PHARMACOLOGY OF LEGAL AND ILLICIT DRUGS

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Introduction

The increasing incidence of drug abuse has wide forensic and legal implications, both nationally and internationally. Whether involved in toxicological analyses or drug seizure analyses, forensic practitioners should be aware of the pharmacological effects of the substances they encounter.

Pharmacology is the study of the biochemical and physiological effects of drugs and their mechanisms of action. The magnitude of a pharmacological response correlates to the concentration of drug at the site of action. Drug concentration is in turn affected by how well the drug is absorbed into the systemic circulation after administration, how it distributes throughout the body, and its subsequent metabolism and elimination.

Absorption, Distribution, Metabolism, and Excretion

Most drugs are administered orally and absorbed via the gastrointestinal (GI) tract . The rate and extent of appearance of drug in the systemic circulation depends on a series of processes: rate of release of drug from the dosage form, solubility, absorption across membranes, gastric emptying, and first-pass metabolism.

Biodistribution depends on the lipid solubility of each drug and the rate at which a drug crosses membrane barriers into the peripheral circulation and the central nervous system (CNS). Once absorbed, the drug may undergo significant chemical modification to render it into a water-soluble form that facilitates elimination and excretion by the body.

Most drugs are metabolized by membrane-bound liver enzymes. The cytochrome P450 mixed-function oxidase system catalyzes oxidation and conjugation with glucuronide. Metabolism generally occurs in the liver and, to a limited extent, the plasma, GI tract, kidneys, and lungs. Enhanced drug metabolism creates lower circulating levels of the parent drug and, as a result, higher drug doses are needed to achieve the same blood levels of the parent drug and an equivalent drug response.

The excretion of drugs and metabolites terminates their activity and presence in the body. Drugs may be eliminated by various routes; the kidney plays a major role by facilitating drug excretion into the urine. Some drugs are also excreted in feces, bile, lungs, sweat, saliva, and breast milk.

Similar drug concentrations do not produce the same pharmacological effects in all subjects. These differences may be due to several factors.

Age

The young and elderly have a lowered metabolic capacity. The very young may have enhanced sensitivity to drugs because the microsomal enzymes responsible for metabolism (particularly conjugation) are not fully active until several months after birth. Older children metabolize drugs at a similar rate as adults.

Patients older than 60 years have a decreased capacity for drug metabolism due to a gradual decline in physiological efficiency. In the elderly, protein binding may be decreased and renal excretion reduced, resulting in higher blood levels of a drug compared to younger patients.

Disease

Diseases can affect all drug absorption, distribution, and elimination processes. GI disturbances can decrease drug absorption; cardiovascular diseases affecting peripheral blood flow can decrease the rate at which drugs cross tissue membranes. Endogenous free fatty acids released into the plasma during trauma displace weak acidic drugs from albumin-binding sites. Diseases affecting the liver and/or kidneys probably have the greatest effect on drug concentration by compromising metabolism and excretion. Impaired liver function due to disease or chronic drug use greatly increases blood drug levels.

Weight

A patient's weight determines the volume of distribution of a drug, directly impacting blood drug concentrations. Drug metabolism is also generally faster in males than in females.

Genetic Factors

The genetic control of the number of receptor sites, the extent of protein binding, and the rate and extent of drug metabolism cause variations in drug concentrations and responses. Some drug-metabolizing enzymes are polymorphic, resulting in slow, rapid, or ultrarapid drug metabolizers. The incidence of

some polymorphism may be higher in some ethnic groups.

Diet

Diet can influence drug metabolism: changing the diet of an asthmatic patient from high to low protein increases the half-life of theophylline. Patient exposure to other drugs (alcohol) can significantly affect the metabolism of certain drugs.

Drug Classes

Depressants

These substances cause CNS depression and include ethanol, barbiturates, methaqualone, and tranquilizers. They cause relaxation, feelings of well-being, and sleepiness.

Barbiturates Barbiturates are derivatives of barbituric acid, and Figure 1 shows the chemical structure of a selection of barbiturates. Generally, barbiturates suppress activity of all excitable tissues in the CNS, peripheral nervous system (PNS), and cardiovascular system (CVS). Barbiturates bind to a site on the GABAA receptor and mediate major CNS effects by depressing neuronal excitability, inhibiting gamma-aminobutyric acid (GABA) binding to its postsynaptic receptor. The GABAA receptor is the main inhibitory receptor in the CNS. Receptor activation opens a Cl^- channel that mediates neuronal inhibition.

Barbiturates were once used to treat anxiety and insomnia, but the side-effects were found to be undesirable and possibly lethal. Since the introduction of the benzodiazepine anxiolytics, the clinical use, and abuse, of barbiturates has declined. Long-acting barbiturates such as phenobarbital have continued to be used as anticonvulsants and have the least potential for abuse (Table 1).

Barbiturates are administered orally or parenterally. As weak acids, they are absorbed rapidly from the stomach and small intestine into the systemic circulation. They rapidly penetrate the CNS and redistribute to other tissues. These drugs are highly bound to plasma proteins.

Long-acting barbiturates have the lowest lipid solubility, are less bound to plasma proteins, and have the shortest onset of action and the longest duration of action, slowly penetrating the CNS and slowly redistributing to other tissues. Biotransformation involves hepatic oxidation and glucuronidation. Metabolism is usually slow and the metabolites produced are generally inactive. Insignificant amounts of barbiturate substances are excreted unchanged. Barbiturates have relatively narrow therapeutic indexes, so there is a high risk of toxicity associated with these drugs, especially when combined with other depressants such as alcohol.

Chronic use induces metabolic and tissue drug tolerance. Cellular tolerance results in diminished tissue response, despite the maintenance of constant plasma drug levels.

Barbiturate withdrawal occurs 12–20 h after the last dose and is characterized by anxiety, irritability, increased heart rate and respiration rate, muscle pain, nausea, tremors, hallucinations, confusion, and seizures. Barbiturates decrease rapid eye movement (REM) sleep, and withdrawal is associated with

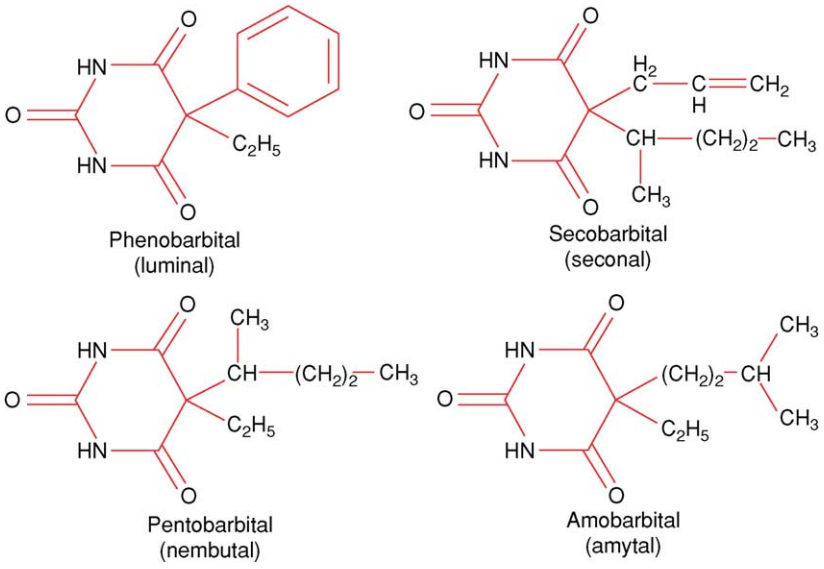


Figure 1 Chemical structures of barbiturates.

Table 1 Pharmacological responses of barbiturates

Peripheral nervous system	*Cardiovascular system*	*Long-term use*
Inhibit autonomic nicotinic receptors, causing hypotension and reduced cardiac function Anesthetic properties may inhibit skeletal muscle nicotinic receptors, suppressing neuromuscular transmission and causing slight muscle relaxation	Inhibition of autonomic nicotinic receptors causing mild hypotension Overdose associated with shock, renal failure, and death Associated with decreased cardiac output, cerebral blood flow, and myocardial contractility	Induces cytochrome P450 enzyme systems, increasing barbiturate metabolism; increases the biotransformation of other drugs, decreasing blood drug levels and promoting tolerance

sleep disruptions (nightmares, insomnia, or vivid dreams).

Benzodiazepines Benzodiazepines are synthetic depressant drugs. Their varied chemical structures impart a variety of chemical properties and pharmacological effects. Benzodiazepines are short acting and routinely used as hypnotics and preoperative anesthetics. Benzodiazepines with half-lives greater than 24 h are used as anxiolytics in the treatment of anxiety and insomnia. Unlike barbiturates, a wide range of doses can be used to treat anxiety, making dose determination easier to relieve anxiety without inducing sleep. Rebound insomnia may occur with some short-acting benzodiazepines but the effects are less severe than those seen with barbiturates. Rebound insomnia does not occur with longer-acting benzodiazepines.

Benzodiazepines also have clinical indications as anticonvulsants, antidepressants, and for the treatment of acute alcohol withdrawal. These agents may also reduce stress-induced GI disorders.

The physiological effects of benzodiazepines are similar to those of the barbiturates, but their mechanism of action is slightly different. Like barbiturates, the major effect of benzodiazepines is the CNS depression of neuronal excitability, mediated by the effect of benzodiazepines on the binding of GABA to its postsynaptic receptor. Benzodiazepines are allosteric modulators that bind to the benzodiazepine binding site of the GABA receptor and increase the receptor affinity for GABA. A GABA receptor γ subunit is required for a response to benzodiazepines; variants of this receptor subunit determine receptor selectivity for certain benzodiazepines.

Peak plasma concentrations occur within a few hours of oral administration. Most benzodiazepines are administered orally or intravenously; diazepam and midazolam may be administered rectally, and alprazolam may be administered sublingually. Diazepam and triazolam are more lipophilic than chlordiazepoxide and lorazepam and penetrate the CNS rapidly, providing a fast onset of action. Benzodiazepines are extensively plasma protein-bound (60–95%), so they are susceptible to drug interactions. Displacement of benzodiazepine from plasma proteins increases the amount of free drug and its pharmacological effect. Benzodiazepines undergo microsomal oxidation followed by glucuronidation prior to urinary excretion. Several phase 1 metabolites of benzodiazepines are active, with longer half-lives than the parent drug (e.g., nordiazepam).

Tolerance to the sedative effects of benzodiazepines often develops within about 1 week of treatment; tolerance to the anxiolytic effects does not occur in short-term use. Tolerance occurs more during benzodiazepine abuse, requiring doses many times greater than the therapeutic dose to achieve desired effects. Benzodiazepine use is associated with physical dependence. Mild withdrawal symptoms include anxiety, dizziness, headache, insomnia, tremor, muscle stiffness, and sensitivity to light and sound. Severe symptoms include intense anxiety, nausea, vomiting, delirium, hallucinations, hyperthermia, sweating, panic attacks, paranoid psychoses, increased heart rate, increased blood pressure, and seizures. Short-acting and high-potency benzodiazepines are most likely to result in dependence, although long-term use is probably the major risk factor.

Ethanol The beneficial effects of ethanol have been well documented. Moderate ethanol consumption – less than two drinks per day (a standard drink being 30 ml of 100-proof liquor, 120 ml of wine, or a 10-oz. bottle of beer) – has been associated with lowered risk of coronary heart disease (red wine has been shown to be most beneficial). The hypnotic properties of ethanol have been exploited to induce sleep, and the treatment for methanol and ethylene glycol toxicity is the administration of ethanol. Ethanol is a more effective substrate for alcohol dehydrogenase, the enzyme that produces toxic metabolites (Table 2).

CNS effects of ethanol are related to blood alcohol concentration (BAC) (Table 3). Effects are more

Table 2 Physiological effects of ethanol

Cardiovascular system (CVS)	Cardiomyopathy, arrhythmia, congestive heart failure; moderate doses associated with higher high-density lipoprotein levels and less cardiovascular disease. Vasodilation causes warm flushed skin, which is why alcohol has traditionally been used to warm the body in cold weather. Vasodilation increases heat loss, leaving the person colder than before. Excessive ethanol consumption may promote hypertension; people consuming more than three drinks per day generally have higher systolic and diastolic blood pressure than those consuming fewer than three drinks per day
Central nervous system (CNS)	Small amounts depress complex CNS pathways promoting relaxation, loss of inhibition, and increased talkativeness. As blood ethanol increases, judgment, decision-making abilities, and reflex reactions are impaired. Very high doses further depress the CNS, inducing sleepiness, coma, and death via respiratory depression
Gastrointestinal (GI) tract	Ethanol stimulates the production of gastric juices and decreased pepsin. At concentrations above 40%, mucosal membranes become irritated, causing hyperemia or gastritis; chronic alcoholics often have chronic gastrointestinal irritation
Kidney	Diuretic effects due to increased liquid intake, and suppression of antidiuretic hormone
Liver	Acute ethanol ingestion has little effect. Long-term consumption causes liver damage and steatosis; hepatic exposure to large amounts of ethanol decreases fatty acid oxidation processes of ethanol metabolism; acetaldehyde accumulation causes lipid peroxidation. Initial effects are reversible; over time liver repair causes collagen deposition, irreversible fibrotic changes; cirrhosis; liver failure, and death

Table 3 Central nervous system effects related to blood alcohol concentration (BAC)[a]

BAC (g 100 ml^{-1})	*Stage of impairment*	*Behavioral effects*
0.01–0.05	No noticeable impairment	Apparent normal behavior; impairment detected by specialized tests
0.03–0.12	Euphoric effects	Slight euphoria, increased sociability, talkativeness, and self-confidence; slowed information processing; decreased judgment, attention, and control; sensory motor impairment begins
0.09–0.25	Excitation	Emotional instability, impaired memory, comprehension, and perception; critical judgment decreases. Increased reaction times, decreased visual acuity, impaired balance, drowsiness
0.18–0.30	Confusion	Disorientation, confusion, dizziness, visual disturbances, increased pain threshold, staggering, slurred speech, apathy, lethargy
0.25–0.40	Stupor	Diminished motor functions; decreased responsiveness and inability to stand or walk; vomiting, incontinence, sleep/stupor
0.35–0.50	Coma	Unconsciousness, coma, depressed reflexes, hypothermia, impaired circulation, and respiration, possible death
+0.45	Death	Respiratory arrest

[a]These are guidelines – the effects are altered by a number of different factors.

pronounced with increasing blood levels compared to decreasing blood levels. However, these are only guidelines and the effects, and their correlation with blood alcohol level, depend on a person's regular intake of alcohol and whether he or she is dependent on alcohol. Ethanol mediates its CNS-depressant effects by suppressing the actions of GABA at the GABAA receptor and blocking the N-methyl-D-aspartate (NMDA) glutamate receptor.

After oral ingestion, some ethanol is absorbed directly from the stomach and the rest is absorbed in the small intestine. Absorption of alcohol is affected by a number of factors, including gastric emptying rate, the presence of food in the stomach, and the concentration of ethanol consumed. Higher ethanol concentrations increase alcohol absorption, but very high concentrations decrease absorption by restricting passage through the pyloric sphincter into the stomach.

BAC is also affected by weight and gender. The heavier the person, the larger the volume of body water and the lower the BAC obtained from a given amount of ethanol. Women generally have a higher proportion of fat tissue and a smaller volume of body water than men of the same weight; therefore, women may achieve a slightly higher BAC when consuming the same quantity of ethanol as men of the same weight. Men also have higher levels of gastric alcohol dehydrogenase, causing some ethanol metabolism before it can be absorbed. Ethanol distributes throughout the body, crossing the blood–brain and placental barriers.

Alcohol dehydrogenase, the main enzyme of ethanol metabolism, is abundant in the liver and present in smaller amounts in the stomach and kidney. This enzyme converts ethanol to acetaldehyde, which is further metabolized by mitochondrial aldehyde

Table 4 The three distinct phases of ethanol withdrawal symptoms

Phase	*Time after discontinuation*	*Symptoms*
Initial	A few hours	Tremulousness, weakness, headache, perspiration, anxiety, nausea, abdominal cramps, vomiting, mild hallucinations
Seizures	2–3 days	Generalized seizures
Delirium tremens	3–4 days	Auditory, visual and tactile hallucinations, insomnia, agitation, disorientation, restlessness, fever, sweating, tachycardia; death may occur

dehydrogenase to acetate and eventually carbon dioxide. The alcohol dehydrogenase step is the rate-limiting step in alcohol metabolism, becoming saturated at or above a BAC of 0.02 mg per 100 ml. Polymorphisms exist in the mitochondrial aldehyde dehydrogenase enzyme (ADH2), resulting in gain or loss of function. For example, approximately 90% of Asians have a polymorphism in this enzyme, resulting in increased function, which in turn leads to accumulation of acetaldehyde. This acetaldehyde accumulation results in a severe flushing reaction.

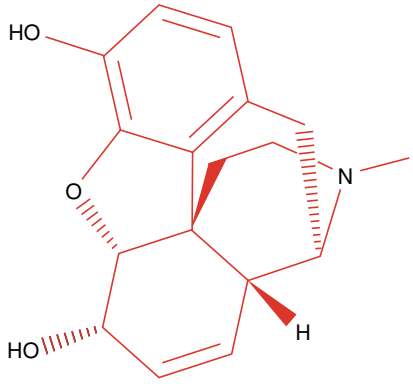
Ethanol is also metabolized by the cytochrome P450 system, particularly CYP2E1. CYP2E1 is induced by regular ethanol consumption and may significantly contribute to ethanol metabolism in frequent users. Approximately 5–10% of the ingested ethanol is eliminated in breath, sweat, urine, and feces.

Unlike most drugs, ethanol elimination is a zero-order process: initially, elimination is dose-dependent but, as alcohol dehydrogenase becomes rapidly saturated, elimination becomes almost linear (pseudolinear). Ethanol is normally eliminated from the blood at a rate of 0.01–0.025 g % h^{-1}, but this rate can vary significantly between individuals. The elimination rate may also depend on the amount of alcohol normally consumed. The following are general guidelines:

- nondrinker: 0.012% h^{-1}
- social drinker: 0.015% h^{-1}
- alcoholic: 0.03% h^{-1}.

Pharmacokinetic and pharmacodynamic ethanol tolerance occurs quickly. As a consequence of pharmacodynamic tolerance, some alcoholics can have BACs of up to 0.35 mg per 100 ml without appearing impaired. Cognitive and psychomotor functions remain impaired and the lethal dose of alcohol remains the same even when tolerance occurs to other effects. Cross-tolerance occurs with ethanol and other CNS-depressants (barbiturates and benzodiazepines).

Withdrawal (not hangover) symptoms are characterized into three distinct phases (Table 4). Death often occurs during delirium tremens (there is a mortality rate of approximately 10%). Symptom severity depends on the ethanol dose and the duration and continuity of administration. Psychological dependence may occur with moderate use, manifesting as ethanol cravings before or during social events.



Morphine

Figure 2 Chemical structure of morphine.

Opioids Opiate agonists are drugs that produce effects similar to those of morphine (Figure 2). Morphine antagonists include naloxone and naltrexone. Partial agonists/antagonists include buprenorphine and pentazocine. These agents behave like morphine but have some antagonist activity. Clinically, opioids are administered orally, transdermally (skin patches), intravenously, or rectally to treat pain, cough suppression, and diarrhea. Side-effects include respiratory depression, nausea and vomiting, constipation, miosis, cardiovascular effects, pulmonary edema, and seizures.

Opioids cross the blood–brain barrier and bind to specific opioid receptors. There are three main opioid receptors: mu (μ), kappa (κ), and sigma (σ).

Receptor distribution varies within the CNS and is species-specific. Stimulation of each of the receptors produces different clinical effects. Many opioid drugs have different affinities to more than one receptor type, producing variations in the observed clinical effect.

There are three main families of endogenous opioid peptides; each elicits analgesic and physiological

functions (Table 5). Each peptide has a high affinity for one receptor type, but each binds to all the opioid receptors with different affinities. Enkephalins have a high affinity for the δ receptor, dynorphins have a high affinity for the κ receptor, and endorphins have a high affinity for the μ and δ receptors.

Morphine is well absorbed from most routes of administration. Opioids have relatively short half-lives; morphine has a half-life of a few hours, whereas methadone has a half-life of approximately 24 h.

Opioids bind to plasma proteins but rapidly leave the circulation and accumulate in highly perfused tissues (lungs, liver, kidneys, and spleen). Long-term use of high doses of lipophilic opioids (fentanyl) may cause accumulation in fatty tissue. Codeine and heroin cross the blood–brain barrier more rapidly than amphoteric drugs such as morphine.

Opioids are metabolized and excreted via the kidney. Morphine's free hydroxyl groups are glucuronidated at the 3- or 6-positions to form morphine-6-glucuronide (an active metabolite that may have greater analgesic activity than morphine) or morphine-3-glucuronide (Figure 3). Morphine glucuronides, with small amounts of unchanged drug, are excreted in the urine, with up to 85% of the dose being recovered in a day. Some opiate–glucuronide conjugates are excreted in the bile.

Significant tolerance to analgesic and euphoric effects occurs rapidly with opiates, especially those with high affinity for μ receptors (heroin, morphine, meperidine, fentanyl, and methadone), resulting in users administering up to 40–50 times the normal lethal dose. Tolerance to the effects of constipation and meiosis occurs more slowly, even after extensive use.

Opiate withdrawal is extremely uncomfortable but not life-threatening. Symptoms tend to be the opposite of the acute drug effect and include muscle aches/pains, joint aches/pains, abdominal cramps, anxiety, diarrhea, pupillary dilation, lacrimation, rhinorrhea, "gooseflesh," sweating, and vomiting.

Withdrawal begins within 12 h of the last dose, peaking at 36–48 h. Symptoms usually disappear within 7–10 days.

Withdrawal is most severe when opioids are displaced from the receptors by the administration of an opioid antagonist. In opioid overdose cases, the drug naloxone competes with the opioid agonist for opioid receptors, reversing the overdose. If the dose of naloxone exceeds the amount required, severe withdrawal symptoms occur. Opiates produce severe psychological dependence, especially heroin, because the euphoria experienced is so intense.

Heroin Illicit opiate use is usually associated with heroin (diacetylmorphine), a semisynthetic agent produced by reacting morphine and acetic anhydride. Usually encountered in the form of a white to brown powder, or a brown to black tar. It has effects

Table 5 The three main families of endogenous opioid peptides

Endogenous peptide family	*Peptides in family*	*Amino acid structure*
Enkephalins	Leu-enkephalin	Tyr-Gly-Gly-Phe-Leu
	Met-enkephalin	Tyr-Gly-Gly-Phe-Met
Dynorphins	Dynorphin A	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln
	Dynorphin B	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr
Endorphins	α-Neoendorphin	Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro-Lys
	β-Neoendorphin	Tyr-Gly-Gly-Phe-Leu-Arg-Lys-Tyr-Pro
	β_h-Endorphin	Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu

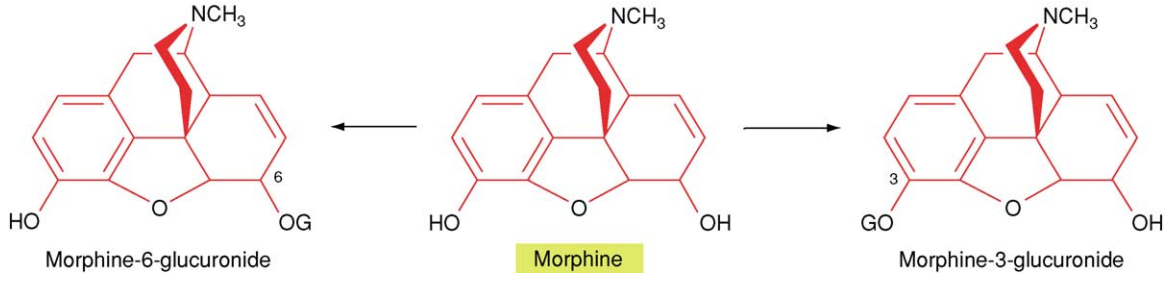


Figure 3 Morphine glucuronidation, forming morphine-6-glucuronide and morphine-3-glucuronide.

similar to those of morphine, lasting 4–6 h, and is significantly more powerful and addictive. Street heroin in the USA is about 2% pure. Other components of the street preparation include cutting agents (sugar, starch, household cleanser, and brick dust) and adulterants (strychnine and quinine). Heroin can be injected intravenously after dissolving in water, lemon juice, or vinegar (the acidity inhibits hydrolysis of heroin and facilitates dissolution). Heroin vapors are often inhaled after heating the drug on aluminum foil. Characteristic effects of heroin and related opiates include drowsiness, euphoria, constricted pupils, and, occasionally, nausea.

Stimulants

Stimulant drugs include cocaine, amphetamine, methamphetamine, caffeine, and methylphenidate (Ritalin). These agents stimulate the CNS, induce a sense of well-being, increase alertness, decrease fatigue, suppress appetite, and can lead to strong psychological dependence.

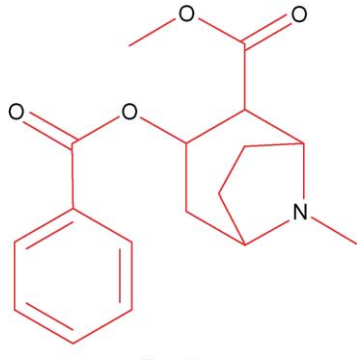
Cocaine Cocaine (Figure 4), derived from the coca plant grown in the Andean mountains of South America, is legitimately used in the USA as a local anesthetic in ear, nose, and throat surgery. Crack is a smokeable form of cocaine produced by combining hydrochloride salt with water and baking soda to make cocaine freebase. The drug is rapidly absorbed through the lungs. The salt form is snorted (insufflated) and absorbed across nasal membranes. Common diluents in street preparations include lidocaine (lignocaine), procaine, sodium bicarbonate, and starch.

At low doses, cocaine increases arousal and motor activity. At moderate doses, heart rate increases. Hypertension results from the increased peripheral resistance (due to vasoconstriction) and the increase in heart rate. Body temperature is increased and the pupils dilate. At high doses, cocaine can induce convulsions. Cardiac arrest is not uncommon due to a direct action of the drug on the heart muscle. Cocaine prevents conduction of sensory impulses by blocking ion channels in the neuronal membrane. This block inhibits the propagation of electrical signals along the axon, inhibiting sensory messages to the CNS (Table 6).

Cocaine can potentiate neurotransmission in catecholaminergic neurons using norepinephrine (noradrenaline), dopamine, or 5-hydroxytryptamine as neurotransmitters. In the periphery, this occurs mainly at noradrenergic terminals in the sympathetic component of the autonomic nervous system, and in the brain it occurs at monoaminergic terminals. Cocaine blocks the reuptake of monoamine into the synaptic terminal, potentiating neurotransmitter effects. Potentiation of norepinephrine (noradrenaline) causes mydriasis, vasoconstriction, hypertension, tachycardia, and tachypnea.

The potentiation of dopamine in the brain is largely responsible for the behavioral effects of cocaine, such as intense euphoria, heightened sexual excitement, and self-confidence; paranoia, hallucinations, and dysphoria may also occur. The initial "rush" experienced with cocaine is followed by a "crash" corresponding to respective increases and decreases in brain dopamine levels.

Cocaine hydrochloride is water-soluble and is administered orally, intranasally, or intravenously. Oral administration results in low bioavailability (20%) and less CNS distribution due to first-pass metabolism. Intravenous administration ("mainlining") allows 100% bioavailability and dramatic CNS effects. Insufflation produces less intense effects and is associated with atrophy and necrosis of the nasal mucosa and septum. Freebase cocaine is smoked, producing rapid and intense effects. Cocaine crosses the blood–brain barrier and is concentrated in the spleen, kidneys, and brain.



Cocaine

Figure 4 Chemical structure of cocaine.

Table 6 Pharmacological effects of cocaine

	Physiological effect
Cardiovascular system	Increased heart rate and blood pressure; constriction of coronary arteries reduces blood supply to the heart
Central nervous system	Short-lived euphoria, arousal, alertness, tremor, seizures, and dysphoria may occur with higher doses; tactile hallucinations
Local anesthetic	Blocks nerve conduction; effective as a topical anesthetic
Other effects	Rhinitis

Cocaine has two primary metabolites, ecgonine methyl ester and benzoylecgonine. Both are inactive and excreted in the urine. Smaller amounts of ecgonine and the active metabolite norcocaine are also formed. Breakdown of cocaine to ecgonine methyl ester is rapidly catalyzed by cholinesterases present in serum and the liver. Hydrolysis of the other ester linkage to form benzoylecgonine may be nonenzymatic. Demethylation of cocaine to form norcocaine occurs through the hepatic mixed-function oxidase system. Cocaethylene is a metabolite of cocaine formed when taken concomitantly with ethanol. It is an active metabolite and has a longer half-life than cocaine. Cocaine is excreted fairly quickly, with a half-life of about 40 min.

Tolerance occurs rapidly (within days of use) in chronic drug users due to the upregulation of cocaine-binding sites in the brain. Significant tolerance is not associated with occasional or binge users.

Cocaine is not associated with severe withdrawal syndromes. However, reported symptoms include anhedonia, anergia, craving, depression, fatigue, lethargy, hypersomnolence, mood disorders, and suicidal behavior.

Stimulant drugs are associated with very strong psychological dependence; users exhibit extreme drug-seeking behavior, that is often detrimental to their health and lives.

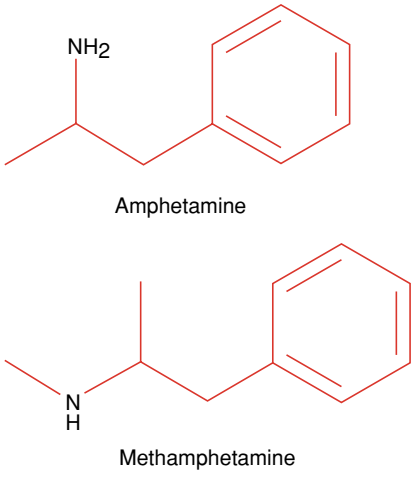


Figure 5 Chemical structures of amphetamine and methamphetamine.

Amphetamine and methamphetamine Amphetamine and methamphetamine drugs are commonly illegitimately produced in clandestine laboratories in the form of white or tan powders that are snorted, injected, smoked, and ingested (Figure 5). Ice is a very pure smokeable form of methamphetamine. Amfetamines, including methamphetamine, methylene dioxyamphetamine, and methylenedioxymethamfetamine (MDMA), are similar to cocaine in pharmacological action (Table 7). Like cocaine, amphetamines cause restlessness, stimulation, appetite suppression, paranoia, and psychosis. Their effects last 4–12 h.

The following amphetamines are used clinically:

- D-Amphetamine is marketed as Dexedrine and is used to treat attention deficit hyperactivity disorder (ADHD) and narcolepsy.
- Methylphenidate is marketed as Ritalin and is used to treat ADHD and narcolepsy.
- Phentermine is used to treat obesity.

Amphetamine, like cocaine, is a sympathomimetic drug, although its mechanism is slightly different. Amphetamines increase monoaminergic activity by stimulating the release of dopamine and norepinephrine (noradrenaline) from the nerve terminals, increasing their synaptic concentration. Amphetamines inhibit dopamine reuptake at the nerve terminal and inhibit monoamine oxidase, the enzyme that metabolizes monoamine neurotransmitters, prolonging their availability. Amphetamine may also directly activate catecholamine receptors.

Amphetamines are weak bases (pK_a of 9 or 10); ionization in the digestive system after oral administration slows their rate of absorption. Amphetamines

Table 7 Pharmacological effects of amphetamines

	Physiological effects
Cardiovascular system	Increased blood pressure, heart rate, and force of contraction; reflex heart rate decreases are encountered due to increased blood pressure; myocarditis is common and potentially fatal. Vascular effects include vasospasm, edema, necrosis, and paresthesia
Smooth muscle	Increased muscle tone, tremors; contraction of bladder sphincter and difficulty in urination; reduced gastric motility and drug absorption; rhabdomyolysis may cause muscle necrosis and renal failure
Central nervous system	Euphoria, mood elevation, increased alertness; increased confidence and physical strength. Euphoric effects last longer than with cocaine; enhanced concentration and physical performance; appetite suppression
Other effects	High doses produce stereotopy (repetitive fixing of objects, cleaning, bathing, grooming, or repetition of words or sentences)

are more potent when taken intravenously or by inhalation. Amphetamines cross the blood–brain barrier and are concentrated in the spleen, kidneys, and brain. Amphetamine and other similar drugs are metabolized by the liver. Some drug is excreted unchanged in the urine. Methamphetamine undergoes *p*-hydroxylation and demethylation, generating a small amount of amphetamine; again, some drug is excreted unchanged.

Both the clearance and the half-life of amphetamine depend on urinary pH. In acidic conditions, amphetamine is ionized and reabsorption from the nephron does not occur. The clearance is rapid and the half-life ranges from 7 to 14 h. In basic conditions, the drug is un-ionized and renal reabsorption occurs. Excretion depends on metabolic processes, and the half-life is extended to 16–34 h. Urinary pH can be altered by drug use and diet.

As with cocaine, tolerance to the effects of amphetamine rapidly develops with chronic drug use; no significant tolerance is associated with occasional or binge use. Amphetamine is not associated with severe withdrawal syndromes, but reported symptoms are similar to those experienced with cocaine. The effects of psychological dependence are also similar to those experienced with cocaine.

Hallucinogens

Hallucinogenic agents cause alterations in the normal thought processes, perceptions, and moods. These drugs include marijuana, lysergic acid diethylamide (LSD), phencyclidine (PCP), peyote, and psilocybin.

Marijuana Marijuana, derived from the plant *Cannabis sativa*, is encountered in different forms, the most common being a smokeable form called cannabis. Its use elicits hallucinations, relaxation, increased appetite, a distorted sense of time, reduced judgment and coordination, and uncontrollable laughter. The high lasts 3 h or more.

The main active component of cannabis is Δ^9-tetrahydrocannabinol (THC). However, cannabis contains an entire family of constituents known as the cannabinoids (more than 60 have been identified). The effects of cannabis result from the effects of each of the cannabinoids.

Cannabis has been shown to have legitimate clinical uses for treatment of nausea and vomiting in cancer patients undergoing chemotherapy and the stimulation of appetite in acquired immunodeficiency syndrome (AIDS) and cancer patients. Nabilone and dronabinol are Δ^9-THC analogs and can be used clinically as antiemetics for cancer patients undergoing chemotherapy and to stimulate appetite in AIDS or cancer patients. Nabilone is marketed for these indications in the UK, whereas dronabinol (Marinol) is marketed in the USA.

Despite being considered a relatively harmless drug, cannabis has a number of significant physiological effects, including tachycardia (heart rate may increase by 20–50%), increased blood pressure (users may experience orthostatic hypotension), decreased body temperature, dry mouth and throat, reddening of the conjunctivae of the eyes, decreased intraocular pressure, decreased pupil size, and hunger.

Smoking cannabis can cause adverse effects such as lung disease, wheezing, and coughing. Cannabis elicits behavioral effects that are dependent on the dose and form of cannabis taken as well as the state of mind, mood, and expectations of the individual prior to use. Moderate doses can cause euphoria, heightening of senses, altered sense of time (time appears to pass much more slowly), and short-term memory impairment. High doses can cause anxiety, aggression, confusion, hallucinations, nausea, and vomiting.

Behavioral effects are not well correlated with plasma THC concentrations since there is a delay before the onset of the long-lasting psychological effects that remain when blood THC levels decrease. Cannabis alters the ability of a user to perform skilled tasks, including driving.

Cannabinoids bind to G-protein-linked (G_i) cannabinoid receptors inactivating adenylyl cyclase, which directly inhibits calcium channel function. CB_1 cannabinoid receptors in the CNS are localized in areas that correspond to the effects of cannabis:

- hippocampus and cortex: memory and learning
- basal ganglia and cerebellum: balance and coordination
- mesolimbic dopamine pathways: reward.

CB_2 cannabinoid receptors located in the PNS may be involved in inflammation and immunity suppression associated with cannabis use.

THC is a weak acid ($pK_a = 10.6$), un-ionized at physiological pH. Cannabinoids are highly lipid-soluble and are slowly absorbed from the stomach and small intestine. Absorption can be increased by adding oil to the plant material before consumption, which is often achieved by baking the material in cookies. Significant first-pass metabolism occurs with oral ingestion of cannabis; a much larger dose must be ingested to achieve the same effects experienced when the drug is inhaled. Bioavailability after oral administration is about 6%, and peak effects occur 1–3 h after ingestion, lasting up to 5 h.

After inhalation, 10–25% of the cannabinoids enter the lungs. Drug effects are experienced within

a few minutes, peaking at 30 min. Bioavailability after inhalation is estimated to be 14–50%. Cannabinoids distribute throughout the body but tend to accumulate in the lungs, kidney, and bile. Approximately 1% of a dose crosses the blood–brain barrier.

Some metabolism occurs in the lungs or stomach or intestine, but most occurs in the liver. Δ^9-THC is metabolized extensively to produce the major metabolite, 11-hydroxy-Δ^9-THC (reported to have significant THC-like activity). 9-Carboxy-Δ^9-THC is also produced in significant quantities; it is conjugated with glucuronic acid to form 9-carboxy glucuronide, the major metabolite in blood and urine.

In low to moderate cannabis users, metabolites can be detected in blood for up to 5 days and in urine for up to 12 days after administration. In regular high-dose users, detection times may be up to 25 days after use.

Onset of cannabis tolerance is rapid but short-lived. Both behavioral and physiological tolerance occur. Fewer mood-altering effects are experienced by regular users of cannabis, and regular users experience less of a "high" than naive users. There is significant individual variation in the development of tolerance to the effects of cannabis.

Cross-tolerance occurs between the effects of cannabis and alcohol; regular cannabis users experience reduced effects to alcohol and vice versa. Relatively few substance abusers seek treatment for cannabis addiction, but long-term users may experience withdrawal symptoms that include restlessness, irritability, mild agitation, insomnia, sleep disturbances, and nausea and cramps.

Psychological dependence may occur with cannabis use; users believe they need the drug in order to function in their everyday lives.

Serotonin-like hallucinogenic agents LSD is a semisynthetic substance produced from ergot alkaloids with serotonin-like properties that was originally developed as a treatment for schizophrenia. Extremely small doses (25 μg) can result in a 12-h high. This drug causes marked mood changes and distortion of sensory perceptions (time and distance). Synesthesia may occur: this is a condition in which colors are "heard" and sounds are "seen." The effects experienced depend on the setting and the user's mental state. Although considered impossible to overdose, LSD-related deaths have been attributed to accidents occurring while under the drug's influence. Flashbacks – spontaneous and fragmentary recurrences of a previous "trip" – have been reported days or months after use. The drug is usually taken orally. It is sold as blotters or sugar cubes, with each hit containing about 100 μg. Other pharmacological effects include dilated pupils, elevated blood sugar levels, tingling of extremities, drowsiness, nausea, vomiting, diarrhea, and spontaneous abortion due to uterine muscle stimulation.

The CNS effects of LSD may include altered time perception (time appears to pass very slowly) and mood changes; distorted perception of size and shape of objects, movements, color, sound, touch, and body image; and anxiety or depression following use.

LSD resembles the CNS neurotransmitter serotonin (5-HT) and is a serotonin agonist with specific activity for the following receptor subtypes: 5-HT_{1A}, 5-HT_{1C}, and 5-HT_2. LSD is orally and sublingually absorbed with a 2- or 3-h half-life. Effects are felt after 40–60 min, with peak effects occurring after 2–4 h and disappearing after 6–8 h. LSD is distributed throughout the body, but only 1% of a dose reaches the brain. It concentrates in the liver, where it is rapidly metabolized before being excreted in the bile and feces.

N-desmethyl-LSD and 2-oxo-3-hydroxy-LSD are the major metabolites found in the urine (**Figure 6**). Together with the glucuronide of the 13-hydroxy metabolite, they can be detected up to 96 h after drug use. Only a small amount (1–3%) is excreted as unchanged drug.

LSD tolerance occurs rapidly. Within a few days of repeated drug administration, the user stops experiencing drug effects. The tolerance is short-lived and disappears after approximately a week of abstinence, enabling the user to experience all the drug effects. Cross-tolerance occurs between LSD, psilocybin, and mescaline, indicating that these drugs may have a common mechanism of action. There have been no reports of a physical withdrawal syndrome from LSD, but its use is associated with psychological dependence.

Psilocybin Psilocin and psilocybin naturally occur in the *Psilocybe* mushroom. Pharmacological action is similar to that of LSD but the agents are less active. Ten to 15 *Psilocybe* mushrooms induce hallucinogenic effects when taken orally. *Psilocybe* mushrooms are also dried and smoked with tobacco or extracted with boiling water to produce infusions. Abuse was popular at approximately the same time as LSD was popular. Although it is 100 times less potent than LSD, the effects are the same when dosage adjustments are made. Once absorbed, psilocybin is converted to the active agent psilocin, thought to be responsible for behavioral effects.

Dimethyltryptamine Dimethyltryptamine (DMT) is recovered from the bark of certain trees indigenous to

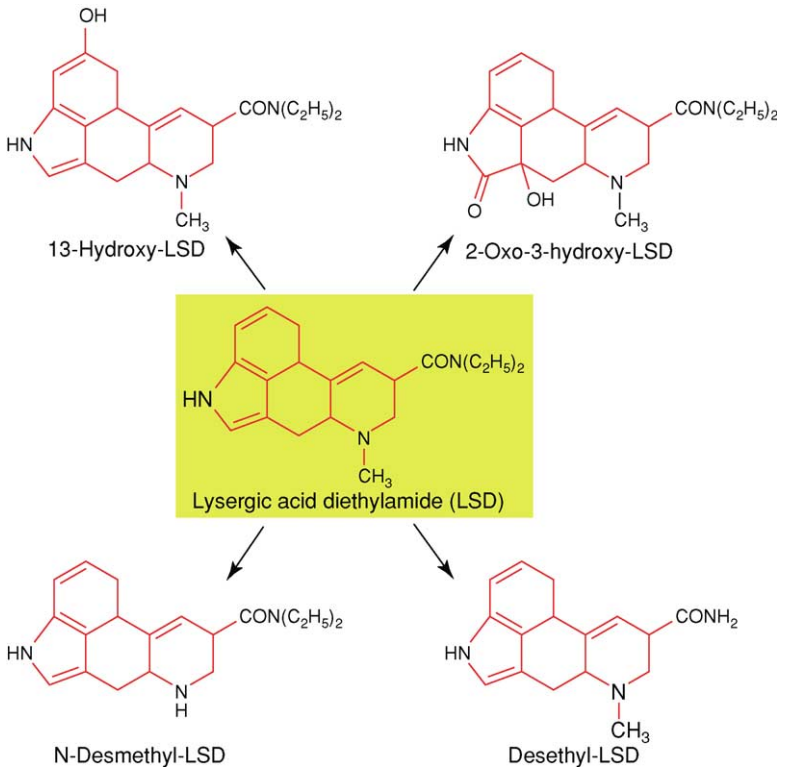


Figure 6 Chemical structure and metabolism of LSD.

the jungles of South and Central America. It is much less potent than LSD and very short-acting. For this reason, it is known as the "businessman's lunch" since the effects disappear within 1 h.

Bufotenine The chemical name for this agent is 5-hydroxy-DMT, a derivative of DMT. The drug is obtained from the beans of several trees from the genus *Anadenanthera* and the flesh of a fish called the "dream fish." It was originally discovered in the skin of a species of toad from the family Bufonidae, and it is not hallucinogenic when taken orally. The drug must be injected or inhaled for effects to be experienced.

Norepinephrine (noradrenaline)-like hallucinogens Obtained from the peyote cactus, mescaline's use was legalized by the US Congress in 1970 due to its central use in Native American ceremonies. Today, laws can still be passed against its use at the state level. The drug is readily absorbed when taken orally, and hallucinogenic effects are experienced within about 1 h of consumption, producing effects similar to those of LSD that last for several hours. This drug is approximately 2000 times less potent than LSD.

Ecstasy and other "designer drugs" Designer drugs encompass a drug group originally synthesized by altering the chemical structure of mescaline to circumvent the law when it only covered specific named drugs. These agents became known as designer drugs and include dimethoxyamphetamine (DMA), 2,5-dimethoxy-4-methylamphetamine (DOM), 2,5-dimethoxy-4-ethylamphetamine (DOET), and others. Many of these drugs have effects similar to those of amphetamine.

Ecstasy refers to MDMA, originally made by Merck in 1914. It was first used as a drug of abuse in the 1960s and is commonly known as X, Adam, E, and XTC. It induces effects similar to those of marijuana or low-dose PCP. Ecstasy causes a heightened sense of emotions and does not cause hallucinations. It is abused for its ability to increase energy and for the sense of euphoria and well-being. It sharpens perceptions and causes users to be more sociable.

Other hallucinogens

Phencyclidine (phenylcyclhexyl, piperidine, and PCP) This was first used as an anesthetic animal tranquilizer in the USA but is no longer legitimately produced. PCP is produced illegally in clandestine labs as a white powder that is taken orally, smoked (often with marijuana), or snorted in combination with cocaine.

Symptoms rapidly appear that resemble schizophrenia: euphoria, depression, agitation, violence,

Table 8 Absorption rates for different routes of administration of PCP

Route of administration	*Time to effect*	*Time to peak effect*
Oral	20–40 min	90 min
Inhalation	1 min	5–30 min
Intravenous	1 min	10 min

hallucinations, paranoia, panic, and suicidal tendencies. As a dissociative anesthetic, the user is aware of what is happening but does not feel involved. The user is insensitive to pain and is able to run on two broken legs or continue to fight after being shot. The drug is smoked, ingested, snorted, or injected; adverse effects include hypertension, tachycardia, coma, cardiac failure, and psychosis.

The effects caused by PCP include tachycardia, elevated blood pressure, sweating, miosis, and vertical and horizontal nystagmus. Other CNS effects include detachment, disorientation, euphoria, a feeling of floating in space, alterations in perception of body image, relaxation, and a warm, tingly feeling. Users may experience a period of depression following use. This drug is associated with violent criminal behavior.

PCP has been shown to have effects on a variety of neurotransmitter systems: dopaminergic system (agonist actions), cholinergic system (complex actions), NMDA receptors (antagonistic effect), noradrenergic system (undefined), and serotonergic system (undefined).

The probable mechanism responsible for the main effects of PCP is its interaction with a PCP receptor. It is thought that the receptor is responsible for the behavioral effects of the drug since other drugs with PCP-like effects have been shown to act at this site. This site has been identified as a site on the NMDA receptor complex.

PCP is absorbed well via various routes of administration (Table 8). The effects of PCP can last for up to 8 h. This long duration of action is due to the fact that it is rapidly taken up into the brain and fatty tissues, from which it is then slowly released.

PCP is extensively metabolized by the cytochrome P450 system. The metabolites are not active and do not contribute to the effects caused by PCP. The polar metabolites are excreted in the urine. Also, about 10% of the dose is excreted unchanged, making urine an ideal choice for testing for PCP use. Because PCP is rapidly distributed to fatty tissue, the drug and its metabolites can be detected in urine for a prolonged period after use. In fact, in chronic users, they can be detected for a period of weeks after use.

As with LSD, tolerance occurs rapidly and is short-lived. There have been very few reports of physical dependence associated with PCP use. However, a few cases have reported a withdrawal syndrome consisting of anxiety, nervousness, and depression. As with LSD, psychological dependence may occur such that users experience an intense craving for the drug.

Ketamine This drug, usually taken orally or intravenously, is an anesthetic used in children and animals, and it has a shorter duration of action than PCP. It is available as a drug of abuse (known as K or Special k) and has been reportedly used as a date rape drug.

See Also

Alcohol: Acute and Chronic Use, Postmortem Findings; **Autopsy, Findings:** Drug Deaths; **Substance Misuse:** Cocaine and Other Stimulants; Substitution Drugs; Sedatives

Further Reading

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