THE BIOLOGY AND EFFICACY OF COMBINATION STRATEGIES FOR ANXIETY DISORDERS

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INTRODUCTION

Optimal treatment of anxiety disorders is important as they are the most prevalent psychiatric disorders in community studies, and generalized anxiety disorder is the most prevalent psychiatric disorder in primary care (Kessler et al. 2010). In addition, anxiety disorders begin early in life, and predispose to the development of comorbid disorders such as depression and substance use disorders; early and robust treatment may therefore be important in secondary prevention (Goodwin and Gorman 2002). Anxiety disorders are not only associated with significant suffering in affected individuals and families, but also contribute enormously to the societal burden of disease; a number are among the most disabling of all medical conditions (Lopez et al. 2006).

Fortunately, there have been significant advances in the treatment of anxiety disorders. A range of medications have been approved in the past few decades for the major anxiety disorders on the basis of randomized controlled trials showing efficacy and safety. Similarly, during the same period, a number of psychotherapies have been rigorously studied, and shown to have both short-term and longer-term efficacy. Expert guidelines, often incorporating systematic meta-analyses of the research literature, have been developed, and highlight the evidence base for first-line interventions, such as selective serotonin uptake inhibitors (SSRIs) and cognitive behavioral therapy (CBT) (Ipser and Stein 2009). The majority of patients with anxiety disorders can be expected to respond to such first-line interventions.
At the same time, underdiagnosis and undertreatment of, and resistance to treatment in, anxiety disorders remain significant problems. Underdiagnosis and undertreatment may reflect a range of structural and attitudinal barriers, including insufficient numbers of well-trained therapists and insufficient mental health literacy in both the general population and primary care practitioners. First-line treatments may work in the majority of cases, but even when appropriately diagnosed and treated, 40% or more of patients may fail to respond (Pallanti et al. 2002; Bandelow and Ruther 2004). There is a relative lack of effectiveness trials in anxiety disorders, but in real-world settings, where patients may have increased comorbidity, and where clinicians are required to be generalists rather than specialists, treatment response rates may be lower, and tolerability concerns more obvious, particularly over the longer term.

Combination treatment is an important consideration in attempts to improve the efficacy and effectiveness of intervention in anxiety disorders. Given the multiple factors, including neurobiological and psychological variables, involved in anxiety disorder pathogenesis, there is a prima facie case for a comprehensive treatment approach including pharmacotherapy and psychotherapy. Indeed, early thinking suggested pharmacotherapy was useful for a rapid treatment response, while psychotherapy was valuable for a maintained response, even after discontinuation of short-term intervention (Riba and Ballon 2005). It has therefore been surprising to see a growing evidence base suggesting relatively little advantage in combining pharmacotherapy and psychotherapy for anxiety disorders (Foa et al. 2002; Otto et al. 2005; Black 2006; Bandelow et al. 2007; Hofmann et al. 2009).

Perhaps one of the most exciting developments in combination treatment of anxiety disorders, if not in all of medicine, has been the adoption of a rigorous translational neuroscience approach (Davis et al. 2006; Otto et al. 2007; Hofmann et al. 2011; Kaplan and Moore 2011). Advances in a range of basic neuroscience areas, including animal models of anxiety disorders, have allowed combination interventions to be studied in the laboratory. Rather than relying on standard first-line pharmacotherapies, such work has focused on targets (e.g. in glutamatergic systems) that may be specifically relevant to enhancing cognitive-behavioral interventions. Such work provides a rigorous foundation for moving findings through to the bedside, in the form of proof-of-principle clinical studies. This approach appears to have significant potential and has therefore attracted considerable interest from researchers, making this book extremely timely.

This chapter will briefly focus on a number of background issues relevant to combination treatment in anxiety disorders. First, we will review some of the psychobiology relevant to an understanding of how combined treatments work. Second, we will review some of the findings addressing, and issues concerning, the efficacy of such combined treatments.
PSYCHOBIOLOGY OF COMBINATION TREATMENTS

There is a growing understanding of the neurocircuitry underlying the fear response in animals and anxiety disorders in humans. Advances in structural and functional neuro-imaging have been key in developing our understanding of such circuitry in clinical conditions (Shin and Liberzon 2010). Thus, a growing body of evidence suggests that anxiety disorders are characterized by abnormalities in both prefrontal and subcortical (e.g. amygdala, hippocampus) circuitry (Grillon 2002; Anderson and Insel 2006). Neurotransmitters involved in such pathways include serotonergic, noradrenergic, glutamatergic, gamma-aminobutyric acid (GABA)ergic, and neuropeptide systems, and many available pharma-cotherapies act on such systems (Charney 2003).

One approach to understanding the psychobiology of combined pharma-cotherapy and psychotherapy is to argue that pharmacotherapy acts predominantly on bottom-up neurotransmitter-mediated mechanisms, while psychotherapy acts mainly on top-down cognitive-affective processes. Medications, such as SSRIs, may act on the amygdala and its efferent pathways (e.g. to hypothalamus and brainstem) to reduce panic attacks, which in turn leads to reduced anticipatory anxiety and phobic avoidance (Gorman et al. 2000). However, interventions such as CBT, may act upstream of the amgydala, strengthening the ability of medial prefrontal areas to inhibit sub-cortically mediated processes, by decreasing cognitive misattributions and deconditioning the fear response (Mayberg 2002).

While such an approach may be heuristically useful, it may entail some over-simplification. First, neurocircuitry alterations following psychotherapy are not limited to prefrontal areas; instead they may be widespread (Roffman et al. 2005; Frewen et al. 2008). Conversely, the effects of pharma-cotherapy are unlikely to be limited to sub-cortical neurotransmitter activity; rather they may lead to significant changes in high-level cognitive and affective processing. Furthermore, such an approach does not explain why certain combinations of pharmacotherapy and psychotherapy appear ineffective or even contra-indicated (Otto et al. 2005). Indeed, both pharmacotherapy and psychotherapy are interventions that have complex and interactive effects on the brain-mind.

Another question that requires a more complex approach is whether combination strategies are likely to be similar across different anxiety disorders, or whether specific combined treatment approaches will be needed for each disorder. On the one hand, imaging studies suggest that there are a number of overlapping mechanisms that cut across different anxiety disorders. A recent meta-analysis of brain imaging studies in anxiety disorders, for example, found an increase in the activity of the amygdala and insula in participants with post-traumatic stress disorder (PTSD), social anxiety disorder, and with specific phobia, relative to healthy control subjects (Etkin and Wager 2007). Thus, it may be predicted
that SSRIs act to decrease insula activity, while CBT acts to decrease amygdala activity, in a number of these conditions (Furmark et al. 2002; Carey et al. 2004). On the other hand, there is also involvement of distinctive neurocircuitry in different anxiety disorders (Etkin and Wager 2007). Furthermore, within a particular disorder, different neuronal circuitry may be involved in different symptom presentations (Lueken et al. 2011). Thus, it is possible that different forms of combined treatment may be effective, not only for different anxiety disorders, but also for different subtypes of particular anxiety disorders.

Imaging studies in humans will no doubt continue to be important in answering such questions. For example, particular neurocircuitry findings predict response to pharmacotherapy, while others predict response to psychotherapy, or to combined treatment (Brody et al. 1998; Furmark et al. 2002; 2005). Data from studies that address the impact of particular gene variants on neuro-imaging findings are also likely to be important in developing more integrative models. Also, in order to develop more complex models of combined treatments, it would be helpful to have good laboratory models of anxiety disorders and interventions. Fortunately, there is a range of ongoing work in this area. We briefly review some of the relevant work targeting neurotransmitter systems (e.g. glutamatergic, noradrenergic, and adenosine systems), neuroendocrine systems (e.g. glucorticorticoids), and social neuropeptides (e.g. oxytocin (OT)).

Neurotransmitter Systems

Laboratory research has suggested the glutamatergic system as a target for combined pharmacotherapy and psychotherapy; this research demonstrated that the N-methyl-D-aspartate (NMDA)-glutamate receptor of the lateral and basolateral amygdaloid nuclei was involved in fear conditioning and fear extinction in rodents (Davis et al. 1993). Given that antagonists of the NMDA receptor prevented both the acquisition and extinction of fear (Lee and Kim 1998), the question arose of whether an NMDA agonist would facilitate the extinction of conditioned fear (Walker et al. 2002). Indeed, rats that received the partial NMDA agonist D-cycloserine (DCS), in combination with repeated exposure to the conditioned stimulus, had enhanced extinction of their fear as compared to the rats that received DCS alone (Walker et al. 2002). The work provided a solid foundation for clinical trials of combined DCS and CBT; the first of these seminal proof-of-principle clinical studies was undertaken in acrophobia (Ressler et al. 2004), and several others soon followed.

Animal research has also questioned the extent to which the effects of DCS on fear extinction are generalized. Rats given DCS and fear extinction training to one stimulus, also exhibited reduced fear to another stimulus (Ledgerwood et al. 2005). Furthermore, some animal work has indicated that DCS may prevent the relapse of learned fear (Ledgerwood et al. 2004).
However, it has also been suggested that if DCS enhances fear extinction by improving learning, then it may also facilitate recall of aversive memories (Lee et al. 2006). Perhaps, to reduce the potential for sensitization of negative memories, it will prove preferable to administer DCS after an exposure session that is determined by the clinician to be successful (Hofmann et al. 2011).

There is also some concern about developing tolerance to DCS, thereby reducing efficacy of combined treatment over time. Perhaps DCS should be used on an acute rather than chronic basis (Hofmann et al. 2006). Indeed, poorer results have been found in studies that used DCS at higher or more frequent doses (Kushner et al. 2007; Wilhelm et al. 2008; Storch et al. 2010). Ultimately, additional clinical research is needed to determine the extent of precise benefits and risks of using DCS in combined treatments (Krystal 2007). Combination strategies using DCS are further discussed in Chapter 5 of this book.

Ongoing animal research has provided additional insight into the specific mechanisms whereby DCS exerts its effects. DCS acts on the NMDA receptor complex’s strychnine-insensitive glycine-recognition binding site, facilitating the movement of calcium, which in turn initiates intracellular processes that are involved in learning. The effects of DCS appear to be mediated in particular by intra-amygdala signaling cascades involving mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI-3K), both of which are known to play a role in fear conditioning (Yang and Lu 2005). Such work may ultimately lead to additional pharmacological interventions for use in clinical employment of combined treatment.

A range of neurotransmitter systems, other than the glutamatergic system, are also likely involved in facilitating prefrontally-mediated fear extinction. The noradrenergic system, for example, plays a key role in prefrontal processes. Yohimbine hydrochloride is a selective competitive alpha2-adrenergic receptor antagonist that stimulates c-Fos expression in the medial prefrontal cortex (Singewald 2003). Administration of yohimbine hydrochloride in rats enhanced extinction learning and improved the time needed to reduce conditioned fear, providing a foundation for subsequent translation to human studies (Cain 2004; Powers 2009). Combination strategies using yohimbine hydrochloride in the treatment of anxiety disorders are further discussed in Chapter 6.

Various neutraceuticals may also act on neurotransmitters mediating fear and anxiety. Caffeine, a psychostimulant that acts on adenosine receptors, is one of the most widely used. It induces positive feelings such as alertness and increased mental performance. However, individuals with a history of anxiety disorders, particularly panic disorder, experience more unpleasant physical symptoms, suggesting adenosine receptor sensitivity; hence the hypothesis that administration of caffeine during exposure based treatment might enhance and sustain fear extinction. Neutraceutical combination treatments are discussed further in Chapter 9.
Neuroendocrine Systems

Glucocorticoids are steroid hormones that are synthesized in the adrenal cortex, and are released along with catecholamines as part of the hypothalamic-pituitary-adrenal neuroendocrine response to stress. Laboratory research has shown that adrenalectomy and administration of corticosteroid synthesis inhibitors reduces the unconditioned startle response and increases time spent in a fearful environment (Cordero 1998; Takehashi 1998). Conversely, administration of GR agonists prior to fear extinction facilitates fear extinction on repeated exposure of the stimulus, an effect that is blocked by co-administration of a GR antagonist (Yang et al. 2006). This work again provides a foundation for clinical trials of GR agonists together with psychotherapy (see below).

Laboratory research again suggests particular clinical research directions. For example, administration of a GR agonist after the extinction phase continues to have a facilitatory effect, suggesting that glucocorticoids influence memory consolidation (Yang et al. 2006), a finding that may be particularly relevant in the context of a condition such as PTSD. Further extensions of laboratory research may ultimately lead to additional clinical targets. It is notable, for example, that it is glucocorticoid receptors, rather than mineralocorticoid receptors, which are associated with memory consolidation (Oitzl and de Kloet 1992; Roozendaal and McGaugh 1996). As the neurobiology of these receptors becomes increasingly better understood, so additional clinical routes of investigation open up (Cahill and McGaugh 1996; Lupien and McEwen 1997). A broad range of other neuroendocrine targets (e.g. gonadal hormonal systems) may also be relevant to combined treatments.

One important area of glucocorticoid research lies in developmental psychobiology. The effects of early adversity of the developing brain-mind, for example, are mediated by a range of neurochemical and neuroendocrine pathways, including the glucocorticoid system (Stein et al. 2005). Administration of an SSRI may reverse some of these effects in rodent models of early life trauma (Uys et al. 2006). Although there has been some literature on both the pharmacotherapy and psychotherapy of patients presenting with psychopathology in the context of a history of early adversity (Nemeroff et al. 2003; Stein et al. 2003), much further work is needed to establish optimal combined treatments for such patients. Combination strategies using glucocorticoids are further discussed in Chapter 7.

Social Neuropeptides

OT and arginine vasopressin (AVP) are highly conserved neuropeptides that play an important role in social interaction, including parental care, pair-bonding, sexual behavior, and social memory. Across species, OT
often mediates female-specific behavior such as parturition and lactation, while AVP often mediates male-specific behavior including aggression (Donaldson and Young 2008). Both OT and AVP appear critical for linking social signals to mesocorticolimbic reward circuitry (Insel 2003). These basic scientific findings raise the question of whether such social neuropeptides may be usefully incorporated into combined treatments of clinical disorders. A broad range of other peptide systems (e.g. opioid system) may also be relevant to the clinical setting (Stein et al. 2007).

In humans, intranasal administration of OT increases feelings of trust (Kosfeld et al. 2005) and enhances emotion recognition (Domes et al. 2007). OT attenuates behavioral or amygdala responses to breaches of trust, aversive stimuli, or fear-conditioned responses to social stimuli (Kirsch et al. 2005; Domes et al. 2007; Baumgartner et al. 2008; Petrovic et al. 2008). Depending on the paradigm studied, there may also be reduced coupling of amygdala to brainstem regions involved in the fear response (Kirsch et al. 2005), or decreased activation in regions involved in facial recognition (Petrovic et al. 2008). However, further work is needed to determine whether such effects are also seen during combined treatment of clinical disorders.

While laboratory studies give insight into general cognitive-affective processes, they may not necessarily be devised with specific clinical conditions in mind. Given the role of OT and AVP in social interaction, these peptides have been postulated to play a role in autism (Hammock and Young 2006). OT may be decreased in autism and association studies have suggested a role for OT receptor variants in autism (Israel et al. 2008). Arginine vasopressin 1a receptor (AVPR1a) knockout mice have social dysfunction that is redolent of autism, and both linkage and association data in clinical samples have pointed to involvement of AVPR1a in autism (Hammock and Young 2006). However, there is also some evidence that these neuropeptides or their receptors may play a role in a broad range of other psychiatric conditions, including schizophrenia, post-traumatic stress disorder, obsessive-compulsive disorder, depression, and substance use disorders (Stein 2009). Thus, should OT be found useful as part of combined treatment, study of a broad range of conditions may be relevant. Combination strategies using OT are further discussed in Chapter 8.

**EVIDENCE FOR COMBINATION THERAPY IN ANXIETY DISORDERS**

Although a psychobiological perspective may be used to support the combination of some pharmacotherapies and psychotherapies, and although laboratory research has provided a basis for the development of specific agents to augment exposure based therapies in the clinic, ultimately the proof of the pudding is, of course, in the eating. In this section,
we briefly review some of the clinical data on combined treatments in anxiety disorders, in order to draw some general conclusions regarding work in this area. Later chapters in this book will discuss combination strategies with specific agents in further detail; Chapter 2 will discuss benzodiazepines, Chapter 3 will discuss tricyclics and monoamine oxidase inhibitors, and Chapter 4 will discuss selective serotonin re-uptake inhibitors, reversible inhibitors of monamine oxidase-A, and buspirone.

Panic Disorder

A relatively large number of studies of combined pharmacotherapy (i.e. antidepressants or benzodiazepines, plus CBT) have been undertaken in panic disorder. An early meta-analysis indicated that 20 studies provided data on the efficacy of combined treatment compared to psychotherapy. Combined treatment was found to be slightly more effective than CBT alone. However, in those studies which included a follow-up, there was no significant difference between a combination approach and CBT alone (Mitte 2005). A subsequent meta-analysis reviewing trials, combining antidepressants with CBT for panic disorder (Furukawa et al. 2007), confirmed that during short-term treatment, combination therapy was more effective than single modality treatment, and found that during long-term follow-up, combined treatment was as effective as psychotherapy alone, and was more effective than pharmacotherapy alone.

Bandelow et al. (2007) have emphasized that by using different methods, meta-analyses of treatments in anxiety disorders may reach different conclusions. In their meta-analysis of combined treatments for different anxiety disorders, they restricted their analysis to studies which directly compared pharmacotherapy, psychotherapy, or the combination of these therapeutic modalities. Furukawa et al. concluded that combined pharmacological and psychological treatment was superior to monotherapy for panic disorder. Effect sizes range between $d = 0.23$ and $d = 0.61$ (which corresponds to small to medium effect sizes, Cohen 1988), thus indicating that combined therapy is the most effective treatment strategy.

Medications studied in combination with CBT for panic disorder are, however, heterogenous, including various antidepressants, buspirone, and benzodiazepines (Marks et al. 1993; Cottraux et al. 1995; Barlow et al. 2000). Although there are arguably too few studies of combined benzodiazepines and CBT in panic disorder to draw definitive conclusions (Watanabe et al. 2009), a study with alprazolam showed that improvements made early in combined treatment were lost when alprazolam was tapered off (Barlow et al. 2000). However, improvements made in the groups receiving CBT alone, or placebo alone, were maintained. This finding suggests that alprazolam weakens the effects of CBT, perhaps due to interference with learning or suppression of affect during exposure therapy (Black 2006; Hofmann 2006; Otto et al. 2010).
More recently, DCS has been combined with exposure-based CBT for panic disorder (Otto et al. 2010). The results indicated large effect sizes for the additive benefit of DCS augmentation, consistent with the view that DCS consolidates extinction memory. The authors also emphasized that this was the first DCS study to have emphasized exposure to feared internal sensations (i.e. interoceptive exposure). Furthermore, the treatment targeted participants who in most cases were refractory to previous pharmacotherapy. A more recent trial was unable to show a significant additive benefit of DCS to panic disorder due to the fact that patients responded well to CBT; however, there was evidence that in more severely measure ill patients, DCS accelerated symptom reduction in the primary outcome (Siegmund et al. 2011).

Social Anxiety Disorder

Sertraline, fluoxetine, phenelzine, and moclobemide are some of the medications that have been studied in combination with CBT for the treatment of social anxiety disorder (Blomhoff et al. 2001; Davidson et al. 2004; Prasko et al. 2006; Blanco et al. 2010). Early meta-analysis found that there was insufficient data to demonstrate an advantage for combined over unimodal treatment (Bandelow et al. 2007). However, in the largest of the comparative studies, combined phenelzine and CBT treatment was superior to either treatment alone (Blanco et al. 2010). Furthermore, as discussed below, combined treatment is more effective than unimodal therapy in children and adolescents with social anxiety disorder (Walkup et al. 2008).

However, few of these studies of combined treatment for social anxiety disorder have compared outcomes in acute and long-term treatment. The sertraline study suggested that a combination of treatment and exposure therapy had enhanced efficacy (Blomhoff et al. 2001), but this did not hold true over a 1-year follow-up (Haug et al. 2003). The moclobemide study followed-up participants over 2 years (Prasko et al. 2006). Although there were no significant advantages between the groups in the first 3 months, the combined treatment group had quicker onset of symptom reduction. The moclobemide group showed a greater reduction in subjective anxiety over the 3 months, while the CBT group showed a greater reduction in avoidant behavior. However, by 6 months, there was no significant difference in outcomes between the groups.

Social anxiety disorder, like other anxiety disorders, is a heterogeneous condition. Most pharmacotherapy studies have focused on patients with generalized social anxiety disorder. Nevertheless, there are reports of the efficacy of both pharmacotherapy and psychotherapy in patients with specific performance phobia, and it would be useful to assess the relative efficacy of combined treatments in this condition.

Of particular interest to translational medicine, two studies have now found that DCS has an additive advantage to exposure-based CBT for
social anxiety disorder (Hofmann et al. 2006; Guastella et al. 2008). Controlled effect sizes in this work were in the medium to large range. In their meta-analysis of the early literature on DCS in the augmentation of CBT, Norberg et al. (2008) suggested that DCS may be useful early in treatment. However, further work with larger samples is clearly needed to fully demonstrate the therapeutic profile of DCS in social anxiety disorder, and to determine predictors of response.

**Generalized Anxiety Disorder**

There are too few studies that have combined psychotherapy and pharmacotherapy in the treatment of generalized anxiety disorder to reach definitive conclusions (Bandelow et al. 2007). In a study of buspirone and various forms of anxiety treatment, combined treatment conferred some additional benefits (Lader and Bond 1998). In one study of diazepam and CBT, the combined treatment was superior to the drug alone, but with a smaller effect in comparison to CBT plus placebo, and inconsistent findings for the combined treatment in comparison to CBT alone (Power et al. 1990). Additional work is clearly needed in this area.

Walkup et al. (2008) conducted a study of combination treatment in children and adolescents with various anxiety disorders, including GAD, separation anxiety disorder, and social anxiety disorder. In this study, the combination of CBT and sertraline was significantly more effective than either treatment modality alone for each of these anxiety disorders. This finding raises the important question of whether combined treatments are equally effective at different development stages; it may, for example, be hypothesized that combined treatments are most effective at developmental periods when neuroplasticity is highest.

The literature on combined treatment for GAD also questions the use of an integrated approach to help improve outcomes of benzodiazepine discontinuation. Cognitive-behavioral treatment has shown efficacy in preventing relapse and facilitating BZ discontinuation in panic disorder (Otto et al. 1993; 2002; Spiegel et al. 1994). CBT provides specific efficacy for the successful discontinuation from BZs, even when controlling for therapist contact and relaxation training (Otto et al. 2010). Similarly, CBT appears useful in preventing relapse and increasing the tolerability of withdrawal in patients with GAD (Gosselin et al. 2006).

**Post-traumatic Stress Disorder**

A meta-analysis of trials of combined pharmacotherapy and psychotherapy for post-traumatic stress disorder found four trials eligible for inclusion (Hetrick et al. 2010). All used an SSRI and prolonged exposure or a cognitive behavioral intervention. Two trials compared combination
treatment with pharmacological treatment and two compared combination treatment with psychological treatment. There was no strong evidence to show group differences. The authors concluded that there is not enough evidence available to support or refute the effectiveness of combined psychological therapy and pharmacotherapy compared to either of these interventions alone.

The literature on combined treatment in PTSD also questions how the sequencing of combined treatments affects outcome. In one study, CBT was added to sertraline in PTSD subjects who had already demonstrated a poor response to sertraline alone, and combined treatment was effective in these treatment-refractory patients (Otto et al. 2003). However, in PTSD patients who were symptomatic after prolonged exposure therapy, the addition of paroxetine was no more effective than placebo (Simon et al. 2008). Further work is needed to determine what specific individual factors predict response to combined and sequenced treatments. In the interim, when combining modalities, clinicians need to weigh up a range of considerations, including issues of counter-transference, and the possible symbolic meaning of medications for both therapists and patients (Southwick and Yehuda 1993).

The developmental of good animal models of PTSD will hopefully facilitate the translation of combined treatment approaches from ‘bench to bedside’ (Harvey et al. 2004; Cohen and Zohar 2004). Clearly, there is a prima facie case for considering the use of DCS in the combined treatment of PTSD (Choi et al. 2010; Ganasen et al. 2010). In addition, approaches which focus on the use of glucorticoid and other neuroendocrine and neuropeptide targets are worthy of further investigation in the clinical setting (Cohen et al. 2008; Kaplan and Moore 2011).

Obsessive-Compulsive Disorder

Medications studied in combination with CBT in treatment of obsessive-compulsive disorder include clomipramine and fluvoxamine (Marks et al. 1980; Cottraux et al. 1990; Hohagen et al. 1998; van Balkom et al. 1998; Foa et al. 2005). The combined results from these studies provide little evidence that combined treatment is better than monotherapy in obsessive-compulsive disorder (OCD). Nevertheless, individual studies have suggested that combined treatment, perhaps with more intensive CBT, may be more effective (Hohagen et al. 1998; Foa et al. 2005). As with PTSD, it may be particularly relevant to consider the use of an augmentation approach in those patients who are treatment-refractory.

Unfortunately, studies of DCS in OCD have also not been entirely persuasive (Kushner et al. 2007; Storch et al. 2007; Wilhelm et al. 2008). Obsessive-compulsive disorder arguably has different psychobiologic underpinnings from other anxiety disorders. Perhaps the investigation of
more specific animal models of OCD at the bench, will ultimately lead to specific targets for combined treatments at the bedside (Joel et al. 2008).

As with PTSD, another important possible target of CBT in combination therapy for OCD is in addressing cognitive distortions about medication (Julius et al. 2009). For example, patients with OCD may view their medication as somehow ‘contaminated.’ Or some patients with religious obsessions may view their medications as somehow contributing to their inability to remain ‘pure.’ In general, there is little literature on how schemas and their products (cognitions, affects) may influence patients’ attitudes toward medication, and therapeutic responses to pharmacotherapy (Pontoski 2010).

CONCLUSION

Anxiety disorders can take pride in a number of aspects of research on combined treatments for these conditions. First, there is a long tradition of systematically comparing pharmacotherapy, psychotherapy, and their combination in anxiety disorders (Westra 1998). This work is arguably more rigorous and extensive for anxiety disorders than for most other psychiatric disorders. Second, the first work comparing the mediating functional neuro-anatomy of pharmacotherapy versus psychotherapy was undertaken in an anxiety disorder (Baxter et al. 1992). This tradition of research continues, and there is data on the comparative effects of pharmacotherapy and psychotherapy on a number of anxiety disorders. Third, laboratory discoveries on fear extinction led to the first examplar of a translational approach to combined treatments in psychiatry (Davis et al. 2005). A range of ongoing work is attempting to move from bench to bedside to optimize combined treatment approaches in anxiety disorders (Hofmann et al. 2011).

However, the number of trials comparing pharmacotherapy, psychotherapy, and combined treatments remains rather limited. In addition, almost all of this work has been undertaken in highly specialized centers with adult patients with a single disorder, and there is a real need for extension to more complex populations, including different age groups, with effectiveness and cost-efficiency trials in real-world settings. Second, our understanding of the psychobiological mechanisms underlying pharmacotherapy and psychotherapy of anxiety disorders remains limited. More work is needed in order to understand fully the relevant neurocircuitry and molecular mechanisms, as well as contributing genetic and epigenetic variance, so that additional targets for the full range of anxiety disorders and their subtypes are developed. Finally, translational work is at an early stage with many questions regarding which disorders respond best to which augmenting agents, optimal timing and dosing of these agents, and long-term efficacy and effectiveness in real-world settings.
Finding resources for conducting larger trials, in the absence of industry support, will be a challenge.

From a practical perspective, meta-analysis of combined pharmacotherapy and psychotherapy treatments are perhaps disappointing, in that they show only limited benefits for combined treatments. However, meta-analyses are only as good as the contributing studies, and given the heterogeneity of this work, the conclusions are perhaps not surprising. Furthermore, a number of clinically relevant conclusions also flow from this literature. First, not all pharmacotherapies and psychotherapies should be combined; there is some reason, for example, to be cautious about using benzodiazepines with CBT. Second, the effects of combined treatments may vary at different points in time, both during development and during the course of an illness; the early clinical rule of thumb that medications work quicker, while CBT lasts longer, may have some truth, although not all data are supportive (Bandelow et al. 2007). Third, it is important to consider the optimal sequencing of pharmacotherapy and psychotherapy. Although there are admittedly few research data that support particular sequences of pharmacotherapy and psychotherapy in anxiety disorders (Fava et al. 2005; Simon et al. 2009), it may be hypothesized, for example, that some patients respond better to CBT once their anxiety is somewhat diminished by pharmacotherapy.

A particularly important lesson, from the work on combined treatment, is that an integrated approach to understanding patients and their disorders is needed. Clearly, advances at the intersection of gene x environmental studies, or studies of the association between gene variants and brain imaging, have emphasized the importance of understanding the contribution of multiple causal mechanisms to psychopathology. Translational neuroscience of combined treatment has provided proof-of-principle evidence that, as we better understand the psychobiology of psychiatric disorders, we will be able to optimize the development of integrated treatments. A translational approach to understanding the placebo effect may further contribute to enhanced treatments (Stein and Mayberg 2005; Furukawa et al. 2007). Taken together, although we clearly need to be cautious about the extent of our progress to date, we can be hopeful that over time, there will be further developments in the crucially important area of anxiety disorders. The remaining chapters provide a comprehensive overview of current progress and future directions.

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