Mechanisms of Action in the Treatment of Anxiety

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Anxiety and depressive disorders share many features, suggesting a common set of physiologic substrates. Recent research has indicated that mood can be categorized into 3 components by factor analysis: (1) somatic anxiety (a factor relatively specific to panic disorder), (2) anhedonic depression (which includes symptoms related to motivation and enjoyment and found to be specific to depression), and (3) general distress (a factor that cuts across all depressive and anxiety disorders studied). Antidepressant drugs, particularly serotonin reuptake inhibitors and serotonin receptor modulators, are effective for a wide variety of anxiety and depressive disorders. The impact on both anxiety and depression may be a result of an effect on a common set of physiologic targets relevant to the general distress dimension. At a cellular level, the antidepressants target components of the stress-adaptation system in brain, which may explain these common effects. On the other hand, there appear to be differences in the relative impact of serotonergic and noradrenergic drugs on the spectrum of distress and motivational symptoms. Basic research and clinical research suggest that serotonergic agents may be preferentially effective for symptoms of general distress, whereas catecholaminergic agents may target anhedonic depression symptoms. *(J Clin Psychiatry 2001;62[suppl 12]:10–15)*

A better understanding of both the fundamental nature of anxiety disorders and the ways in which they relate to depressive disorders is essential in order to achieve full syndromal remission in the anxiety disorders. Anxiety and depressive disorders share certain common features, but maintain unique characteristics as well. Shared symptom features suggest a final common pathway of symptom expression between the anxiety and depressive disorders. A better understanding of such shared features would likely lead to a better understanding of both the fundamental physiopathology and treatment response of these disorders.

Most antidepressant drugs are not limited in their scope of action to depressive disorders. Clearly, these drugs, especially the serotonin reuptake inhibitors and serotonin receptor modulators, are broadly effective for a range of depressive and anxiety disorders. We would posit that this suggests that serotonergic antidepressants act on a set of mechanisms that are common to the full range of anxiety and depression. In this article, we will first review literature (mostly from the field of experimental psychology) that informs our current thinking about the nature of mood. We then will discuss possible mechanisms of action of antianxiety and antidepressant drugs. The biological mechanisms underlying anxiety and the mechanisms of action of antianxiety drugs have been reviewed extensively elsewhere and will not be the focus of discussion here.[1–5] Rather, the focus will be on the interface of anxiety and depressive disorders and the actions of antidepressant drugs on these conditions.

THE ANXIETY-DEPRESSION CONTINUUM

The interface between anxiety and depressive disorders often is an area of confusion for clinicians and researchers alike. This is due to several factors. While it seems clear that anxiety and depression are distinct constructs, it also is apparent that there is a significant overlap in symptoms.[6,7] This overlap is exemplified in the proposed mixed anxiety and depression syndrome, in which there is sufficient overall symptomatology to impair function, but full diagnostic criteria for either an anxiety or depressive disorder are not met.[8,9] Moreover, there is a high degree of comorbidity between diagnoses, such that having any one diagnosis significantly enhances the likelihood of having another. Curiously, diagnostic comorbidity is greater between the anxiety and depressive disorders than within the anxiety disorder continuum.[10] For example, estimates for the comorbidity of depressive disorders with generalized anxiety disorder run as high as 70%.[10] Finally, both anxiety and depressive disorders share similar responses to both pharmacologic and psychotherapeutic treatments. More specifically, treatments for any one anxiety or depressive disorder often are effective for a variety of disor-

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ders within the continuum. For example, serotonin reuptake inhibitors appear to be almost globally effective for anxiety and depressive disorders. Furthermore, cognitive-behavioral therapy (CBT) or the variations on CBT clearly reduce symptoms in most of these disorders. When treatment is effective, there often is joint remission of syndromes. When one disorder improves or remits, any comorbid disorder also seems to improve concomitantly.[11,12]

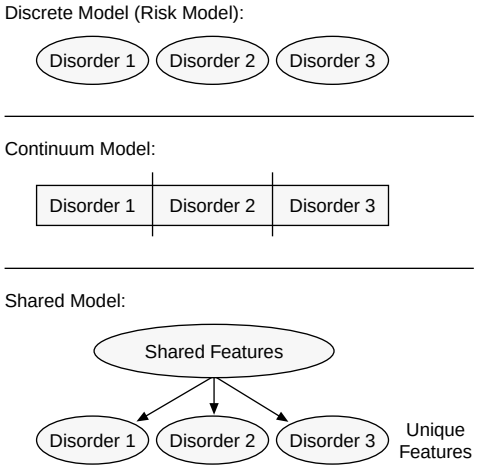
Nosologically, there are a variety of possibilities that may explain this overlap. One possibility is a shared diathesis (i.e., continuum model). Considering possible genetic and environmental influences, this model would posit a limited set of diatheses that produce a range of symptoms. Multiple sclerosis, a condition with a limited, well-defined physiopathology but a variety of symptoms, is an example of a disorder for which this particular model might be useful. Under this model, any diagnostic distinctions would be considered artificial or epiphenomenal.

A second perspective might propose that there are multiple discrete and unrelated disorders. The co-occurrence of 2 or more disorders, then, would have at least 2 explanations. First, any shared characteristics could represent minor or trivial components of the individual disorders and be unrelated to their essential features. An example of this would be headache associated with migraine versus a brain tumor, 2 disorders with entirely different causes but with similar symptoms. Second, the presence of one disorder could simply increase the risk of developing another disorder in the continuum. The usefulness of this model can be seen in the case of HIV/AIDS and *Pneumocystis carinii* pneumonia. One disorder increases the risk of developing another, but the 2 disorders are etiologically distinct. Support for this model with respect to anxiety and depressive disorders is the often-observed sequential development of comorbid disorders; that is, there often is an initial (or primary) diagnosis that is followed in time by the development of one or more additional disorders.

A final explanatory model is one in which there is true overlap; that is, there are unique syndromes that have shared features. Such a model would suggest that the joint characteristics share a final common pathway of physiopathology. For example, connective tissue diseases like lupus and rheumatoid arthritis have unique characteristics as well as common or shared features and often respond to similar treatments.

There are, therefore, at least 3 models that might describe the relation between anxiety and depressive syndromes (Figure 1): (1) The discrete or risk model in which all the disorders are distinct from one another and similarities either are epiphenomenal or are related to the fact that one disorder increases the risk of developing a second one; (2) The continuum (or shared diathesis) model in which there would be a limited number of causes that are common to all the disorders; and (3) The shared model in which there are certain joint features (and, presumably, a common physiopathology for those characteristics) as well as unique characteristics that separate the disorders in meaningful ways.

Figure 1. Nosologic Models of the Anxiety-Depression Continuum[a]



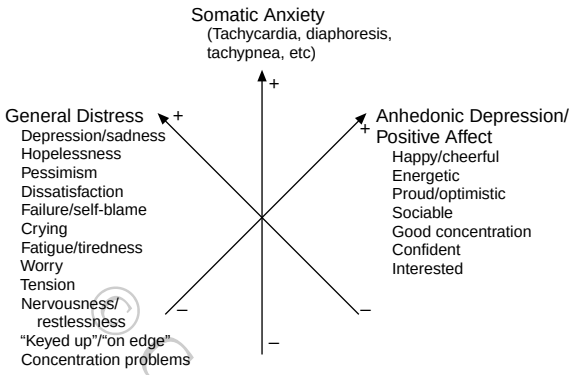
[a]Adapted in part from Frances et al.[64]

THE EVIDENCE FOR A SHARED MODEL OF DEPRESSION AND ANXIETY

The bulk of research evidence suggests that depressive and anxiety disorders are distinct disorders. Watson et al.[13 (p3)] captured the state of affairs well when they stated: "Anxiety is centered on the emotion of fear and involves feelings of worry, apprehension, and dread; in contrast, depression is dominated by the emotion of sadness and is associated with feelings of sorrow, hopelessness, and gloom. Nevertheless, despite their seeming distinctiveness, it has proven difficult to distinguish these constructs empirically." Using factor analysis of mood ratings, Clark and Watson[14] proposed a 3-factor or tripartite model of mood (Figure 2). The first element of this model focuses on symptoms of physical arousal (somatic anxiety) that appear to be specific to the anxiety disorders, particularly to panic disorder. The second component involves low levels of positive emotion such as pleasure, motivation, and sociability (referred to as "anhedonic depression" or "positive affect"). These appear to be specific to depressive disorders. The final factor involves a broad category of negative emotions (general distress) that are common to both anxiety and depressive disorders.

In order to test this model, Watson and colleagues[13–15] evaluated a large group of both normal volunteers and patients with a broad range of anxiety, depressive, and substance abuse disorders using the Mood and Anxiety Symptom Questionnaire (MASQ). The MASQ is a self-report instrument in which participants endorse the presence or

Figure 2. The Tripartite Model of Mood[a]



[a]Based on Clark and Watson[14] and Watson et al.[15]

absence, as well as the intensity, of various mood and anxiety symptoms. The data gathered using the MASQ were subjected to a best-fit factor analysis, in which a variety of possible factor solutions were considered. As predicted, the factor analysis supported the tripartite model with the 3 proposed dimensions of somatic anxiety, anhedonic depression, and general distress.

These factor solutions are related to the fact that symptoms were strongly correlated within each factor; that is, if one symptom was present within a factor, other symptoms within that factor were also more likely to be present. Further, there also appears to be coherence of intensity; that is, when a given symptom worsens, other symptoms within that component also tend to worsen. Finally, the 3 factors appear to be orthogonal. Correlations across dimensions are significantly lower than those within a dimension.

The somatic anxiety factor includes symptoms, such as tachycardia, tachypnea, dizziness, and tremor, that map closely onto symptoms of panic. Additionally, somatic anxiety symptoms can be seen normally under conditions of threat, or with exposure to a phobic stimulus. Alternatively, the anhedonic depression factor includes mood states such as feeling up, lively, energetic, confident, cheerful, sociable, talkative, or optimistic. The factor loading for general distress includes symptoms that are typically associated with anxiety disorders, such as feeling tense, on edge, restless, or keyed up; being afraid of losing control or going crazy; worry; and rumination. However, this general distress category also includes symptoms commonly associated with depression, such as feeling down, sad, discouraged, hopeless, disappointed, dissatisfied, and tearful and having problems with concentration.[13,15] Therefore, the general distress factor represents the set of symptoms common to anxiety and depressive disorders.

This tripartite model was supported in a study by Brown et al.[7] of another broad group of subjects with well-defined depressive and anxiety disorders. This study tested a variety of competing models using a structural modeling method and used a wide variety of symptom measurements. When the components of the tripartite model were examined in the anxiety and depressive disorders, general distress loaded on all diagnoses (depression, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, and social phobia). Somatic anxiety, on the other hand, loaded only on panic disorder, as predicted by the model. The positive affect component (anhedonic depression) loaded inversely on both depression and social phobia. It appears, then, that the positive affective component captures elements associated specifically with depression and, possibly, the social withdrawal associated with social phobia.

These and similar data offer strong support for the shared or true overlap model of depressive and anxiety psychopathology involving the category of general distress. In summary, this model proposes that there exists a subset of symptoms that are shared between depressive and anxiety disorders and separate symptom clusters that appear to distinguish them. The sharing of general distress symptoms suggests that there may also exist a common set of genetic vulnerabilities or a final common physiologic pathway that cuts across diagnostic categories. The fact that a range of anxiety and depressive disorders respond to serotonin reuptake inhibitors/serotonin receptor modulators may relate to the impact of these drugs on a common set of symptoms.

From this perspective, comorbidity might be better understood by considering relatively independent vulnerability factors that might operate at various points in time over the life span. Interestingly, trait or personality dimensions such as harm avoidance or neuroticism appear to confer increased risk for both depressive and anxiety disorders and track closely to the general distress dimensions of mood.[6,16] Therefore, vulnerability to general distress may be a chronic trait, with periods of anhedonia or somatic anxiety superimposed, resulting in comorbid diagnoses. If this is in fact the case, successful treatment of the general distress component would be expected to reduce the overall intensity of symptoms of both anxiety and depressive disorders.

THE CELLULAR EFFECTS OF ANTIDEPRESSANT DRUGS

Antidepressant drugs, particularly the serotonin reuptake inhibitors and serotonin receptor modulators, appear to be effective for the treatment of anxiety and depressive disorders.[17–20] These findings have recently been further supported by the demonstration of the effectiveness of the serotonin-norepinephrine reuptake inhibitor venlafaxine extended release for generalized anxiety disorder (GAD).[21] It should also be noted that other serotonin reuptake inhibitors and serotonin receptor modulators, as well as tricyclics and monoamine oxidase inhibitors, have been shown to have effect in GAD and other anxiety disorders.[17–20] Since the data presented above indicate that there is a set of symptoms common to both anxiety and depressive disor-

ders, is there evidence to indicate that a set of pharmacologic responses might also relate to these specific, common symptoms?

Antidepressants modulate receptor-dependent activation of neuronal signal transduction cascades linked to serotonin, norepinephrine, and dopamine.[22] These cascades, in turn, appear to modulate the expression of specific genes and their protein products. Relevant to the ideas presented above, antidepressant treatments have been shown to enhance steady-state messenger RNAs (mRNAs) for glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs),[23,24] brain-derived neurotrophic factor (BDNF) and its receptor trkB,[25,26] and preproenkephalin[27] and to reduce the mRNA expression for corticotropin-releasing hormone (CRH).[23,24] The hypothalamic-pituitary-adrenal axis plays a key role in the modulation of the neuronal response to stress. Therefore, the importance of the effects of antidepressants on GR, MR, and CRH levels might explain some of the common effects of antidepressants in anxiety and depressive disorders.[22] Their effects on BDNF, a nerve growth factor involved in the differentiation and survival of neurons in brain,[25,26] may also be of importance in this regard. Interestingly, in an animal model of depression, BDNF appears to reduce symptoms of learned helplessness.[28] These findings support the notion that antidepressants activate a group of integrative stress-adaptational mechanisms, which, together, may account for their broad set of therapeutic actions.[22,23,25,26,29–32] When viewed from this perspective, it becomes easier to envision how antidepressant drugs might produce therapeutic effects in both anxiety and depressive disorders.

However, it remains to be seen whether these actions are common to all antidepressants and whether there may be differences in the scope of therapeutic effects between drugs. The impact of serotonin reuptake inhibitors and serotonin receptor modulators in disorders of general distress such as depression, GAD, or conditions involving somatic anxiety (i.e., panic disorder, social phobia) is evident from clinical research.[17,18,20] It is further supported by a prodigious literature on the modulation of anxiety in the central nervous system by serotonin and serotonergically active drugs.[33–37] Therefore, the combination of basic and clinical research would predict that serotonin reuptake inhibitors and serotonin receptor modulators (including drugs such as nefazodone, mirtazapine, and buspirone) would be effective in reducing general distress and somatic anxiety.

On the other hand, the anhedonic depression (positive affectivity) component appears to be relatively specific to depressive disorders.[12,13,15] Therefore remission of depression (and remission of anxiety disorders that are comorbid with depression) should also involve normalization of the anhedonic depression domain.

The effects of antidepressant drugs on positive affect, however, appear to be somewhat complex. For instance, elements of positive affectivity, such as arousal, alertness, pleasure, and motivation, appear to be substantially regulated by the actions of norepinephrine and dopamine in areas of the brain such as nucleus accumbens or frontal cortex.[38–41] Serotonin has a complex role in regulating forebrain catecholamine (particularly dopamine) activity. Depending on the receptor subtype involved, serotonin can either activate or inhibit dopaminergic activity. Although the research in this area is controversial, serotonin 1A, 1B, and 2A receptors appear to activate dopamine release, while 2B and 2C receptors appear to be inhibitory.[42–53] The effects of serotonergic drugs on dopaminergically mediated positive affectivity are, therefore, difficult to predict.

On the other hand, some findings suggest that relatively selective serotonin reuptake inhibitors inhibit prefrontal dopamine activity[54,55] and dopaminergically mediated behaviors,[56–58] although at least one study failed to replicate these findings.[59] In any case, the bulk of evidence would indicate that relatively selective serotonin reuptake inhibitors (what we might refer to as "unopposed serotonin") would be inhibitory to forebrain dopamine and, by implication, positive affectivity. Alternatively, catecholaminergically active antidepressants, or drugs with mixed and potent serotonin and catecholamine effects, might be expected to enhance positive affectivity via frontal and accumbens pathways.

This notion has been supported by work of Ichikawa and colleagues[55] in which rats were administered either the relatively selective serotonin reuptake inhibitor fluoxetine or the mixed norepinephrine and serotonin reuptake inhibitor imipramine for 24 to 28 days. By using in vivo microdialysis, extracellular dopamine levels were measured in the nucleus accumbens. In comparison to a vehicle-treatment control, chronic imipramine administration enhanced accumbens dopamine, whereas levels were somewhat decreased by fluoxetine. These investigators concluded that the effects of these 2 medications on frontal dopamine activity could not be the basis for their shared antidepressant effects. However, these findings do offer support for the notion that these drugs work via shared effects on serotonergically mediated symptoms (i.e., general distress) but may produce differential effects on catecholaminergically regulated symptoms such as anhedonic depression.

The enhancement or broadening of the therapeutic effects of antidepressants by multiple mechanisms of action also has been demonstrated by studies evaluating the effects of combining noradrenergic and serotonergic antidepressants. This approach appears to enhance therapeutic response in some patients who have not responded to either individual agent. For example, Nelson[60] has shown that adding desipramine, a potent and selective norepinephrine reuptake inhibitor, appears to augment the effects of fluoxetine. These relatively selective effects of serotonin- and norepinephrine-acting antidepressants on symptoms of general distress (i.e., the common set of anxiety

and depressive symptoms) and anhedonic depression (the symptoms that are fairly unique to depression) have been emphasized recently by Stahl.[61–63]

In summary, anxiety and depressive disorders, clearly, represent a complex set of symptom types and neurobiological substrates. Certain features, particularly those involving general distress, are substantially shared across the spectrum of these disorders. Antidepressant medications appear to exert common effects on symptoms of general distress across the anxiety-depression spectrum. However, these medications may produce unique but variable actions on positive affectivity. Further research is needed to further elucidate these concepts in clinical settings.

Drug names: buspirone (BuSpar), desipramine (Norpramin and others), fluoxetine (Prozac), mirtazapine (Remeron), nefazodone (Serzone), venlafaxine (Effexor).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, desipramine is not approved by the U.S. Food and Drug Administration to augment SSRIs.

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