Effects of Drugs on the Nervous System

Alcohol

Alcohol, a drug, is consumed at some time by up to 80% of the population. At low doses alcohol can have some beneficial effects such as decreased rates of myocardial infarction, stroke, gallstones, and possibly vascular or Alzheimer's dementias, but the consumption of more than two standard drinks per day increases the risk for health problems in many organ systems. Heavy repetitive drinking, as is seen in alcohol abuse and dependence, cuts short the life span by an estimated decade in both genders, all cultural groups, and all socioeconomic strata. Even low doses of alcohol have a significant effect on many organ systems, adversely affecting most preexisting disease states and altering the effectiveness or blood levels of most over-the-counter and prescribed medications.

The intoxicating effects of alcohol appear to be due to actions at a number of neurotransmitter receptors and transporters. Alcohol enhances γ-aminobutyric acid A ($GABA_A$) receptors and inhibits N-methyl-D-aspartate (NMDA) receptors. In vitro studies suggest that additional effects involve inhibition of adenosine uptake and a translocation of the cyclic AMP–dependent protein kinase catalytic subunit from the cytoplasm to the nucleus. Neurons adapt quickly to these actions, and thus different effects may be present during chronic administration and withdrawal.

Nicotine

Tobacco, which comes primarily from the plant nicotiana tabacum, has been used for centuries. It can be smoked, chewed, or sniffed. The first description of addiction to tobacco is contained in a report from the New World in which Spanish soldiers said that they could not stop smoking. When nicotine was isolated from tobacco leaves in 1828, scientists began studying its effects in the brain and body. This research eventually showed that, although tobacco contains thousands of chemicals, the main ingredient that acts in the brain and produces addiction is nicotine. More recent research has shown that the addiction produced by nicotine is extremely powerful and is at least as strong as addictions to other drugs such as heroin and cocaine. Some of the effects of nicotine include changes in respiration and blood pressure, constriction of arteries, and increased alertness. Many of these effects are produced through its action on both the central and peripheral nervous system.

Nicotine activates cholinergic receptors. Cholinergic receptors are present in many brain structures, as well as in muscles, adrenal glands, the heart, and other body organs. These receptors are normally activated by the neurotransmitter acetylcholine, which is produced in the brain, and by neurons in the peripheral nervous system. Acetylcholine and its receptors are involved in many activities, including respiration, maintenance of heart rate, memory, alertness, and muscle movement.Unlike acetylcholine, when nicotine enters the brain and activates cholinergic receptors, it can disrupt the normal functioning of the brain.

Regular nicotine use causes changes in both the number of cholinergic receptors and the sensitivity of these receptors to nicotine and acetylcholine. Some of these changes may be responsible for the development of tolerance to nicotine. Once tolerance has developed, a nicotine user must regularly supply the brain with nicotine in order to maintain normal brain functioning. If nicotine levels drop, the nicotine user will begin to feel uncomfortable withdrawal symptoms.

Recently, research has shown that nicotine also stimulates the release of the neurotransmitter dopamine in the brain's pleasure circuit. Using microdialysis, a technique that allows minute quantities of neurotransmitters to be measured in precise brain areas, researchers have discovered that nicotine causes an increase in the release of dopamine in the nucleus accumbens. This release of dopamine is similar to that seen for other drugs of abuse, such as heroin and cocaine, and is thought to underlie the pleasurable sensations experienced by many smokers.

However nicotine may not be the only psychoactive ingredient in tobacco. Using positron emission tomography (PET), scientists discovered that cigarette smoking causes a dramatic decrease in the levels of an important enzyme that breaks down dopamine. The decrease in this enzyme, known as monoamine-oxidase-A (MAO-A), results in an increase in dopamine levels. Importantly, this particular effect is not caused by nicotine but by some additional, unknown compound in cigarette smoke. Nicotine itself does not alter MAO-A levels; it affects dopamine through other mechanisms. Thus, there may be multiple routes by which smoking alters the neurotransmitter dopamine to ultimately produce feelings of pleasure and reward.

Opioids

It is difficult to imagine modern medical practice without the use of opioid analgesics. These drugs have been part of health care since 300 B.C. Opium and codeine were isolated in the early nineteenth century, opioid-like substances produced by the body were recognized in the 1970s, and the first endogenous opioid was isolated in 1995. As important as these substances are to modern medicine, opioid drugs have many disadvantages, including overdosage and dependency; close to 1 million individuals in the United States are opioid-dependent. All opioid drugs are capable of producing a heroin-like intoxication, as well as tolerance and withdrawal.

The prototypic opiates, morphine and codeine (3-methoxymorphine), are derived from the milky juice of the poppy Papaver somniferum. The semisynthetic drugs produced from the morphine or thebane molecules include hydromorphone, diacetylmorphine (heroin), and oxycodone. The purely synthetic opioids and their cousins include meperidine, propoxyphene, diphenoxylate, fentanyl, buprenorphine, tramadol, methadone, and pentazocine.

Endogenous opioid peptides (i.e., enkephalins, endorphins, dynorphins, and others) have distinct distributions in the central nervous system (CNS) and appear to be natural ligands for opioid receptors. As summarized in the following, the receptors with which opioid peptides interact differentially produce analgesia, respiratory depression, constipation, euphoria, and other actions. Substances capable of antagonizing one or more of these actions include nalorphine, levallorphan, cyclazocine, butorphanol, buprenorphine, and pentazocine, each of which has mixed agonist and antagonist properties, as well as naloxone, nalmefene, and naltrexone, which are pure opiate antagonists. The availability of relatively specific antagonists has helped identify at least three different receptor subtypes, including μ receptors, which influence some of the more classic opioid actions such as pain control, reinforcement, constipation, hormone levels, and respiration; κ receptors, with possible similar functions along with sedation and effects on hormones; and δ receptors, thought to relate mostly to analgesia, mood, reinforcement, and breathing. A fourth possible receptor subtype, sensitive to another endogenous peptide, is sometimes called nociceptin or orphanin and may influence pain. The major features of tolerance, dependence, and withdrawal are thought to be mediated primarily by μ receptors, and these are affected by all prescription opioids.

TABLE 373-1 Actions of Opioid Receptors

Receptor Type	*Actions*
Mu (μ) (e.g., morphine)	Analgesia, reinforcement euphoria, cough and appetite suppression, decreased respirations, decreased GI motility, sedation, hormone changes, dopamine and acetylcholine release
Kappa (κ) (e.g., butorphanol)	Decreased dysphoria, decreased GI motility, decreased appetite, decreased respiration, psychotic symptoms, sedation, diuresis, analgesia
Delta (δ) (e.g., etorphine)	Hormone changes, appetite suppression, dopamine release

Note: GI = gastrointestinal.

Cocaine

Cocaine is a stimulant and local anesthetic with potent vasoconstrictor properties. The leaves of the coca plant (Erythroxylon coca) contain ~0.5 to 1% cocaine. The drug produces physiologic and behavioral effects when administered orally, intranasally, intravenously, or via inhalation following pyrolysis (smoking). Cocaine increases synaptic concentrations of the monamine neurotransmitters dopamine, norepinephrine, and serotonin by binding to transporter proteins in presynaptic neurons and blocking reuptake. The reinforcing effects of cocaine appear to be related to effects on dopaminergic neurons in the mesolimbic system.

Cocaine produces a brief, dose-related stimulation and enhancement of mood and an increase in cardiac rate and blood pressure. Body temperature usually increases following cocaine administration, and high doses of cocaine may induce lethal pyrexia or hypertension. Because cocaine inhibits reuptake of catecholamines at adrenergic nerve endings, the drug potentiates sympathetic nervous system activity. Protracted cocaine abuse may cause paranoid ideation and visual and auditory hallucinations, a state that resembles alcoholic hallucinosis. Psychological dependence on cocaine, indicated by inability to abstain from frequent compulsive use, has also been reported. Although the occurrence of withdrawal syndromes involving psychomotor agitation and autonomic hyperactivity remains controversial, severe depression ("crashing") following cocaine intoxication may accompany drug withdrawal.

Marijuana and Cannabis Compounds

Cannabis sativa contains >400 compounds in addition to the psychoactive substance, delta-9-tetrahydrocannabinol (THC). Marijuana cigarettes are prepared from the leaves and flowering tops of the plant, and a typical marijuana cigarette contains 0.5 to 1 g of plant material. Although the usual THC concentration varies between 10 and 40 mg, concentrations >100 mg per cigarette have been detected. Hashish is prepared from concentrated resin of C. sativa and contains a THC concentration of between 8 to 12% percent by weight. "Hash oil," a lipid-soluble plant extract, may contain a THC concentration of 25 to 60% percent and may be added to marijuana or hashish to enhance its THC concentration. Smoking is the most common mode of marijuana or hashish use. During pyrolysis, >150 compounds in addition to THC are released in the smoke. Although most of these compounds do not have psychoactive properties, they do have potential physiologic effects.

Specific cannabinoid receptors (CB_1 and CB_2) have been identified in the central nervous system, including the spinal cord, and in the peripheral nervous system. High densities of these receptors have been found in the cerebral cortex, basal ganglia, and hippocampus. B lymphocytes also appear to have cannabinoid receptors. A naturally occurring THC-like ligand has been identified in the nervous system, where it is widely distributed.

Acute intoxication from marijuana and cannabis compounds is related to both the dose of THC and the route of administration. THC is absorbed more rapidly from marijuana smoking than from orally ingested cannabis compounds. Acute marijuana intoxication usually consists of a subjective perception of relaxation and mild euphoria resembling mild to moderate alcohol intoxication. This condition is usually accompanied by some impairment in thinking, concentration, and perceptual and psychomotor function. Higher doses of cannabis may produce behavioral effects analogous to severe alcohol intoxication. Although the effects of acute marijuana intoxication are relatively benign in normal users, the drug can precipitate severe emotional disorders in individuals who have antecedent psychotic or neurotic problems. As with other psychoactive compounds, both set (user's expectations) and setting (environmental context) are important determinants of the type and severity of behavioral intoxication. As with abuse of cocaine, opioids, and alcohol, chronic marijuana abusers may lose interest in common socially desirable goals and steadily devote more time to drug acquisition and use. However,

THC does not cause a specific and unique "amotivational syndrome." The range of symptoms sometimes attributed to marijuana use is difficult to distinguish from mild to moderate depression and the maturational dysfunctions often associated with protracted adolescence. Chronic marijuana use has also been reported to increase the risk of psychotic symptoms in individuals with a past history of schizophrenia. Persons who initiate marijuana smoking before the age of 17 may subsequently develop severe cognitive and neuropsychological disorders, and may be at higher risk for later polydrug and alcohol abuse problems.

Methamphetamine

The abuse of methamphetamine, also referred to as "meth," "speed," "crank," "chalk," "ice," "glass," or "crystal," has been declining in many metropolitan areas and communities throughout the United States. This decrease is attributed in part to drug seizures and the closures of clandestine laboratories that produce methamphetamine illegally. Prevention programs focusing upon methamphetamine abuse have also increased.

Methamphetamines increase the release of monoamine neurotransmitters (dopamine, norepinephrine, and serotonin) from presynaptic neurons. It is thought that the euphoric and reinforcing effects of this class of drugs are mediated through dopamine and the mesolimbic system, whereas the cardiovascular effects are related to norepinephrine.

Adverse physiologic effects observed as a consequence of methamphetamine abuse include headache, difficulty concentrating, diminished appetite, abdominal pain, vomiting or diarrhea, disordered sleep, paranoid or aggressive behavior, and psychosis. Severe, life-threatening toxicity may present as hypertension, cardiac arrythmia or failure, subarachnoid hemorrhage, ischemic stroke, intracerebral hemorrhage, convulsions, or coma. MRS studies suggest that chronic abuse may injure the frontal areas and basal ganglia of the brain.

MDMA (Ecstasy)

MDMA (3,4-methylenedioxymethamphetamine) is a derivative of methamphetamine. It is most commonly known by the street names ecstasy or XTC, is a synthetic entactogen of the phenethylamine family, whose primary effect is believed to be the stimulation of secretion as well as inhibition of re-uptake of large amounts of serotonin as well as dopamine and norepinephrine in the brain, inducing a general sense of openness, empathy, energy, euphoria, and well-being. Serotonin is a neurotransmitter believed to play a role in the regulation of mood and pleasure. MDMA causes serotonin vesicles in the neurons to release quantities of serotonin into the synapses. The effects of ecstasy depend on the strength of the dose, the physiology of the user and their state of mind at the time of taking the drug. Generally some of the immediate effects of ecstasy include: Feelings of confidence, happiness and benevolence, Accelerated heart rate and breathing, Rise in blood pressure, Sweating and dehydration, Nausea, Jaw clenching and teeth grinding, Loss of appetite, Hallucinations, An increased urge for sex, Loss of inhibitions. Acute dehydration is a risk among users who are highly physically active and forget to drink water, as the drug may mask one's normal sense of exhaustion and thirst. In high doses, ecstasy can cause seizures and vomiting. The symptoms of overdose include a sharp rise in body temperature and blood pressure, dizziness, cramps, heart palpitations and vomiting. Ecstasy can cause death in a number of ways, including: Cardiac arrest, Stroke, Kidney failure, Overheating (hyperthermia) and dehydration, Dilutional hyponatremia, when the user 'drowns' their brain by drinking too much water.

During the past decade, an eighteenfold increase in MDMA-related emergency room incidents has been reported in the United States. Recent studies have revealed that MDMA induces both brain dopaminergic and serotonergic neurotoxicity. Thus, use of recreational use of MDMA by young persons may significantly increase the risk for subsequent occurrence of severe neuropsychiatric disorders.

Lysergic Acid Diethylamide (LSD)

The discovery of the psychedelic effects of LSD in 1947 led to an epidemic of LSD abuse during the 1960s. Imposition of stringent constraints on the manufacture and distribution of LSD (classified as a Schedule I substance by the U.S. Food and Drug Administration), as well as public recognition that psychedelic experiences induced by LSD were a health hazard, have resulted in a reduction in LSD abuse. The drug still retains some popularity among adolescents and young adults, however, and there are indications that LSD use among young persons has been increasing in some communities in the United States.

LSD is a very potent drug; oral doses as low as 20 μg may induce profound psychological and physiologic effects. Tachycardia, hypertension, pupillary dilation, tremor, and hyperpyrexia occur within minutes following oral administration of 0.5 to 2 μg/kg. A variety of bizarre and often conflicting perceptual and mood changes, including visual illusions, synesthesias, and extreme lability of mood, usually occur within 30 min after LSD intake. These effects of LSD may persist for 12 to 18 h, even though the half-life of the drug is only 3 h.

Tolerance develops rapidly for LSD-induced changes in psychological function when the drug is used one or more times per day for >4 days. Abrupt abstinence following continued use does not produce withdrawal signs or symptoms. There have been no clinical reports of death caused by the direct effects of LSD.

The most frequent acute medical emergency associated with LSD use is panic episode (the "bad trip"), which may persist up to 24 h. Management of this problem is best accomplished by supportive reassurance ("talking down") and, if necessary, administration of small doses of anxiolytic drugs. Adverse consequences of chronic LSD use include enhanced risk for schizophreniform psychosis and derangements in memory function, problem solving, and abstract thinking. Treatment of these disorders is best carried out in specialized psychiatric facilities.

Phencyclidine (PCP)

Phencyclidine (PCP), a cyclohexylamine derivative, is widely used in veterinary medicine to briefly immobilize large animals and is sometimes described as a dissociative anesthetic. PCP binds to ionotropic n-methyl-d-aspartate (NMDA) receptors in the nervous system, blocking ion current through these channels. PCP is easily synthesized; its abusers are primarily young people and polydrug users. It is used orally, by smoking, or by intravenous injection. It is also used as an adulterant in THC, LSD, amphetamine, or cocaine. The most common street preparation, angel dust, is a white granular powder that contains 50 to 100% percent of the drug. Low doses (5 mg) produce agitation, excitement, impaired motor coordination, dysarthria, and analgesia. Users may have horizontal or vertical nystagmus, flushing, diaphoresis, and hyperacusis. Behavioral changes include distortions of body image, disorganization of thinking, and feelings of estrangement. Higher doses of PCP (5 to 10 mg) may produce profuse salivation, vomiting, myoclonus, fever, stupor, or coma. PCP doses of ≥10 mg cause convulsions, opisthotonus, and decerebrate posturing, which may be followed by prolonged coma.