Alcohol (ethanol) is a CNS depressant. Large amounts consumed rapidly can cause respiratory depression, coma, and death. Large amounts chronically consumed damage the liver and many other organs. Alcohol withdrawal manifests as a continuum, ranging from tremor to seizures, hallucinations, and life-threatening autonomic instability in severe withdrawal (delirium tremens). Diagnosis is clinical.

About 45 to 50% of adults are current drinkers, 20% are former drinkers, and 30 to 35% are lifetime abstainers. For most drinkers, the frequency and amount of alcohol consumption does not impair physical or mental health or the ability to safely carry out daily activities. However, acute alcohol intoxication is a significant factor in injuries, particularly those due to interpersonal violence, suicide, and motor vehicle crashes. Chronic abuse interferes with the ability to socialize and work. About 7 to 10% of adults meet criteria for an alcohol use disorder (abuse or dependence) in any given year. Binge drinking, defined as consuming ≥ 5 drinks per occasion for men and ≥ 4 drinks per occasion for women, is a particular problem among younger people.

Pathophysiology

One serving of alcohol (one 12-oz can of beer, one 6-oz glass of wine, or 1.5 oz of distilled liquor) contains 10 to 15 g of ethanol. Alcohol is absorbed into the blood mainly from the small bowel, although some is absorbed from the stomach. Alcohol accumulates in blood because absorption is more rapid than oxidation and elimination. The concentration peaks about 30 to 90 min after ingestion if the stomach was previously empty. About 5 to 10% of ingested alcohol is excreted unchanged in urine, sweat, and expired air; the remainder is metabolized mainly by the liver, where alcohol dehydrogenase converts ethanol to acetaldehyde. Acetaldehyde is ultimately oxidized to CO₂ and water at a rate of 5 to 10 mL/h (of absolute alcohol); each milliliter yields about 7 kcal. Alcohol dehydrogenase in the gastric mucosa accounts for some metabolism; much less gastric metabolism occurs in women.
Alcohol exerts its effects by several mechanisms. Alcohol binds directly to γ-aminobutyric acid (GABA) receptors in the CNS, causing sedation. Alcohol also directly affects cardiac, hepatic, and thyroid tissue.

**Chronic effects:** Tolerance to alcohol develops rapidly; similar amounts cause less intoxication. Tolerance is caused by adaptational changes of CNS cells (cellular, or pharmacodynamic, tolerance) and by induction of metabolic enzymes. People who develop tolerance may reach an incredibly high blood alcohol content (BAC). However, ethanol tolerance is incomplete, and considerable intoxication and impairment occur with a large enough amount. But even these drinkers may die of respiratory depression secondary to alcohol overdose. Alcohol-tolerant people are susceptible to alcoholic ketoacidosis (see Diabetes Mellitus and Disorders of Carbohydrate Metabolism: Alcoholic Ketoacidosis), especially during binge drinking. Alcohol-tolerant people are cross-tolerant of many other CNS depressants (eg, barbiturates, nonbarbiturate sedatives, benzodiazepines).

The physical dependence accompanying tolerance is profound, and withdrawal has potentially fatal adverse effects.

Chronic heavy alcohol intake typically leads to liver disorders (eg, fatty liver, alcoholic hepatitis, cirrhosis); the amount and duration required vary (see Alcoholic Liver Disease). Patients with a severe liver disorder often have coagulopathy from decreased hepatic synthesis of coagulation factors, increasing the risk of significant bleeding from trauma (eg, from falls or vehicle crashes) and of GI bleeding (eg, due to gastritis, from esophageal varices due to portal hypertension); alcohol abusers are at particular risk of GI bleeding.

Chronic heavy intake also commonly causes the following:

- Gastritis,
- Pancreatitis
- Cardiomyopathy, often accompanied by arrhythmias and hypertension
- Peripheral neuropathy
- Brain damage, including Wernicke's encephalopathy, Korsakoff's psychosis, Marchiafava-Bignami disease, and alcoholic dementia
- Certain cancers (eg, head and neck, esophageal), especially when drinking is combined with smoking

Indirect long-term effects include malnutrition, particularly vitamin deficiencies.

On the other hand, low to moderate levels of alcohol consumption (≤ 1 to 2 drinks/day) may decrease the risk of death from cardiovascular disorders. Numerous explanations, including increased high density lipoprotein (HDL) levels and a direct antithrombotic effect, have been suggested. Nonetheless, alcohol should not be recommended for this purpose, especially when there are several safer, more effective approaches to reduce cardiovascular risk.

**Special populations:** Young children who drink alcohol are at significant risk of hypoglycemia because alcohol impairs gluconeogenesis and their smaller stores of glycogen are rapidly depleted. Women may be more sensitive than men, even on a per-weight basis, because their gastric (first-pass) metabolism of alcohol is less. Drinking during pregnancy increases the risk of fetal alcohol syndrome (see Metabolic, Electrolyte, and Toxic Disorders in Neonates: Alcohol).
Symptoms and Signs

**Acute effects:** Symptoms progress proportionately to the BAC. Actual levels required to produce given symptoms vary with tolerance, but in typical users:

- 20 to 50 mg/dL: Tranquility, mild sedation, and some decrease in fine motor coordination
- 50 to 100 mg/dL: Impaired judgment and a further decrease in coordination
- 100 to 150 mg/dL: Unsteady gait, nystagmus, slurred speech, loss of behavioral inhibitions, and memory impairment
- 150 to 300 mg/dL: Delirium and lethargy (likely)

Emesis is common with moderate to severe intoxication; because emesis usually occurs with obtundation, aspiration is a significant risk.

In most US states, the legal definition of intoxication is a BAC of ≥ 0.08 to 0.10% (≥ 80 to 100 mg/dL); 0.08 is used most commonly.

**Toxicity or overdose:** In alcohol-naive people a BAC of 300 to 400 mg/dL often produces unconsciousness, and a BAC ≥ 400 mg/dL may be fatal. Sudden death from respiratory depression or arrhythmias may occur, especially when large quantities are drunk rapidly. This problem is emerging in US colleges but has been known in other countries where it is more common. Other common effects include hypotension and hypoglycemia.

The effect of a particular BAC varies widely; some chronic drinkers seem unaffected and appear to function normally with BAC in the 300 to 400 mg/dL range, whereas nondrinkers and social drinkers are impaired at a BAC that is inconsequential in chronic drinkers.

**Chronic effects:** Stigmata of chronic use include Dupuytren's contracture of the palmar fascia, vascular spiders, and, in men, signs of hypogonadism and feminization (eg, smooth skin, lack of male-pattern baldness, gynecomastia, testicular atrophy). Malnutrition may lead to enlarged parotid glands.

**Withdrawal:** A continuum of symptoms and signs of CNS (including autonomic) hyperactivity may accompany cessation of alcohol intake.

A mild withdrawal syndrome includes tremor, weakness, headache, sweating, hyperreflexia, and GI symptoms. Symptoms usually begin within about 6 h of cessation. Some patients have generalized tonic-clonic seizures (called alcoholic epilepsy, or rum fits) but usually not > 2 in short succession.

Alcoholic hallucinosis (hallucinations without other impairment of consciousness) follows abrupt cessation from prolonged, excessive alcohol use, usually within 12 to 24 h. Hallucinations are typically visual. Symptoms may also include auditory illusions and hallucinations that frequently are accusatory and threatening; patients are usually apprehensive and may be terrified by the hallucinations and by vivid, frightening dreams. The syndrome may resemble schizophrenia, although thought is usually not disordered and the history is not typical of schizophrenia. Symptoms do not resemble the delirious state of an acute organic brain syndrome as much as does delirium tremens (DT) or other pathologic reactions associated with withdrawal. Consciousness remains clear, and the signs of autonomic lability that occur in DT are usually absent. When hallucinosis occurs, it usually precedes DT and is transient.
DT usually begins 48 to 72 h after alcohol withdrawal; anxiety attacks, increasing confusion, poor sleep (with frightening dreams or nocturnal illusions), profuse sweating, and severe depression also occur. Fleeting hallucinations that arouse restlessness, fear, and even terror are common. Typical of the initial delirious, confused, and disoriented state is a return to a habitual activity; eg, patients frequently imagine that they are back at work and attempt to perform some related activity. Autonomic lability, evidenced by diaphoresis and increased pulse rate and temperature, accompanies the delirium and progresses with it. Mild delirium is usually accompanied by marked diaphoresis, a pulse rate of 100 to 120 beats/min, and a temperature of 37.2 to 37.8°C. Marked delirium, with gross disorientation and cognitive disruption, is accompanied by significant restlessness, a pulse of > 120 beats/min, and a temperature of > 37.8°C; risk of death is high.

During DT, patients are suggestible to many sensory stimuli, particularly to objects seen in dim light. Vestibular disturbances may cause them to believe that the floor is moving, the walls are falling, or the room is rotating. As the delirium progresses, resting tremor of the hand develops, sometimes extending to the head and trunk. Ataxia is marked; care must be taken to prevent self-injury. Symptoms vary among patients but are usually the same for a particular patient with each recurrence.

**Diagnosis**

- Usually, clinical
- Acute: BAC, evaluation to rule out hypoglycemia and occult trauma
- Chronic: CBC, Mg, liver function tests, and PT/PTT
- Withdrawal: Evaluation to rule out CNS injury and infection

In acute intoxication, laboratory tests, except for fingerstick glucose to rule out hypoglycemia and tests to determine BAC, are generally not helpful; diagnosis is usually made clinically. Confirmation by breath or blood alcohol levels is useful for legal purposes (eg, to document intoxication in drivers or employees who appear impaired). However, finding a low BAC in patients who have altered mental status and smell of alcohol is helpful because it expedites the search for an alternate cause. Clinicians should not assume that a high BAC in patients with apparently minor trauma accounts for their obtundation, which may be due to intracranial injury or other abnormalities. Such patients should also have toxicology tests to search for evidence of toxicity from other substances.

Chronic alcohol abuse and dependence are clinical diagnoses; experimental markers of long-term use have not proven sufficiently sensitive or specific for general use. However, heavy alcohol users may have a number of metabolic derangements that are worth screening for, so CBC, electrolytes (including Mg), liver function tests including coagulation profile (PT/PTT), and serum albumin are often recommended.

In severe withdrawal and toxicity, symptoms may resemble those of CNS injury or infection, so medical evaluation with CT and lumbar puncture may be needed. Patients with mild symptoms do not require routine testing unless improvement is not marked within 2 to 3 days.

**Treatment**

*Toxicity or overdose:* Treatment may include the following:

- Airway protection
- Sometimes IV fluids with thiamin, Mg, and vitamins
The first priority is ensuring an adequate airway; endotracheal intubation and mechanical ventilation are required for apnea or inadequate respirations. IV hydration is needed for hypotension or evidence of volume depletion but does not significantly enhance ethanol clearance. When IV fluids are used, a single dose of thiamin 100 mg IV is given to treat or prevent Wernicke's encephalopathy. Many clinicians also add multivitamins and Mg to the IV fluids.

Disposition of the acutely intoxicated patient depends on clinical response, not a specific BAC.

Withdrawal: Patients with severe withdrawal or DT should be managed in an ICU until these symptoms improve. Treatment may include the following to prevent Wernicke-Korsakoff syndrome and other complications:

- IV thiamin
- Benzodiazepines

Thiamin 100 mg IV is given to prevent Wernicke-Korsakoff syndrome.

Alcohol-tolerant people are cross-tolerant of some drugs commonly used to treat withdrawal (eg, benzodiazepines).

Benzodiazepines are the mainstay of therapy. Dosage and route depend on degree of agitation, vital signs, and mental status. Diazepam, given 5 to 10 mg IV or po hourly until sedation occurs, is a common initial intervention; lorazepam 1 to 2 mg IV or po is an alternative. Chlordiazepoxide 50 to 100 mg po q 4 to 6 h, then tapered, is an older acceptable alternative for less severe cases of withdrawal. Phenobarbital may help if benzodiazepines are ineffective, but respiratory depression is a risk with concomitant use. Phenothiazines and haloperidol are not recommended initially because they may lower the seizure threshold. For patients with a significant liver disorder, a short-acting benzodiazepine (lorazepam) or one metabolized by glucuronidation (oxazepam) is preferred. (Note: Benzodiazepines may cause intoxication, physical dependence, and withdrawal in alcoholics and therefore should not be continued after the detoxification period. Carbamazepine 200 mg po qid may be used as an alternative and then tapered). For severe hyperadrenergic activity or to reduce benzodiazepine requirements, short-term therapy (12 to 48 h) with titrated β-blockers (eg, metoprolol 25 to 50 mg po or 5 mg IV q 4 to 6 h) and clonidine 0.1 to 0.2 mg q 2 to 4 h can be used.

A seizure, if brief and isolated, needs no specific therapy; however, some clinicians routinely give a single dose of lorazepam 1 to 2 mg IV as prophylaxis against another seizure. Repeated or longer-lasting (ie, > 2 to 3 min) seizures should be treated and often respond to lorazepam 1 to 3 mg IV. Routine use of phenytoin is unnecessary and unlikely to be effective. Outpatient therapy with phenytoin is rarely indicated for patients with simple alcohol withdrawal seizures when no other source of seizure activity has been identified because seizures occur only under the stress of alcohol withdrawal, and patients who are withdrawing or heavily drinking may not take the anticonvulsant.

DT may be fatal and thus must be treated promptly with high-dose IV benzodiazepines, preferably in an ICU. Dosing is higher and more frequent than in mild withdrawal. Very high doses of benzodiazepines may be required, and there is no maximum dose or specific treatment regimen. Diazepam 5 to 10 mg IV or lorazepam 1 to 2 mg q 10 min is given as needed to control delirium; some patients require several hundred mg over the first few hours. Patients refractory to high-dose benzodiazepines may respond to phenobarbital 120 to 240 mg IV q 20 min as needed. Severe drug-resistant DT can
be treated with a continuous infusion of lorazepam, diazepam, midazolam, or propofol, usually with concomitant mechanical ventilation. Physical restraints should be avoided if possible to minimize additional agitation, but patients must not be allowed to elope, remove IVs, or otherwise endanger themselves. Intravascular volume must be maintained with IV fluids, and large doses of vitamins B and C, particularly thiamin, must be given promptly. Appreciably elevated temperature with DT is a poor prognostic sign.

ALCOHOL PROBLEMS AND REHABILITATION

Definitions

At-risk drinking is defined solely by quantity and frequency of drinking:

- > 14 drinks/wk or 4 drinks per occasion for men
- > 7 drinks/wk or 3 drinks per occasion for women

Compared with lesser amounts, these amounts are associated with increased risk of a wide variety of medical and psychosocial complications.

Alcohol abuse refers to a maladaptive pattern of episodic drinking that results in failure to fulfill obligations, drinking in physically hazardous situations (eg, driving, boating), legal problems, or social and interpersonal problems without evidence of dependence.

Alcohol dependence refers to frequent consumption of large amounts of alcohol with ≥ 3 of the following:

- Tolerance
- Withdrawal symptoms
- Drinking larger amounts than intended
- Persistent desire to reduce use without success
- Substantial time spent obtaining, drinking, or recovering from alcohol
- Sacrifice of other life events for drinking
- Continued use despite physical or psychologic problems

Alcoholism is often used as an equivalent term for alcohol dependence, especially when drinking results in significant toxicity and tissue damage.

Etiology

The maladaptive pattern of drinking that constitutes alcohol abuse may begin with a desire to reach a state of feeling high. Some drinkers who find the feeling rewarding then focus on repeatedly reaching that state. Many who abuse alcohol chronically have certain personality traits: feelings of isolation, loneliness, shyness, depression, dependency, hostile and self-destructive impulsivity, and sexual immaturity. Alcoholics may come from a broken home and have a disturbed relationship with their family. Societal factors—attitudes transmitted through the culture or child rearing—affect patterns of drinking and consequent behavior. However, such generalizations should not obscure the fact that alcohol use disorders can occur in anyone, regardless of their age, sex, background, ethnicity, or social situation. Thus, clinicians should screen for alcohol problems in all patients.

The incidence of alcohol abuse and dependence is higher in biologic children of people with alcohol problems than in adoptive children, and the percentage of biologic children of alcoholics who are problem drinkers is greater than that of the general population. There is evidence of genetic or biochemical predisposition, including data that suggest some people who become alcoholics are less easily intoxicated; ie, they have a higher
threshold for CNS effects.

**Symptoms**

Serious social consequences usually occur. Frequent intoxication is obvious and destructive; it interferes with the ability to socialize and work. Injuries are common. Eventually, failed relationships and job loss due to absenteeism may result. People may be arrested because of alcohol-related behavior or be apprehended for driving while intoxicated, often losing driving privileges for repeated offenses; in most US states, the maximum legal blood alcohol concentration (BAC) while driving is 80 mg/dL (0.08%), and this level is likely to be reduced in the future.

**Diagnosis**

Some alcohol-related problems are diagnosed when people seek medical treatment for their drinking or for obvious alcohol-related illness (eg, DT, cirrhosis). However, many of these people remain unrecognized for a long time. Female alcoholics are, in general, more likely to drink alone and are less likely to manifest some of the social signs. Therefore, many governmental and professional organizations recommend alcohol screening during routine health care visits. A scaled approach (see Table 2: Drug Use and Dependence: Levels of Screening for Alcohol Problems) can help identify patients who require more detailed questioning; several validated detailed questionnaires are available.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Levels of Screening for Alcohol Problems</th>
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<tbody>
<tr>
<td><strong>Screening Level</strong></td>
<td><strong>Criteria for Use</strong></td>
</tr>
<tr>
<td>1</td>
<td>If only one question is possible</td>
</tr>
</tbody>
</table>
| 2 | For all patients who report drinking alcohol if time allows | 1. On average, how many days per week do you drink alcohol?  
2. On a typical day when you drink, how many drinks do you have?  
3. What is the maximum number of drinks you had on any given day in the past month? |
| 2 | For patients who respond "yes" to a level 1 screening question |  |
| 3 | If level 2 screening identifies risk of alcohol-related problems (ie, for men, > 14 drinks/wk or 4 drinks/day; for women, > 7 drinks/wk or 3 drinks/day) or If the clinician suspects that patients are minimizing their alcohol use | The 10-question Alcohol Use Disorders Identification Test (AUDIT†) |

*A drink is defined as 12 oz of beer, 5 oz of wine, or 1.5 oz of distilled spirits.  
†The AUDIT questionnaire is available at [National Institute of Alcohol Abuse and Alcoholism (NIAAA) web site](http://www.niaaa.nih.gov). Adapted from Fleming MF: Screening and Brief Intervention in Primary Care Settings. At the [NIAAA web site](http://www.niaaa.nih.gov).

**Treatment**

- Rehabilitation programs
- Outpatient counseling
- Self-help groups
Consideration of drugs (eg, naltrexone, disulfiram)

All patients should be counseled to decrease their alcohol use to below at-risk levels.

For patients identified as at-risk drinkers, treatment may begin with a brief discussion of the medical and social consequences and a recommendation to reduce or cease drinking, with follow-up regarding compliance (see Table 3: Drug Use and Dependence: Brief Interventions for Alcohol Problems).

For patients with more serious problems, particularly after less intensive measures have been unsuccessful, a rehabilitation program is often the best approach. Rehabilitation programs combine psychotherapy, including one-on-one and group therapy, with medical supervision. For most patients, outpatient rehabilitation is sufficient; how long patients remain enrolled in programs varies, typically weeks to months, but longer if needed. Inpatient rehabilitation programs are reserved for patients with more severe alcohol dependence and those with significant and comorbid medical, psychoactive, and substance abuse problems. Treatment duration is usually briefer (typically days to weeks) than that of outpatient programs and may be dictated in part by patients’ insurance.

Psychotherapy involves techniques that enhance motivation and teach patients to avoid circumstances that precipitate drinking. Social support of abstinence, including the support of family and friends, is important.

Maintenance: Maintaining sobriety is difficult. Patients should be warned that after a few weeks, when they have recovered from their last bout, they are likely to find an excuse to drink. They should also be told that, although they may be able to practice controlled drinking for a few days or, rarely, a few weeks, they will most likely lose control eventually.

In addition to the counseling provided in outpatient and inpatient alcohol treatment programs, self-help groups and certain drugs may help prevent relapse in some patients.

Alcoholics Anonymous (AA) is the most common self-help group. Patients must find an AA group they feel comfortable in. AA provides patients with nondrinking friends who are always available and a nondrinking environment in which to socialize. Patients also hear others discuss every rationalization they have ever used for their own drinking. The help they give other alcoholics may give them the self-regard and confidence formerly found only in alcohol. Many alcoholics are reluctant to go to AA and find individual counseling or group or family treatment more acceptable. Alternative organizations, such as LifeRing Recovery (Secular Organizations for Sobriety), exist for patients seeking another approach.

Drug therapy should be used with counseling rather than as sole treatment.

Disulfiram, the first drug available to prevent relapse in alcohol dependence, interferes with the metabolism of acetaldehyde (an intermediary product in the oxidation of alcohol) so that acetaldehyde accumulates. Drinking alcohol within 12 h of taking disulfiram causes facial flushing in 5 to 15 min, then intense vasodilation of the face and neck with suffusion of the conjunctivae, throbbing headache, tachycardia, hyperpnea, and sweating. With high doses of alcohol, nausea and vomiting may follow in 30 to 60 min and may lead to hypotension, dizziness, and sometimes fainting and collapse. The reaction can last up to 3 h. Few patients risk drinking alcohol while taking disulfiram because of the intense discomfort. Drugs that contain alcohol (eg, tinctures;
elixirs; some OTC liquid cough and cold preparations, which contain as much as 40% alcohol) must also be avoided. Disulfiram is contraindicated during pregnancy and in patients with cardiac decompensation. It may be given on an outpatient basis after 4 or 5 days of abstinence. The initial dosage is 0.5 g po once/day for 1 to 3 wk, followed by a maintenance dosage of 0.25 g once/day. Effects may persist for 3 to 7 days after the last dose. Periodic physician visits are needed to encourage continuation of disulfiram as part of an abstinence program. Disulfiram’s general usefulness has not been established, and many patients are noncompliant. Compliance usually requires adequate social support, such as observation of drinking. For these reasons, use of disulfiram is now limited. Disulfiram is most effective when given under close supervision to highly motivated patients.

Naltrexone, an opioid antagonist (see Drug Use and Dependence: Maintenance), decreases the relapse rate and number of drinking days in most patients who take it consistently. Naltrexone 50 mg po once/day is typically given, although there is evidence that higher doses (eg, 100 mg once/day) may be more effective in some patients. Even with counseling, adherence rates with oral naltrexone are modest. A long-acting depot form is also available: 380 mg IM once/mo. Naltrexone is contraindicated in patients with acute hepatitis or liver failure and in those who are opioid dependent.

Acamprosate, a synthetic analogue of γ-aminobutyric acid, is given as 2 g po once/day. Acamprosate may decrease the relapse rate and number of drinking days in patients who relapse.

Nalmefene, an opioid antagonist, and topiramate are under study for their ability to decrease alcohol craving.

### Table 3

<table>
<thead>
<tr>
<th>Intervention Level</th>
<th>Criteria for Use</th>
<th>Brief Intervention Technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>If screening results determine that intervention is necessary but time is limited</td>
<td>Simply stating concern that the patient’s drinking exceeds recommended limits and could lead to alcohol-related problems; recommending that the patient minimize or stop drinking</td>
</tr>
<tr>
<td>2</td>
<td>If referral to a specialist is not necessary; if abstinence is not necessarily the goal</td>
<td>Project TrEAT (Trial for Early Alcohol Treatment) protocol: 2 brief face-to-face sessions scheduled 1 mo apart, with a follow-up telephone call 2 wk after each session</td>
</tr>
<tr>
<td>3</td>
<td>If the patient has symptoms of alcohol abuse or dependence; if abstinence is the primary goal</td>
<td>Motivational enhancement; referral to a specialist</td>
</tr>
</tbody>
</table>

**Wernicke’s Encephalopathy**

Wernicke’s encephalopathy is characterized by acute onset of confusion, nystagmus, partial ophthalmoplegia, and ataxia due to thiamin deficiency. Diagnosis is primarily clinical. The disorder may remit with treatment, persist, or degenerate into Korsakoff’s psychosis. Treatment consists of thiamin and supportive measures.

Wernicke’s encephalopathy results from inadequate intake or absorption of thiamin plus continued carbohydrate ingestion. Severe alcoholism is a common underlying condition. Excessive alcohol intake interferes with thiamin absorption from the GI tract and hepatic storage of thiamin; the poor nutrition associated with alcoholism often precludes
adequate thiamin intake. Wernicke's encephalopathy may also result from other conditions that cause prolonged undernutrition or vitamin deficiency (eg, recurrent dialysis, hyperemesis, starvation, gastric plication, cancer, AIDS). Loading carbohydrates in patients with thiamin deficiency (ie, refeeding after starvation or giving IV dextrose-containing solutions to high-risk patients) can trigger Wernicke's encephalopathy.

Not all thiamin-deficient alcohol abusers develop Wernicke's encephalopathy, suggesting that other factors may be involved. Genetic abnormalities that result in a defective form of transketolase, an enzyme that processes thiamin, may be involved.

Characteristically, CNS lesions are symmetrically distributed around the 3rd ventricle, aqueduct, and 4th ventricle. Changes in the mamillary bodies, dorsomedial thalamus, locus ceruleus, periaqueductal gray matter, ocular motor nuclei, and vestibular nuclei are common.

**Symptoms and Signs**

Clinical changes occur suddenly. Oculomotor abnormalities, including horizontal and vertical nystagmus and partial ophthalmoplegias (eg, lateral rectus palsy, conjugate gaze palsies), are common. Pupils may be abnormal; they are usually sluggish or unequal.

Vestibular dysfunction without hearing loss is common, and the oculovestibular reflex may be impaired. Gait ataxia may result from vestibular disturbances and cerebellar dysfunction; gait is wide-based and slow, with short-spaced steps.

Global confusion is often present; it is characterized by profound disorientation, indifference, inattention, drowsiness, or stupor. Peripheral nerve pain thresholds are often elevated, and many patients develop severe autonomic dysfunction characterized by sympathetic hyperactivity (eg, tremor, agitation) or hypoactivity (eg, hypothermia, postural hypotension, syncope). In untreated patients, stupor may progress to coma, then to death.

**Diagnosis**

Diagnosis is clinical and depends on recognition of underlying undernutrition or vitamin deficiency. There are no characteristic abnormalities in CSF, evoked potentials, brain imaging, or EEG. However, these tests, as well as laboratory tests (eg, blood tests, glucose, CBC, liver function tests, ABG measurements, toxicology screening), should be done to rule out other etiologies. Thiamin levels are not routinely measured.

**Prognosis**

Prognosis depends on timely diagnosis. If begun in time, treatment may correct all abnormalities. Ocular symptoms usually begin to abate within 24 h after early thiamin administration. Ataxia and confusion may persist days to months. Untreated, the disorder progresses; mortality is 10 to 20%. Of surviving patients, 80% develop Korsakoff psychosis; the combination is called Wernicke-Korsakoff syndrome.

**Treatment**

- Parenteral thiamin
- Parenteral Mg

Treatment consists of immediate administration of thiamin 100 mg IV or IM, continued daily for at least 3 to 5 days. Mg is a necessary cofactor in thiamin-dependent metabolism, and hypomagnesemia should be corrected using Mg sulfate 1 to 2 g IM or IV q 6 to 8 h or Mg oxide 400 to 800 mg po once/day. Supportive treatment includes
rehydration, correction of electrolyte abnormalities, and general nutritional therapy, including multivitamins. Patients with advanced disease require hospitalization. Alcohol cessation is mandatory.

Because Wernicke's encephalopathy is preventable, all malnourished patients should be treated with parenteral thiamin (typically 100 mg IM followed by 50 mg po once/day) plus vitamin B₁₂ and folate (1 mg po once/day for both), particularly if IV dextrose is necessary. Thiamin is also prudent before any treatment is begun in patients who present with a reduced level of consciousness. Patients who are malnourished should continue to receive thiamin as outpatients.

**KORSAKOFF'S PSYCHOSIS**

*Korsakoff's psychosis is a late complication of persistent Wernicke's encephalopathy and results in memory deficits, confusion, and behavioral changes.*

Korsakoff's psychosis (Korsakoff's amnestic syndrome) occurs in 80% of untreated patients with Wernicke's encephalopathy. Why Korsakoff's psychosis develops in only some patients with Wernicke's encephalopathy is unclear. A severe or repeated attack of post-alcoholic delirium tremens can trigger Korsakoff's psychosis whether or not a typical attack of Wernicke's encephalopathy has occurred first.

Other triggers include head injury, subarachnoid hemorrhage, thalamic hemorrhage, thalamic ischemic stroke, and, infrequently, tumors affecting the paramedian posterior thalamic region.

**Symptoms and Signs**

Immediate memory is severely affected; retrograde and anterograde amnesia occurs in varying degrees. Patients tend to draw on memory of remote events, which appears to be less affected than memory of recent events. Disorientation to time is common. Emotional changes are common; they include apathy, blandness, or mild euphoria with little or no response to events, even frightening ones. Spontaneity and initiative may be decreased.

Confabulation is often a striking early feature. Bewildered patients unconsciously fabricate imaginary or confused accounts of events they cannot recall; these fabrications may be so convincing that the underlying disorder is not detected.

**Diagnosis**

Diagnosis is based on typical symptoms in patients with a history of severe chronic alcohol dependence. Other causes of symptoms (eg, CNS injury or infection) must be ruled out.

**Prognosis and Treatment**

Prognosis is fairly good for patients with head injury, subarachnoid hemorrhage, or both; the amnesia is transient. Prognosis is poor when the cause is thiamin deficiency or stroke; prolonged institutional care is required for about 25% of patients, and only about 20% recover completely. However, they may improve up to 12 to 24 mo after onset, and patients should not be prematurely institutionalized.

Treatment consists of thiamin and adequate hydration.

**MARCHIAFAVA-BIGNAMI DISEASE**

*Marchiafava-Bignami disease is a rare demyelination of the corpus callosum that occurs in chronic alcoholics, predominantly men.*
Pathology and circumstances link this disorder to osmotic demyelination syndrome (previously called central pontine myelinolysis), of which it may be a variant (see Fluid and Electrolyte Metabolism: Osmotic demyelination syndrome). In Marchiafava-Bignami disease, agitation and confusion occur with progressive dementia and frontal release signs. Some patients recover over several months; others experience seizures and coma, which may precede death.