantly improve therapeutic outcomes and expedite treatment gains for individuals with SP when provided in close proximity to exposures sessions (within 1 hour before or after) and in the context of within-session fear habituation.

Panic Disorder (PD)—Two RCTs have evaluated the therapeutic benefit of DCS in enhancing exposure-based therapy for individuals with PD. Although only using a brief five session treatment protocol, Otto et al. [37] found that DCS enhanced therapeutic outcomes at post-treatment and follow-up assessments. Contrary to Otto et al. [37], Siegmund et al. [38] did not find any significant difference between DCS or placebo augmented exposure-based group CBT that was delivered over eight sessions (three exposure sessions) over a month. Post-hoc analyses of Siegmund et al. [38] identified that participants with a higher baseline panic symptom severity experienced greater therapeutic benefit on DCS relative to placebo on the Panic and Agoraphobia Scale (PAS). Neither trial examined whether DCS expedited therapeutic gains during treatment. Taken together, these findings suggest that DCS-augmented exposure-based therapy can enhance therapeutic outcomes for individuals with PD, but may be particularly beneficial for individuals with higher baseline panic symptom severity. Although promising, a well-powered clinical trial would useful to replicate and confirm these initial findings and examine expedited treatment gains.

Social Anxiety Disorder (SAD)—Four RCTs have examined the enhancing properties of DCS among individuals with SAD. In three of the four RCTs, participants receiving DCS and exposure-based treatment exhibited enhanced therapeutic outcomes at post-treatment and follow-up assessments on either the Liebowitz Social Anxiety Scale (LSAS)[39,40], Social Phobia and Anxiety Inventory (SPAI)[39,40] or the Social Phobia Scale (SPS)[42]. Although treatment response and symptom remission rates favored DCS over placebo, no significant group differences were found in a well-powered multi-center RCT that administered 12 sessions of group exposure-based CBT to 169 participants [41]. When examining expedited treatment gains, Guastella et al. [40] found no significant difference until the fifth therapy session that occurred immediately prior to the post-treatment assessment. Alternatively, Hofmann et al. [41] identified that DCS participants exhibited faster improvement on the weekly administered LSAS and the Social Phobic Disorders Scale (SPD). Similarly, Rodebaugh et al. [42] found that a single exposure session augmented with DCS produced significant benefit on the SPS relative placebo augmentation

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(Cohen's $d = 1.06$), with treatment effect sizes being comparable to treatment studies using abbreviated treatment protocols (e.g., $d = 0.98$ [39]). Findings from these trials provide evidence that DCS can improve therapeutic outcomes for individuals with SAD, however this enhanced benefit may be minimized or not significant in the context of a full-course of treatment (e.g., 12 exposure-based CBT sessions). These findings also suggest that DCS expedites therapeutic improvement, which may account for enhanced therapeutic outcomes in trials using an abbreviated treatment protocol.

Obsessive Compulsive Disorder (OCD)—Six RCTs have examined the benefit of DCS in exposure-based treatments for individuals with OCD, with three RCTs focused specifically on youth with OCD. In four RCTs, participants receiving DCS and exposure-based treatment exhibited small-to-moderate enhanced treatment effects at post-treatment and follow-up assessments on the Children's/Yale-Brown Obsessive-Compulsive Scale (C/Y-BOCS) that did not reach statistical significance [43,45,46,48]. Similarly, two other studies found no significant difference between groups, but identified that results favored placebo-augmented exposure therapy over DCS [44,47]. Notably, the timing of dose administration differed for these two studies (e.g., four hours before exposure sessions, immediately after exposure sessions) relative to trials that found small-to-moderate DCS treatment effects (e.g., one to two hours before exposure sessions). When evaluating the presence of expedited treatment gains, Kushner et al. [43] found that participants receiving DCS reached subjective units of distress scale (SUDS) reduction criteria for discontinuing treatment in two fewer treatment sessions compared to the placebo group (SUDS ratings reduced by 50% of initial baseline rating), and had a lower treatment dropout rate (6% versus 35%). Wilhelm et al. [46] identified improvement among participants receiving DCS relative to placebo at the mid-treatment assessment, with post-hoc analyses identifying that therapeutic gains were achieved more quickly for participants receiving DCS relative to placebo [54]. Storch et al. [45] also found greater effects for youth receiving DCS relative to placebo at mid-treatment, but the difference was not statistically significant. Contrary to this emerging evidence of expedited treatment gains, Mataix-Cols et al. [47] did not find a significant difference between group at mid-treatment with results favoring placebo receiving participants.

Taken together, these findings suggest that small-to-moderate enhanced therapeutic outcomes may be observed in trials administering DCS one to two hours before exposure therapy sessions, with participants receiving DCS exhibiting expedited therapeutic improvement earlier in treatment. Given that most of these studies have small-to-moderate sized samples, a soon-to-be completed large-scale RCT will prove useful to evaluate these findings in a well-powered study [55]. Compared to DCS trials in related psychiatric conditions, DCS utilization in OCD presents a unique challenge. For instance, evidence suggests that DCS can enhance fear learning and extinction, however not all OCD symptoms are fear based. Indeed, there is some evidence that youth with fear-based and non-fear based symptoms exhibit differential neuropsychological [56] and clinical outcomes [57,58]. Thus, future examinations should assess whether enhanced therapeutic outcomes and expedited treatment gains differ across these two broad symptom subtypes.

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Posttraumatic Stress Disorder (PTSD)—Five RCTs that have evaluated DCS-augmented exposure-based treatments for individuals with PTSD, with only a single trial focused on youth. In two of the five RCTs, enhanced therapeutic outcomes were observed at post-treatment or follow-up assessments on the Clinician Administered PTSD Scale (CAPS) for participants receiving DCS-augmented exposure therapy relative to placebo [49,51]. Further analysis by de Kleine et al. [49] found that participants with a greater baseline PTSD symptom severity who completed a full treatment course exhibited greater effects when therapy was augmented with DCS relative to placebo. Countering these findings, Litz et al. [50] identified that participants receiving placebo-augmented therapy had greater therapeutic outcomes compared to DCS on the CAPS at post-treatment. Similarly, Scheeringa and Weems [52] found greater treatment effects that trended toward significance on the Child/PTSD Symptom Scale (C/PSS) for youth receiving placebo-augmented treatment at post-treatment. While Rothbaum et al. [59] found no significant difference between DCS or placebo-augmented virtual reality exposure therapy on the CAPS or PSS in a large-scale RCT, treatment effects favored placebo over DCS. When examining expedited treatment gains, Difede et al. [51] found that participants receiving DCS-augmented treatment exhibited a greater reduction on the CAPS that trended toward significance by the sixth therapy session, and achieved statistical significance at post-treatment. Interestingly, when Litz et al. [50] conducted post-hoc analysis on SUDS ratings at each session, participants receiving DCS reported higher pre-exposure distress only after the first exposure therapy session. Furthermore, when Scheeringa and Weems [52] conducted a detailed session-by-session analysis of the CPSS, they found a relatively linear decline in PTSD symptoms in the placebo group but greater variability among participants receiving DCS. Collectively, available evidence suggests that DCS can enhance therapeutic outcomes and expedite treatment gains for exposure-based treatment among individuals with PTSD, but other factors such as fear habituation may influence these results. For instance, Litz et al. [50] found that participants in the DCS group experienced higher pre-exposure distress only after the initial exposure session, suggesting that DCS administration may have inadvertently enhance reconsolidation of feared memories rather than improving fear extinction learning. Similarly, Rothbaum et al. [59] found that participants in the DCS group who had greater between-session fear learning (i.e., average decrease in peak SUDS ratings across exposures sessions) experienced greater therapeutic improvement on the CAPS and PSS, whereas those DCS group participants with lower between-session fear learning had worse therapeutic outcomes. The relationship between between-session fear learning and therapeutic outcome was not significant for the placebo group. These findings highlight the importance of within-session habituation and between-session fear learning when implementing DCS-augmented exposure therapy to maximize therapeutic outcomes and prevent enhancement of existing fear memories.

Yohimbine Hydrochloride (YHCL)

While some cognitive enhancers like DCS focus on augmenting NMDA receptors to enhance fear learning, other cognitive enhancers target the adrenergic/noradrenergic system to facilitate fear extinction. The noradrenergic system and its neurotransmitter norepinephrine are important in emotional memory as they are responsible for increased sympathetic nervous system reactivity (i.e., the fight-or-flight response), and serve as an

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indicator of stress. Norepinephrine is associated with memory for emotion evoking stimuli, and its release during extinction may enhance memory formation [60,61]. Yohimbine hydrochloride (YHCL) is an over-the-counter supplement that acts as a selective alpha2-adrenergic receptor antagonist, and increases norepinephrine in brain region areas implicated in extinction learning (e.g., medial prefrontal cortex, amygdala, hippocampus) [62,63]. As noradrenergic activity has been implicated in the consolidation of emotional memories [64,65], YHCL's increase in central noradrenergic activity vis-a-vis norepinephrine may serve as the mechanism for its influence on fear extinction [66,67]. A series of animal studies have demonstrated that YHCL can accelerate and enhance fear extinction [68], with mixed findings emerging among human studies. When examining group differences between YHCL and placebo administered prior to conditioning, O'Carroll et al. [69] found that participants receiving YHCL exhibited a stronger physiological reaction and recalled more emotion-related slides relative to participants receiving placebo. Contrary to these findings, Southwick et al. [70] found no significant difference in emotion-related recall between groups when YHCL and placebo were administered post conditioning. Similarly, when YHCL was administered during a differential fear conditioning paradigm, it was found to impair fear extinction and increased fear during a subsequent conditioning paradigm relative to placebo [71,72]. Taken together, these findings suggest that a nuanced relationship exist between YHCL and fear enhancement among humans, with findings influenced by timing of dose administration. Translating these findings into a treatment context, there have been three RCTs that have examined whether YHCL enhances outcomes and expedites fear extinction among individuals receiving exposure-based treatments [73–75], with at least one ongoing trial examining its benefit among veterans with PTSD [76]. Table 2 presents the characteristics and findings from these three completed RCTs.

Specific Phobia (SP)—Two RCTs have evaluated the added benefit of YHCL relative to placebo among individuals with SP such as claustrophobia (e.g., fear of small spaces) [73] and aerophobia (e.g., fear of flying)[74]. There were no significant group differences at post-treatment in either trial, however the results from one trial favored YHCL with large treatment effects [73]. Although one trial did not conduct a follow-up assessment, the other trial identified enhanced therapeutic outcomes on several measures with large treatment effects [73]. Neither RCT examined whether YHCL produced expedited treatment gains relative to placebo augmentation, which may be attributed to the brief treatment duration (2–4 weeks) and few treatment sessions provided (2–4 sessions). Given the contrasting results, further research is needed to clarify whether YHCL enhances therapeutic outcome and expedites treatment gains for individuals with SP receiving exposure-based treatment.

Social Anxiety Disorder (SAD)—One RCT has evaluated the benefit of YHCL augmented exposure-based treatment for individuals with SAD. Although no comparisons were reported at the post-treatment assessment, Smits et al. [75] found that participants receiving YHCL augmented exposure-based CBT exhibited improved therapeutic outcomes on the LSAS relative to participants receiving placebo. Smits et al. [75] identified that participants receiving YHCL exhibited expedited treatment gains on the LSAS relative to participants receiving placebo. When conducting a session-by-session analysis, Smits et al. [75] found a significant relationship between end of session fear (i.e., within-session fear

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habituation) and the LSAS rating at the following session for participants receiving YHCL, but not placebo. Although future studies are needed to replicate these findings, this preliminary evidence suggests that YHCL enhances therapeutic outcome and expedites treatment gains for individuals with SAD. Concurrently, these findings draw attention to the fear enhancing properties of YHCL and highlight the importance of within-session fear habituation for positive treatment outcomes.

Glucocorticoids and Cortisol (G-CORT)

Glucocorticoids and cortisol (G-CORT) are a class of naturally occurring steroid hormones released from the adrenal cortex that regulate stress responses to changing internal and external environments. Building upon the existing relationship between the release of cortisol in response to fear and its impact on memory, detailed investigations have explored the influence of G-CORT on learning and memory processes (see De Quervain et al. [77] for a comprehensive review). There is evidence to suggest that G-CORT can enhance memory consolidation [78,79], with systemic administration of C-CORT enhancing long-term memory consolidation when administered either prior to or immediately after training [78,80,81]. Animal studies suggest that G-CORT effects on memory consolidation are dose dependent, with moderate doses enhancing memory and higher doses potentially impairing memory consolidation [81]. Beyond impacting memory consolidation, studies have also identified that administration of G-CORT can impair retrieval of non-feared based memories [82,83] and fear-related memories [84–86]. Integrating these findings into a therapeutic context, there have been three RCTs examining whether G-CORT can enhance fear extinction among phobic individuals receiving exposure-based treatment [87–89], with no examination of G-CORT in other anxiety disorders, OCD, or PTSD. Table 3 presents the characteristics and findings from the three RCTs that have evaluated G-CORT.

Specific Phobia (SP)—Three RCTs have evaluated the additive benefit of G-CORT relative to placebo in enhancing exposure-based treatment of individuals with SP (e.g., arachnophobia, acrophobia) [87–89]. Across all three RCTs, there is consistent evidence of enhanced therapeutic outcome at either post-treatment or follow-up assessments, with moderate-to-large effects observed. Unfortunately, there has been no direct examination of whether G-CORT augmented exposure-based therapy produces expedited treatment gains. Thus, while G-CORT appears to consistently enhance therapeutic outcomes, there is no evidence for that it produces expedited treatment gains.

While these results are promising, there are several considerations that warrant caution. First, no large-scale well-powered RCT of G-CORT exists with most studies having small-to-moderate sample sizes. Second, G-CORT has only been evaluated for specific phobias and findings may not generalize to other anxiety disorders, OCD, or PTSD. Third, there has been no direct evaluation of expedited treatment gains among RCT augmenting treatment with G-CORT. Given that these three RCTs had a short duration (1–2 weeks) and provided few therapy sessions (2–6 sessions), this examination would prove critical toward understanding how G-CORT improves therapeutic outcomes at post-treatment and follow-up assessments. For instance, it may be that expedited treatment gains are driving the moderate-to-large between group differences found at the short post-treatment and one-

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month follow-up assessments. Future studies would benefit from a longer treatment duration and evaluation of G-CORT in augmenting exposure-based treatments among other anxiety disorders, OCD, and PTSD.

Brain-Derived Neurotrophic Factor (BDNF)

Brain-derived neurotrophic factor (BDNF) is the most abundant neurotrophin in the central nervous system, and has a high affinity receptor tropomyosin-related kinase B (TrkB) [90]. Brain-derived neurotrophic factor and its high affinity receptor TrkB are found throughout brain regions associated in fear learning (e.g., prefrontal cortex, amygdala, hippocampus), and are essential for synaptic plasticity processes that are a prerequisite for long-term learning and memory [91]. Indeed, BDNF and TrkB have been implicated in fear learning, fear extinction, and fear memory reconsolidation across several studies (see Andero and Ressler [92] for a comprehensive review). Single-nucleotide polymorphism (SNP) evaluations have established genetic associations between BDNF and several psychiatric conditions (e.g., schizophrenia, depression, PTSD)[93]. Specifically, individuals with the Val66Met polymorphism that consists of a substitution of *Met* for *Val* at position 66 in the pro-region of BDNF, have been reported to experience decreased BDNF availability [93–95], and exhibit deficits in memory and extinction learning [96]. While the presence of the BDNF Val66Met variation did not definitively predict BDNF levels among non-clinical populations [97], BDNF and the TrkB system has been found to influence treatment outcomes in antidepressant studies [98,99]. Moreover, some evidence suggests that the BDNF and TrkB system may also modulate other cognitive enhancers (e.g., DCS) as BDNF increases glutamate release and enhances glutamate receptor NMDA subtype activity [91]. Indeed, animal studies demonstrate that mice withVal66Met exhibit impaired NMDA receptor dependent synaptic plasticity [94] and impaired fear extinction that is ameliorated by systemic administration of DCS [100]. Recognizing the clinical implications of these findings, several studies have examined the association between BDNF biomarkers (e.g., BDNF levels, BDNF Val66Met) and treatment outcome to exposure-based therapies. Table 4 presents the characteristics and findings from the three RCTs.

Panic Disorder (PD)—One RCT has examined the association between BDNF biomarkers and therapeutic response to exposure-based treatment among individuals with PD [101]. Kobayashi et al. [101] found that participants who exhibited at least a 40% reduction in symptom severity on the PDSS (classified as a treatment responder) exhibited significantly higher levels of BDNF serum at baseline relative to participants who were non-responders to treatment. There was no examination between the association of baseline BDNF serum levels and expedited treatment gains. Furthermore, the relationship between antidepressant medication status and BDNF serum was not reported, and may have influenced results. Although promising, there is a clear need to replicate these findings in well-powered clinical trials.

Obsessive Compulsive Disorder (OCD)—One RCT has examined the association between BDNF biomarkers and treatment outcome in OCD [102]. Participants were partial or non-responders to a 12-week trial of a selective serotonin reuptake inhibitors (SSRIs), who were on a stable antidepressant dose and received exposure-based CBT [102]. Fullana

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et al. [102] found no significant difference in symptom severity reductions on the Y-BOCS between individuals with and without the BDNF Val66Met polymorphism after 20 weekly sessions of exposure-based CBT. However, chi-square analyses revealed that the number of participants who exhibited at least a 35% reduction on the Y-BOCS (classified as a treatment responder) significantly differed between groups (36% treatment response in BDNF Val66Met carriers versus 60% response in BDNF Val66Met non-carriers, χ^2=4.89, p=0.03) [102]. A follow-up examination by symptom dimensions revealed this difference to be particular salient for individuals with contamination/cleaning symptoms (n = 46), in which participants possessing the BDNF Val66Met allele had a markedly lower response rate (0%) relative to participants without the allele (58%) [102]. Despite the promising results of this initial investigation, Fullana et al. [102] only included adults with OCD who were partial or non-responders to SSRIs. Future research studies are needed to replicate these findings in a more representative sample, and also examine whether BDNF biomarkers are associated with expedited treatment gains in exposure-based therapies for individuals with OCD.

Posttraumatic Stress Disorder (PTSD)—One RCT has evaluated the association between BDNF biomarkers and treatment outcome to exposure-based therapy for individuals with PTSD [103]. In a sample of 55 medication-free civilians adults, Felmingham et al. [103] found that participants with the BDNF Met allele exhibited less improvement on the CAPS (40% reduction in symptom severity) relative to participants without the BDNF Met Allele (62% reduction in symptom severity). Additionally, participants without the BDNF Met allele had lower overall CAPS scores at post-treatment, with no follow-up assessment completed. Although these initial findings are promising, future research is needed to replicate these results and also examine whether BDNF biomarkers are also associated with expedited treatment gains.

DISCUSSION

Translating basic science findings on fear conditioning into clinical applications, considerable progress has been made in enhancing and expediting therapeutic outcomes using cognitive enhancers in the treatment of individuals with anxiety disorders, OCD, and PTSD. This paper reviewed the evidence of four cognitive enhancers (DCS, YHCL, G-CORT, and BDNF biomarkers) in improving therapeutic outcomes and expediting treatment gains in RCTs that used exposure-based treatments. D-cycloserine was the most well-studied cognitive enhancer. Collectively, findings from the 22 RCTs that used DCS-augmented exposure-based treatments suggest that DCS can produce small-to-moderate improvements in therapeutic outcomes and expedite treatment gains. Most trials used 50mgs of DCS to augment exposure treatments, with few trials using dosages greater than 50mg. Although Ressler et al. [32] found no significant difference between exposure sessions augmented by either 50mg or 500mg of DCS, further replication of these findings in other psychiatric disorders would prove informative to ascertain a more definitive relationship between DCS dose and outcome in human trials. Although the findings on DCS-augmented exposures treatment are generally positive, there remains some question about the additive benefit of DCS in treatment studies with longer durations. An updated meta-analysis on

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RCTs of DCS would prove useful to quantitative evaluate treatment effects using consistent treatment outcome measures, and identify potential moderators of treatment (e.g., number of sessions, trial duration). Moreover, the findings by Smits et al. [53] and Rothbaum et al. [59] highlight the importance of within-session habituation and between-session fear learning in achieving therapeutic benefit in DCS-augmented exposure therapy. Beyond replicating these results in other DCS trials, there is a clear need to identify other therapeutic ingredients to maximize exposure sessions, and develop protocols to monitor these treatment components in future RCTs and eventual clinical practice. Indeed, small-to-moderate improvements in therapeutic outcomes reported in current RCTs may be more robust when within-session habituation and between-session fear learning are achieved throughout treatment. Research has begun to examine components of within-session [104] and between-session exposure treatments [105], with further research needed to expand upon the preliminary findings reported in two DCS trials [53,59]. Furthermore, as fear learning continues beyond the treatment session, it would prove informative to examine other factors such as homework compliance and its relation to improved therapeutic outcomes and expedited treatment gains [106].

Yohimbine hydrochloride (YHCL) is another promising cognitive enhancer that has been evaluated in three RCTs, with a fourth RCT soon-to-be completed. Preliminary evidence highlights YHCL's potential to enhance therapeutic outcomes and expedite treatment gains in exposure-based treatments, with benefits being more evident at follow-up assessments. Although promising, additional well-powered RCTs are needed to assess YHCL's utility in other anxiety disorders, OCD, and PTSD. Moreover, as YHCL has demonstrated tolerability among youth [107], future studies should examine YHCL's enhancement ability for childhood anxiety disorders, OCD, and PTSD. Consistent with DCS-augmented exposure treatments, findings by Smits et al. [75] draw attention to the importance of within-session habituation during YHCL-augmented exposure session. Further studies are needed to replicate these findings, and also explore between-session fear learning findings reported by Rothbaum et al. [59]. A detailed evaluation of YHCL-augmented exposure sessions would prove useful to determine if relevant therapeutic ingredients differ between cognitive enhancers. Moreover, there is a need to identify and evaluate these therapeutic ingredients to maximize fear extinction rather than facilitating the reconsolidation of existing fear memories.

Glucocorticoids and cortisol (G-CORT) exhibit a consistent benefit for enhancing therapeutic outcomes of exposure-based treatments, but have only been evaluated in three RCTs for specific phobias. Moreover, there is no examination of expedited treatment gains in any of these studies, with all studies excluding youth. Future studies are needed to evaluate the utility of G-CORT beyond adults with specific phobias, and also examine whether the findings pertaining to within-session fear habituation and between-session fear learning observed in other cognitive enhancers generalize to G-CORT. Furthermore, there is a need to evaluate an optimal dose range of G-CORT in exposure augmentation. To date, the three existing RCTs have used between 10mg to 20mg of G-CORT to augment exposure sessions. Given the dose dependent relationship of G-CORT observed in animal studies [81], it would prove useful to determine an optimal dose range to facilitate fear extinction rather than impair memory consolidation during treatment. Thus, a large-scale and well-

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powered RCT would prove useful to providing more definitive results for G-CORT's use in augmenting exposure-based treatments.

Brain-derived neurotrophic factor (BDNF) and its biomarkers (e.g., BDNF levels, BDNF Val66Met) have consistent empirical support for their association with improved therapeutic outcomes. However, there has been no evaluation of expedited treatment gains for BDNF biomarkers, with no studies including youth. Given that only three RCTs have evaluated the association between BDNF biomarkers and exposure-based treatments, future studies are needed to replicate and generalize these findings to other psychiatric conditions (e.g., SP, SAD). Moreover, given the purported overlap in receptors and shared mechanisms with DCS, it would prove interesting to examine BDNF biomarkers among treatment studies using DCS to augment exposure-based treatments.

There is clear and consistent evidence that cognitive enhancers can improve therapeutic outcomes and expedite treatment gains for exposure-based treatments, with the most well-tested cognitive enhancer being DCS. The relationship between cognitive enhancers and treatment outcomes has been found to nuanced, with within-session fear habituation and between-session fear learning serving as key ingredients in either enhancing fear extinction or reconsolidating existing fear memories. As the field continues to advance, there is a need to closely monitor adverse events (e.g., enhancement of fear, etc.) among these augmentation psychotherapy trials that may go initially unnoticed [108]. Moreover, future research is needed to determine whether specific cognitive enhancers are more or less appropriate for specific individuals, conditions, and treatment durations. Given the challenges that currently confront the implementation of exposure-based treatment for anxiety disorders, OCD, and PTSD, cognitive enhancers present an optimal option to safely enhance therapeutic outcomes and expedite treatment gains that may limit treatment attrition, and abbreviate treatment duration for patients that can increase the availability of trained practitioners.

EXPERT COMMENTARY

Based on the available evidence, DCS has some preliminary support as a cognitive enhancer for anxiety disorders, OCD, and PTSD due to its demonstrated benefit, widespread evaluation, and minimal side effects, albeit findings are mixed. Although YHCL and G-CORT demonstrate potential promise as cognitive enhancers, these compounds require further evaluation to generalize their findings and would benefit from evaluations in samples of youth with anxiety disorders, OCD, and PTSD. Finally, BDNF and its biomarkers are naturally occurring substances within human physiology that have been associated with therapeutic outcomes. Given the few number of studies examining BDNF and its biomarkers, we would encourage further evaluation in clinical and community settings prior to making any substantive recommendations. Although cognitive enhancers offer the promise of improved therapeutic outcomes and expedited treatment gains, these compounds are still in experimental stages and are not recommended for common clinical use until conclusive trials have been completed. Moreover, given the emerging importance of within-session fear habituation and between-session fear learning, there is a potential benefit of

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refining treatment guidelines to ensure that fear extinction is enhanced during exposure-based treatment rather than allowing the reconsolidation of fear to occur.

FIVE YEAR VIEW

As the field continues to develop, there are several goals to achieve. First, a consistent trial design (e.g., trial duration, dose administration, uniform measurement of within-session habituation and between-session fear learning) would prove beneficial to consistently evaluate cognitive enhancers and facilitate comparison across compounds. Second, the findings pertaining to within-session habituation and between-session fear learning should be evaluated and replicated across all cognitive enhancers. If these findings are consistently replicated across RCTs or cognitive enhancers, guidelines should be developed to aid clinicians practicing exposure-based treatments augmented by cognitive enhancers in maximizing the therapeutic benefit of exposure sessions. Specific modifications to cognitive enhancer augmented exposure treatment may include: implementing preliminary exposure sessions to ascertain a patient's level of fear habituation prior to augmentation; discontinuing the session once within-session fear habituation is achieved rather than a typical session length; and focusing on the patient's habituation to fear rather than the number of exposures achieved in session. Thus, a patient's treatment would be driven by their within-session fear habituation, and may incorporate specific exercises to enhance between-session fear learning. Third, it would prove useful to identify specific populations for whom cognitive enhancers would be most useful (e.g., difficult-to-treatment cases [48], patients likely to discontinue exposure treatment [109]). In doing so, treatment algorithms could be developed and evaluated to match specific patients and disorders with specific cognitive enhancers and treatment protocols to promote therapeutic outcomes. Fourth, while cognitive enhancers appear to promote reductions in symptom severity at post-treatment and at follow-up assessments, there is further need to evaluate whether these enhancements are more likely to result in sustained symptom remission and recovery. Finally, given the purported overlap between pathways for DCS and BDNF biomarkers, studies that delineate mechanisms of action and pathways to achieving enhanced fear extinction would provide critical information in understanding the interplay between these two cognitive enhancing agents.

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KEY ISSUES

- Cognitive enhancers are compounds that influence signaling pathways involved in brain regions (e.g., amygdala, hippocampus, prefrontal cortex) associated with fear learning to enhance the neurological circuitry of fear extinction.
- Cognitive enhancers can address several of the challenges confronting exposure-based treatments such as improving therapeutic outcomes, expediting treatment gains to reduce attrition, and reducing treatment duration to increase the availability of treatment providers.
- Although several cognitive enhancers have been evaluated, only D-cycloserine (DCS), yohimbine hydrochloride (YHCL), glucocorticoids and cortisol (G-CORT), and brain derived neurotrophic factor (BDNF) have been evaluated in the context of randomized controlled trials (RCTs) for anxiety disorders, obsessive compulsive disorder (OCD), and posttraumatic stress disorder (PTSD).
- Across the 22 RCTs of DCS, small-to-moderate improvements in therapeutic outcomes and expedited treatment gains have been observed. Although findings are generally positive, questions remain about the additive benefit of DCS in trials with longer durations.
- Across 3 RCTs, YHCL has demonstrated preliminary evidence of enhancing therapeutic outcomes and expediting treatment gains, with benefits being more evident at follow-up assessments.
- Across 3 RCTs, G-CORT has demonstrated a consistent benefit for enhancing therapeutic outcomes, with no examination of expedited treatment gains.
- Across 3 RCTs, BDNF biomarkers have been associated with improved therapeutic outcomes, with no examination of expedited treatment gains.
- Collectively for DCS and YHCL, within-session fear habituation and between-session fear learning have been associated with improved therapeutic outcomes. This highlights the fear enhancing properties of these compounds, as well as the importance of monitoring these constructs within emerging treatment protocols.
- Future research is needed to expand the limited evidence for YHCL, G-CORT and BDNF, as well as develop empirically-support guidelines to monitor within-and-between sessions therapeutic components to enhance fear extinction (rather than reconsolidate existing fear memories).

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Table 1

Randomized Controlled Trials of D-cycloserine (DCS) Augmented Exposure-based Therapies

Study	Diagnosis	Sample	Dose & Timing	# of Doses	Type of Therapy	# of Sessions	Expedited Tx. Gains	Outcome at Post-Tx.	Tx. Outcome at Follow-up Assessment
Ressler et al. [32]	Acrophobia	27 adults	50 mg or 500 mg 2–4 hours before exposure sessions	2	VRE	2 sessions (up to45 min)	Lower SUDS at start of session 2 for DCS	Lower SUDS on BAT of acrophobia, and greater improvement on CGI-I for DCS	After 3 months, lower SUDS on BAT of acrophobia, and greater improvement on AAVQ and ATHI for DCS
Hoffman et al. [39]	SAD	27 adults	50 mg 1 hour before exposure sessions	5	Individual or group EXP-based CBT	5 sessions (up to 90 min)	Not assessed	Improved scores on LSAS (d = 0.72) and SPAI (d = 0.98) for DCS	After 1 month, continued improved scores on LSAS (d = 0.69) and SPAI (d = 1.43) for DCS
Guastella et al. [34]	Sub-threshold Arachnophobia	63 adults	50 mg 2–3 hours before exposure	1	EXP	1 (approx. 65 min)	Not assessed	No sig. difference on SUDS or BAT	No sig. difference on SUDS or BAT
Kushner et al. [43]	OCD	32 adults	125mg 2 hours before exposure	Up to 10	EXP-based CBT	Up to 10 sessions	Greater reduction in SUDS (d = 0.77) for DCS	No sig. difference on SUDS or Y-BOCS	After 3 months, no sig. difference on SUDS or Y-BOCS
Storch et al. [44]	OCD	24 adults	250mg 4 hours before exposure	12	EXP-based CBT	12 sessions (60 min)	Not assessed	No sig. difference on Y-BOCS but results favored placebo (d = 0.17)	No. After 2 months, no sig. difference on Y-BOCS but results favored placebo (d = 0.35)
Guastella et al. [40]	SAD	56 adults	50mg 1 hour before exposure	4	EXP-based CBT	5 sessions (up to 90 min)	DCS lower LSAS scores after 5 sessions of tx.	Improvement on LSAS (d = 0.68) for DCS, but not sig. on SPAI (d = 0.22)	After 1 month, continued improvement

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Study	Diagnosis	Sample	Dose & Timing	# of Doses	Type of Therapy	# of Sessions	Expedited Tx. Gains	Outcome at Post-Tx.	Tx. Outcome at Follow-up Assessment
									on LSAS for DCS (on LSAS for DCS (0.52), but not sig. on SPAI (*d* = 0.26)
Wilhelm et al. [46]	OCD	23 adults	100mg 1 hour before exposure	10	EXP-based CBT	11 sessions (60 min)	Greater improvement on Y-BOCS at mid-tx for DCS (*d* = 1.17)	Large non-sig. effect in favor of DCS on Y-BOCS (*d* = 0.63)	After 1 month, large non-sig. effect in favor of DCS on Y-BOCS (*d* = 0.66)
Otto et al. [37]	PD or PDA	31 adults	50mg 1 hour before exposure	3	EXP-based CBT	5 sessions (up to 90 min)	Not assessed	Improvement on the PDSS and CGI-S for DCS	After 1 month, DCS continued improvement on the PDSS and CGI-S
Storch et al. [45]	OCD	30 youth	Up to 50mg 1 hour before exposure	7	EXP-based CBT	10 sessions (60 min)	Moderate non-sig. effect in favor of DCS on CY-BOCS (*d* = 0.40).	Small non-sig. effect in favor of DCS on CY-BOCS (*d* = 0.31)	Not assessed
Siegmund et al. [38]	PDA	44 adults	50mg 1 hour before exposure	3	group CBT w/ EXP	8 sessions (90 min)	Not assessed	No sig. difference on PAS, but effects favored DCS group	After 5 months, no sig. difference on PAS, but effects favored DCS group
de Kleine et al. [49]	PTSD	67 adults	50mg 1 hour before exposure	9	EXP-based CBT	10 sessions	Not assessed	DCS group more likely to respond, but not remit to tx. on CAPS	After 3 months, no difference in response or remission rates on CAPS
Gutner et al. [35]	Sub-threshold Arachnophobia	48 adults	50mg 1 hour before exposure	1	Subliminal EXP	1 session	Not assessed	DCS group had lower scores on DSR. Non-sig. but better performance on BAT for DCS	Not assessed
Litz et al. [50]	PTSD	26 adults	50mg 30 min before exposure	4	EXP-based CBT	6 sessions (90 min)	Not assessed	Placebo group outperformed DCS	No changes from post-tx.

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Study	Diagnosis	Sample	Dose & Timing	# of Doses	Type of Therapy	# of Sessions	Expedited Tx. Gains	Outcome at Post-Tx.	Tx. Outcome at Follow-up Assessment
								on CAPS (g = 0.73) and PCL (g = 0.73) and BAT (g = 0.46)	6 month follow-up
Nave et al. [36]	Ophidiophobia	20 adults	50mg 1 hour before exposure	1	EXP	1 session (up to 180 min)	DCS group completed 13-step EXP hierarchy in less time	No sig. difference on SQ, CGI-S or CGI-I	Not assessed
Tart et al. [33]	Acrophobia	29 adults	50mg immediately after exposure	2	VRE	2 sessions (30–60 min)	Not assessed	No sig. difference on BAT, AAVQ, AAQ, CGI-S, or CGI-I	After 1 month, no sig. difference on BAT, AAVQ, AAQ, CGI-S, or CGI-I
Difede et al. [51]	PTSD	25 adults	100mg 90 min before exposures	10	VRE	12 sessions (90 min)	DCS exhibited a non-sig. greater reduction on CAPS	No sig. difference, but effects favored DCS group on CAPS (g = 0.68) and PCL (g = 0.20)	After 6 months, DCS exhibited sig. difference on the CAPS (g = 1.13) and PCL (g = 1.19)
Farrell et al. [48]	OCD	17 youth	Up to 50mg 1 hour before exposure	5	EXP-based CBT	9 sessions (90 min)	Not assessed	No sig. difference, but response and remission rates favored DCS	After 3 months, no sig. difference but CY-BOCS scores lower in DCS group (d = 0.40)
Hofmann et al. [41]	SAD	169	50mg 1 hour before exposure	5	Group EXP-based CBT	12 sessions (150 min)	Greater symptom improvement on the SPDS and LSAS	Sig. lower scores on SPDS, and approached sig. on LSAS for DCS. But no sig. difference in response or remission rates	After 6 months, no sig. difference in response or remission rates
Rodebaugh et al. [42]	SAD	34 adults	250mg at start of exposure	1	EXP	1 session	Not assessed	DCS group had a sig. reduction on SPS, and had a trend toward sig. lower SUDS ratings	Not assessed

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Study	Diagnosis	Sample	Dose & Timing	# of Doses	Type of Therapy	# of Sessions	Expedited Tx. Gains	Outcome at Post-Tx.	Tx. Outcome at Follow-up Assessment
Mataix-Cols et al. [47]	OCD	27 youth	50mg 1 hour after exposure	10	EXP-based CBT	14 session	No sig. difference at mid-tx	No sig. difference on CY-BOCS, with parent-rated ChOCI favoring placebo (*d* = 1.25)	After 12 months, no sig. difference on CY-BOCS or parent-rated ChOCHI
Scheeringa & Weems [52]	PTSD	56 youth	50mg 1 hour before exposure	7	EXP-based CBT	12 session	No sig difference, but DCS group had more variability in symptom decrease	No sig. difference on CPSS, but results favored placebo (*d* =1.9) over DCS (*d* = 1.5)	After 3 months, no sig. difference between groups on CPSS, with effects favoring placebo (*d* =2.0) over DCS (*d* = 1.5)
Rothbaum et al. [59]	PTSD	106 veterans[a]	50mg 30 minutes before exposure	5	VRE	6 sessions (90 min)	Not assessed	No sig. difference on CAPS or the PSS between DCS and placebo groups	After 12 months, no sig. difference on CAPS or the PSS between DCS and placebo groups

Note: DCS = D-cycloserine; VRE = Virtual Reality Exposure; SUDS = Subjective Units of Distress; BAT = Behavioral Avoidance Test; CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; AAVQ = Acrophobia Questionnaire with Avoidance, ATHI = Anxiety Toward Heights Inventory; EXP = Exposure; SAD = Social Anxiety Disorder; CBT = Cognitive Behavioral Therapy; LSAS = Liebowitz Social Anxiety Scale; SPAI = Social Phobia and Anxiety Inventory; OCD = Obsessive Compulsive Disorder; C/Y-BOCS = Children's/Yale-Brown Obsessive Compulsive Scale; PD = Panic Disorder; PDA = Panic Disorder w/ Agoraphobia; PDSS = Panic Disorder Severity Scale; PAS = Panic and Agoraphobia Scale; PTSD = Posttraumatic Stress Disorder; CAPS = Clinician Administered PTSD Scale; PCL= PTSD Checklist; SQ = Snake Questionnaire; SPDS = Social Phobic Disorders Scale; SPS = Social Phobia Scale; DS-R= Disgust Scale-Revised; ChOCI = Child Obsessive Compulsive Inventory; C/PSS = Child/PTSD Symptom Scale.

[a]Total sample included 156 participants in all three conditions (53 in DCS-augmentation, 50 in alprazolam-augmentation, and 53 in placebo augmentation).

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Table 2

Randomized Controlled Trials of Yohimbine Hydrochloride (YHCL) Augmented Exposure-based Therapies

Study	Diagnosis	Sample	Dose & Timing	# of Doses	Type of Therapy	# of Sessions	Expedited Tx. Gains	Outcome at Post-Tx.	Tx. Outcome at Follow-up Assessment
Powers et al. [73]	Sub-threshold and threshold Claustrophobia	24 adults	10.8mg 1 hour before exposure sessions	2	EXP	2 sessions (approx. 60 min)	Not assessed	No sig. difference but large effect favoring YHCL (h^2 = 0.14)	After 1 week, YHCL group exhibited sig. large effects on the CCQ (h^2 = 0.230, CLQ (h^2 = 0.18), and BAT (h^2 = 0.35)
Meyerbroeker et al. [74]	Aerophobia	67 adults	10mg 1 hour before exposure sessions	4	VRE	4 sessions (60 min)	Not assessed	No sig. difference between groups	Not assessed
Smits et al. [75]	SAD	40 adults	10.8mg 1 hour before exposure sessions	4	Exposure-based CBT	5 sessions (60–90 min)	YHCL exhibited expedited gains on LSAS	Not assessed	After 3 weeks, YHCL exhibited large and significant effects on LSAS (d = 0.53).

Note: EXP = Exposure therapy; CCQ = Claustrophobic Concerns Questionnaire; CLQ = Claustrophobia Questionnaire; BAT = Behavioral Avoidance Task; VRE = Virtual Reality Exposure Therapy; FAM = Flight Anxiety Modality Questionnaire; FAQ = Flight Anxiety Situation Questionnaire; SUDS = Subjective Units of Distress; CBT = Cognitive Behavioral Therapy; LSAS = Liebowitz Social Anxiety Scale; CGI-S = Clinical Global Impression of Severity; PE = Prolonged Exposure; CAPS = Clinician Administered PTSD Scale; PCL = PTSD Checklist.

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Table 3

Randomized Controlled Trials of Glucocorticoids and Cortisol (G-CORT) Augmented Exposure-based Therapies

Study	Diagnosis	Sample	Dose & Timing	# of Doses	Type of Therapy	# of Sessions	Expedited Tx. Gains	Outcome at Post-Tx.	Tx. Outcome at Follow-up Assessment
Soravia et al. [87]	Arachnophobia	20 adults	10mg 1 hour before exposure sessions	4	EXP	6	Not assessed	G-CORT exhibited sig. reduced fear on VAS. No difference on STAI between groups	Not assessed
De Quevain et al. [88]	Acrophobia	40 adults	20mg 1 hour before exposure sessions	3	VRE	3	Not assessed	G-CORT exhibited lower scores on AQ (d = 0.60), and SUDS (d = 1.00), but not ATHQ	After 1 month, G-CORT exhibited lower scores on AQ (d = 0.60), but no sig. difference on SUDS and ATHQ
Soravia et al. [89]	Arachnophobia	22 adults	20mg 1 hour before exposure sessions	2	Group exposure-based CBT	2 (up to 150 min)	Not assessed	No sig. difference, but results favored G-CORT on FSQ (d = 0.69).	After 1 month, G-CORT exhibited lower FSQ scores (d = 1.04), SPQ (d = 0.98), and less subjective fear after viewing 20 pictures of spiders (d = 1.61)

Note: G-CORT = Glucocorticoids and Cortisol; VAS = Visual Analog Scale; STAI = State Trait Anxiety Inventory; VRE = Virtual Reality Exposure; AQ = acrophobia questionnaire; ATHQ = Attitude Toward Heights Questionnaire; BAT = Behavioral Avoidance Test; SUDS = Subjective Units of Distress; CBT = Cognitive Behavioral Therapy; SPQ = Spider Phobia Questionnaire, FSQ = Fear of Spider Questionnaire.

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Table 4

Randomized Controlled Trials of Brain-Derived Neurotrophic Factor (BDNF) Augmented Exposure-based Therapies

Study	Diagnosis	Sample	Type of Therapy	# of Sessions	Expedited Tx. Gains	Outcome at Post-Tx.	Tx. Outcome at Follow-up Assessment
Kobayashi et al. [101]	PD	42 adults	Exposure-based group CBT	10 (60min)	Not assessed	Treatment responders exhibited a higher level of BDNF serum at BL relative to poor responders	Not assessed.
Fullana et al. [102]	OCD	98 adults who were SSRI partial or non-responders	Exposure-based CBT	20 sessions (45 min)	Not assessed	BDNF Val66Met group exhibited lower treatment response on Y-BOCS (36%) relative to non-carriers (60%)	Not assessed.
Felmingham et al. [103]	PTSD	55 adults	Exposure-based CBT	8 sessions	Not assessed.	BDNF MET group exhibited lower treatment response (40% reduction) relative to non-BDNF Met Group (62% reduction). Significant difference in CAPS scores at post-tx, favoring non-BDNF group	Not assessed.

Note: PD = Panic Disorder; CBT = Cognitive Behavioral Therapy; Panic Disorder Severity Scale; SSRI = Selective Serotonin Reuptake Inhibitors; Y-BOCS = Yale-Brown Obsessive Compulsive Scale; CAPS = Clinician Administered PTSD Scale.

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