

## How Do Alcohol and Drugs Influence Seizure Activity?

**Abuse of either one can exacerbate seizure activity, but should epilepsy patients refrain from moderate alcohol consumption or be concerned about prescription drug use?**

**M**ost neurologists will have encountered, at some point in their training and general practice, a patient who experiences seizures as the result of alcohol or drugs (both illicit and prescribed). In addition, most neurologists have encountered persons who have seizures as a result of the withdrawal of these agents. It has long been thought that a person with epilepsy is prone to seizures, and therefore more sensitive to the effects that these drugs might have. In most instances, the seizures are induced by acute over-use (or abrupt withdrawal following long-standing use) of these drugs. However, what should be the medical advice given to people whose seizures are well-controlled? Is the occasional glass of wine allowable?

### Alcohol-induced Seizures

Reports of increasing alcohol use and abuse, especially among young adults and adolescents, are frequently featured in the news. It is estimated that up to 10 to 20 percent of people are heavy drinkers; men are more likely to have a problem than women. Up to 10 percent of heavy drinkers will have seizure(s). Most often the type of seizure that occurs is a generalized tonic-clonic (GTC) seizure, also known as a convulsion. However, partial seizures may also occur.<sup>1</sup> In rat models, the GTC seems to be triggered by a substrate in the brainstem. This is a different mechanism than that proposed for the spontaneous seizures which occur in epilepsy patients: in epilepsy, the seizures begin in the cere-



bral neocortex. This difference may account for the observation that epileptiform EEG discharges occur only rarely in people who have had alcohol-related seizures.<sup>2</sup>

Although alcohol, a central nervous system depressant, may induce seizures when acutely ingested, this is uncommon. Instead, most alcohol-related seizures occur during withdrawal. The longer the chronic use of alcohol occurs, the more likely that the withdrawal symptoms will be severe, and the greater likelihood of seizures in that instance. When alcohol withdrawal seizures occur, 40 percent of the time there is a single seizure. Sixty percent of people will experience multiple seizures, most often in the range of two to four events. Three percent of people will experience alco-

hol-related status epilepticus, a medical emergency that could result in permanent neurological injury if not aggressively treated.<sup>1</sup> For most, the withdrawal seizure(s) occurs six to 48 hours after their last drink, with the majority falling in the 12-24 hour range (Figure 1).<sup>1,2</sup>

The link between alcohol and the occurrence of withdrawal seizures is unclear. In rats, changes in the regulation of specific gamma-amino-butyric-acid (GABA) receptors may play a role. As these receptors are chronically exposed to alcohol, there is an adaptation of certain GABA receptor subtypes. When alcohol is withdrawn, the inhibitory effect of these receptors is lost, resulting in over-excitation and seizures.<sup>2</sup> This is almost certainly an oversimplification of the mechanism involved in alcohol-withdrawal seizures; NMDA, kainate, serotonin and glycine receptors have also been implicated in the chain of events that lead to these episodes. The reason this has been studied is simple: by understanding the mechanism, we may be able to design better treatments for the consequences of alcohol withdrawal, and perhaps alcoholism itself.

In heavy drinkers, up to 4.5 percent will be diagnosed with epilepsy; specifically, the syndrome of recurrent unprovoked seizures. In other words, these people did not have epilepsy but, after heavy drinking, developed this syndrome later in life. Here again, the link between alcohol and the development of epilepsy is unclear. Perhaps the chronic changes in neurotransmitter receptors leads to a chronically hyperexcitable state. It has been proposed that chronic exposure to

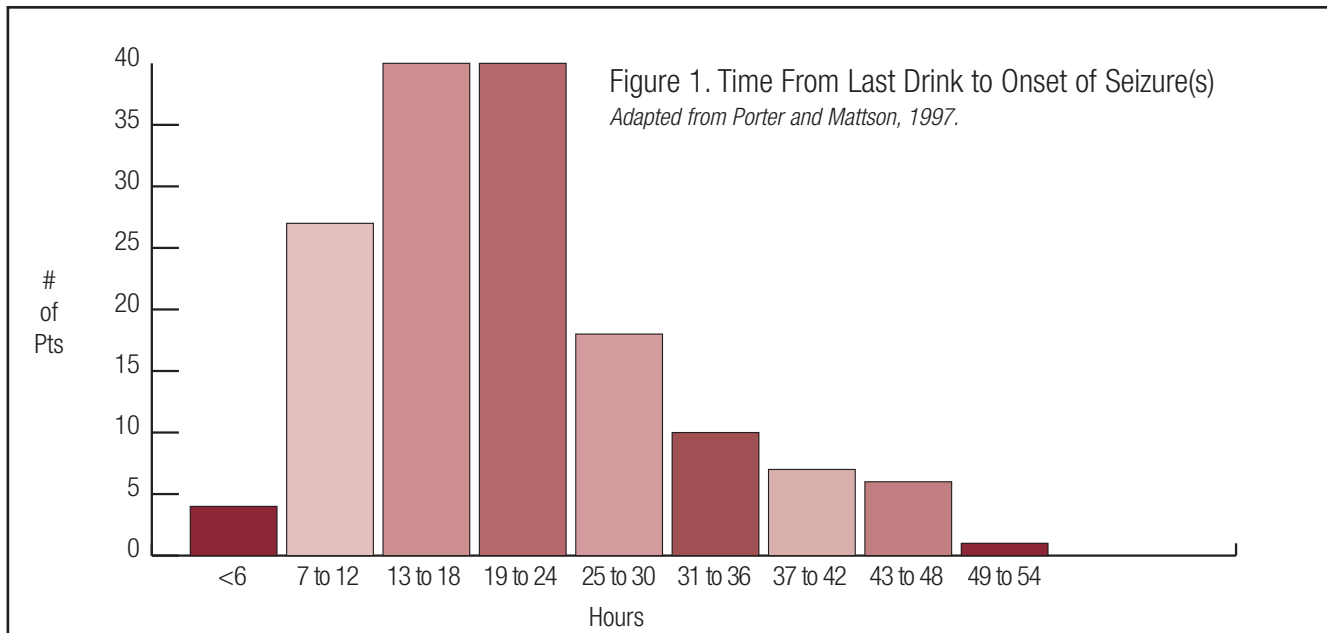


Figure 1. Time From Last Drink to Onset of Seizure(s)  
Adapted from Porter and Mattson, 1997.

alcohol leads to a phenomenon similar to kindling. There is some evidence to support this theory: rats that were induced to have alcohol-withdrawal seizures experienced longer and more severe seizures,<sup>3</sup> the longer the exposure to alcohol, the worse the withdrawal seizures become.

There are other possible explanations as well. Many drinkers have also had serious head injuries, often incurred when intoxicated. Head injuries are a risk factor for the development of epilepsy, especially if the injury causes loss of awareness for more than 30 minutes. Chronic alcohol use may lead to undernourishment or malnourishment: if hypoglycemia occurs, seizures may result. Similarly, alcohol abuse may lead to acute electrolyte abnormalities, a known cause of seizures. Finally, chronic alcohol use can result in cirrhosis and other medical problems, each of which can independently pose a risk for the development of seizures. For instance, chronic alcoholism may lead to an immunocompromised state, and therefore expose the person to an increased risk of CNS infection.

The long-term treatment of alcohol withdrawal seizures is simple: stop drink-

ing. However, in the Emergency Department (ED), when a person is in the midst of seizures due to alcohol withdrawal, benzodiazepines may be needed. Studies have shown that administration of benzodiazepines reduces the number of alcohol withdrawal seizures. Interestingly, neither phenytoin nor carbamazepine are effective in this situation.<sup>2</sup> Why then are so many people who arrive in the ED, with what seem like alcohol-related seizures, given phenytoin intravenously? Usually phenytoin is given for all of the other reasons listed above: what if the person has seizures at baseline? What if there are risk factors for epilepsy such as a past history of head injury? Some of these questions may be answered in the ED by the patient's friends or relatives; however, the history can sometimes be unavailable, especially if the person is post-ictally confused or somnolent.

Although phenytoin and carbamazepine are ineffective for acute alcohol-withdrawal seizures, some studies have suggested that several of the "newer" antiepileptic drugs may be effective. Gabapentin, topiramate and valproate may have a role in this setting.

Furthermore, there is some suggestion that gabapentin and topiramate may be useful in reducing the other systemic symptoms of alcohol withdrawal as well. Additional study is needed, however.<sup>2</sup>

Because of the effect that alcohol can have on seizures, many people with epilepsy ask, "Can I have a glass of wine or beer? Will it cause me to have seizures?" The answer to both questions is somewhat vague. However, alcohol-related seizures most often occur in the setting of overuse, abuse and withdrawal. This has led to the widespread thought, shared by most neurologists, that the occasional alcoholic drink is unlikely to cause seizures.

### Drug-Induced Seizures

Illicit excitotoxic drugs like cocaine have long been known to cause seizures. Unlike alcohol-related seizures, which occur up to two days after drinking, cocaine-induced seizures occur at the time of ingestion. As with alcohol withdrawal, cocaine withdrawal can cause single seizures, seizure clusters or status epilepticus. Here again, the treatment is aimed at the use of the drug: stop using the drug and the seizures will stop.

## Table 1. Selected Commonly Used Medicines Reported to Cause Seizures

### Often Cause Seizures

- meperidine (Demerol)
- clozapine (Clozapine)
- phenothiazines, such as promethazine (Phenergan)

### Occasionally Cause Seizures

- isoniazid
- theophylline
- beta-lactam antibiotics (such as the penicillins and cephalosporins)

### Rarely Cause Seizures

- antidepressants
- anticonvulsants
- quinolone antibiotics, such as ciprofloxacin (Cipro)
- acyclovir or its congeners, such as valacyclovir (Valtrex)
- beta-blockers, such as propranolol (Inderal)

More often than illicit drug use, the neurologist is challenged by patients who present with new-onset seizures that could possibly be related to a prescribed drug they are taking (see Table 1). Many medications have been reported to cause seizures; in fact, the list is so long that it would be nearly impossible to list them all. However, as a general rule, medications that cause seizures do so in two specific instances: (1) during use at very high doses (or during overdose) which translates into very high serum concentrations of the drug, or (2) during very rapid titration of the prescribed medication.

A good example is antidepressants: most often serotonin-specific reuptake inhibitors (SSRIs) are used. In the October 2005 installment of *Epilepsy Essentials*, attention was focused on comorbid mood disorders and epilepsy. In other words, many people with a

seizure disorder also have depression, anxiety or both. This person may need an antidepressant for mood control and an anticonvulsant for their seizures. If the antidepressants cause seizures, can they be used safely in people with epilepsy? The answer is “yes.” In fact, they are used very often for three reasons: (1) they are very effective, (2) they are well-tolerated (in general), and (3) they infrequently-to-rarely cause seizures. As we discussed last October, treating the mood disorder is probably just as important as treating the seizures in order to improve the quality of life of people with epilepsy (and comorbid mood disorders).

Even more confusing is the fact that many anticonvulsants have been reported to make seizures worse. Of course, this phenomenon is rare and not well understood. Since many of the reports occur as a case study or case series, the information is not gathered in a prospective way. Several factors may account for the perceived worsening of seizures, including a spontaneous increase in seizure activity that happens to coincide with the initiation of a new anticonvulsant. In order for the worsening to be more likely a drug effect, it should occur soon after initial exposure, reverse with withdrawal of the drug, and re-occur with re-introduction. Of course, many neurologists would understandably be unwilling to re-try a medication that they had already observed made seizures worse.<sup>3</sup>

There are several situations where anticonvulsant-induced seizures occur. The first occurs when very high doses are used or during overdose (both situations result in very high serum anticonvulsant levels). A second instance occurs when an inappropriate drug is chosen. For instance, some anticonvulsants, such as carbamazepine, have been shown to exacerbate myoclonic seizures. If a person has juvenile myoclonic epilepsy (JME), this drug would not be a good choice for two reasons: it may be less effective against

generalized-from-onset seizures (the kind that occur in JME), and it may exacerbate the seizures. Third, there may simply be a paradoxical response to the chosen AED. In this instance, the levels are “therapeutic” (*i.e.*, not toxic); however, the seizures get worse.<sup>3</sup> Many investigators are currently studying this phenomenon: little is known why this occurs or who is at the greatest risk.

Interestingly, there are two mechanisms of action that are common to the AEDs which have been reported to cause an exacerbation of seizures: those that block voltage-gated sodium channels and those that increase GABA-mediated transmission. GABA was implicated as well in the setting of alcohol-related seizures; perhaps there are common pathways through which foreign molecules (like drugs or alcohol) induce seizures. Again, further study is needed.

## Conclusions

There are many instances where seizures are provoked. Alcohol withdrawal, stimulant use and prescribed drugs are a few examples. Alcohol-withdrawal seizures may require acute treatment, usually with benzodiazepines; however, the long-term treatment is to remove the offending agent. The same is true for stimulant use: stop taking the drug. Prescribed drugs can also cause seizures, though most often this occurs in the setting of toxicity or overdose. Even anti-seizure medications, given at therapeutic doses, can exacerbate seizures. When identified, removal of the drug is required. **PN**

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2. Rogawski MA. Update on the Neurobiology of Alcohol Withdrawal Seizures. *Epilepsy Currents* 2005;5(6):225-230.

3. Sanzgar M and Bourgeois FD. Aggravation of Epilepsy by Antiepileptic Drugs. *Pediatric Neurology* 2005;33:227-234.

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