CLINICAL REVIEWS

Alcohol Withdrawal Syndromes:

A Review of Pathophysiology, Clinical Presentation, and Treatment

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ALCOHOLISM REMAINS one of the most common and devastating problems that the general internist encounters in both ambulatory and hospital settings. This paper reviews alcohol syndromes withdrawal, including their pathophysiology, clinical presentation, and management. We attempt to help the physician who faces decisions about how to manage alcohol withdrawal in an outpatient setting, when and whom to admit to the hospital, and how to manage the more severe withdrawal syndromes and related complications. Although most alcoholics can be withdrawn from alcohol with little or no drug therapy as outpatients or in detoxification centers, we focus on the more serious alcohol withdrawal syndromes requiring hospital admission. In addition, we hope to encourage the primary care physician to consider withdrawal as only the initial phase of ongoing treatment and support of the alcoholic patient.

Of the 1.2 million patients hospitalized annually in this country for manifestations of alcohol abuse, approximately 5% will develop delirium tremens.[1,2] Using these figures, approximately 60,000 patients will experience delirium tremens (and a much larger number will exhibit minor withdrawal symptoms) yearly. While in the past the mortality rate from delirium tremens has been as high as 20%,[3] current appropriate treatment may reduce mortality to 1%, resulting in 600 to 9,000 deaths annually that can be attributed directly to alcohol withdrawal. At our institution there were 56 patients discharged with a diagnosis of delirium tremens between November 1986 and June 1988. Of these patients, three died, for a mortality rate of 5%.

PATHOPHYSIOLOGY OF ALCOHOL WITHDRAWAL

In the 1960s Victor and Wolfe proposed that the hypomagnesemia and respiratory alkalosis commonly observed during early withdrawal might be of etiologic importance in the alcohol withdrawal syndrome.[4] Subsequent studies have not supported the hypomagnesemia hypothesis, as low magnesium levels are not always present in the serum or cerebrospinal fluid (CSF) of patients withdrawing from alcohol.[5,6] The respiratory alkalosis described by Wolfe and Victor is probably the result rather than the cause of generalized arousal. Other proposed but unsupported etiologies for the alcohol withdrawal syndrome have included hypovitaminosis, exogenous toxins from various alcoholic beverages, and endogenous toxins from liver failure.[5]

Kalant has suggested that withdrawal symptoms result from an acquired tolerance of and a physical dependence on alcohol.[7] Physical dependence can be operationally defined as the biochemical or biophysical abnormalities that develop progressively during chronic alcohol administration. Tolerance refers to the alcoholic's need to consume more alcohol to obtain the desired effect. The withdrawal reaction consists of the signs and symptoms that develop as the blood alcohol level decreases. These manifestations are generally opposite in nature to the primary central nervous system (CNS) depressant effect of the drug. Kalant's model of withdrawal views the body as a physiological system which adapts to the continuous CNS depressant effects of alcohol through a compensatory increase in neuronal activity. When the blood alcohol level falls, the chronic adaptive mechanisms produce a state of generalized CNS arousal.[7-10] Alcohol's diffuse effects on the brain are mediated by interactions with the constituent lipids and proteins of cell membranes. This generalized effect on neurons differs from opiates and benzodiazepines, which act on specific receptors located in the specific areas of the brain. Alcohol-induced changes in cell membranes exert a depressant effect on neuronal excitability, impulse conduction, and transmitter release. Alcohol also reduces neuronal activity resulting in decreased neuronal oxygen utilization, adenosine triphosphate (ATP) turnover, and neurotransmitter release. During chronic alcohol ingestion, poorly understood compensatory changes appear to offset these depressant effects on the brain. When alcohol intake is abruptly discontinued or blood and CNS levels rapidly decrease, the compensatory changes can produce signs of CNS overactivity such as seizures, hallucinations, and delirium.[9]

Much recent research has been directed at the biochemical mediators of the withdrawal response, yet the

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exact mechanisms have not been fully clarified. Increased levels of plasma norepinephrine and its metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), have been demonstrated in subjects withdrawing from alcohol.[11, 12] There is evidence that increased norepinephrine levels are due to decreased inhibitory activity of alpha-2 receptors on presynaptic neurons. There are also complex alterations in the function of the hypothalamic-pituitary-adrenal axis.[13] Serotonin may be involved in the development of tolerance and craving for alcohol. Impairment of normal serotonergic nerve function in experimental animals increases their preference for alcohol. Investigators have described varied levels of serotonin in the brain during alcohol administration; however, it seems that there may be a shift in the usual degradation pathway, which leads to the formation of biologically active products that increase craving for alcohol.[14, 15]

Gamma-aminobutyric acid (GABA) is thought to be an inhibitory neurotransmitter throughout the brain. Acute alcohol intoxication potentiates GABA's inhibitory effect; however, during withdrawal, the activity of cortical GABA neurons is reduced. Barbiturates and benzodiazepines have binding sites in the GABA receptor complex. Their withdrawal may produce symptoms similar to alcohol withdrawal.[14-16]

Metabolic byproducts of alcohol metabolism may play a role in promoting alcohol consumption and in subsequent withdrawal. For example, acetaldehyde has been found to sharply enhance voluntary drinking of alcohol in some laboratory animals.[14] Aldehydes can also react with biogenic amines, such as neurotransmitters, to form active products such as tetrahydroisoquinolines (TIQs). One TIQ is the biological precursor of morphine and could therefore contribute to the addictive properties of alcohol. Infusion of certain TIQs into the brain of rats has been shown to cause a marked increase in alcohol consumption.[14, 15, 17] When acetaldehyde reacts with serotonin, a product called tetrahydro-beta-carbolines, which is longer-acting than TIQs, is formed. This compound also enhances alcohol consumption in rats.[14, 15, 17]

It appears that multiple mechanisms are responsible for the development of alcohol tolerance and subsequent withdrawal symptoms. The significance and exact roles of many of the biochemical changes in alcoholism and withdrawal have yet to be elucidated.

ACUTE INTOXICATION VERSUS WITHDRAWAL

Physicians inexperienced in treating alcohol-related problems may have difficulty distinguishing between acute alcohol intoxication and alcohol withdrawal. Alcohol intoxication is characterized by one or more of the following: relaxation, sedation, euphoria, ataxia, reduced inhibitions, memory loss, poor judgment, variable moods, nausea, vomiting, obtundation, and coma. Acute intoxication rarely causes an idiosyncratic excitation response.[18] The blood alcohol level is usually more than 100 mg/dl in acute intoxication whereas it is either zero or falling in alcohol withdrawal. In the withdrawal state, the alcoholic is hypervigilant, easily startled, and hyperventilating in contrast to being obtunded in the state of acute intoxication. Higher blood levels of alcohol will be required to produce acute intoxication in alcoholics than in occasional drinkers because of the increased metabolism of ethanol in chronic alcoholics. The following case is an example of a patient in acute alcohol intoxication.

> J.T. was a 100-pound, 21-year-old black female who had consumed little alcohol in her life. At a party her boyfriend encouraged her to drink heavily. She was brought to the emergency room when she became comatose. She suffered a respiratory arrest requiring mechanical ventilation. Her blood alcohol level was 400 mg/dl. Twelve hours after admission she began to wake up. After 18 hours she was extubated. She was discharged 48 hours after admission with no signs of alcohol withdrawal.

This case illustrates that an acute alcohol overdose can cause severe obtundation and respiratory suppression.[19] With respiratory support in the intensive care unit, she recovered without sequelae.

In some circumstances it may be more difficult to distinguish acute intoxication from withdrawal. This may occur when withdrawal develops in a patient who is in hepatic encephalopathy. This patient will be confused and lethargic as in acute intoxication, however, the patient's blood alcohol level will be low and the ammonia will be high. This patient may also have asterixis, hepatomegaly, and ascites. Acute alcohol intoxication may be difficult to distinguish from alcohol withdrawal when the following coexisting complications occur: head injury, use of multiple drugs in addition to alcohol, pancreatitis, and hypoglycemia. A thorough history from the patient's friends or relatives in addition to the physical exam and appropriate laboratory tests will help the physician distinguish between alcohol intoxication and withdrawal in unclear situations.

CLINICAL WITHDRAWAL SYNDROMES

Once addicted, the alcoholic enters a cycle of drinking to avoid the uncomfortable symptoms of early alcohol withdrawal. He or she treats withdrawal on a daily basis through continued alcohol consumption.[20] The amount of alcohol required to avoid withdrawal gradually increases as tolerance develops. When something occurs to keep the alcoholic from drinking, such as an infection, gastritis, or a lack of money, withdrawal symptoms may become more prominent and may develop into one of the more severe alcohol withdrawal syndromes.

There is, unfortunately, no uniform system for classifying the more serious alcohol withdrawal syn-

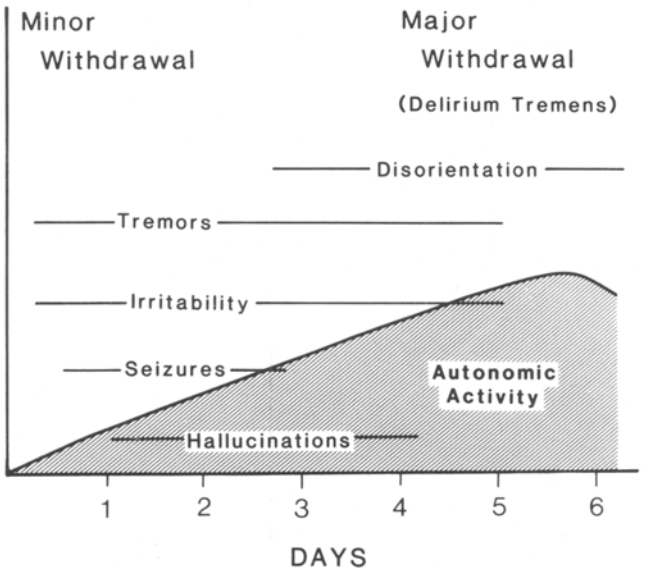

FIGURE 1. Characteristics of alcohol withdrawal.

dromes, which are the focus of this paper. The American Psychiatric Association's Diagnostic and Statistical Manual, 3rd edition, Revised (DSM III-R) lists nine alcohol-related syndromes including seven alcohol-induced organic mental disorders.[19] Three of these disorders that result from alcohol withdrawal are uncomplicated alcohol withdrawal, alcohol withdrawal delirium, and alcohol hallucinosis. Withdrawal seizures are mentioned in the text of DSM III-R but are not listed as a separate, alcohol-related disorder.

Most clinical references classify withdrawal syndromes by time (early and late) and severity (minor and major).[19-24] Early withdrawal refers to the symptoms and signs that develop during the first 24 to 48 hours after alcohol consumption has significantly declined or ceased. Conditions arising more than 48 hours after cessation are classified as signs of late withdrawal. Severity is more difficult to describe and categorize. Several withdrawal severity scales have been developed for research purposes but have found little acceptance in clinical practice.[24, 25] The two pivotal measures of severity are the degree of autonomic hyperactivity and the presence or absence of delirium. In all classification systems, delirium tremens is clearly distinguished as a late and major withdrawal syndrome.[26, 27] Alcoholic hallucinosis and alcohol withdrawal seizures are usually included with the early or minor withdrawal syndromes, but some authors place them in a category of intermediate severity or prefer to describe them as distinct, clinical syndromes.[22-24] Whatever classification system is used, it is widely accepted that alcohol withdrawal is a clinical syndrome that evolves over time and forms a continuum of severity from the earlier, mild symptoms to the later and more severe physiologic changes of delirium tremens (Fig. 1). It is also clear that although many patients experience some degree of early or minor withdrawal, only a small minority enter the more severe and later stages.

Clinical descriptions of severe alcohol withdrawal first appeared in the early 19th century in the case descriptions of Sutton. His observations were vivid and still relevant today, as this excerpt[28] shows:

> It is preceded by tremors of the hands, restlessness, irregularity of thought, deficiency of memory, anxiety to be in company, dreadful nocturnal dreams when the quantity of liquor through the day has been insufficient; much diminution of appetite, especially an aversion to animal food; violent vomiting in the morning and excessive perspiration from trivial causes. Confusion of thought arises to such height that objects are seen of the most hideous forms, and in positions that it is physically impossible they can be so situated; the patient generally sees flies or other insects; or pieces of money, which he anxiously desires to possess. . . .

A systematic study of severe alcohol withdrawal was not published until 1953, when Victor and Adams reported their observations of 286 consecutive patients admitted to an inner-city hospital for neurologic complications of alcohol consumption.[2] Their findings were supported in 1955 by Isbell et al.'s study of ten former morphine addicts who were given large quantities of ethyl alcohol for seven to 87 days and then were withdrawn abruptly from it without sedation.[29] Mendelson and LaDou performed similar studies in 1964 on ten chronic alcoholics who were withdrawn from alcohol after three weeks of daily alcohol consumption.[30] These studies provide much of the foundation for the clinical descriptions of alcohol withdrawal and are included in the following discussion.

Early or Minor Alcohol Withdrawal

Early withdrawal produces a constellation of symptoms and signs that vary with the intensity and duration of the patient's prior consumption of alcohol. Symptoms may appear within eight hours of the patient's last drink and may arise before the blood alcohol level has returned to zero. Early withdrawal was observed in more than 80% of the patients studied by Victor and Adams.[2] The common morning hangover may represent the mildest form of withdrawal, developing after drinking has been interrupted for eight to 12 hours by sleep. The morning eye-opener may represent the alcoholic's attempt to treat this early withdrawal symptom, thus avoiding progression to the more uncomfortable symptoms that follow. After 12 hours of abstinence, the untreated patient may complain of increasing jitters or shakes and have an intense craving to resume intake of alcohol. Other symptoms of early or minor withdrawal include insomnia, vivid dreams, anxiety, anorexia, nausea, vomiting, paroxysmal sweating, weakness, and myalgias. The intensity of the symptoms peaks between 24 and 36 hours, at which time the patient often appears agitated, irritable, and hypervigi-

lant. Tachycardia, systolic hypertension, and a coarse tremor of the extended hands or the tongue are common. This tremor is 6–8 cps, and appears on electromyography (EMG) to be an exaggeration of the normal physiologic tremor.[31] The tremor may last up to 14 days.[2] Sleep abnormalities include insomnia with marked sleep fragmentation, increased rapid eye movement (REM) sleep, and decreased Stage 4 sleep.[32] These sleep changes may persist for months after the patient's last drink.[33]

Alcohol Hallucinosis

Alcohol hallucinosis occurs in about 25% of hospitalized patients who have been drinking heavily for at least ten years.[34] Withdrawal-induced hallucinosis is not, however, a predictor of delirium tremens.[23] Withdrawal hallucinations can occur as soon as eight to 12 hours after the last drink, but the majority of them begin 24 hours after the last drink and stop within another 24 to 48 hours.[35] On rare occasions, hallucinosis may persist as an isolated symptom or may blend into a condition indistinguishable from that of chronic paranoid schizophrenia.[36]

The hallucinations are most often visual, although auditory hallucinations are common. Visual phenomena include the common report of bugs crawling on the walls or the patient's bed. Auditory hallucinations may begin as unformed sounds (such as clicks or buzzing) and progress to formed voices.[23] These voices are frequently accusatory in nature, and patients may respond to their content in a fearful or overtly paranoid fashion. Visual and auditory hallucinations may occur simultaneously. It is important to note that during alcohol hallucinosis, the patient's sensorium is otherwise clear, thus distinguishing this syndrome from the diffusely impaired sensorium of delirium tremens. The electroencephalogram (EEG) is usually normal[32] and the autonomic arousal may be minimal or absent,[23] causing the relationship of the hallucinosis to alcohol withdrawal often to be overlooked. Alcohol hallucinosis occurs during the peak of REM-sleep rebound, suggesting that these hallucinations may represent the insertion of dream material into waking reality.[33]

Alcohol Withdrawal Seizures

Withdrawal seizures occurred in 23% of the patients studied by Victor and Adams,[2] and in 33% of the patients in Isbell's study who drank for 48 to 87 days.[29] Seizures appear to be more common in patients with a prior history of epilepsy. Withdrawal seizures usually begin within eight to 24 hours after the patient's last drink and may occur before the blood alcohol level has returned to zero.[37] A falling blood alcohol level can itself provoke withdrawal seizures, particularly after a binge of excessive drinking.[38] Seizures peak 24 hours after the last drink and almost always occur before the onset of delirium. Most are generalized, major motor seizures occurring singly or in a rapid burst of several seizures. Withdrawal seizures occur at the peak of withdrawal-induced EEG abnormalities that include an increased amplitude, a photomyoclonic response, and spontaneous paroxysmal activity.[32] Although less than 3% of withdrawal seizures evolve into status epilepticus, a recent study of 98 patients cited alcohol withdrawal as the major cause of status epilepticus in 15 individuals.[39] Four of these individuals had no prior history of epilepsy, while for the other 11, failure to take their antiseizure medication as well as the alcohol withdrawal itself was thought to be a major factor in triggering the onset of status epilepticus. An etiology other than alcohol withdrawal must be sought for any seizures that begin after the onset of delirium, are either focal or multiple, or occur in a patient who has a temperature of 100.5 F° or more or a history of head trauma.

Late or Major Withdrawal — Delirium Tremens

The hallmark of the late withdrawal syndrome is clouding of consciousness and delirium. This syndrome occurs in a small minority of all cases of alcohol withdrawal.[23] It is rarely observed in patients under the age of 30 years, appears to be restricted to patients with a long and intense history of alcohol exposure (especially if there has been a recent binge followed by abrupt cessation), and is more common in patients with a prior history of major withdrawal episodes.[40] The syndrome typically begins about 48 hours after the patient's last drink, but its onset may be delayed for as long as 14 days or masked by intercurrent medical problems such as trauma, surgery, and narcotic analgesics.[41] The early symptoms of withdrawal usually precede delirium tremens, although these may be masked by other medical problems and the use of CNS depressants. Delirium tremens is frequently precipitated by illnesses such as pancreatitis, alcoholic gastritis, trauma, or an infectious disease. In 80% of the cases of withdrawal, the syndrome resolves within 72 hours.[2]

Late withdrawal may begin after a brief period of apparent clinical improvement that follows early withdrawal seizures or hallucinosis. In this stage, the patient develops signs of confusion and appears hyperactive and disoriented. Signs of autonomic hyperactivity may be profound, with the patient experiencing systolic hypertension, tachycardia, fever, diaphoresis, and volume depletion. Circulating levels of catecholamines are markedly elevated and are associated with increases in cardiac output, stoke volume, and oxygen consumption.[42, 43] Surprisingly, during the height of delirium, the EEG either shows a moderate increase in fast frequencies or, more frequently, is within the normal range.[32] The EEG abnormalities associated with withdrawal seizures, as a rule, resolve before the onset of delirium tremens. If the EEG shows gross slowing in a

delirious patient, other diagnoses such as acute Wernicke's syndrome or hepatic encephalopathy should be considered.

The late withdrawal syndrome is easily recognized when the patient exhibits its classic symptoms. However, in as many as 50% of the patients, the syndrome is modified or masked by an intercurrent illness, trauma, or therapeutic drugs, such as sedatives or analgesics.[41] The syndrome may therefore be overlooked in the postoperative, pregnant, or elderly patient and in other patients if the possibility of alcohol withdrawal is not considered. Suggestive signs pointing toward the diagnosis of alcohol withdrawal in patients who do not show the classic symptoms include unexplained hypertension, tachycardia, fever, and diaphoresis. The following case history is an example of classic delirium tremens:

> A 51-year-old white woman was brought to the emergency room after having a generalized seizure with tonic-clonic movements. Her husband reported that she drank three to four shots of whiskey per day and a fifth on weekends. The weekend prior to admission she had drunk less, for an unknown reason.
> On physical examination she was lethargic but arousable with no findings compatible with chronic alcohol abuse. A lumbar puncture was performed because her temperature was 102°F. This was normal, as was a CT scan of the head. An EEG was normal. She became more agitated and was disoriented as the postictal state waned. Her blood alcohol level was zero. All other laboratory findings were normal except for moderately elevated liver enzymes. The patient was treated with Dilantin, decremental doses of Valium, and intravenous fluids. She was discharged on no medication after the seventh hospital day in an apparently lucid state. On the tenth day after her seizure she went back to her job as a bookkeeper but was unable to perform her work because of a clouded sensorium. She stayed home from work four more days, abstained from alcohol, and returned to work on the fifteenth day after hospital admission. She was then able to perform her job at her previous level of competence. She refused further treatment for her alcoholism. A review of her medical records revealed that she had experienced delirium tremens twice before under similar circumstances.

This case illustrates several points about alcohol withdrawal. First, alcoholics show similar patterns of behavior each time they withdraw. The individual in the case study experienced a third episode of delirium tremens. Also, she had only one grand mal seizure preceding her clouded sensorium, a characteristic seizure pattern in alcohol withdrawal. Finally, the clouded sensorium of alcohol withdrawal may persist either continuously or intermittently for two weeks or longer after the discontinuation of alcohol consumption.

It should be noted that there are other causes of delirium in the alcoholic patient in addition to alcohol withdrawal alone. These include sepsis, meningitis, hypoxia, hypoglycemia, hepatic or renal disease, thiamine deficiency, the postictal state, the use of another CNS toxin, or subdural bleeding.[21] These other causes of delirium often produce mental confusion earlier in a patient's history than alcohol withdrawal does. They should be searched for and ruled out before assuming that the alcoholic patient is experiencing delirium tremens.

Twenty years ago the mortality rate from delirium tremens was as high as 20%, but with current treatment, this figure has fallen to about 1%.[3, 23] Mortality increases if there is a delayed diagnosis, severe illness (such as pancreatitis), a temperature higher than 104°F, malnutrition, or general debility.[3] The recent decrease in mortality rate probably is the result of an earlier diagnosis of this syndrome, a greater recognition of its severity, improved pharmacologic therapy, and the use of invasive monitoring in critically ill patients.

Wernicke's Encephalopathy and Korsakoff's Syndrome

Victor and Adams[2] carefully analyzed the clinical features of acute Wernicke's encephalopathy, confirming that the diagnostic triad of cognitive impairment, ocular dysfunction (horizontal and vertical nystagmus and ophthalmoplegia), and ataxia appeared in a large number of patients. This syndrome may be precipitated in the malnourished alcoholic patient by the administration of glucose-containing fluids without the prior administration of thiamine. Thiamine promptly arrests the syndrome. Its delayed administration may lead to permanent neurologic deficits. This highly curable syndrome may be overlooked by physicians, as Harper noted in his study of 51 patients post mortem with Wernicke's encephalopathy, only seven of whom had had the condition diagnosed during life.[44]

Korsakoff's syndrome may follow an acute episode of Wernicke's encephalopathy or may occur in patients with no preceding history of ophthalmoplegia, ataxia, or acute delirium.[45] DSM-III-R refers to this syndrome as an alcohol-induced, amnestic disorder and, like Wernicke's encephalopathy, it is caused by a thiamine deficiency.[21] The clinical manifestations of this syndrome may be altered by some of the other CNS changes seen in chronic alcoholism, but it is characterized predominantly by an impairment of memory (particularly recent memory) out of proportion to other cognitive disturbances. The patient with Korsakoff's syndrome remains alert and has a clear sensorium, but often displays confabulation. Confabulation may represent the patient's conscious or unconscious attempt to compensate for this amnestic disorder, a feature not unique to Korsakoff's syndrome.

Other Complications of Alcohol Withdrawal

A comprehensive discussion of each of the many complications that occur in patients experiencing alcohol withdrawal is beyond the scope of this article. However, we provide a brief discussion of the problems that

most often arise in the care of these patients. The complications, of course, vary with the population being treated, but they are often multiple and overlapping, resulting in patients with complicated symptoms.

The comatose alcoholic patient presents an important diagnostic challenge to the physician. The diagnostic considerations in this situation are numerous and include acute alcoholic poisoning, mixed-drug overdosage, toxic ingestion of a substance such as methanol or ethylene glycol, head trauma, hypoglycemia, meningitis, hypothermia, and alcoholic ketoacidosis. This patient requires a comprehensive evaluation that may include computed tomography or magnetic resonance imaging of the head (which may reveal intracranial trauma or masses), an EEG (to differentiate delirium tremens from other causes of a clouded sensorium), or an analysis of the cerebrospinal fluid to rule out hemorrhaging or a CNS infection. A complete screening of the blood and urine for other toxins, along with calculation of the osmolar gap, may alert the physician to the possibility of mixed-drug intoxication or withdrawal. It must be remembered that many alcoholics abuse other substances that may alter the clinical presentation of alcohol withdrawal and lead to withdrawal syndromes of their own.

The patient's volume depletion may be profound and may be accompanied by hypokalemia, hypomagnesemia, hypoglycemia, and hypophosphatemia.[46] Acute rhabdomyolysis is a well-recognized complication of the combined effects of alcohol toxicity, hypokalemia, and hypophosphatemia. Prompt correction of these deficits is necessary to prevent its occurrence, and early recognition of the condition is necessary to prevent renal damage secondary to myoglobinuria.[47] Alcoholic ketoacidosis in non-diabetic patients results from the effects of alcohol ingestion on carbohydrate and lipid metabolism. Its etiology and management are well reviewed elsewhere.[48] Atrial and ventricular cardiac arrhythmias are common, reflecting the combined influence of direct alcoholic cardiac toxicity and the extreme elevations of circulating catecholamines. Alcohol withdrawal should be considered as a diagnosis when any middle-aged patient has unexplained atrial fibrillation.[49] The patient's systolic blood pressure is frequently elevated in this case and may not return to normal until seven days after alcohol intake is stopped.[29] Alcohol withdrawal in hospitalized patients is frequently accompanied by nutritional problems such as pellagra, scurvy, folate deficiency, protein-calorie malnutrition, and thiamine deficiency.

Gastrointestinal complications are present in many alcoholic patients. Pancreatitis, alcoholic gastritis, upper gastrointestinal bleeding, and alcoholic hepatitis often complicate the management of the withdrawal syndrome in hospitalized patients. Evidence of severe hepatic dysfunction, manifested by coagulopathies, esophageal varices, ascites, and hepatic encephalopathy, should be sought in all alcoholic patients. Infectious problems, including aspiration pneumonia, other bacterial pneumonias, cellulitis, meningitis, and spontaneous bacterial peritonitis are also common.

TREATMENT

The initial step in the treatment of a patient undergoing alcohol withdrawal is the taking of a thorough history and the performance of a complete physical examination. Because of the recalcitrant nature of many chronic alcoholic patients, however, there is often a tendency to carry out a cursory performance of these steps. The primary care physician must remember that alcoholism is a chronic, relapsing, and potentially fatal disease. An awareness of the emotional responses that alcoholics can elicit from health care professionals will do much to reduce the frustration that working with this population often produces and will ensure that alcoholic patients receive the same quality of care as patients with other disorders.

If the patient is delirious or hallucinating, his or her history frequently must be obtained from a relative or friend. An attempt should be made to determine the amount of alcohol and length of time the patient has been drinking, and when and why the patient stopped drinking. The use of other narcotics such as cocaine and barbiturates also should be ascertained since these may have withdrawal symptoms of their own.[21] The physician should ask whether there is a previous history of alcohol withdrawal seizures or delirium tremens, since the patterns of withdrawal tend to be similar with each withdrawal episode.[40] The physician should look for the specific symptoms of common alcohol-related disorders, such as gastritis and pancreatitis, and should perform a standard review of symptoms.

The usual signs of chronic alcohol abuse, such as hepatomegaly, ascites, telangiectasias, gynecomastia, and testicular atrophy, frequently will be found on physical examination. However, if the patient has been drinking heavily for only a few months, these signs may not be present. The patient experiencing alcohol withdrawal characteristically will have a tremor (most noticeably in the hands), a fever (with or without infection), tachycardia, and systolic hypertension. The examining physician should assume that an infection is present in the withdrawing alcoholic who has a fever. Signs of aspiration pneumonia, meningitis, or spontaneous bacterial peritonitis should be sought on physical examination. Special attention should be directed to the scalp and skull for signs of trauma that may be causing subdural bleeding. Abdominal problems may be present in the withdrawing alcoholic who has alcoholic hepatitis, gastritis, a peptic ulcer, or pancreatitis. Laboratory blood tests may reveal an anemia with high mean corpuscular volume (MCV), elevated liver enzymes, hyperamylasemia, hyperuricemia, hypocholesterolemia, and hypoalbuminemia. The serum alcohol level will be zero or lower than normal for the patient.

The serum sodium and potassium as well as the serum magnesium and phosphorus frequently will be low.[18] (We do not perform lumbar punctures routinely in alcohol withdrawal patients unless they are febrile and delirious.)

Once the physician has determined that a patient is withdrawing from alcohol, he or she must decide whether the patient requires admission to the hospital or can be treated as an outpatient. Frequently, when an alcoholic stops drinking unexpectedly because of a concomitant medical problem, admission to the hospital is required. For those whose withdrawal is treated on an outpatient basis, withdrawal is most successful when there is a voluntary decision to stop drinking, there is a friend or relative available to give medications and monitor the situation, and there is a preexisting relationship with a physician who will see the patient daily during the initial withdrawal period.[50, 51]

There are those who advocate the detoxification of alcoholic patients without the use of psychoactive drugs. This requires frequent staff participation in the treatment, using reassurance and reality orientation in the therapy.[52, 53] This method of alcohol withdrawal, however, is not appropriate for the many alcoholic patients who present with concomitant medical problems requiring hospital admission. A patient who is withdrawing from alcohol and has other medical problems may be admitted to either an intensive care unit or a regular ward in a general hospital, depending on the severity of the symptoms and the sophistication of the nurses who will be caring for the patient. At our institution, most patients who appear in the Emergency Department with alcohol withdrawal are admitted to a general medicine ward where the nurses are experienced with the management of the withdrawal syndromes. Sensitive nursing care and the presence of a family member in the patient's room frequently will help to reduce the agitation of the withdrawing alcoholic. Restraining the patient's extremities should be avoided unless absolutely necessary since this may increase the patient's agitation. Orders to restrain the patient should be given as needed and reviewed frequently rather than left as a standing "prn" order.

Goals for treatment can be divided into several categories. These include an attenuation of the symptoms of withdrawal, replacement of identified metabolic deficiencies, management of any associated conditions and complications, and attempts at rehabilitation.

Sedation

The most important pharmacologic treatment is the administration of a substance that is cross-tolerant with alcohol to relieve agitation, hallucinosis, and tremulousness. More than 100 medications have been used to treat alcohol withdrawal,[19, 54-63] although none is a specific antidote. Alcohol itself may be given as part of the treatment; however, this is not recommended because it promotes the acceptability of alcohol and also has a short half-life, thus requiring frequent administration. At least five randomized, controlled trials have demonstrated that benzodiazepines are superior to placebos in the treatment of alcohol withdrawal.[64] The benzodiazepines largely have replaced previously used drugs such as chloral hydrate, paraldehyde, and barbiturates. Paraldehyde is available only as a liquid and may be difficult to give orally or rectally in the agitated patient. Also, intramuscular injection of this may cause a sterile abscess. Barbiturates cause excessive sedation more frequently than do benzodiazepines.[19, 23, 65]

The data showing that benzodiazepines are superior to other therapeutic agents are, however, conflicting. Kaim et al. showed that chlordiazepoxide is clearly superior to chlorpromazine, hydroxyzine, and thiamine in preventing seizures and the progression to delirium tremens.[59] Golbert et al. found that paraldehyde given with chloral hydrate is more effective than alcohol, chlordiazepoxide, or promazine in the treatment of alcohol withdrawal syndromes.[60] Thompson et al. showed that intravenous diazepam was superior to rectally administered paraldehyde in patients with severe delirium tremens.[65] A more recent study showed that barbital and diazepam were equally effective in mild withdrawal, but barbital was superior in the treatment of fully developed delirium tremens.[61] These and other trials have been criticized for several reasons: failures and dropouts were not accounted for, sample sizes were too small, allowing for Type II (beta) errors, side effects were not considered, the criteria for inclusion or rejection were not specified, and an endpoint was not specified.[64] Nevertheless, we conclude that benzodiazepines are used widely in treating alcohol withdrawal syndromes in the United States because they are easily administered, clinically effective, and are recommended by experts.

Diazepam (Valium), chlordiazepoxide (Librium), lorazepam (Ativan), oxazepam (Serax), and clorazepate (Tranxene) are the benzodiazepines used most frequently in the treatment of alcohol withdrawal (Table 1).[19, 63] Alprazolam (Xanax) has also been used, but experience with this drug is limited.[62] Several reports of withdrawal reactions from alprazolam suggest a high potential for addiction.[66] We do not recommend its use in the treatment of alcohol withdrawal.

The pharmacokinetics of the benzodiazepines must be understood by the physician using them. Since chlordiazepoxide, diazepam, and clorazepate have long half-lives and are metabolized by the liver (Table 1),[67] they should not be given to the alcoholic with severe liver disease, after head trauma, or in the postoperative period because of the potential for oversedation. Because of their shorter half-lives and lower dependence on hepatic metabolism, oxazepam and lorazepam are the preferred drugs in the treatment of

TABLE 1

Guidelines for Use of Benzodiazepines in Alcohol Withdrawal

	Dose*	Interval	Half-Life†	Comments
Diazepam (Valium)	5–20 mg, po or iv	q 6h	30–60 hours	Lower doses required in liver failure[67]
Chlordiazepoxide (Librium)	25–100 mg, po or iv	q 6h	5–15 hours	Effective half-life is 50–100 hours because of active metabolites[67]
Lorazepam (Ativan)	1–2 mg, po, iv, or im	q 4h	10–20 hours	Recommended in liver failure and for the elderly[68, 71]
Oxazepam (Serax)	15–30 mg, po	q 4h	5–10 hours	Same as above[68]
Clorazepate (Tranxene)	30 mg, po	q 12h	50–80 hours	May be less euphorogenic[57]

*Doses should be reduced by approximately 25%–50% each succeeding day.
†Half-life will be longer in hepatic failure.

alcohol withdrawal in patients with liver disease and in the elderly.[68] We once treated an alcoholic who had variceal bleeding and delirium tremens with 400 mg of diazepam iv, in 48 hours. Because the metabolism of diazepam was delayed, the patient remained oversedated for three weeks. Since then, we have chosen to use oxazepam or lorazepam in similar instances.

Benzodiazepines, if given early to the withdrawing alcoholic, may prevent the progression to delirium tremens.[57] One group advocates giving a loading dose of 20 mg of diazepam po every hour until the patient is sedated and then withholding therapy because of the long half-life of diazepam.[69] We do not advocate this regimen because of the danger of oversedation. Once a withdrawing alcoholic has developed the signs and symptoms of delirium tremens, however, large doses of benzodiazepams, iv, may be required to achieve adequate sedation. One tested method of therapy is the administration of diazepam, 5–10 mg, iv, every five minutes until the patient is awake but calm. This method usually requires an initial dose of 15–215 mg of diazepam.[65] Doses of diazepam as high as 2,640 mg, iv, during the first 48 hours for the treatment of severe delirium tremens have been reported.[70] When high doses of diazepam must be used, the patient should be observed closely for respiratory depression.

Chlordiazepoxide may be given in an initial oral dose of 25–100 mg followed by an additional 25–100 mg dose every six hours.[19] Intravenous administration is inconvenient because chlordiazepoxide must be mixed with its diluent immediately before its use.[71] With the exception of lorazepam, the benzodiazepines are erratically absorbed by the intramuscular (im) route and should not be given in this manner.[68, 72] The doses of all benzodiazepines should be decreased by approximately 25% to 50% or more on each succeeding day of treatment to avoid oversedation. Length of treatment with benzodiazepines is usually between three and five days. We prefer to give benzodiazepines on a regular, tapering basis rather than on a prn basis to avoid over- or undersedation, although doses will frequently have to be individualized for each patient.

Phenothiazines are not recommended for the treatment of alcohol withdrawal since they may lower the seizure threshold, potentiate the hyperthermia seen in withdrawal, and cause hypotension.[19, 59] Haloperidol (Haldol) is effective in controlling the agitation and hallucinations of alcohol withdrawal, although it also lowers the seizure threshold and therefore should be used with caution.[73, 74]

Beta-blockers have been used to reduce the adrenergic signs of withdrawal, including increased heart rate, elevated blood pressure, and tremor.[75, 76] In a randomized, double-blind clinical trial of patients with mild to moderate withdrawal symptoms, Kraus et al. showed that a daily dose of 50 mg of atenolol (Tenormin) reduced the patient's mean hospital stay from 5.1 days to 4.4 days and significantly reduced the total dose of benzodiazepine required for treatment.[77] Critics of this study attacked it from several sides. Some felt that atenolol would alleviate the symptoms of minor withdrawal but not lessen the likelihood of seizures and delirium.[78] Others pointed out that the clinical and statistical significance of the shortened hospital stay was questionable.[79] Finally, there was concern that the short-acting benzodiazepine (oxazepam) given to patients in the study on an as-needed basis was not enough to treat withdrawal symptoms and may have led to the significant differences in the results of the atenolol group.[80] It is clear that the routine use of atenolol in the withdrawing alcoholic shows promise but requires further study.

Clonidine (Catapres) has been used to treat opiate, nicotine, and alcohol withdrawal. Its effect is related to its alpha-2-receptor-mediated inhibition of brain noradrenergic activity, leading to sedation, a lowering of blood pressure, and a lowering of the heart rate.[81, 82] In a recent study, clonidine in a fixed, tapered dosage was superior to chlordiazepoxide in the management of mild to moderate alcohol withdrawal syndrome.[83] It would appear that clonidine is an effective alternative to benzodiazepines in the treatment of mild to moderate alcohol withdrawal syndrome. Studies using clonidine in the treatment of major withdrawal syndromes have not been reported.

Many other treatments have been used to sedate patients undergoing alcohol withdrawal. One of the most unusual is a therapy requiring ventilation with 100% oxygen and nitrous oxide.[84] Chlormethiazole, an antiepileptic drug, is favored worldwide as a treatment

for withdrawal but it has not been approved for use in the United States.[85]

Seizures

Since 10%–25% of withdrawing alcoholics will have a generalized grand mal seizure within the first 48 hours of alcohol withdrawal, it is frequently a dilemma as to whether these patients should be treated with anticonvulsant medications. Status epilepticus is an uncommon alcoholic withdrawal seizure, usually occurring in only 3%–4% of the cases (it was more frequent in one previously mentioned study[39]). Treatment with both phenytoin (Dilantin), iv, and diazepam (Valium), iv, has been recommended for these rare occurrences.

The routine use of phenytoin to prevent withdrawal seizures in patients withdrawing from alcohol is controversial. Three studies have shown contradictory results. In one study of 200 patients, treatment with chlordiazepoxide alone was compared with treatment using chlordiazepoxide and phenytoin.[86] There were no withdrawal seizures when either treatment was used. The authors concluded that when adequate doses of chlordiazepoxide are given, phenytoin is not required. Others have agreed with this view.[69] In another study of 157 patients, the use of chlordiazepoxide and placebo was compared with the use of chlordizepoxide and phenytoin. Eleven of 66 patients in the placebo-treated group and none in the phenytoin-treated group experienced seizures within the first 48 hours of administration.[87] The authors of this study concluded that even in withdrawing alcoholics who receive adequate benzodiazepine therapy, seizures may occur. Another recent study followed 292 randomly selected patients admitted to an inpatient alcoholism program.[88] Most of these patients received prophylactic anticonvulsants. Three per cent of the patients had seizures. In this uncontrolled study, the authors concluded that the use of anticonvulsants in withdrawing alcoholics may actually increase the incidence of seizures.

It is our practice to give phenytoin with a benzodiazepine only to withdrawing patients with a documented history of non-alcohol-related seizures, a history of withdrawal seizures in the past, or recurrent multiple withdrawal seizures during the current admission. In these patients, phenytoin is given in a loading dose of 15 mg/kg dissolved in 250–500 ml of 5% D_5W over four hours, followed by 100 mg, po, q 8h, for three or four days or chronically if the EEG is abnormal.[89]

A differential diagnosis that includes the many other causes of seizures in alcohol-dependent patients should be considered. These include idiopathic or posttraumatic epilepsy, hypoglycemia, electrolyte imbalance, meningitis, hemorrhage, and cerebrovascular accident. If there is a high index of suspicion for any of these other conditions, the individual should be evaluated with the appropriate studies.[90]

Magnesium Replacement

Hypomagnesemia is found frequently in chronic alcoholic patients as well as in those undergoing alcohol withdrawal. It has become a common practice to replace this magnesium deficit. Wolf and Victor demonstrated that stroboscopic stimulation in withdrawing alcoholics caused photomyoclonus more frequently in those individuals with a serum magnesium level significantly below normal, and that administering magnesium to these patients abolished the response to or elevated the threshold for photomyoclonus.[4] They concluded that the routine administration of magnesium sulfate raised the seizure threshold, but did not prevent the development of delirium tremens. In a more recent study, im injections of magnesium sulfate were given in a double blind, placebo-controlled fashion to 100 alcoholic patients being treated for withdrawal.[91] All patients received chlordiazepoxide for sedation. The authors found no significant differences between the treatment and placebo groups in the occurrences of diaphoresis, tremor, vomiting, hallucinations, grand mal seizures, the overall severity of withdrawal, or the changes in diastolic blood pressure or heart rate. They concluded that the routine administration of magnesium sulfate does not affect alcohol withdrawal. It is known, however, that magnesium deficiency produces several physical signs and symptoms, including ataxia, vertigo, hyperacusis, hyperactive reflexes, a positive Babinski sign, tremor, and athetoid and choreiform movements.[92] Hypomagnesemia may also cause cardiac arrhythmias.[93]

Although the therapeutic value of magnesium sulfate in the treatment of alcohol withdrawal remains undefined, it is our practice to administer it to patients who are hypomagnesemic to prevent the various signs and symptoms mentioned above. The routine use of magnesium sulfate in alcoholics with normal serum magnesium levels is not recommended. Magnesium sulfate may be administered in a dose of 1 g, im or iv, every 6–12 hours for 48 hours.[94] Magnesium oxide also may be given orally in a dose of 250–500 mg four times daily for 48 hours, although diarrhea is a common side effect.[95] We give magnesium supplementation to approximately 30% of our withdrawing alcoholics.

Fluid and Electrolyte Disturbances

The management of fluid and electrolyte disturbances in the alcoholic patient often is difficult because of the variations in symptoms among individuals. Beard and Knott[96] reported that alcoholics in the early stages of withdrawal were often over-hydrated, perhaps because of a falling blood alcohol level, which leads to an over-production of antidiuretic hormone. In patients who have not had significant gastrointestinal fluid losses, the result has been over-hydration. Patients with mild to moderate alcohol withdrawal symptoms and no fever may have fluids replaced orally to com-

TABLE 2

Suggested Treatment Protocol for Severe Delirium Tremens

1. Make the diagnosis of delirium tremens based on the patient's history and a physical examination. Perform a lumbar puncture in febrile patients.
2. Search for infections, or other sequelae of alcohol abuse (such as gastrointestinal bleeding or pancreatitis) and treat as indicated.
3. Sedate the patient with 5 – 10 mg diazepam, iv, every 5 minutes until the patient is awake but calm. Use lorazepam, 1 – 2 mg, iv, in place of diazepam in liver-impaired or elderly patients. Reduce the doses of benzodiazepines as the patient recovers.
4. Administer 100 mg of thiamine, po, iv, or im. Give multivitamins daily.
5. Estimate the patient's fluid deficit and replace with normal saline if the serum sodium concentration is more than 120 mEq/L. If the serum sodium concentration is less than 120 mEq/L, raise the serum sodium to 125 mEq/L with 3% or 5% saline at a rate of 2 mEq/L/hr, then use normal saline. Monitor for fluid overload.
6. Replace potassium, magnesium, and phosphorus if the serum levels are low. Potassium may be given in the intravenous fluids at a rate of 20 mEq/hr. Give magnesium sulfate, 1 g, iv or im, every 6 – 12 hours for 48 hours or give magnesium oxide, 250 – 500 mg, po, qid, for 48 hours. Give doses of 12 – 18 mM potassium phosphate in the intravenous fluids every eight hours.
7. Load with Dilantin, 15 mg/kg, only if the patient has an untreated, non-alcohol-related seizure disorder, a history of previous withdrawal seizures, or multiple seizures during the current admission.
8. Consider giving a beta-blocker, po or iv, if the patient's systolic blood pressure is more than 180 mm Hg or the heart rate is more than 120/min.
9. Keep the patient in a quiet room. Restrain in bed if necessary, but avoid if possible since this may increase feelings of paranoia and agitation.
10. Provide frequent monitoring of the patient's status by a nurse and/or physician.

pensate for their considerable fluid losses. The patient with delirium tremens, however, may have a more significant fluid loss from the skin, respiratory tract, and gastrointestinal system. Losses of 1 – 3 L in 24 hours may occur from diaphoresis alone, with an additional 1-L loss from the respiratory tract during this same period. Urinary and intestinal fluid losses may result in another 2 – 3 L of fluid loss per day, thus requiring at least 6 L of fluid in a 24-hour period. Intravascular volume status can be determined by measuring the urinary specific gravity and the urinary sodium concentration. A specific gravity of more than 1.025 with a sodium concentration of less than 10 mEq/L is an indication of volume depletion. Orthostatic hypotension can also be used to determine the patient's hydration status, but it may be difficult to measure in agitated patients. Volume deficits are best replaced by an infusion of 5% dextrose, iv, in half-normal saline if the serum sodium is normal.[89] Other electrolytes may be added as needed. Frequent clinical and laboratory reevaluations of the patient should be made to determine the individual's volume status and continuing needs.

The reduction of total body potassium in most withdrawing alcoholics is a result of poor nutritional intake, vomiting, and diarrhea. This deficiency may be exacerbated by the concurrent administration of thiazide diuretics. Watson et al. suggested that hypokalemia might be caused by the ethanol-induced overactivity of the sodium-potassium pump.[97] There are those who believe that hypokalemia may be a factor in the genesis of delirium tremens[98], although potassium replacement does not reverse the symptoms. Hypokalemia diffusely affects the patient's neuromuscular function and is manifested by skeletal muscle weakness, intestinal ileus, and abnormalities of cardiac electrical conduction. It also may promote rhabdomyolysis. For these reasons, hypokalemia should be corrected, usually in a conservative manner, by administering not more than 20 mEq of potassium chloride, po or iv, per hour (unless there are ECG or other changes showing severe hypokalemia).[99]

Hyponatremia in the alcoholic patient may be a result of the combined effects of gastrointestinal losses from vomiting and diarrhea, the inadequate dietary intake of sodium, and antidiuretic hormone (ADH) stimulation secondary to volume contraction. Beer drinkers seem to develop hyponatremia from excessive ADH secretion.[100] In most instances, hyponatremia in withdrawing alcoholics should be treated with normal saline solution rather than fluid restriction because these patients tend to experience volume contraction. As mentioned previously, fluid status can be determined by examining for orthostatic hypotension and checking the urinary specific gravity and urinary sodium concentration. Symptomatic, acutely hyponatremic patients with a serum sodium level below 120 mEq/L should receive either 3% or 5% hypertonic saline at a rate sufficient to raise the serum sodium concentration by 2 mEq/L/hr to a final concentration of 125 – 130 mEq/L. Central pontine myelinolysis (CPM) has been reported to occur in hyponatremic patients who had a rapid increase in their serum sodium concentrations.[101] The relationship between the rate of correction and this syndrome is controversial. Most experts agree that CPM should not occur if the above guidelines are followed.

Hypophosphatemia secondary to malnutrition may produce symptoms such as bone pain, stiffness, weakness, loss of appetite, and intention tremors at serum phosphate levels below 1 mg/dl. The most serious complications of hypophosphatemia are rhabdomyolysis and cardiac failure.[46, 47] If the patient cannot maintain a normal diet, potassium phosphate should be given in the intravenous fluids in a dose of 12 – 18 mM, q 8 h.[99]

Alcoholic ketoacidosis, as previously noted, may be seen in the malnourished, non-diabetic alcoholic. Restoration of normal fluid balance with a glucose-containing saline solution usually reverses this syndrome.[48] A marked acidosis may be associated with methanol or ethylene glycol ingestion. Hypoglycemia also may occur in the withdrawing alcoholic, since malnutrition and liver disease impair the storage of gly-

cogen. The serum glucose level should be monitored in the withdrawing alcoholic, and episodes of hypoglycemia should be treated with 50-ml boluses of 50% glucose after the patient has been given adequate thiamine replacement. If the serum glucose level remains low, a continuous infusion of 10% dextrose, iv, in an appropriate saline solution may be administered.

Nutritional Deficiencies

As mentioned above, withdrawing alcoholics have many nutritional deficiencies. To prevent Wernicke's encephalopathy and Korsakoff's syndrome, withdrawing alcoholics should immediately receive 100 mg of thiamine, po, iv, or im, depending on how ill the patient is. Again, this should be given before any glucose infusion, since a glucose load may further exhaust the body's reserves of thiamine and precipitate the onset of Wernicke's encephalopathy. The patient should receive supplements of multivitamins containing thiamine, folic acid, and vitamin C, either iv or po, throughout his or her hospital stay.[102] A single dose of vitamin K (10 mg) may be given subcutaneously to treat a prolonged prothrombin time.[99]

Suggested Treatment Protocol for Severe Delirium Tremens

The patient with severe delirium tremens who is agitated, delirious, and febrile is a therapeutic challenge for any physician. In Table 2, we outline our approach to the patient with severe delirium tremens. This protocol is distributed to our new housestaff each year.

Post-withdrawal Care

Patients who have been admitted to a hospital for treatment of any of the alcohol withdrawal syndromes should not be discharged before an attempt has been made to intervene in their alcoholism. At our institution, a full-time alcoholism counselor is available to see any patient on a consultation basis. The alcoholism counselor assesses the patient's desire for abstinence and makes specific recommendations for rehabilitation. This may include a referral to Alcoholics Anonymous, an alcohol rehabilitation center, or an outpatient mental health center. The counselor may also recommend the involvement of the primary care physician in an ongoing treatment program. The use of disulfuram (Antabuse) is often recommended as an adjunct to rehabilitation. The patient's primary care physician should provide close and frequent follow-ups for the patient after the individual is discharged to monitor any ongoing medical problems and to support the patient's abstinence from alcohol. General internists will find the recently published book by Barnes et al. helpful in the management of alcoholic patients, since alcoholism and alcohol withdrawal are common problems encountered in their practices.[103]

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