

Anticonvulsants as Anxiolytics, Part 1

Tiagabine and Other Anticonvulsants With Actions on GABA

Stephen M. Stahl, M.D., Ph.D.

Issue: *Anticonvulsants that enhance GABA neurotransmission may also have potential as novel anxiolytics.*

GABA AND ANXIETY

Anticonvulsants are proving to have much broader utility in psychiatry and neurology than in just the treatment of seizure disorders, with the expanded indications dependent on the specific pharmacologic mechanism of action of a given anticonvulsant.¹ Increasing evidence shows dysfunction of the γ -aminobutyric acid (GABA)-ergic system to be pivotal to the pathogenesis of anxiety²⁻⁴; thus, augmenting GABA neurotransmission may be expected to have anxiolytic actions.²

POTENTIAL ANXIOLYTIC ACTIONS OF ANTICONVULSANTS

Direct GABAergic Mechanisms

An association between enhancement of GABA neurotransmission and anxiolytic actions is supported by the well-documented efficacy of benzodiazepines (also anticonvulsants) in anxiety disorders.⁵ Other anticonvulsants may enhance GABA neurotransmission via other mechanisms, including selective inhibition of GABA reuptake, inhibition of the enzyme GABA transaminase (GABA-T), and increased synthesis and release of GABA secondary to inhibition of voltage-gated ion channels.^{1,6,18} These actions are not only appealing as possible novel anxiolytics,

but are also beginning to show anxiolytic efficacy in early trials.

Selective GABA reuptake inhibitors (SGRIs). The synaptic actions of GABA are terminated by high-affinity reuptake systems on presynaptic GABA neurons and neighboring glia and can be blocked by SGRIs such as tiagabine.⁶⁻⁸ These actions are analogous to those of SSRIs (selective serotonin reuptake inhibitors) on the high-affinity reuptake system of serotonin neurons.

Four distinct genes for GABA transporters have been cloned: GAT-1, GAT-2, GAT-3, and BGT-1.⁷ GAT-1 is the most abundant and may act not only to terminate GABA action by transporting GABA into presynaptic GABAergic terminals but also to influence excitatory and inhibitory transmission by modulating the spread of GABA from within the synaptic cleft to extrasynaptic receptors.⁸ The precise roles of GAT-2, GAT-3, and BGT-1 have yet to be elucidated. At present, the only SGRI clinically available is tiagabine, an analog of the GABA reuptake inhibitor nipecotic acid.⁶⁻⁸ Of the GABA transporters, tiagabine is the most highly selective for GAT-1.⁶

Small, open-label studies⁹⁻¹¹ have shown that tiagabine monotherapy may improve anxiety symptoms and sleep quality in patients with generalized anxiety disorder and posttrau-

matic stress disorder (PTSD). Augmentation with tiagabine also improves anxiety symptoms in patients with treatment-refractory anxiety disorders,¹²⁻¹⁴ and preliminary data are encouraging in patients with PTSD and comorbid disorders, anxiety and comorbid depression, and panic disorder with or without agoraphobia.¹⁵⁻¹⁷

Selective GABA-T inhibitors. Vigabatrin is an anticonvulsant that robustly increases brain GABA levels by irreversibly inhibiting GABA-T, the enzyme responsible for the degradation of GABA.¹⁸ Preliminary results suggest that vigabatrin may have anxiolytic activity in humans, given that 7-day vigabatrin treatment produced a marked reduction in cholecystokinin-tetrapeptide-induced panic in healthy volunteers.¹⁹ Drug toxicity causing the development of visual field defects in some patients taking vigabatrin is expected to preclude availability of the drug in the United States, but develop-

BRAINSTORMS is a monthly section of The Journal of Clinical Psychiatry aimed at providing updates of novel concepts emerging from the neurosciences that have relevance to the practicing psychiatrist.

From the Neuroscience Education Institute in Carlsbad, Calif., and the Department of Psychiatry at the University of California San Diego.

Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, BRAINSTORMS, Neuroscience Education Institute, 5857 Owens Street, Ste. 102, Carlsbad, CA 92009.

Take-Home Points

- ◆ GABA is the major inhibitory neurotransmitter in the central nervous system and plays a key regulatory role in neuroanatomic circuits that hypothetically mediate fear in anxiety disorders.
- ◆ Numerous anticonvulsants may enhance GABA neurotransmission via several different mechanisms, including selective inhibition of GABA reuptake, inhibition of GABA transaminase, and increased synthesis and release of GABA secondary to inhibition of voltage-gated ion channels.
- ◆ Anticonvulsants with robust GABA-enhancing actions may eventually prove to be effective anxiolytics.

ment of other GABA-T inhibitors that lack this toxicity may be warranted.

Indirect GABAergic Mechanisms

Many anticonvulsants are inhibitors of voltage-gated ion channels for calcium (Ca^{2+}) and/or sodium (Na^+).¹ Whether these indirect actions are also related to putative GABA-enhancing effects or any anxiolytic actions is unclear.

Valproate, carbamazepine, lamotrigine, and topiramate. These 4 anticonvulsants hypothetically have primary actions as modulators of voltage-gated Na^+ channels and may also possess GABAergic activity due to downstream consequences of blocking sodium channels.¹ However, a definitive association of their Na^+ channel blocking actions and any GABA activity remains to be proved, and these agents have only very limited data suggesting anxiolytic actions. Thus, valproate,²⁰ lamotrigine,²¹ and topiramate²² may possess some preliminary evidence of anxiolytic action in PTSD, and valproate²³ but not carbamazepine²⁴ may have some efficacy in panic disorder. The lack of more impressive anxiolytic efficacy data from these agents may be related to their lack of demonstrable robust actions on GABA.

REFERENCES

1. Stahl SM. Psychopharmacology of anticonvulsants: do all anticonvulsants have the same mechanism of action? [BRAINSTORMS] *J Clin Psychiatry* 2004;59:149–150
2. Stahl SM. Independent actions on fear circuits may lead to therapeutic synergy for anxiety when combining serotonergic and GABAergic agents [BRAINSTORMS]. *J Clin Psychiatry* 2002; 63:854–855
3. Coplan JD, Lydiard RB. Brain circuits in panic disorder. *Biol Psychiatry* 1998;44:1264–1276
4. Stutzmann GE, LeDoux JE. GABAergic antagonists block the inhibitory effects of serotonin in the lateral amygdala: a mechanism for modulation of sensory inputs to fear conditioning. *J Neurosci* 1999;19:RC8
5. Stahl SM. Essential psychopharmacology of depression and bipolar disorder. 2nd ed. New York, NY: Cambridge University Press; 2002
6. Borden LA, Murali Dhar TG, Smith KE, et al. Tiagabine, SK&F 89976-A, CI-966, and NNC-711 are selective for the cloned GABA transporter GAT-1. *Eur J Pharmacol* 1994;269: 219–224
7. Borden LA. GABA transporter heterogeneity: pharmacology and cellular localization. *Neurochem Int* 1996;29:335–356
8. Minelli A, Brecha NC, Karschin C, et al. GAT-1, a high-affinity GABA plasma membrane transporter, is localized to neurons and astroglia in the cerebral cortex. *J Neurosci* 1995;15:7734–7746
9. Connor K, Weisler R, Zhang W, et al. Tiagabine for posttraumatic stress disorder. In: New Research Abstracts of the 156th Annual Meeting of the American Psychiatric Association; May 22, 2003; San Francisco, Calif. Abstract NR822:307
10. Papp L, Ray S. Tiagabine treatment of generalized anxiety disorder. In: New Research Abstracts of the 156th Annual Meeting of the American Psychiatric Association; May 22, 2003; San Francisco, Calif. Abstract NR818:306
11. Rosenthal M. Tiagabine for the treatment of generalized anxiety disorder: a randomized, open-label, clinical trial with paroxetine as a positive control. *J Clin Psychiatry* 2003;64: 1245–1249
12. Crane D. Tiagabine for the treatment of anxiety. *Depress Anxiety* 2003;18:51–52
13. Schwartz TL. The use of tiagabine augmentation for treatment-resistant anxiety disorders: a case series. *Psychopharmacol Bull* 2002;36: 53–57
14. Schwartz TL, Nouman A, Husain J, et al. Tiagabine as augmentation therapy for anxiety. In: New Research Abstracts of the 156th Annual Meeting of the American Psychiatric Association; May 19, 2003; San Francisco, Calif. Abstract NR258:96–97
15. Taylor FB III. Tiagabine for the treatment of posttraumatic stress disorder. In: New Research Abstracts of the 156th Annual Meeting of the American Psychiatric Association; May 22, 2003; San Francisco, Calif. Abstract NR772:289
16. Carpenter L, Tyrka A, Schecter J, et al. Tiagabine for major depression with anxiety. In: New Research Abstracts of the 156th Annual Meeting of the American Psychiatric Association; May 20, 2003; San Francisco, Calif. Abstract NR501:187
17. Zwanzger P, Baghai TC, Schüle C, et al. Tiagabine improves panic and agoraphobia in panic disorder patients [letter]. *J Clin Psychiatry* 2001;62:656–657
18. Sills GJ. Pre-clinical studies with the GABAergic compounds vigabatrin and tiagabine. *Epilepsia* 2003;5:51–56
19. Zwanzger P, Baghai TC, Schuele C, et al. Vigabatrin decreases cholecystokinin-tetrapeptide (CCK-4) induced panic in healthy volunteers. *Neuropsychopharmacology* 2001;25:699–703
20. Baetz M, Bowen RC. Efficacy of divalproex sodium in patients with panic disorder and mood instability who have not responded to conventional therapy. *Can J Psychiatry Rev Canadienne de Psychiatrie* 1998;43:73–77
21. Hertzberg MA, Butterfield MI, Feldman ME, et al. A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. *Biol Psychiatry* 1999;45:1226–1229
22. Berlant J, van Kammen DP. Open-label topiramate as primary or adjunctive therapy in chronic civilian posttraumatic stress disorder: a preliminary report. *J Clin Psychiatry* 2002;63:15–20
23. Clark RD, Canive JM, Calais LA, et al. Divalproex in posttraumatic stress disorder: an open-label clinical trial. *J Trauma Stress* 1999;12:395–401
24. Uhde TW, Stein MB, Post RM. Lack of efficacy of carbamazepine in the treatment of panic disorder. *Am J Psychiatry* 1988;145: 1104–1109