# The Functional Anatomy, Neurochemistry, and Pharmacology of Anxiety

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The functional anatomy of anxiety involves amygdala-based neurocircuits with critical reciprocal connections to the medial prefrontal cortex. Traumatic experiences leave emotional imprints involving the amygdala, with facilitated fear-conditioned associations involving declarative memory traces. Avoidance conditioning is an additional component. An understanding of the functional anatomy of anxiety allows for a new perspective on the various anxiety disorders. The neurotransmitters involved in these circuits are reviewed for their relevance to the pharmacologic choices in the treatment of anxiety. Potent serotonin reuptake inhibitors appear to have superior efficacy in many of the anxiety disorders, with indications that norepinephrine reuptake inhibitors have an advantage in severe forms of major depression. Medications with dual effects—blocking reuptake of both serotonin and norepinephrine (e.g., clomipramine and venlafaxine XR)—have superior benefits in achieving remission in major depression and GAD. These medications may also offer a faster onset of action and theoretically superior benefits in patients with comorbid anxiety disorder and major depression.

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*If the human brain were so simple that we could understand it, we would be so simple that we couldn't.*

—Emerson Pugh, 1997

Current psychiatric nosology, codified in the DSM-IV, defines diagnostic categories using signs and symptoms. Thus, generalized anxiety disorder (GAD) has the key component of worry, with associated symptoms of restlessness, fatigue, impaired concentration, irritability, muscle tension, and sleep disturbance. Diagnostic categories that share core symptoms are grouped as disorders. The core symptom in the anxiety disorders is the excessive experience of anxiety, which can manifest in different forms such as panic, avoidance, intrusive experiences, or patterns of cognition. Anxiety, however, is not unique to anxiety disorders. The majority of patients with major depression experience pathologic anxiety as a symptom.[1] Confusion arises as terms like *anxiety* can encompass different experiences and observed behaviors. Thus, nervousness, tension, irritability, agitation, restlessness, worry, and somatization all describe overlapping or equivalent experiences for individuals.

If symptomatic overlap occurs in different diagnostic conditions, it is not surprising that syndromal overlap also occurs, given that our syndromal labels are derived from symptomatic criteria. The National Comorbidity Survey reported that 58% of patients with major depression also suffered from an anxiety disorder.[2] Additionally, major depression is a common lifetime comorbidity in GAD, panic disorder, social phobia, obsessive-compulsive disorder (OCD), and posttraumatic stress disorder (PTSD). Thus, comorbidity of anxiety and mood disorders is the rule rather than the exception. In 68% of such individuals with both an anxiety disorder and major depression, the anxiety disorder preceded the major depression. There was an average of 11 years between the development of the anxiety disorder and major depression in these individuals.[2] For clinicians, the implication is that successful treatment of such individuals would require adequate management of both the anxiety disorder as well as the major depression. Only then will the individual have a chance of achieving wellness.

## THE FUNCTIONAL ANATOMY OF ANXIETY

Fear is a normal response to threat, while anxiety can be defined as unwarranted or inappropriate fear.[3] The protective response to aversive threat is an evolutionarily maintained, unconditioned response "hard-wired" in the brain. The fear/anxiety response does not have to be learned and includes defensive behaviors, autonomic arousal, hypoalgesia, potentiation of somatic reflexes, and

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activation of the "stress" axis through the hypothalamic-pituitary-adrenal (HPA) axis.[3] An amygdala-based neurocircuit has been proposed to mediate the fear and anxiety response.[4] The amygdala is central to registering the emotional significance of stimuli and the development of emotional memories. The output pathways of the central nucleus of the amygdala (CnA) can explain various symptoms experienced in anxiety states (Table 1).[4]

Optimal activity in the anxiety circuits is associated with a normal readiness to respond to situations and a flexible, motivated state of being. Exaggerated challenges induce anxiety, and resources are marshaled to respond. Life-threatening challenges result in the permanent imprinting of the experience in the emotional circuits through the amygdala, encompassing the full emotional memory of the experience. Associated cues are stored through the declarative memory circuits involving the hippocampus. This allows for associated cues to trigger the emotional memory of the trauma, bringing it to conscious awareness (conditioned fear). Avoidance conditioning allows for the individual to avoid associated sensory, cognitive, or other stimuli that potentially trigger the emotional imprint of the trauma.

The medial prefrontal cortex is reciprocally connected with the amygdala, allowing for self-imposed regulation of affect and the modulation of autonomic and neuroendocrine function.[5] This allows for the "cognitive" control of the "anxiety" response. New memories with more benign associations can result in the extinction of the emotionally traumatic memory. However, the original imprint still exists, as it can be reawakened with new experiences of similar threat or specific association cues.

In times of increased challenge, the control shifts from the prefrontal "executive" centers to primordially lower centers such as the amygdala.[6] Behaviors are then guided by patterns conditioned from earlier anxious/traumatic experiences or species-typical–programmed ones. The prefrontal cortical functions such as working memory are taken "off-line" under these circumstances.

The functional anatomy of the anxiety response with its various elements allows a different conceptual perspective on the nature of anxiety disorders. The emotional and somatic experience of anxiety is mediated by output from the CnA. Anxiety is associated with a loss of otherwise broader cognitive capabilities to drive behavior, as emotionally driven circuits result in characteristic limited patterns of thinking and behavior. The potential cues for triggering the anxiety response include psychological threat, novelty, social or performance situations, cognitive mechanisms, and conditioned associative memories. Thus, the common element in the anxiety disorders is exaggerated output through the CnA, with different anxiety disorders having different but often overlapping mechanisms for such an activation. Thus, in panic attacks, the fear is of imminent death; in social phobia, the concern is with embarrassment; in PTSD, the emotional memory of the trauma; in OCD, the intrusive obsessional ideas; and in GAD, anxiety, not conditioned to specific triggers (i.e., free-floating).

**Table 1. Mediation of the Fear/Anxiety Response Through the CnA Output Pathways[a]**

| CnA Output Pathway | | Fear/Anxiety Response |
|---|---|---|
| Lateral hypothalamus | → | Sympathetic activation |
| DMN of vagus/nucleus ambiguous | → | Parasympathetic activation |
| Parabrachial nucleus | → | Dyspnea/hyperventilation |
| VTA/locus ceruleus/dorsolateral tegmental nucleus | → | Behavioral and EEG arousal, increased vigilance |
| Nucleus reticularis pontis caudalis | → | Increased startle |
| Midbrain central gray | → | Freezing, fear of dying |
| Trigeminal/facial motor nerve | → | Facial expression of fear |
| Paraventricular nucleus | → | HPA axis activation |

[a]Adapted with permission from Davis.[4] Abbreviations: CnA = central nucleus of the amygdala, DMN = dorsomedial nucleus, HPA = hypothalamic-pituitary-adrenal, VTA = ventral tegmental area.

Normality, derived from this model, can be defined as the capacity to vary, choose, and control the emotional, cognitive, behavioral, and interpersonal responses to a given situation. Pathology is the limitation of those choices to a specific pathway. In anxiety disorders, that pathway is through amygdala-mediated circuits, resulting in the experience of anxiety and characteristic patterns of cognition. The anxiety circuits can be seen as having "hijacked" the larger repertoire of choices the brain is otherwise capable of.

## THE NEUROCHEMISTRY OF ANXIETY

Several neurotransmitters mediate the different components of anxiety, including excitatory amino acids such as glutamate, inhibitory amino acids such as γ-aminobutyric acid (GABA), and monoaminergic neurotransmitters such as catecholamines and indoleamines. Different aspects of the anxiety response are mediated by various neurotransmitters in anatomically distinct areas. Thus, imprinting of emotionally traumatic memories is mediated, in part, by norepinephrine action through the β-adrenergic receptor in the amygdala. Administration of a β-blocker prior to a trauma may prevent the emotional imprinting of the traumatic memory.[7] The development of conditioned fear is mediated by dopamine-1 ($D_1$) receptors in the amygdala, leading to facilitation of the declarative memory associations through the hippocampus.[8] LeDoux[3] suggests that avoidance conditioning is mediated through the prefrontal cortex and also through the $D_1$ receptor.

For the practicing clinician, the neurotransmitters of interest are those tied to currently available pharmacologic treatments—benzodiazepines, serotonin-1A ($5\text{-}HT_{1A}$) agonists such as buspirone, and antidepressant medications affecting norepinephrine and serotonin. The response to pharmacologic treatments and their time course in relieving symptoms[9–16] through a "reverse engineering ap-

proach" indicate relevance of these neurotransmitters in anxiety.

### Benzodiazepines

The recognition of the anxiolytic potency of the barbiturates,[17] and subsequently the benzodiazepines, led to a benzodiazepine receptor–mediated model of anxiety.[18] The benzodiazepines act mainly through the GABA-A receptor subtype[19,20] by potentiating GABA transmission. GABA is a ubiquitous neurotransmitter, involved in the majority of inhibitory synapses in the brain. Thus, GABA suppresses neuronal firing, inhibiting or regulating other neurotransmitters, including serotonin, norepinephrine, and dopamine. It accomplishes this by decreasing their turnover in limbic areas, including the amygdala, as well as the locus ceruleus and raphe nuclei.

In addition to their anxiolytic effect, benzodiazepines also have sedative, muscle relaxant, and amnesic effects, as well as the potential for dependence. These effects can contribute to reducing symptoms of anxiety, such as insomnia and tension, but also mediate side effects such as delayed reaction time, forgetfulness, and dependence/withdrawal symptoms seen with chronic use.

### Norepinephrine

The locus ceruleus is a nucleus situated in the dorsal pons containing the majority of noradrenergic neurons. Stimulation of the locus ceruleus leads to amplification of both inhibitory and excitatory messages, with autonomic arousal and other symptoms commonly associated with anxiety.[20] Elevated levels of norepinephrine are associated with somatic manifestations of anxiety, such as rapid heart rate, increased blood pressure, dry mouth, and cessation of intestinal peristalsis.[21] Increases in both norepinephrine and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) are correlated with the state of anxiety.[22] Drugs that increase the firing of noradrenergic cell bodies in the locus ceruleus, such as yohimbine, induce anxiety in humans, and drugs that reduce their firing, such as clonidine, inhibit the symptoms of anxiety.[20]

GABA receptors are found in high concentrations on noradrenergic cell bodies in the locus ceruleus. Thus, one of the possible pathways by which benzodiazepines exert their beneficial effects in anxiety may be through GABA-facilitated reductions in noradrenergic activity.

A modified version of the monoamine hypothesis links higher activity of the noradrenergic system with anxiety and lower activity with depression.[20,22–24] Paul[25] proposed that norepinephrine plays a role in initiating a cascade of events that begins with states of anxiety that gradually evolve into states of depression. In chronic anxiety, increased neuronal excitability and firing of the locus ceruleus cells over time result in depletion of norepinephrine associated with the development of depression.[9] Reduced activity of the noradrenergic system has been correlated with a lack of initiative and decisiveness, as well as an increased tendency to fatigue and apathy.[21]

Many tricyclic antidepressants (TCAs) potently block only the reuptake of norepinephrine, and their chronic use is associated with down-regulation and desensitization of presynaptic $\alpha_2$-autoreceptors. These effects are believed to contribute to their antidepressant effects.[26,27]

**Table 2. Abnormalities in Serotonin Function in Affective Disorders[a]**

| |
|---|
| Decreased tryptophan |
| Decreased platelet uptake of serotonin |
| Increased serotonin receptor binding in |
| Platelets |
| Cortex of subjects who commit suicide |
| Decreased prolactin response to |
| Intravenous tryptophan |
| Oral fenfluramine |
| Decreased hypothermic response to ipsapirone |
| Relapse of depression after rapid depletion of tryptophan in antidepressant-treated depressed patients |

[a]Adapted with permission from Delgado et al.[29]

### Serotonin

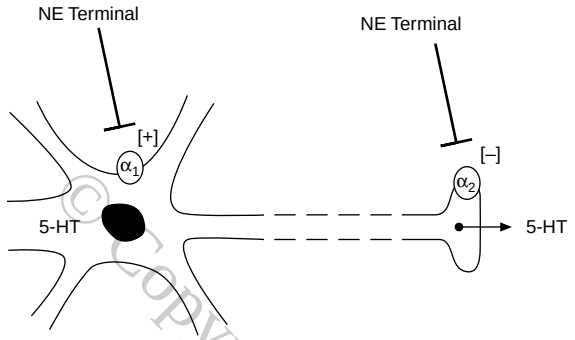
The neurons located in the dorsal and median raphe nuclei of the brain stem are the primary source of serotonin production in the brain. The serotonergic system has been implicated in the alterations in appetite, energy, sleep, mood, libido, and cognitive function in anxiety and affective disorders.[23] Additionally, serotonin is important in regulating anxiety as well as impulsivity in suicidal and other violent acts.

The role of serotonin in anxiety is supported by its modulatory effects on the locus ceruleus and its dense projections to the amygdala.[28] Decreased serotonergic activity is associated with depression (Table 2),[29] and most effective antidepressants have been shown to enhance the function of serotonin.[29] Low activity of serotonin may permit the dysregulation of other neurotransmitters including norepinephrine.[10,20] These 2 systems are linked so closely that notable changes in one are reflected in the other. Interactions between these systems appear to be reciprocal.[29] The precise nature of the reciprocal interaction can vary, and the activity of norepinephrine at presynaptic serotonergic terminals may lead to a decreased release of serotonin, whereas its activity at postsynaptic adrenoceptors may lead to an increase in the release of serotonin (Figure 1).[26]

### The HPA Axis

Neuroendocrine function is a "window" into the activity of the human brain relevant to psychopathology. Less information is available about the neuroendocrine changes in the anxiety disorders than in major depression.[30] The HPA axis is the prototypical "stress" axis and has been extensively studied in mood disorders and, to a lesser degree,

Figure 1. Interactions Between Noradrenergic and Serotonergic Systems in the Brain[a]




[a]Data from Heninger et al.[26] Abbreviations: 5-HT = serotonin, NE = norepinephrine, $\alpha_1$ = postsynaptic $\alpha_1$-adrenergic receptors, $\alpha_2$ = presynaptic $\alpha_2$-adrenergic receptors.

in anxiety disorders. The HPA axis is activated in anxiety but becomes dysregulated with the development of major depression.

The response of adrenocorticotropic hormone (ACTH) to the administration of corticotropin-releasing hormone (CRH) appears to be normal or slightly increased in patients with panic disorder, in contrast with patients who have depression. Studies of social phobia, although limited by the small numbers of patients, have suggested that the function of the HPA axis is normal.[31,32] Data from studies that measured 24-hour urinary free cortisol in GAD show levels to be normal.[33] In major depression, on the other hand, as many as 75% of patients have overactivity of the HPA axis, characterized by hypercortisolemia.[23,34]

## THE PHARMACOLOGY OF ANXIOLYSIS

In the pharmacologic treatment of anxiety, the clinician has several choices, with different mechanisms of action.[21,29] These include the benzodiazepines, 5-$HT_{1A}$ agonists (buspirone), and antidepressant medications. Antidepressant medications were discovered initially as treatments for depression, but more recent data suggest their value in multiple other conditions including the different anxiety disorders. Relevant antidepressant medications are the TCAs, the monoamine oxidase (MAO) inhibitors, the selective serotonin reuptake inhibitors (SSRIs), and newer agents such as venlafaxine extended release (XR), which act through mixed inhibition of serotonin and norepinephrine reuptake.

### Benzodiazepines

Benzodiazepines provide powerful and rapid relief from the symptoms of anxiety.[19] High-potency benzodiazepines (e.g., lorazepam, alprazolam, clonazepam), in particular, have also demonstrated syndromal benefits in GAD, panic disorder, and social phobia. Most studies have limited their use to durations from several weeks to a few months (with the notable exception of some long-term studies with alprazolam in panic disorder). However, benzodiazepines are not effective in major depression, which is a relevant issue given the high comorbidity of major depression in all the anxiety disorders. There is some suggestion that benzodiazepines may even potentiate or aggravate depression.[35]

The utility of the benzodiazepines has been limited by their potential for tolerance, dependence, and psychomotor and cognitive impairment.[36,37] Thus, patients who are treated for periods longer than 2 weeks or so may experience a withdrawal syndrome if therapy is discontinued abruptly. This syndrome is characterized by anxiety, dysphoria, depersonalization, hyperacusis, and unsteadiness.[37] The risk of physical dependence increases with higher doses and longer durations of treatment.[36] The risk for abuse of benzodiazepines in clinical populations is generally low, but their use should be avoided in patients who are abusing drugs or alcohol.

Cognitive impairment associated with benzodiazepine therapy may be particularly problematic in older patients, and it may be magnified when these agents are used in combination with other sedatives, such as alcohol.[19]

### Buspirone

Buspirone is a partial agonist of the 5-$HT_{1A}$ receptor and the only one in its class available in the United States. It has demonstrated efficacy in GAD,[17] but not in other anxiety disorders, nor does it have a powerful antidepressant effect. It has the advantage of a benign side effect profile. Its value as an augmentation agent in complex anxiety patients is in need of systematic evaluation.

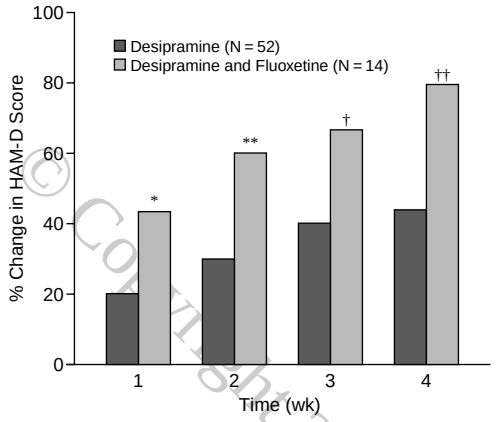
### Antidepressants

The TCAs have been available in the United States for close to half a century. Their dominant mechanism of therapeutic action is through potent reuptake inhibition of norepinephrine. One TCA, clomipramine, also has powerful effects in blocking the reuptake of serotonin, to the degree seen with SSRIs. The clinical use of TCAs is limited by their side effect profile, potential cardiac toxicities, and lethality in overdose.

The benefit provided by TCAs in major depression is well documented,[23,27] and TCAs have particular advantages in severely ill populations, including hospitalized depressed patients and those suffering from melancholia.[38] The benefits of TCAs have also been demonstrated in GAD, panic disorder, OCD, social phobia, and PTSD.[14]

MAO inhibitors have also been available in the United States for several decades with documented benefits in major depression, particularly in patients with the "atypical" subtype. These individuals have a form of depression marked by high levels of anxiety (including panic attacks), mood responsivity to positive events, rejection sensitivity,

**Figure 2. Percentage Change in Hamilton Rating Scale for Depression (HAM-D) Scores in Patients Given Desipramine and Fluoxetine and in Those Given Desipramine Alone[a]**




[a]Reprinted with permission from Nelson et al.[46] Comparisons by the Mann-Whitney U test.
*p = .007. **p = .001. †p = .004. ††p = .0001.

and reverse vegetative symptoms of hypersomnia and hyperphagia. MAO inhibitors have also been documented in controlled studies to be effective in social phobia and panic disorder, but their value in OCD and PTSD is more limited.[14] Their clinical utility is limited by their side effect profile and potentially lethal drug and food interactions.

With the introduction of the first SSRI in the United States in 1988, a considerable shift in practice occurred in the treatment of major depression, largely driven by ease of use, a more benign side effect profile, lack of cardiotoxic effects, and relative safety in overdose.[23,29] However, the selectivity of SSRIs for serotonin has been implicated in their lesser potency in down-regulating β-adrenergic receptors with chronic treatment.[27]

Treatment studies document that medications that powerfully inhibit the serotonin transporter (e.g., SSRIs) are often more effective in the anxiety disorders than medications that inhibit the norepinephrine transporter.[14] This is best documented in OCD, where the only agents that have consistently demonstrated efficacy are the TCA clomipramine and the SSRI fluvoxamine.[39] In social phobia, serotonin reuptake inhibitors have documented efficacy,[40,41] while TCAs are not very effective.[42] A recent meta-analysis of the PTSD literature reported superior effect sizes for SSRIs compared with other pharmacologic treatments, including noradrenergic reuptake inhibitors such as the TCAs.[43] In panic disorder, although TCAs have documented efficacy over placebo, the efficacy of SSRIs is superior to that of TCAs.[44] The efficacy of SSRIs in GAD is less well documented. The efficacy of venlafaxine XR in GAD is reviewed elsewhere in this supplement (see Dr. Sheehan's article[45]).

Combinations of SSRIs with a TCA may accelerate down-regulation of β-adrenergic receptors, leading to more robust antidepressant effects with more rapid onset in major depression.[26] One study of fluoxetine and desipramine, given alone and in combination, found a more rapid and robust antidepressant response with the combined administration, supporting the value of a serotonergic-noradrenergic interaction for effective antidepressant response (Figure 2).[46] Medications that powerfully inhibit both serotonin and norepinephrine transporters may provide an advantage from several perspectives. They may provide a more rapid and powerful down-regulation effect on β-adrenergic receptors, postulated to be a measure of antidepressant action.[27] Faster and more robust antidepressant activity has also been shown with the use of an α-adrenergic antagonist, such as yohimbine, or an SSRI in combination with a drug that primarily affects noradrenergic activity, such as desipramine.[24,26,27,46]

Additionally, if there is greater value with serotonin transport inhibition in the anxiety disorders and superior benefit of norepinephrine transport inhibition in severe depression, would not a dual action agent be particularly effective in those patients with comorbid anxiety disorder and major depression? There are limited direct data available in the full comorbid anxiety and major depression group of patients. However, the superior efficacy of venlafaxine XR in achieving remission in major depression might be the result of addressing both depressive and anxious symptoms in these patients.[24,28,47,48]

## CONCLUSION

Recent advances in the understanding of the functional anatomy of anxiety allow a new perspective on the different anxiety disorders. Current pharmacologic options provide a wide repertoire for the clinician to choose from. However, the common comorbidity of anxiety disorders with major depression suggests the use of antidepressants as the first line, with dual-action antidepressants having an advantage in providing a greater likelihood of remission and the achievement of wellness.

*Drug names:* alprazolam (Xanax and others), buspirone (BuSpar), clomipramine (Anafranil and others), clonazepam (Klonopin and others), clonidine (Catapres and others), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), lorazepam (Ativan and others), venlafaxine XR (Effexor XR), yohimbine (Yocon and others).

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