

### LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital (MGH) sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. Such consultations require the integration of medical and psychiatric knowledge. During their thrice-weekly rounds, Dr. Roffman and Dr. Stern discuss the diagnosis and management of conditions confronted. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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# Alcohol Withdrawal in the Setting of Elevated Blood Alcohol Levels

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**H**ave you ever wondered who was at risk for alcohol withdrawal or its most serious manifestation, the delirium tremens (DTs)? Have you failed to consider that alcohol withdrawal may still occur in the presence of an elevated blood alcohol level (BAL)? If you have, then the following case vignette (of a man with alcohol withdrawal that arose precipitously in the emergency department) should serve to provide the forum for answers to these and other questions related to alcohol use, abuse, and abstinence.

### Case Presentation

Mr. A, a 46-year-old man with a history of depression, alcohol abuse, and hypertension, presented to the emergency department with a complaint of suicidal ideation. At the triage desk, he acknowledged that he typically consumed approximately 12 beers every day and that his last drink had occurred 8 hours ago. He had also missed his morning dose of atenolol. His vital signs included a heart rate of 90 beats/minute and a blood pressure of 148/92 mm Hg. He appeared anxious and was mildly tremulous, although he was fully alert and oriented to person, place, and time. Although Mr. A's vital signs were mildly elevated, this was attributed to a rebound effect from his having failed to take his antihypertensive medication.

Mr. A was taken to a secured area of the emergency department, where a BAL was drawn. He was given thiamine, folate, and a multivitamin orally. One hour later, while he awaited psychiatric evaluation, Mr. A's BAL results returned, and his BAL was 150 mg/dL. At this point, Mr. A appeared increasingly tremulous and mildly agitated. He was immediately given lorazepam 2 mg orally, and other causes of delirium (including hypoglycemia and subdural hematoma) were ruled out. However, within the hour, his clinical status continued to deteriorate. Despite additional doses of lorazepam, Mr. A's heart rate and blood pressure continued to rise, and he began to respond to internal stimuli. Antipsychotics were administered but were insufficient to control his agitation, and, because higher doses of benzodiazepines were to be used, Mr. A was intubated for airway protection and transferred to the medical intensive care unit (ICU), where he eventually required a propofol drip to achieve a state of calm.

### What Is Alcohol Withdrawal and Why Is It Important to Diagnose and Treat?

Alcohol abuse is highly prevalent, occurring in 15% to 20% of primary care and hospitalized patients.<sup>1</sup> Chronic alcohol use can lead to physiologic dependence, believed to be mediated by changes in type A  $\gamma$ -aminobutyric acid (GABA) and glutamate transmission.<sup>2</sup> Abrupt cessation or decline in alcohol intake in this setting can trigger a withdrawal syndrome characterized by affective, behavioral, and cognitive changes.

These changes range from mild effects (such as anxiety and irritability) in the early stages to more pronounced effects (such as agitation, psychosis, and confusion) as withdrawal continues. However, physicians tend to pay most attention to physiologic changes consistent with adrenergic hyperactivity (as described below). Failure to recognize and treat alcohol withdrawal in its early stages can lead to more intense and problematic symptoms, such as seizures and DTs.

### **What Are the Early Signs and Symptoms of Alcohol Withdrawal?**

Mr. A's initial presentation in the emergency department included several elements consistent with early alcohol withdrawal. Any elevation in heart rate, blood pressure, or temperature, in any combination, is suggestive of the syndrome. Physical examination may also reveal tremulousness, diaphoresis, flushing, and hyperreflexia. The initial stages of alcohol withdrawal can occur as early as 8 hours after the last drink and usually involve measurable autonomic changes.

In most cases, although patients in the early stages of withdrawal experience prominent anxiety and physical discomfort, they do not exhibit gross impairment in orientation or attention, and they do not report perceptual disturbances. The presence of confusion, an altered level of alertness, or hallucinations usually signals a more advanced (and dangerous) stage of alcohol withdrawal.

### **How Much Alcohol Must Be Ingested (and over what period) for a Person to Develop Alcohol Dependence and to Be at Risk for Alcohol Withdrawal?**

There is no absolute relationship between pattern of alcohol use and the risks of physiologic dependence and withdrawal, which most likely reflects the significant number of variables, in addition to duration and quantity of alcohol use, that can contribute to dependence and withdrawal risk for a given individual. Some of these additional variables include age, medical comorbidities (such as hepatic dysfunction), concomitant medication use, and seizure threshold.

It has been easier to quantify the risk of benzodiazepine withdrawal, based on degree of benzodiazepine use (even though benzodiazepines act at the same receptor as does alcohol and are cross-reactive with it). For example, daily use of 20 mg of diazepam for 3 weeks or longer is believed to be sufficient to induce physiologic dependence.<sup>3</sup> However, the shorter half-life of alcohol (1–2 hours) has made similar predictions elusive in the case of alcohol abuse. In general, any suspicion of daily alcohol use over several weeks or more, regardless of quantity, should raise concern over possible alcohol withdrawal.

### **Can One Always Tell When the DTs Will Develop?**

Delirium tremens is a dread and sometimes fatal complication of alcohol withdrawal. In general, the DTs occur after 48 to 72 hours of abstinence from alcohol and follow a prodromal period manifest by characteristic signs and symptoms. However, for a patient with a chronically elevated BAL, the DTs may begin even when alcohol is still present in the bloodstream. Unfortunately, many clinicians in general hospital settings gain a false sense of security from a positive toxicologic screen for alcohol in patients who drink alcohol. Believing that they have a window of several hours to days before alcohol withdrawal begins, clinicians may turn their focus to other presenting or comorbid medical or psychiatric problems. However, without rapid recognition and treatment, such patients may quickly deteriorate.

### **How Can Alcohol Withdrawal Arise Despite the Presence of Alcohol in the Bloodstream?**

In patients with chronic alcohol dependence, any acute decline in the BAL can precipitate withdrawal. Such a decline may be relative or absolute. Thus, for patients who normally have high BALs secondary to large daily intake of alcohol, a notable drop in the BAL will precipitate withdrawal even if the BAL does not reach zero. In the case of Mr. A, who had a "baseline" alcohol level of 300 to 400 mg/dL, a decline to 150 mg/dL was sufficient to cause his initial symptoms of alcohol withdrawal.

Patients who use both alcohol and benzodiazepines chronically are also susceptible to alcohol withdrawal. Alcohol and benzodiazepines exert cross-reactive effects on alcohol-benzodiazepine-barbiturate receptors in the brain. Therefore, the effects of alcohol and benzodiazepines are additive in patients who abuse both substances. In patients such as these who consume alcohol daily, a reduction in the dose and frequency of benzodiazepines can precipitate a withdrawal syndrome, even in the setting of a "baseline" BAL.

### **What Additional Factors May Hinder Prompt Recognition of Alcohol Withdrawal?**

Certain medications and comorbid medical conditions can render the usual warning signs of alcohol withdrawal unreliable. In Mr. A's case, he had missed his usual dose of  $\beta$ -blocking medication, which may have contributed to elevations of his vital signs. While rapid tapering of all antihypertensive medications may cause rebound hypertension, discontinuation of  $\beta$ -blockers can also cause tachycardia. Given the overlapping effects of antihypertensive medication discontinuation and alcohol withdrawal on the autonomic nervous system, one cannot safely assume that the cause of vital sign elevations is antihypertensive withdrawal in a patient who may be experiencing both conditions. On the other hand, elevated vital

signs due to alcohol withdrawal may be masked in a patient who is taking antihypertensive medications. The ability of  $\beta$ -blockers to minimize tremor may also prevent the tremulousness associated with alcohol withdrawal.

Patients with diabetes or other conditions (including other neuropathies, infection, and advanced age) that affect the autonomic nervous system may fail to exhibit reliable changes in heart rate, blood pressure, and temperature in the early stages of alcohol withdrawal. In these patients, the only manifestations of withdrawal may be a change in mental status. By the time these mental status changes have occurred, a patient may have already progressed into the late stages of alcohol withdrawal and be more difficult to treat.

### What Consequences May Arise if the Early Warning Signs of Alcohol Withdrawal Are Overlooked?

If inadequately treated in its initial stages, alcohol withdrawal can lead to life-threatening complications within a matter of hours. These complications can be especially severe for a patient in the general hospital setting who is already compromised by active medical conditions.<sup>4</sup>

Generalized seizures (“rum fits”), if present, usually occur within the first 2 days of alcohol withdrawal. In severe cases, seizures may continue for longer periods. In addition to placing a patient at risk for mechanical injury and aspiration, continuous seizures can cause irreversible excitotoxic injury to brain tissue.

After 48 hours, an insufficiently treated patient is at risk to develop the DTs, which are characterized by profound disorientation, hallucinations (usually visual), and worsening autonomic hyperactivity. Typically, such patients become agitated and increasingly tremulous, often with marked psychomotor agitation. In severe cases, multiorgan failure and death may occur, as a consequence of hyperthermia, rhabdomyolysis, or infection.

Patients dependent on alcohol are also at risk for Wernicke’s encephalopathy and Korsakoff’s syndrome due to thiamine deficiency. Signs and symptoms of Wernicke’s encephalopathy include mental status changes, ataxia, and oculomotor abnormalities (including ophthalmoplegia and nystagmus); however, patients do not always manifest each of these warning signs, and the presence of any of them should raise one’s index of suspicion about the condition. Persistent memory deficits and confabulation may indicate progression to Korsakoff’s syndrome, which is believed to reflect bilateral degeneration of the dorsomedial thalamic nuclei. Because Korsakoff’s syndrome is irreversible, it is essential to initiate treatment with thiamine as soon as alcohol dependence is suspected. Although as little as 2 mg of thiamine may be enough to reverse Wernicke’s encephalopathy, it is routinely administered in 100-mg doses. Thiamine should always be

Table 1. The CAGE Questionnaire<sup>a</sup>

|   |  |
|---|--|
| C | Have you ever felt you should Cut down on your drinking?   |
| A | Have people Annoyed you by criticizing your drinking?  |
| G | Have you ever felt bad or Guilty about your drinking?  |
| E | Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover ( <i>Eye opener</i> )? |

<sup>a</sup>Based on Mayfield et al.<sup>5</sup>

given before glucose solutions or symptoms may acutely worsen.

### What Interventions Can Prevent Progression of Alcohol Withdrawal in These Patients?

Early intervention is essential for the treatment of alcohol withdrawal. While the potential medical complications become more severe as withdrawal progresses, with delayed intervention withdrawal becomes much more difficult to treat; it often requires large doses of parenteral benzodiazepines, ICU monitoring, and a longer duration of treatment. For example, had Mr. A been given the 2 mg of lorazepam early in the course of his alcohol withdrawal, it is possible that this dose would have been more effective in preventing the syndrome’s progression.

A history of the pattern of alcohol use, prior episodes of withdrawal, use of medications, and comorbid medical conditions can be obtained rapidly, and it should be a part of the triage process for every patient who is suspected of abusing alcohol. If there is concern about the reliability of a patient’s history, a quick search of available medical records or conversation with a family member can be invaluable.

Even in the absence of elevated vital signs or a change in mental status, the prophylactic use of benzodiazepines should be considered if the patient’s history is sufficiently concerning. Notable “red flags” include a history of withdrawal seizures or the DTs, a daily alcohol consumption of greater than 2 drinks each day, and 2 or more items of the CAGE questionnaire answered in the affirmative (Table 1).<sup>5</sup> Treatment with benzodiazepines carries its own set of risks, including disinhibition, hypotension, and respiratory compromise, especially in patients who may be predisposed to these side effects due to underlying medical conditions. Administration of benzodiazepines may also psychologically reinforce alcohol (or benzodiazepine) addiction in a patient who craves these substances. However, each of these risks must be weighed carefully against the potentially life-threatening consequences of advanced alcohol withdrawal.

Patients who already exhibit signs and symptoms of withdrawal should be treated early and aggressively. While several institutions have guidelines for which benzodiazepine to give, at what dose, and how often, no “gold standard” currently exists. At the MGH, a protocol is on-line for use by physicians from all disciplines; this

protocol relies on a patient's CAGE score, vital signs, and evidence of other withdrawal symptoms to assign varying doses of benzodiazepines for prophylaxis or treatment of alcohol withdrawal. Vital signs should be monitored frequently (e.g., as often as every 1–2 hours) as an index of dosing effectiveness. If the vital signs remain elevated, one should consider giving higher doses, or dosing at a higher frequency. Drowsiness, especially in a patient at high risk for withdrawal, should not impede dosing (in fact, this may be a good indication that the desired effect is being achieved); medication should be diminished or stopped in the setting of poor arousability or respiratory compromise. Close monitoring should continue until stabilization has been reached for 24 hours, at which point a benzodiazepine taper may be initiated. With careful attention to these measures, the dangerous complications of alcohol withdrawal may be avoided, and better medical outcomes may be achieved.

REFERENCES

1. O'Connor PG, Schottenfeld RS. Patients with alcohol problems. *N Engl J Med* 1998;338:592–602
2. Davis KM, Wu JY. Role of glutamatergic and GABAergic systems in alcoholism. *J Biomed Sci* 2001;8:7–19
3. Gonzales JJ, Stern TA, Emmerich AD, et al. Recognition and management of benzodiazepine dependence. *Am Fam Phys* 1992;45:2269–2276
4. Castenada R, Cushman P. Alcohol withdrawal: a review of clinical management. *J Clin Psychiatry* 1989;50:278–284
5. Mayfield D, McLeod G, Hall P. The CAGE questionnaire: validation of a new alcoholism screening instrument. *Am J Psychiatry* 1974;131:1121–1123

ANNOTATED BIBLIOGRAPHY

Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. *N Engl J Med* 2003;348:1786–1795  
 –This review describes the clinical presentation and management of

alcohol from the standpoint of a general practitioner. The authors discuss the use of benzodiazepines as well as adjuvant treatments, such as haloperidol,  $\alpha$ - and  $\beta$ -blocking medications, and anticonvulsants. They also review the presentation and treatment of withdrawal from opiates and stimulants.

Mayo-Smith MF. Pharmacological management of alcohol withdrawal: a meta-analysis and evidence-based practice guideline: American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. *JAMA* 1997;278:144–151  
 –In this meta-analysis, the author reviews studies of alcohol withdrawal treatment conducted through mid-1995. The use of benzodiazepines reduced the severity and duration of alcohol withdrawal, as well as the incidence of withdrawal seizures. The best results were obtained when treatment regimens were individualized and based on withdrawal scales, comorbid illness, and a history of withdrawal seizures.

Nutt D. Alcohol and the brain: pharmacological insights for psychiatrists. *Br J Psychiatry* 1999;175:114–119  
 –The author reviews the neurochemical effects of acute alcohol use as well as the putative neural mechanisms of alcohol withdrawal. Primary effects of alcohol on amino acid neurotransmitter systems and related effects on monoamine neurotransmitters are described.

Bayard M, McIntyre J, Hill KR, et al. Alcohol withdrawal syndrome. *Am Fam Physician* 2004;69:1443–1450  
 –The authors describe the recognition and treatment of alcohol withdrawal in the outpatient population, focusing on the use of benzodiazepine tapers and the use of carbamazepine. They describe the importance of follow-up treatment for alcohol abuse to prevent relapse.

Bostwick JM, Seaman JS. Hospitalized patients and alcohol: who is being missed? *Gen Hosp Psychiatry* 2004;26:59–62  
 –In this retrospective investigation of patients admitted to medical, trauma, and psychiatric inpatient wards, the authors found that patients who present to the hospital with a BAL > 300 ng/dL were often not identified as in need of alcohol-related treatment. This problem was especially pronounced on trauma services. The authors discuss the need for greater hospital-wide efforts to recognize the contributions of alcohol to medical and trauma-related illness.

Kraemer KL, Mayo-Smith MF, Calkins DR. Independent clinical correlates of severe alcohol withdrawal. *Subst Abus* 2003;24:197–209  
 –The authors retrospectively identified 6 risk factors associated with severe alcohol withdrawal in 284 patients admitted to a detoxification unit. Use of a morning eye-opener, initial Clinical Institute Withdrawal Assessment for Alcohol (CIWA) score  $\geq$  10, serum aspartate aminotransferase 80 U/L, past benzodiazepine use, self-reported history of delirium tremens, and history of participation in 2 or more alcohol treatment programs were independently correlated with severe withdrawal. An especially high risk was seen for patients with 3 or more of these factors.