

GABA

**THE ROLE OF GABA IN THE PATHOGENESIS AND TREATMENT
OF ANXIETY AND OTHER NEUROPSYCHIATRIC DISORDERS
PART 2: THE TREATMENT OF ALCOHOL WITHDRAWAL**



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Robert Malcolm, M.D.: **Research support:** GlaxoSmithKline and Sanofi. **Consultant:** GlaxoSmithKline, Cephalon, and Sanofi.

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Statement of Educational Need

This activity is designed to respond to the needs of psychiatrists and other physicians who treat patients undergoing alcohol and/or benzodiazepine withdrawal by updating their knowledge of GABA-enhancing agents, which are emerging as potentially important agents in the treatment of alcohol dependence and other substance abuse disorders.

Educational Objectives

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

- Better understand the roles of GABA and glutamate in the central nervous system
- Better understand the neuropsychiatric effects of acute alcohol withdrawal
- Describe the drawbacks of benzodiazepines in the treatment of alcohol withdrawal
- Understand the rationale for using GABAergic anticonvulsants to treat alcohol and benzodiazepine withdrawal syndromes
- Describe 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 compact disc.

Statement of Evaluation Instrument

A 10-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 treat patients with alcohol withdrawal syndrome.

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, Part 2. Your credit certificate will be returned. Participation is confidential. Estimated program completion time: 1 hour.

Activity Number: END 00 11 101 02

Release date: 12-01-02. Expiration date: 11-30-03.

Answer key to CME Post-Test

1. C 2. B 3. A 4. B 5. D 6. B 7. A 8. C 9. D 10. D

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GABA

PART 2: THE TREATMENT OF ALCOHOL WITHDRAWAL

Introduction

Gamma aminobutyric acid (GABA) is the brain’s major inhibitory neurotransmitter. When GABA binds to a GABA receptor in the brain, it causes a reduction in the ability of that neuron to conduct a neural impulse. Thus, GABA has the ability to “shut down” nerve cells throughout the central nervous system (CNS).

The brain has three types of GABA receptors, GABA_A, GABA_B, and GABA_C. GABA_A receptors mediate fast inhibitory synaptic transmissions. They regulate neuronal excitability, such as the seizure threshold, and rapid mood changes, such as panic. GABA_A receptors are the targets of sedating drugs, such as benzodiazepines, barbiturates, neurosteroids, and ethanol.^{1,2} GABA_B receptors mediate slow inhibitory potentials. They play an important role in memory, depressed moods, and pain.³ Stimulation of GABA_B receptors can also reduce the release of dopamine, thereby inhibiting the reward/reinforcing response to drug abuse. GABA_C receptors are found in the retina; their physiologic role is poorly understood.

Interest in the behavioral and psychological roles of GABA has focused on the bonding of GABA to the GABA_A receptor, which is widely distributed throughout the brain; 60-75% of all synapses in the CNS are GABAergic.⁴ GABA_A receptors are very heterogeneous, with at least 16 different subunits producing potentially over 150,000 different receptor types. It has recently been discovered that some of these subunits mediate specific behavioral and pharmacological effects. For example, the high-affinity binding of GABA_A receptors to benzodiazepines requires the presence of a $\gamma 2$ subunit and an adjacent $\alpha 1$, $\alpha 2$, $\alpha 3$, or $\alpha 5$ subunit.⁵ The anxiolytic and sedating effects of the benzodiazepines appear to be governed by different subunits of the GABA_A receptor. Sedation is mediated through interaction with $\alpha 1$ -containing GABA_A receptor complexes. Thus, mice that lack the gene for the $\alpha 1$ subunit experience the anxiolytic effects of benzodiazepines, but not the sedative effects. Similarly, drugs that do not evoke potentials in GABA_A receptors containing the $\alpha 1$ subunit may produce the desirable anxiolytic effects of benzodiazepines without the undesirable effects of sedation and ataxia.⁶

GABA and alcohol withdrawal

In addition to anxiolytic and sedative effects, GABA_A receptors are responsible for the intoxicating effects of alcohol and other sedative hypnotics. With chronic use, alcohol, and to a lesser extent, benzodiazepines modify the five protein areas of GABA_A receptors. This down-regulation is responsible for the phenomenon of alcohol withdrawal seen when alcohol is ceased abruptly in individuals who are alcohol-dependent.

The phenomenon of alcohol dependence can be explained on a molecular basis. When GABA binds to the GABA_A receptor, it opens a chloride channel, which permits extracellular chloride to move into the intracellular compartment. Because the chloride ion is negatively charged, it hyperpolarizes the neuron, which makes it refractory to excitatory postsynaptic potentials. Several compounds, such as neurosteroids, benzodiazepines, ethanol, and barbiturates, potentiate the activity of GABA. When an individual ingests alcohol, it facilitates the ability of GABA to open chloride ion channels, so that greater amounts of chloride ion move from the extracellular to the intracellular space. With chronic use of alcohol, the GABA system is down-regulated and the neuron may eventually become dependent on alcohol to enable GABA to function.

TABLE 1

The role of GABA receptors

GABA_A receptors:

- Mediate fast inhibitory synaptic transmissions
- Regulate neuronal excitability
- Responsible for rapid mood changes (e.g., anxiety, panic, and stress response)

GABA_B receptors:

- Mediate slow inhibitory potentials
- Effects on memory and mood (depression)
- Effects on pain response

GABA_C receptors: Physiologic role yet to be described

At the same time, the excitatory glutamate system is up-regulated, as well as calcium-channel activity. If alcohol is withdrawn, GABA alone is no longer capable of opening the chloride ion channel, which results in a very excitable cell that is easily stimulated by excitatory postsynaptic potentials. This cellular hyperexcitability is responsible for the irritability, insomnia, hallucinations, tachycardia, hypertension and, in the case of abrupt cessation of long-time alcohol use, seizures. As one faculty member (RM) expressed it, an apt analogy might be an automobile with a stuck accelerator and no brakes.

Alcohol withdrawal is also associated with neurotoxicity. Chronic ethanol ingestion results in an up-regulation of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors, a phenomenon associated with withdrawal seizures.⁷ Together, alcohol and glutamate cause increases in the number of neuronal calcium receptors. When chronic alcohol use suddenly ceases, calcium floods into the cell, a phenomenon associated with cell death. The neurotoxicity tends to worsen with each successive withdrawal, a “kindling” process similar to that seen in epilepsy. The symptoms are more severe and seizures are likely to worsen. Yet, even mild withdrawal can be associated with neuronal damage. People undergoing mild alcohol withdrawal who were not treated with any agent have been found to have increased levels of oxidative radicals and glutamate metabolites in the cerebrospinal fluid. These are suggestive of oxidative damage to cells, damaging calcium influx into cells, and damaging intracellular proteins. This suggests that even mild withdrawal may lead to CNS damage, particularly if it is repeated several times over the course of alcohol dependency, and therefore needs to be treated.

Preventing neurotoxicity and controlling symptoms during alcohol withdrawal

One approach to mitigating the damage of alcohol withdrawal is to down-regulate the glutamate system with acamprosate. Acamprosate has been approved for use in over 70 countries, and Phase III trials have been completed in the U.S. While trials of acamprosate have generally had positive outcomes, the current faculty emphasized that it must be combined with established psychosocial therapies to be of real benefit. These may include cognitive behavioral therapy, motivational therapies, or 12-step programs.

In a 2001 study of animals undergoing ethanol withdrawal, acamprosate was shown to reduce increases in glutamate-induced calcium entry into cells and prevent glutamate-induced neurotoxicity.⁸ A 2001 Montreal symposium provided additional support for the neuroprotective effects of acamprosate.⁹ A meta-analysis of controlled trials of naltrexone and acamprosate showed both drugs to have significant but modest benefits on treatment retention and/or drinking outcomes.¹⁰ Similarly, a clinical

review of published double-blind, placebo-controlled trials of acamprosate showed a greater rate of treatment completion, time to first drink, and abstinence rate and/or duration compared with placebo.¹¹

In a recent study of 627 people (almost all men) with severe alcohol dependence, naltrexone was not shown to be effective.¹² However, the current faculty noted that their experience with naltrexone has often been positive. They emphasized the need for concomitant psychosocial support; in fact, none of the pharmacologic therapies for alcohol withdrawal, opiate addiction, or smoking cessation are effective as stand-alone therapies. One faculty member (RM) had a remarkable response from naltrexone from a patient in his 70s who had been alcohol-dependent for 50 years and had refused most forms of psychosocial treatment. Naltrexone,

he said, removed his desire to drink; it was “like turning off a switch.” As an opiate-receptor antagonist, naltrexone shuts down the “reward” response to drinking. Unlike the patient described above, the faculty felt that patients most likely to respond to naltrexone are young and in the early stages of alcohol dependence.

Despite their drawbacks, benzodiazepines are still commonly used to treat alcohol withdrawal. The present faculty try to avoid using benzodiazepines in substance abusers, especially severe alcoholics. In addition to the dangers of combining the drugs with alcohol, RM and HM have noted that patients on benzodiazepines often don't recognize drug-induced ataxia when it occurs. Nevertheless, it may be necessary to use this class of drugs for brief periods in some patients. For example, in patients with a history of delirium tremens or withdrawal seizures, HM uses a combination of a benzodiazepine and an anticonvulsant; these patients generally receive inpatient treatment.

Another danger is that benzodiazepines may actually “prime” alcoholics to start drinking again. A recent randomized trial by RM and HM compared carbamazepine and lorazepam in 136 patients undergoing single and multiple previous alcohol withdrawals.¹³ The two drugs were found to be equally effective in decreasing withdrawal symptoms, while carbamazepine was superior to lorazepam in reducing anxiety and improving sleep. Furthermore, lorazepam-treated patients had a significantly higher risk of rebound of alcohol-withdrawal symptoms post-treatment ($p=0.007$), and the risk of having a first drink was three times greater with the lorazepam-treated patients than with the carbamazepine-treated patients ($p=0.04$).

Benzodiazepines are themselves abusable drugs and, if a patient decides to drink while taking them, the interaction can lead to increased sedation, motor incoordination, and ataxia. Furthermore, when the benzodiazepine is withdrawn after five to seven days, the patient is often left with symptoms of generalized anxiety disorder and may even experience

Drugs that do not evoke potentials in GABA_A receptors containing $\alpha 1$ subunit may produce desirable anxiolytic effects of benzodiazepines without the undesirable effects of sedation and ataxia.

panic attacks. The question then becomes how to manage the anxiety symptoms. Chronic benzodiazepines are inappropriate in such individuals. JG noted that, while selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) can be helpful, people with substance abuse problems generally do not like these drugs; they tend to experience more side effects from antidepressants than people without abuse problems. In his practice, JG has had more success treating anxiety symptoms with atypical antipsychotic agents, such as quetiapine.

Anticonvulsants for alcohol withdrawal

There is growing support in the literature for the use of anticonvulsants, both for detoxification and the management of subsequent anxiety symptoms. However, clinical experience has generally been limited to outpatient treatment of mild to moderate alcohol withdrawal. Among the anticonvulsants used to treat alcohol withdrawal are valproate, gabapentin, carbamazepine, and tiagabine. The efficacy of these drugs in the treatment of acute alcohol withdrawal is probably related to their GABAergic effects. To date, most of the studies of these agents have been small and/or open-label, and large-scale controlled studies of anticonvulsants for acute alcohol withdrawal are clearly needed. The current faculty has had some success with carbamazepine, while noting that, because of its numerous interactions with other drugs, it is impractical to use in patients on multiple drug regimens. There have been numerous case reports on the use of valproate for alcohol withdrawal suggesting that the drug is helpful in decreasing seizures and other withdrawal symptoms. Valproate was recently evaluated in three pilot studies of acute alcohol withdrawal.¹⁴⁻¹⁶ While the effect on alcohol-related outcomes was modest in these studies, valproate did appear to be useful in decreasing the irritability and mood disturbances associated with alcohol withdrawal. This effect is consistent with the mood-stabilizing benefits of the agent seen in the treatment of bipolar disorder. A major drawback of valproate in long-term therapy is weight gain, an adverse effect that appears to be dose-related.

Gabapentin is an anticonvulsant that has also shown efficacy in the treatment of mood and anxiety disorders.¹⁷⁻²⁰ It appears to act primarily by increasing the release of nonsynaptic GABA from glia.²¹ In a published case report, three patients with alcohol withdrawal were treated with gabapentin 400 mg tid for three days, 400 mg bid for one day, and 400 mg qd for one day.²² Withdrawal symptoms subsided and no adverse effects were observed.

The anticonvulsant tiagabine also has shown efficacy in a variety of neuropsychiatric disorders, including anxiety.²³⁻²⁸ Tiagabine has a highly specific mode of action: the selective inhibition of GABA reuptake at

the GAT-1 GABA transporter (selective GABA-reuptake inhibition, or SGRI). Tiagabine acts at both the GABA_A and GABA_B receptors, so it is theoretically able to enhance GABA activity while inhibiting the “reward” effect of substance abuse by preventing the release of dopamine. Unlike the benzodiazepines, tiagabine does not interact pharmacokinetically or pharmacodynamically with alcohol.²⁹ And, unlike carbamazepine, tiagabine has virtually no drug interactions. Among the faculty, JG and RM have had extensive experience using tiagabine in patients with substance abuse problems, including patients undergoing withdrawal from benzodiazepines. HM added that tiagabine and other GABAergic medications also have potential in the treatment of cocaine and nicotine dependency.

We now have a variety of drugs that increase GABA levels in several different ways, from the highly specific mechanism of tiagabine to the multiple GABAergic mechanisms of valproate.

Patients with anxiety or bipolar disorder who respond to tiagabine generally do so at doses of 4-12 mg day. The same dose range is recommended for the treatment of alcohol withdrawal, although the useful upper limit to this range has not been established. During treatment, response to therapy may be assessed by the *Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-AR)*.³⁰ The latest, simplified version of this scale rates the severity of alcohol withdrawal using 10 clinical parameters, such as anxiety, tremor, and nervousness. Each parameter is scored on a scale of 0 - 7 and patients generally require treatment only if the score is 10 or higher. Hospitalized patients are rated every eight hours by the nursing staff. This scale can be used in a variety of clinical settings, including detoxification units, psychiatric units, and general medical/surgical wards.³⁰ It provides an objective measurement of the need for medication, of the need to increase the dose, or if inpatient treatment might be required.

It was previously believed that after five to seven days of detoxification, the brain returned to homeostasis. It is now understood, however, that there is a protracted abstinence syndrome, with symptoms of anxiety, irritability, moodiness, and sleep disturbances. Even 12 to 18 months after drinking has ceased, patients may exhibit abnormal sleep patterns, with an absence of deep slow-wave Delta sleep. These patients have frequent awakenings, which may lead some to return to drinking or abuse sedative hypnotics in an effort to sleep. While not a hypnotic, tiagabine appears to normalize sleep architecture by increasing Stage 3 and Stage 4 Delta sleep. Patients report subjectively that the next day they feel more refreshed; they had a “deeper” night’s sleep. The effect of a single oral dose of 5 mg tiagabine on sleep was studied in 10 healthy elderly subjects.³¹ During the placebo night, the subjects had high amounts of intermittent wakefulness and little slow-wave sleep. During the tiagabine night, the subjects had greatly improved sleep quality, with decreased wakefulness and increases in both slow-wave sleep and low-frequency activity on the EEG within non-REM sleep.

Baclofen, a centrally acting muscle suppressant, is an older drug that, like tiagabine, has activity at the GABA_B receptor. One recent study showed it to be effective in rapidly suppressing the alcohol withdrawal syndrome.³² However, the drug must be given three times daily, interacts with CNS depressants, is abusable, and can be fatal in overdose.

Benzodiazepine withdrawal

As noted above, tiagabine may be useful in decreasing the symptoms of benzodiazepine withdrawal. The faculty still see patients who have been on high doses of benzodiazepines for many years. Often, they are obtaining prescriptions from several physicians. The abuse problem may only come to a physician's attention as the patient ages and experiences greater cognitive and motor impairment from the drug. In some cases, the patient falls or is in an automobile accident. As the benzodiazepine is withdrawn, the patient begins to experience symptoms of agitation and anxiety; if this isn't treated, the patient is likely to return to benzodiazepine abuse for symptomatic relief. JG recommends a cross taper of the benzodiazepine and tiagabine over a period of 4 to 8, or even 12 weeks if the patient has been on chronic benzodiazepines at high doses. As the benzodiazepine is slowly withdrawn, tiagabine is initiated at a dose of 2 mg qd and titrated to 4 mg bid or, in some patients, 8 mg bid. This is approximately the dose range used for tiagabine in the treatment of anxiety and is lower than the doses generally used to treat seizures (32-56 mg/day). This procedure, which is done on an outpatient basis can increase both the comfort of the patient and the likelihood of success. HM employs a slight variant on this procedure, maintaining patients on their current benzodiazepine doses until the dose of tiagabine or other anticonvulsant has reached a steady state. At this point, he initiates a slow taper of the benzodiazepine.

Conclusion

One of the most remarkable developments in psychopharmacology in recent decades has been the targeting of specific neurotransmitters, including serotonin, norepinephrine, dopamine and, recently, GABA and glutamate. For the first time, tools have been developed that enable clinicians to manipulate systems in the brain responsible for widespread neurotransmission. For example, we now have a variety of drugs that increase GABA levels in several different ways, from the highly specific mechanism of tiagabine to the multiple GABAergic mechanisms of valproate. GABAergic drugs have already shown potential in many neuropsychiatric disorders, not the least of which is alcohol withdrawal syndrome. In the treatment of alcohol withdrawal, some of these agents appear to have the potential to be both neuroprotective and to ameliorate the disabling symptoms associated with the syndrome.

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POST-TEST QUESTIONS

Seven correct answers are required for a passing score

- What is the role of GABA_A receptors in the CNS ?
 - A. Increase the release of dopamine
 - B. Mediate slow inhibitory potentials
 - C. Mediate fast inhibitory synaptic transmissions
- Stimulation of GABA_B receptors enhances the reward response to drugs susceptible to abuse.
 - A. True
 - B. False
- The sedating effect of benzodiazepines is mediated by which GABA_B subunit?
 - A. α 1
 - B. α 2
 - C. α 3
 - D. γ 2
 - E. Any of the above
- After alcohol detoxification, the brain returns to homeostasis in five to seven days?
 - A. True
 - B. False
- Which of the following are potential drawbacks of baclofen ?
 - A. tid dosing
 - B. Potential for abuse
 - C. Interaction with CNS depressants
 - D. All of the above
- What is the primary mechanism of gabapentin?
 - A. Inhibition of GABA reuptake by glia and postsynaptic neurons
 - B. Increasing release of nonsynaptic GABA from glia
 - C. Inhibition of GABA metabolism by GABA transaminase
- What is the mode of action of tiagabine?
 - A. Inhibition of GABA reuptake at the GAT-1 GABA transporter
 - B. Increasing release of nonsynaptic GABA from glia
 - C. Inhibition of GABA metabolism by GABA transaminase
- Which of the following is a potential drawback with the use of carbamazepine for alcohol withdrawal?
 - A. Weight gain
 - B. Pharmacodynamic interaction with ethanol
 - C. Numerous interactions with other drugs
- Which of the following are benefits of acamprosate in the treatment of alcohol withdrawal?
 - A. Neuroprotection
 - B. Greater rate of treatment completion compared with placebo
 - C. Longer time to first drink compared with placebo
 - D. All of the above
 - E. B and C above
- What happens at the cellular level when GABA binds to a GABA_A receptor?
 - A. There is a calcium influx into the neuron
 - B. A chloride channel is opened, permitting extracellular chloride to move into the cell
 - C. The neuron becomes hyperpolarized, making it resistant to excitatory stimuli
 - D. B. and C. above

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

PART 2: THE TREATMENT OF ALCOHOL WITHDRAWAL

Activity Number: END 00 11 101 02

Expiration date: 11-30-03

To earn one (1) hour of category 1 CME credit after reading this monograph and listening to the accompanying audio CD, please mail the completed post-test answers, activity evaluation, and personal information questionnaire in the enclosed envelope.



POST-TEST ANSWERS

Circle the appropriate letter for each question.

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

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If yes, what changes? _____

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