EDITOR'S NOTE

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 twice-weekly rounds, Dr Stern and other members of the Consultation Service 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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Dr Stern is an employee of the Academy of Psychosomatic Medicine; has served on the speaker's board of Reed Elsevier; is a stock shareholder in WiFiMD (Tablet PC); and has received royalties from Mosby/Elsevier and McGraw Hill. **Drs Gross**, **Nejad**, and **Maldonado** and **Mr Stern** report no financial or other affiliations relevant to the subject of this article.

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Current Approaches to the Recognition and Treatment of Alcohol Withdrawal and Delirium Tremens: "Old Wine in New Bottles" or "New Wine in Old Bottles"

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Have you ever wondered how much alcohol a person has to drink (and for how long) before he or she risks developing a withdrawal syndrome after sudden abstinence? Have you ever wondered which methods are best to diagnose and quantify the severity of alcohol withdrawal? Have you been uncertain about which strategies can best manage alcohol withdrawal? If you have, then the following discussion and review of the literature should serve as a stimulus to enhance your understanding of the problem and to create effective solutions.

HISTORICALLY, HOW HAS ALCOHOL WITHDRAWAL BEEN VIEWED?

Descriptions of alcohol withdrawal, including delirium tremens (DTs), have filled the medical literature since the late 1700s.[1] Decades later in 1813, Pearson[2] labeled alcohol withdrawal as "brain fever" secondary to "frequent and excessive intoxication."(p327) In that same year, Sutton[3,4] coined the syndrome *delirium tremens*. More than a century later in 1953, Fraser[5] induced an abstinence syndrome (manifest by tremulousness, seizures, and "canine delirium") in chronically alcohol-intoxicated canines. Our understanding of these syndromes grew when Victor and Adams[6] used a naturalistic setting to study 206 patients hospitalized for alcoholism. After their patients' intake of alcohol ceased upon hospitalization, 12% developed seizures, 18% had hallucinations, and 5% developed DTs. Victor and Adams[6] as well as others[7,8] believed that these symptoms were related to the cessation of alcohol consumption.

Several years later, Isbell[9] conducted a classic study on 10 former morphine addicts who had consumed large quantities of alcohol for prolonged periods and then abruptly discontinued their alcohol consumption. Four of the participants drank 266–346 mL of 95% alcohol daily for 7–34 days; they developed mild symptoms of withdrawal (including tremulousness).[9] The 6 subjects who drank 383–489 mL of 95% alcohol (approximately 1 L of whiskey a day) for 48–87 consecutive days exhibited more significant signs and symptoms of alcohol withdrawal: all exhibited tremulousness and autonomic instability, 2 developed seizures, 5 had hallucinations, and 3 developed DTs.[9] This study was instrumental in demonstrating the principles of dose dependence (as the dose and frequency of alcohol consumption increased, alcohol-dependent subjects suffered from more serious withdrawal symptoms upon abstinence), tolerance over time to sedative qualities of alcohol, and withdrawal despite drinking (1 subject who reduced his intake by 50% [ie, he did not abstain] suffered from symptoms of alcohol withdrawal).[8,9]

HOW HAS ALCOHOL WITHDRAWAL BEEN TREATED?

Over the years, a variety of treatments (eg, poultice, digitalis, alcohol, chloroform, paraldehyde, chloral hydrate, lumbar punctures, hydrotherapy, electroconvulsive therapy, insulin coma therapy, and morphine) have been tried for symptoms of alcohol withdrawal.[4] In 1902, Burnke[10] determined that paraldehyde effectively treated alcohol withdrawal and DTs (in fact, it became the standard treatment for alcohol withdrawal in the mid-1900s). In the 1910s, lumbar punctures were utilized, in the 1930s, hydrotherapy became a common treatment, and in the 1940s, both electroconvulsive shock therapy and insulin coma therapy were seen as choices for the treatment of alcohol withdrawal.[4,11]

With the introduction of the phenothiazines in the 1950s, these agents also gained acceptance as a treatment for alcohol withdrawal.[12] In 1958, Laties and colleagues[13] determined that promazine and chlorpromazine were equally efficacious in the treatment of DTs. In 1959, Friedhoff and Zitrin[14] demonstrated that those who received paraldehyde recovered more quickly than did those who received chlorpromazine. Gruenwald et al[15] determined in 1960 that patients with mild-to-moderate symptoms of alcohol withdrawal responded to either promazine or triflupromazine, but those with severe symptoms of alcohol withdrawal did not respond as well to either medication and often required use of additional sedating medications. In 1961, Hart[16] demonstrated that there was no difference in the recovery time for patients treated with promazine and paraldehyde for DTs; however, those with less severe illness recovered faster with paraldehyde.

Thomas and Freedman[12] conducted a study in 1964 that compared paraldehyde and promazine in the treatment of a continuum of conditions from alcohol withdrawal to DTs. They studied 106 male patients who were admitted to a state hospital (with a diagnosis of alcohol withdrawal or DTs); these 2 groups were then divided into treatment groups that received promazine (200 mg q 4–6 h) or paraldehyde (10 mL q 4–6 h) utilizing a fixed-dosage schedule.[12] Among those with alcohol withdrawal, 65% became symptom free in 2 days after taking promazine, while only 18% became symptom free in 2 days after treatment with paraldehyde. However, promazine nonresponders did poorly (4 developed DTs and 1 died). Those with DTs who were treated with paraldehyde became symptom free in 4 days, while promazine-treated patients had a high mortality rate.[12]

In 1969, Kaim et al[7] evaluated the efficacy and safety of 4 drugs commonly used in the treatment of alcohol withdrawal (chlordiazepoxide, chlorpromazine, hydroxyzine, and thiamine); these agents were matched against placebo for the treatment of alcohol withdrawal and the prevention of seizures and DTs. The incidence of delirium for the entire sample (N = 537) was 4.5%; chlordiazepoxide-treated patients showed the lowest rate, while chlorpromazine-treated patients had the highest rate (which was equal to placebo).[7] Seven percent of the entire sample had seizures; those treated with chlordiazepoxide had the lowest rate of seizures, while chlorpromazine-treated patients had the highest rate of seizures.[7]

Widely used reference manuals have recommended a wide range of treatments for alcohol withdrawal syndrome (AWS).[17–19] In 1972, *The Merck Manual of Diagnosis and Therapy*[17] suggested that alcohol withdrawal should be treated with medications that have a similar chemical structure to alcohol. The use of paraldehyde (10 mL q 4 h–10 mL q 2 h) and chloral hydrate (0.5–1 gm q 6 h, max 1 gm q 4 h) was recommended; and it was noted that chlordiazepoxide (50–100 mg q 2 h) could be combined with these medications if clinically necessary.[17] In the same year, *The Principles and Practice of Medicine*[18] suggested the use of diazepam or barbiturates for the treatment of alcohol withdrawal seizures. While no specific treatment for DTs was stated, it was recommended that agitation be managed with environmental cues (including keeping the room well lit and avoiding phenothiazines, as the medication class decreases the seizure threshold).

In 1978, the *Massachusetts General Hospital Handbook of General Hospital Psychiatry*[19] described the treatment of DTs as being similar to the treatment of other types of delirium; it was advised that the most important intervention included surveillance with constant nursing and that physicians must be aware that these patients are at a high risk for unsafe behaviors (including falling from windows and through glass doors). The chapter author of that text also recommended that restraints be avoided unless absolutely necessary. Medication recommendations included the use of chlordiazepoxide until the patient becomes "quiet"; if the patient did not respond, augmentation with haloperidol was recommended, especially among patients with an underlying psychosis or borderline personality disorder.[19]

Another study in 1983 compared the use of barbital and diazepam in the treatment of alcohol withdrawal symptoms; barbital was found to be superior to diazepam in the treatment of DTs.[20] In 1987, an uncontrolled study assessed the utility of intravenous (IV) phenobarbital in patients who presented to the emergency department with symptoms of alcohol withdrawal.[21] None of the 38 patients treated with phenobarbital who presented with seizures had recurrent seizures 4 hours after treatment began.[21] In 1994, *Harrison's Principles of Internal Medicine*[22] recommended adequate nutrition and diligent recognition of central nervous system (CNS) symptoms of withdrawal, with the subsequent administration of another CNS depressant (with a taper of the medication over 3–5 days).

Benzodiazepines with a short half-life (eg, oxazepam or lorazepam) were recommended for patients with liver disease; however, medications with longer half-lives (eg, chlordiazepoxide or diazepam) were generally preferred.[22]

At present, benzodiazepines are the most commonly used class of medication for the treatment of alcohol withdrawal. The 4 most commonly used benzodiazepines include diazepam (which is characterized by a rapid onset and a long half-life), lorazepam (which has an intermediate onset and half-life and an absence of oxidative metabolism in the liver), chlordiazepoxide (which has an intermediate onset of action and a long half-life), and oxazepam (which has a slow onset, a short half-life, and absence of oxidative metabolism in the liver). In addition, a few reports have suggested that barbiturates are useful in the treatment of alcohol withdrawal.[23] Several alcohol withdrawal treatment pathways have been produced[24]; some utilize fixed-dosing schedules, while others recommend symptom-based dosing.[25]

WHAT INFORMATION IS AVAILABLE TO PATIENTS AND THEIR FAMILY MEMBERS REGARDING RISK FACTORS FOR ALCOHOL WITHDRAWAL?

In the digital age of the 21st century, a simple Internet search of "alcohol withdrawal" yields approximately 1.63 million results in 0.38 seconds. Ranging from Google Health[26] to WebMD[27] to Wikipedia[28] to the American Academy of Family Physicians,[29] results for information on alcohol withdrawal for patients and their family members come from far and wide. However, the Internet is not the only source for information concerning alcohol withdrawal and its risks. Many books on alcohol withdrawal have been published. These include *A Choice Theory Approach to Drug and Alcohol Abuse,*[30] *Alcohol Withdrawal Treatment Manual,*[31] and *Alcohol Withdrawal: A Medical Dictionary, Bibliography, and Annotated Research Guide to Internet References*.[32] Also in circulation are learning tools for those on the go, such as *Alcohol Withdrawal Pocketcards*,[33] alcohol withdrawal's version of flash cards, made popular by students studying for tests.

Described as referring to symptoms that may occur when a person who has been drinking too much alcohol every day suddenly stops drinking alcohol, some patients are more susceptible to alcohol withdrawal than are others. Information regarding risk factors for alcohol withdrawal are readily available to the general public (including patients and their family members). One article from the National Institute of Mental Health stated: "Risk factors for prolonged or complicated alcohol withdrawal include lifetime or current long duration of alcohol consumption, lifetime prior detoxification, prior seizures, prior episodes of DTs, and current intense craving for alcohol."[34(p62)]

Manifestations of alcohol withdrawal (as listed on the Internet) include mild-to-moderate psychological symptoms (eg, jumpiness/nervousness, shakiness, anxiety, irritability or easy excitability, rapid emotional changes, depression, fatigue, difficulty thinking clearly, bad dreams) and mild-to-moderate physical symptoms (eg, headache, sweating, nausea and vomiting, loss of appetite, insomnia, pallor, rapid heart rate, eye pupils enlarged, clammy skin, tremor of the hands, and involuntary and abnormal movements of the eyelids), as well as severe symptoms (eg, DTs, agitation, fever, convulsions, and blackouts).

Information about the onset of alcohol withdrawal after excessive use followed by abstinence includes its development within 5–10 hours after one's last drink; however, it may not appear until 7–10 days following cessation of use. The more heavily one drinks, the greater the likelihood that symptoms of alcohol withdrawal will appear once drinking ceases. The likelihood of developing severe withdrawal symptoms also increases if the patient has or experiences other medical problems.

WHAT IS CONSIDERED COMMON KNOWLEDGE ABOUT THE TREATMENT OF ALCOHOL WITHDRAWAL?

When evaluating the treatment of alcohol withdrawal's symptoms, goals range from the immediate to the long term. The most pressing goal is to treat the withdrawal symptoms in a timely fashion; thereafter, one needs to prevent complications of alcohol withdrawal and to begin long-term therapy to promote and ensure abstinence (so that the patient does not drink in the future). The information available to the general public reflects the fact that in most cases, the patient should stay at the hospital or in an inpatient facility for constant observation that will include, but is not limited to, the monitoring of blood pressure, body temperature, breathing, and heart rate, as well as fluid and electrolyte levels.[26] Often, patients are told they will receive IV fluids, and some may need drugs to depress the CNS to reduce the symptoms of alcohol withdrawal.

The Internet informs readers that a variety of treatments are available and may consist of sedating the patient (moderately) for over a week until withdrawal has completely run its course.[26] During this time, the doctor/medical staff must be careful to observe the possibility of signs of DTs. Testing for and treatment of various other medical problems associated with alcohol use (including liver disease, blood clots, brain and heart disorders, malnutrition, and nerve damage) are both recommended and necessary.

The final step in the treatment of alcohol withdrawal (as presented on the Internet) is the "drying-out period," during which time no alcohol is allowed. The best long-

term treatment for those who have undergone alcohol withdrawal is lifelong abstinence, which can be aided by rehabilitation involving social, as well as medical, support.

WHAT IS THE PRESUMED PATHOPHYSIOLOGY OF ALCOHOL WITHDRAWAL?

In the normal human brain, extracellular dopamine levels in the nucleus accumbens are controlled by inhibitory γ-aminobutyric acid (GABA) transmission and by excitatory glutamatergic activity.[35–37] Acute alcohol ingestion has an inhibitory effect at *N*-methyl-D-aspartate (NMDA) receptors, reducing excitatory glutamatergic transmission and exerting an agonistic effect at $GABA_A$ receptors.[38–40] Thus, acute alcohol intake decreases the activity of GABAergic neurons in the ventral tegmental area, disinhibits the GABA-mediated dopaminergic afferents to the nucleus accumbens, and therefore increases dopamine levels.[36,37] The initially stimulating response of alcohol is associated with the pleasurable effects of, and craving for, alcohol.[41]

In the short term, alcohol intake depresses the inhibitory centers of the cerebral cortex resulting in early symptoms of intoxication (eg, euphoria, exaggerated feelings of well-being, ataxia, loss of self-control, and dose-dependent sedation). Conversely, long-term alcohol intake leads to an up-regulation of NMDA receptors and down-regulation of $GABA_A$ receptors leading to the development of tolerance. In the case of habituated individuals, abstinence from alcohol leads to a rebound stimulatory effect and increased excitability of the nervous system (eg, with enhanced NMDA receptor function, dysregulation of the dopaminergic system, and reduced GABAergic function).[42–44]

With regard to the catecholamine system, chronic alcohol consumption is associated with desensitization of α_2 receptors and/or impaired α_2 agonist activity. Conversely, a rise in the amount of extracellular dopamine leads to eventual increases in available norepinephrine (NE), as dopamine is metabolized to NE by dopamine-β-hydroxylase. These changes inhibit the sensitivity of the autonomic adrenergic system with a resulting receptor up-regulation and adrenergic hypersensitivity.[45] In fact, animal studies have demonstrated that a relatively large acute dose of alcohol produces sympathetic innervation with a decrease in the turnover of NE in both the brain and peripheral organs. Studies have shown a significant decrease in hypothalamic NE levels 1 hour after a single dose of alcohol.[46] Yet, with chronic alcohol intake, the opposite effect is observed. In fact, chronic alcohol intake led to acceleration in the turnover of central and some peripheral NE-containing neurons (eg, in the heart and in the adrenal medulla).[46]

Animal studies have also confirmed that alcohol administered as either an acute or chronic dose affects both central and peripheral NE neurons and the adrenal medulla.[46] To examine the turnover in NE neurons, 3H-tyrosine was injected subcutaneously in rats that had been receiving either ethanol or sucrose diets. The animals were then sacrificed (10, 30, 60, 180, or 360 minutes later). At every interval, the labeled NE was found at a higher level in the alcohol group, suggesting that the synthesis of NE was higher in the ethanol-treated rats. The rate of release of 3H-NE also appeared to be higher in these animals, since the accumulation of 3H-metabolites was also significantly greater.[46]

Since the synthesis of NE (controlled mainly by the activity of tyrosine hydroxylase)[47] was increased, tyrosine hydroxylase activity in the brain was probably higher in rats exposed chronically to ethanol; this leads to higher levels of 3H-NE metabolite by-products. In fact, cerebrospinal fluid (CSF) concentrations of 3-methoxy-4-hydrophenylglycol (MHPG) were markedly elevated during acute alcohol intoxication and successively declined during 1 and 3 weeks of abstinence.[48,49] Similarly, CSF levels of MHPG were increased in patients undergoing alcohol withdrawal and eventually improved during recovery.[50,51]

HOW EFFICACIOUS IS DEXMEDETOMIDINE FOR ALCOHOL WITHDRAWAL AND OTHER TYPES OF DELIRIUM?

Dexmedetomidine is a lipophilic imidazole derivative approved by the US Food and Drug Administration in 1999 for sedation in the intensive care setting. It has an affinity for α_2 adrenoceptors that is 1,620 times higher than for α_1 receptors and 8 times higher than the other α_2-agonist drug, clonidine, available in the United States.[52] Like all α-agonist agents, dexmedetomidine works by binding the presynaptic α_2-adrenergic receptors and decreasing the release of NE at the locus ceruleus; this leads to a non-GABAergic–mediated sedation. Dexmedetomidine's sedative, anxiolytic, and analgesic effects are produced through specific and selective activation of postsynaptic α_2-adrenoreceptors.

Given the effects of chronic alcohol abuse and withdrawal on the catecholamine system, it makes sense to consider the role of α_2 agonists (eg, clonidine) in the management of alcohol withdrawal. Clonidine has been efficacious in managing the physical (eg, elevated heart rate and blood pressure) as well as the psychological (eg, anxiety) symptoms associated with alcohol withdrawal.[53–60]

For example, Baumgartner and associates[53] randomly assigned 50 adults experiencing AWS to receive either prophylactic chlordiazepoxide or transdermal clonidine (Catapres patch). They found that no patient in either group developed seizures or progressed to DTs. Yet, the group that received clonidine had a better overall

response to medical therapy (as assessed by the Alcohol Withdrawal Assessment Scale), were less anxious (as assessed by the Hamilton Anxiety Rating Scale), and had lower heart rates and blood pressure readings.[53]

Similarly, Dobrydnjov and coworkers[56] evaluated the prophylactic use of an α_2 agonist (clonidine) and a benzodiazepine (diazepam) on the attenuation of postoperative AWS (in those with daily alcohol use > 60 g) following transurethral resection of the prostate performed under spinal anesthesia. Eighty percent of the diazepam-treated patients developed symptoms of alcohol withdrawal, as compared with only 10% in the clonidine-treated group.[56] Of note, 13% of patients in the diazepam-treated group developed DTs, while none of those treated with clonidine did. Finally, patients who received diazepam were more likely to develop tachycardia and an elevated blood pressure 24 to 72 hours after surgery; whereas, none of the clonidine-treated patients manifest a hyperdynamic circulatory reaction.[56]

Unfortunately, there are less data on the use of dexmedetomidine in alcohol withdrawal; this may be more a function of how new and expensive this agent is than of its efficacy. However, Riihioja and colleagues[61–64] have demonstrated that dexmedetomidine effectively controls alcohol withdrawal in laboratory animals. Numerous case reports of dexmedetomidine's efficacy for management of severe alcohol withdrawal exist; typically, these are cases that have failed more conventional management strategies (eg, use of benzodiazepines).[65–70]

To date, no randomized clinical trials have been published on the use of dexmedetomidine for treatment of AWS; however, 3 abstracts containing case series were presented at the American Society of Anesthesiology on the potential of this drug in AWS. The first by Cooper and colleagues[71] presented a case series of 64 patients collected over a 6-month period; all had a history of heavy alcohol use and were admitted for elective surgical procedures. Of these, 8 patients (12.5%) developed symptoms consistent with DTs and were transferred to the intensive care unit (ICU). In an attempt to control heart rate, blood pressure, and agitation, each patient underwent (and failed) an IV lorazepam trial (2–4 mg every 6 h).[71] Each patient required further sedation, thereby increasing their risk of respiratory depression and endotracheal intubation. Then, dexmedetomidine was initiated (via a 1.0 μg/kg bolus, followed by a continuous infusion at 0.2–1.0 μg/kg/h) to supplement sedation with benzodiazepines. None of the patients required adjunctive support of their airway, had a decrease in O_2 saturation, or required endotracheal intubation. No complications were noted, and dexmedetomidine was weaned slowly after 48 hours without signs or symptoms of further withdrawal.[71]

Prieto and coworkers'[72] case series was based on a retrospective review of medical-surgical patients with AWS during a 4-year period (2003–2007) treated with dexmedetomidine after failure to respond to benzodiazepine treatment. Of those with AWS, 68% (n = 17) were successfully treated with dexmedetomidine alone or as an adjunct to typical AWS therapy; clinical endpoints were extubation and/or control of agitation and other AWS symptoms. In 3 patients (16%), use of dexmedetomidine failed to control agitation; 2 patients (11%) developed hypotension that required discontinuation of dexmedetomidine. The researchers concluded that dexmedetomidine was a safe and effective treatment for AWS but warned that "due to its lack of anticonvulsant activity, however, dexmedetomidine may be inappropriate as sole therapy for AWS."[72(pA1313)]

Kandiah and colleagues[73] reported on the use of dexmedetomidine in 7 critically ill patients who failed a trial of IV benzodiazepines. Their results suggested that agitation and autonomic control was achieved within 2 hours of the initiation of dexmedetomidine. None of the patients developed seizures. Patients were extubated while taking dexmedetomidine, and its discontinuation was not associated with recurrence of AWS.[73]

Dexmedetomidine has been found to be an excellent alternative for sedation in ICU settings, and studies suggest its use has been associated with a significant reduction in the development of postoperative withdrawal.[74] Changes in the noradrenergic system have been described as potential causative factors in delirium, with increased levels of plasma free MHPG concentrations observed in some delirious states.[75,76] It is possible that the evolution to DTs involves a similar alteration of the catecholamine system.[77]

Given that α_2-agonist agents (eg, clonidine and dexmedetomidine) effectively control the autonomic manifestations of AWS and have been shown to reduce agitation and other behavioral manifestations of AWS (eg, anxiety), their use in the management of AWS should be considered. The use of α_2 agonists should be limited to an adjunctive role with other agents (eg, benzodiazepines or barbiturates) for the management of AWS since they have no known anticonvulsant properties. Because α_2 agents (particularly dexmedetomidine) control symptoms of withdrawal and agitation without causing respiratory depression or contributing to the development of delirium (as benzodiazepines do), their use in the control of AWS should be investigated further.

WHAT IS PROPOFOL AND HOW DOES IT WORK?

The first clinical trial of propofol (an alkyl phenol administered intravenously) was conducted in 1977 by Kay and Rolly[78] and established the potential benefit of propofol as an anesthetic induction agent.[78] Since then, laboratory studies have suggested that propofol has many pharmacologic effects, including the ability to reduce cerebral blood flow, cerebral metabolic rate,

and intracranial pressure and the ability to act as an antioxidant (by decreasing lipid peroxidation) and as a free radical scavenger, activating $GABA_A$ receptors, inhibiting glutamate receptors, and reducing extracellular glutamate levels by inhibiting Na^+ channel-dependent glutamate release.[79–83] Currently, propofol is widely used for the induction and maintenance of anesthesia and for the maintenance of sedation in the ICU.

Although a variety of agents act in a similar fashion at the benzodiazepine-barbiturate-alcohol receptor and are cross-reactive with alcohol, benzodiazepines have become the cornerstone of therapy for AWS. However, other medications (eg, β-blockers, clonidine, antiepileptic drugs, serotonin-dopamine antagonists) have served as adjunctive agents for treatment of alcohol withdrawal.[84] In patients suffering from AWS refractory to conventional treatments (eg, with escalating doses of benzodiazepines), propofol has been efficacious in the rapid control of autonomic instability and agitation associated with the syndrome.[85–91]

How Does Propofol Work?

Several of propofol's properties account for its efficacy in severe complicated alcohol withdrawal and DTs. Propofol appears to have less cross-tolerance than benzodiazepines, is easily titratable, and is rapidly cleared from the body.[92,93] Furthermore, propofol is similar to alcohol in that it affects both $GABA_A$ and glutamate receptors.[94]

How Efficacious Is Propofol?

Case series have described the use of propofol in treatment-refractory AWS. McCowan and Marik[88] described 4 patients with AWS initially (and inadequately) treated with escalating doses of benzodiazepines. These patients improved (ie, they achieved autonomic stability and became calm) with subsequent treatment with propofol. Subramaniam and colleagues[90] described 3 patients with AWS refractory to benzodiazepines alone; however, they were treated successfully with addition of propofol.

Propofol distributes rapidly throughout the body, including the CNS; its pharmacokinetic profile is best described by a 3-compartment model.[93] In phase 1, there is fast distribution of the drug from the blood to the tissues, with a half-life of several minutes. In phase 2, there is rapid metabolic clearance from the blood, with a half-life of 34 to 56 minutes. In phase 3, there is a slow return of the drug from poorly perfused tissue compartments into the bloodstream, with an mean half-life of 3–8 hours.[95]

How Is Propofol Used?

Maintenance of sedation (via an infusion at 25–75 μg/kg/min) or anesthesia (at 100–200 μg/kg/min) can be achieved and titrated to the patient's response.[91] Recovery from propofol is short; typically after 30 minutes or less following discontinuation of prolonged infusion, propofol concentrations drop to less than 1 mg/L.[95] There is no standard protocol for the taper of propofol when used for the control of AWS; some clinicians abruptly discontinue the infusion while others prefer to wean the drug over a few hours.

CAN ALCOHOL BE USED TO TREAT ALCOHOL WITHDRAWAL IN THE GENERAL HOSPITAL?

Numerous clinical trials and published reports have described the use of ethanol for the prevention and treatment of alcohol withdrawal.[96–104] Spies and colleagues[96] conducted a randomized open-label controlled trial and compared IV ethanol and other drug regimens. They studied 197 alcohol-dependent patients undergoing resection of upper gastrointestinal carcinomas and randomly assigned them to 1 of 4 prophylactic treatment regimens: flunitrazepam-clonidine, chlormethiazole-haloperidol, flunitrazepam-haloperidol, or ethanol. The investigators found no difference between the groups with respect to the development of AWS and detected no significant differences in the length of stay in the ICU or in the frequency of complications.[96]

In a prospective uncontrolled study of 153 patients with thermal injury, 10% IV ethanol (at initial infusion rates of 50–100 mL/h) was used to prevent AWS.[98] None of the patients developed signs of alcohol withdrawal during the course of the ethanol infusion, and only 1 patient developed undue sedation due to ethanol administration.[98]

Large variability exists in the quality of the methodology (including doses used and monitoring of blood alcohol concentrations) as well as the results regarding use of IV ethanol. Treatment regimens have combined IV and enteral administration, used different concentrations of ethanol (5% versus 10%), and used different rates of administration. Goal blood level concentrations have ranged from undetectable in asymptomatic patients to maintaining a state of intoxication with concentrations of 0.38% (380 mg/dL) in patients.[97,99,104] In addition, the literature describing the use of ethanol has focused almost entirely on the prevention of AWS and alcohol-associated delirium rather than on the treatment of ongoing symptoms of alcohol withdrawal or DTs. Due to ethanol's pharmacokinetic profile and its relatively narrow therapeutic index, its use has not been advised in critically ill individuals.[104]

Typically in general hospital settings, 5% ethanol has been administered via use of a central line or the largest available peripheral vein as long as there are no contraindications to its use (eg, acute intracranial

hemorrhages, partial spinal cord injuries, extensive hepatic disease, pancreatitis, and epilepsy).[97] Initial infusions begin at a rate of 50 mL/h, and if symptoms of alcohol withdrawal improve, the infusion is maintained for at least 48 hours. If withdrawal symptoms continue, the infusion rate is increased by 25–50 mL/h until control of symptoms is achieved. Therapeutic serum levels of alcohol with this method have not been established, although levels would be expected to vary among patients given differences in patients' alcohol histories. Once symptoms are controlled, the ethanol drip may be weaned (as tolerated), generally at a rate of 25% daily. Patients should not be discharged from the hospital less than 24 hours after discontinuation of the infusion to allow the metabolism and excretion of ethanol and to ensure that relapse (with autonomic instability) from re-emerging alcohol withdrawal does not develop.

WHAT TYPES OF TEACHING STRATEGIES CAN GUIDE THE RECOGNITION AND TREATMENT OF ALCOHOL WITHDRAWAL?

Since clinicians working at the bedside must collaborate on the identification and treatment of alcohol withdrawal (as well as on safety interventions and interpersonal management of the confused patient), strategies to improve both knowledge and skills are sorely needed. Overlapping symptoms of alcohol withdrawal, delirium from other causes, dementia, and comorbid conditions can contribute to diagnostic errors.[105,106] Therefore, educational efforts are needed to help clinicians navigate the course of delirious patients.

Teaching should target nurses, medical students, residents, and faculty from medical and surgical specialties. Traditional models of education have included lectures, reading materials,[23,24,66,106–114] and bedside rounds (that provide a breadth of opportunities to hone individual skills). Recently, simulation training has gained wider use as a teaching tool. Simulation provides the opportunity for participants to learn the requisite assessment and treatment skills and to provide them in a safe environment.[117,118] This approach allows participants to fully engage in the learning experience, and it facilitates the integration of clinical experience, reflective observation, and the conceptualization of the clinical challenge. Active participation generates an emotional engagement that helps to solidify knowledge learned.[119]

While simulation has been used for decades in the field of medicine and psychiatry, the advent of voiced high-fidelity manikins has generated an unlimited variety of clinical encounters that may be replicated.[120] Physiologic parameters (eg, respiratory rate, blood pressure, heart rate, and O_2 saturation) and verbal responses may be programmed to mimic myriad clinical conditions and then be manipulated in response to interventions enacted by participants.

At our institution, an interdisciplinary simulation training program was created to evaluate and care for patients with delirium (including alcohol withdrawal).[121] Physician/nurse teams are presented with a clinical scenario involving a patient with an altered mental status; clinicians then collaborate to treat the "patient." Immediately following the training scenario, a debriefing session offers the participants the opportunity to process their reactions to the scenario and to reflect on their performance (both as an individual and as a member of a team).[122] A didactic presentation that emphasizes a systematic approach to life-threatening etiologies of delirium (including alcohol withdrawal) concludes the training program.

CONCLUSION

Alcohol withdrawal is prevalent and problematic among general hospital patients. Timely recognition and treatment (with benzodiazepines, alcohol, and/or other cross-reacting agents, as well as β-blockers and α_2 agonists) is required to reduce its morbidity and mortality. In addition, supportive care (including use of IV fluids and nutritional supplementation with multivitamins, thiamine, and glucose) should be administered to prevent Wernicke's encephalopathy (a disorder of thiamine deficiency associated with gait abnormalities, mental status changes, and ophthalmoplegia) and Korsakoff's psychosis.[123]

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