GABA Systems, Benzodiazepines, and Substance Dependence

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Alterations in the γ-aminobutyric acid (GABA) receptor complex and GABA neurotransmission influence the reinforcing and intoxicating effects of alcohol and benzodiazepines. Chronic modulation of the $GABA_A$-benzodiazepine receptor complex plays a major role in central nervous system dysregulation during alcohol abstinence. Withdrawal symptoms stem in part from a decreased GABAergic inhibitory function and an increase in glutamatergic excitatory function. $GABA_A$ receptors play a role in both reward and withdrawal phenomena from alcohol and sedative-hypnotics. Although less well understood, $GABA_B$ receptor complexes appear to play a role in inhibition of motivation and diminish relapse potential to reinforcing drugs. Evidence suggests that long-term alcohol use and concomitant serial withdrawals permanently alter GABAergic function, down-regulate benzodiazepine binding sites, and in preclinical models lead to cell death. Benzodiazepines have substantial drawbacks in the treatment of substance use–related disorders that include interactions with alcohol, rebound effects, alcohol priming, and the risk of supplanting alcohol dependency with addiction to both alcohol and benzodiazepines. Polysubstance-dependent individuals frequently self-medicate with benzodiazepines. Selective GABA agents with novel mechanisms of action have anxiolytic, anticonvulsant, and reward inhibition profiles that have potential in treating substance use and withdrawal and enhancing relapse prevention with less liability than benzodiazepines. The $GABA_B$ receptor agonist baclofen has promise in relapse prevention in a number of substance dependence disorders. The $GABA_A$ and $GABA_B$ pump reuptake inhibitor tiagabine has potential for managing alcohol and sedative-hypnotic withdrawal and also possibly a role in relapse prevention.

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Alcohol dependence is among the most common psychiatric disorders in the general population. Current prevalence of alcohol dependence is fairly stable in the United States at approximately 6% of men and 2% of women,[1] although 14% of Americans may be alcohol dependent at some point during their lives.[2] According to the DSM-IV, a diagnostic criterion of physiologic alcohol dependence is the presence of an alcohol withdrawal syndrome during acute reduction in or cessation of drinking (Table 1).

MECHANISMS OF ALCOHOL WITHDRAWAL

The alcohol withdrawal syndrome is the result of the brain's adaptation to the long-term presence of alcohol in the central nervous system (CNS). During continuous exposure to alcohol, neuroadaptive changes occur to compensate for alcohol's destabilizing effects.[3] When alcohol use is discontinued, the maladaptive nature of these changes becomes evident. Gamma-aminobutyric acid (GABA)—the main inhibitory neurotransmitter in the mammalian CNS—is implicated in multiple aspects of alcohol intoxication, dependency, and withdrawal. GABA systems are sensitive to both the initial and the chronic effects of alcohol exposure.

The neuropathology of withdrawal is opposite to that of intoxication. Alcohol intoxication enhances the function of the GABAergic system, resulting in enhanced inhibitory neurotransmission and, thus, depression of the CNS. Conversely, withdrawal is marked by increased glutamatergic action and reduced GABA activity, resulting in heightened excitatory neurotransmission and brain hyperexcitability. In untreated alcohol withdrawal, the neuronal firing rate and recruitment of neighboring neurons increase while CNS levels of oxidative free radicals, peroxidases, and intracellular calcium rise.[4] Cell damage or cell death is possible. Cortical, brain stem, and limbic function are disrupted. At the clinical level, alcohol withdrawal can cause a host of autonomic and CNS effects, including hypertension, tachycardia, excessive sweating,

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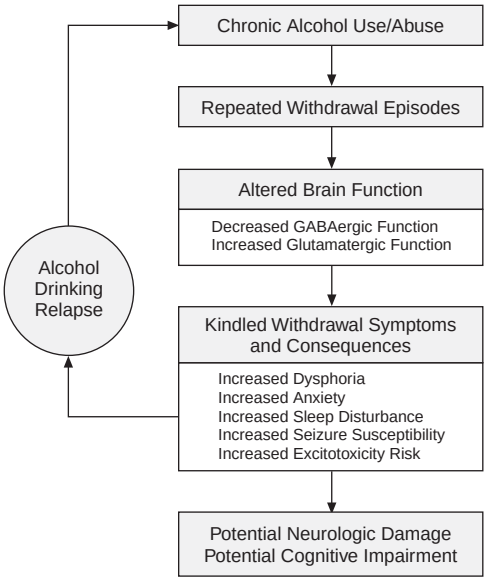
Table 1. Diagnostic Criteria for Alcohol Withdrawal[a]

Decrease in (or cessation of) prolonged and heavy alcohol use
2 or more of the following symptoms developing within several hours to a few days of the above
Autonomic hyperactivity (eg, elevated pulse rate or diaphoresis)
Tremor
Psychomotor agitation
Insomnia
Transient hallucinations or illusions
Anxiety
Nausea or vomiting
Seizures
The above symptoms cause considerable distress or impairment and are not better accounted for by another mental disorder or medical condition

[a]Adapted with permission from DSM-IV.[2]

Figure 1. Cycle of Alcohol Dependence[a]



[a]Adapted with permission from Becker.[3]

hypothermia, tremor and other motor incoordination, cognitive disruption, dysphoria, anxiety, insomnia, hallucinations, delirium, seizures, and—in about 1% of inadequately treated cases—death.

Chronic alcohol use renders $GABA_A$ receptors dysfunctional, permanently dampening GABAergic function. Autopsies of histologically normal brains of human alcoholics found benzodiazepine receptor sites, which are located on the $GABA_A$ receptor complex, reduced by 30% in the hippocampus and by 25% in the frontal cortex.[5] Diminished inhibition via $GABA_A$ receptors may contribute to the worsening of withdrawals over time. Also, repeated withdrawals may increase the number of glutamatergic receptors, making the brain more vulnerable to neural excitability and excitotoxic damage.[3]

In a process of sensitization, sometimes clinically referred to as neuronal "kindling," withdrawal symptoms intensify as withdrawal episodes grow in number.[6] Prior withdrawal experience is associated with more severe and medically complicated later withdrawal episodes. This progression is not solely attributable to a worsening of alcoholic drinking over the course of alcoholism. Rather, having a previous withdrawal episode reduces the duration and extent of intoxication necessary to provoke subsequent withdrawal episodes.[3] For example, mice exposed to alcohol for 3 cycles of 16 hours showed more severe withdrawal symptoms than mice exposed to alcohol for 48 hours straight.[7] Further, chronic intermittent alcohol exposure led to hippocampal cell loss in rats, but continuous alcohol exposure did not.[8,9] In mammals, cycles of binge-drinking followed by abstinence initially provoke no withdrawal symptoms, then mild withdrawal symptoms, then moderate and finally severe withdrawal symptoms. Through "kindling," the alcoholic brain ultimately becomes hyperexcitable (Figure 1).

Kindling is a term originally used in the study of epilepsy to describe the augmentation process by which low level, intermittent, subconvulsant stimulus eventually provokes seizure.[3] Seizure can be a symptom of severe alcohol withdrawal and as such is associated with poor prognosis and relatively high mortality rate.[10] Patients with withdrawal-related seizures are more likely to have undergone numerous previous detoxifications than patients without seizures.[6,11,12]

TREATMENT OF ALCOHOL WITHDRAWAL

For more than 4 decades, benzodiazepines have been first-line treatment for patients with alcohol withdrawal. Their anxiolytic and anticonvulsant properties appear to address both psychological and physiologic symptoms. More recently, research suggests that benzodiazepines may have substantial drawbacks in the treatment of alcohol-related disorders. Benzodiazepines combined with alcohol in the outpatient setting can lead to death, even with relatively low levels of blood alcohol.[13] Benzodiazepines also interact with alcohol to produce motor impairment that patients may not recognize. Additionally, some patients treated with benzodiazepines experience rebound (a reversal of the medication's effects and return of symptoms) upon discontinuation of treatment. Benzodiazepines ameliorate withdrawal symptoms at any one episode of withdrawal, but they do not appear to interrupt the kindling process.[11,14,15] Because benzodiazepines are potentially habit-forming, there may be a risk of substituting one dependence (or abuse) for another when benzodiazepines are used chronically to treat patients with alcoholism.

My colleagues and I conducted a series of studies[16,17] in which we compared the anticonvulsant carbamazepine—which has a long history of use in the detoxification of alcohol-dependent patients in Europe—to the benzodiaze-

pine lorazepam. One such study[16] focused on the pharmacologic treatment of psychosocial factors associated with alcohol withdrawal (sleep quality, ability to return to work, anxiety, and depression). Psychiatric withdrawal symptoms such as sleep disturbance may increase the likelihood of relapse as outpatients seek relief by self-medicating with alcohol. In this study, 136 outpatients with mild-to-moderate withdrawal symptoms were grouped according to their number of previous treated withdrawals, 0-to-1 or multiple (> 2). Subjects from each group received 600 to 800 mg carbamazepine on day 1, 600 mg/day in 3 divided doses through day 4, and a single dose of 200 mg on day 5. Or, they received 6 to 8 mg lorazepam on day 1, 6 mg/day in 3 divided doses through day 4, and a single dose of 2 mg on day 5. (Carbamazepine/lorazepam dosage equivalency was extrapolated from the literature.) All subjects completed the Zung Anxiety Scale, the Beck Depression Inventory, and visual analogue scales describing their sleep quality and subjective ability to work. Mood symptoms improved for all patients regardless of detoxification history or the drug they received.[16]

In examining the effect of kindling on symptom severity, we found that the outpatients with a history of multiple withdrawals experienced more severe anxiety than those with no or 1 previous withdrawal. Oddly enough, anxiety symptoms responded better to carbamazepine than to lorazepam. The multiple withdrawal group also felt less able to return to work and experienced more sleep problems than the group with no or 1 previous withdrawal. In the posttreatment period, subjects who had received carbamazepine reported better sleep than subjects who had received lorazepam.[16]

Postdetoxification relapse can be predicted in part by the intensity of alcohol withdrawal symptoms at the end of withdrawal treatment.[18] The progressive re-intensification of symptoms may influence a patient's motivation to drink again. Further, protracted withdrawal symptoms—symptoms such as anxiety, irritability, mood lability, and sleep disturbance lasting beyond the 5 to 7 days of detoxification—present a relapse risk. My colleagues and I[17] looked at relapse to drinking behaviors. In the immediate 7-day posttreatment period, outpatients with no or 1 previous withdrawal who had received carbamazepine drank on average less than 1 drink per day, while those who had received lorazepam drank about 3 drinks per day. Outpatients with multiple (> 2) previous detoxifications drank less than 1 drink per day following carbamazepine treatment but about 5 drinks per day following lorazepam treatment. Ten percent of the carbamazepine multiple detoxification group (> 2) drank posttreatment; 50% of the lorazepam multiple detoxification group drank in the same 7-day interval. Most outpatients who received lorazepam treatment experienced rebound withdrawal symptoms posttreatment. Rebound withdrawal symptoms may encourage relapse.[17] In addition to having a higher risk for taking a first drink after detoxification, 20% of lorazepam-treated patients experienced dizziness or ataxia but did not recognize their impairment. Outpatients' unawareness of their impairment could put benzodiazepine-treated patients at risk for automobile or other accidents, including overdoses. Although carbamazepine was superior to lorazepam in the experimental setting, carbamazepine has several liabilities that limit its clinical utility. It interacts to increase the clearance of many other therapeutic agents. In some patients, confusion, decreases in serum sodium, and, rarely, hematologic and hepatic damage can occur.

Relapse Prevention

Benzodiazepines may have other qualities that limit their usefulness in the treatment of alcohol dependence. In a study by Deutsch and Walton,[19] rats subjected to forced intragastric intubation of alcohol later showed an increase in free-choice self-administration of alcohol. Once dependence was established, rats were acclimatized to a free-choice situation in which they could always choose between flavored water and flavored water containing alcohol. During these free-choice situations, rats treated with diazepam showed no decline in their level of alcohol drinking, while untreated rats tapered their drinking over time. In a second study by Hedlund and Wahlstrom,[20] rats were made psychologically alcohol dependent by a regimen of once-weekly injections of alcohol accompanied by once-weekly 24-hour periods in which alcohol was available for drinking. During the first phase of the study, dependence was established when the rats consistently drank until they had self-administered a certain dose of alcohol regardless of the differential alcohol concentration in the solution offered them. After dependence was established, alcohol-dependent rats began a 3-week treatment course in which randomly selected rats were treated with diazepam and offered alcohol only on the first and final days of the treatment. On the first day, when these rats received both a diazepam injection and the choice to drink alcohol, they showed a 56% decrease in mean intake of alcohol compared with the previous week. Then alcohol was denied the rats for 3 weeks while diazepam treatment continued. On the final day, the rats were again offered alcohol to drink, and they showed a 140% increase in mean alcohol intake over their pretreatment alcohol intake. Increased drinking lasted for 1 week. In yet another preclinical study not involving alcohol withdrawal, benzodiazepines increased the consumption of alcohol use.[21] These data[19,20] suggest that a distinct effect of diazepam on alcohol intake may arise early in treatment and that diazepam may help prime for alcohol use during the course of withdrawal treatment. Our study, while not definitive, supports this premise in humans.[18]

Baclofen, an agent used to treat spasticity, has also been studied in the treatment of alcoholic patients and cocaine dependence. In contrast to benzodiazepines, which influ-

ence neurotransmission via the $GABA_A$ receptor complex, baclofen is an agonist at the less-understood $GABA_B$ presynaptic receptors. Baclofen blocks motor activation of cocaine and prevents development of cocaine-induced behavioral sensitization.[22] Krupitsky and colleagues[23] conducted a study of baclofen among 90 alcoholic inpatients with comorbid secondary, subclinical anxiety and depression. Anxiety and depression frequently accompany alcohol dependence, but alcohol-dependent individuals tend to have poor self-recognition of these disorders. Affective disorders alongside alcohol dependence can increase withdrawal severity and vulnerability to relapse. The study subjects had been abstinent for 3 to 4 weeks, and thus were without symptoms of alcohol withdrawal syndrome. They were randomly divided into 4 groups, and for 3 weeks received only 37.5 mg/day baclofen, 15 mg/day diazepam, 75 mg/day of the antidepressant amitriptyline, or placebo. The Zung Anxiety Scale, the Minnesota Multiphasic Personality Inventory, and Spielberger's State-Trait Anxiety Inventory, as well as blood and plasma measurements of dopamine, serotonin, and GABA and an electroencephalogram (EEG) were administered before and after medication trial. The results of the posttreatment rating scale scores showed a decrease in anxiety and depression in all 3 treatment groups; these results were confirmed by the electrophysiologic tests. Baclofen provoked no side effects, while diazepam and amitriptyline caused sedation. Blood and plasma measurements revealed no significant changes. The results indicated that selective ligands of $GABA_B$ receptors can be as efficacious in treating anxiety/affective disorders as $GABA_A$ receptor ligands. A recent case report suggested that baclofen also may be of value in treating alcohol withdrawal.[24]

Another agent with potential in the management of alcohol withdrawal is tiagabine. Tiagabine is an antiepileptic GABA pump uptake inhibitor; it increases available extracellular concentrations of GABA in various brain regions in both $GABA_A$ and $GABA_B$ synapses.[25] In a study by Cleton et al.,[26] tiagabine resulted in higher maximal GABA concentrations in the brains of rats kindled to seizures versus the brains of unkindled controls. The researchers inferred from EEG results during the study that tiagabine-induced enhancement of GABAergic inhibition was less sensitive to functional adaptation in response to epileptic activity than modulation of GABAergic inhibition by midazolam. Another interesting feature of tiagabine is that it does not appear to interact with alcohol. In a study of 20 healthy men and women, Kastberg and colleagues[27] found that the pharmacokinetic and pharmacodynamic features of tiagabine were unchanged by alcohol, and vice versa. The investigators concluded that individuals taking tiagabine could ingest moderate amounts of alcohol and drive and operate machinery safely. In a small double-blind trial of relapse prevention of cocaine use, tiagabine was superior to placebo on several subjective measures in reducing cocaine use.[28] Although tiagabine has not been studied for relapse to alcohol use in humans, tiagabine did not increase free-choice alcohol use in alcohol-dependent rats, whereas diazepam did.[29]

Repeated exposure to amphetamine-like psychostimulants such as cocaine produces in animals a sensitization of effects similar to kindling.[22] The threshold for cocaine to produce seizures is lowered in animals exposed repeatedly to cocaine over time.[30] Stimulant drugs inhibit $GABA_A$ receptor action and block the reuptake or promote the release of dopamine and glutamate, thereby increasing seizure potential. Polysubstance users frequently self-medicate with benzodiazepines[31] and show preference for some types of benzodiazepines over others.[32]

Dopamine plays a role in the rewarding aspects of intoxication, and GABA (via $GABA_B$ receptors) inhibits dopamine neurons. Baclofen is an agonist at $GABA_B$ receptors and inhibits the release of several neurotransmitters including dopamine and glutamate. Cocaine-abusing humans treated with baclofen experienced reduced craving for cocaine but unattenuated highs.[33] In rats, acute pretreatment with baclofen has been shown to decrease cocaine self-administration in a dose-dependent manner.[34] Tiagabine also appears to have promise in the treatment of patients with cocaine dependence.[28]

Gasior and colleagues[30] tested several drugs in the treatment of cocaine-induced seizures in mice. Of these drugs, felbamate, gabapentin, loreclezole, losigamone, progabide, remacemide, stiripentol, tiagabine, and vigabatrin protected against cocaine-induced seizures. Tiagabine offered the most potent neuroprotection with seizure suppression but also produced the most pronounced side effects (namely motor impairment). The researchers concluded that many classic antiepileptics are ineffective in murine models of cocaine-induced seizures, but drugs that enhance GABA-mediated neuronal inhibition in a manner distinct from benzodiazepines offer the best anticonvulsant profile in relation to side effects.

CONCLUSION

$GABA_A$ and $GABA_B$ inhibitory systems play substantial roles in addiction including intoxication, reward inhibition and motivation, sensitization, and kindling. Disturbances in GABA are presumed to lead to clinical manifestations of withdrawal from alcohol and sedative-hypnotics in humans. Until recently, clinical alterations of GABA receptor activity in addiction were limited to the use of benzodiazepines, but benzodiazepines have substantial drawbacks in the treatment of alcohol-related disorders. These drawbacks include serious interactions with alcohol, rebound, priming, and the risk of supplanting the alcohol dependence with benzodiazepine dependence.

Selective $GABA_B$ receptor ligands such as baclofen and tiagabine, with $GABA_A$ and $GABA_B$ activity, show

promise in the treatment of alcohol-dependent patients. Medication-assisted detoxification should provide a safe withdrawal from alcohol or other drugs and prepare the patient for ongoing rehabilatory treatment.

Drug names: amitriptyline (Endep, Elavil, and others), baclofen (Lioresal and others), carbamazepine (Tegretol, Epitol, and others), diazepam (Valium and others), felbamate (Felbatol), gabapentin (Neurontin), lorazepam (Ativan and others), midazolam (Versed and others), tiagabine (Gabatril).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, amitriptyline is not approved by the U.S. Food and Drug Administration for the treatment of depression; baclofen is not approved for the treatment of alcohol withdrawal and relapse prevention; carbamazepine, diazepam, lorazepam, and midazolam are not approved for the treatment of alcohol withdrawal; felbamate, gabapentin; loreclezole, losigamone, progabide, remacemide, stiripentol, and vigabatrin are not approved for the treatment of cocaine withdrawal seizures; and tiagabine is not approved for treating alcohol withdrawal and relapse.

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