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Alcohol and Alcohol

Use Disorders Most patients drink alcohol, including many who take this drug at levels that can adversely affect their medical conditions or interfere with the effects of prescribed medications. Therefore, it is important to note that this chapter presents information relevant to all patients, not just those with alcohol problems. Alcohol (beverage ethanol) has diverse and widespread effects on the body and impacts directly or indirectly on almost every neurochemical system in the brain. At even relatively low doses, this drug can exacerbate most medical problems and affect medications metabolized in the liver, and at higher doses, it can tempo rarily mimic many medical (e.g., diabetes) and psychiatric (e.g., depres sion) conditions. Frequent and heavier drinking is also associated with the treatable but life-threatening condition of alcohol use disorder (the modern term for alcoholism). Physicians from all specialties play an important role in screening, using brief interventions, and treating or referring for treatment individuals with repetitive alcohol problems, a process abbreviated as SBIRT. The lifetime risk for repetitive serious alcohol problems (e.g., alcohol use disorder) in patients is at least 20% for men and 10% for women, regardless of a person's education or income, and U.S. yearly costs for these disorders exceed $249 billion. Although low doses of alcohol might have healthful benefits, drinking more than three stan dard drinks per day enhances the risk for cancer and vascular disease, and alcohol use disorders decrease the life span by ~10 years. Unfortu nately, most clinicians have had only limited training in identifying and treating alcohol-related disorders. ■ ■PHARMACOLOGY AND NUTRITIONAL IMPACT

OF ETHANOL Ethanol blood levels are expressed as milligrams or grams of ethanol per deciliter (e.g., 100 mg/dL = 0.10 g/dL), with values of ~0.02 g/dL resulting from the ingestion of one typical drink. In round figures, a standard drink is 10–12 g of ethanol, as seen in 340 mL (12 oz) of beer, 115 mL (4 oz) of nonfortified wine, and 43 mL (1.5 oz) (a shot) of 80-proof (40% ethanol by volume) beverage (e.g., whisky); 0.5 L (1 pint) of 80-proof beverage contains ~160 g of ethanol (~16 standard drinks), and 750 mL of wine contains ~60 g of ethanol. These beverages also have additional components (congeners) that affect the drink's taste and might contribute to adverse effects on the body. Congeners include methanol, butanol, acetaldehyde, histamine, tannins, iron, and lead. As a depressant drug, alcohol acutely decreases neuronal activity and has similar behavioral effects and cross-tolerance with other depressants, including benzodiazepines,

barbiturates, and some anticonvulsants. Alcohol is absorbed from mucous membranes of the mouth and esophagus (in small amounts), from the stomach and large bowel (in modest amounts), and from the proximal portion of the small intestine (the major site). The rate of absorption is increased by rapid gastric emp tying (as seen with carbonated beverages); by the absence of proteins, fats, or carbohydrates (which interfere with absorption); and by dilution to a modest percentage of ethanol (maximum at ~20% by volume). Between 2% (at low blood alcohol concentrations) and 10% (at high blood alcohol concentrations) of ethanol is excreted directly through the lungs, urine, or sweat, but most is metabolized to acetaldehyde, primarily in the liver. The most important pathway occurs in the cell cytosol where alcohol dehydrogenase (ADH) produces acetaldehyde, which is then rapidly destroyed by aldehyde dehydrogenase (ALDH) in the cytosol and mitochondria (Fig. 464-1). A second pathway occurs in the microsomes of the smooth endoplasmic reticulum (the microsomal ethanol-oxidizing system [MEOS]) that is responsible for ≥10% of ethanol oxidation at high blood alcohol concentrations. Although a standard drink contains ~300 kJ, or 70–100 kcal, these are devoid of minerals, proteins, and vitamins. In addition, alcohol

MEOS 20% Acetaldehyde Ethanol Alcohol 80% Acetaldehyde dehydrogenase Aldehyde dehydrogenase Acetyl CoA Acetate Citric acid cycle Fatty acids CHAPTER 464 CO2 + Water FIGURE 464-1 The metabolism of alcohol. CoA, coenzyme A; MEOS, microsomal ethanol oxidizing system. interferes with absorption of vitamins in the small intestine and decreases their storage in the liver with modest effects on folate (folacin or folic acid), pyridoxine (B6), thiamine (B1), nicotinic acid (niacin, B3), and vitamin A. Alcohol and Alcohol Use Disorders Heavy drinking in a fasting, healthy individual can produce tran sient hypoglycemia within 6–36 h, secondary to the acute actions of ethanol that decrease gluconeogenesis. This can result in temporary abnormal glucose tolerance tests (with a resulting erroneous diagnosis of diabetes mellitus) until the heavy drinker has abstained for 2–4 weeks. Alcohol ketoacidosis, probably reflecting a decrease in fatty acid oxidation coupled with poor diet or persistent vomiting, can be misdiagnosed as diabetic ketosis. With alcohol-related ketoacidosis, patients show an increase in serum ketones along with a mild increase in glucose but a large anion gap, a mild to moderate increase in serum lactate, and a β-hydroxybutyrate/lactate ratio of between 2:1 and 9:1 (with normal being 1:1). In the brain, alcohol affects almost all neurotransmitter systems, with acute effects that are often the opposite of those seen follow ing desistance after a period of heavy drinking. The most prominent acute actions relate to boosting γ-aminobutyric acid (GABA) activity, especially at GABAA receptors. Enhancement of this complex chloride channel system contributes to anticonvulsant, sleep-inducing, anti anxiety, and muscle relaxation effects of all GABA-boosting drugs. Acutely administered alcohol produces a release of GABA, and con tinued use increases density of GABAA receptors, whereas alcohol withdrawal states are characterized by decreases in GABA-related activity. Equally important is the ability of acute alcohol to inhibit postsynaptic N-methyl-d-aspartate (NMDA) excitatory glutamate receptors, whereas chronic drinking and desistance are associated with an upregulation of these excitatory receptor subunits. The relationships between greater GABA and diminished NMDA receptor activity dur ing acute intoxication and diminished GABA with enhanced NMDA actions during alcohol withdrawal explain much of intoxication and withdrawal phenomena. As with all pleasurable activities, alcohol acutely increases dopamine levels in the ventral tegmentum and related brain regions, and this effect plays an important role in continued alcohol use, craving, and relapse. The changes in dopamine pathways are also linked to increases in “stress hormones,” including cortisol and adrenocorticotropic hor mone (ACTH), during

intoxication and in the context of the stresses of withdrawal. Such alterations are likely to contribute to both feelings of reward during intoxication and depression during falling blood alcohol concentrations. Also closely linked to alterations in dopamine (especially in the nucleus accumbens) are alcohol-induced changes in opioid receptors, with acute alcohol causing release of β-endorphins. Additional neurochemical changes include increases in synaptic levels of serotonin during acute intoxication and subsequent upregula tion of serotonin receptors. Acute increases in nicotinic acetylcholine

TABLE 464-1 Effects of Blood Alcohol Levels in the Absence

of Tolerance BLOOD LEVEL, g/dL USUAL EFFECT 0.02 Decreased inhibitions, a slight feeling of intoxication 0.08 Decrease in complex cognitive functions and motor performance 0.20 Obvious slurred speech, motor incoordination, irritability, and poor judgment 0.30 Light coma and depressed vital signs 0.40 Death systems contribute to the impact of alcohol in the ventral tegmental region, which occurs in concert with enhanced dopamine activity. In the same regions, alcohol impacts on cannabinol receptors, with result ing release of dopamine, GABA, and glutamate as well as subsequent effects on brain reward circuits. PART 13 Neurologic Disorders ■ ■BEHAVIORAL EFFECTS, TOLERANCE,

AND WITHDRAWAL The acute effects of a drug depend on the dose, the rate of increase in plasma, the concomitant presence of other drugs, and past experience with the agent. “Legal intoxication” with alcohol in most states is based on a blood alcohol concentration of 0.08 g/dL, some states are con sidering lowering acceptable levels to <0.05 g/dL, and levels of 0.04 g/dL

are cited for pilots in the United States and automobile drivers in some other countries. However, behavioral, psychomotor, and cognitive changes are seen at 0.02–0.04 g/dL (i.e., after one to two drinks) (Table 464-1). Deep but disturbed sleep can be seen at 0.15 g/dL in individuals who have not developed tolerance, and death can occur with levels between 0.30 and 0.40 g/dL. Beverage alcohol is probably responsible for more overdose deaths than any other drug. Repeated use of alcohol contributes to the need for a greater number of standard drinks to produce effects originally observed with fewer drinks (acquired tolerance), a phenomenon involving at least three compensatory mechanisms. (1) After 1–2 weeks of daily drinking, metabolic or pharmacokinetic tolerance can be seen, with up to 30% increases in the rate of hepatic ethanol metabolism. This alteration disappears almost as rapidly as it develops. (2) Cellular or pharmacody namic tolerance develops through neurochemical changes that main tain relatively normal physiologic functioning despite the presence of alcohol. Subsequent decreases in blood levels contribute to symptoms of withdrawal. (3) Individuals learn to adapt their behavior so that they can function better than expected under the influence of the drug (learned or behavioral tolerance). The cellular changes caused by chronic ethanol exposure may not resolve for several weeks or longer following cessation of drinking. Rapid decreases in blood alcohol levels before that time can produce a withdrawal syndrome, which is most intense during the first 5 days, but with some symptoms (e.g., disturbed sleep and anxiety) lasting up to 4–6 months as part of a “protracted withdrawal” syndrome. THE EFFECTS OF ETHANOL ON

ORGAN SYSTEMS Relatively low doses of alcohol (one or two drinks per day) may have mild potential beneficial effects by, for example, decreasing aggregation of platelets and potentially

decreasing the risk for vascular dementia and Alzheimer’s disease. However, any potential healthful effects dis appear with the regular consumption of three or more drinks per day, and knowledge about the deleterious effects of alcohol can both help the physician to identify patients with alcohol use disorders and supply them with information that might help motivate changes in behavior. ■ ■NERVOUS SYSTEM Approximately 35% of drinkers overall, including as many as 50% of drinking college students and a much higher proportion of individu als with alcohol use disorders, ever experience a blackout. This is an episode of temporary anterograde amnesia, in which the person was

awake but forgot all (en bloc blackouts at blood alcohol levels

> 0.20 mg/dL) or part (fragmentary blackouts at >0.12 mg/dL) of what occurred during a drinking period. Another common problem, one seen after as few as one or two drinks shortly before bedtime, is disturbed sleep. Although alcohol might initially help a person fall asleep, it disrupts sleep throughout the rest of the night. The stages of sleep are altered, and times spent in rapid eye movement (REM) and deep sleep early in the night are reduced. Alcohol relaxes muscles in the pharynx, which can cause snoring and exacerbate sleep apnea; symptoms of the latter occur in 75% of men with alcohol use disorders aged ≥60 years. Patients may also experience prominent and sometimes disturbing dreams later in the night. All these sleep impairments can contribute to relapses to drinking in persons with alcohol use disorders. Other common consequences of alcohol use even at relatively low alcohol levels are impaired judgment and coordination, which increase the risk of injuries. In the United States, ~40% of drinkers have at some time driven while intoxicated. Heavy drinking can also be associated with headache, thirst, nausea, vomiting, and fatigue the following day, a hangover syndrome that is responsible for much missed work and school time and temporary cognitive deficits. Chronic high alcohol doses cause peripheral neuropathy in ~10% of individuals with alcohol use disorders. Similar to diabetes, patients experience bilateral limb numbness, tingling, and paresthesias, all of which are more pronounced distally. Approximately 1% of those with alcohol use disorders develop cerebellar degeneration or atrophy, producing a syndrome of progressive unsteady stance and gait often accompanied by mild nystagmus. Perhaps 1 in 500 individuals with alcohol use disorders develop full Wernicke’s (ophthalmoparesis, ataxia, and encephalopathy) and Korsakoff’s (severe retrograde and antero grade amnesia) syndromes. These result from low levels of thiamine, especially in predisposed individuals with transketolase deficiencies. Repeated heavy drinking can contribute to cognitive problems and temporary memory impairment lasting for weeks to months after abstinence. Brain ventricular enlargement and widened cortical sulci on magnetic resonance imaging (MRI) and computed tomography (CT) scans occurs in ~50% of individuals with long-term alcohol use disorders; these changes are usually reversible if abstinence is main tained. Adolescents may be especially vulnerable to alcohol-related brain changes, as indicated by

> preclinical studies and prospective investigations in humans suggesting that alcohol exposure in the devel oping brain may adversely impact future cognitive processes related to cognition, reward recognition, and cue processing. There is no single “alcoholic dementia” syndrome; rather, this label describes patients who have irreversible cognitive changes (possibly from diverse causes) in the context of chronic alcohol use disorders. Psychiatric Comorbidity Alcohol temporarily alters brain neu rochemistry in a manner similar to ways observed in some psychi atric conditions, resulting in mood, anxiety, and psychotic disorders. However, those alcohol-induced psychiatric symptoms that are only observed during intense intoxication or withdrawal syndromes are likely to disappear within days to weeks of abstinence. For example, while about 40% of individuals with alcohol use disorder will at some point meet criteria for a major depressive episode, about half of those conditions are temporary substance-induced mood disorders that are likely to disappear within a month of abstinence without the use of antidepressant medications. In addition, several preexisting psychiat ric disorders increase the risk for future alcohol use disorder includ ing schizophrenia, manic-depressive disease, posttraumatic stress disorder, and anxiety syndromes such as panic disorder (Chap. 463). The comorbidities of alcohol use disorders with independent psychi atric disorders might represent an overlap in genetic vulnerabilities, impaired judgment regarding the use of alcohol as a consequence of the independent psychiatric condition, or an attempt to use alcohol to alleviate symptoms of the disorder or side effects of medications. Treatment of all forms of alcohol-induced psychopathology includes helping patients achieve abstinence and offering supportive care, as well as reassurance and “talk therapy” such as cognitive-behavioral

approaches. However, with the exception of short-term antipsychotic medications for substance-induced psychoses, substance-induced psy chiatric conditions only rarely require medications. Recovery is likely within several days to 4 weeks of abstinence. Conversely, because alcohol-induced conditions are temporary and do not indicate a need for long-term pharmacotherapy, a history of heavy alcohol intake is an important part of the workup for any patient who presents with any of these psychiatric syndromes. ■ ■THE GASTROINTESTINAL SYSTEM Esophagus and Stomach Alcohol can cause inflammation of the esophagus and stomach causing epigastric distress and gastrointestinal bleeding, making alcohol one of the most common causes of hemor rhagic gastritis. Violent vomiting can produce severe bleeding through a Mallory-Weiss lesion, a longitudinal tear in the mucosa at the gastro esophageal junction. Pancreas and Liver The incidence of acute pancreatitis (~25 per 1000 per year) is almost threefold higher in individuals with alcohol use disorders than in the general population, accounting for an esti mated 10% or more of the total cases. Alcohol impairs gluconeogenesis in the liver, resulting in a fall in the amount of glucose produced from glycogen, increased lactate production, and decreased oxidation of fatty acids. These contribute to an increase in fat accumulation in liver cells. In healthy individuals, these changes are reversible, but with repeated exposure to ethanol, especially daily heavy drinking, more severe changes in the liver occur, including alcohol-induced hepatitis,

perivenular sclerosis, and cirrhosis, with the latter observed in an estimated 15% of individuals with alcohol use disorders (Chap. 353). Perhaps through an enhanced vulnerability to infections, individuals with alcohol use disorders have an elevated rate of hepatitis C, and drinking in the context of that disease is associated with more severe liver deterioration. ■ ■CANCER As few as 1.5 drinks per day increases a woman's risk of breast cancer 1.4-fold. For both sexes, four drinks per day increases the risk for oral and esophageal cancers approximately threefold and rectal cancers by a factor of 1.5; seven to eight or more drinks per day produces an approximately fivefold increased risk for many other cancers. These consequences may result directly from cancer-promoting effects of alcohol and acetaldehyde or indirectly by interfering with immune homeostasis. ■ ■HEMATOPOIETIC SYSTEM Ethanol causes an increase in red blood cell size (mean corpuscular volume [MCV]), which reflects its effects on stem cells. If heavy drinking is accompanied by folic acid deficiency, there can also be hypersegmented neutrophils, reticulocytopenia, and a hyperplastic bone marrow; if malnutrition is present, sideroblastic changes can be observed. Chronic heavy drinking can decrease production of white blood cells, decrease granulocyte mobility and adherence, and impair delayed-hypersensitivity responses to novel antigens (with a possible false-negative tuberculin skin test). Associated immune deficiencies can contribute to vulnerability toward infections, including hepatitis and HIV, and interfere with their treatment. Finally, many individuals with alcohol use disorders have mild thrombocytopenia, which usually resolves within a week of abstinence unless there is hepatic cirrhosis or congestive splenomegaly. ■ ■CARDIOVASCULAR SYSTEM Acutely, ethanol decreases myocardial contractility and causes periph eral vasodilation, with a resulting mild decrease in blood pressure and a compensatory increase in cardiac output. Exercise-induced increases in cardiac oxygen consumption are higher after alcohol intake. These acute effects have little clinical significance for the average healthy drinker but can be problematic when persisting cardiac disease is present. The consumption of three or more drinks per day results in a dosedependent increase in blood pressure, which returns to normal within

weeks of abstinence. Thus, heavy drinking is an important factor in mild to moderate hypertension. Chronic heavy drinkers also have a sixfold increased risk for coronary artery disease, related, in part, to increased low-density lipoprotein cholesterol, and carry an increased risk for cardiomyopathy through direct effects of alcohol on heart muscle. Symptoms of the latter include unexplained arrhythmias in the presence of left ventricular impairment, heart failure, hypocontractility of heart muscle, and dilation of all four heart chambers with associated potential mural thrombi and mitral valve regurgitation. Atrial or ven tricular arrhythmias, especially paroxysmal tachycardia, can also occur temporarily after heavy drinking in individuals showing no other evidence of heart disease—a syndrome known as the "holiday heart."

■ ■GENITOURINARY SYSTEM CHANGES, SEXUAL FUNCTIONING, AND FETAL DEVELOPMENT Heavy drinking in adolescence can affect normal sexual development and reproductive onset. At any age, modest ethanol doses (e.g., blood alcohol concentrations of 0.06 g/dL) can increase sexual drive but also decrease erectile capacity in men. Even in the absence of liver impair ment, a significant minority of chronic heavy-drinking men show irre versible testicular atrophy with shrinkage of the seminiferous tubules, decreases in ejaculate volume, and a lower sperm count (Chap. 403). CHAPTER 464 Alcohol and Alcohol Use Disorders The repeated ingestion of high doses of ethanol by women can result in amenorrhea, a decrease in ovarian size, absence of corpora lutea with associated infertility, and an increased risk of spontaneous abor tion. Drinking during pregnancy

results in the rapid placental transfer of both ethanol and acetaldehyde, which may contribute to a range of consequences known as fetal alcohol spectrum disorder (FASD). One severe result is the fetal alcohol syndrome (FAS), seen in ~5% of children born to heavy-drinking mothers, which can include any of the following: facial changes with epicanthal eye folds; poorly formed ear concha; small teeth with faulty enamel; cardiac atrial or ventricular septal defects; an aberrant palmar crease and limitation in joint move ment; and microcephaly with intellectual impairment. Less pervasive FASD conditions include combinations of low birth weight, a lower intelligence quotient (IQ), hyperactive behavior, and some modest cognitive deficits. The amount of ethanol required and the time of vul nerability during pregnancy have not been defined, making it advisable for pregnant women to abstain from alcohol completely. ■ ■OTHER EFFECTS Between one-half and two-thirds of individuals with alcohol use disor ders have skeletal muscle weakness caused by acute alcoholic myopathy, a condition that improves but that might not fully remit with absti nence. Effects of repeated heavy drinking on the skeletal system include changes in calcium metabolism, lower bone density, and decreased growth in the epiphyses, leading to an increased risk for fractures and osteonecrosis of the femoral head. Hormonal changes include an increase in cortisol levels, which can remain elevated during heavy drinking; inhibition of vasopressin secretion at rising blood alcohol concentrations and enhanced secretion at falling blood alcohol con centrations (with the final result that most individuals with alcohol use disorders are likely to be slightly overhydrated); a modest and revers ible decrease in serum thyroxine (T4); and a more marked decrease in serum triiodothyronine (T3). Hormone irregularities may disappear after a month or more of abstinence. ■ ■ALCOHOL USE DISORDERS Because many drinkers occasionally imbibe to excess, temporary alcohol-related problems are common, especially in the late teens to the late twenties. However, repeated problems in multiple life areas can indicate an alcohol use disorder as defined in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). ■ ■DEFINITIONS AND EPIDEMIOLOGY An alcohol use disorder (also called alcoholism or alcohol dependence in prior diagnostic manuals) is defined in DSM-5 of the American Psy chiatric Association as repeated alcohol-related difficulties in at least 2 of 11 life areas that cluster together in the same 12-month period (Table 464-2). Ten of the 11 items in DSM-5 (published in 2013) were

TABLE 464-2 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Classification of Alcohol Use Disorder (AUD) Criteria Two or more of the following items occurring in the same 12-month period must be endorsed for the diagnosis of an alcohol use disordera: Drinking resulting in recurrent failure to fulfill role obligations Recurrent drinking in hazardous situations Continued drinking despite alcohol-related social or interpersonal problems Tolerance Withdrawal, or substance use for relief/avoidance of withdrawal Drinking in larger amounts or for longer than intended Persistent desire/unsuccessful attempts to stop or reduce drinking Great deal of time spent obtaining, using, or recovering from alcohol Important activities given up/reduced because of drinking Continued drinking despite knowledge of physical or psychological problems caused by alcohol Alcohol craving PART 13 Neurologic Disorders aMild AUD: 2–3 criteria required; moderate AUD: 4–5 items endorsed; severe AUD: 6 or more items endorsed. taken directly from the dependence and abuse criteria in DSM-IV, after deleting legal problems and adding craving. Thus, diagnoses estab lished across the two systems agree at >.84. Severity of DSM-5 alcohol use disorder is based on the number of items endorsed: mild is two or three items; moderate is four or five; and severe is six or more of the 11 criterion items. The lifetime risk for an alcohol use disorder in most Western coun tries is ~10–20% for men and 5–10% for women; higher rates are seen in individuals who seek help from health care deliverers. Between 2001 and 2013, the proportion of

the U.S. population with a current (i.e., past 12 months) alcohol use disorder increased by 49% with increases of almost 100% in women, African Americans, and individuals aged ≥45. Rates are similar in the United States, Canada, Germany, Australia, and the United Kingdom; tend to be lower in most Mediterranean countries, such as Italy, Greece, and Israel; and may be higher in Ireland, France, Eastern Europe (e.g., Russia), and Scandinavia. An even higher lifetime prevalence has been reported for most native cultures, including Native Americans, Eskimos, Maori groups, and aboriginal tribes of Australia. These differences in prevalence reflect both cultural and genetic influences, as described below. In Western countries, the typical individual with alcohol use disorder has a family and a career, and the lifetime risk among physicians is similar to that of the general population. ■ ■GENETICS Some of the most exciting recent research developments into alcohol-related disorders have clarified the contribution of genetic influences to these conditions. These investigations include how variations in genes relate to environmental and attitudinal mediators of genetic effects. Understanding how specific gene variations contribute to the risk for a condition has the potential to help with early identifica tion of individuals at high risk, development of effective prevention efforts, and, perhaps, identifying individuals most likely to respond to specific medications. Approximately 60% of the risk for alcohol use disorder is attributed to genes, as indicated by the fourfold higher risk in children with an alcohol use disorder parent (even if adopted early in life and raised by nonalcoholics) and a higher risk in identical twins compared to fraternal twins of affected individuals. Like most medical and psychi atric conditions that are referred to as complex genetically influenced disorders, the risk for alcohol use disorders is related to hundreds of gene variations, many of which explain <1% of the risk. As a result, vul nerabilities toward the condition are often approached by considering multiple gene variations at the same time using polygenic risk scores. These genetic variations operate primarily through intermediate characteristics that subsequently combine with environmental influ ences to alter the risk for heavy drinking and alcohol problems. These

include genes relating to a high risk for all substance use disorders that operate through impulsivity, schizophrenia, and bipolar disorder. Another characteristic, an intense skin flushing response when drink ing, decreases risk for only alcohol use disorders, and not substance use conditions related to other drugs, through gene variations for several alcohol-metabolizing enzymes, especially ALDH (a mutation only seen in Japanese, Chinese, and Korean individuals), and to a lesser extent, variations in ADH. An additional genetically influenced characteristic that increases the risk for heavy drinking, a low level of response or low sensitivity to alcohol, can be seen very early in the drinking career and before acquired tolerance or alcohol used disorders develop. The low response per drink operates, in part, through variations in genes relating to calcium and potassium channels, GABA, nicotinic, dopamine, and serotonin systems. Prospective studies have demonstrated that this need for higher doses of alcohol to achieve effects predicts future heavy drinking, alcohol problems, and alcohol use disorders, but not prob lems with drugs other than alcohol. The impact of a low response to alcohol on adverse drinking outcomes is partially mediated by a range of environmental and attitudinal influences, including the selection of heavier-drinking friends, more positive expectations of the effects of high doses of alcohol, and using alcohol to cope with stress. Several studies of college freshmen demonstrated that helping students who have a low sensitivity to alcohol modify these influences was associated with lower drinking quantities and fewer alcohol-related problems over the subsequent year. ■ ■NATURAL HISTORY Although the average age of the first drink (~15 years) is similar in individuals who do and do not go on to develop alcohol use disorders, an earlier onset of regular drinking and

drunkenness, especially in the context of conduct problems, is associated with a higher risk for later alcohol-related diagnoses. By the mid-twenties, most nonalcoholic men and women begin to moderate their drinking (perhaps learning from negative consequences), whereas those with alcohol use disorders are likely to escalate their drinking despite difficulties. The first major life problem from alcohol often appears in the late teens to early twen ties, and a pattern of multiple alcohol difficulties by the mid-twenties. Once established, the course is likely to include exacerbations and remissions, with little difficulty in temporarily stopping or controlling alcohol use when problems develop, but without help desistance usu ally gives way to escalations in alcohol intake and subsequent problems. Following treatment, for at least a year, more than half of those with alcohol use disorder maintain a marked decrease in alcohol use and related problems or achieve full abstinence, including many who stop drinking permanently. Even without formal treatment or self-help groups, there is at least a 20% chance of spontaneous remission with long-term abstinence. However, should the individual continue to drink heavily, the life span is shortened by ~10 years on average, with the leading causes of early death being enhanced rates of heart disease, cancer, accidents, and suicide. ■ ■IDENTIFICATION AND TREATMENT The approach to treating alcohol-related conditions is relatively straightforward: (1) recognize that at least 20% of patients have an alcohol use disorder; (2) learn how to identify and treat acute alcoholrelated conditions (e.g., severe intoxication); (3) know how to help patients begin to address their alcohol problems; (4) know how to treat alcohol withdrawal symptoms; and (5) learn how to appropriately treat or refer patients for additional help. ■ ■IDENTIFICATION OF PATIENTS WITH ALCOHOL USE DISORDERS Even in affluent locales, the ~20% of patients who have an alcohol use disorder can be identified by asking questions about alcohol problems and noting laboratory test results that can reflect regular consump tion of six to eight or more drinks per day. The two blood tests with ≥60% sensitivity and specificity for heavy alcohol consumption are γ-glutamyl transferase (GGT) (>35 U) and carbohydrate-deficient

TABLE 464-3 The Alcohol Use Disorders Identification Test (AUDIT)a 5-POINT SCALE (LEAST

TO MOST) ITEM 1. How often do you have a drink containing Never (0) to 4+ per week (4) alcohol? 2. How many drinks containing alcohol do you 1 or 2 (0) to 10+ (4) have on a typical day? 3. How often do you have six or more drinks on Never (0) to daily or almost daily (4) one occasion? 4. How often during the last year have you found Never (0) to daily or almost daily (4) that you were not able to stop drinking once you had started? 5. How often during the last year have you failed Never (0) to daily or almost daily (4) to do what was normally expected from you because of drinking? 6. How often during the last year have you Never (0) to daily or almost daily (4) needed a first drink in the morning to get yourself going after a heavy drinking session? 7. How often during the last year have you had a Never (0) to daily or almost daily (4) feeling of guilt or remorse after drinking? 8. How often during the last year have you been Never (0) to daily or almost daily (4) unable to remember what happened the night before because you had been drinking? 9. Have you or someone else been injured as a No (0) to yes, during the last year (4) result of your drinking? 10. Has a relative, friend, doctor, or other health No (0) to yes, during the last year (4) worker been concerned about your drinking or suggested that you should cut down? aThe AUDIT is scored by simply summing the values associated with the endorsed response. A score ≥8 may indicate harmful alcohol use. transferrin (CDT) (>20 U/L or >2.6%); the combination of the two tests is likely to be more accurate than either alone. The values for these serologic markers are likely to return toward normal within several weeks of abstinence. Other useful blood tests include high-normal

MCVs (≥91 μm3) and serum uric acid (>416 mol/L, or 7 mg/dL). The diagnosis of alcohol use disorder ultimately rests on the docu mentation of a pattern of repeated difficulties associated with alcohol (Table 464-2). The criteria can be paraphrased as reaching a point where alcohol means more to the person than the significant repetitive problems that it causes. Thus, in screening, it is important to probe for marital or job problems, legal difficulties, histories of accidents, medi cal problems, evidence of tolerance, and so on, and then attempt to relate these issues to use of alcohol. Some standardized questionnaires can be helpful, including the 10-item Alcohol Use Disorders Identifica tion Test (AUDIT) (Table 464-3), but these are only screening tools, and a face-to-face interview is still required for a meaningful diagnosis. The diagnostic criteria in the fourth and fifth versions of the American Psychiatric Association DSM (DSM-IV and DSM-5) are very similar, both are reliable across different clinicians, and both labels are very good at predicting future problems, especially for individuals with moderate or severe disorders. TREATMENT Alcohol-Related Conditions ACUTE INTOXICATION The first priority in treating severe intoxication is to assess vital signs and manage respiratory depression, cardiac arrhythmias, and blood pressure instability, if present. The possibility of intoxication with other drugs should be considered by obtaining, if needed, toxicology screens for other central nervous system (CNS) depres sants such as benzodiazepines and for opioids. Aggressive behavior should be handled by offering reassurance but also by calling for help from an intervention team. If the aggressive behavior contin ues, relatively low doses of a short-acting benzodiazepine such as lorazepam (e.g., 1–2 mg PO or IV) may be used and can be repeated as needed, but care must be taken not to destabilize vital signs or

worsen confusion. An alternative approach is to use an antipsy chotic medication (e.g., olanzapine 2.5–10 mg IM repeated at 2 and 6 h, if needed). INTERVENTION The steps presented here follow the acronym of SBIRT, indicating screening, brief interventions, and treatment or referral to treat ment. There are two main elements to highlighting the need for compliance with treatment in a person with an alcohol use disorder: motivational interviewing and brief interventions. During motiva tional interviewing, the clinician helps the patient to think through the assets (e.g., comfort in social situations) and liabilities (e.g., health- and interpersonal-related problems) of the current pat tern of drinking. The clinician should listen empathetically to the responses, help the patient weigh options, and encourage the taking of responsibility for needed changes. Patients should be reminded that only they can decide to avoid the consequences that will occur if heavy drinking continues. The process of brief intervention, a similar approach, has been summarized by the acronym FRAMES: Feedback to the patient; Responsibility to be taken by the patient; Advice, rather than orders, on what needs to be done; Menus of options that might be considered; Empathy for understanding the patient’s thoughts and feelings; and Self-efficacy, i.e., offering sup port for the capacity of the patient to make changes.

 Once the patient begins to consider change, the discussions can focus more on the consequences of high alcohol consumption, suggested approaches to stopping drinking, and help in recogniz ing and avoiding situations likely to lead to heavy drinking such as going to bars or associating with heavy-drinking friends. Both motivational interviewing and brief interventions can be carried out in 15-min sessions, but because patients often do not change behavior immediately, multiple meetings are often required to explore the problem and possible options, discuss optimal treat ments, and explain the benefits of abstinence. ALCOHOL WITHDRAWAL If the patient agrees to stop drinking, sudden decreases in alcohol intake

can produce withdrawal symptoms, most of which are the opposite of those produced by intoxication. Features include tremor of the hands (shakes); agitation and anxiety; autonomic nervous system overactivity including an increase in pulse, respiratory rate, sweating, and body temperature; and insomnia. These symptoms usu ally begin within 5–10 h of decreasing ethanol intake, peak on day 2 or 3, and improve by day 4 or 5, although mild levels of these problems may persist for 4–6 months as a protracted abstinence syndrome. About 2% of individuals with alcohol use disorder experience a withdrawal seizure, with the risk increasing in the context of older age, concomitant medical problems, misuse of additional drugs, and higher alcohol quantities. The same risk factors also contribute to the ~1% rate of withdrawal delirium, also known as delirium tremens (DTs), where the withdrawal includes a severe agitated delirium (mental confusion, agitation, and fluctuating levels of con sciousness) associated with a tremor and autonomic overactivity (e.g., marked increases in pulse, blood pressure, and respirations). The risks for seizures and DTs can be diminished by identifying and treating underlying medical conditions early in the course of with drawal and by instituting adequate doses of depressant medications such as benzodiazepines. Thus, the first step in dealing with possible withdrawal phenom ena is a thorough physical examination in all heavy drinkers who are considering abstinence. This includes evaluation of possible liver impairment, gastrointestinal bleeding, cardiac arrhythmias, infection, and glucose or electrolyte imbalances. It is also important to offer adequate nutrition and oral multiple B vitamins, includ ing 50–100 mg of oral thiamine daily for a week or more. Because most patients with alcohol use disorders who enter withdrawal are either normally hydrated or mildly overhydrated, IV fluids should be avoided unless there is a relevant medical problem or significant recent bleeding, vomiting, or diarrhea.

The next step is to recognize that because withdrawal symptoms reflect the acute decrease in the usual blood levels of a CNS depres sant (i.e., alcohol), the symptoms can be controlled by administer ing any other depressant in doses that decrease symptoms (e.g., a rapid pulse and tremor) and then tapering the dose over 3–5 days. Although most depressants are effective, benzodiazepines (Chap. 463) have the most supportive data for use in this situa tion, combining a high level of safety and low cost. Short-half-life benzodiazepines can be considered for patients with serious liver impairment or evidence of significant brain damage, but they must be given every 4 h to avoid abrupt blood-level fluctuations that may increase the risk for seizures. Therefore, most clinicians use drugs with longer half-lives (e.g., chlordiazepoxide), adjusting the dose if signs of withdrawal escalate and withholding the drug if the patient is sleeping or has orthostatic hypotension. The average patient requires 25–50 mg of chlordiazepoxide or 10 mg of diazepam given PO every 4–6 h on the first day, with doses then decreased to zero over the next 5 days. Although alcohol withdrawal can be treated in a hospital, patients in good physical condition who demonstrate mild signs of withdrawal despite low blood alcohol concentrations and who have no prior history of DTs or withdrawal seizures can be considered for outpatient detoxification. For the next 4 or 5 days, these patients should receive only 1 or 2 days of medications at a time and return daily for evaluation of vital signs. They can be hos pitalized if signs and symptoms of withdrawal markedly escalate.

PART 13 Neurologic Disorders Treatment of patients with DTs can be challenging, and the con dition is likely to run a course of 3–5 days regardless of the therapy used. However, conditions that meet the criteria for DTs outlined above represent medical emergencies that carry an estimated mor tality as high as 5%, and treatment is best carried out in an intensive care unit by well-trained

clinicians who closely monitor vital signs. Medications can include high-dose benzodiazepines (e.g., as much as 800 mg/d of chlordiazepoxide has been reported) or, for those who do not respond to that regimen, closely monitored doses of propofol or dexmedetomidine. The focus of care is to identify and correct medical problems and to control behavior and prevent injuries. Antipsychotic medications are not recommended for treat ment of alcohol withdrawal symptoms; although antipsychotics are less likely than benzodiazepines to exacerbate confusion, they may increase the risk of seizures. Generalized withdrawal seizures rarely require more than the administration of an adequate dose of benzodiazepines. There is little evidence that anticonvulsants such as phenytoin or gabapentin are more effective than benzodiazepines for alcohol-withdrawal sei zures, and the risk of seizures has usually passed by the time effec tive drug levels are reached. The rare patient with status epilepticus must be treated aggressively (Chap. 436). HELPING INDIVIDUALS WITH ALCOHOL USE DISORDERS TO STOP OR SIGNIFICANTLY DECREASE DRINKING: THE REHABILITATION PHASE An Overview After completing alcoholic rehabilitation, ≥50% of individuals with alcohol use disorders, especially highly function ing patients, maintain abstinence or significant diminution of alco hol intake for at least a year; many also achieve long-term sobriety. The ideal outcome is abstinence, but treatment trials are increasing recognizing that outcomes shy of total abstinence can still improve levels of functioning and quality of life. The core components of the rehabilitation phase of treatment include cognitive-behavioral approaches to help patients recognize the need to change, while working with them to alter their behaviors to enhance compliance. A key step is to optimize motivation toward abstinence through education of patients and their significant others about alcohol use disorders and their likely course over time. It is important to recognize that contrary to what some physicians might think, the typical person with an alcohol use disorder is likely to have a job and a family and not fit the inaccurate “down and out” stereotype. However, after years of heavy drinking, some patients require voca tional or avocational counseling to help to structure their days, and

all patients should try self-help groups such as Alcoholics Anony mous (AA) to assist them in developing a sober peer group and to learn how to deal with life’s stresses while remaining sober. Relapse prevention education helps patients identify situations in which a return to drinking is likely (e.g., stopping in a bar to meet friends but planning to only have a nonalcoholic beverage), formulate ways to avoid the risky situation, and when that is not possible, to mitigate the risks to which they are exposed. It is also important to develop coping strategies that increase the chances of a quick return to abstinence after an episode of drinking. Although many individuals can be treated as outpatients, more intense interventions are more effective and some individuals with alcohol use disorders do not respond to just AA or outpatient groups. Whatever the setting, ongoing contact with outpatient treatment staff should be maintained for at least 6 months and pref erably for a year after abstinence. Counseling focuses on areas of improved functioning in the absence of alcohol (i.e., why it is a good idea to continue abstinence), helping patients to manage free time without alcohol, encouraging them to develop a nondrinking peer group, and discussions of ways to handle stress without drinking. The physician serves an important role in identifying the alcohol problem, diagnosing and treating associated medical and inde pendent or substance-induced psychiatric syndromes, oversee ing detoxification, referring the patient to outpatient or inpatient rehabilitation programs, providing counseling, and, if appropriate, selecting which (if any) medication might be needed. For insomnia, patients should be reassured that troubled sleep is likely to improve over subsequent weeks. They should be taught the elements of “sleep hygiene” including maintaining consistent schedules for bedtime and awakening, avoiding exercise or consumption of large meals before bedtime, and keeping the bedroom cool, dark, and quiet at

night (Chap. 33). Depressant sleep medications are not the optimal approach for this type of insomnia that often continues for several weeks or months. Patients are likely to develop rebound insomnia when the depressant dose is decreased or stopped. The rebound increases the chance they will increase the dose and potentially develop problems controlling the prescribed depressant drug. Sedating antidepressants (e.g., trazodone) should not be used because they interfere with cognitive functioning the next morning and disturb the normal sleep architecture, but occasional use of over-the-counter sleeping medications (sedating antihistamines) can be considered. An additional problem, anxiety symptoms, can be addressed by increasing patients' insights into the temporary nature of the symptoms and helping them develop strategies to achieve relaxation by using forms of cognitive therapy. Medications for the Alcohol Rehabilitation Treatment Phase The core of the rehabilitation phase for any chronic relapsing condition, including alcohol use disorder, relates to cognitive and behavioral approaches that help people comply with treatment goals and improve health and quality of life. Any medication for this disorder is likely to operate optimally in the context of such cognitivebehavioral approaches. As a result, the efficacy of a medication is best measured as the gain in functioning over and above improvements associated with the motivational interviewing, brief interventions, and related behavioral approaches. Such additional treatments (e.g., medications) are likely to have modest effect sizes, which can be diffi cult to document. Adding to the challenge of establishing the efficacy of a medication for this condition are the fluctuations of the inten sity of alcohol-related symptoms over time and the 20% or higher spontaneous remission for alcohol use disorder. Recognizing that all treatments might cause harm through side effects and financial costs, it is important to demonstrate that a medication has a beneficial asset-to-liability ratio using double-blind controlled treatment trials. In that light, to date, well-structured controlled trials have revealed only a few medications that have even modest benefits when used in the first 6–12 months of recovery from an alcohol use disorder. The opioid antagonist naltrexone may shorten sub sequent relapses, whether used in the oral form (50–150 mg/d) or

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