

# New Molecular Targets for Antianxiety Interventions

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Recent advances in neuroscience and understanding in the etiology of anxiety have led researchers to new targets for treatments that are proving to be at least as effective as benzodiazepines, which have been the traditional treatment for anxiety for over 40 years. The  $\gamma$ -aminobutyric acid (GABA) system has long been targeted in anxiety interventions via benzodiazepines, but better understanding of its role in anxiety disorders has led to the development of partial benzodiazepine-GABA receptor antagonists and agents that target specific subunits of the GABA-A receptor and that manipulate GABA levels. The recognition that antidepressants are effective in anxiety even in nondepressed patients has caused researchers to develop antianxiety agents that affect the serotonin and norepinephrine systems. Other neurotransmitter systems such as corticotropin-releasing factor and substance P appear to be abnormally regulated in patients with anxiety disorders, so antagonists of these neurotransmitters may prove to be beneficial anxiolytics. Meanwhile, antistress and antianxiety effects through neurogenesis may be possible with the use of agents that decrease glutamate neurotransmission, such as metabotropic glutamate receptor agonists. Finally, the stimulation of neurotrophic factors, such as brain-derived neurotrophic factor, which appears to enhance neurogenesis, may also prove to have anxiolytic effects.

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The prevalence of anxiety disorders is, by now, well known and the need for safe, effective anxiety treatments, well substantiated. For over 40 years, benzodiazepines were the traditional treatment for anxiety. However, recent advances in neuroscience and understanding the etiology of anxiety have led researchers to new targets for treatments that are proving to be at least as effective as benzodiazepines. Although some new anxiety treatments are variations on earlier, more established treatments, such as agents that partially stimulate the benzodiazepine- $\gamma$ -aminobutyric acid (GABA) receptor or the 5-HT<sub>1A</sub> receptor, other potential treatments involve previously untargeted neurotransmitters like corticotropin-releasing factor (CRF) and substance P, receptors *N*-methyl-D-aspartate (NMDA) and metabotropic glutamate (mGluR), and brain neurotrophins.

## GABA SYSTEM

Benzodiazepines potentiate the effects of the inhibitory neurotransmitter GABA. Benzodiazepines and GABA also

enhance the binding of one another to the benzodiazepine-GABA receptor, which is located on the GABA-A receptor complex. Benzodiazepine-GABA receptors, also known as benzodiazepine receptors, are found ubiquitously throughout the central nervous system, making benzodiazepines effective anxiolytics because they rapidly decrease excitatory neurotransmission everywhere in the brain. However, because the distribution of benzodiazepine-GABA receptors is widespread in the central nervous system, modulating them also leads to many of the adverse events associated with benzodiazepines such as sedation, potentiation of the effects of alcohol, memory and motor disturbances, and psychological and physical dependence. The need for anti-anxiety treatments with the effectiveness but not the side effects of benzodiazepines has led researchers to develop agents that partially stimulate benzodiazepine-GABA receptors.

## Partial Benzodiazepine-GABA Receptor Agonists

Pagoclone is a partial benzodiazepine-GABA receptor agonist that is currently under development for the treatment of panic and other anxiety disorders. In a randomized crossover study, Sandford et al.<sup>1</sup> assessed the effectiveness of pagoclone as an antipanic agent as well as its side effect profile. After a 2-week screening period, patients with DSM-IV panic disorder entered a 6-week trial with 2-week treatment periods followed by a 1-week washout. Patients were randomly assigned to receive pagoclone, 0.1 mg t.d.s., or placebo during the first treatment period and were crossed over for the second period. The number of

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panic attacks decreased with both pagoclone ( $p = .05$ ) and placebo ( $p = .14$ ), but, compared with each other, there was no statistically significant difference between pagoclone and placebo in the change in panic attack frequency. The authors concluded that the study provided evidence of pagoclone's anxiolytic properties without the usual side effects of benzodiazepines. Pagoclone may also be effective in generalized anxiety disorder.

### GABA-A Receptor Subunits

The GABA-A receptor is composed of several different subunits. Research conducted in recent years has targeted some of these subunits in order to explore how they mediate specific physiologic effects of benzodiazepines. McKernan and colleagues<sup>2</sup> created genetically modified mice lacking the gene for the  $\alpha_1$  subunit. The results revealed that the  $\alpha_1$  subunit mediated the sedative but not the anxiolytic properties of benzodiazepines. In a similar study, Löw et al.<sup>3</sup> created mice lacking the gene for the  $\alpha_2$  or  $\alpha_3$  subunit. The authors found that anxiolytic effects were absent in the mice lacking  $\alpha_2$  subunits but not in the mice lacking  $\alpha_3$  subunits, which led to the conclusion that the  $\alpha_2$  subunit mediates the anxiolytic effect of benzodiazepines. Mice with a deletion of the  $\alpha_1$  subunit failed to show the sedative, amnesic, and some of the anticonvulsant effects of the benzodiazepine in research by Rudolph et al.<sup>4</sup> However, the anxiolytic, myorelaxant, motor-impairing, and alcohol-potentiating effects of the benzodiazepine did remain and were attributed to being mediated by the  $\alpha_2$  and  $\alpha_5$  subunits found in the limbic system and motoneurons and in the  $\alpha_3$  subunit found in monoaminergic neurons. Studies such as these on the GABA-A  $\alpha$  subunits have led to the development of agents that activate specific subunits.

### Selective GABA Reuptake Inhibitors

Manipulation of GABA levels may be another effective antianxiety treatment. The anticonvulsant tiagabine, which is a selective GABA reuptake inhibitor (SGRI), increases GABA levels by selectively inhibiting the GAT-1 GABA transporter responsible for the reuptake of GABA in the central nervous system.<sup>5</sup> Both preclinical and clinical trials with tiagabine suggest that this agent may be useful as an anxiolytic.

Schmitt and Hiemke<sup>6</sup> analyzed the behavior of rats after the administration of SGRIs. The rats were put into 8 groups and received either saline or the SGRIs tiagabine or SKF 89976-A. Behavior was analyzed 30 minutes after the dosing in a standard open field, an enriched open field, and an elevated plus-maze. Tiagabine, 18.5 mg/kg, impaired motor coordination, enhanced exploratory activity, and reduced anxiety-related behavior, whereas SKF 89976-A had few behavioral effects. The authors acknowledged, however, that the doses of SKF 89976-A used were quite likely too low.

**Table 1. Clinical Global Impressions (CGI) Scale Ratings After 4 Weeks of Tiagabine Treatment<sup>a</sup>**

Number of Patients	Baseline CGI-S Rating	Endpoint CGI-I Rating
3	Moderately ill	Very much improved
6	Markedly ill	Much improved
1	Severely ill	Much improved

<sup>a</sup>Data from Crane.<sup>5</sup> Abbreviations: CGI-I = CGI-Improvement scale, CGI-S = CGI-Severity of Illness scale.

Crane<sup>5</sup> conducted an open 4-week study confirming the anxiolytic effects of tiagabine in patients with treatment-refractory anxiety disorders. During the first week of the study, 5 patients received tiagabine, 2 mg/day, as monotherapy, and 5 patients received the same dose in combination with other anxiolytic agents. During the remainder of the study, doses were increased for patients who reported insufficient control of anxiety. Patients were assessed using the Clinical Global Impressions (CGI)-Improvement scale. Most patients improved within the first week of tiagabine treatment, with all patients rated as much improved or very much improved at the end of the study (Table 1). No side effects related to tiagabine treatment were reported, and the efficacy of tiagabine in these patients was sustained for at least 9 months. On the basis of these results, the author concluded that tiagabine may be effective for patients with partially or completely treatment-refractory anxiety disorders. However, placebo-controlled trials are necessary before this impression can be confirmed.

Tiagabine has also been assessed as an augmentation to antidepressant treatment in posttraumatic stress disorder (PTSD).<sup>7</sup> In a 6-week, open-label, case series study, 6 patients with PTSD and comorbid mood disorders were administered tiagabine, 2 mg/day to 4 mg/day, in addition to an antidepressant to target symptoms of increased arousal. Patients were assessed using the Davidson Trauma Scale and the Overt Aggression Scale (Modified), and results were compared with 2 control patients (1 treated with only a selective serotonin reuptake inhibitor [SSRI] and 1 treated with an antidepressant and a benzodiazepine). All patients treated with antidepressant and tiagabine therapy had a decrease in PTSD symptoms at a rate comparable with the patient treated with antidepressant and benzodiazepine therapy and at a more rapid rate than that of the patient treated with antidepressant therapy alone. The antidepressant and tiagabine therapy also decreased aggression and impulsivity more than the other therapies did. Side effects were minimal, and no patients discontinued tiagabine because of side effects. Again, small open-label studies such as this must be interpreted with great caution.

### CALCIUM CHANNEL MODULATOR

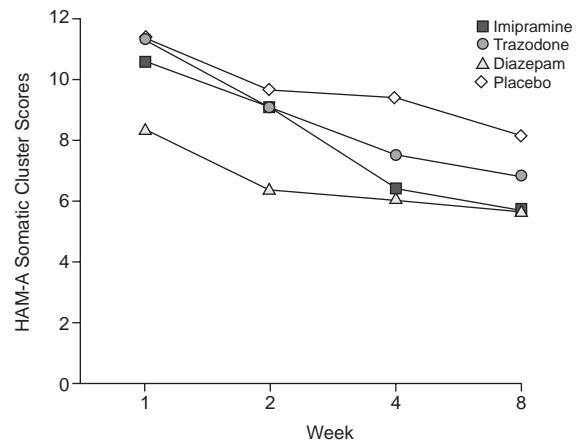
Pregabalin has been shown to be effective for anxiety disorders in several controlled trials.<sup>8,9</sup> Although its mechanism of action in treating anxiety is not yet clear, it may

work by modulation of a subtype of calcium ion channel in the central nervous system. In a 4-week randomized, double-blind trial,<sup>8</sup> 455 patients with generalized anxiety disorder (GAD) were treated with pregabalin, 300, 450, or 600 mg/day; the benzodiazepine alprazolam, 1.5 mg/day; or placebo. All treatments were dosed t.i.d. Pregabalin and alprazolam were significantly more effective than placebo in reducing anxiety. The most common side effects for pregabalin and alprazolam were dizziness and somnolence, but withdrawal due to adverse events was low. Another study<sup>9</sup> compared pregabalin, the antidepressant venlafaxine, and placebo in patients with GAD. Over 400 patients were randomized to 6 weeks of double-blind treatment with pregabalin, 400 or 600 mg/day; venlafaxine, 75 mg/day; or placebo. Both doses of pregabalin and venlafaxine were superior to placebo in ameliorating the symptoms of GAD. Patients in the venlafaxine group withdrew because of adverse events more often than patients in the pregabalin and placebo groups.

### SEROTONIN AND NOREPINEPHRINE SYSTEMS

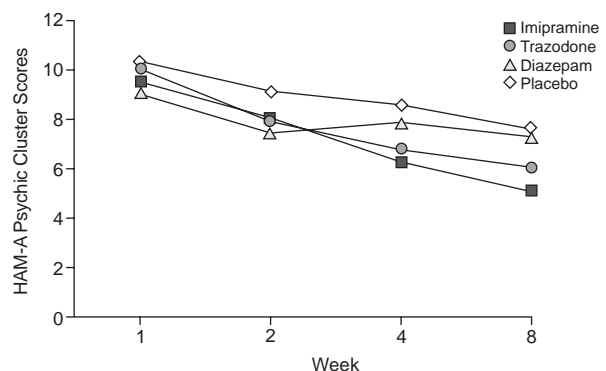
A somewhat recent development in treating anxiety disorders has been the recognition that antidepressants may be more effective than benzodiazepines in the treatment of anxiety disorders, even in patients with little to no depression. In a randomized, double-blind, placebo-controlled, flexible-dose, 8-week study, Rickels et al.<sup>10</sup> compared the anxiolytic efficacy of the antidepressants imipramine and trazodone and the benzodiazepine diazepam. Patients (N = 230) with a DSM-III diagnosis of GAD were treated with 143 mg/day of imipramine, 225 mg/day of trazodone, 26 mg/day of diazepam, or placebo. To be included in the study, patients had to have a score of 18 or higher on the Hamilton Rating Scale for Anxiety (HAM-A) and have no major depression or panic disorder. In the first 2 weeks of treatment, patients treated with diazepam showed the most improvement in anxiety ratings. During weeks 3 through 8, however, patients treated with trazodone showed an improvement in anxiety ratings similar to that of patients treated with diazepam, while patients treated with imipramine showed the most improvement in anxiety ratings. For patients who completed the study, moderate to marked improvement in the treatment groups was reported as follows: 73% of imipramine group, 69% of trazodone group, and 66% of diazepam group. Somatic symptoms improved most in diazepam-treated patients early in the study (Figure 1). Later, diazepam and imipramine improved somatic symptoms at a comparable rate, with trazodone producing slightly less improvement. Initially, imipramine and diazepam ameliorated psychic symptoms at a similar rate, but at the end of the study imipramine showed significantly more amelioration than diazepam in the total psychic factor in addition to psychic symptoms such as anxious mood and tension (Figure 2).

Figure 1. HAM-A Somatic Cluster Scores at Weeks 1, 2, 4, and 8<sup>a</sup>



<sup>a</sup>Data from Rickels et al.<sup>10</sup> Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

Figure 2. HAM-A Psychic Cluster Scores at Weeks 1, 2, 4, and 8<sup>a</sup>



<sup>a</sup>Data from Rickels et al.<sup>10</sup> Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

Rocca et al.<sup>11</sup> found similar results when they compared the anxiolytic efficacy of the SSRI paroxetine with imipramine and the benzodiazepine 2'-chlorodesmethyldiazepam in 81 patients with a DSM-IV diagnosis of GAD. The study lasted 8 weeks, and, as in the Rickels et al. study,<sup>10</sup> patients taking the benzodiazepine improved the most during the first 2 weeks of treatment. However, from week 4 onward, the patients treated with the antidepressants experienced greater amelioration than those treated with 2'-chlorodesmethyldiazepam. Again, the antidepressants were more effective than the benzodiazepine in treating psychic symptoms of anxiety, whereas the benzodiazepine was more effective in treating the somatic symptoms. The authors point out that given the emphasis placed on the psychic symptoms of GAD in DSM-IV, the effectiveness of antidepressants on psychic symptoms is relevant.

More recent studies have proven the efficacy of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) in anxiety disorders. In a large placebo-controlled, flexible-dosage trial,<sup>12</sup> 324 patients with DSM-IV GAD and baseline HAM-A scores of at least 20 were given paroxetine, 20–50 mg/day, or placebo for 8 weeks. Patients were assessed with the HAM-A, the anxiety subscale of the Hospital Anxiety and Depression Scale, and the Sheehan Disability Scale. At week 8, patients taking paroxetine had a statistically significant greater reduction of GAD symptoms than patients taking placebo did. Meanwhile, the efficacy of the SNRI venlafaxine for the treatment of GAD has been verified in both short- and long-term studies. Patients with GAD but not depression were randomly assigned to receive placebo or venlafaxine extended release (XR), 75, 150, or 225 mg/day, for 8 weeks<sup>13</sup> or 6 months.<sup>14</sup> In the 8-week study,<sup>13</sup> the total number of patients entering the study was 377, with 370 patients included in the safety analysis and 349 patients included in the efficacy analysis. Patients receiving venlafaxine XR scored statistically significantly lower than patients receiving placebo on both primary and secondary outcome measures. In the 6-month study,<sup>14</sup> 251 patients participated. Compared with placebo, venlafaxine XR improved anxiety scores on primary efficacy measures. The effectiveness of paroxetine and venlafaxine XR in GAD have led to these agents being approved by the U.S. Food and Drug Administration for the treatment of this anxiety disorder.

### Selective 5-HT<sub>1A</sub> Agonists

As an SSRI, an antidepressant like paroxetine, even at low doses, produces a rapid blockade of all the available serotonin transporters in the brain. The result of this blockade is a widespread change in serotonin neurotransmission throughout the brain, which leads to antianxiety and antidepressant effects. Unfortunately, altering serotonin neurotransmission also leads to adverse events such as sexual side effects. Thus, here again, researchers want to understand what the actual target of the increased synaptic serotonin is in order to develop agents that are more selective. A research group from Columbia University is studying the behavioral effects of mice who have had their 5-HT<sub>1A</sub> receptors knocked out.<sup>15–18</sup> Mice without 5-HT<sub>1A</sub> receptors exhibit anxious and fear-related behaviors and are insensitive to SSRIs. These findings suggest that SSRIs may be effective in anxiety through the stimulation of postsynaptic 5-HT<sub>1A</sub> receptors in the forebrain and hippocampus. Strategies are being developed to find selective 5-HT<sub>1A</sub> agonists that will mimic this effect.

## OTHER NEUROTRANSMITTERS

### CRF Antagonists

Studies by Rauch et al.<sup>19</sup> in PTSD and Birbaumer et al.<sup>20</sup> in social phobia indicate that the amygdala is critical in the

experience and expression of fear and anxiety. Additionally, the amygdala appears to be overactive in people with anxiety disorders. Rauch et al.,<sup>19</sup> using a method for measuring automatic amygdala responses to general threat-related stimuli, compared combat-exposed veterans with PTSD with combat-exposed veterans without PTSD. The veterans with PTSD had exaggerated amygdala responses to masked faces with fearful expressions versus masked faces with happy expressions. The authors noted that although patients with PTSD had exhibited amygdala recruitment in response to reminders of traumatic events, their findings were the first evidence for exaggerated amygdala responses to general negative stimuli in PTSD. Birbaumer et al.<sup>20</sup> used functional magnetic resonance imaging (fMRI) to determine the activation of the amygdala when exposed to potentially fearful stimuli in 7 patients with social anxiety disorder and 5 healthy controls. In an fMRI session, patients and controls were exposed to 2 slides of neutral faces, an aversive odor (fermented yeast), and a neutral air puff 10 times each. Participants rated the stimuli for valence, arousal, and intensity. fMRI data revealed that odors elicited amygdala activation. Further, the amygdalae of the patients with social phobia, but not those of controls, were activated when exposed to the neutral faces. The subjective responses of the patients with social anxiety disorder indicated that they knew the faces were not harmful, but the activation of the amygdala suggests the faces induced an affective response.

Because of the amygdala's role in the expression of fear and anxiety, researchers have targeted a neurotransmitter released by the amygdala, CRF, as a possible antianxiety intervention. CRF produces stress- and anxiety-related behavior in animals.<sup>21</sup> When CRF is injected into the locus ceruleus, an anxiogenic response occurs<sup>22</sup> and the expression of tyrosine hydroxylase in the locus ceruleus is increased.<sup>21</sup> Consequently, alterations in the CRF system are believed to contribute to the pathophysiology of anxiety.

The CRF system has been measured peripherally in panic disorder by Coplan et al.<sup>23</sup> through the evaluation of plasma cortisol concentrations. Patients with panic disorder (N = 170) who panicked (N = 101) or did not panic (N = 69) with lactate infusion were compared with healthy controls (N = 44) who also received lactate infusions. Prior to the lactate infusion, the patients who panicked had higher plasma cortisol levels than non-panicking patients or controls. Fear, dyspnea, and diastolic blood pressure were also highest in the group who panicked compared with the other groups. On the basis of these findings, the researchers suggested that particular biological and emotional states are present before a panic attack occurs, including activation of the CRF system. Bremner et al.<sup>24</sup> measured the CRF system directly by comparing the cerebrospinal fluid concentrations of CRF of Vietnam combat veterans (N = 11) with DSM-III-R PTSD with the concentrations of comparison subjects (N = 17). The cerebrospi-

nal fluid concentrations of CRF were higher in the patients with PTSD than in the comparison group. Finally, the finding of decreased hippocampal volume in patients with PTSD has been speculated to be linked to excessive CRF activity.

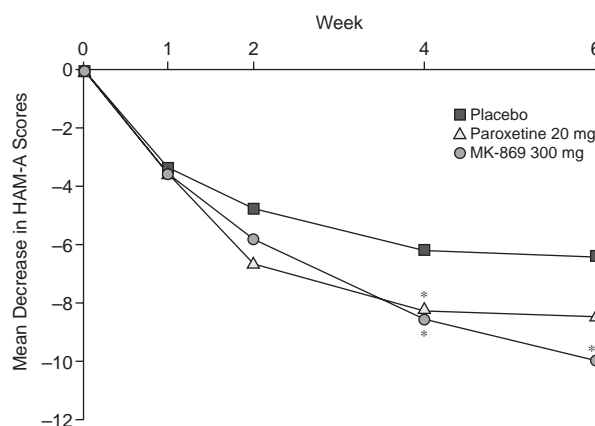
A CRF antagonist has been developed to block the effects of CRF in the central nervous system. In the brain, 2 main receptors bind CRF and activate the CRF system. R121919 is a CRF(1) receptor antagonist that, in vivo, significantly inhibited stress-induced CRF release in rats selectively bred for high and low anxiety behavior.<sup>25</sup> However, the agent appeared to have anxiolytic effects for only high anxiety rats. Zobel and colleagues<sup>26</sup> administered R121919 to 24 patients with a major depressive episode to investigate whether it would compromise the stress-hormone system and whether it had other safety and tolerability issues. The 20 patients who completed the study were enrolled in 2 dose-escalation panels. A group of 10 had the dose increased from 5 mg to 40 mg and the other group of 10 had the dose increased from 40 mg to 80 mg, each within 30 days. R121919 did not appear to impair the stress-hormone system and was safe and well tolerated. Significant reductions in depression and anxiety scores in both clinician- and patient-rated scales were observed. Unfortunately, due to liver toxicity in other studies, R121919 is no longer under development. However, a number of other CRF antagonists are now available and are being tested in depressed and anxious patients.

### Substance P Antagonists

A group of neurotransmitters that may be released in excess during times of emotional stress, and therefore may be related to anxiety, are the neurokinin neurotransmitters (known previously as the tachykinins). The most well-known neurokinin neurotransmitter is substance P, which is an 11 amino acid neuropeptide that is localized in the brain, sensory afferents, lungs, and intestines. Substance P—the P refers to preparation or powder—also binds preferentially to neurokinin-1 (NK-1) receptors that are widely distributed in the brain and limbic system. The distribution of substance P receptors in the rat brain has been found in brain regions that are key areas for the expression of anxiety, such as the amygdala and the hippocampus.<sup>27</sup> Further evidence for substance P playing a role in anxiety disorders is that the central injection of substance P into rat brains produces defensive cardiovascular and behavioral changes.<sup>28,29</sup>

Several substance P antagonists studied in preclinical and clinical trials appear to have antidepressant and anxiolytic effects. Rupniak and colleagues<sup>30</sup> found that the behavioral response of animals treated with the substance P antagonists L-760735 or GR205171 in the resident intruder and forced swim tests was similar to the behavioral response seen with the SSRI fluoxetine. Using the chronic mild stress model of depression, Papp et al.<sup>31</sup> studied the

Figure 3. Mean Decrease in HAM-A Scores After 6 Weeks of MK-869, Paroxetine, or Placebo<sup>a</sup>



<sup>a</sup>Reprinted with permission from Kramer et al.<sup>32</sup> Abbreviation: HAM-A = Hamilton Rating Scale for Anxiety.

\*p = .05 versus placebo.

\*\*p = .002 versus placebo.

antidepressant effects of the NK-1 receptor antagonist NKP608. Rats exposed to various mild stressors were administered NKP608 once daily for 5 weeks, and the observed effect of NKP608 was comparable to that following imipramine treatment. In a proof of concept study, Kramer et al.<sup>32</sup> sought to validate the hypothesis that substance P receptor antagonists have clinical antidepressant and/or anxiolytic efficacy. The 6-week, randomized, double-blind study had 210 patients who were administered the substance P receptor antagonist MK-869, 300 mg/day; the SSRI paroxetine, 20 mg/day; or placebo. Patient criteria included a DSM-IV diagnosis of major depressive disorder (single episode or recurrent), a current depressive episode lasting longer than 4 weeks but less than 2 years, a score of 22 or higher on the 17-item Hamilton Rating Scale for Depression (HAM-D), a score of 15 or higher on the HAM-A, and a score of 4 or higher on the CGI scale. MK-869 proved to be equal in antidepressant efficacy to paroxetine and to have robust antianxiety effects as well (Figure 3).

### NEUROGENESIS

The discovery that the adult mammalian brain, including the human brain, is capable of neurogenesis has led to more molecular targets for anxiety interventions. Eriksson and colleagues<sup>33</sup> found that new neurons are generated from dividing progenitor cells in the dentate gyrus of adult humans. These neurons become mature neurons and function like other mature neurons, and neurogenesis in the human hippocampus appears to be possible throughout life. However, neurogenesis can be impeded by stress and thereby CRF, glucocorticoids, and the glutamate system,

all of which are associated with stress-related behavior. Thus, preventing stress or reversing the effects of stress through neurogenesis may be a treatment strategy for anxiety disorders. Evidence suggests that blocking glutamate activity and drugs that stimulate its NMDA class of receptors may lead to antistress, antianxiety effects that may in turn act to restore normal neurogenesis in the brain. Additionally, neurogenesis may be improved by stimulating neurotrophic factors in the brain.

### NMDA Receptor Antagonists

Preclinical studies have been conducted to determine the anxiolytic effectiveness of NMDA receptor antagonists. The noncompetitive NMDA receptor antagonist MK-801 was investigated for antianxiety effect using the elevated plus-maze paradigm in rats.<sup>34</sup> Additionally, the interactional effects of MK-801 were compared with the benzodiazepine diazepam, the anxiogenic beta-carboline FG-7142, and the central benzodiazepine receptor antagonist Ro 15-1788. MK-801 had anxiolytic effects in rats at all doses (0.025 mg/kg to 0.1 mg/kg). This effect was potentiated by diazepam. However, the effect of MK-801 and diazepam when administered together was reversed by both FG-7142 and Ro 15-1788. In another study, Xie and Commissaris<sup>35</sup> examined the effects of MK-801 on the behavior of rats in the conditioned suppression of drinking paradigm. Their findings led them to conclude that MK-801 may exert antianxiety effects in humans.

Several preclinical and clinical studies have found that NMDA antagonists have antidepressant action, which suggests that such agents may be potential anxiolytics given the effectiveness of some antidepressants in the treatment of anxiety. Trullas and Skolnick<sup>36</sup> examined the actions of a competitive NMDA antagonist (2-amino-7-phosphonoheptanoic acid), a noncompetitive NMDA antagonist (dizocilpine [MK-801]), and a partial agonist at strychnine-insensitive glycine receptors (1-aminocyclopentanecarboxylic acid [ACPC]) on the NMDA receptor complex. They found that the antagonists mimicked the effects of antidepressants in animal models. These findings lend support to the idea that the NMDA receptor complex is involved in behavioral deficits as a result of stress and that agents that reduce neurotransmission at the NMDA receptor complex may be potential antidepressants.

Other studies with MK-801<sup>37</sup> and ACPC<sup>38</sup> showed that these agents had antidepressant effects in rats. In a placebo-controlled, double-blind trial, Berman et al.<sup>39</sup> administered the NMDA receptor antagonist ketamine to 7 patients meeting criteria for DSM-IV major depressive episodes. Patients completed 2 test days in which they were treated intravenously with either ketamine, 0.5 mg/kg, or saline solutions. Those who received ketamine had significant improvement in HAM-D scores within 72 hours of administration. Skolnick<sup>40</sup> reviewed these and

several other studies that demonstrate that NMDA antagonists are antidepressants.

### mGluR Receptor Agonists

The glutamate system has also been targeted for anti-anxiety activity through the use of mGluR agonists, which decrease the presynaptic release of glutamate and block yohimbine-stimulated cortisol release. Shekhar and Keim<sup>41</sup> administered the mGluR agonist LY354740 and the benzodiazepine alprazolam to panic-prone rats in order to test the efficacy of LY354740 in preventing the lactate-induced panic-like response. The authors found LY354740 to be as efficacious as alprazolam in preventing lactate-induced panic attacks. In a recent study, Coplan et al.<sup>42</sup> administered yohimbine to monkeys to induce anxiety and then gave them LY354740, which was potent in blocking the subsequent cortisol release associated with induced anxiety. In a case report,<sup>43</sup> striking changes in the glutamate resonance in the caudate nucleus were observed in a 9-year-old boy with obsessive-compulsive disorder treated with the SSRI paroxetine for 12 weeks.

### Neurotrophic Factors

Neurotrophic factors are crucial to the survival, development, orientation, maintenance, and plasticity of neurons. Because of the ways in which they provide trophic support for neurons, neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), may be able to improve neurogenesis when stimulated. BDNF expression in the hippocampus is reduced by stress, and, when infused into the hippocampus of rats, BDNF has been shown to produce an antidepressant effect comparable with that of a chemical antidepressant.<sup>44</sup> To date, there appear to be no studies of BDNF or neurotrophic factor agonists administered to humans. However, in a recent postmortem study,<sup>45</sup> frozen anterior hippocampus sections were taken from patients with major depression, bipolar disorder, schizophrenia, and controls with no psychiatric illness. The tissue samples were stained for BDNF using immunohistochemistry. Patients treated with antidepressants at the time of death had increased BDNF expression. This and several preclinical studies suggest that stimulation of BDNF expression may be involved in the mechanism of action of antidepressant medications.

### SUMMARY

Several new molecular targets are being investigated for the treatment of anxiety. The GABA system has long been used in anxiety interventions, but better understanding of its role in anxiety disorders has recently led to the development of partial benzodiazepine-GABA receptor antagonists and agents that target specific subunits of the GABA-A receptor and that manipulate GABA levels. The recognition that antidepressants like the SSRIs and SNRIs

are effective in anxiety even in nondepressed patients has caused researchers to develop antianxiety agents that affect the serotonin and norepinephrine systems. Neurotransmitters such as CRF and substance P appear to be involved in patients with anxiety disorders, so antagonists of these neurotransmitters may prove to be beneficial anxiolytics. Meanwhile, antistress and antianxiety effects through neurogenesis may be possible through the modulation of glutamate system receptors such as NMDA and mGluR. Finally, the stimulation of neurotrophic factors such as BDNF appears to enhance neurogenesis and could play a role in the mechanism of action of anxiolytics.

*Drug names:* alprazolam (Xanax and others), diazepam (Valium and others), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), ketamine (Ketalar and others), paroxetine (Paxil), tiagabine (Gabitril), trazodone (Desyrel and others), venlafaxine (Effexor).

*Disclosure of off-label usage:* The author of this article has determined that, to the best of his knowledge, imipramine is not approved by the U.S. Food and Drug Administration for the treatment of generalized anxiety disorder; ketamine is not approved for the treatment of depression; tiagabine is not approved for the treatment of generalized anxiety disorder and posttraumatic stress disorder; and pagoclone is not approved for the treatment of generalized anxiety disorder and panic disorder.

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