

The Potential Role of
Selective GABA-Reuptake Inhibitors (SGRIs)
in the Treatment of Anxiety
and Other Psychiatric Disorders

Supported by an educational grant from Cephalon, Inc.

Normal release and reuptake of GABA

After GABA is released into the synapse, its synaptic action is normally terminated by diffusion and reuptake into nerve terminals and astrocytic processes.¹

Reference

1. Meldrum BS, Chapman AG. Basic mechanisms of Gabitril (tiagabine) and future potential developments. *Epilepsia*. 1999;35(Suppl 9):S2-S6.

The physiologic role of GABA

- γ -aminobutyric acid (GABA) is the major inhibitory neurotransmitter of the CNS
- Decreases in GABA involved in pathogenesis of several neurologic disorders
- Drugs that enhance GABA activity often effective in treating these disorders

The physiologic role of GABA

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter of the central nervous system. A decrease in GABAergic neurotransmission is involved in the pathogenesis of several neurologic disorders, including epilepsy, chronic pain, and anxiety.¹⁻³ A recent positron emission tomography (PET) study showed that patients with panic disorder have decreased binding at the GABA-A receptor.⁴ On the other hand, drugs that enhance activity at the GABA-A receptor are often effective in the treatment of these disorders.⁵ GABAergic mechanisms appear to be important in both anxiolytic and sedative medications.^{6,7}

References

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GABA-A receptors and mood

- GABA-A receptors regulate rapid mood changes:
 - anxiety
 - panic
 - stress response
- Drugs that stimulate GABA-A receptors (BZs, PB) have anticonvulsive effects and anxiolytic effects

GABA-A receptors and mood

There are two principal postsynaptic GABA receptors, the GABA -A and GABA -B receptor complexes. Activation of the GABA-B receptor by GABA causes 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.¹

The GABA-A receptor subtype regulates neuronal excitability and rapid mood changes, such as anxiety, panic, and stress response. Drugs that stimulate GABA-A receptors, such as the benzodiazepines and barbiturates, have anticonvulsive effects (by reducing neuronal excitability and raising the seizure threshold) as well as anxiolytic effects.¹ GABA-A receptor antagonists produce convulsions in animals.² Decreased GABA-A receptor binding has been observed in a PET study of patients with panic disorder.³ Low plasma GABA may, in fact, be a useful trait marker for mood disorders.^{4,5}

1. Tunnicliff G, Raess BU. GABA neurotransmitter activity in human epileptogenic brain. In: Tunnicliff G, Raess BU, eds. *GABA mechanisms in epilepsy*. New York: Wiley-Liss, 1991:105-120. 2. Schwartz RD. The GABA-A receptor-gated ion channel: biochemical and pharmacological studies of structure and function. *Biochem Pharmacol*. 1988;27:3369-3378. 3. 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. 4. 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. 5. Petty F. GABA and mood disorders: a brief review and hypothesis. *J Affect Disord*. 1995;34:275-281.

Possible mechanisms for enhancement of GABA function

- Direct receptor agonism (benzodiazepines)
- Inhibition of enzymatic breakdown of GABA (vigabatrin)
- Action at GABA-coupled ion channels (topiramate)
- Inhibition of reuptake of synaptic GABA (tiagabine)

Possible mechanisms for enhancement of GABA function

Enhancement of GABA function can theoretically be effected through several mechanisms. These include direct receptor agonism, the mode of action of the benzodiazepines, inhibition of the extraneuronal enzymatic breakdown of GABA, which is the mechanism of vigabatrin, modulation of GABA-coupled ion channels, which is the primary mode of action of topiramate, and inhibition of the reuptake of synaptic GABA by neurons and glial cells, which is the mechanism of tiagabine.¹

Reference

1. 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.

SGRI: A physiologic approach to GABA enhancement

- Selective GABA-reuptake inhibitor (SGRI)
- SGRIs show preliminary evidence of safety and efficacy in anxiety
- Only one SGRI currently available, tiagabine (Gabitril®, Cephalon)
- Tiagabine shown in animal models to increase GABA up to 200%

SGRI: A physiologic approach to GABA enhancement

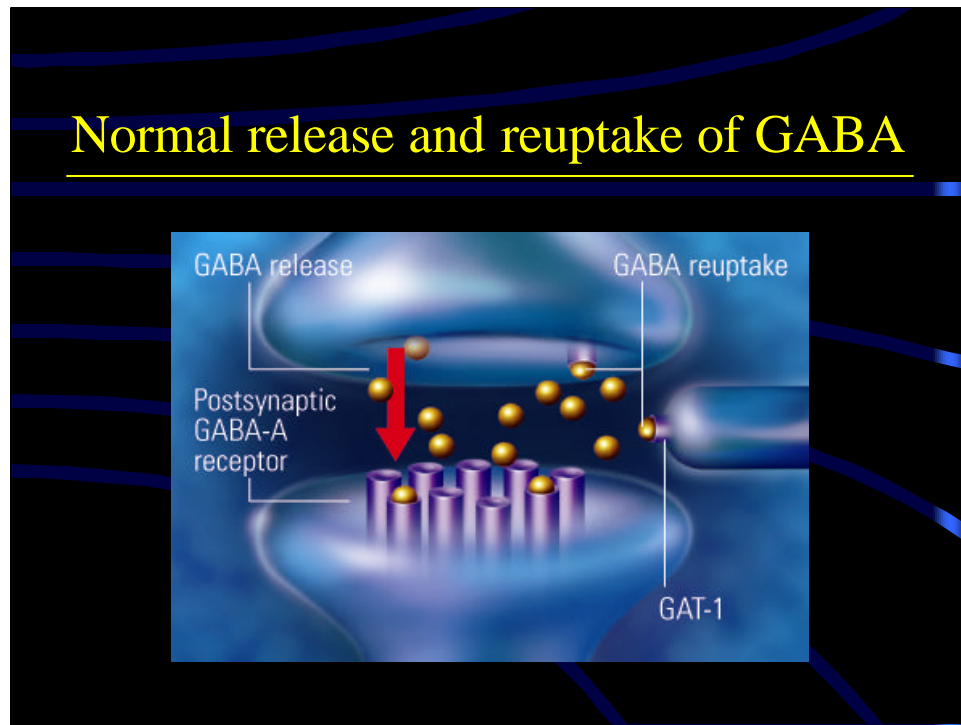
Among the most promising new treatments for anxiety disorders are the selective GABA-reuptake inhibitors, or SGRIs, a class of drugs with a mechanism of action that has shown preliminary evidence of safety and efficacy in the treatment of anxiety.

The only currently available SGRI, tiagabine, was shown in animal studies to increase extracellular GABA levels up to 200%.^{1,2}

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Normal release and reuptake of GABA



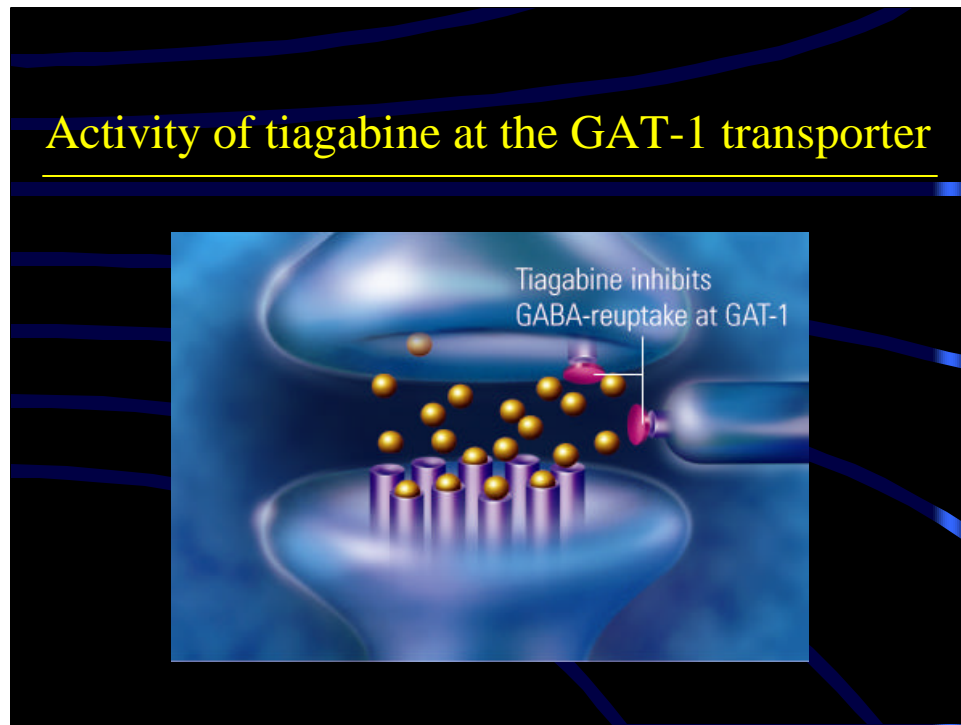
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Reference

1. Meldrum BS, Chapman AG. Basic mechanisms of Gabitril (tiagabine) and future potential developments. *Epilepsia*. 1999;35(Suppl 9):S2-S6.

Activity of tiagabine at the GAT-1 transporter



Activity of tiagabine at the GAT-1 transporter

Tiagabine acts by selectively blocking the reuptake of GABA at the GAT-1 GABA transporter. As a result, available GABA is increased without increasing the total amount of GABA in the central nervous system. By blocking the reuptake of extracellular GABA via the GAT-1 transporter, tiagabine enhances its normal inhibitory function. With an SGRI, therefore, GABA remains under normal physiologic control. Several commentators have speculated that this mode of action may reduce the potential for adverse effects, since enhancement of GABA-mediated function is limited by the total amount of GABA released.^{1,2}

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Tiagabine: potential utility in neuropsychiatric disorders

- Positive psychiatric effects seen in patients taking tiagabine for epilepsy
- Investigated in animal, open-label, or preclinical studies of:
 - sleep disorders
 - postherpetic neuralgia
 - diabetic neuropathy
 - migraine
 - tardive dyskinesia
 - spasticity
 - anxiety

Tiagabine: potential utility in neuropsychiatric disorders

The potential of tiagabine in the treatment of anxiety and other psychiatric disorders was recognized in part because of positive psychiatric effects observed in patients who were taking the drug for epilepsy.^{1,2}

Tiagabine has been investigated in animal, open-label, or preclinical studies of a variety of CNS disorders where GABA may play a role, including sleep disorders,³ postherpetic neuralgia, diabetic neuropathy,⁴ migraine,⁵ tardive dyskinesia,⁶ spasticity,⁷ and anxiety.^{1,8}

References

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Tiagabine case report: adjunctive use in severe psychiatric disorders

- Controlled paranoid features when added to paroxetine and olanzapine in a patient with schizoaffective disorder
- Controlled bipolar symptoms when added to mood stabilizer and antidepressant in two patients with severe mania

Tiagabine case reports: adjunctive use in severe psychiatric disorders

Case reports of patients with severe psychiatric disorders reported clear benefits from the addition of tiagabine.¹ 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.² 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.

References

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

- Middle-aged woman with a history of post-traumatic stress disorder, dissociated identity disorder, severe anxiety symptoms, refractory auditory hallucinations, and substance abuse
- Treated unsuccessfully with mood stabilizers and psychotropics
- Addition of tiagabine to carbamazepine and quetiapine produced dramatic improvement in PTSD symptoms

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

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).¹ Her sleep was often disturbed by nightmares, flashbacks, and hallucinations. She had proved very difficult to stabilize and had 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 at the time of publication had been abstinent for 18 months. She became stabilized, and remained greatly improved, on a regimen of carbamazepine (2000 mg/day), quetiapine (400-600 mg/day), and tiagabine (2 mg t.i.d. plus 16 mg at bedtime). In addition, her weight declined to 165 lbs.

Reference

1. Unpublished case report submitted by Ethan Kisch, M.D., Assistant Clinical Professor, Tufts University School of Medicine, Boston, MA, psychiatrist in private practice, Providence, RI.

Summary

- Clinical experience with SGRIs in psychiatric disorders is preliminary but promising
- Many patients with psychiatric disorders have comorbidities requiring multiple-drug therapies
- Potential role for SGRIs in anxiety and as adjunctive agents in patients with complex neuropsychiatric disorders

Summary

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 SGRI tiagabine is preliminary but promising. Controlled studies of this and other GABA-enhancing agents are in the planning stages and will be useful in clarifying their potential clinical utility across a range of psychiatric disorders.

Most people 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 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.