

GABA

THE ROLE OF GABA IN THE PATHOGENESIS AND TREATMENT OF ANXIETY AND OTHER NEUROPSYCHIATRIC DISORDERS



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This educational activity was planned in accordance with Accreditation Council for Continuing Medical Education (ACCME) Essentials and Standards.

Statement of Educational Need

This activity is designed to respond to the needs of psychiatrists and other physicians who treat patients with anxiety and other neuropsychiatric disorders by updating their knowledge of GABA-enhancing agents, which are emerging as potentially important agents in the treatment of these disorders.

Educational Objectives

After reading this monograph, listening to the audio CD, and completing the post-test, the participant should be able to:

- Describe the historical background of the current treatment of anxiety disorders
- Describe the role of benzodiazepines in the treatment of anxiety disorders
- Better understand the role of GABA in the central nervous system
- Understand the rationale for using GABAergic drugs to treat anxiety and other neuropsychiatric disorders
- Understand the potential clinical utility of the newer, specific GABA-enhancing agents

Statement of Educational Method

The educational information is presented in an 8-page monograph and the accompanying 30-minute audio CD.

Statement of Evaluation Instrument

A 12-question multiple-choice post-test is used as the evaluation instrument. An activity evaluation questionnaire will be completed by each participant.

Statement of Intended, or Target, Audience

This activity is intended for, but not limited to: psychiatrists and other physicians who care for patients with anxiety and other neuropsychiatric disorders.

Statement of Unlabeled Usage

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Instructions

To earn 1 hour of category 1 credit, listen to the accompanying audio CD and read the material in this monograph carefully. Complete the activity evaluation and answer the post-test questions on the accompanying questionnaire. Send the questionnaire in the enclosed envelope to: OCME Registrar, P.O. Box 980048, Richmond, VA 23298-0048. ATTN: GABA PROGRAM. Your credit certificate will be returned. Participation is confidential. Estimated program completion time: 1 hour.

Course Number: END 00 02 101 02

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Answer key to CME Post-Test

1. B 2. E 3. A 4. C 5. E 6. E 7. B 8. A 9. A 10. A 11. A 12. E

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GABA

THE ROLE OF GABA IN THE PATHOGENESIS AND TREATMENT OF ANXIETY AND OTHER NEUROPSYCHIATRIC DISORDERS

This monograph is a companion piece to a 30-minute audio CD that contains an edited version of a roundtable discussion that took place in New York City on October 26, 2001.

The treatment of anxiety disorders: a brief overview

The treatment of anxiety disorders has evolved considerably in the past 50 years. There was early use of alcohol and barbiturates to treat anxiety, but both were associated with significant problems. The situation changed in the 1950s and 60s, when the benzodiazepines were developed as effective anxiolytics; these agents are still commonly used today. The benzodiazepines work quickly and are generally well tolerated. Their primary disadvantages are initial sedation, ataxia, incoordination, impaired memory, and cognition and, after chronic administration, physiological dependence and the potential for withdrawal symptoms upon discontinuation. Some of these adverse effects occur more frequently in older patients. The current faculty has also observed occasional undesirable behavioral disinhibition in pediatric patients and in patients with a comorbid Cluster B Personality Disorder (Antisocial, Borderline, Histrionic, or Narcissistic). People with a history of or propensity for alcohol or drug abuse are at risk for abusing benzodiazepines. Due to their lack of significant antidepressant effects, these drugs are also not optimal for long-term monotherapy treatment of patients with generalized anxiety disorder (GAD) or other anxiety disorders. As a result, there has been a continued search for new anxiolytic agents. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) proved to be effective in the treatment of some anxiety disorders, but enthusiasm for their use is limited by side effects, especially during long term therapy. Over the past several years, the selective serotonin reuptake inhibitors (SSRIs) have become first-line monotherapy for the anxiety disorders, because they are generally better tolerated and have a broader spectrum of efficacy than older agents. Benzodiazepines are now recommended as adjunctive treatment for anxiety disorders, and as monotherapy for those intolerant of or unresponsive to other agents. Venlafaxine, a serotonin and

norepinephrine reuptake inhibitor (SNRI), and paroxetine, an SSRI, were recently approved for the treatment of GAD and there is preliminary evidence that, like the SSRIs, the efficacy of venlafaxine may extend to other anxiety disorders.¹ These newer agents represent a significant advance, but side effects in some patients, including weight gain, sexual dysfunction, and increases in anxiety upon initiation of treatment remain troublesome. With the currently available agents, the majority of patients with anxiety disorders can be successfully treated. Nevertheless, as many as one-third of patients in controlled studies are unresponsive to any one of these medications.² Thus, there remains a need for new safe and effective anxiolytic agents.

The role of GABA in psychiatric disorders

The brain's principal inhibitory neurotransmitter, γ -aminobutyric acid (GABA), along with serotonin and norepinephrine, is one of several neurotransmitters that appear to be involved in the pathogenesis of anxiety and mood disorders.

There are two principal subtypes of postsynaptic GABA receptor complexes, the GABA-A and GABA-B receptor complexes. Activation of the GABA-B receptor by GABA causes neuronal membrane hyperpolarization and a resultant inhibition of neurotransmitter release. In addition to binding sites for GABA, the GABA-A receptor has binding sites for benzodiazepines, barbiturates, and neurosteroids. GABA-A receptors are coupled to chloride ion channels; activation of the receptor induces increased inward chloride ion flux, resulting in membrane hyperpolarization and neuronal inhibition.³

After release into the synapse, free GABA that does not bind to either the GABA-A or GABA-B receptor complexes can be taken up by neurons and glial cells. Four different membrane transporter proteins, known as GAT-1, GAT-2, GAT-3, and BGT-1, which differ in their distribution in the CNS, are believed to mediate the uptake of synaptic GABA into neurons and glial cells.⁴

As many as one-third of patients in controlled studies of anxiety are unresponsive to currently used agents.



The GABA-A receptor subtype regulates neuronal excitability and rapid changes in fear arousal, such as anxiety, panic, and the acute stress response. Drugs that stimulate GABA-A receptors, such as the benzodiazepines and barbiturates, have anxiolytic and anti-seizure effects via GABA-A-mediated reduction of neuronal excitability, which effectively raises the seizure threshold.³ In support of the anticonvulsant and anxiolytic effects of the GABA-A receptor are findings that GABA-A antagonists produce convulsions in animals⁵ and the demonstration that there is decreased GABA-A receptor binding in a positron emission tomography (PET) study of patients with panic disorder.⁶ Low plasma GABA has been reported in some depressed patients and, in fact, may be a useful trait marker for mood disorders.^{7,8}

GABA enhancement in psychiatric treatment: different mechanisms for different patients?

Enhancement of GABA function can theoretically be effected through several mechanisms, including direct receptor agonism (benzodiazepines), inhibition of the extraneuronal enzymatic breakdown of GABA (vigabatrin), modulation of GABA-coupled ion channels (topiramate), and inhibition of the reuptake of synaptic GABA by neurons and glial cells (tiagabine). In a review article by one of the program faculty (Terence Ketter) and colleagues, two categories of anticonvulsant drugs were identified on the basis of their clinical psychotropic profiles.⁷ These categories provide a theoretical model for the potential usefulness of GABA-enhancing agents in the treatment of anxiety and other neuropsychiatric disorders. Two important mechanisms of anticonvulsant drugs are: (1) enhancement of GABA inhibitory action and (2) attenuation of glutamatergic excitatory action. Drugs that enhance GABA receptor-mediated inhibitory neuro-

transmission include benzodiazepines, tiagabine, valproate, vigabatrin, and gabapentin; all of these agents have “sedating” clinical profiles. In addition to anxiolytic effects, they can also cause fatigue and impaired cognition. Valproate has known anti-manic properties, while others in this group show promise in this therapeutic area. Agents that attenuate glutamatergic excitatory neurotransmission, such as felbamate or lamotrigine, have “activating” clinical profiles; they tend to improve alertness and, in some patients, may have anxiogenic and possibly antidepressant effects. Table 1 shows the GABAergic and antiglutamatergic actions of several drugs with distinctive GABA-enhancing activity: tiagabine, gabapentin, vigabatrin, and valproate. Ketter et al note that patients with seizure disorders often exhibit a variety of mood and anxiety symptoms. The authors suggested that it may be clinically useful to select a drug with a side effect profile that may actually benefit the patient. For example, a “sedating” GABA-enhancing agent may be better tolerated or even beneficial in a patient who manifests seizure-related symptoms of chronic anxiety.⁷

The faculty concurred that GABA-enhancing agents have shown early evidence of efficacy in several neuropsychiatric disorders. The benzodiazepines, valproate, carbamazepine, tiagabine, gabapentin and vigabatrin, all have GABAergic mechanisms, and produce anxiolytic effects in preclinical models of anxiety, and varying degrees of clinically relevant anxiolytic effects.^{7,9-15} Several GABAergic agents (tiagabine, topiramate, valproate, and carbamazepine) have shown evidence of efficacy in post-traumatic stress disorder (PTSD). One of the cardinal features of PTSD is nocturnal awakening associated with vivid and very frightening nightmares. Two of the faculty (EK and TAK) have found that tiagabine normalizes sleep architecture or sleep disturbance in many patients with PTSD and, in addition, reduced arousal, agitation, anxiety, and the frequency of flashbacks. EK made a clinical distinction between PTSD

TABLE 1.

Psychotropic profiles of selected GABAergic drugs (adapted from Ketter et al)⁷

Drug	GABAergic potency	GABAergic effects	Antiglutamatergic potency	Antiglutamatergic effects	Profile
Tiagabine	Strong	GABA- reuptake inhibition	Absent	None	Sedating
Gabapentin	Strong	↑ glial GABA release ↑ cerebral GABA	Modest	↓ glutamate synthesis	Sedating
Vigabatrin	Strong	↑ GABA - transaminase inhibition ↑ cerebral GABA	Absent	None	Sedating
Valproate	Strong	↑ GABA _B -R ↓ GABA T/O ↑ cerebral GABA/GAD ↑ synthesis /release, SSADH inhibition, GABA-transaminase inhibition	Modest	↓ cerebral aspartate	Sedating
Carbamazepine	Modest	↑ GABA _B -R ↓ GABA T/O	Modest	↓ glutamate release	Partially sedating

patients who develop PTSD following a single episode of trauma, such as victims of violent crimes, and those who experience repetitive trauma, such as incest victims or combat veterans. Patients who experience a single traumatic episode appear to respond to SSRIs, while those with repetitive trauma tend not to respond well to SSRIs. The latter patients may benefit from treatment with GABAergic mood stabilizers. GABA-enhancing agents (carbamazepine, valproate, and vigabatrin) have also been shown to have activity in the behavioral despair model of depression¹⁶ and, in a recently completed study, valproate also appears to be effective in impulsive-aggressive or agitated patients.¹⁷

There are promising preliminary reports of the clinical utility of the GABA-enhancing agents gabapentin and tiagabine in the treatment of anxiety disorders. Gabapentin increases GABA primarily by enhancing release of GABA from glia.⁷ Although the structure of gabapentin is similar to that of GABA, it does not directly act on GABA receptors.⁷ Gabapentin has shown promise in neuropathic pain syndromes,¹⁸ and anxiety.^{19,23} It has also demonstrated potential usefulness for the treatment of bipolar disorder,²⁴ and intermittent explosive disorder.²⁵

In preclinical studies, gabapentin was shown to have anxiolytic effects similar to those of diazepam, but did not produce the memory-impairing effects of the latter drug.²¹ Gabapentin has also been shown to be beneficial in clinical studies of patients with panic disorder (PD),²⁰ social phobia (SP),¹⁸ obsessive-compulsive disorder (OCD),²³ and PTSD.²⁴ In a randomized, double-blind, placebo-controlled, parallel-group study, 69 patients with SP were randomly assigned to gabapentin or placebo for 14 weeks.¹⁹ A significant reduction ($p < 0.05$) in the symptoms of SP were seen in patients on gabapentin compared with placebo. The adverse events reported were consistent with the known side-effect profile of gabapentin.

Various case reports have appeared in which gabapentin has been reportedly useful in PTSD²² and refractory PD, OCD, and GAD.²⁶ One case report described 18 patients with a variety of serious psychiatric illnesses and comorbid anxiety disorders. Gabapentin was administered for up to 38 months.²⁵ Fifteen patients were treated for at least 12 months. The authors found that the anxiolytic effects of gabapentin were sustained over several months in most patients, with no evidence of tolerance or physical dependence after abrupt discontinuation. In these 18 patients, the most common adverse effects were drowsiness and dizziness during initiation of treatment. This is consistent with the literature, which indicates that gabapentin is generally well tolerated; the most common adverse effects include somnolence, dizziness, ataxia, fatigue, and weight gain.²⁷

Tiagabine potentiates CNS GABAergic function through its unique ability to inhibit GABA reuptake at the GAT-1 GABA transporter. Tiagabine is the only currently available selective GABA-reuptake inhibitor (SGRI). Tiagabine increases the amount of available extracellular GABA by up to 200%,²⁸ without perturbing normal physiologic control and without increasing total brain GABA. Some researchers have speculated that this unique mechanism of action may result in fewer adverse effects compared with other GABA-enhancing mechanisms.^{14,29}

Tiagabine has been investigated in open-label clinical studies of a variety of CNS disorders in which GABA may play a role, including migraine,³⁰ sleep disorders,³¹ postherpetic neuralgia, diabetic neuropathy,³² and tardive dyskinesia.³³ Preclinical studies also suggest potential usefulness in models of anxiety,^{14,34} spasticity,³⁵ and neuroprotection against ischemia-induced cell loss.³⁶ Tiagabine is generally well tolerated. Adverse effects include dizziness, fatigue, somnolence, tremor, cognitive slowing, nausea, and abdominal pain.

A conclusive demonstration of the clinical utility of tiagabine and other GAT-1 agents with GABAergic-potentiating properties which provide anxiolytic efficacy comparable to benzodiazepines but without the liability of physiological dependence or withdrawal would represent a significant advance in treatment of anxiety disorders.

Finally, case reports of patients with severe psychiatric disorders reported clear benefits from the addition of tiagabine.³⁷ In one patient, with schizoaffective disorder (manic type) tiagabine 8 mg daily was added as an adjunct to paroxetine and olanzapine. The adjunctive tiagabine successfully controlled paranoid features that appeared when the patient stopped taking lamotrigine. Two other patients in this case report and two patients in another report presented with severe, uncontrolled mania (mixed mania, with and without mood-congruent psychosis in the second report) were reported to benefit from the addition of tiagabine to ongoing mood stabilizer and antidepressant treatment. Tiagabine treatment was followed by complete remission of bipolar symptoms.^{33,38} One patient began to experience a manic episode at 3 mg/day tiagabine, but these symptoms resolved after the dose was raised to 4 mg/day.

A small-scale European trial evaluated the use of tiagabine in eight patients with acute mania.³⁹ The patients received higher initial doses (20 mg daily) and a more rapid titration than is typically employed (5 mg per day until limiting side effects occurred or 40 mg daily is reached). Three patients with moderate mania showed slight improvements, but none of the patients with severe mania showed a clear benefit. The authors suggested that tiagabine may not be effective as acute therapy for mania, but recommended further research on the drug as a mood stabilizer.

Three major mood stabilizers, lithium, carbamazepine, and valproate, share GABAergic effects (at GABA-B receptors and/or on GABA turnover) as one possible common mechanism for mood stabilization. The GABAergic activity of valproate is believed to be an important mechanism underlying both its anticonvulsive and mood-stabilizing effects.⁴⁰ Recent work conducted at Yale University (not yet published) suggests that unipolar patients have mean plasma GABA levels that are only 50% of those of normal volunteers; these rise to 100% with SSRI treatment. They also reported that depressed bipolar patients, in contrast to non-bipolar depressives, have near-normal GABA levels, which become significantly higher than normal as clinical improvement occurs.

Tiagabine
is the only
currently available
selective
GABA-reuptake
inhibitor
(SGRI).



TAK noted that two of the main mood stabilizers, lithium and carbamazepine, are ineffective as anxiolytics, suggesting that therapeutic actions unrelated to GABA are important for these agents. There is a relatively high prevalence of comorbid anxiety disorders in patients with bipolar disorder. Thus, agents that provide a combination of anxiolysis and mood stabilization would be clinically useful. While neither tiagabine nor gabapentin have yet been studied sufficiently to determine if either is effective as monotherapy in bipolar disorder, the faculty have found that they appear to be clinically useful as adjunctive agents, because of their anxiolytic effects (and, in the case of tiagabine, beneficial effects on sleep). Further study is needed to clarify whether these agents may be useful in controlling comorbid anxiety in patients with chronic psychosis. An additional advantage of both gabapentin and tiagabine as adjunctive agents is that they have a low propensity for drug interactions.

EK described his clinical experience using tiagabine to treat severe neuropsychiatric disorders. Based on published case reports, he became interested in using tiagabine to treat patients with bipolar disorder who had failed to respond to lithium, valproate, or carbamazepine, either alone, in combination with each other, or in combination with antipsychotic agents. Some of the patients with the most refractory illness had comorbid anxiety disorders, including some with PTSD resulting from chronic childhood sexual abuse.

In patients with epilepsy, the dose range of tiagabine is 32-56 mg per day, while patients with anxiety or bipolar disorder appear to benefit from doses of 4-12 mg day. Based on clinical reports and personal experience, the faculty recommend initiating tiagabine at a dose of 2-4 mg and increasing the dose by 2-4 mg weekly until efficacy is achieved or limit-

ing side effects occur. Low initial dosing and gradual upward titration may prevent significant adverse effects, such as those observed in the European trial described above.

The accompanying *Case Report* (Table 2) illustrates one of the more dramatic successes achieved with tiagabine in a particularly complex and refractory patient.

Summary and Conclusions

GABA appears to play a role in the pathogenesis of several neuropsychiatric disorders. Many of the traditional agents used to treat psychiatric disorders are known to act, at least in part, by enhancing GABA activity, while some of the newer agents may exert their therapeutic effects exclusively via GABAergic actions. Clinical experience with the newer agents, tiagabine and gabapentin, are preliminary but promising. Controlled studies of these agents are in the planning stages and will be useful in clarifying their potential clinical utility across a range of psychiatric disorders.

The cliché “If you find one thing wrong in the brain, you’ll find more than one” clearly applies to psychiatric disorders. Most individuals with psychiatric disorders suffer from one or more additional disorders at some point, and it is not surprising that many patients require multiple-drug therapy to control their symptoms. Unfortunately, many individuals with comorbid psychiatric disorders fail to respond optimally to treatment. It is likely that specific GABA-enhancing agents will play important roles as treatment for patients with anxiety disorders, with or without comorbidity, and as adjunctive therapy in patients with more complicated neuropsychiatric disorders.

TABLE 2.

Case Report: A patient with refractory PTSD, anxiety, and substance abuse

Ethan Kisch, M.D.

Ellen P. (not her real name) is a middle-aged woman with a history of post-traumatic stress disorder, dissociated identity disorder, severe anxiety symptoms, refractory auditory hallucinations, and substance abuse (cocaine and alcohol). Her sleep was often disturbed by nightmares, flashbacks, and hallucinations. She had proved very difficult to stabilize and has been hospitalized many times, ending up in an inpatient unit or outpatient program nearly every month. She has been treated successively with the classic mood stabilizers; lithium, valproate (2500 mg/day), and finally carbamazepine (2000 mg/day). She was also treated with a succession of psychotropic agents, including risperidone (up to 6 mg/day, reduced to 4 mg when tiagabine was started), olanzapine (up to 30 mg/day), and clozapine (up to 700 mg/day). Unfortunately, she became very obese (305 lbs) as a side effect of her therapy. After she failed to respond to clozapine, she was switched to quetiapine (up to 800 mg/day, later reduced to 400-600 mg), which seemed to have a lesser tendency to cause weight gain. On carbamazepine and quetiapine her response was less than optimal, so tiagabine was added to the regimen. The addition of tiagabine produced a dramatic improvement. Her sleep pattern was normalized, with a marked reduction in nightmares, flashbacks, and hallucinations. With the exception of a three-day relapse of cocaine use, her drinking and drug-taking ceased and she has now been abstinent for 18 months. She is currently stabilized, and remains greatly improved, on her regimen of carbamazepine (2000 mg/day), quetiapine (400-600 mg/day), and tiagabine (2 mg t.i.d. plus 16 mg at bedtime). Her weight has declined to 165 lbs. 🍀 🍀 🍀

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POST-TEST QUESTIONS

Eight correct answers are required for a passing score

- Which of the following is the mode of action of venlafaxine?
 A. Selective inhibition of serotonin reuptake
 B. Selective inhibition of serotonin and norepinephrine reuptake
 C. Selective inhibition of GABA reuptake
- Drugs that stimulate GABA-A receptors tend to have which of the following effects?
 A. A reduction in neuronal excitability
 B. Increasing alertness
 C. A reduction in symptoms of anxiety
 D. All of the above
 E. A. and C. above
- Panic disorder (PD) has been associated with decreased binding at GABA-A receptors.
 A. True B. False
- Which of the following is one of the modes of action of topiramate?
 A. GABA-A receptor agonism
 B. Inhibition of the enzymatic breakdown of GABA
 C. Modulation of GABA-coupled ion channels
 D. Inhibition of the reuptake of synaptic GABA
- Which of the following drugs enhance GABA inhibitory neurotransmission?
 A. Phenobarbital
 B. Benzodiazepines
 C. Valproate
 D. Tiagabine
 E. All of the above
 F. B. and D. above
- Which of the following drugs have shown evidence of efficacy in post-traumatic stress disorder (PTSD)?
 A. Tiagabine
 B. Topiramate
 C. Valproate
 D. Carbamazepine
 E. All of the above
 F. A. and B. above
- Which of the following is the primary mode of action of gabapentin?
 A. Selective inhibition of GABA reuptake from the synapse
 B. Increasing the release of nonsynaptic GABA from glia
 C. Inhibition of the enzymatic breakdown of GABA
- Which of the following is the mode of action of tiagabine?
 A. Selective inhibition of GABA reuptake from the synapse
 B. Increasing the release of nonsynaptic GABA from glia
 C. Inhibition of the enzymatic breakdown of GABA
- The GABAergic activity of valproate is probably responsible for both its anticonvulsive and mood-stabilizing effects.
 A. True B. False
- Both tiagabine and gabapentin have potential utility as adjunctive therapy in bipolar disorder.
 A. True B. False
- What is the typical dose range for tiagabine when it is used as an anxiolytic agent?
 A. 4-12 mg/day
 B. 16-32 mg/day
 C. 32-56 mg/day
- Which of the following are potential disadvantages of benzodiazepines?
 A. Impairment of memory and cognition
 B. Motor impairment
 C. Disinhibition in patients with a comorbid Cluster B Personality Disorder
 D. Ataxia
 E. All of the above
 F. A., B., and D. above

POST-TEST ANSWERS

Circle the appropriate letter for each question.

1. A B C 2. A B C D E 3. A B 4. A B C D 5. A B C D E F
6. A B C D E F 7. A B C 8. A B C 9. A B 10. A B 11. A B C
12. A B C D E F

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If yes, what changes? _____

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THE ROLE OF GABA IN THE PATHOGENESIS AND TREATMENT OF ANXIETY AND OTHER NEUROPSYCHIATRIC DISORDERS

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