
Mechanisms for enhancing GABAergic activity and their potential therapeutic implications

A supplement to the CME program: The Role of GABA in the Pathogenesis and Treatment of Anxiety and Other Neuropsychiatric Disorders

Mechanisms for enhancing GABAergic activity and their potential therapeutic implications

A supplement to the CME program: The Role of GABA in the Pathogenesis and Treatment of Anxiety and Other Neuropsychiatric Disorders

GABA: the principal inhibitory neurotransmitter

The principal inhibitory neurotransmitter in the central nervous system (CNS) is γ -aminobutyric acid (GABA), which is widely distributed throughout the brain. Approximately 60-75% of all synapses in the CNS are GABAergic.¹ GABA binds to at least three receptors, each of which has a different physiological function. GABA-A receptors mediate fast inhibitory synaptic transmissions; they regulate neuronal excitability and rapid changes in mood. Thus, the seizure threshold, anxiety, panic, and response to stress (i.e., the “fight or flight” response) are regulated by GABA-A receptors.^{2,3} In addition to binding sites for GABA, GABA-A receptors have binding sites for ben-

zodiazepines, ethanol, barbiturates, and neurosteroids. GABA-B receptors mediate slow inhibitory transmissions, which appear to be important in memory, mood, and pain.⁴ GABA-C receptors have been identified, but their physiologic role has not yet been described.

GABA and neurologic disorders

A decrease in GABAergic neurotransmission is involved in the pathogenesis of several neurologic disorders, including some forms of epilepsy, chronic pain, and anxiety and other mood disorders.^{2,5,6} For example, a positron emission tomography (PET) study showed that patients with panic disorder have decreased GABA-A receptor binding.² Low plasma GABA may be characteristic of a subgroup of

patients with mood disorders.^{6,7} Similarly, research conducted at Yale showed that unipolar patients have GABA levels approximately 50% lower than those of normal controls.⁸ Drugs that enhance GABA activity, such as benzodiazepines, valproate, and phenobarbital, are often effective in the treatment of these disorders.³ GABAergic mechanisms appear to be important in both anxiolytic and sedative medications.^{9,10} Not surprisingly, GABAergic drugs that have anticonvulsant effects may also have clinically useful mood-stabilizing or antimanic effects (e.g., valproate).

Mechanisms for enhancing GABA activity

There are at least five known mechanisms by which drugs can increase the availability and activity of GABA. (1) **Stimulation of GABA-A receptors.** GABA-A receptors are coupled to chloride ion channels; activation of the GABA-A receptor induces increased inward chloride ion flux, resulting in membrane hyperpolarization and neuronal inhibition.¹¹ This can be effected by increasing either the frequency (benzodiazepines) or the duration (phenobarbital) of opening of the chloride ion channels.⁶ (2) **Increasing the release of GABA from glial cells.** This is believed to be the mode of action of gabapentin, which is structurally similar to GABA but does not interact with GABA-A receptors. (3) **Inhibition of GABA transaminase,** (the enzyme that metabolizes GABA). Vigabatrin (not approved for use in the U.S.) works primarily and valproate works in part through this mechanism. (4) **Increases in GABA**

synthesis and release. This is also one of the multiple GABAergic mechanisms of valproate. (5) **Inhibition of reuptake of GABA by neurons and glial cells.** Tiagabine prevents GABA reuptake by inhibiting the action of GAT-1 GABA transporters. Table 1 summarizes the mechanisms of potent GABAergic drugs that are currently used for neuropsychiatric disorders or have shown a potential for such use. The subsequent discussion of the potential clinical uses of these agents omits phenobarbital (because of its serious adverse cognitive effects) and vigabatrin (because it is not approved for U.S. use).

The benzodiazepines

The benzodiazepines act primarily through direct agonism at GABA-A receptors by increasing the frequency, but not the duration of opening of GABA-activated chloride channels.¹² These agents have potent anxiolytic and sedative effects as well as hypnotic, muscle relaxing, and anticonvulsant effects. They may also have modest antimanic and antidepressant effects.¹³⁻¹⁵

Benzodiazepines continue to be among the most widely prescribed psychotropic drugs. Their use for the acute treatment of generalized anxiety disorder (GAD) was described by Schweizer as "one of the early successes in the field of psychopharmacology."¹⁶ Benzodiazepine prescriptions peaked in 1974 and have generally been declining ever since, in response to a growing awareness about their potential for abuse. As a percentage of total prescriptions

Table 1. Mechanisms of drugs with strong GABAergic activity⁶

Drug	GABAergic mechanism(s)	GABAergic potency	Comments
Benzodiazepines	Direct agonism at GABA-A receptors	Strong	Increases frequency of GABA-A chloride channel opening
Phenobarbital	Direct agonism at GABA-A receptors	Strong	Prolongs duration of opening of GABA-A chloride channel
Gabapentin	Increases GABA release from glial cells	Strong	Increases total cerebral GABA
Vigabatrin (not approved in U.S.)	Inhibits GABA transaminase	Strong	Increases total cerebral GABA
Valproate	Multiple GABAergic mechanisms, including GABA transaminase inhibition and increases in GABA synthesis and release	Strong	Increases total cerebral GABA
Tiagabine	Selective inhibition of GABA reuptake by neurons and glial cells	Strong	GABA release remains under physiologic control; no increase in total CNS GABA

for anxiety, benzodiazepine usage has been declining. Nevertheless, the absolute number of benzodiazepine prescriptions, including prescriptions for anxiety, has increased in recent years.¹⁶ The significance of this trend is not known.

Benzodiazepines continue to be among the most widely prescribed psychotropic drugs.

The usefulness of benzodiazepines in long-term therapy is limited by concerns over tolerance, abuse, dependence, and withdrawal symptoms. For these reasons, they no longer represent first-line therapy for long-term treatment of GAD,¹⁷⁻¹⁹ but are still used for acute anxiety and as adjunctive treatment for chronic anxiety disorders. Depression may emerge with long-term treatment, especially in patients with a history of affective disorder.¹⁷ Patients who receive long-term treatment (six months or longer) with benzodiazepines also have a high relapse rate if the drug is discontinued¹⁹ and there have been several reports of loss of anxiolytic effect over time.^{20,21} Particular care should be taken in elderly patients, who may be more susceptible to the cognitive adverse effects of these agents. In addition, because the elderly metabolize benzodiazepines more slowly, they may accumulate toxic levels if the long-acting formulations are used.²²

Patients who abuse street drugs and/or alcohol are at highest risk for benzodiazepine abuse.²³ Physicians should be

concerned about possible dependence if patients take more than 30 mg/day of diazepam (or its equivalent) for longer than four months.²² Patients who have taken a benzodiazepine for a month or longer should have the drug tapered slowly; sudden discontinuation may lead to a withdrawal syndrome similar to that seen with alcohol. Withdrawal symptoms may include anxiety, irritability, delirium, and/or psychosis.²⁴ In general, the adverse effects of benzodiazepines include sedation, ataxia, slurred speech, difficulty with memory and cognition, and motor impairment.

Tiagabine

One of the more promising new approaches to enhancing GABAergic activity is the inhibition of GABA reuptake. The inhibition of GABA reuptake preferentially accentuates the pattern of endogenous GABA release in the brain without affecting the amount of total available synaptic GABA, which remains under physiologic control.²⁵

The inhibition of GABA reuptake preferentially accentuates the pattern of endogenous GABA release without affecting the amount of available synaptic GABA.

The only currently available selective GABA-reuptake inhibitor (SGRI) is tiagabine, which is a nipecotic acid derivative with a lipophilic anchor covalently attached to the amino nitro-

gen. Tiagabine interacts preferentially with the GAT-1 GABA transporter, which is most important in the cortex, cerebellum, and hippocampus.^{3,4}

Tiagabine is currently approved for the treatment of epilepsy. Meldrum and Chapman make a strong case for investigating the drug's potential in a variety of additional neuropsychiatric disorders related to GABAergic mechanisms.⁴ In addition to expanded epilepsy-related indications, such as *status epilepticus* and infantile spasms, tiagabine is being investigated for the pain of postherpetic neuralgia and diabetic neuropathy,²⁶ migraine,²⁷ sleep disorders,²⁸ (including the disturbed sleep architecture of post-traumatic stress disorder),¹⁶ movement disorders (including tardive dyskinesia),^{29,30} bipolar disorder,³¹ anxiety disorders,^{32,33} and neuroprotection against ischemia-induced cell loss.³⁴ Anxiety disorders are perhaps the most promising of the potential new uses for tiagabine. In obsessive-compulsive disorders, for example, tiagabine has shown efficacy both in normalizing sleep disturbances and in treating avoidance/numbing symptoms (detachment and avoidance of people or places related to the trauma).¹⁶ In addition, because tiagabine does not compete with ethanol at GABA-A receptors, it may prove to be preferable to benzodiazepines in the treatment of alcohol withdrawal.³⁵ Tiagabine is generally well tolerated; adverse effects include

dizziness, fatigue, somnolence, tremor, cognitive slowing, nausea, and abdominal pain.

Gabapentin

Gabapentin increases GABA through a different mechanism than that of tiagabine; it appears to act 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 interact with GABA receptors and does not inhibit either GABA reuptake or metabolism.⁶ Like tiagabine, gabapentin shows potential for the treatment of a variety of psychiatric disorders, including bipolar disorder,³⁶ intermittent explosive disorder,³⁷ pain syndromes,³⁸ and anxiety.³⁹⁻⁴³ Gabapentin has also been shown to be beneficial in preclinical and clinical studies of patients with panic disorder,⁴⁰ social phobia,³⁹ obsessive-compulsive disorder,⁴³ and post-traumatic stress disorder.⁴² In case reports, gabapentin has also showed promising results in patients with post-traumatic stress disorder⁴² and refractory panic disorder, obsessive-compulsive disorder, and generalized anxiety disorder.⁴⁴ Gabapentin is generally well tolerated; adverse effects include somnolence, dizziness, ataxia, fatigue, and weight gain.⁴⁵ Both gabapentin and tiagabine have a low potential for clinically important drug interactions.

The structure of gabapentin is similar to that of GABA, but the agent does not interact with GABA receptors and does not inhibit either GABA reuptake or metabolism.

Valproate

Valproate is notable for having multiple biochemical effects. Its GABAergic mechanisms include the inhibition of GABA metabolism and increases in GABA synthesis and release; these result in an increase in total brain, CSF, and plasma GABA.⁶

Valproate has multiple biochemical effects, including the inhibition of GABA metabolism and increases in GABA synthesis and release.

Valproate was approved as an anticonvulsant in 1978 and has become established as a broad-spectrum antiepilepsy drug that is not contraindicated for any seizure type.⁴⁶ Valproate has since been approved for the treatment of mania in bipolar illness and for the prophylaxis of migraine. An intravenous form of the drug has been shown to have potential in the treatment of acute migraine and *status epilepticus*. The results of a recently completed study suggest that valproate may be effective in impulsive-aggressive or agitated patients.⁴⁷ The drug may also have utility in paroxysmal pain syndromes, panic disorder, and obsessive-compulsive disorder. Preclinical studies suggest that valproate has anxiolytic and antidepressant effects.⁶ These observations are consistent with the sedating, mood-stabilizing profile of the drug. Compared with tiagabine and gabapentin, the usefulness of valproate is limited somewhat by its adverse effects, which

include GI upset, weight gain, tremor, hair loss, and teratogenic effects. It should be noted that some of these effects appear to be dose-related and valproate is generally used at relatively low doses for non-epilepsy neuropsychiatric disorders.⁴⁸

Summary

There have been a number of research initiatives investigating alternatives to benzodiazepines in the treatment of neuropsychiatric disorders characterized by a reduction in GABAergic activity. Most of these initiatives have produced compounds of limited therapeutic utility because of side effects related to generalized, possibly non-physiological, stimulation of GABA receptors or the development of drug tolerance. For these reasons, alternatives to direct GABA-receptor stimulation appeared to offer promising therapeutic approaches. Valproate has already become established as a broad-spectrum anticonvulsant, a major mood stabilizer, and an effective prophylactic agent for migraine. It is likely to prove useful in a variety of other neuropsychiatric disorders. Where tiagabine and gabapentin may prove superior to valproate is in the areas of safety, tolerability, and absence of drug interactions. Tiagabine and gabapentin have highly specific ranges of activity and are well tolerated at efficacious dose ranges. The important role of GABA in both normal and abnormal neurological function suggests that these agents may have a variety of future therapeutic applications.



References:

1. Schwartz, RD. The GABA_A receptor-gated ion channel: Biochemical and pharmacological studies of structure and function. *Biochem Pharmacol.* 1988;37:3369.
 2. Neilson EB, Suzdak PD, Andersen KE, et al. Characterization of tiagabine (NO-328), a new potent and selective GABA uptake inhibitor. *Eur J Pharmacol.* 1991;257-266.
 3. Borden LA, Murali Dhar TG, Smith KE, et al. Tiagabine, SK&F 89976-A, CI-996, and NNC-711 are selective for the cloned GABA transporter GAT-1. *Eur J Pharmacol.* 1994;219-224.
 4. Meldrum BS, Chapman AG. Basic mechanisms of Gabitril (tiagabine) and future potential developments. *Epilepsia.* 1999;40(Suppl 9):S2-S6.
 5. Mengel H. Tiagabine. *Epilepsia.* 1994;35(Suppl 5):S81-S84.
 6. Ketter TA, Post RM, Theodore WH. Positive and negative psychiatric effects of antiepileptic drugs in patients with seizure disorders. *Neurology.* 1999; 53(Suppl 2):S53-S67.
 7. Malizia AL, Cunningham VJ, Bell CJ, et al. Decreased brain GABA(A)-benzodiazepine receptor binding in panic disorder: preliminary results from a quantitative PET study. *Arch Gen Psychiatry.* 1998;55:715-720.
 8. Petty F. GABA and mood disorders: a brief review and hypothesis. *J Affect Disord.* 1995;34:275-281.
 9. Personal communication, Bruce Lydiard, M.D.
 10. Salzman C, Miyawaki EK, le Bars P, et al. Neurobiologic basis of anxiety and its treatment. *Harv Rev Psychiatry.* 1993;1:197-206.
 11. Graham D, Besnard F, Faure C, et al. GABA_A receptor subtype diversity: implications for new generation hypnotic drug discovery. *Sleep.* 1996; 19:S43-S54.
 12. Tunnickliff G, Raess BU. GABA neurotransmitter activity in human epileptogenic brain. In: Tunnickliff G, Raess BU, eds. *GABA mechanisms in epilepsy.* New York: Wiley-Liss, 1991:105-120.
 13. Twyman RE, Rogers CJ, Macdonald RL. Differential regulation of gamma-aminobutyric acid receptor channels by diazepam and phenobarbital. *Ann Neurol.* 1989;2:213-220.
 14. Bradwejn J, Shriqui C, Koszycki D, et al. Double-blind comparison of the effects of clonazepam and lorazepam in acute mania. *J Clin Psychopharmacol.* 1990;10:403-408.
 15. Rickels K, Chung HR, Csanalosi IB, et al. Alprazolam, diazepam, imipramine, and placebo in outpatients with major depression. *Arch Gen Psychiatry.* 1987;44:862-866.
 16. Schweizer E. Generalized anxiety disorder. Longitudinal course and pharmacologic treatment. *Psychiatr Clin North Am.* 1995;18(4):843-857.
 17. Data on file, Cephalon, Inc.
 18. Lydiard RB. An overview of generalized anxiety disorder: disease state — appropriate therapy. *Clin Ther.* 2000;22(Suppl A):A3-A24.
-

-
-
19. Hales RE, Hilty DA, Wise MG. A treatment algorithm for the management of anxiety in primary care practice. *J Clin Psychiatry*. 1997;58(Suppl 3):76-80.
 20. Ballenger JC. Current treatments of the anxiety disorders in adults. *Biol Psychiatry*. 1999;46:1579-1594.
 21. Mahe V, Balogh A. Long-term pharmacological treatment of generalized anxiety disorder. *Int Clin Psychopharmacol*. 2000;15:99-105.
 22. Lader M. Anxiolytic drugs: dependence, addiction, and abuse. *Eur Neuropsychopharmacol*. 1994;4:85-91.
 23. Enkelman R. Alprazolam versus buspirone in the treatment of outpatients with generalized anxiety disorder. *Psychopharmacology*. 1991;105:428-432.
 24. Berkow R (ed.) *The Merck Manual, 16th ed.* Rahway, NJ: Merck Research Laboratories, 1992, 1631-1635.
 25. Hauser P, Devinsky O, De Bellis M, et al. Benzodiazepine withdrawal delirium with catatonic features. Occurrence in patients with partial seizure disorders. *Arch Neurol*. 1989;46:696-699.
 26. Suzdak PD, Jansen JA. A review of the preclinical pharmacology of tiagabine: a potent and selective anticonvulsant GABA uptake inhibitor. *Epilepsia*. 1995;36:612-626.
 27. Sheardown MJ, Weis JU, Knutsen LJ. Analgesic effect of the GABA uptake inhibitor NO-328 (N-(4,4-D1 (3-methyl-2-thienyl) but-3-1-yl) nipecotic acid). *Soc Neurosci Abstr*. 1989;15:602.
 28. Freitag FG, Diamond S, Diamond ML, et al. An open use trial of tiagabine in migraine. *Headache Q*. 2000;11:133-134.
 29. Lancel M, Faulhaber J, Deisz RA. Effect of the GABA uptake inhibitor tiagabine on sleep and EEG power spectra in the rat. *Br J Pharmacol*. 1998;123:1471-1477.
 30. Gao XM, Kakigi T, Friedman MB, et al. Tiagabine inhibits haloperidol-induced oral dyskinesias in rats. *J Neurol Transm*. 1994;95:63-69.
 31. Holden KR, Titus MO. The effect of tiagabine on spasticity in children with intractable epilepsy: a pilot study. *Pediatr Neurol*. 1999;21:728-730.
 32. Kaufman KR. Adjunctive tiagabine treatment of psychiatric disorders: three cases. *Ann Clin Psychiatry*. 1998;10:181-184.
 33. Dodrill CB, Arnett JL, Sommerville KW. Cognitive and quality of life effects of differing dosages of tiagabine in epilepsy. *Neurology*. 1997;48:1025-1031.
 34. Neilson EB. Anxiolytic effect of NO-328, a GABA-uptake inhibitor. *Psychopharmacology*. 1988;96:S42.
 35. Johansen FF, Diemer NH. Enhancement of GABA neurotransmission after cerebral ischemia in the rat reduces loss of hippocampal CA1 pyramidal cells. *Acta Neurol Scand*. 1991;84:1-5.
 36. Kastberg H, Jansen JA, Cole G, et al. Tiagabine: absence of kinetic or dynamic interactions with ethanol. *Drug Metab and Drug Interact*. 1998;14(4):259-273.
-

-
-
37. Letterman L, Markowitz JS. Gabapentin: a review of published experience in the treatment of bipolar disorder and other psychiatric conditions. *Pharmacotherapy*. 1999; 19(5):565-572.
 38. Ryback R, Ryback L. Gabapentin for behavioral dyscontrol. *Am J Psychiatry*. 1995;152:1399.
 39. Mellick GA, Mellick LB, Mellick JD. Gabapentin in the management of reflex sympathetic dystrophy. *J Pain Symptom Manage*. 1995;10:265-266.
 40. Pande AC, Davidson JRT, Jefferson JW, Greist JH et al. Treatment of social phobia with gabapentin: a placebo-controlled study. *J Clin Psychopharmacol*. 1999;19(4):341-348.
 41. Crockatt JG, Greiner M, Clift LL, et al. Treatment of panic disorder with gabapentin. Proc 38th Ann Meet New Clin Drug Evaluation Unit Prog, 1998 (abstr);154.
 42. de-Paris F, Busnello JV, Vianna MR, et al. The anticonvulsant gabapentin possesses anxiolytic but not amnesic effects in rats. *Behav Pharmacol*. 2000; 11(2):169-173.
 43. Brannon N, Labbate L, Huber M. Gabapentin treatment for posttraumatic stress disorder. *Can J Psychiatry*. 2000; 45(1):84.
 44. Chouinard G, Beauclair L, Bélanger M-C. Gabapentin: long-term antianxiety and hypnotic effects in psychiatric patients with comorbid anxiety-related disorders. *Can J Psychiatry*. 1998; 43(3):305.
 45. Pollack MH, Mathews J, Scott ER. Gabapentin as a potential treatment for anxiety disorders. *Am J Psychiatry*. 1998; 155(7):992.
 46. Neurontin® package insert, Parke-Davis.
 47. Richens A, Perucca E. Clinical pharmacology and medical treatment. In: Laidlaw J, Richens A, Chadwick D (eds). *A Textbook of Epilepsy*. Edinburgh: Churchill Livingstone, 1993, pp 495-559.
 48. Data on file, Abbott Laboratories.
-