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The Future of D-Cycloserine and Other Cognitive Modifiers in Obsessive-Compulsive and Related Disorders

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Abstract

Variants of exposure therapy are effective for treating obsessive-compulsive and related disorders (OCRDs). However, significant numbers of patients do not respond adequately to exposure therapy resulting in continued distress and functional impairment. Therefore, novel approaches to augmenting exposure therapy are needed to adequately treat non- and partial-responders. Emerging research suggests that interventions that augment learning and memory processes associated with exposure therapy (i.e., extinction training) may display promise in enhancing

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treatment response in OCRDs. As the most studied example, d-cycloserine (DCS) is a relatively safe cognitive enhancer that appears to accelerate treatment gains associated with exposure therapy. This article reviews research on the use of DCS and other putative cognitive modifiers as they relate to the treatment (or prospective treatment) of obsessive-compulsive disorder and other OCRDs.

Keywords

Cognitive enhancer; D-cycloserine; Glucocorticoids; Memory reconsolidation; Obsessive-compulsive disorder; Brain-derived neurotrophic factor; Yohimbine

Obsessive-compulsive and related disorders (OCRDs) such as obsessive-compulsive disorder (OCD), body dysmorphic disorder (BDD), and health anxiety/hypochondriasis are characterized by the presence of intrusive/anxiety-provoking thoughts (i.e., obsession) and anxiety preventing/reducing behaviors (i.e., compulsions, avoidance) [1][1]. These disorders were once considered rare and treatment refractory; however, recent research suggests that they occur with relative frequency and are amenable to psychological and pharmacological treatments [2, 3]. Specifically, cognitive-behavioral therapy with exposure and response prevention (CBT[2]) and serotonin reuptake inhibitor (SRI) medication have been established as effective treatments for different OCRDs [4]. However, despite notable improvements in psychological and pharmacological treatments for OCRDs, many individuals with these disorders do not respond adequately to extant treatments [5, 6] and others continue to display significant symptomology following treatment. For example, research on children with OCD, indicates that as 50% to 75% of patients may still display symptoms following a full course of treatment [5, 7].

Researchers have speculated that combining treatment modalities (e.g., CBT and SRI medication) would improve treatment outcomes [8]. However, a recent meta-analysis that compared the addition of pharmacotherapy to CBT for treating anxiety disorders found only modest benefits associated with combined treatment relative to CBT with placebo treatment at post-treatment (d = .59) and no added value at 6-month follow-up [9]. Thus, although augmenting CBT with medication is a common practice and subsequent research is needed to investigate this treatment approach in large samples of patients with OCRDs, room for improvement exists in extant treatment approaches, especially for refractory cases and treatment non-responders [10, 11].

“Cognitive modifiers” or interventions that aim to enhance/modify cognitive functions such as memory and extinction learning represent a promising new approach to improve treatment outcomes for individuals with anxiety and OCRDs [10, 12, 13, 14]. D-cycloserine, catecholamines, yohimbine, endocannabinoids, glutocorticoids, modafinil, methylene blue,

[1]Note: Several other disorders are classified as OCRDs. Hypochondriasis, OCD, and BDD were included because of their favorable response to exposure therapy and similarities in their phenomenology (e.g., functional similarities in symptom presentation). However, no mechanism has been established for classifying which disorders warrant classification as OCRDs despite numerous efforts to refine the scope of the putative OCRDs.

[2]Note: CBT for OCRDs includes variants of exposure therapy as the core therapeutic mechanism. Later portions of this article will discuss the use of exposure therapy independent from other CBT interventions.

brain-derived neurotrophic factor (BDNF), and various nutrients and botanicals (e.g., omega-3 fatty acids, nicotine, caffeine) have been investigated as potential cognitive modifiers in treating anxiety and many of these agents also may have possible indications for augmenting treatment for OCRDs with anxiety as a central phenomenological feature [10, 13, 15]. Other agents such as *N*-acetylcysteine and inositol also may enhance treatment for OCRDs as suggested in preliminary studies [16, 17, 18]. However, additional research is needed to determine if these supplements enhance cognitive functions or exert their therapeutic effects through different mechanisms.

Empirical support for the use of cognitive modifiers is still emerging and the mechanisms behind the effectiveness of many of cognitive modifiers await validation in humans. Furthermore, in addition to establishing putative mechanisms of action, translational research is needed to establish feasibility, safety/tolerability, and efficacy of using these agents in conjunction with exposure therapy. Although research on the use of cognitive modifiers with exposure therapy for OCRDs currently is limited, findings obtained in studies that involve individuals with non-OCD anxiety disorders highlight potential applications for the use of cognitive modifiers in the treatment of OCRDs. To add to a growing dialogue on augmenting psychotherapy for OCRDs, this article reviews relevant findings obtained in studies of various cognitive modifiers and suggests potential applications for these agents in the treatment of OCRDs.

D-cycloserine

One novel approach to augmenting CBT involves the use of d-cycloserine (DCS; d-4-amino-3-isoxazolidone), an antibiotic that is an analogue of the enzyme D-alanine [14]. The precise mechanisms by which DCS works as a cognitive enhancer have received empirical attention yet still requires elucidation. For example, DCS may indirectly increase glutamatergic activity because of its role as a partial agonist of the neuronal N-methyl-D-aspartate (NMDA) glutamate receptor, an excitatory amino acid receptor implicated in the development of associative fear/anxiety-based learning [19, 20]. However, DCS also may reduce NMDA receptor functioning because of its ability to saturate glycineB sites when surrounding glycine levels are high [21, 22]. Therefore, treatment gains associated with DCS may be related to its role in enhancing NMDA activity which increases neuroplasticity and extinction learning during exposure-based therapy or by its role in reducing NMDA receptor activity and interfering with the reconsolidation or reinstatement of fear memories [21, 23].

Regardless of its specific mechanism of action, DCS' action as a cognitive modifier is distinctly different from traditional psychotropic medications that are used to treat OCRDs (e.g., SRIs, atypical antipsychotics). First, DCS is not anxiolytic in that it does not relieve anxiety by itself [12, 13]. Second, side effects associated with DCS are relatively rare and mild and patients generally are not aware of whether they ingested it or a placebo [24]. Third, the efficacy of DCS is dependent on successful exposure therapy [12]. Thus, the therapeutic utility of DCS is solely as a cognitive modifier or treatment augmentation agent. Lastly, DCS dosing is targeted or acute as opposed to chronic dosing. D-cycloserine actually may lose its therapeutic utility when dosed repeatedly [11, 25], suggesting that its primary

indication may be to amplify early treatment gains or speed up the efficacy of exposure therapy [11, 26].

D-cycloserine as a Cognitive Modifier

An emerging body of research investigates the efficacy of DCS as a cognitive modifier when it is paired with exposure therapy. The first successful clinical trial that involved using DCS to augment exposure therapy was conducted by Ressler et al. [14] and included patients (N = 28) with acrophobia [14]. This randomized controlled trail (RCT) included two active DCS treatment groups (50 mg, 500 mg)[3] and a placebo group. All participants received two sessions of virtual reality exposure therapy and DCS was administered 2.5 hours before exposure. Regardless of the DCS dose patients received, patients who received DCS reported lower levels of fear at post-treatment compared to those who received a placebo. Stronger treatment effects were found in the DCS group that received 500 mg of DCS at post treatment (d = .86) compared to the group that received 50 mg of DCS (d = . 36). However, no differences were observed between DCS groups at follow-up, suggesting that relatively low doses of DCS can still facilitate gains associated with exposure therapy.

Hofmann et al. [27] investigated the use of DCS as a cognitive modifier for treating social phobia. This RCT included 27 patients and in comparison to a placebo group, participants who received DCS (50 mg) one hour before exposure therapy displayed superior reductions at post treatment (d = .43) and one-month follow-up (d = .80). Guastella et al. [28] also conducted a RCT to investigate the effects of DCS augmentation of exposure therapy (e.g., public speaking exposures) compared to an exposure therapy plus placebo condition. In comparison to participants who received placebo and exposure therapy (N = 28), participants who received DCS (50 mg) one hour prior to exposure therapy (N = 28) displayed greater improvements on measures of symptom social phobia symptomology (d = .26 – .51), maladaptive cognitions (d = .42), and functional impairment (d = .52). Furthermore, these results generally were durable at one-month follow-up.

Two studies have investigated the use of exposure therapy with DCS augmentation for treating panic disorder. In one RCT, participants (N = 28) received five interoceptive exposure therapy sessions either alone (placebo control) or with DCS (50 mg) augmentation one hour before therapy [29]. Results of this investigation suggest that DCS augmentation of interoceptive exposure therapy results in superior outcomes at post treatment (d = 1.20) and follow-up (d = .88) in patients with panic disorder. In a similar RCT that included patients with either severe panic disorder and/or agoraphobia, 11 sessions of CBT (including three sessions of exposure therapy) with DCS (50 mg) augmentation were provided to patients (N = 20) or a placebo control (N = 19) [25]. Although no differences were observed between groups on measures of panic and agoraphobia, patients' successful response to CBT may have mitigated DCS-related treatment effects at post-treatment. However, in support of DCS as a cognitive enhancer, DCS appeared to accelerate treatment gains in patients who

[3]*Note:* Optimal DCS dose levels await further elucidation. Common dose levels include 25, 50, 125, and 500 mg. Often dose levels are governed by levels reported in previous trials or the relative size of DCS capsules available to researchers. Higher dose levels might be used to protect against inadequate dosing. However, research on DCS dose levels and treatment outcome is mixed across assessment time points, suggesting that a non-linear relationship may exist between dose level and treatment outcome.

displayed more severe levels of psychopathology at baseline compared to patients who displayed lower levels of psychopathology (d = .84). Thus, additional research is needed to support the role of DCS as an adjunctive treatment for severe or treatment refractory cases of panic disorder.

A recent study including participants (N = 100) with elevated yet sub-clinical levels of spider phobia (i.e., arachnophobia) investigated the role of DCS when it was administered 2.5 hours before exposure therapy [30]. Overall, regardless of dose level (50 mg, 500 mg), results of this investigation indicated that DCS augmentation of single-session exposure therapy did not reduce arachnophobia (d = −.41 – .00). However, a ceiling effect may have attenuated the utility of DCS as a cognitive modifier because of the high efficacy of single-session exposure-based therapy for phobias—especially for arachnophobia [31]. Additionally, mildly phobic participants may quickly habituate to phobic stimuli, which might then obscure or overshadow the role of DCS in facilitating extinction [11].

D-cycloserine as a cognitive modifier for OCRDs

Five studies have investigated DCS as a potential cognitive modifier for exposure and response prevention (E/RP) in individuals with OCD. Kushner et al. [32] investigated the use of DCS-augmented E/RP (N = 15; 125 mg) compared to E/RP monotherapy (N = 17). In this RCT, all participants were adults with principal OCD diagnoses and they received 10 E/RP sessions; DCS was administered two hours prior to E/RP treatment. Participants who took DCS prior to engaging in E/RP displayed greater reductions in OCD symptoms early in treatment (i.e., between sessions 1 and 4) when compared to participants who received E/RP monotherapy (d = .77). However, these differences were not observed at post-treatment or at three-month follow-up. More recently, Wilhelm et al. [33] replicated results of this investigation in another sample of adult patients with OCD (d = .70). Participants (N = 23) in this RCT received 10 E/RP therapy sessions and DCS (100 mg) was administered one hour prior to each session. Although no differences were observed in OCD symptoms between individuals who received DCS or a placebo at post-treatment or at one-month follow-up, individuals who received DCS displayed lower levels of depression at follow-up. This finding may suggest that DCS may have other indications that warrant empirical attention. Additionally, and more importantly, subsequent research suggests that DCS's role of as a cognitive enhancer may have been obscured at post treatment and follow-up. Thus, in this regard, a reanalysis of data obtained by Wilhelm et al. [33] by Chasson et al. [26] found that the course of E/RP was 2.3 times faster in participants receiving DCS compared to controls across ten therapy sessions [26] and the effects of DCS were approximately six times faster across the first five E/RP sessions, suggesting that DCS is an effective cognitive enhancer. Overall, similar to previous findings [32], this result suggests that DCS expedites initial treatment effects associated with E/RP but does not result in superior outcomes in treatment completers. Thus, DCS may accelerate E/RP gains but eventually exhausts its efficacy as treatment progresses and patients experience benefits from exposure therapy.

One RCT that included adults (N = 24) diagnosed with OCD found that DCS (250 mg) did not appear to enhance exposure therapy as no differences were observed in OCD symptoms between patients who received DCS and those who received a placebo control at post-

treatment ($d = -.19$) and at two-month follow-up ($d = -.36$) [34]. However, subsequent findings that the effects of DCS largely depend on timing and dosage scheduling (e.g., Norburg et al. [11]) suggest that the aforementioned results [31] may have been affected by the relatively long delay between DCS administration and exposure therapy (four hours) and the high number of DCS doses ($N = 12$).

Only one study investigated the role of DCS as a cognitive modifier in youth (e.g., Storch et al. [35]). In this RCT, children in the treatment condition received seven sessions of E/RP and weight-adjusted doses of DCS (25 or 50 mg) that were administered one hour prior to therapy. Results indicated that youth who received DCS ($N = 15$) and E/RP displayed moderate reductions in OCD symptoms as measured on the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS [36]) symptom severity scale relative to youth who received placebo and E/RP at post treatment ($N = 15$), which is noteworthy because two active treatments were compared and a moderately strong treatment effect was found between groups ($d = .67$). Although between-group symptom reductions were not statistically significant at post treatment ($p < .05$), perhaps due to the relatively small sample size included in the study ($N = 30$), Storch et al. [32] conclude that DCS is safe and may be an effective cognitive modifier, especially for youth who do not initially experience declines in OCD symptoms during treatment and may be at risk for not completing a trial of E/RP. To expand on these findings, researchers at the University of South Florida and Massachusetts General Hospital currently are conducting a large randomized double-blind placebo-controlled study to assess the efficacy of DCS augmentation of E/RP for pediatric OCD. This study will enroll 150 youth across two sites and it aims to provide the most comprehensive investigation of DCS augmentation to date.

Although individuals with OCRDs generally respond favorably to variants of exposure therapy [35, 37, 38, 39, 40, 41], with the exception of OCD, no studies have investigated the use of DCS as a potential cognitive modifier for these disorders. This may be surprising in light of phenomenological similarities between various OCRDs and in their treatment [4, 42, 43]. Additionally, although understudied compared to OCD and other anxiety disorders, symptoms of disorders such as BDD and health anxiety are relatively common in clinical [44, 45, 46] and non-clinical samples [3, 47]. Thus, the role of DCS as a potential cognitive modifier for treating OCRDs remains an open and promising area for investigation.

Other Cognitive Modifiers

In addition to DCS, other agents may modify extinction-based learning and have applications for augmenting exposure-based therapy for OCRDs. However, literature on other potential cognitive modifiers is nascent and with the exception of DCS, no cognitive modifiers have been tested with patients with OCRDs. Therefore, although some of the following cognitive modifiers may display potential utility, significant work is needed to translate these treatment approaches into clinical practice for OCRDs.

Glucocorticoids

The effects of glucocorticoids (corticosterone in animals and cortisol in humans) on memory are complex and dependent on multiple variables (e.g., dosing levels, time of

administration). However, under certain conditions, cortisol can enhance memory consolidation (i.e., the stabilization of memories after initial acquisition) in humans and potentially facilitate extinction learning within exposure therapy [48, 49]. In this regard, cortisol may impede the development of anxiety/fear-based memories and enhance the consolidation of extinction learning [50]. Although additional research is needed to establish specific mechanisms of action, one study that involved administering cortisol one hour before exposure to spider photos found greater reductions in fear in individuals who received cortisol compared to those who received a placebo [51]. Similarly, another study found that individuals who were administered cortisol (10 mg) one hour before each of three virtual reality exposure to heights displayed a significantly greater reduction in their fear of heights at post-treatment (d = 1.00) and one-month follow-up (d = .60) relative to a placebo [52]. Additionally, although not directly related to cortisol reactivity, patient levels of cortisol have been linked to their response to exposure therapy. For example, preliminary research suggests that patients with PTSD and panic disorder who respond well to exposure therapy tend to have low cortisol levels at post-treatment [53, 54].

Yohimbine

Yohimbine is an alkaloid and noradrenaline agonist that may enhance emotional memory and fear extinction through its potential to increase noradrenaline levels in humans [55]. In this regard, one recent study supports the cognitive enhancing effects of yohimbine for treating claustrophobia [56]. In this study, individuals receiving two session of exposure therapy displayed markedly greater reductions in fear at one-week follow-up if the therapy had been augmented by yohimbine hydrochloride (10.8 mg) instead of placebo (d = 1.68). Additionally, yohimbine was well tolerated by all patients, which is important because of previous findings suggesting yohimbine can exacerbate anxiety in individuals who are sensitive to somatic sensations and signs of physiological arousal [57]. However, as suggested by Hofmann et al. [34], increases in somatic arousal actually may aid in the therapeutic effects associated with yohimbine. For example, yohimbine may produce feelings similar to sensations that are purposely engendered during interoceptive therapy (i.e., exposure therapy for panic disorder) such as tachycardia, shortness of breath, and dizziness. If this is the case, yohimbine might not be an effective cognitive modifier for other anxiety disorders and OCRDs that are not characterized by the presence of somatic symptoms. A recent study of patients (N = 67) undergoing virtual reality exposure therapy for specific fear of flying symptoms found that therapy was equally effective when augmented by yohimbine (10 mg) or placebo [58]. Thus, in light of this finding, additional research is needed to replicate findings obtained by Powers et al. [56] and establish specific mechanisms related to yohimbine use that may result in advantageous clinical outcomes for OCRDs.

Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) affects the central nervous system in adults as well as activity of neurons associated with learning and memory [59]. Specifically, BDNF is hypothesized to mediate the consolidation of extinction memory or learning that occurs during exposure therapy [13]. Additionally, BDNF levels may predict exposure therapy response rates. In a sample of patients with panic disorder, Kobayashi et al. [60] found that

patients with high BDNF levels displayed superior treatment gains relative to patients with low BDNF levels. Thus, interventions that increase BDNF levels may enhance treatment outcomes for some individuals receiving exposure therapy.

Growing evidence supports the efficacy of aerobic exercise for increasing BDNF levels [61, 62]. In a recent study, Ströhle et al. [63] found that patients with panic disorder (N = 12) had lower BDNF levels when compared to normal controls (N = 12). However, following 30 minutes of moderate exercise, these patients BDNF levels were comparable to BDNF levels observed in normal controls at baseline. No increases in BDNF were observed in normal controls. Thus, this study suggests that short bouts of exercise can increase BDNF levels in anxious individuals. Furthermore, although not discussed as a standalone treatment, Ströhle et al. [63] suggest that exercise might enhance effects associated with exposure therapy for anxiety disorders. Similarly, aerobic exercise may be a safe and reliable cognitive modifier for treating OCRDs.

Cognitive Modifiers and Memory Consolidation/Reconsolidation

Disrupting the consolidation of memory following a traumatic/highly anxiety-provoking experience may prevent the development of impairing stress/anxiety reactions [64, 65]. This process involves mitigating the impact of emotionally overwhelming experiences yet not declarative memory for the potentially traumatic/highly anxiety-provoking experience. Alternatively, even after the consolidation of traumatic/highly anxiety-provoking memories, interventions that interfere with the reconsolidation of these memories when they are rendered labile (i.e., when they are being re-experienced and reconsolidated) may reduce the emotional valence of the memories [65, 66, 67, 68]. Therefore, in contrast to d-cycloserine, agents that either forestall the consolidation of traumatic/stressful memories or modify these memories when they are pliable (i.e., during reconsolidation) may mitigate processes contributing to the development and/or maintenance of anxiety.

Modifiers of memory consolidation

The release of stress hormones (e.g., epinephrine, glucocorticoids) following stressful or emotionally intense experiences leads to the consolidation of episodic and emotional memory [69, 70]. However, recent research suggests that this process can be disrupted through providing beta-adrenergic blockers such as propranolol that attenuate the memory-strengthening effects of stress hormones shortly after exposure to a traumatic experience (i.e., within six hours of the event) [65, 71]. Thus, the impact of traumatic/highly stressful memories can be lessened if specific agents are administered shortly after the traumatic or stressful experience when memories about the experience are being consolidated.

In a seminal study, Pitman et al. [65] administered propranolol to individuals receiving emergency medical care shortly after they survived a traumatic event to test if the medication would disrupt memory consolidation and render memories of the traumatic event less emotionally poignant. Compared to placebo controls (N = 23), individuals who received propranolol (N = 18) displayed lower physiological reactivity in response to script-driven imagery trauma triggers compared to placebo controls at follow-up. Thus, agents that disrupt the consolidation of traumatic or stress-induced memories may protect against the

development of subsequent stress or trauma associated with initial memories. More recently, these results were replicated in a study that employed a similar design and involved treating patients with propranolol immediately after a traumatic experience (i.e., a motor vehicle accident or physical assault) and over the course of seven days [71]. These findings, although noteworthy in that they challenge the notion that memory consolidation is an immutable process, may not generalize broadly to the treatment of OCRDs because symptoms of these disorders tend to have an onset that is more gradual and unpredictable compared to PTSD and may not be fear based. However, these findings do underscore the importance of memory mechanisms as cognitive modifiers.

Modifiers of memory reconsolidation

Memories were once considered indelible following consolidation yet recent research suggests that consolidated memory is amenable to change following reactivation [67, 72]. In contrast to administering propranolol right after a traumatic experience, Kindt, Soeter, and Vervliet [74] found that administering the medication before memory reactivation erased the behavioral expression of the fear memory 24 hours later as well as prevented the return of fear. More specifically, in a laboratory study, they found that a previously conditioned stimulus (i.e., acoustic startle response) no longer elicited fear in participants following reconsolidation even though they were still aware of the paired relationship between conditioned and unconditioned stimulus (i.e., shock expectancy), suggesting that only the fear component of memory had been eliminated. In other words, this study suggests that the emotional content in consolidated memories is amenable to modification during reconsolidation even if declarative memory of the initial events/stressors remains intact.

Another conditioning study by Schiller et al. [68] involved the use of a behavioral intervention (i.e., presenting non-fearful information) to disrupt the reconsolidation of fear memories in lieu of a biological agent. In this study, non-clinical participants ($N = 20$) were first conditioned to fear a visual object (e.g., colored square) followed by a reminder of the object (memory reactivation) 24 hours later, which was intended to initiate the reconsolidation process. Extinction training was then provided shortly after memory reactivation (reconsolidation) to demonstrate that the conditioned stimulus was then benign and render the associated fear memory labile. Then, the following day, participants were tested to determine if they continued to display a fear in response to the presentation of the conditioned stimulus. Results of this study indicated that extinction training only resulted in the elimination of fear responses if it occurred during the reconsolidation window when memory was rendered temporarily labile. Furthermore, as a testament to the durability of study results, fear memories generally did not return in subjects who received extinction training during the reconsolidation window at one-year follow-up, suggesting that the conditioned fear memory was successfully eliminated.

Modifying memory reconsolidation in the treatment of OCRD

Extinction results from new learning about a conditioned stimulus as opposed to erasing consolidated memory [15, 74]. Therefore, treatments that encourage patients to confront anxiety provoking stimuli/situations within the context of therapy may already modify consolidated highly stressful/anxiety-provoking memories through reactivating these

memories in the absence of legitimate or perceived threat [67, 75]. For example, after watching a therapist model an exposure task (e.g., touching a toilet seat) and then participating in the exposure task itself, patients' consolidated fears (e.g., contamination) are reactivated and may be rendered temporarily labile. Then, following exposure without the use of any compulsive rituals (e.g., washing, avoidance), the patient may reconsolidate new information that s/he learns during the exposure task (e.g., "the therapist doesn't seem anxious," "my anxiety went down naturally—I didn't need to wash," "the exposure wasn't as bad as I thought it would be").

No published studies have investigated the potential of targeting reconsolidation in the treatment of OCRD. However, as suggested by research involving fear conditioning (e.g., [64]), the use of agents such as propranolol and/or behavioral interventions to target reconsolidation may augment exposure therapy for OCRD. Though research in this vein is speculative and it will have to overcome some particular obstacles such as whether general or specific stimuli should be used during reminder trials to activate the reconsolidation window. In other words, research is needed to determine whether general fear/anxiety, disorder specific fear/anxiety, or even symptom specific stimuli should be used to reactivate consolidated memories. Additionally, research is needed to distinguish between mechanisms involved in memory modification during reconsolidation and overlapping mechanisms that already may be active during exposure therapy. Lastly, despite research suggesting that extinction training can eliminate fear memories during the reconsolidation window (e.g., [73, 68]), no studies have translated this finding to clinical practice. In other words, it remains unclear whether similar findings would be found in clinical trials or in studies that compare exposure therapy that is augmented with tasks designed to modify memory reconsolidation against established treatments relative to exposure therapy alone or other treatment agents (e.g., SRI therapy).

Conclusion

Exposure therapy is an effective treatment for OCRDs; however, not all patients with these disorders adequately respond to treatment. Therefore, alternative ways to help treatment refractory or treatment non-responding patients are needed. Unfortunately, combined psychotherapy and SRI treatment may convey limited benefit over either monotherapy [9]. As an alternative, augmenting exposure therapy with cognitive modifiers may result in new, promising, and well-tolerated approaches to treating OCRDs. Although research on the use of cognitive modifiers in patients with OCRDs is limited or non-existent depending on the disorder or intervention paradigm, several different cognitive modifiers have been investigated in studies that include individuals with anxiety symptoms. These include DCS, cortisol, yohimbine, BDNF and agents/procedures that have been shown to impact memory consolidation and/or reconsolidation. Currently, DCS displays the greatest potential as a method of treatment augmentation because of its potential to accelerate treatment gains associated with exposure therapy for OCD. However, research on the use of cognitive modifiers is in its infancy and the forthcoming decades may be marked by exciting developments in the use of other cognitive modifiers to augment exposure therapy for OCRDs.

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