Patients With Alcohol Use Disorder

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OVERVIEW

Alcohol remains one of the most prevalent and clinically relevant drugs of abuse, with an estimated 75 million people worldwide meeting criteria for an alcohol use disorder (AUD) in 2004.[1] In the United States, two-thirds of all adults consume alcoholic beverages; an estimated 8 million Americans meet criteria for a severe AUD. Furthermore, approximately 500,000 individuals each year experience acute alcohol withdrawal severe enough to require pharmacologic management.[2] The annual healthcare cost related to alcohol use exceeds US$250 billion, and an estimated 85,000 deaths a year in the United States alone can be attributed to alcohol use.[3,4] Alcohol accounts for roughly one-tenth of all deaths among working-age US adults.[5] Thus, it is no surprise that alcohol is responsible for more psychiatric and neuropsychiatric problems in general hospitals than from all other substances combined. Studies estimate that 25% to 50% of all patients hospitalized for injuries are intoxicated at the time of their trauma and that the prevalence of alcohol-related problems in medical inpatients ranges from 12.5% to 30%.[5,6]

Given the prevalence of alcohol use in our society and the potential for significant medical, psychiatric, and psychosocial complications associated with chronic use and alcohol withdrawal, all psychiatrists who work in general hospitals should be skilled in the recognition and treatment of AUD. In fact, failure to diagnose and effectively treat alcohol use in hospitalized patients is exceedingly costly (in terms of morbidity and expense); a retrospective study at a major teaching hospital estimated that $4.3 million of charges were sustained by 160 patients with a substance use disorder (SUD) over a 23-day period and these could be attributed directly to the patients' SUD.[7] Prompt identification of patients with AUD in particular, and initiation of acute inpatient treatment (including acute withdrawal management, engagement with an addiction consultation service and identification of suitable aftercare resources), has been associated with improved outcomes (e.g., abstinence, longer time since the last drink, job performance, and personal happiness).[8,9]

CASE 1

Mr. T, a 55-year-old unkempt homeless man was admitted to the hospital after sustaining 30% total body surface area burns to his face, chest, and upper extremities. His examinations fluctuated between profound sedation and assaultive behavior, when attempts were made to arouse him. Examiners also commented on the "smell of alcohol" on his breath. Review of prior notes indicated an extensive history of visits for alcohol intoxication, albeit without concerns for self-harm. EMT notes indicated that Mr. T's injuries were not self-inflicted, and instead resulted from an altercation. There was no clear history of alcohol and substance use (beyond presumed daily drinking), and no history of complicated withdrawal. His medical record was replete with requests to leave the hospital against advice after acute intoxication resolved.

Mr. T was admitted to the burn service with a plan for urgent wound exploration and management. Psychiatry consult was requested "STAT" for assistance with agitation, as well as for prophylaxis and management of alcohol withdrawal.

His initial examination was notable for tachycardia (with a heart rate of 120 beats/minute), systolic hypertension (with a blood pressure, BP, of 165/80 mmHg), and an oxygen level of 96% on 3L nasal cannula. Laboratory tests were notable for a blood alcohol level (BAL) of 3,600 mg/mL, as well as for cannabis detected on the urine toxicology screen. Otherwise, labs indicated elevated transaminases (ALT 120 U/L, AST 235 U/L), but a normal MCV (95) and a normal PTT/INR.

Mr. T received a total of 10 mg of intravenous (IV) lorazepam while in the Emergency Department (ED), and he was deeply sedated. His neurologic exam did not reflect any signs, including tremor, suggestive of imminent alcohol withdrawal, but did reveal mild horizontal nystagmus. The mental status exam remained consistent with encephalopathy, but was without paranoid ideation or hallucinations. When he awoke, Mr. T stated that he "drinks a lot, 100 beers a day," and then he fell asleep.

Following surgery, Mr. T was started on a phenobarbital taper (based on his ideal body weight, his expected high risk for withdrawal, and his high risk of associated complications). He tolerated the treatment well. His mental status remained "pleasantly confused" and his vital signs showed persistent low-grade tachycardia, although both improved with wound debridement and treatment of his infectious contributors. As his mental status continued to improve further, Mr. T also agreed to meet with clinicians from the addiction consultation team to manage his alcohol use disorder (AUD). After 3 weeks on the inpatient burn surgical service, Mr. T was transferred to an inpatient medical rehabilitation program with a plan to transition him to an outpatient addiction treatment program after discharge.

SCREENING FOR ALCOHOL USE DISORDER

Alcohol use is widespread; roughly 50% of the adult US population reports using alcohol within the past 30 days, although there is considerable variation in the pattern and severity of use. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines two categories of problematic drinking:

- Use of more than 14 drinks per week or more than 4 drinks on any day, for men under the age of 65 years
- Use of more than 7 drinks per week or more than 3 drinks on any day for women and/or any adult 65 years and older.[10]

Nearly 30% of all US adults who use alcohol do so in a potentially unhealthy manner, including 15% who exceed the recommended daily limit, 10% who exceed both daily and weekly limits, and 2% who exceed the weekly limit alone.[10] The highest rates of risky alcohol use occur in younger adults (18–29 years old), males, and Native Americans.[11]

Many tools are available to providers to help identify risky alcohol use. These include a variety of questionnaires that can be administered to inpatients or outpatients. Laboratory testing can be useful (especially if there is a concern for minimization of reported use), although such tests are not routinely recommended for screening purposes. The most commonly encountered screening tools are outlined in Tables 14-1 and 14-2, and include the AUDIT-C screening test (Table 14-1) and the CAGE questionnaire (Table 14-2). The AUDIT-C asks three questions and is considered positive when scores are >4 in men or are >3 in women, with a 90% sensitivity, and an 80% specificity rate. The CAGE asks four questions; >2 positive responses carries 77% sensitivity and 79% specificity for the detection of an AUD.[12] If the CAGE is used for screening, even a single response should be considered as screening positive.

TABLE 14-1 AUDIT-C Questionnaire for Alcohol Problems Screening[a]

1. How often did you have a drink containing alcohol in the past year?
   - Never (0 points)
   - Monthly or less (1 point)
   - 2–4 times per month (2 points)
   - 2–3 times per week (3 points)
   - >4 times per week (4 points)
2. In the past year, how many drinks did you have on a typical day when you were drinking?
   - 1–2 (0 points)
   - 3–4 (1 point)
   - 5–6 (2 points)
   - 7–9 (3 points)
   - >10 (4 points)
3. How often did you have six or more drinks on one occasion in the past year?
   - Never (0 points)
   - Less than monthly (1 point)
   - Monthly (2 points)
   - Weekly (3 points)
   - More than once a week, or daily (4 points)

[a]AUDIT-C is scored 0–12, with score >4 (men) and >3 (women) considered positive for problematic drinking.

ACUTE INTOXICATION AND THE PSYCHIATRIC SEQUELAE OF ALCOHOL USE

Ethanol, the primary active component of alcoholic beverages, is a water-soluble alcohol compound primarily absorbed via the gastrointestinal (GI) mucosa of the duodenum and small intestine (80%) and the stomach (20%).[13] The compound undergoes hepatic metabolism via alcohol dehydrogenase; in fact, a smaller distribution volume and reduced expression of this enzyme in women is believed to account for their increased susceptibility to alcohol intoxication. In most individuals, peak serum alcohol levels are reached 30–90 minutes following ingestion. Resolution of the acute toxidrome follows steady-state kinetics, so that a 70-kg male is expected to metabolize approximately 10 mL of absolute ethanol or 1.5 to 2 drink equivalents (1.5 oz whiskey = 5 oz wine = 12 oz beer) per hour.[14]

The effect of alcohol on the central nervous system (CNS) is surprisingly complex, and involves changes across multiple neurotransmitter systems. The primary mechanism of action is achieved through gamma amino butyric acid (GABA) agonism, which accounts for the CNS depressant effects of alcohol as well as for the behavioral disinhibition seen with use of the compound. With chronic exposure, further CNS changes occur, primarily in response to exogenously increased GABA tone, including a decrease in GABA receptors, decreased GABA production and decreased binding affinity to the receptor complex.[15] More importantly, these changes also lead to an increase in endogenous glutaminergic tone (an attempt to maintain homeostasis) and the development of complicated alcohol withdrawal symptoms.[16–18]

Signs and symptoms associated with acute alcohol intoxication are undoubtedly familiar to virtually all clinicians. Mild intoxication can present as impulsivity, elation, slight slurring of speech, and gait impairment. As the blood alcohol content increases, these findings become more pronounced, and include marked disinhibition, irritation, or even frankly aggressive behavior. The neurologic examination is notable for nystagmus, impaired coordination (ataxia), and unsteady gait. Attention and memory consolidation are commonly impaired, resulting in reduced recall of the intoxication, or even full "blackouts" in more severe cases. With severe

TABLE 14-2 CAGE Questionnaire for Alcohol Problems Screening[a]

C	Have you felt the need to **C**ut down on your drinking?
A	Have people **A**nnoyed you by criticizing your drinking?
G	Have you ever felt bad or **G**uilty about your drinking?
E	Have you had a drink first thing in the morning to steady your nerves or to get rid of a hangover (i.e., an "**E**ye opener")?

[a]A score of two positive items indicates the need for detailed assessment.

alcohol poisoning, CNS depression becomes prominent, leading to stupor and coma.

The clinical effect is dose-dependent, although much variability (based on the patient's gender, genetics, amount/rate of intake, co-ingestion of other drugs, and overall duration of alcohol use) exists. While the blood alcohol level (BAL) can reliably predict clinical effects in patients who only use alcohol socially, habituation and tolerance are common with chronic use, and in these individuals, little clinical evidence of intoxication may be seen despite an extremely elevated BAL.[19] In patients who use alcohol intermittently, a BAL <100 mg/dL, will produce euphoria, problems with coordination, and impaired attention. Higher levels (e.g., BAL 100–200 mg/dL) are associated with a worsening of motor deficits, impaired judgment, and an increased chance of assaultive/aggressive behavior. As BAL exceeds 300 mg/dL encephalopathy and CNS depression become prominent, and coma (and even death) can occur at BAL 400–500 mg/dL.

Initial work-up of acute alcohol intoxication should involve checking basic chemistry studies (as electrolyte imbalance is common with acute intoxication), a serum glucose, hepatic function, and a BAL. If co-ingestion is suspected, screening for other drugs of abuse is recommended, though it may not always be necessary with isolated alcohol intoxication. Treatment depends largely on the degree of intoxication observed:

- Mild to moderate intoxication can be managed supportively and patients may require little more than observation and serial assessments. IV fluids may be warranted if there is evidence (e.g., persistent tachycardia) of volume depletion. Agitation, if present, may respond to reduced stimulation/isolation, and in more severe cases, use of dopamine antagonists such as intravenous (IV) haloperidol (e.g., 2–5 mg), as it does not exacerbate sedation, and can be administered easily. In patients with a preference for the parenteral route, various atypical agents (e.g., olanzapine, quetiapine) should be considered. Benzodiazepines are also commonly used in this setting, although using them as sole agents for management of agitation may exacerbate acute intoxication and worsen agitation, over-sedation, and respiratory depression. Once an individual is no longer intoxicated, he or she can usually be discharged home, after screening for the severity/extent of use and discussing aftercare resources.
- Severe intoxication may require intensive supportive measures, including frequent assessment of physiologic parameters. With severe obtundation, patients may not be able to protect their airway and may require intubation. Hemodynamic changes may be seen, including tachycardia and hypotension, and patients may require IV hydration.

ALCOHOL WITHDRAWAL SYNDROME: IDENTIFICATION AND MANAGEMENT

Alcohol withdrawal can range from a state of mild discomfort that requires no medication to multi-organ failure that requires intensive care. In large part, this variability is a reflection of a series of changes in CNS receptor expression and function associated with chronic alcohol use (Figure 14-1). As previously discussed, alcohol enhances GABA activity and inhibits glutamate activity; this leads to a CNS depressant effect. In the setting of chronic alcohol use, the GABA system habituates, leading to a decrease in the number of GABA receptors, to changes in configuration of the receptor subunits, and to reduced rates of GABA synthesis. The result is one of decreased *endogenous* GABA tone. Similarly, chronic exposure to alcohol leads to changes in the glutamate neurotransmitter system, namely with an increase in the number of glutamate receptors. The overall effect is that of increased *endogenous* excitatory tone, representing an attempt to restore homeostasis and balance the increase in *exogenous* GABA tone caused by the use of alcohol. With abrupt cessation of alcohol use, this tenuous balance becomes disturbed quickly and a state marked by over-expression of excitatory neurotransmitters (glutamate, norepinephrine, dopamine) and reduced GABA tone develops. The specific types of neurotransmitters affected and the severity of aberration seen determine the clinical symptoms and the severity of the alcohol withdrawal syndrome observed.[16–18]

Table 14-3 summarizes three key clusters of symptoms observed in alcohol withdrawal. Type A symptoms are associated with minor (uncomplicated) withdrawal and reflect an overall decrease in GABA activity. The most common clinical findings with this type are anxiety, restlessness/irritability, insomnia, general malaise, and a *fine* tremor. Symptoms of types B and C are more prevalent in cases of severe (complicated) withdrawal and reflect an increase in noradrenergic and dopaminergic tone, respectively. Type B withdrawal symptoms include the hallmark increased

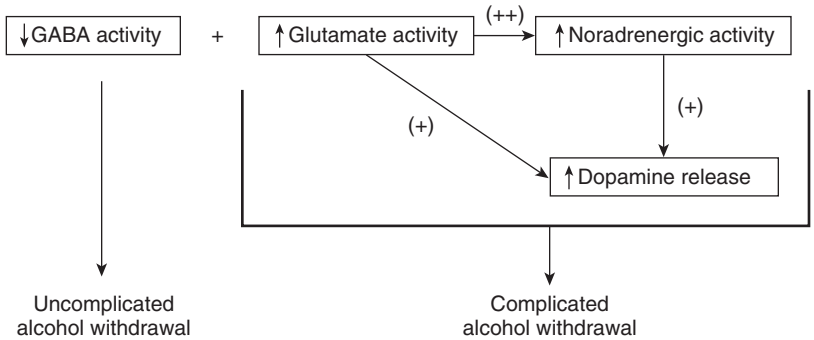

Figure 14-1 Neurotransmitters affected in alcohol withdrawal syndrome.

TABLE 14-3 Alcohol Withdrawal Syndrome Symptom Clusters, Receptors and Recommended Treatment Options

SYMPTOM CLUSTERS	COMMON SYMPTOMS	NEUROTRANSMITTERS AFFECTED	RECOMMENDED TREATMENT
A	Anxiety, restlessness, general malaise, nausea/emesis; *fine* tremor	Decreased GABA activity	GABA-agonists
B	*Coarse* tremor, hypertension, tachycardia, fever, diaphoresis	Increased glutamate and norepinephrine activity	Beta-blockers, alpha-agonists
C	Confusion, encephalopathy, hallucinations, paranoid ideation, agitation	Increased glutamate and dopamine activity	Dopamine antagonists

sympathetic tone, with resultant *coarse* bilateral tremor, hypertension, tachycardia, fever, and diaphoresis. Since some patients attempt to fabricate type B findings (e.g., tremor), clinicians should examine patients for tongue fasciculations and monitor for the absence of tremor with distraction (e.g., observation from outside the room or providing a glass of water to consume while conducting the examination and observing for the presence of end-point tremor). Type C symptoms are marked by impairments of attention and by confusion, as well as by the symptoms of acute psychosis, including hallucinations (visual more often than auditory), paranoid ideation, and delusional thinking.

Given the range of neurotransmitters involved, treatment of alcohol withdrawal should be tailored to the specific symptom cluster observed, including use of benzodiazepines for type A symptoms, use of beta-blockers and alpha-adrenergic agents to treat refractory tachycardia/hypertension (type B symptoms), and use of dopamine antagonists for management of hallucinations, agitation, and paranoid delusions (type C symptoms). The clinician, however, should always ensure that one prioritizes type A > type B > type C unless there are type B or type C emergencies that need to be managed and treated acutely (e.g., concern for demand ischemia or hypertensive emergency).

Types of Alcohol Withdrawal Syndromes

Clinical hallmarks of the four major alcohol withdrawal syndromes are outlined below.

Early/uncomplicated withdrawal syndrome generally reflects CNS hyperactivity in the setting of alcohol discontinuation, and includes subjective sensations of anxiety and restlessness, as well as insomnia, fine tremor, changes in appetite/GI upset, diaphoresis, and headaches. These symptoms generally develop within the first 6–12 hours after cessation of use, and may even be observed in those with elevated BALs (a reflection of chronic use and habituation). Unless the patient progresses to a complicated withdrawal state, an early withdrawal syndrome is self-limited and will remit spontaneously within 24–48 hours. The vast majority of patients who experience alcohol withdrawal present with minor withdrawal symptoms, and respond well to treatment with benzodiazepines.

Alcohol withdrawal seizures occur within the 12–48 hours after the last drink, though they have been described as early as 1–2 hours after last use. Despite significant concerns in the hospital setting, alcohol withdrawal seizures are uncommon events seen in only 1% of unmedicated patients who undergo alcohol withdrawal. Moreover, the incidence of alcohol withdrawal seizures increases in patients with a pre-existing seizure disorder, prior head trauma, and a history of seizures related to alcohol discontinuation.[20] Classically, most alcohol withdrawal seizures fit the description of singular, self-limited, tonic-clonic convulsions and a report of multiple, prolonged seizures and/or progression to status epilepticus should raise concerns for alternative etiologies and prompt further diagnostic assessment. Although most patients do not require head imaging, CT and/or MRI scans can help exclude causes of ictal activity, and should be strongly considered in those who demonstrate focal neurologic findings, those with suspected head trauma, and those with an altered sensorium not due to acute intoxication. Multiple prior detoxifications predict withdrawal seizures more than the quantity or duration of a drinking history; this implies a kindling phenomenon with chronic alcohol use and detoxifications, similar to that observed in those patients with epilepsy. Most cases of alcohol withdrawal seizures are treated with benzodiazepines (e.g., IV/PO lorazepam) or longer-acting barbiturates (e.g., phenobarbital). There are limited data to support the use of other anti-epileptic drugs (AEDs) over benzodiazepines, unless the patient has a history of a seizure disorder, however care should be noted that no other AED, outside of phenobarbital, has been shown to be effective for moderate to severe alcohol withdrawal seizures in the acute setting. In other words, while they may reduce seizure activity from epilepsy, they do not influence seizure activity due to alcohol withdrawal seizures.

Alcoholic hallucinosis is a rare syndrome reflective of increased dopaminergic activity; it is commonly confounded by alcohol withdrawal delirium (AWD), which is often referred to as *delirium tremens*. The onset of symptoms is typically seen within 12–24 hours after the last drink. Without treatment, most symptoms will remit within 48 hours after the last drink (the earliest time point associated with delirium tremens).[18] The patients who experience alcoholic hallucinosis classically describe vivid visual hallucinations that may occur in an otherwise clear sensorium. Olfactory and tactile hallucinations are also noted with alcoholic hallucinosis, along with the presence of paranoid delusions. Unlike AWD, patients with alcoholic hallucinosis do not exhibit significant attention deficits, tremor, or autonomic dysregulation (the combination of these sets of

symptoms essentially constitutes the diagnosis of alcohol withdrawal delirium). While alcoholic hallucinosis will invariably (and eventually) remit even without treatment, most patients will benefit from a brief course of dopamine antagonists, along with some GABA-agonists to provide a degree of anxiolysis. As with other types of acute psychosis, attention should be paid to patient safety and all patients with alcoholic hallucinosis should be assessed for self-harm and harm to others.

Alcohol withdrawal delirium (AWD), delirium tremens is a clinical syndrome characterized by autonomic hyperactivity (tachycardia, hypertension, hyperthermia), confusion/disorientation, hallucinations, and not uncommonly agitation. Visual hallucinations, including those of animals ("white mice" and "pink elephants"), are common, although hallucinations involving other sensory modalities have also been described. Delusional thinking and paranoia may exacerbate a patient's distress and lead to agitation or frank aggression. Most patients will develop AWD within 48–72 hours of discontinuing alcohol, although later onset has also been described. Untreated, the condition typically persists for 3–4 days, although it may persist longer and is associated with a significant risk for mortality and morbidity. While only 5% of all patients with AUD will develop AWD, the risk appears to be greater in the following populations:

- Patients with a history of AWD (strongest predictor)
- Patients with a history of chronic sustained daily drinking
- Older individuals (age >40)
- Patients with significant concurrent medical/surgical illnesses, including long bone fractures, burns, and head trauma
- Patients who develop withdrawal symptoms in the context of an elevated BAL
- Patients admitted >2 days since their last drink.[21–23]

While AWD was associated with a 37% mortality rate at the beginning of the last century, more recent estimates describe a mortality rate closer to 5%, undoubtedly a reflection of improved diagnosis, and management, particularly with advances in critical care. Most AWD-associated morbidity and mortality occurs in the setting of cardiopulmonary failure (e.g., arrhythmias, ischemic events, aspiration), infectious (e.g., aspiration pneumonia), metabolic derangements (e.g., acute hepatitis, pancreatitis, electrolyte abnormalities), and CNS injury.

Treatment of Alcohol Withdrawal

Uncomplicated alcohol withdrawal (accounting for the majority of patients) responds adequately to treatment with GABA-agonists, including various benzodiazepines or phenobarbital. Long-acting benzodiazepines (e.g., diazepam, chlordiazepoxide) have been preferred due to their longer half-life and associated self-tapering properties, which helps to create a smoother taper. One key exception is the populations with significant liver injury who require a taper with a short-acting agent (e.g., oxazepam, lorazepam) that does not undergo first pass hepatic metabolism; such agents are less likely to accumulate and to cause over-sedation. The duration of the taper, and overall dose required, will depend on a number of factors (e.g., the patient's pattern of alcohol use, genetics, hepatic metabolism, and the pharmacokinetics of the chosen drug). Thus, no single taper schedule may prove effective for all patients, and clinicians should expect considerable variation from patient-to-patient, particularly in those with co-morbid medical and surgical illness. In general, one should aim for light sedation as a target of treatment, to a degree that ensures patient comfort, and staff safety, and does not significantly obscure the neurologic examination.

Benzodiazepines can be administered either on a fixed schedule (i.e., a dose is given at fixed intervals even if symptoms of withdrawal are absent) or as symptom-triggered therapy. The latter method is most commonly utilized in detoxification centers and psychiatric units as it requires nursing staff with expertise in identification and treatment of alcohol withdrawal. In the general hospital setting, symptom-triggered therapy often proves to be challenging, as medical/surgical clinicians may lack familiarity with the CIWA scale, and its downstream consequences (e.g., a number of symptoms reported on the CIWA scale may be non-specific in the medically ill and may result in administration of sedatives due to other etiologies, leading to benzodiazepine excess and iatrogenic delirium). Fixed-dosing helps to avoid some of the unpredictability associated with symptom-triggered treatment, albeit at a risk of over-medicating and becoming benzodiazepine-intoxicated.

Regardless of the method used, management of withdrawal involves the use of increasingly large benzodiazepine doses until the patient appears comfortable and light sedation is attained. Subsequently, a benzodiazepine taper can be initiated and the dose is decreased by 25% to 30% per day until it has been discontinued.

One common clinical pitfall is using benzodiazepines for the management of symptoms associated with alcohol withdrawal, including type B and C symptoms. While benzodiazepines are excellent agents for managing symptoms related to decreased GABA tone, benzodiazepines have little impact on the management of refractory tachycardia and hypertension; these symptoms may be better addressed by hydration and by administration of beta-blockers, and/or alpha-adrenergic agents. Similarly, benzodiazepines should not be the sole agents for the management of alcohol withdrawal-related hallucinations or agitation; dopamine antagonists often offer better symptom control with less risk for over-sedation and intoxication.

Phenobarbital, the most commonly used AED in the world, presents an excellent alternative to benzodiazepines in general hospital settings. This medication demonstrates both GABA-agonism and glutamate-antagonism, and can thus directly address both major neurotransmitter-associated and acute withdrawal. Furthermore, it has reliable pharmacokinetics, and a long half-life, and it lacks a narrow therapeutic index; its only absolute contraindication is a history of Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) or acute intermittent porphyria. Patients can be dosed based on their ideal body weight, with the target dose adjusted according to the patient's overall risk of withdrawal as well as the expected risk of complications. Initial loading doses are administered at 3-hour intervals as IM injections, while the subsequent taper can be administered orally. A serum level is obtained following the last IM dose and is used to monitor metabolic function, and to adjust subsequent dosing.[24–29]

Various AEDs (e.g., gabapentin, carbamazepine, valproate), have been proposed as agents for management of alcohol withdrawal, but none of these agents has appeared to confer the same degree of benefit as seen with benzodiazepines or phenobarbital.[30] Similarly, ethanol has been used, especially in patients who report their intention to resume drinking immediately on discharge.[31] Although the notion of administering ethanol in the hospital may appear novel and exciting, a number of practical complications arise that make other agents preferred alternatives in nearly all cases. Ethanol is difficult to titrate, has many adverse metabolic effects, and is overall unsafe in the general medical setting. Lastly, in the intensive care unit (ICU), dexmedetomidine and propofol have both been used as viable alternatives to benzodiazepines/phenobarbital for the treatment of alcohol withdrawal. Respiratory compromise and sedation with propofol, along with bradycardia and hypotension associated with dexmedetomidine, limits the use of these medications to the ICU setting.

In addition to the medications described, all patients treated for alcohol withdrawal should receive thiamine given their increased risk for Wernicke encephalopathy and Korsakoff psychosis. Doses of 200 mg daily are recommended for the prevention of the syndrome and carry no safety risk to the patient, while higher doses are recommended if an actual thiamine deficiency is suspected.

WERNICKE–KORSAKOFF SYNDROME

Victor and associates in their classic monograph *The Wernicke–Korsakoff syndrome* stated that "Wernicke's encephalopathy and Korsakoff's syndrome in the alcoholic, nutritionally deprived patient may be regarded as two facets of the same disease."[32] Although uncommon (by some estimates, <5% of all patients with chronic alcohol use) the diagnosis is often missed and should be considered in all patients who present with heavy alcohol use, especially if they may have other reasons for malnutrition (e.g., homelessness, head/neck cancer, cognitive impairment).

Wernicke's Encephalopathy

Wernicke's encephalopathy arises acutely and is classically characterized by a triad of ophthalmoplegia, ataxia, and mental status disturbance.[32] The ocular disturbance, which is necessary for the diagnosis, consists of paresis or paralysis of the lateral rectus muscles, nystagmus, and a disturbance in conjugate gaze. A global confusional state consists of disorientation, unresponsiveness, and derangement of perception and memory. Exhaustion, apathy, and profound lethargy are also part of the picture.

Once treatment with thiamine has been initiated for Wernicke's encephalopathy, improvement in the ocular findings is often evident within hours, while full recovery follows over days or weeks. Classically, it has been estimated that approximately one-third of patients recover from the state of global confusion within 6 days of treatment, another third recover within 1 month, and the remainder improve within 2 months. The global confusional state is almost always reversible, in marked contrast to the memory impairment of Korsakoff's psychosis.

Korsakoff's Psychosis

Korsakoff's psychosis, also referred to as *confabulatory psychosis* and *alcohol-induced persisting amnestic disorder*, is characterized by impaired memory in an otherwise alert and responsive person. Hallucinations and delusions are rarely encountered. Curiously, confabulation, long regarded as the hallmark of Korsakoff's psychosis, is not seen in the majority of cases and its absence should not preclude this diagnosis. The memory loss is generally bipartite. The retrograde component involves the inability to recall the past, and the anterograde component involves the lack of capacity for retention of new information. In the acute stage of Korsakoff's psychosis, the memory gap may be so blatant that the patient cannot recall simple items (such as the examiner's first name, the day, or the time) after a few minutes, even though the patient is provided with this information several times. As memory improves, usually within weeks to months, simple problems can be solved, limited always by the patient's span of recall.

The EEG may be unremarkable or might show diffuse slowing, while an MRI scan might demonstrate changes in the periaqueductal gray area, hippocampal formations, and the medial dorsal nucleus of the thalamus.[19]

Although often regarded as irreversible, a significant number of patients with Korsakoff's psychosis show some improvement over time. Classically, one expects 20% of the patients to recover more or less completely; however, 25% showed no recovery, and the rest recovered partially.

Treatment

Administration (IV or IM) of the B vitamin, thiamine, should be considered a routine component of early treatment for all intoxicated patients, preferably while still in the ED or immediately upon admission, whichever comes earlier.[33] Because subclinical cognitive impairment can occur even in apparently well-nourished patients, we recommend routine treatment with IV thiamine (as prophylaxis) for all intoxicated patients, as this prevents advancement of the disease and reverses at least a portion of the lesions affecting CNS territories.

For preventive measures, we often recommend using >100 mg of IV thiamine immediately, followed by 200 mg of thiamine (orally) while the patient remains in the hospital. If Wernicke/Korsakoff is suspected, treatment should consist of high-dose thiamine (500 mg IV three times per day for at least 3 days) followed by 500 mg IV/IM daily while symptoms persist. Because GI absorption of thiamine may be erratic, IV/IM formulations are much preferred to oral formulations. Lastly, thiamine should be administered before giving glucose, as the latter may precipitate or even exacerbate Wernicke's encephalopathy.[33,34]

PHARMACOTHERAPY FOR ALCOHOL USE DISORDER

Most of the treatment for AUD is centered on modifying the reinforcing effects that the compound has on the corticomesolimbic dopamine reward pathways. Thus, medications

used for treatment of AUD will work on a variety of receptor systems (e.g., endogenous opioids, GABA, glutamate, and serotonin). Treatment should be initiated while the patient is hospitalized, and patients should remain on the medication for at least 6 months after attaining sobriety. Treatment courses longer than 6 months have not been well studied.

First-line treatment for AUD involves naltrexone and acamprosate. The two are briefly summarized below:

- Naltrexone, available in oral and IM depot form, exerts its pharmacologic effect through mu (μ)-opioid receptor blockade, which reduces the reinforcing effects of alcohol consumption. In animal studies, naltrexone has been found to reduce alcohol self-administration.[35] In humans, naltrexone has been found to reduce the rate and severity of alcohol consumption compared with placebo.[36,37] Oral naltrexone is commonly used at doses of 50 to 100 mg/day, while the IM formulation (Vivitrol) is used at doses of 380 mg every 4 weeks. Patients who require opioid agents (e.g., for pain management) should not be started on naltrexone; otherwise the drug is well tolerated with its most common side effects including nausea, fatigue, and low appetite. Rare cases of interstitial pneumonia and eosinophilic pneumonia have been reported with use of naltrexone.
- Acamprosate works through modulation of glutamate CNS transmission, and has been shown to reduce alcohol consumption rates compared to placebo in patients with severe AUD, as well as to increase the duration of abstinence by an average of 11%.[36,38] The drug is safe and is generally well tolerated, although dose adjustments may be needed in patients with renal failure (owing to primarily renal metabolism). The primary barrier to treatment may be reduced adherence in the setting of TID dosing.

In addition to these agents, a variety of other compounds have been use for pharmacologic management of AUD. Some of the most common are summarized below:

- Topiramate has been shown to reduce alcohol use in patients with severe AUD, but it does not carry FDA approval for this indication. It is believed to work through antagonizing kainate glutamate receptors and by interacting with GABA receptors.[39,40] Compared with other drugs listed here, topiramate initiation may require a gradual taper (to both initiate and discontinue the medication) and is associated with more frequent side effects, including cognitive dulling, weight loss, mood changes, and depression. As with many AEDs, topiramate should be avoided by pregnant women.
- Gabapentin, baclofen, SSRIs, and ondansetron have all been studied as potential options for treatment of AUD, although the data for most of these compounds have not been encouraging. A recent prospective placebo-controlled randomized trial of gabapentin in patients with AUD noted improvements with regard to rates of complete abstinence, reduction in heavy drinking, and improved mood/sleep and cravings in the treatment group. These results were more pronounced at higher doses of the medication (e.g., 1800 mg daily).[24]
- Disulfiram discourages drinking through negative reinforcement, as it precipitates an unpleasant physical reaction when an individual consumes alcohol while on this medication. The compound works by inhibiting aldehyde dehydrogenase, thus preventing the metabolism of acetaldehyde (the primary hepatic metabolite of alcohol breakdown). Accumulation of acetaldehyde leads to flushing, sweating, headache, palpitations, nausea, and vomiting. Efficacy of the compound is limited, and it often requires strong motivation or supervised conditions. With unsupervised treatment, disulfiram is less effective, as most patients will self-discontinue the medication before they resume drinking. Disulfiram should be avoided in patients with severe cardiovascular disease, pregnant women, and patients with psychosis. In general, the use of this medication has waned, given the alternatives.

PSYCHOSOCIAL TREATMENT OF ALCOHOL USE DISORDER

Brief substance use intervention in the general medical setting is well-developed and effective.[41] Even brief contact with an addiction consultant has led to improvement rates in 30% to 50% of patients several months after hospitalization. This effect is even more pronounced in those with no prior psychiatric illness and with good social function and resources.[42] Addiction consultation services to hospital physicians should assist with diagnosis, intervention, pharmacologic management, and post-acute care referral.

AUD causes diverse disruptions in people's self-awareness, communication skills, capacity for relationships, sense of purpose, and spirituality. Alcoholics Anonymous (AA), SMART recovery, and other peer-driven recovery services, have a record of success and benefit greatly from accessibility and low cost. If already established within AA, patients may benefit from visits from their sponsor or other group members while hospitalized. Alternatively, some hospitals have established AA meetings on-campus, and (if able and interested) patients should be encouraged to attend these while hospitalized. Recovery coaches offer an excellent alternative to the classic addiction clinician's approach and may be able to engage patients on a deeply personal level through shared experiences. Working with individuals in recovery may motivate the patient to engage with the team and be more trusting of the treatment options offered.

Key features of central intake include directly assisting patients with access to treatment, helping patients to call programs, subsidizing transportation to treatment program interviews, obtaining concrete services to diminish treatment obstacles (such as homelessness or lack of child care), and motivational interviewing. Motivational interviewing is a directed, patient-centered counseling for eliciting behavioral change by helping to explore and resolve ambivalence to change.[43] With this technique, the provider assesses the patient's losses and risks, helps the patient to recognize the underlying cause as substance abuse, and uncovers ambivalence about the potential value of treatment. By avoiding a threatening style of confrontation about denial, motivational

interviewing has been found to enhance motivation for recovery.[43]

To be successful, any attempt at treating AUD in the inpatient setting should focus on much more than diagnosis of the disorder and management of the potential withdrawal syndrome. Patients should be assessed for their understanding of the problem and readiness to engage with addiction work. Pharmacologic treatments should be initiated while in the hospital, and patients should engage with substance use specialists to review outpatient resources and services to assist with recovery. Issues that may impede recovery, such as housing and legal issues, should be acknowledged and addressed whenever possible.

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Access the reference list online at https://expertconsult.inkling.com/.

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