The Role of GABA in Anxiety Disorders

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Anxiety stems from and perpetuates dysregulation of neurobiological systems, but the exact mechanisms of anxiety disorders are still only partially understood. Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter known to counterbalance the action of the excitatory neurotransmitter glutamate. Several pharmacologic agents target the GABA system and modulate the overall effect of GABA. This article highlights multiple neurobiological interactions that play a role in anxiety and reviews selected studies of plasma neurosteroid levels, plasma GABA levels, and benzodiazepine binding site sensitivity and density in patients with anxiety disorders. The article concludes with further support for the role of the GABA system in anxiety by summarizing the current evidence supporting the use of novel GABAergic agents including tiagabine in the treatment of anxiety disorders. *(J Clin Psychiatry 2003;64[suppl 3]:21–27)*

Gamma-aminobutyric acid (GABA) is the primary inhibitory transmitter in the central nervous system (CNS). One third of all CNS neurons are thought to be GABAergic. GABA is present in relatively high concentrations in the spinal cord and in all regions of the brain but does not exist in neurons outside the CNS.

The inhibitory action of GABA on neuronal activity in the CNS counterbalances the action of the excitatory neurotransmitter glutamate (Figure 1). The mutual homeostasis between glutamate and GABA works to modulate neuronal excitability and CNS arousal. This balance prevents excessive levels of neuronal hyperexcitability, which are known to occur in seizure disorders and pathologic anxiety and anxiogenesis.

NEUROBIOLOGICAL SYSTEMS IN STRESS AND ANXIETY

Interactions between multiple neurobiological systems, including the GABAergic system, are important to the adaptation to stress and protection against the development of pathology of anxiety disorders. Normal anxiety is a natural evolutionary response to stressful stimuli; pathologic anxiety, however, is situationally debilitating and harmful.[1] Extreme anxiety, whether generalized or characterized by episodes of panic, can have lasting disruptive effects on cerebral function and even structure. In effect, severe pathologic anxiety can result in brain damage, as shown by an 8% reduction in hippocampal volume in war veterans with posttraumatic stress disorder (PTSD).[2] Thus, persistent, pathologic levels of anxiety may lead to disruption of normal homeostasis in neurobiological systems over the long term.

Vermetten and Bremner[3] recently reviewed preclinical literature on the neurobiological effects of stress in animal models. The most important neuronal circuits regulating the stress response system are the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system. One of the most important neurobiological components of the stress response is corticotropin-releasing hormone (CRF), a neuropeptide found in the hypothalamus and other brain areas. Under acute stress, CRF is released from the paraventricular nucleus of the hypothalamus (PVN). This release initiates a cascade of events: pituitary adrenocorticotropic hormone is released, which in turn stimulates adrenal synthesis and release of cortisol (Figure 2). Cortisol is often referred to as the "stress hormone." The neuropeptide arginine vasopressin, which is co-localized in the PVN, has effects on HPA function similar to those of CRF; the 2 neuropeptides interact in complementary ways, especially during chronic stress. After activation by stress, HPA axis activity can be inhibited via cortisol via a negative feedback mechanism. Outside the hypothalamus, CRF-containing neurons exist in several brain nuclei and, along with other neurotransmitters, are involved in the expression of fear, mediation of conditioned fear, and stress reactivity. These areas include the amygdala, locus ceruleus, hippocampus, prefrontal cortex, and anterior cingulate gyrus.[5] Pathologic stress, depression, and/or anxiety sustains overactivity of the HPA axis that cannot be sufficiently controlled by the fear/stress systems. This may

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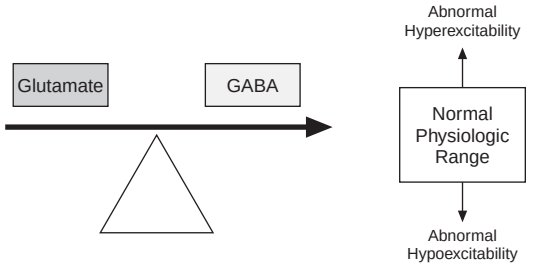
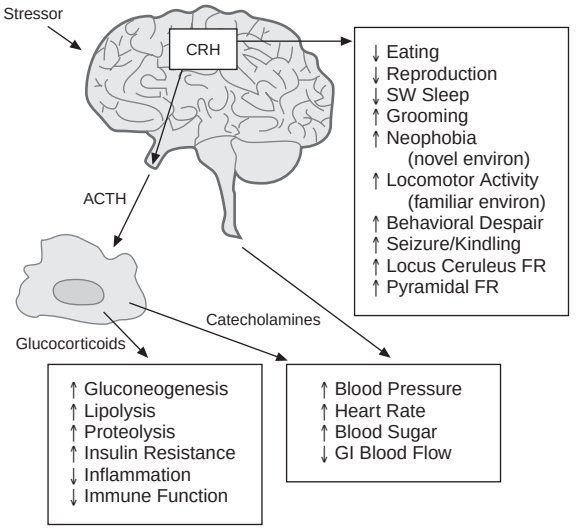
Figure 1. GABAergic-Glutamatergic Balance[a]



[a]Abbreviation: GABA = γ-aminobutyric acid.

Figure 2. Stress and the HPA Axis[a]



Abbreviations: ACTH = adrenocorticotropic hormone, CRH = corticotropin-releasing hormone, FR = firing rate, GI = gastrointestinal, HPA = hypothalamic-pituitary-adrenal, SW = slow wave.
[a]Adapted with permission from Heit et al.[4]

lead to chronic hypercortisolemia, a condition associated with the destruction of hippocampal neurons.[3]

The GABA system plays a role in homeostasis during stress. As with cortisol, GABA opposes the actions of CRF/arginine vasopressin on HPA axis function and interacts with numerous other neurotransmitter systems related to stress modulation at both the hypothalamic and extrahypothalamic level. The many neurotransmitter systems involved in stress-related neurobiological events that are known to interact with GABA are presented in Table 1.[3,5]

GABA ROLE IN ANXIETY DISORDERS

Alterations in the GABA system have been linked to the pathophysiology of anxiety disorders.[6–10] It is widely accepted that patients with anxiety disorders (e.g., panic disorder, PTSD, and generalized anxiety disorder) have reduced benzodiazepine binding in various brain regions, in comparison with controls.[6,7,9,10] Consistent with this theme of a downregulated GABA system, patients with panic disorder were found to have lower brain levels of GABA than healthy controls.[8] However, the results of studies measuring GABA concentrations in plasma and cerebrospinal fluid (CSF) in patients with anxiety are contradictory, partially due to differences in study design/methodology, site of biologic sampling, and patient population.

Roy-Byrne et al.[11] studied the acute effects of intravenous diazepam on plasma GABA in 18 benzodiazepine-naive patients with panic disorder, 13 patients with generalized anxiety disorder (GAD), and 20 healthy controls. All subjects were given logarithmically increasing doses of diazepam or placebo on separate days, and plasma GABA level was measured prior to and 3 minutes following the highest dose of diazepam or placebo. In the combined group, there was a significant overall decrease in plasma GABA level that was significantly greater following treatment with diazepam compared with placebo, but no group differences in response were found. When the authors evaluated a separate group of 18 panic disorder patients who were receiving chronic alprazolam treatment, the same diazepam infusion procedure (no placebo day was included) produced decreases in plasma GABA similar to those seen in the untreated panic disorder patients. Balon et al.[12] measured plasma GABA concentrations before and after panic attacks were induced via lactate infusion in 9 healthy subjects. Plasma GABA levels were found to significantly decrease during infusions of sodium lactate, but not during infusions of dextrose.

Goddard et al.[13] compared plasma GABA levels in 10 patients with panic disorder and 10 nonanxious controls; no significant difference between groups was detected, in part due to highly variable levels of disease severity in the panic disorder sample. Rimon et al.[14] studied CSF GABA concentrations in 11 patients with panic disorder, prior to and after 7 months' treatment with either alprazolam or

Table 1. CNS $GABA_A$ Receptor: Multiple Neurobiological Interactions

Neurosteroids
Corticotropin-releasing factor/arginine vasopressin
Neuropeptide Y
Cholecystokinin
Substance P
Somatostatin
Neurotensin
Glutamate
Norepinephrine
Serotonin
Dopamine
Acetylcholine
N-methyl-D-aspartate

Abbreviations: CNS = central nervous system, GABA = γ-aminobutyric acid.

imipramine, and in 6 controls. A clear treatment response in patients treated with either agent and no decrease in CSF GABA concentrations were observed. Furthermore, there was a negative correlation between baseline lumbar CSF GABA and psychopathology measures post-treatment (measures of anxiety, depression, and panic attack frequency).

The relationship between brain, plasma, and CSF GABA concentrations and the degree to which they singly or collectively reflect CNS GABA activity remain unclear. Taken together, the findings from the studies discussed above suggest that there are no baseline differences between panic disorder patients and healthy subjects in either plasma or CSF GABA concentrations. This would be consistent with the hypothesis that episodic underactivity of CNS GABA system plasma may occur and might not be detected at baseline. As noted, lactate infusion was accompanied by a reduction in plasma GABA concentrations.[12] It is possible that lactate infusion provokes panic and anxiety in part by reducing central GABA function. The observed reduction of peripheral GABA may reflect enhancement of CNS GABA function with reduced need for GABA release. Reduced turnover may result in reduced amounts of GABA diffusing into peripheral blood. The question of why similar changes in CNS GABA concentration did not occur makes these findings difficult to interpret. It may be that CSF and plasma GABA represent different pools of CNS GABA. Taken together, these findings indicate variable results. However, small experimental sample sizes, open versus blinded treatment, and differences in assay measures utilized, or other methodological differences, may have contributed to these seemingly conflicting findings. Additional research replicating the above findings and a more complete understanding of how to interpret plasma and CSF GABA concentrations will be required to put such findings into perspective.

THE GABA SYSTEM

GABA is known to act on 3 GABA receptor subtypes, $GABA_A$, $GABA_B$, and $GABA_C$.[15] The $GABA_A$ and $GABA_C$ receptors are oligomeric transmembrane glycoproteins composed of 5 subunits that are arranged around a central chloride channel. Upon activation, there is an augmentation in chloride influx, which causes the membrane to hyperpolarize and results in neuronal inhibition. Whereas, the $GABA_B$ receptor comprises two 7-transmembrane-spanning proteins that are coupled to either a calcium or potassium channel via G proteins.[16] When activated, either calcium currents are suppressed or membrane potassium conductance is increased leading to neuronal hyperpolarization. The $GABA_A$ receptor plays a role in anxiety (see previous section), epilepsy, alcoholism, and other psychiatric and neurologic disorders[17]; however, the involvement of the $GABA_B$ and $GABA_C$ receptors in these disorders has yet to be determined.

$GABA_A$ RECEPTOR

$GABA_A$ receptors comprise 5 protein subunits.[17] The subunit composition determines the receptor's sensitivity to different ligands and its diversity of function. Receptors with an α_1 subunit preferentially bind zolpidem and other similar agonists with high affinity[17] and have been linked to the sedative/hypnotic effects associated with benzodiazepine treatment.[18] Conversely, receptors with α_2, α_3, or α_5 subunits bind with low affinity to these same substances.[17] Receptors with the α_2 subunit are thought to mediate the anxiolytic effects of the benzodiazepines.[19] Although α_4 and α_6 subunits are diazepam-insensitive, α_1, α_2, α_3, and α_5 subunits bind diazepam as well as other benzodiazepines.[17]

Receptor subunit distribution is heterogeneous within regions of the brain but does show some brain region specificity. Receptors containing the α_1 subunit constitute the majority of $GABA_A$ receptors and are expressed predominantly in the cerebellum and thalamus. Whereas, the receptors with α_2, α_3, or α_5 subunits appear mainly in the hippocampus. However, receptors containing any of these 4 subunits (i.e., α_1, α_2, α_3, and α_5) may be found in the cortex.[17]

The $GABA_A$ receptor is the known target of a number of pharmacologic agents, including the benzodiazepines and neurosteroids. The therapeutic benefits of these agents are thought to derive from the modulation (enhancement) of the GABA-mediated inhibition of neuronal overexcitability. The importance of the GABA system in the pathophysiology of anxiety has been firmly established by the proven efficacy of the benzodiazepines in the treatment of anxiety disorders.[20]

$GABA_A$ RECEPTOR MODULATORS

Modulators of the $GABA_A$ receptor may be endogenous (e.g., benzodiazepines and neurosteroids) and/or exogenous (benzodiazepines) in nature. Endogenous regulation of neuronal excitability suggests a number of theoretical roles for endogenous ligands and/or abnormalities in the coupling between GABA and $GABA_A$-benzodiazepine receptors in the pathophysiology of anxiety disorders. For example, the brains of overanxious individuals may underproduce an endogenous agonist or they may overproduce an endogenous inverse agonist.

Endogenous Modulators: Benzodiazepines and Neurosteroids

Benzodiazepines occur naturally in mammals, including humans; however, data is lacking in regard to their involvement in the treatment of anxiety disorders. Rather,

the efficacy of the exogenous benzodiazepines has been well-documented in the literature.[20]

Neurosteroids are progesterone-derived neuromodulators of the $GABA_A$ receptors as well as some G-protein-coupled receptors. The neurosteroids allopregnanolone and pregnanolone produce an inhibitory, anxiolytic effect similar to that of benzodiazepines.[21] Whereas, 3-b,5a tetrahydroprogesterone may exert the opposite effects.

Experimental stress in rodents was found to be associated with altered concentrations of neurosteroids in the brain and plasma, along with downregulation of GABA receptors. These effects of stress were modified by pretreatment with anxiolytics.[22–24]

The literature is not entirely consistent, however, in demonstrating correlations between psychiatric state and plasma neurosteroid concentrations. In a study[21] of 10 patients with panic disorder matched to 10 nonanxious controls, plasma neurosteroid levels were monitored at intervals over a 24-week course of paroxetine treatment. Patients with panic disorder had higher plasma concentrations of allopregnanolone and pregnanolone compared with controls. Serotonin reuptake inhibitor antidepressants tend to increase agonist neurosteroids.[25] Although all panic disorder patients experienced improvement as a result of paroxetine treatment, the concentrations of allopregnanolone, pregnanolone, and steroid GABA agonist metabolite of these neurosteroids remained the same. These findings were markedly different from those in patients with major depression, in which baseline neurosteroid agonist concentrations were lower and antagonist steroid concentrations were higher than in control subjects.[20] Following successful treatment with a serotonin selective uptake inhibitor antidepressant, the profile resembled that seen in control subjects at baseline.

The authors[21] suggested that these unexpected findings in panic disorder patients may be due to ongoing biological compensatory mechanisms (i.e., higher concentrations of baseline agonist neurosteroids) accounting for the lack of paroxetine effects on this parameter even with the observed therapeutic efficacy.

Further studies that examine the function of endogenous benzodiazepines and neurosteroids in anxiety and other psychiatric disorders, as well as the effects of different treatments, will be necessary to increase our understanding of what role this pool of endogenous anxiolytic neurosteroids may play in either normal or pathologic anxiety states.

Exogenous Modulators: Benzodiazepines

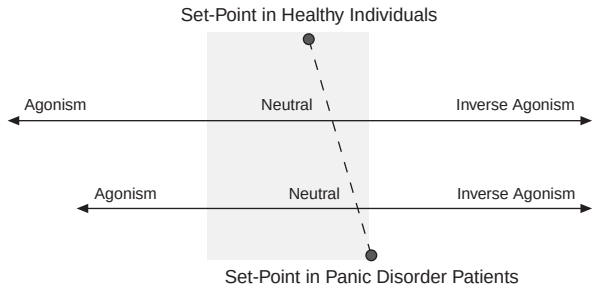
As previously stated, panic disorder is associated with abnormalities in the GABA system and may be effectively treated with benzodiazepines. Collectively, the benzodiazepines exert a full spectrum of pharmacologic effects on the $GABA_A$ receptor. They may act as full agonist, partial agonist, antagonist, partial inverse agonist, and full inverse agonist. Studies have employed various benzodiazepines with different pharmacologies to further probe into the involvement of GABA in anxiety disorders, with contradictory conclusions.

Roy-Byrne and colleagues[26] tested benzodiazepine receptor sensitivity by administering intravenous diazepam to 9 patients with panic disorder and 10 healthy controls. Of the 9 panic disorder patients, 8 were benzodiazepine-naive; one patient had been treated with alprazolam 8 months prior to the study. All subjects received logarithmically increasing doses of diazepam during 1 session and propylene glycol vehicle of equal volumes during the other session. Subjects completed the Beck Depression Inventory, Spielberger Anxiety scale, and Lader Mood Analogue Scale, among other measures. Pharmacologic results were measured by saccadic eye movement velocity, memory, and self-rated sedation. Results showed that diazepam was significantly less potent in subjects with panic disorder than in controls. All panic disorder patients were able to perform the saccadic eye velocity test without difficulty after receiving the highest dose of diazepam, but 5 of 9 controls were physically unable to perform the test after receiving the highest dose. All panic disorder patients tolerated diazepam at all doses, but 1 control subject was dropped from the study when extreme sedation prevented the subject from safely completing the dose range. This evidence strongly suggests benzodiazepine-receptor subsensitivity among individuals with panic disorder.

Flumazenil has been used to study the role that the GABA system plays in anxiety. A 1990 study by Nutt et al.[27] administered the neutral benzodiazepine antagonist flumazenil to 10 patients with panic disorder and 10 healthy comparison subjects to test the hypothesis suggested by Roy-Byrne and colleagues[26] that panic disorder is associated with benzodiazepine receptor abnormalities. No subject had taken benzodiazepines for at least 3 months prior to the study, and 6 of the 10 subjects were benzodiazepine-naive. Each subject received a single 2-mg injection of flumazenil (predicted to achieve 50% receptor occupancy) and an injection of inert vehicle over approximately 1 minute. Subjects were informed in advance that they might experience either an increase or a decrease in their level of anxiety. Heart rate and blood pressure were measured throughout the study. Following each infusion, subjects gave a verbal report of their test experience, rated their symptoms via visual analogue scales, and again completed the Spielberger State Anxiety Scale. The occurrence of a panic attack was determined by using DSM-III-R criteria.

At the end of the double-blind study,[27] both physicians and subjects were asked which of the 2 infusions had been active. In 8 of the 10 patients with panic disorder, the neutral antagonist flumazenil prompted a full panic attack; some described this attack as the most severe they had ever experienced. The placebo (vehicle) was slightly anxi-

Figure 3. Alterations in the Endogenous Benzodiazepine Receptor "Set-Point"[a]



[a]Adapted with permission from Nutt et al.[27]

ogenic, but was clearly identified as different from flumazenil by all study subjects (and by all physicians). Panic disorder patients experienced elevated heart rate and blood pressure with flumazenil, but controls experienced no change in heart rate and only a small and fleeting change in blood pressure. Subjective and physiologic ratings indicated that flumazenil induced anxiety in patients with panic disorder compared with control subjects, who reported only sedation and dizziness. The authors proposed that this study provided evidence for a shift in the benzodiazepine receptor "set-point" (Figure 3). In individuals with panic disorder, benzodiazepine receptor function was shifted in the same way as in individuals who have developed physiologic dependence on benzodiazepines. In such a condition, full agonists may be less effective in producing some $GABA_A$ agonist effects, and neutral antagonists would act as partial inverse agonists.

Woods et al.[28] conducted a study to evaluate the possibility that benzodiazepine receptor function in panic disorder may be abnormal. They administered 2 doses of flumazenil and placebo to 11 panic disorder patients in a double-blind, randomized, crossover design. The 200-mg dose appeared to be anxiogenic and precipitated panic attacks in 4 of the 10 subjects who received that dose, while the higher 600-mg dose and placebo had no significant effect. None of the treatments caused a significant change in heart rate, blood pressure, or levels of the norepinephrine metabolite 3-methoxy-4-hydroxy-phenylethylene glycol. After receiving 200 mg of flumazenil, panic patients' anxiety ratings on a visual analogue scale were significantly increased compared with those receiving placebo. It may be that the lack of anxiogenic effects of flumazenil at the higher 600-mg dose is due to other pharmacologic effects. For example, it may be that flumazenil at higher doses is sufficient to exert full neutral-antagonist effects.

Other studies[29,30] of flumazenil have yielded more conflicting results. Maddock[29] administered a flicker sensitivity test to 6 medication-free panic disorder patients and 5 nonanxious controls after treatment with either intravenous flumazenil (0.1–0.5 mg), which was intended to induce anxiety but not panic, or a placebo infusion. Only 1 patient, who was given 0.5 mg of flumazenil, experienced a panic attack (with no change in flicker sensitivity). All of the other doses administered were lower, and no other subject experienced panic or a significant change in flicker sensitivity. The author concluded that the study provided no evidence to support a benzodiazepine receptor inverse-agonist effect for flumazenil in panic disorder patients and suggested that the findings of Nutt et al.[19] were due to nonspecific, unpleasant interoceptive effects of flumazenil. Given the small sample size and the novel paradigm used by Maddock, it is difficult to interpret the results without replication of the findings in a larger sample.

Ströhle et al.[30] challenged 10 patients with panic disorder with 0.5 M of sodium lactate (which is known to induce panic attacks in approximately 70% of panic disorder patients),[29] 2 mg of flumazenil, or saline placebo. A panic attack was defined a priori as an Acute Panic Inventory total score ≥ 20 and at least 14 points above the preinjection score. Neither flumazenil nor saline placebo produced panic attacks, but sodium lactate produced panic attacks in 8 of 10 patients. Again, results argued against the conclusions of Nutt et al.[27] Two groups have assessed the effects of flumazenil in patients with PTSD and reported no significant anxiogenic activity for flumazenil in patients compared with healthy subjects.[31,32]

Overall, the findings for flumazenil are inconclusive. As noted above, methodological differences may play a major role in the findings reported. However, the findings suggest that the degree to which $GABA_A$ receptors play a role in the pathogenesis of anxiety may differ.

A few studies of benzodiazepine inverse agonists have been conducted. In 1983, Dorow et al.[33] challenged 5 nonanxious male volunteers aged 30 to 45 years with increasing oral doses of the full inverse agonist FG 7142. The incremental doses generally stopped at 200 mg, but 1 volunteer received a 400-mg dose of FG 7142. In 2 of 12 trials, the volunteer experienced a severe, almost debilitating panic reaction. In 1 instance, the volunteer demanded intravenous benzodiazepine rescue. The intense discomfort of the volunteers who experienced panic discouraged further experimentation with FG 7142 in humans. A study[34] in which the partial inverse agonist S-8510 was administered to rats found that the agent enhanced memory at dosages that did not cause anxiety.

Although the benzodiazepines are highly effective in the treatment of anxiety disorders, therapy is associated with the dependence and withdrawal syndromes and abuse.[35] Thus, other GABAergic agents with different mechanisms of action have been explored.

NOVEL GABAERGIC AGENTS

GABAergic neurotransmission may also be enhanced by increasing the synthesis and release of GABA (e.g.,

gabapentin) and inhibiting the reuptake of GABA (e.g., tiagabine).

Increase GABA Release: Gabapentin

There are promising early reports of the efficacy of gabapentin in the treatment of anxiety disorders. Gabapentin enhances GABA activity primarily by increasing the release of nonsynaptic GABA from glia. The structure of gabapentin is similar to that of GABA, but the agent does not appear to act on GABA receptors. Gabapentin has shown potential for the treatment of a variety of psychiatric disorders, including bipolar disorder, intermittent explosive disorder, pain syndromes, and anxiety disorders such as panic disorder, social phobia, GAD, and PTSD.[36–40]

To assess the efficacy of gabapentin in social phobia, researchers utilized a randomized, double-blind, placebo-controlled, parallel-group, multicenter study. Sixty-nine patients with social phobia were randomly assigned to receive gabapentin or placebo for 14 weeks.[41] A significant reduction ($p < .05$) in the symptoms of social phobia was seen in patients treated with gabapentin compared with placebo. The adverse events reported were consistent with the known side effect profile of gabapentin.

In a case report of 18 psychiatric patients with a variety of psychiatric illnesses and comorbid anxiety disorders, gabapentin was administered for up to 38 months.[3] Fifteen patients were treated for at least 12 months. The authors reported that the anxiolytic effects of gabapentin were long lasting and were still present after several months without dose increases and without problems of dependence or withdrawal. In these patients, the most common adverse effects were drowsiness and dizziness at initiation of treatment. Gabapentin is generally well tolerated; adverse effects include somnolence, dizziness, ataxia, fatigue, and weight gain.[20]

Inhibition of GABA Reuptake: Tiagabine

Tiagabine elevates GABA levels via inhibition of GABA reuptake and is the only currently available selective GABA-reuptake inhibitor (SGRI). Clinical reports of the use of tiagabine in patients with refractory anxiety have suggested its potential utility in treating anxiety, including panic disorder.[42]

A 4-week, case-series study[43] enrolled 10 moderately to severely ill patients with refractory anxiety disorders that had been unresponsive to treatment with other antianxiety agents. Patients received 2 mg of tiagabine daily (either as monotherapy or adjunctive therapy) for 1 week, after which time dosage was increased as necessary for efficacy. At the end of the trial, effective daily doses ranged from 2 mg to 8 mg of tiagabine, and all patients were rated as "much improved" or "very much improved" on the Clinical Global Impression of Change scale. Further, treatment was well tolerated, and effect was sustained for at least 9 months. Gruener[44] reported the utility of tiagabine in 7 women and 3 men with treatment-resistant anxiety disorder, 6 of whom also had neuropathic pain. Anxiety diagnoses included panic disorder in 5 patients and GAD in 5 patients. Several patients also had major depression and pain syndromes. The final mean dose was 12 mg/day (range, 2 mg b.i.d. to 8 mg b.i.d.). All patients derived benefit from treatment after 4 weeks of therapy; most continued treatment. One patient developed nausea early in treatment and stopped tiagabine treatment with resolution of symptoms. Lara[45] indicated that tiagabine may be a useful adjunct in the treatment of anxiety. This case series comprised 6 women with recent-onset PTSD, 4 of whom had major depression and 2 of whom had bipolar II disorder. All of the patients had residual PTSD symptoms that were unresponsive to 1 or more antidepressants and, in the 2 bipolar patients, unresponsive to mood stabilizers plus antidepressants. Lara found that a mean dose of 12 mg (range, 8–16 mg) given at bedtime was associated with clinically significant additional improvement.

Tiagabine allows for increased accumulation of intrasynaptic GABA without affecting the normal release of GABA, which remains under normal physiologic control. Thus, the total amount of GABA in the CNS is unchanged. With such a mechanism, it is possible that fewer adverse effects might be observed with tiagabine compared with other GABA-enhancing mechanisms due to the extremely high CNS GABA levels caused by other mechanisms in some circumstances.

CONCLUSION

GABA is the primary inhibitory transmitter in the CNS that maintains homeostasis by counterbalancing neuronal overexcitability that is associated with conditions such as seizure and anxiety disorders. There is a wealth of information supporting the role of the GABA system in the pathophysiology of anxiety; however, some individual studies have conflicting results, in part due to differences in study design/methodology, site of biologic sampling, and patient population. With the proven efficacy of the benzodiazepines in the treatment of anxiety, other GABAergic agents have been evaluated for anxiolytic properties, including gabapentin and tiagabine. Both agents show promise as therapeutic options in the treatment of anxiety disorders and provide hope for the many sufferers with an unsatisfactory response to currently available treatments.

Drug names: alprazolam (Xanax and others), diazepam (Valium and others), flumazenil (Romazicon), gabapentin (Neurontin), imipramine (Tofranil, Surmontil, and others), paroxetine (Paxil), tiagabine (Gabitril), zolpidem (Ambien).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, gabapentin and tiagabine are not approved by the U.S. Food and Drug Administration for the treatment of anxiety disorders.

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