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Combined Pharmacotherapy and Cognitive-Behavioral Therapy for Anxiety Disorders: Medication Effects, Glucocorticoids, and Attenuated Treatment Outcomes

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Abstract

Despite the success of both pharmacologic and cognitive-behavioral interventions for the treatment of anxiety disorders, the combination of these modalities in adults has not resulted in substantial improvements in outcome relative to either strategy alone, raising questions about whether there are interfering effects that attenuate the magnitude of combination treatment benefits. In this article, we introduce an accounting of potential interference effects that expands upon arguments asserting the necessity of arousal for successful fear exposure. Specifically, recent advances in the study of the effects of cortisol on memory--suggesting that glucocorticoids are crucial to the learning of emotional material--have led us to posit that the attenuation of glucocorticoid activity by anxiolytic medications may interfere with extinction learning in exposure-based therapies. Implications for the efficacy of combination treatments for the anxiety disorders are discussed.

Keywords

Combination Therapy; Anxiety Disorders; Extinction; Glucocorticoids; Cognitive-Behavioral Therapy; NMDA

Despite the individual achievements of pharmacotherapy and cognitive-behavioral therapy (CBT) in offering efficacious treatment for anxiety disorders, the expectation that the combination of these modalities will provide a particularly powerful treatment has met with disappointment in studies of adults. The evidence is most clear for the treatment of panic disorder, where there are enough studies available for meta-analytic review of the literature to show modest effects for the advantage of combined pharmacotherapy and exposure-based CBT relative to CBT alone (Furukawa, Watanabe, & Churchill, 2006; Watanabe, Churchill, & Furukawa, 2009). Qualitative reviews support this perspective for other anxiety disorders (Foa, Franklin, & Moser, 2002; Otto, Smits, & Reese, 2005), as do recent multi-site trials. For example, a large-scale randomized trial of the individual and combined effects of fluoxetine and CBT for social anxiety disorder, revealed a combination treatment response rate of 54.2% relative to a response rate of 51.7% for CBT alone, and a response rate of 50.8% for fluoxetine alone (Davidson et al., 2004). Similar modest effects for combination

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treatment were evident in a large-scale trial of the individual and combined effects of exposure-based CBT (exposure plus response prevention) and clomipramine for obsessive-compulsive disorder; rates of responders for CBT were 62% for the intent-to-treat sample and 86% for treatment completers, compared to 70% and 79%, respectively, for combination treatment (Foa et al., 2005).

Across the literature, there is evidence for occasional significant findings for improved outcomes with combination treatment relative to exposure-based CBT alone (e.g., Hohagen et al., 1998). Hence, we are not asserting that there is no advantage for combined treatment, but that the advantage, when examined across the literature, is particularly modest. The overall limited performance for combined treatment is also interesting given evidence, at least for panic disorder, for strong and durable treatment effects when non-responders to one treatment are switched to a second modality of treatment (Heldt et al., 2006; Otto, Pollack, Penava, & Zucker, 1999). Indeed, if combined treatment strategies simply offered benefit to nonresponders to monotherapy, then one would expect to see more promising combination treatment effects than has been observed in the clinical trial literature. The absence of this effect raises questions about whether medication treatment, when used concurrently with exposure-based CBT, might have *interfering as well as facilitative effects*, so that only subtle advantages are seen over monotherapy. That is, the limited magnitude of combination treatment effects may reflect benefit from pharmacologic anxiolysis in combination with attenuated benefit from exposure-based CBT, such that the sum of these two powerful treatments in combination fares only slightly better than either monotherapy.

Otto and associates (Otto, Basden, Leyro, McHugh, & Hofmann, 2007; Otto, Smits, & Reese, 2005) have argued that the changes in internal context (affect) brought by medication treatment may also undermine some of the beneficial effects of exposure-based CBT and place patients at relatively greater risk of relapse when medications are discontinued. This account relied on evidence from animal (see for review, Rescorla, 2001) and human studies (see for review, Mystkowski, Craske, & Echiverri, 2002) indicating that exposure-based CBT is sensitive to shifts in internal context, preventing generalization between the context of being on medication to that of being medication free. Thus when the internal context created by medication is changed, a return of fears may ensue. Although this hypothesis is consistent with the lack of evidence for additive effects of medication and exposure-based CBT in large efficacy trials for panic disorder when medication is later discontinued (Barlow, Gorman, Shear, & Woods, 2000; Marks et al., 1993), it does not explain the absence of substantial additive effects when medication and CBT are combined acutely.

In this article, we posit a mechanism for the absence of reliable additive effects when antidepressant or benzodiazepine treatments are combined with exposure-based CBT for the treatment of anxiety disorders. Our hypotheses are a result of recent advances that have led to a reconceptualization of the effects of glucocorticoids on learning and memory. We propose that although these pharmacologic treatments add anxiolytic efficacy, they may also hinder the efficacy of exposure-based CBT by attenuating beneficial effects of glucocorticoids (i.e., cortisol and corticosterone) on extinction learning.

Glucocorticoids and Learning

Glucocorticoid release is increased in response to both acute and chronic stress and has a number of important effects on cognition (Lupien & McEwen, 1997). Although evidence initially suggested that cortisol was detrimental to cognition (e.g., Heffelfinger & Newcomer, 2001; Newcomer et al., 1999), ongoing research on the nature of the relationship between glucocorticoids and cognition has made it clear that this association is complex and dependent on several variables, such as the timing of cortisol release and the type of cognition. For example, whereas chronic elevations in glucocorticoids appear to impair memory functioning, recent research with both animals and humans indicates that acute increases in glucocorticoids play an important role in enhancing emotional consolidation and extinction-based learning (for review see Lupien et al., 2005). For example, animal studies indicate that corticosterone activated by emotionally arousing learning experiences serves to regulate consolidation of memory (Hui et al., 2004; Roozendaal, Hui et al., 2006), and can enhance extinction (Barreto, Volpato, & Pottinger, 2006; Micheau, Destrade, & Soumireu-Mourat, 1982; Yang, Chao, Ro, Wo, & Lu, 2007). In contrast, acute corticosterone increases also have some memory impairing effects, but these appear to be more specific to retrieval of a memory that had been activated at the time of corticosterone release (Cai, Blundell, Han, Greene, & Powell, 2006; Pakdel & Rashidy-Pour, 2007; Sajadi, Samaei, & Rashidy-Pour, 2006).

In research with humans, cortisol has been linked to enhanced consolidation of verbal and pictorial memory (Beckner, Tucker, Delville, & Mohr, 2006; Cahill, Gorski, & Le, 2003) particularly for emotional material (Abercrombie, Speck, & Monticelli, 2006; Buchanan & Lovallo, 2001; Putman, Van Honk, Kessels, Mulder, & Koppeschaar, 2004). Additionally, cortisol administration appears to facilitate fear extinction. In a study of spider phobics, Soravia et al. (2006) administered oral cortisol (10 mg) or pill placebo one hour before exposure to a spider photograph, repeated six times over two weeks. The cortisol group reported significantly greater fear reduction over time than the placebo group with maintenance of this effect through the final session. Furthermore, at the final session no cortisol was administered, suggesting that the facilitation of extinction was durable over time. Similar findings have been identified for cue exposure in substance use disorders, where alcohol dependent individuals who demonstrated greater cortisol reactivity during 60 minute cue exposure sessions were less likely to relapse by 6 weeks post-treatment (Junghanns et al., 2005).

Additionally, several studies have examined naturally-occurring cortisol reactivity during exposure interventions and have found that endogenously-released cortisol increases in clinical populations in the context of a feared stimulus. Alpers and colleagues (Alpers, Abelson, Wilhelm, & Roth, 2003) studied salivary cortisol response during driving exposure in individuals with a diagnosis of specific phobia of driving and controls. The phobic group had significantly greater cortisol response to exposures than the control group. Notably, cortisol response did not decrease over the three days of exposure, but self-reported anxiety did significantly decrease. A study of physiological response during a one-session exposure to body shape among individuals with and without eating disorders demonstrated higher cortisol levels prior to exposure in the eating disorders group which remained significantly

higher throughout the exposure (Vocks, Legenbauer, Wachter, Wucherer, & Kosfelder, 2007). Thus, cortisol appears to be elevated during exposure-based therapy. Extinction in the context of exposure therapy may be further enhanced by the role of cortisol in attenuating the recall of traumatic memories (Roozendaal, Okuda, Van der Zee, McGaugh, 2006; Vocks, Legenbauer, Wachter, Wucherer, & Kosfelder, 2007); hence, cortisol may both facilitate extinction learning while also attenuating recall of the original fear association.

In summary, this body of findings provides a mechanism for the enhancement of exposure effects with cortisol. We posit that cortisol release may be a crucial aspect of this fear activation; under conditions of cortisol stimulation, more effective exposure therapy should result. This proposition is consistent with hypotheses that emotional activation is necessary for successful exposure-based CBT (Foa & Kozak, 1986), but offers greater specificity to this hypothesis, where it is not arousal alone, but arousal-linked stimulation of cortisol that may be important for enhancement of extinction learning.

Are Glucocorticoids Enough?

Recent research in both animals (Roozendaal, Okuda, Van der Zee, & McGaugh, 2006) and humans (Abercrombie et al., 2006; van Stegeren et al., 2007) suggests that emotional arousal associated with activation of the amygdala is necessary for the modulating effect of glucocorticoids on memory. This effect has been noted for the modulation of both memory consolidation (Cahill et al., 2003) and retrieval (Buchanan & Lovallo, 2001). Additionally, studies utilizing beta-blockers (Power, Roozendaal, & McGaugh, 2000; Roozendaal, Hui et al., 2006) or glucocorticoid antagonists (Jin, Lu, Yang, Ma, & Li, 2007; Roozendaal, Nguyen, Power, & McGaugh, 1999) to isolate the mechanisms of memory facilitation have demonstrated that the combination of arousal and cortisol is necessary for the effects of stress on learning.

A large number of animal studies (McGaugh & Roozendaal, 2008) indicate that the consolidation process for emotional memory requires glucocorticoid release and β-adrenergic receptor activation within the basolateral nucleus of the amygdala (BLA). Much of this literature bases this conclusion on post-training/pre-retrieval intra-BLA infusions of either agonists (e.g., norepinephrine, RU 28362) or antagonists (e.g., propranolol, RU38486). Arousal is obligatory for memory consolidation and appears to be due to noradrenergic activation. A study in rats demonstrated that administration of the α_2A autoreceptor antagonist yohimbine, which increases norepinephrine levels, enabled corticosterone enhancement of memory that was otherwise unaffected by corticosterone treatment due to the low-arousing testing conditions (Roozendaal, Okuda et al., 2006). These findings suggest that norepinephrine release mimics the effects of emotional arousal and support the need for noradrenergic activation for glucocorticoid facilitation of memory.

The mechanism by which cortisol aids memory is not altogether clear, although one mechanism may be through stimulation of N-methyl-d-aspartate (NMDA) receptors in the amygdala (Yang et al., 2007). There is evidence that glucocorticoids elevate calcium conductance and calcium channel subunit expression in the BLA (Karst et al., 2002), providing a mechanism by which glucocorticoids can facilitate NMDA receptor function.

The NMDA receptor has been shown to be crucially important for extinction learning. In animal studies, consolidation of extinction learning is blocked by antagonists at the NMDA receptor in the amygdala (Falls, Miserendino, & Davis, 1992). Likewise, administration of d-cycloserine (DCS), a partial NMDA receptor agonist, facilitates extinction when given in individual doses prior to extinction trials in animals (Davis, Ressler, Rothbaum, & Richardson, 2006; Richardson, Ledgerwood, & Cranney, 2004), and may also aid the generalization of extinction to related cues (Ledgerwood, Richardson, & Cranney, 2004, 2005). It has been shown that subthreshold doses of DCS and the synthetic glucocorticoid agonist dexamethasone facilitate extinction, suggesting that NMDA receptors within the amygdala participate in the modulatory effect of glucocorticoids on extinction (Yang et al., 2007). In humans, use of DCS in exposure-based CBT has been shown to facilitate clinical treatment of height phobia (Ressler et al., 2004), social anxiety disorder (Guastella et al., 2008; Hofmann et al., 2006), and obsessive compulsive disorder (Kushner et al., 2007; Wilhelm et al., 2008). Furthermore, there is a potential for synergistic effects between noradrenergic agents and exposure-based CBT. This effect has been shown in animal extinction models using yohimbine, which facilitates extinction of fear-conditioned responses associated with cue exposure (Cain, Blouin, & Barad, 2004). Initial extension of this model to humans has met with success. Specifically, Powers and associates have shown that single doses of yohimbine taken prior to each of two one-hour *in vivo* exposure sessions successfully augmented exposure-based treatment for claustrophobic fears in adults (Powers, Smits, Otto, Sanders, & Emmelkamp, 2009).

The success of DCS augmentation of exposure therapy (Anderson & Insel, 2006; Norberg, Krystal, & Tolin, 2008) as well as initial findings for yohimbine (Powers et al., 2009), have helped usher in a new focus for pharmacotherapy. Rather than targeting anxiolysis directly, pharmacotherapy is used to promote therapeutic learning (Otto et al., 2007). In the sections below, we evaluate the role of pharmacotherapy in therapeutic learning. Specifically, we review evidence that antidepressant and benzodiazepine treatments can inhibit glucocorticoids and propose that these treatments applied in conjunction with exposure-based CBT may reduce cortisol levels (or noradrenergic activation) thereby attenuating therapeutic learning in exposure-based CBT.

Cortisol Activity and Anxiolytic Medications

Benzodiazepines are linked with dose-dependent suppression of cortisol (Gram & Christensen, 1986; Pomara, Willoughby, Sidtis, Cooper, & Greenblatt, 2005) and attenuate stress-related increases in cortisol (Fries, Hellhammer, & Hellhammer, 2006; Rohrer, von Richthofen, Schulz, Beyer, & Lehnert, 1994). Indeed, acute use of these agents to decrease cortisol has been used to reduce stress response to pending surgery (Duggan et al., 2002; Jerjes et al., 2005) and to myocardial infarction (Pruneti, Giusti, Boem, & Luisi, 2002). Decreases in cortisol with benzodiazepine treatment have been noted in both control (Santagostino et al., 1996) and anxiety disordered samples (Abelson, Curtis, & Cameron, 1996; Curtis, Abelson, & Gold, 1997; Roy-Byrne et al., 1991). Although there is some evidence for the development of tolerance to the impact of benzodiazepines on cortisol (Pomara et al., 2005), the initiation of benzodiazepine treatment *co-occurring* with the initiation of exposure-based CBT is a common combination treatment strategy (Marks et al.,

1993). Fewer disrupting effects on cortisol by chronic benzodiazepine administration is consistent with the observation that exposure-based CBT works well for patients refractory to chronically administered medication treatment (Heldt et al., 2006; Otto et al., 1999).

The relationship between cortisol levels and antidepressants, such as monoamine oxidase inhibitors and serotonin and norepinephrine reuptake inhibitors, is more complex. In animals, these agents appear to not only reduce general levels of glucocorticoids (Badawy & Morgan, 1991), but to also attenuate stress-induced increases in cortisol in some (Reul, Stec, Soder, & Holsboer, 1993), but not all paradigms (Duncan, Knapp, Carson, & Breese, 1998). In humans, this general (Schule, Sighart, Hennig, & Laakmann, 2006) and stress-induced (Michelson et al., 1997) attenuation of cortisol is also noted, and reduced levels of cortisol and reduced cortisol reactivity have been documented clinically in treatment of PTSD with paroxetine (Vermetten et al., 2006). Moreover, a variety of antidepressant agents, including imipramine, amitriptyline, desipramine, fluoxetine, tianeptine, mianserin, moclobemide reboxetine, venlafaxine, citalopram, and mirtazapine can attenuate some of the effects of glucocorticoids by inhibition of their action on gene transcription (Augustyn et al., 2005; Budziszewska, Jaworska-Feil, Kajta, & Lason, 2000).

Studies in animals provide evidence that anxiolytic and antidepressant actions in the amygdala and hippocampus are disruptive to memory consolidation. Lesions of the BLA block the memory-impairing effect of systemic administration of the benzodiazepine receptor agonist diazepam (Tomaz, Dickinson-Anson, & McGaugh, 1991). Moreover, benzodiazepine-induced memory impairment is also blocked by intra-BLA infusions of the GABAergic antagonist bicuculline (Dickinson-Anson & McGaugh, 1997). In contrast, blockade of benzodiazepine receptors in the BLA with flumazenil produces a memory-enhancing effect (Da Cunha, Roozendaal, Vazdarjanova, & McGaugh, 1999). In hippocampal slices, the benzodiazepine agonist midazolam was found to inhibit long-term potentiation (Evans & Viola-McCabe, 1996), a process important for memory formation. Studies have documented that benzodiazepines interact with stress-related behaviors and cause a dose-dependent inhibition of stress-induced rise in corticosteroid levels (De Souza, 1990). Thus, while benzodiazepines may be beneficial for reducing stress-related symptoms, they are likely to be disruptive to memory consolidation. In complement to these findings, post-training infusion of the tricyclic antidepressant imipramine into the hippocampus was found to disrupt memory consolidation for passive avoidance (Zarrindast et al., 2003). The memory impairing effects of imipramine were reduced by co-infusion of the α_2A receptor antagonist yohimbine. Moreover, as noted, yohimbine has the ability to facilitate extinction learning (Cain et al., 2004) and may enhance resistance to relapse (Morris & Bouton, 2007).

The mechanisms by which benzodiazepines and antidepressants disrupt memory consolidation may relate to the effects of these agents on expression of the immediate early gene *Arc* (activity-regulated cytoskeleton-associated protein). *Arc* gene expression in the hippocampus is critical for memory consolidation (Miyashita, Kubik, Lewandowski, & Guzowski, 2008). Within the hippocampus, *Arc* is expressed transiently in CA1 and for a prolonged period in dentate gyrus following learning. It has been demonstrated that β-adrenergic receptor activation in the BLA enhances learning-induced *Arc* gene expression in hippocampus (McIntyre et al., 2005). Thus, β-adrenergic and glucocorticoid receptor

interactions in the BLA during emotional arousal may promote memory consolidation by enabling *Arc* gene expression in hippocampus. In various learning paradigms, *Arc* gene expression is enhanced approximately 260% above control levels in both CA1 and dentate gyrus subregions (Guzowski, Setlow, Wagner, & McGaugh, 2001; Huff et al., 2006). It may be of significance that chronic administration of a variety of antidepressant agents (tranylcypromine, paroxetine, venlafaxine, desipramine) produces little or no change in *Arc* gene expression in dentate gyrus and only modest (125%-160%) enhancement in CA1 (Pei, Sprakes, Millan, Rochat, & Sharp, 2004; Pei, Zetterstrom, Sprakes, Tordera, & Sharp, 2003). Consistent with these small changes in *Arc* gene expression, it has been demonstrated that several noradrenergic and serotonergic antidepressants reduce plasma corticosterone levels in response to chronic unpredictable mild stress (Dronjak, Spasojevic, Gavrilovic, & Varagic, 2007). In comparison, chronic fluoxetine produces a 3-fold increase in hippocampal *Arc* gene expression (Alme, Wibrand, Dagestad, & Bramham, 2007) and is the least disruptive of antidepressant agents to memory consolidation, at least in animal subjects (Flood & Cherkin, 1987; Lee, Lin, Chen, Shiu, & Liang, 1992). Nonetheless, the facilitation of extinction learning from exposure-based CBT has not been evident in clinical trials with SSRIs, including fluoxetine (Davidson et al., 2004). The effects of benzodiazepines on *Arc* gene expression in hippocampus have not been studied, though it is likely that this class of anxiolytics also precludes robust learning-induced *Arc* gene expression in hippocampus, due to benzodiazepine-induced lowering of plasma corticosterone levels (De Souza, 1990).

It is also important to note that our focus in this article is on acute changes in cortisol activity. These acute changes may occur against a backdrop of changing basal activity, in part driven by levels of chronic stress and affective disorders. For example, anxiety disorders are associated with a range of hypothalamic-pituitary-adrenal (HPA) axis challenges, including increased responsivity to stress, high basal levels, and downregulation of cortisol receptors due to chronically high levels of cortisol or corticotrophin-releasing factor (Abelson, Khan, Liberzon, & Young, 2007; Miller, Chen, & Zhou, 2007). Furthermore, depression has long been characterized by dysfunction in the negative feedback loop of the HPA axis, providing additional complexity when examining co-occurrence with anxiety (Gillespie & Nemeroff, 2005). Both pharmacologic (Vermetten et al., 2006) and psychosocial (Tafet, Feder, Abulafia, & Roffman, 2005) treatments have demonstrated reduction in basal cortisol level or response to stress following successful treatment outcomes and recent research has successfully sought to target dysregulation of the HPA axis through the use of CRF antagonists, which attenuate cortisol release (Ising et al., 2007). Nonetheless, the association between basal cortisol levels and/or HPA axis hyper-reactivity and treatment response is an issue potentially distinct from the enhanced learning associated with the acute release of cortisol.

Cortisol Blockade: Therapeutic Applications and Cautions

Whereas cortisol blockade has the potential to attenuate safety learning when applied during fear extinction, cortisol blockade also has the potential for beneficial effects if applied during the consolidation of fear memory. Following a traumatic event, reduction of physiological arousal in the context of memory retrieval is believed to reduce facilitation of memory consolidation modulated by increased cortisol response. Propanolol, a β-adrenergic

receptor blocker administered acutely following the occurrence of a traumatic event has been shown to reduce the likelihood of development of PTSD as compared with placebo when administered following recall of a traumatic memory outside an extinction paradigm (Pitman et al., 2002; Vaiva et al., 2003). The rationale for such interventions is that interruption of the consolidation of a traumatic memory by decreasing cortisol will prevent the development of PTSD symptoms. This differs from exposure therapies which rely on consolidation of *new* learning for extinction to occur. The salience of the traumatic memory may be weakened by reducing cortisol acutely during consolidation or reconsolidation processes; however, by also attenuating the consolidation of new memory, the re-learning of safety following a trauma may be compromised.

Accordingly, propanolol administration may have beneficial effects if applied acutely after trauma (perhaps one week or less), but may slow re-acquisition of safety in response to trauma-related cues if this treatment is continued too long – during a period when patients are exposed to trauma cues under safe circumstances. Indeed, Cain et al. (2004) demonstrated an attenuation of extinction learning with propanolol administration in mice. Thus, propanolol may be exactly the wrong treatment if administered into the period of safety learning (i.e. fear extinction) during the post-acute period following the trauma. Study of propanolol as a preventive treatment for PTSD is ongoing, and analysis of the length of treatment may shed light on the degree to which this treatment may be acutely beneficial or harmful if medication administration is maintained into the post-acute period.

Discussion

In this article, we introduce an account that posits a specific mechanism for poorer extinction learning when stress and fear-related glucocorticoid and NMDA receptor activity is modulated by traditional pharmacotherapy for anxiety disorders. Evidence in both animals and humans indicates that acute impairment of glucocorticoid responsivity is linked to poorer memory consolidation and may interfere with extinction learning. However, this reactivity is dampened by treatment with many benzodiazepine and antidepressant medications, thereby attenuating extinction learning. It is important to note that this hypothesis is consistent with the model introduced by Foa and Kozak two decades ago. Foa and Kozak (1986) hypothesized that two conditions are necessary for fear reduction via exposure: activation of a “network” of fear associations and incorporation of new information into this network. According to this model, affect modulation from medication may prevent adequate activation of the fear network, and hence attenuate extinction of fear. Our accounting is consistent with concerns about the affect modulating properties of medication on the therapeutic learning offered by exposure interventions, but offers greater specificity by hypothesizing that it is the blockade of acute cortisol release that may underlie the attenuation of additive effects in combination treatment. Focusing on cortisol release instead of the degree of anxious arousal is also consistent with recent data showing that the degree of anxiety during exposure is not a predictor of treatment outcome (Hayes, Hope, & Heimberg, 2008; Pitman et al., 1996), although more complex relationships (e.g., curvilinear, Foa & Kozak, 1986) between anxious arousal and outcome may exist. Regardless, it appears that the degree of cortisol release during exposure is independent of degree of anxiety (Alpers et al., 2003).

An important feature of our model is the timing of cortisol release. Rather than considering the utility of the facilitation or attenuation of cortisol release for clinical treatment, we draw attention to the type of learning that is ongoing at the time of this release. If it is extinction learning, then cortisol release may facilitate treatment of anxiety disorders. Our concerns about combined treatments are also specific to the timing of administration. Use of agents that may attenuate cortisol during core learning sessions of exposure-based CBT would, according to the evidence reviewed above, be expected to attenuate treatment effects from CBT. As noted, these predictions are consistent with the limited performance of combined treatment strategies when exposure-based CBT and pharmacotherapy are initiated together. Predictions of adding CBT to patients undergoing longer-term medication maintenance are less clear, and exposure-based CBT may be better combined with medications under conditions of longer-term pharmacotherapy in treatment refractory patients (Otto et al., 1999). Likewise, our expectations of relative benefit vs. harm in the use of beta blockers following a traumatic stressor are based fully on the time course of their use, with the expectation that these agents may inhibit extinction learning as well as fear learning, raising questions about how quickly their use should be discontinued as patients work to reacquire a sense of safety in the post-acute phase of adjustment to trauma.

Limitations and Rival Hypotheses

It is important to note that studies of the combination of exposure-based CBT and pharmacotherapy in children and adolescents have provided at least some evidence of additive effects of combined treatment (see Pediatric OCD Treatment Team, 2004; Walkup et al., 2008). Unfortunately, no studies have specifically evaluated the impact of cortisol on extinction learning in children, and thus it is unclear whether the effects of glucocorticoids on learning processes function similarly in children. However, the discrepancy between child and adult combination treatment studies may be explained by the central role of parents in CBT for anxiety disorders in children (e.g., Walkup et al., 2008). Due to the sessions focused on parent education and intervention, parents in these protocols facilitate exposure by providing the child with opportunities for therapeutic learning at home in addition to what is provided in session. With such additional opportunities for therapeutic learning, the role of in-session attenuation of learning effects (should they occur with combination treatment) would be expected to play less of a role in the overall efficacy of CBT for children in these protocols. Also, the role of cortisol activity in children may be more difficult to assess given that parental stress and depression itself influences cortisol levels among children (see Lupien et al., 2005). Accordingly, additional research with children is needed to clarify both the importance of glucocorticoids for therapeutic learning and the impact of medications on cortisol and learning among children with anxiety disorders.

Also, the failure to find additive treatment effects for the anxiety disorders stands in at least partial contrast to combination treatments for major depression. Although effects are variable (see Otto, Smits, & Reese, 2005) and modest according to meta-analytic review (Cuijpers, van Straten, Warmerdam, & Andersson, 2009), there is evidence that combining pharmacotherapy with CBT for unipolar depression can provide additive effects in both adults (e.g., Manber et al., 2008) and adolescents (e.g., March et al., 2004) than is typically

evident in the treatment of anxiety disorders. Hence, our hypotheses are specific to the effects of cortisol on extinction-based learning offered by exposure-based CBT for anxiety disorders.

In this manuscript, we focused on explicating a cortical-based mechanism that may explain the limited combination treatment effects observed in the anxiety literature. Other potential explanations for combination treatment effects also should be noted. It is possible that the learning of safety from exposure is altered simply because patients may attribute their therapeutic successes to medication. Indeed, for the treatment of claustrophobia, there is evidence that the perception of rescue alternatives (e.g., calling the therapist or opening a window) significantly reduced both acute anxiety and the efficacy of the exposure (Powers, Smits, & Telch, 2004; Sloan & Telch, 2002). Likewise, knowing that a medication was taken may calm anxiety but also alter the perception that phobic cues are truly manageable or safe. As noted above in our discussion of context effects, there is strong evidence for this effect when patients are later discontinued from the medication available during the exposure (Otto et al., 2005; Powers, Smits, Whitley, Bystritsky, & Telch, 2008), but the strength of these findings is difficult to estimate for patients who remain on medication. Indeed, there is evidence for facilitative effects of pill placebo in clinical trials of panic disorder when patients continue pill taking (Barlow et al., 2000). Hence, support for this alternative explanation is limited. Also, we cannot rule out other brain changes that may be redundant between exposure-based CBT and pharmacotherapy. For example, there is evidence that CBT and medications may both affect some of the same brain regions in depressed individuals, but may affect these regions in different ways (for review see Otto et al., 2005). Such redundant sites of action may reduce the degree to which additive effects can be obtained from two treatments. However, current research does not allow adequate elaboration of the mechanism of such an effect, if any, in the treatment of anxiety disorders.

Conclusions

In summary, here we propose a mechanism for the absence of reliable additive effects for the addition of anxiolytics to exposure-based CBT for the anxiety disorders. We posit that the blockade of cortisol activity with traditional antidepressants and anxiolytics may cause attenuated learning during exposure. This proposition is supported by animal and human studies showing cortisol activation during exposure therapy, cortisol enhancement of extinction learning in experimental paradigms, and attenuation of cortisol levels with benzodiazepine treatment and at least some antidepressant treatments. This proposition is made more complex by variable memory-facilitative effects of some antidepressants, with expectations of greater facilitation of memory processes with drugs having relatively more robust effects on the expression of *Arc* and other immediate early genes in the hippocampus. Attention to the effects of pharmacotherapy on therapeutic learning in exposure-based CBT is in line with recent successes of translational research (Anderson & Insel, 2006) showing the efficacy of DCS in enhancing exposure therapy (Norberg et al., 2008; Otto et al., 2007). This article provides a complement to this perspective, drawing cautionary attention to the potential extinction-attenuating effects of traditional anxiolytic medications.

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