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New Developments in the Neurobiological Basis of Anxiety Disorders

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ABSTRACT *~ Generalized anxiety disorder (GAD) is a chronic disorder that often precedes the development of, and is comorbid with, depression. Investigation of the neurobiological basis of GAD has provided suggestive evidence to implicate dysfunction of serotonergic and noradrenergic systems in the expression of GAD, as well as the depressive disorders. Hence, there may be a neurobiological link between GAD and depression through the activity of the serotonin and norepinephrine systems. The use of various anxiolytics and antidepressants, including benzodiazepines, tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin and norepinephrine reuptake inhibitors in the treatment of GAD is reviewed. The neurobiological relationship between GAD and depression, and the frequent comorbidity of these disorders, suggests that agents with a dual action on the serotonin and norepinephrine systems may potentially offer superior benefits in the management of patients with anxiety and depressive disorders.* Psychopharmacology Bulletin. *2002;36(Suppl 2):49-67*

Generalized anxiety disorder (GAD) is a chronic disorder with a lifetime prevalence estimated at 5%.[1] GAD was first defined in the *Diagnostic and Statistical Manual of Mental Disorders,* Third Edition,[2] as a residual category characterized by excessive worry, but distinct from a diagnosis of panic disorder or agoraphobia. Further refinement of diagnostic criteria came in the forms of the *Diagnostic and Statistical Manual of Mental Disorders,* Third Edition-Revised *(DSM-III-R),*[3] in 1987 and the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition,[4] in 1994. These reference books have led to the definition of GAD as a distinct anxiety disorder characterized by long-term (>6 months) pathological anxiety, with additional emphasis on uncontrollable worry. A minimum of three associated somatic or psychological symptoms are required for the diagnosis,

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including restlessness, fatigue, muscle tension, irritability, difficulty concentrating, or sleep disturbance.

GAD produces significant impairment in daily functioning[1,5] and has an average duration of 20 years[6]—much longer than the minimum 6 months required for its diagnosis. Patients with GAD may therefore require effective therapy for extended periods of time. Understanding the neurobiology of GAD may help the clinician to make the most optimal choices in treatment.

Different aspects of the anxiolytic response are mediated by various neurotransmitters in anatomically distinct areas.[7] Understanding the pharmacology of effective treatments has led to hypotheses and suggestive evidence of the pathophysiology of GAD. Thus, the focus of research has been primarily on the γ-aminobutyric acid/benzodiazepine (GABA/BZD) complex, and the norepinephrine and 5-HT systems.[8-10] The involvement of 5-HT and norepinephrine systems in both GAD and depression may indicate a neurobiological relationship between these two disorders. There is epidemiological, longitudinal, and genealogical evidence to suggest that GAD and major depression may be linked,[1,11,12] which may have implications for the appropriate choice of therapy for patients with GAD. This article will discuss the neurobiology of GAD and the relationship of this disorder with major depression, and review the therapeutic choices available for the treatment of patients with GAD.

The Neurobiological Basis of Generalized Anxiety Disorder

Research involving patients with GAD has implicated roles for a variety of neurobiological factors in the pathophysiology of this disorder, including the GABA/BZD complex, and the norepinephrine and 5-HT systems (Table 1). These neurotransmitter systems play critical roles in the limbic system, including the amygdala, which is pivotal in the processing of fear and anxiety responses.[13,14] In addition, roles for cholecystokinin, corticotropin-releasing factor, and the hypothalamic-pituitary-adrenal (HPA) axis have also been suggested.[15-19] These factors may exert direct actions in areas critical to the mediation of anxiety responses, or may act indirectly through modulation of the effects of other neurotransmitters.

The GABA/BZD Complex in Generalized Anxiety Disorder

GABA is the predominant inhibitory neurotransmitter in the human brain, mediating its effects through interaction with GABA receptors ($GABA_A$ and $GABA_B$) located throughout the central nervous system (CNS). The $GABA_A$ receptor has a close functional relationship with the benzodiazepine receptor in the modulation of membrane chloride

ion channel activity. Activation of the benzodiazepine receptor by inverse agonists can induce the behavioral, neurochemical, and autonomic symptoms associated with anxiety.[20,21] Benzodiazepines, which interact as agonists at the benzodiazepine receptor, potentiate GABAergic transmission, leading to enhanced suppression of neuronal firing, and thus regulate other neurotransmitters, including norepinephrine and 5-HT.[22] $GABA_A$ receptors, although ubiquitous throughout the CNS, are present in high density in the cortex, hippocampus, striatum, and cerebellum.[23,25] The ability of projections from the GABA/BZD complex to decrease turnover of monoamines in limbic areas, and to suppress firing at the locus coeruleus and raphé nuclei, is therefore likely to modulate anxiety responses.

Benzodiazepine binding sites have also been identified in peripheral tissues, including platelets and lymphocytes,[25-27] although these binding sites are not coupled with GABA receptors and chloride ion channels.[25] The isoquinoline carboxamine derivative, PK-11195, has been shown to bind to the peripheral benzodiazepine receptor and has been used as a marker for studying these receptors. Studies of peripheral benzodiazepine receptors have suggested impairment of these receptors in patients with GAD, which could reflect changes in the GABA/BZD

TABLE 1

Evidence Implicating Changes in the GABA/BZD, Norepinephrine, and Serotonin Systems in the Neurobiology of GAD[6]

The Neurobiology of GAD
The GABA/BZD Complex
• Reduced platelet BZD receptors (increased following treatment)
• Reduced lymphocyte BZD receptors (increased following treatment, coincident with improvement of symptoms)
• Reduced saccadic eye-movement velocity after BZD administration
The Norepinephrine System
• Reduced platelet α_2-adrenergc receptors
• Blunted growth hormone response to clonidine
• Attenuated yohimbine-induced increase in MHPG
The Serotonin System
• Reduced serotonin levels in CSF
• Reduced platelet serotonin transporter sites
• Exaggeration of symptoms by mCPP

GABA/BZD=γ-aminobutyric acid/benzodiazepine; GAD=generalized anxiety disorder; BZD=benzodiazepine; MHPG=3-methoxy-4-hydroxyphenylglycol; CSF=cerebrospinal fluid; mCPP=m-chlorophenylpiperazine.

Adapted from: Connor KM, Davidson JR. Generalized anxiety disorder: neurobiological and pharmacotherapeutic perspectives. *Biol Psychiatry*. 1998;44:1286-1294.

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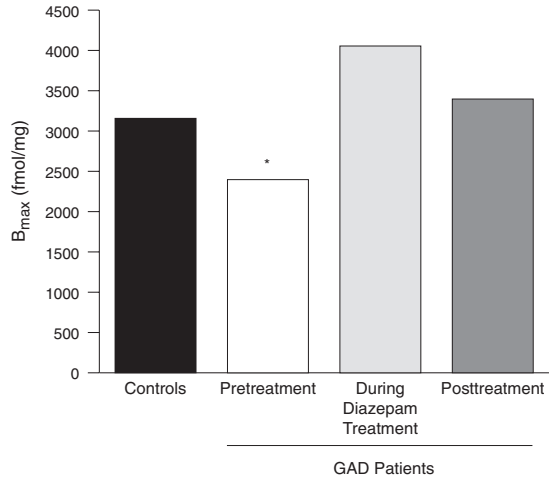
complex in the brain.[28-30] The maximum number of platelet benzodiazepine binding sites (B_{max}), determined from the binding of tritiated hydrogen ([^{3}H])-PK-11195, was reduced by 24% in patients with GAD, but was restored to control levels following treatment with diazepam for 4 weeks (Figure 1).[28]

Similar observations have been made by studying the binding of [^{3}H]-PK-11195 to lymphocytes from patients with GAD.[27] Maximum binding capacity was reduced by 45% on lymphocytes from patients with GAD, but was restored to control both during diazepam treatment and at 1 month after cessation of treatment. Moreover, the increase in lymphocyte benzodiazepine binding sites during anxiolytic therapy coincided with the resolution of patients' anxiety symptoms. The loss of benzodiazepine receptors in GAD may explain the reduction in saccadic eye movement velocity reported in patients with GAD,[29,30] since this measure is an indication of the functional integrity of the benzodiazepine system. If peripheral changes are reflective of changes in the CNS, decreased number and functioning of the benzodiazepine recep-

FIGURE 1

B_{max} determined From the Bindings of [^{3}H]-PK-11195 to Platelets Obtained From Control Subjects (n=10) and Patients With GAD (n=10) Before, During, and After Diazepam Treatment*



* B_{max} determined from platelets obtained at baseline, following treatment with diazepam for 4 weeks, and 1 week after withdrawal of drug treatment.

† *P*<.01 versus control group.

B_{max}=maximum number of binding sites; ^{3}H=tritiated hydrogen; GAD=generalized anxiety disorder.

Adapted from: Weizman R, Tanne Z, Granek M, et al. Peripheral benzodiazepine binding sites on platelet membranes are increased during diazepam treatment of anxious patients. *Eur J Pharmacol*. 1987;138:289-292.

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tors may reduce the GABAergic regulation of other neurotransmitters, including monoamines.

The Norepinephrine System in Generalized Anxiety Disorder

The noradrenergic neurons of the locus coeruleus give rise to diffuse projections innervating most brain areas. The locus coeruleus-norepinephrine-sympathetic nervous system complex is of critical importance in mediating responses to stress, fear, and arousal,[19,31,32] though its role may be limited to providing amplification by enhancing the "signal-to-noise" ratio. Thus, norepinephrine may play a role in the development of anxiety responses, and abnormalities in this system may be relevant in anxiety disorders.

The central effects of norepinephrine are mediated through postsynaptic α_1- or β_1-adrenergic receptors. In addition, presynaptic α_2-adrenergic receptors are important in mediating presynaptic inhibition of norephinephrine release (autoreceptors) or the release of other neurotransmitters when located on terminals of nonadrenergic neurons. The α_2-adrenergic receptor is important in the mediation of anxiety responses. Agents increasing the firing of noradrenergic cell bodies in the locus coeruleus—for example the α_2-adrenergic receptor antagonist yohimbine—induce anxiety, while agents reducing the firing of these neurons—for example the α_2-adrenergic receptor agonist clonidine—inhibit symptoms of anxiety.[33] Interestingly, mirtazapine, which blocks α_2-adrenoceptors, appears to be effective in alleviating the symptoms of anxiety in major depression. However, it should be noted that α_2-adrenoceptor blockade is not the only mechanism of action thought to be involved in the mechanism of action for mirtazapine.

There is some evidence that central α_2-adrenergic receptors could be altered in patients with anxiety disorders.[34,35] The binding of ligands at peripheral α_2-adrenergic receptors has suggested changes in these receptors in GAD. The number of binding sites for [^{3}H]-yohimbine in platelets is reduced by 34% in patients with GAD (Figure 2).[34] Whether or not this is predictive of a downregulation of α_2-adrenergic receptors in the brain is unknown. Further evidence from studies in patients with GAD assessing the functional status of the α_2-adrenoceptor (monitoring plasma growth hormone, 3-methoxy-4-hydroxyphenylglycol [MHPG], heart rate, and blood pressure) has suggested a reduced function of α_2-adrenergic receptors in patients with anxiety disorders.[35,36] In healthy adults, a rapid decrease in the firing of noradrenergic neurons in the locus coeruleus, as induced by clonidine administration, is associated with an immediate release of growth hormone from the pituitary gland.[36] However, administration of clonidine to patients with GAD

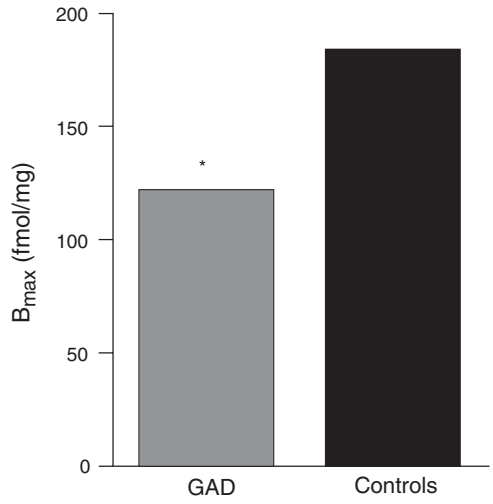
results in a significantly blunted growth hormone response compared with control patients.[35]

Other noradrenergic responses following clonidine administration, including lowering of plasma levels of the norepinephrine metabolite MHPG and decreased blood pressure, were comparable in patients with GAD and control subjects.[35] These responses may indicate that an alteration of α_2-adrenergic receptor function occurs in specific neurons or brain areas of patients with GAD. Consistent with this finding is the observation that behavioral, cardiovascular and stress responses to yohimbine did not differ between patients with GAD and the control group, but the yohimbine-induced rise in plasma MHPG was blunted in those with GAD.[37] These findings are consistent with reduced sensitivity at the presynaptic α_2-adrenergic receptor in patients with GAD, perhaps as a long-term adaptation to high circulating levels of catecholamines.[35] Indeed, the blunted MHPG response to yohimbine[37] could be interpreted as an inability to further stimulate an already overactivated norepinephrine system.

Further supporting this suggestion are observations that plasma norepinephrine and MHPG levels were elevated in patients with GAD,[34] and that there was increased plasma MHPG volatility in response to

FIGURE 2

B_{MAX} Determined From the Bindings of [^{3}H]-Yohimbine to Platelets Obtained From Control Subjects (n=14) and Patients With GAD (n=14)



* *P*<.001 versus control group.

B_{max}=maximum number of binding sites; ^{3}H=tritiated hydrogen; GAD=generalized anxiety disorder.

Adapted from: Sevy S, Papadimitriou GN, Surmont DW, Goldman S, Mendlewicz J. Noradrenergic function in generalized anxiety disorder, major depressive disorder, and healthy subjects. *Biol Psychiatry.* 1989;25:141-152.

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clonidine in patients with panic disorder.[38] Taken together, these data indicate that there may be increased central noradrenergic activity at the locus coeruleus in anxiety disorders.

The Serotonin System in Generalized Anxiety Disorder

Serotonergic neurons arise from the raphe nuclei and project to large areas of the brain, including areas such as the limbic system and hypothalamus that are integrally involved in the mediation of anxiety responses.[10] As with the norepinephrine system, the 5-HT system is also implicated in mediating a variety of behaviors that are altered in anxiety disorders, including appetite, sleep, mood, and cognitive function.[9] The effects of 5-HT in the brain are mediated through interaction with 5-HT receptors located pre- and postsynaptically at serotonergic nerve terminals and on serotonergic nerve cell bodies throughout the CNS.[39] In the mediation and modulation of anxiety responses, the 5-HT_1 and 5-HT_2 receptors appear to have the most prominent roles.[22] Presynaptic 5-HT_1 autoreceptors are important in the modulation of serotonergic activity. Stimulation of somatodendritic 5-HT_{1A} receptors attenuates the firing of serotonergic neurons, and stimulation of terminal 5-HT_{1D} autoreceptors attenuates the release of 5-HT at the nerve ending.[40] The 5-HT_2 receptors predominantly mediate postsynaptic effects of 5-HT.[10] Following release from the nerve terminal, there is rapid reuptake of 5-HT into the terminal via specific transporters.

Studies of 5-HT levels (eg, metabolite studies), 5-HT reuptake, and of 5-HT receptors, have suggested that there may be a dysfunction of the 5-HT system in anxiety disorders.[7,41,42] Levels of 5-HT in the cerebrospinal fluid are reported to be abnormally low in patients with GAD,[7] suggesting that a deficiency of 5-HT may be associated with symptoms of GAD. A long-term reduction in levels of endogenous 5-HT could lead to compensatory changes in receptors and reuptake systems. For example, patients with an anxiety disorder are reported to have a reduced number of 3mechanisms.[42] The maximum number of [^{3}H]-paroxetine binding sites on the platelets of patients with GAD was reduced by 38% compared with control subjects (Figure 3),[42] which may reflect a decreased number of 5-HT reuptake sites in the brain, possibly as a compensatory response to a deficiency of 5-HT. A further response to reduced levels of neurotransmitter may be the upregulation of receptors.

Administration of m-chlorophenylpiperazine, a nonselective 5-HT_1/5-HT_2 receptor agonist, leads to exaggerated anxiety and hostility in patients with GAD.[41] This enhanced response to an exogenous agonist would be consistent with an upregulation of 5-HT receptors. Dysfunction of the 5-HT system may lead to dysregulation of other systems, including increased volatility of the norepi-

nephrine system, with which 5-HT interacts. The relationship between 5-HT and norepinephrine is discussed further below.

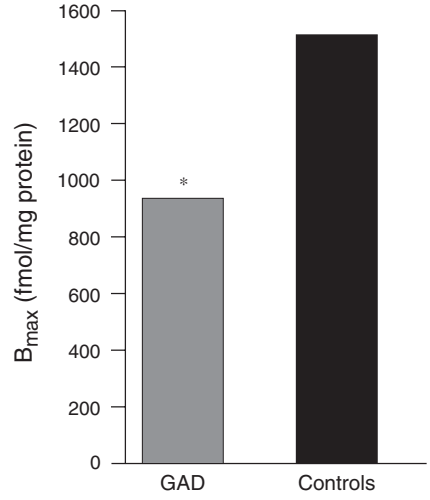
Other Systems Operating in Generalized Anxiety Disorder

In addition to the HPA axis, a variety of agents are implicated in the pathophysiology of GAD, including cholecystokinin (CCK) and corticotropin-releasing factor (CRF).[15-19] CCK is a peptide cotransmitter found throughout the CNS, particularly in the limbic system.[17] Anxiogenic effects of CCK may occur through interaction with CCK receptors or through interaction with, or modulation of the action of, neurotransmitters such as 5-HT and GABA,[17,18,45,46] but the role of this peptide in GAD is unclear at present. CRF is intimately involved in the mediation of stress and anxiety responses through the control of cortisol secretions.[47]

In addition, CRF may influence the activity of the locus coeruleus either directly or through modulation of norepinephrine activity. Although a role for CRF in the mediation of depressive disorder has been suggested (see Nemeroff, pages 6–23), its role in the neurobiology of GAD is not yet fully determined. Abnormalities in the HPA

FIGURE 3

B_{MAX} Determined Rrom the Bindings of [^{3}H]-Paroxetine to Platelets Obtained From Control Subjects (n=13) and Patients With GAD (n=18)



* $P<.05$ versus control group

B_{max}=maximum number of binding sites; ^{3}H=tritiated hydrogen; GAD=generalized anxiety disorder.

Adapted from: Iny LJ, Pecknold J, Suranyi-Cadotte BE, et al. Studies of a neurochemical link between depression, anxiety, and stress from [^{3}H] imipramine and [^{3}H] paroxetine binding on human platelets. *Biol Psychiatry.* 1994;36:281-291.

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axis have been reported in patients with GAD, but data are conflicting and require further characterization.[10] One possibility is that the HPA system is excessively activated in GAD and becomes dysregulated in major depression.

A Pathophysiologic Link Between Serotonin and Norepinephrine in Anxiety and Depression

The 5-HT and norepinephrine systems in the brain do not function independently of each other; there is a close interaction between them through both direct and indirect influences. For example, 5-HT may modulate noradrenergic activity directly via inhibitory serotonergic projections from the brainstem raphé to the noradrenergic neurons of the locus coeruleus, or indirectly by modulation of neurotransmitters (including CRF, glutamate, somatostatin, or substance P) that stimulate brainstem noradrenergic activity.[10] As a consequence of this close interaction between the two systems, changes in one are reflected in the other and, although their precise nature may vary, it seems likely that interactions between the systems are reciprocal.[9]

The relationship between the 5-HT and norepinephrine systems suggests that anxiety disorders may arise from a dysregulation between these systems. Current evidence would suggest that anxiety results from a relative hyperactivity of the norepinephrine system and reduced function of the 5-HT system.

Although there are differences in the neurobiology of anxiety and depression, there is some overlap between these two disorders with respect to the involvement of the norepinephrine and 5-HT systems, and the relationship between them, in the mediation of symptoms (see Nemeroff, pages 6–23). Furthermore, some symptoms of GAD, such as impaired cognitive function and sleep disturbance, are also found in patients with depression.[48]

It has therefore been proposed that there is a pathophysiological link between anxiety and depression.[49] A reduction in the function of the 5-HT system is common to both disorders and it has been suggested that in chronic anxiety (eg, GAD, the elevation of neuronal activity in the locus coeruleus leads to eventual depletion of endogenous norepinephrine and the development of depression). The possibility that a reduction in 5-HT and norepinephrine function may be common to both disorders has led to consideration of GAD as a prodrome for major depression.[50,51]

Generalized Anxiety Disorder as a Prodrome for Major Depressive Disorder

The overlap between the neurobiological changes in GAD and depression indicate that GAD may be important in the development of

depression. There are three lines of evidence from epidemiological, longitudinal and genealogical data to suggest that, in most patients, GAD is a prodrome for major depression.

There is a high degree of comorbidity of GAD and depression.[1,52] Data from the US National Comorbidity Survey (NCS) showed that 39% of patients with GAD had experienced major depression during the 30 days prior to interview.[1] Furthermore, when lifetime prevalence was considered, 62% of patients with GAD could be expected to experience comorbid major depression.[1] The onset of GAD is generally at an earlier age than major depression,[1] and GAD precedes the development of major depression in individuals with both disorders.

Data from the NCS found that 58% of patients with major depression had experienced a previous anxiety disorder, and the depressive episode was most strongly comorbid with GAD.[52] There was a high risk of developing major depression within 1 year of developing GAD (odds ratio=62), and major depression was likely to develop within approximately 1.5 years of diagnosing GAD.[52] In a recent prospective, longitudinal, community study of young adults it was found that most anxiety disorders are primary conditions that substantially increase the risk for secondary depression.[53]

In addition to epidemiological and longitudinal data, there is evidence of a genetic link between GAD and major depression. Genetic factors have a role in the etiology of GAD[54] and the total heritability is estimated at 32%.[55] A similar (41%) risk for major depression is ascribed to genetic factors.[55] Studies suggest that there is likely to be a considerable overlap in the genes responsible for these disorders, although the identity of these genes is unknown at present.[11,12] Relatives of patients with comorbid anxiety and depression have an increased risk of experiencing episodes of GAD or major depression,[11] suggesting that a familial predisposition to the two disorders may be shared. Indeed, a study of twin pairs has determined that the same genes influence the liability to major depression and GAD, although the environmental factors that influence development of the disorders are distinct.[11,12] The genetic link between GAD and major depression indicates that there are likely to be common neurobiological changes in these two disorders. Studies of the neurobiology provide suggestive evidence that dysfunction of the 5-HT and/or norepinephrine systems may be important in the development of both GAD and major depressive disorder, and may have implications for the choice of treatment for these disorders.

Treatment of Generalized Anxiety Disorder

In general, patients with GAD seek treatment for the disorder when associated with comorbidity,[1] probably due to the greater impairment it

causes in their lives.[5] Therefore, for patients with comorbid depression, it is likely that their depressive disorder is treated as the primary indication. Consequently, they may experience symptoms of GAD only. However, pure GAD is associated with significant impairment of patients' lives and also requires effective treatment.[1,5] Moreover, GAD often precedes major depressive disorder and, therefore, early and effective treatment of GAD may prevent the occurrence of comorbidity.

In addition to nonpharmacotherapeutic options, including support counseling and psychotherapy, treatment of anxiety disorders has involved the use of anxiolytics and antidepressants. The agents considered for the treatment of GAD include benzodiazepines, azapirones (buspirone), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs).[8,9,56,57]

Benzodiazepines

Benzodiazepines have been used for the short-term treatment of somatic symptoms of anxiety.[58] The mechanism of action of these agents is believed to be through potentiation of inhibitory GABAergic transmission, thereby suppressing the activity of other, perhaps dysregulated, neurotransmitter systems. Benzodiazepines are effective for very rapid relief from acute anxiety, and have a rapid onset of anxiolytic action in patients with GAD.[59-62] They are relatively inexpensive as they are available in generic formulations, and are widely accepted by the patient population. However, as our understanding and diagnosis of anxiety disorders increases, there is greater recognition that GAD is a chronic disorder characterized by both somatic and psychological symptoms requiring long-term treatment.[63] Benzodiazepines alleviate predominantly somatic symptoms of anxiety while leaving psychic symptoms[64-68] and efficacy may not be sustained during long-term treatment.

In a study comparing alprazolam and imipramine in patients with GAD, alprazolam was more effective in alleviating somatic symptoms, while imipramine was more effective in attenuating psychic symptoms, such as dysphoria and negative thinking.[66] Some studies have reported that although there is early improvement in symptoms, the effects of benzodiazepines are not significantly different from placebo following 4–6 weeks of treatment.[62,69-71] In addition, benzodiazepines have little, if any, efficacy in the treatment of major depression and may even exacerbate the disorder[72]—a major disadvantage in light of the high comorbidity of major depression and GAD.[1] Furthermore, benzodiazepine use is associated with unwanted side effects, including sedation, and psychomotor and cognitive impairment.[22,64]

Contrary to popular belief, observations that patients do not increase dose over prolonged periods of medication,[73] and that abuse is rare in patients without pre-existing substance abuse,[22] indicate that tolerance and abuse have a low likelihood of occurring during treatment with benzodiazepines. However, the use of these agents is associated with a physiological withdrawal syndrome indicating receptor sensitization subsequent to downregulation, and resulting in rebound anxiety. Rebound anxiety may occur when discontinuing medication after only 2 weeks of treatment[9] and usually worsens with longer periods of administration, higher doses, and abrupt discontinuation.[64] In summary, benzodiazepines are effective short-term anxiolytics for the relief of some somatic symptoms of anxiety, but have significant disadvantages for the long-term treatment necessary for GAD.

Buspirone

Buspirone, a member of the azapirone group of drugs, is a partial agonist at the pre- and postsynaptic 5-HT_{1A} receptor.[74] As described earlier, this receptor mediates presynaptic inhibitory effects of 5-HT. An anxiolytic effect of buspirone is therefore likely to occur through activation of 5-HT_{1A} receptors and subsequent modulation of central serotonergic activity. Buspirone appears to be effective in reducing anxiety symptoms in GAD. The anxiolytic effect is comparable to that attained using benzodiazepines, although it is slower in onset, taking an average of 2 weeks to develop.[75-82] Improvement following treatment with buspirone is primarily in psychic symptoms,[65] and the use of this agent is associated with only mild adverse events, including dizziness, headache, and nausea.[74] However, although buspirone has been indicated for GAD (as defined by *DSM-III-R*), its efficacy in major depression is at best modest[49] and there are no studies examining its potential benefits.

Tricyclic Antidepressants

TCAs, well-established agents for the treatment of depressive disorders, mediate their effects by the inhibition of reuptake of norepinephrine, or both norepinephrine and 5-HT.[83,84] TCAs are relatively inexpensive, as they are available in generic formulations, and are effective in alleviating symptoms of GAD.[62,66,68] The efficacy of imipramine is equivalent to or greater than that attained by benzodiazepines, and improvement is primarily in psychic compared with somatic symptoms.[62,66,68] However, TCAs have a poor adverse-event profile associated with their use, possibly attributable to the additional effects of these agents at histaminergic, muscarinic, and adrenergic receptors.[83]

The use of TCAs is associated with dry mouth, sedation, and constipation. TCAs may also pose cardiovascular risks, including orthostatic hypotension and cardiotoxicity. The initial worsening of anxiety symptoms has been reported in some patients with panic disorder.[85,86] Moreover, TCAs have a high potential for fatal overdose with a relatively small supply of medication; caution could be required in prescribing to patients with depression and suicidal thought.[87] Therefore, although the pharmacology of TCAs would recommend their use in the treatment of GAD, in terms of modulating 5-HT and norepinephrine activity, the adverse-event profile associated with them may limit their use for the long-term therapy of GAD.

Selective Serotonin Reuptake Inhibitors

SSRIs bind with the 5-HT transporter to inhibit the reuptake of 5-HT from the synaptic cleft. These agents therefore mediate a selective increase in the availability of 5-HT in the brain, which is believed to underlie the efficacy of SSRIs in the treatment of depression (see Nemeroff, pages 6–23). SSRIs have significant advantages over TCAs, being effective in the treatment of a variety of anxiety disorders (panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, social anxiety disorder, and GAD) without the cardiovascular risks and toxicity associated with TCAs.[84,88]

The use of SSRIs in the treatment of GAD has been studied using paroxetine. Data from two separate studies demonstrate that paroxetine produces an anxiolytic effect significantly greater than placebo.[89] This which is comparable to the effect of imipramine,[68] and, from 4 weeks onwards, is greater than that attained by administration of a benzodiazepine.[68] Improvement was noted in psychic symptoms, and a significant reduction in the anxious mood item of the Hamilton Rating Scale for Anxiety was evident after only 1 week of treatment with paroxetine ($P<.05$).[68,88] Administration of paroxetine for 8 weeks was associated with a significantly greater number of patients responding or remitting compared with placebo, and an improvement in social functioning.[89] This is consistent with the improvement in temperament and character inventory scores following longer-term treatment with paroxetine.[90]

SSRIs are safe and well tolerated, and adverse events, including sleep disturbance, nausea, and sexual dysfunction, are generally mild. This profile of action suggests that SSRIs are likely to be effective in the treatment of GAD, although the longer-term efficacy of paroxetine and other SSRIs in controlled studies beyond the 8 weeks' duration remains to be established.

Serotonin and Norepinephrine Reuptake Inhibitors

SNRIs bind to sites associated with the 5-HT and norepinephrine transporters to inhibit the reuptake of both 5-HT and norepinephrine from the synaptic clefts. These agents therefore have a dual mode of action to mediate increases in the availability of 5-HT and norepinephrine in the brain. Hence, the use of SNRIs in GAD may lie in an ability to restore the functioning of the 5-HT system and, by elevation of endogenous norepinephrine, desensitize an overactive norepinephrine system.

Venlafaxine extended release (XR) is the only SNRI indicated as effective in the treatment of GAD. This agent has been shown to reduce symptoms of anxiety during 8 weeks of administration,[91,92] the mean size of effect determined from five studies being 2.78 (Wyeth Pharmaceuticals, data on file). Improvement was seen particularly in psychic symptoms,[91-93] and on two rating scales (Clinical Global Impressions, and Hospital Anxiety and Depression) the anxiolytic effect of venlafaxine XR was superior to buspirone.[91] Efficacy was maintained during 6 months' administration with no evidence for tachyphylaxis.[94,95] Treatment with venlafaxine XR is associated with a significantly greater number of patients responding or remitting (attaining a virtual symptom-free state) compared with placebo,[93] and improved social functioning.[96] It is also effective in treating both anxiety and depression in patients with comorbid GAD and major depression.[97] Venlafaxine XR is safe and well tolerated, with mild side effects, including nausea, dizziness, dry mouth, and sexual adverse effects being associated with its use, although the incidence of these events declines during long-term use.[98]

Rationale for the Use of Dual Reuptake Inhibitors for GAD

The proposed dysfunction of central serotonergic and noradrenergic function as major factors in the etiology of GAD suggests that the ability of SNRIs to influence both of these systems simultaneously may offer advantages in the treatment of GAD. For example, the physiological links between the norepinephrine and 5-HT systems would indicate that inhibition of norepinephrine reuptake might exert immediate effects on noradrenergic systems and consequential effects on serotonergic systems, and vice versa for inhibition of 5-HT reuptake. However, an SNRI could exert effects on the norepinephrine and 5-HT systems simultaneously. The superior efficacy of the SNRI, venlafaxine/venlafaxine XR, in the treatment of depression (see Thase, pages 24–35, and Keller, pages 36–48) may suggest an advantage of dual reuptake inhibitors in preventing or treating the comorbid depression that is present in many patients with GAD.

Although both 5-HT and norepinephrine are important mediators of anxiety, irritability, mood, and emotion, there is speculation that some aspects of functioning can be ascribed to individual monoamines (eg, aggression to 5-HT, and motivation to norepinephrine).[99,100] It is not known whether this has implications for the extent of response or remission during treatment with agents affecting one system only, such as a norepinephrine-only TCA or an SSRI, compared with a dual reuptake inhibitor.

Efficacy of Dual Reuptake Inhibitors for Anxiety Disorders

Evidence indicating the benefits of a dual reuptake inhibitor in the treatment of anxiety disorders has been obtained using venlafaxine XR. Studies have shown this agent to be well tolerated and effective in the treatment of comorbid moderate-to-severe anxiety in depressed outpatients and those diagnosed with pure GAD.[91,101] In addition, preliminary evidence suggests that venlafaxine may have use in the treatment of panic disorder. In an open study involving 13 patients with panic disorder, administration of very low doses of venlafaxine was associated with a cessation of panic attacks and significant improvement in anxiety scores.[102]

Conclusion

The data reviewed indicate that dysfunction of 5-HT and norepinephrine systems is a factor in the neurobiology of anxiety disorders, including GAD. Furthermore, evidence has been presented to suggest that GAD is a prodrome for major depression and that these two disorders share a common neurobiological abnormality which is likely to involve an imbalance in the serotonergic and noradrenergic systems. Of the treatment options available for GAD, SSRIs and SNRIs provide sustained improvement in symptoms, have a better adverse events profile than benzodiazepines and TCAs, and are effective in treating the depressive symptoms present in many patients. The efficacy of SSRIs and SNRIs supports a role for both the 5-HT and norepinephrine systems in the neurobiology of GAD. ✤

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