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COMMENTARIES

Anxiety and Its Disorders: Implications for Pharmacotherapy

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Otto, McHugh, and Kantak (2010) have crafted a model to account for the observation that pharmacologic treatments do not reliably add to the effectiveness of cognitive-behavioral therapy (CBT) for anxiety disorders. In this commentary, we discuss the nature of anxiety and its disorders and review three approaches to the pharmacotherapy of these psychological disorders. When the implications of these approaches are considered, the use of *N*-methyl-D-aspartate agonists, in theory, holds the greatest promise for a pharmacological treatment to complement CBT for anxiety disorders.

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In their outstanding article, Otto, McHugh, and Kantak (2010) introduce a model to account for the observation that pharmacologic treatments do not reliably add to the effectiveness of cognitive-behavioral therapy (CBT) for anxiety disorders. They propose that the attenuation of glucocorticoid activity by benzodiazepines, as well as by serotonergic medications, interferes with the extinction learning that takes place during exposure-based CBT. Their article raises interesting questions about the role of combined treatment for anxiety disorders, and forces us to turn a critical eye toward the intuitively appealing and widespread clinical "pearl" that *two treatments are better than one*. In this commentary, we briefly discuss the nature of anxiety disorders before turning to a discussion of the implications for three common approaches to pharmacologic treatments.

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ANXIETY AND ITS DISORDERS

Anxiety disorders are psychological disorders that have their basis in one of the most rudimentary and adaptive human functions: the innate stress response (often termed the "fight or flight" response). All of us—whether or not we suffer with an anxiety *disorder*—are familiar with the feeling of stress or anxiety, such as when we have to take an important examination, ask someone on a date, or attend a job interview. In the short term, the stress response is designed to motivate us to protect ourselves by preparing to cope with a perceived threat. But when this stress or fear response is repeatedly triggered in situations that do not pose objective danger (i.e., the anxiety is *irrational*), the person is said to have an anxiety *disorder*. Research on people with such problems (for a review, see Barlow, Gorman, Shear, & Woods, 2000) reveals that inappropriate anxiety and fear responses are learned, and once learned, may be activated and maintained by faulty thinking patterns (the tendency to overestimate threat), information-processing biases (selective attention and memory), and behavioral habits (engaging in excessive active or passive avoidance). Cognitive and behavioral models of the anxiety disorders account extremely well for the nature and maintenance of anxiety symptoms

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and form the basis for the most effective treatments for these problems: CBT (e.g., Barlow et al., 2000).

Pharmacologic treatment approaches, on the other hand, have been traditionally based on the assumption that anxiety disorders are the product of a primary biological dysfunction. However, following many years of research (including the heralded ''Decade of the Brain'') into the possible biological mechanisms in anxiety disorders, no specific biological markers of any anxiety disorders have been identified, and little in the way of advances in biological treatments have been made (Antony & Stein, 2009). Psychiatrist Michael First (2002) noted that ''the field has thus far failed to identify a single neurobiological phenotypic marker or gene that is useful in making a diagnosis of a major psychiatric disorder or for predicting response to psychopharmacological treatment'' (p. 11). This is not to say that biology does not play a role; indeed, research shows that certain regions of the brain are associated with anxiety symptoms. Yet these findings hold for healthy individuals as well as those with anxiety disorders, and therefore likely represent how the experience of anxiety is implemented within certain brain functions, rather than revealing brain abnormalities that directly cause pathological anxiety.

APPROACHES TO PHARMACOTHERAPY FOR ANXIETY

Three broad approaches to the pharmacotherapy of anxiety disorders have been applied over the past century. Beginning in the early 20th century, the barbiturates were widely used to reduce anxiety because of their sedative, hypnotic, and anesthetic properties. In the early 1960s, these drugs were replaced by benzodiazepines (e.g., alprazolam, clonazepam), which were more widely effective and safer agents. Therapeutically, these medicines bring about a rapid and marked reduction in the physiologic arousal that accompanies anxiety. The implication of using benzodiazepines to treat anxiety is that this emotion is an unacceptable, threatening, or unmanageable response in a given situation. Yet as we have discussed, anxiety is a normal, adaptive response that, although uncomfortable (after all, part of its purpose is to be an alarm for potential for danger), is not inherently dangerous to the individual. Thus, the use of benzodiazepines paradoxically implies that anxiety is something to be reduced or avoided at all costs. Overreliance on these medications can prevent patients from developing more adaptive coping strategies, and interferes with the safety learning that occurs when individuals confront feared situations without the use of safety aids (as in treatment by exposure and response prevention). As Otto et al. (2010) and others (e.g., Schmidt, Koselka, & Woolaway-Bickel, 2001) have clearly elucidated, this message is antithetical to the process and goals of effective CBT.

The second, and a newer, approach to the pharmacotherapy of anxiety disorders involves the use of ''antidepressant'' agents that have also been found to have anxiolytic properties. Although antidepressants such as imipramine have been available since the late 1950s, it was not until the late 1980s that newer generation antidepressants—the selective serotonin reuptake inhibitors—were widely used to treat anxiety. These medicines are thought to work by allowing serotonin to remain in the synapse longer, thereby slowing down its activity in the brain and correcting a presumed deficit in the activity of this neurotransmitter. Although these medications have some efficacy for anxiety disorders, about half of the patients who use them show little or no benefit; on average, individuals experience about a 30–50% reduction in their symptoms (Antony & Stein, 2009).

Despite their moderate efficacy, the theoretical basis for use of antidepressant medications in the treatment of anxiety is problematic. There is scant evidence that people with anxiety disorders have abnormally functioning serotonin (or other neurotransmitter) systems. Indeed, the promotion of the ''chemical imbalance'' view of emotional disorders is derived primarily from the marketing departments of pharmaceutical companies rather than scientific evidence (Healy, 2004). Moreover, combined treatment with antidepressants generally fails to augment the benefits of CBT. We note that combined pharmacotherapy with antidepressants also generally fails to outperform the combination of CBT and pill placebo (e.g., Barlow et al., 2000; Davidson et al., 2004), suggesting that the occasional, minor benefits associated with combination treatment in the scientific literature are largely attributable to the psychological aspects of pill-taking. As Otto and colleagues (2010) have observed, the putative pharmacological benefits of these medications may be counterbalanced by the possibility that patients undergoing concurrent CBT may attribute their improvement to the drug. Moreover, endorsement of a ''chemical imbalance'' explanation for one's anxiety

symptoms may foster low self-efficacy and skepticism toward nonbiological treatments (Deacon & Lickel, 2009). Interestingly though, recent findings from a study comparing combination treatment to CBT alone for childhood anxiety suggest that such findings may be specific to adults (Walkup et al., 2008).

The final, and most recent, approach to treating anxiety disorders using medication does not involve the use of psychoactive medicines at all, but instead, as Otto and colleagues (2010) describe, *N*-methyl-D-aspartate (NMDA) receptor agonists that enhance the type of therapeutic learning that takes place during exposure-based CBT. From this framework, the pharmacological and psychological treatments have the same goal, which is to change problematic thinking and behaving patterns through learning. But in this case, the pharmacologic (biological) target is not an otherwise harmless psychological experience (as with benzodiazepines) or a non-empirically supported biological marker (as in the case of the serotonergic medications), but rather, the promotion of a normal process that has been empirically linked to the amelioration of excessive, inappropriate fear and anxiety. In this manner, therapeutic use of medications like D-cycloserine (DCS) does not require the assumption that anxiety disorders are caused by a biological dysfunction. Indeed, NMDA agonists work by facilitating the same *nondisordered* physiological processes thought to underlie fear extinction in the brains of both normal and clinically anxious individuals.

This third approach clearly holds the most promise for the treatment of anxiety disorders. Combination treatment with DCS is the only pharmacotherapy augmentation method that has reliably shown a benefit over CBT monotherapy (Norberg, Krystal, & Tolin, 2008). Yet despite the excitement for the clinical application of this treatment strategy, several formidable barriers may hinder its widespread adoption by physicians. The use of pharmacotherapy as a CBT augmentation strategy, as opposed to a means of correcting faulty brain chemistry, may constitute a potentially threatening paradigm shift for psychiatrists and other biologically oriented prescribers who view anxiety disorders as "brain diseases." Prescribers would also be put in the position of assisting exposure therapists do their job more effectively, rather than serving as the primary (or sole) treatment provider. This form of combined treatment also requires the availability of (and collaboration with) a competent exposure therapist, a species in short supply in many areas of the world. It is our hope that as additional data emerge about the clinical utility of combined CBT and NMDA agonist pharmacotherapy, this treatment strategy will be given the attention and utilization it deserves by treatment providers of all persuasions.

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