especially at $GABA_A$ receptors. Enhancement of this complex chloride channel system contributes to anticonvulsant, sleep-inducing, antianxiety, and muscle relaxation effects of all GABA-boosting drugs. Acutely administered alcohol produces a release of GABA, and continued use increases density of $GABA_A$ 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 during 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 hormone (ACTH) during intoxication and 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 beta endorphins.

Additional neurochemical changes include increases in synaptic levels of serotonin during acute intoxication and subsequent upregulation of serotonin receptors. Acute increases in nicotinic acetylcholine 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 resulting release of dopamine, GABA, and glutamate as well as subsequent effects on brain reward circuits.

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 requires a blood alcohol concentration of 0.08 g/dL, but levels of 0.04 are cited 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 467-1). Deep but disturbed sleep can be seen at twice the legal intoxication level, 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 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 pharmacodynamic tolerance* develops through neurochemical changes that maintain 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 influence of the drug (*learned or behavioral tolerance*).

TABLE 467-1 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

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 some symptoms (e.g., disturbed sleep and anxiety) can take up to 4–6 months to resolve.

THE EFFECTS OF ETHANOL ON ORGAN SYSTEMS

Relatively low doses of alcohol (one or two drinks per day) have potential beneficial effects of increasing high-density lipoprotein cholesterol and decreasing aggregation of platelets, with a resulting decrease in risk for occlusive coronary disease and embolic strokes. Red wine has additional potential health-promoting qualities at relatively low doses due to flavinols and related substances. Modest drinking might also decrease the risk for vascular dementia and, possibly, Alzheimer's disease. However, any potential healthful effects disappear 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 an alcohol use disorder and to supply them with information that might help motivate a change in behavior.

NERVOUS SYSTEM

Approximately 35% of drinkers (and a much higher proportion of alcoholics) experience a *blackout*, an episode of temporary anterograde amnesia, in which the person forgets all or part of what occurred during a drinking evening. 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 time spent in rapid eye movement (REM) and deep sleep is reduced. Alcohol relaxes muscles in the pharynx, which can cause snoring and exacerbate sleep apnea; symptoms of the latter occur in 75% of alcoholic men older than age 60 years. Patients may also experience prominent and sometimes disturbing dreams later in the night. All of these sleep problems are more pronounced in alcoholics, and their persistence may contribute to relapse.

Another common consequence of alcohol use is impaired judgment and coordination, increasing the risk of injury. 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 time and temporary cognitive deficits at work and school.

Chronic high doses cause *peripheral neuropathy* in ~10% of alcoholics: similar to diabetes, patients experience bilateral limb numbness, tingling, and paresthesias, all of which are more pronounced distally. Approximately 1% of alcoholics develop *cerebellar degeneration or atrophy*, producing a syndrome of progressive unsteady stance and gait often accompanied by mild nystagmus; neuroimaging studies reveal atrophy of the cerebellar vermis. Fortunately, very few alcoholics (perhaps as few as 1 in 500 for the full syndrome) develop *Wernicke's* (ophthalmoparesis, ataxia, and encephalopathy) and *Korsakoff's* (retrograde and anterograde amnesia) *syndromes*, although a higher proportion have one or more neuropathologic findings related to these conditions. These result from low levels of thiamine, especially in predisposed individuals with transketolase deficiencies. Alcoholics can manifest *cognitive problems* and temporary memory impairment lasting for weeks to months after drinking heavily for days or weeks. Brain atrophy, evident as ventricular enlargement and widened cortical sulci on magnetic resonance imaging (MRI) and computed tomography (CT) scans, occurs in ~50% of chronic alcoholics; these changes are usually reversible if abstinence is maintained. 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 alcoholism.

Psychiatric Comorbidity As many as two-thirds of individuals with alcohol use disorders meet the criteria for another psychiatric syndrome in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) of the American Psychiatric Association