Alcohol Withdrawal Syndrome

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ABSTRACT
Alcohol withdrawal syndrome is a significant problem that can complicate underlying disease states and lead to serious clinical consequences. The recognition of the early signs and symptoms of this syndrome, as well as the identification of those at highest risk for developing it, is crucial for effective prevention and management. Multiple pharmacotherapy options exist, and therapy should be guided on the basis of patient-specific factors and clinical presentation. The optimal care of these patients is dependent on a multidisciplinary approach to provide appropriate evaluation, treatment, and follow-up. Key words: alcohol, barbiturates, benzodiazepines, delirium tremens, withdrawal

It has been estimated that 126.8 million Americans have had at least one alcoholic drink in the past 30 days (U.S. Department of Health and Human Services, 1999). In addition, 23.3% of Americans reported participating in binge drinking (five or more drinks on the same occasion in the last 30 days), and 17 million people reported “heavy” use of this drug (five or more drinks on the same occasion on at least five different days in the past 30 days). Beyond its inherent effects on the body, alcohol also leads to potentially risky behaviors, as demonstrated by the fact that 31.4 million people are estimated to have driven under the influence of alcohol in the past year. It is of little surprise then that up to 20% of hospitalized patients are dependent on alcohol (Cargiulo, 2007). Those who have developed a biological dependence on alcohol are at risk for developing an alcohol withdrawal syndrome (AWS), typically within the first 24-48 hr of their last drink (McKeon, Frye, & Delanty, 2008). If left undiagnosed and untreated, this withdrawal syndrome can not only significantly complicate the underlying disease state with which the patients present but also lead to severe clinical consequences on its own (Wax, 1996). Therefore, the presentation of these patients to the emergency department is a likely occurrence, and it is essential that all healthcare professionals be familiar with their management. This review will describe the underlying pathology of AWS as well as current treatment modalities to reduce its impact and alleviate its symptoms.
PATHOPHYSIOLOGY

Chronic ingestion of alcohol impacts multiple neurologic processes and systems (Hughes, 2009). Although acute alcohol ingestion has an inhibitory effect at N-methyl-D-aspartate receptors and has an agonistic effect on γ-aminobutyric acid type A (GABA₁) receptors, reducing excitatory neurotransmission and chronic ingestion results in quite different effects on these receptors (Tsai & Coyle, 1998; Tsai, Gastfriend, & Coyle, 1995). When alcohol ingestion is sustained over a period, it eventually leads to the up-regulation of N-methyl-D-aspartate receptors and down-regulation of GABA₁ receptors as part of the body’s natural homeostatic response (Sanna et al., 2003). This adaptation underlies the basis of the hyperexcitable state and many of the symptoms that develop during withdrawal (Hughes, 2009). In addition, chronic alcohol use also leads to a dysregulation of the dopaminergic system, a system whose transmission is enhanced in withdrawal and may contribute to the characteristic hallucinations (Heinz et al., 1996; Nutt, 1999).

SYMPTOMATOLOGY AND DIAGNOSIS

Alcohol withdrawal syndrome is defined as the presence of two or more of the following after cessation or reduction of alcohol use: autonomic hyperactivity (sweating, tachycardia); increased hand tremor; insomnia; nausea or vomiting; transient visual, tactile, or auditory hallucinations or illusions; psychomotor agitation; anxiety; and tonic-clonic seizures. The syndrome can present with a wide spectrum of symptoms ranging from mild to potentially life-threatening (i.e., seizures and delirium tremens; American Psychiatric Association, 2000). In patients with prior episodes of withdrawal, more severe responses tend to be seen, a phenomenon referred to as “kindling” (Ballenger & Post, 1978). Symptoms may develop as soon as a few hours after cessation of alcohol intake (Table 1; Etherington, 1996; Tetrault & O’Connor, 2008). Early symptomatology is rather mild and progresses to more severe symptoms over the next 96 hr.

Table 1. Symptoms of alcohol withdrawal

<table>
<thead>
<tr>
<th>Onset</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>6–8 hr</td>
<td>Tremulousness, anxiety, palpitations, nausea, anorexia</td>
</tr>
<tr>
<td>6–48 hr</td>
<td>Generalized tonic-clonic seizures</td>
</tr>
<tr>
<td>12–48 hr</td>
<td>Hallucinations, visual, tactile, auditory</td>
</tr>
<tr>
<td>48–96 hr</td>
<td>Delirium tremens (tachycardia, hypertension, low-grade fever, diaphoresis, delirium, agitation)</td>
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Following the termination of alcohol consumption after sustained chronic use, the seizure threshold begins to decline, putting the patient at risk for tonic-clonic seizure activity (Hillbom, Pieninkeroinen, & Leone, 2003). This is largely attributable to the multiple neurotransmitter adaptations that occur in the brain and alterations in N-methyl-D-aspartate and GABA₁ receptors. Patients may also be at risk for developing seizure activity even if they have only had a reduction in overall alcohol consumption. When examining patients who are suspected of suffering alcohol-related seizures, care must be taken to exclude other possible etiologies for seizure activity. Very often, patients who are chronically dependent on alcohol have additional factors that may provide an explanation for seizure activity, such as prior brain injury (Verma, Policherla, & Buber, 1992).

The most serious complication of withdrawal, delirium tremens, presents in about 5% of all patient visits and carries a mortality of 5%–15% (Ferguson, Suelzer, Eckert, Zhou, & Dittus, 1996). Delirium tremens is characterized by a severe hyperadrenergic state (i.e., hyperthermia, diaphoresis, tachypnea, tachycardia), disorientation, impaired attention, and consciousness, as well as visual and auditory hallucinations. These patients may exhibit increased oxygen consumption,
increased hyperventilation leading to respiratory alkalosis, and decreased cerebral blood flow (Abraham, Shoemaker, & McCartney, 1985). The risk of delirium tremens increases in patients with a prolonged drinking history, previous episodes of delirium tremens, older than 30 years, comorbid illness, and number of days since their last drink.

Because of poor nutrition as well as the symptoms of delirium tremens that can lead to dehydration, those suffering from AWS frequently present with electrolyte abnormalities. Hypokalemia, hypomagnesemia, and hypophosphatemia are commonly present, and these not only complicate the clinical symptomatology of AWS but can also cause seizures and arrhythmias independently if left untreated (Al-Sanouri, Dikin, & Soubani, 2005; DeBellis, Smith, Choi, & Malloy, 2005). Hyponatremia is also a common presenting abnormality in beer drinkers who have multiple etiologies including acute solute dilution and solute loss (Reynolds, Padfield, & Seckl, 2006). One notable deficiency that may be present is thiamine, which has potential to lead to one of the most damaging consequences of alcohol abuse, Wernicke’s encephalopathy (Pearce, 2008).

Originally described in 1881 by Karl Wernicke, the overall syndrome is poorly understood; however, brain lesions develop with characteristics of vascular congestion, microglial proliferation, and petechial hemorrhages in a symmetric distribution around the third and fourth ventricles as well as atrophy of the mamillary bodies. Symptomatology of this condition typically includes delirium with anterograde amnesia, oculomotor dysfunction, and gait ataxia. This condition is often associated with a subacute dementia known as Korsakoff’s psychosis. Early recognition of Wernicke’s encephalopathy is crucial and is treated with the replacement of thiamine stores.

It is important to gather an accurate history of alcohol intake. Often this is challenging, and individuals may be somewhat reluctant to discuss their alcohol use. To assist with this, several screening tools exist to identify those patients whose alcohol consumption has become hazardous or harmful to their health. Some examples include the Alcohol Use Disorders Identification Test (AUDIT) and the CAGE questionnaire (Ewing, 1984; Reiner & Allen, 2002). The National Institute on Alcohol Abuse and Alcoholism recommends the use of the AUDIT questionnaire developed by the World Health Organization. This is a 10-item, self-administered questionnaire that examines alcohol intake, dependence, and adverse consequences (Reiner & Allen, 2002). A score of 8 or higher for men and 4 or higher for women necessitates further investigation into alcohol use. This evaluation has demonstrated validity in multiple patient populations and has the added benefit of identifying at-risk behavior. However, it does appear to have a lower validity in the elderly population.

The revised Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar) is the most common tool used to quantify AWS symptoms (Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989; Williams, Lewis, & McBride, 2001). This is a 10-item scale that scores the severity of nausea, sweating, agitation, headache, anxiety, tremor, sensory disturbances, and orientation on a 0–7 scale. The higher the score, the more severe the AWS and the greater the possibility that pharmacotherapy will be needed. This scale can be repeated at various periods to assess progression, repeat need for intervention, or resolution of symptoms.

**MANAGEMENT**

It is generally recommended that symptoms of withdrawal be treated aggressively to prevent further complications and limit any neurologic damage that may occur with AWS (Becker, 1998). Multiple drug classes have been utilized as either single therapy or combination therapy for the management of AWS (Table 2; Kosten & O’Connor, 2003).

**GOALS OF THERAPY**

The goals of therapy for AWS include the safe and effective treatment of withdrawal symptoms, prevention of initial and recurrent...
Table 2. Medication treatment for alcohol withdrawal

<table>
<thead>
<tr>
<th>Class</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Decreased severity of withdrawal symptoms; reduced risk of seizures and delirium tremens</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Decreased severity of withdrawal symptoms</td>
</tr>
<tr>
<td>β-adrenergic antagonists</td>
<td>Improvement in vital signs; reduction in craving</td>
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seizures, and the prevention and treatment of delirium tremens. The ideal pharmacotherapy agent would be efficacious while minimizing adverse drug events, preventing addiction, and being cost-effective. However, as any agent that possesses GABA receptor activity has the potential to cause sedation and decrease the ability of the patient to participate in an adequate neurological examination, different administration regimens have been explored in the hopes of minimizing side effects while maximizing efficacy (Hobbs, Rall, & Verdoorn, 1996).

BENZODIAZEPINES

Benzodiazepines are considered to be first-line therapy for the treatment of AWS and the prevention and treatment of seizure activity and delirium tremens (McKeon et al., 2008). Their success in this area is tied to their affinity for binding to GABA receptors in the brain, thus acting as an alcohol substitute. A meta-analysis of 11 trials, comprising 1,286 patients, which compared benzodiazepines with placebo or with an active control drug, showed that the use of benzodiazepines resulted in a clinically significant reduction in symptoms of alcohol withdrawal within 2 days (odds ratio: 3.28; 95% confidence interval: 1.30-8.28; Mayo-Smith, 1997). In prospective trials, benzodiazepines were also more effective than placebo in reducing the incidence of seizures (risk reduction, 7.7 seizures per 1,000 patients treated; \( p = 0.003 \)) and delirium (risk reduction, 4.9 cases of delirium per 100 patients treated; \( p = 0.04 \); Adinoff, 1994; Lejoyeux, Solomon, & Ades, 1998; Mayo-Smith, 1997; Mayo-Smith & Bernard, 1995).

However, there is not a consensus regarding which benzodiazepine is the most effective because randomized controlled trials are limited in sample size. When considering which agent to use, characteristics of the individual agents must be taken into account including the onset and duration of action, metabolism, and the commercially available dosage forms. In addition, the characteristics of the individual patient such as age, specific symptomatology, and severity of withdrawal symptoms must be considered. For example, current European treatment guidelines for the treatment of alcohol withdrawal seizures recommend either diazepam or lorazepam, although lorazepam is recommended over diazepam for the treatment of status epilepticus (Brathen et al., 2005), whereas the use of long-acting benzodiazepines, such as chlor Diazepam and diazepam, has been suggested to be more efficacious in the prevention of delirium (Ntais, Pakos, Kyzas, & Ioannidis, 2005). However, these agents are metabolized to active metabolites that prolong the sedative and anxiolytic effects. In addition, diazepam rapidly redistributes into adipose tissue because of its lipophilicity and can cause oversedation (Miller & McCurdy, 1984). Alternatively, intermediate acting agents, such as lorazepam or oxazepam, which yield into inactive metabolites, may be safer in patients with hepatic dysfunction (Bird & Makela, 1994). Agents with a rapid onset of action, including diazepam, alprazolam, and lorazepam, have a greater potential for abuse than those with a slower onset of action, such as chlor Diazepam and oxazepam, and thus might be inappropriate for susceptible individuals (Griffiths & Wolf, 1990). Therefore, the benzodiazepine choice...
should be individualized on the basis of the characteristics of the drug as well as patient-specific parameters.

BARBITURATES

The barbiturates may also have utility in the treatment of the AWS through a similar mechanism of action of binding to GABA receptors in the brain (Hobbs et al., 1996). Phenobarbital has the benefit of having a lower potential for abuse than the benzodiazepines; however, its efficacy in this area has not been extensively evaluated in clinical trials (Kosten & O’Connor, 2003). In addition, phenobarbital use has been attributed to respiratory depression in high doses or when combined with alcohol. Until more data are available, the role of phenobarbital in AWS resides in the management of patients refractory to standard benzodiazepine therapy, and it may have an additional role in those presenting with delirium tremens (Devetag, Mandich, Zaiotti, & Toffolo, 1983; Hayner, Wuestefeld, & Bolton, 2009).

ANTI-EPILEPTIC THERAPY

Anti-epileptic therapy has long been studied for the prevention of seizures in AWS and lessening the overall syndrome. Interestingly, placebo-controlled trials have demonstrated that phenytoin is ineffective for the secondary prevention of alcohol withdrawal seizures (Hillbom et al., 2003). Valproic acid has also been studied in a few small studies, with limited evidence to support its use over benzodiazepines (Lum, Gorman, & Slavik, 2006). Other pharmacotherapy options with limited evidence include gabapentin, lamotrigine, and topiramate. Currently, the mainstay of treatment of seizure activity secondary to AWS is benzodiazepines.

Perhaps one of the most explored, and most effective, agents in this therapeutic class has been carbamazepine. Despite its apparent inability to treat delirium tremens, it appears to be quite effective at preventing AWS. In a randomized controlled trial, Malcolm et al. (2002) compared tapering doses of carbamazepine (600–800 mg/day initially) and lorazepam (6–8 mg/day initially) in divided doses using the CIWA-Ar score to assess alcohol withdrawal symptoms. Both therapies were equally efficacious in preventing alcohol withdrawal, but carbamazepine was more effective in preventing posttreatment relapses with alcohol consumption over the 12 days of follow-up. Those patients who received carbamazepine reported fewer anxiety symptoms than those patients who received lorazepam. Carbamazepine also does not appear to have significant toxic effects when used in 7-day protocols for alcohol withdrawal (Malcolm, Ballenger, Sturgis, & Anton, 1989; Stuppaec et al., 1992). Oxcarbazepine, an analogue of carbamazepine, has shown similar efficacy in the treatment of AWS in one randomized study (Schik et al., 2005).

ADJUVANT THERAPY

β-Adrenergic antagonist agents (atenolol and propranolol) and clonidine lower heart rate and limit tremor in AWS and may be considered as adjuvant therapy (Bjorkqvist, 1975; Kraus, Gottlieb, Horwitz, & Anscher, 1985; Sellers, Zilm, & Degani, 1977). However, the pharmacodynamic effects of multiple agents including β-adrenergic antagonists, nitrates, and calcium channel blockers may be altered in AWS, increasing both their potency and risk of adverse effects (Kahkonen, 2006). Haloperidol has also been utilized to control the psychiatric symptoms of alcohol withdrawal such as combative ness, delirium, and anxiousness. However, it has been shown to be significantly less effective than benzodiazepines in preventing delirium (difference in risk, 6.6 cases per 100 patients) and seizures (difference in risk, 12.4 seizures per 100 patients; p < 0.01 for both comparisons; Pales tine & Alatorre, 1976). Thus, haloperidol therapy should be reserved for the treatment of psychiatric manifestations of AWS refractory to benzodiazepine therapy. In addition, electrocardiographic monitoring is necessary for
patients receiving both intravenous and oral haloperidol therapy because haloperidol can cause torsade de pointes through prolongation of the QT interval. Secondary to the increased risk of adverse reactions through intravenous administration, this is an unapproved route by the Food and Drug Administration. This agent, however, continues to be administered intravenously with varying levels of efficacy and toxicity throughout the United States (Hassaballa & Balk, 2003).

Correction of electrolyte and intravascular volume disturbances is also important in this population. For the treatment of Wernicke’s encephalopathy and thiamine deficiency, the administration of thiamine 100 mg intravenous/intramuscular for 5 days is typically recommended (Pearce, 2008). The correction of hyponatremia should be done cautiously to avoid the development of central pontine myelinolysis, also known as osmotic demyelination syndrome (Bourgouin, Chalk, Richardson, Duang, & Vezina, 1995; Lien, 1995). This is a complication associated with rapid increases in serum sodium that can lead to a destruction of the myelinated structures of the deep white matter of the brain. Typical recommendations are not to exceed a change in the sodium concentration of 10 mEq/L or more in 24 hr or a rate of rise of approximately 1-1.5 mEq/L/hr (Laureno & Karp, 1997). Hypovolemia, hypokalemia, hypomagnesemia, and hypophosphatemia should also be corrected on an as-needed basis and monitored routinely in the acute setting (Al-Sanouri et al., 2005; DeBellis et al., 2005).

TREATMENT REGIMENS

Benzodiazepines should be administered early to prevent alcohol withdrawal and its related complications. They may be administered using a fixed schedule or a symptom-triggered method. These two methods have different benefits and disadvantages. A fixed schedule therapy provides continuous delivery of medication through a taper and should be utilized in patients with a history of seizures and delirium tremens and in patients with acute medical illness, with surgical illness, or who are pregnant. A symptom-triggered regimen delivers medication only when a patient is symptomatic (CIWA-Ar 8 or higher) and requires a trained and attentive staff.

There is some evidence demonstrating that the use of symptom-triggered regimens, compared with continuous administration, is safe and effective and results in shorter duration of treatment and smaller quantity of medication administered (Daeppen et al., 2002; Hardern & Page, 2005; Jaeger, Lohr, & Pankratz, 2001; Saitz et al., 1994; Segatore, Adams, & Lange, 1999). In a study of symptom-triggered versus fixed schedule doses of oxazepam, only 39% of the symptom-triggered treatment group received any medication during the period of withdrawal and used six times less oxazepam than the fixed-schedule group (Daeppen et al.). In addition, Segatore et al. (1999) reported that patients treated with a symptom-triggered lorazepam protocol did not require intubation and mechanical ventilation for oversedation, and fewer restraining devices were necessary. Symptom-triggered regimens are successful when therapy is individualized for each patient through a protocol-driven approach.

CONCLUSION

Alcohol addiction and withdrawal can have serious physical and mental complications. Various medication options and treatment regimens exist for the treatment of the AWS, with benzodiazepines being the gold standard. The success of any treatment regimen, however, relies on the individualization of therapy for each patient through the use a protocol-driven, multidisciplinary approach.

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