



INFORMATION FOR PROFESSIONALS

Amphetamines

Amphetamines are members of a class of drugs known as stimulants that includes caffeine, cocaine, and nicotine. Stimulants have the common property of increasing activity in the central nervous system (CNS). Some of these drugs are produced naturally by plants; others, like amphetamines, are the result of chemical synthesis.

The amphetamines include methamphetamine, dextroamphetamine, levoamphetamine, and others.

Amphetamine, the original drug of this group, is a mixture of dextro- and levoamphetamine. It was first synthesized in Germany in 1887. In the 1930s, it was discovered that amphetamine had both vasoconstricting and bronchodilating effects and it was marketed as a non-prescription inhaler to treat nasal congestion under the trade name Benzedrine. Amphetamine has also been used in the treatment of asthma, depression, obesity, and narcolepsy. However, early enthusiasm for medical use quickly waned as it was discovered that the therapeutic benefits amphetamines may have in treating obesity and depression are short-lived and offset by the serious liabilities of chronic use, including physical and psychological dependence, sleep disorders, psychological disturbances, and unwanted appetite suppression.

The ability of amphetamines to reduce the need for sleep and increase alertness led to their use by military personnel in World War II. A severe outbreak of methamphetamine addiction occurred in Japan after the war when military supplies of the drug were made available to the public.

Use in North America was sporadic until the late 1950s and early 1960s when amphetamines gained acceptance as an appetite suppressant for weight loss programs and youth experimentation with a variety of drugs, including amphetamines, became more widespread. Severe addiction and serious medical side effects prompted government intervention and, in Canada, the use of amphetamines for weight control was outlawed and prescriptions became much more regulated.

Chemistry

Amphetamine has a chemical structure similar to the neurotransmitters noradrenaline (norepinephrine) and dopamine, and the hormone adrenaline (epinephrine). When amphetamine is ingested, many of the biological reactions normally controlled by neurotransmitters (noradrenaline, dopamine) are elicited. Amphetamine is not metabolized as rapidly as adrenaline, noradrenaline, and dopamine. As a result, it

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remains active in the body longer and effects can still be felt four to six hours after oral ingestion of a relatively small dose. Large doses will have a longer duration of effects.

When amphetamine is synthesized, two mirror image molecules are formed, a “d” form and an “l” form. The “d” form (dextroamphetamine) acts more on the brain while the “l” (levoamphetamine) form acts more on the cardiovascular system.

Amphetamines are usually used for their actions on the brain; therefore, the “d” form is most commonly used, although mixtures of the “l” and “d” form do exist. Many chemical modifications of amphetamine have been synthesized, including MDA and MDMA (ecstasy). Most of these derivatives possess some hallucinogenic properties but are still stimulants. Methamphetamine, one of the derivatives, is a pure stimulant that has become a drug of widespread abuse (see below).

Amphetamine use

Amphetamines can be swallowed, snorted, or injected. Most users begin taking the drug orally but because of the slow onset of action (30 to 60 minutes) and the development of tolerance, intravenous use becomes more and more attractive. Intravenous injection will produce greater effects for the same dose of drug and the effects occur much more rapidly (within minutes). An intense rush is more likely to occur when the drug is taken intravenously. Users can develop a very high degree of tolerance to amphetamine. The normal dose for a new user is 25 to 50 mg taken orally, but some intravenous users are reported to inject several hundred milligrams at a time.

Mechanism of action

Amphetamine enters nerve terminals and displaces neurotransmitter molecules (noradrenaline, dopamine) from storage areas within the nerve terminal. This results in an increase in the release of transmitter from the terminal during periods of rest. It is not necessary for the nerve itself to be stimulated for this sort of release to take place. Such release increases the activity of the organ system serviced by that nerve even when this activity is not needed.

Amphetamine also prevents re-uptake of neurotransmitters (noradrenaline, dopamine) into the nerve terminal after release. Typically, nerves recycle transmitter substances, releasing them in response to a nerve impulse and taking the transmitter back into the terminal during rest periods. Thus, the action of released neurotransmitters is made more powerful by decreased neuronal reuptake, producing exaggerated cellular responses.

Because nerves have efficient reuptake mechanisms, they normally do not need to synthesize large amounts of transmitter; thus, the ability of these nerves to synthesize new transmitter is limited. If the re-uptake mechanism is inhibited by amphetamine, transmitter that cannot get back into the nerve terminal will ultimately be destroyed. If high doses of amphetamines are taken over an extended period, the nerve terminal can become depleted of transmitter. Recovery after long periods of amphetamine use cannot occur until these nerve terminals synthesize enough transmitter to fulfill their functional duties.

Finally, amphetamine can act inside the nerve terminal as well as outside to inhibit the action of monoamine oxidase (MAO), an enzyme normally involved in the breakdown of noradrenaline and dopamine. Inhibition of this enzyme allows released transmitters to remain active longer, to further exaggerate the actions of these transmitters.

In summary, amphetamine is an indirectly-acting drug that enhances the action of endogenous neurotransmitters by (a) enhanced release of transmitters and (b) reduced reuptake and metabolism by MAO. As a consequence, overall nervous activity is stimulated; the user is shifted into “overdrive,” as all systems are running faster and at a higher level than normal.

Amphetamine effects

Amphetamines enhance the actions of noradrenaline and dopamine in the brain and the rest of the body. The brain contains nerve cells that release noradrenaline and others that release dopamine. The rest of the body does not contain the dopamine releasing nerve cells, only the noradrenaline releasing nerve cells.

Amphetamine effects on the body are due to

increased release of noradrenaline from nerve endings in various organ systems. The effects on the heart are significant, increasing heart rate and force of contraction. Blood pressure rises due to the increase in cardiac activity (tachycardia) and also because noradrenaline is released at blood vessels, causing them to contract, which further increases blood pressure. The increases in heart rate and blood pressure are dose-dependent and may be very high, causing palpitations and chest pain with the possibility of heart attack. The cardiovascular effects become severe in patients using high doses and were a major factor in the decision to curtail the use of amphetamines as an appetite suppressant. Amphetamines can cause urinary retention by contracting the sphincter and relaxing the bladder. The effects on the gastrointestinal system are unpredictable.

The effects of amphetamines in the brain result from the release of both noradrenaline and dopamine. Central nervous system (CNS) effects include euphoria, a decreased need for sleep, decreased appetite, decreased need for liquids, increased sense of alertness, increased energy, and an increase in ambition, which may turn into aggressive behaviour at higher doses.

Users usually experience a narrowing of focus and increased fascination with events and concepts that would ordinarily bore them. This effect made these drugs popular among post-secondary students and truck drivers. Amphetamines allowed them to stay up all night and cram for exams or drive without distraction.

Dopamine is known to be an important transmitter in the "reward pathway." The euphoria, appetite suppression (anorexic effect), thirst suppression, and reduction of the need for sleep are likely mediated by dopamine in the brain. Overlying all of these effects is a sense of excitement caused by noradrenaline. Amphetamine-induced dopamine release produces a behavioural syndrome indistinguishable from an acute schizophrenic episode. Thus, amphetamine use is a differential diagnosis for schizophrenia.

Euphoria occurs with most doses of the drug and with most routes of administration. A "rush" may occur if the drug is taken intravenously, but is not as likely if taken orally. A "rush" is an intense sudden feeling of

extreme pleasure, described by some as a "complete body orgasm." Many users cannot describe the sensation except to profess that it is very pleasant.

In summary, the therapeutic uses of amphetamine and related drugs are limited to situations requiring CNS stimulation: for narcolepsy, for excessive morning sedation following morphine (dextroamphetamine), and for hyperactive children (see methylphenidate below). Importantly, amphetamine use produces a number of adverse effects, most notably in the CNS (insomnia, acute psychoses, abuse and dependence) and cardiovascular system (tachycardia and hypertension).

Pharmacokinetics

Amphetamine is well-absorbed orally, penetrates freely into the brain and is excreted unchanged into the urine. The plasma half-life is approximately 12 hours, but varies widely depending on urine pH. If the urine is alkaline, only 2.7% is excreted in 24 hours; acidification of the urine increases excretion to 57%.

Amphetamine use during pregnancy results in maternal vasoconstriction and hypertension that can lead to fetal hypoxia, obstetric complications and adverse effects on the newborn child (abnormal sleep patterns, tremors, poor feeding, hypotonia, fever and vomiting). Amphetamine also accumulates in breast milk, causing irritability and poor sleep patterns. Therefore, amphetamine should not be used during pregnancy and lactation.

Long-term effects

Amphetamines reduce the need for sleep and sleep can be postponed for several days. However, the body cannot sustain this activity and must recover the extra energy used. The price paid for this extra energy is exhaustion following the drug use.

A long period of no sleep is followed by a prolonged period of sleeping. After extended use of amphetamines, the "rebound" sleep is not satisfying and normal sleep patterns do not return for several weeks.

Thinking patterns are often altered by high doses and extended use of amphetamines. Social contacts can become strained due to secretive behaviour. Paranoid

behaviour can occur, and coupled with increased aggression, may lead to violence.

Fatal toxic effects

Seizures, convulsions, and respiratory depression may occur following high doses. These symptoms are dose-related and are more likely to occur following intravenous injection rather than oral ingestion.

High doses of amphetamines can cause rupture of blood vessels in the brain, heart failure, hyperthermia (extremely high fever), seizures, coma, and death.

Methylphenidate

Paradoxically, CNS stimulants (dextroamphetamine, methylphenidate) are used in the treatment of attention deficit/hyperactivity disorder (ADHD) in children, characterized by excessive motor activity, difficulty in sustaining attention and impulsiveness. Methylphenidate is a piperidine derivative that is structurally related to amphetamines. New formulations containing both immediate-release and extended-release methylphenidate are available for once-daily dosing. Use of methylphenidate for ADHD is associated with predictable side effects: anorexia, insomnia, headache, abdominal pain.

Methamphetamine

Methamphetamine is a derivative of amphetamine that was first synthesized in Japan in 1919. Methamphetamine was originally available in a liquid form for injection and was used for emergency treatment of patients who had overdosed on barbiturates. When this treatment became obsolete, the need for an injectable form disappeared. It is likely that much of the mystique about the superior properties of methamphetamine compared to amphetamine have their origins in this era, when methamphetamine was injected and amphetamine was taken orally.

Methamphetamine has a methyl group substituted on the terminal amine portion of the amphetamine molecule. This substitution may be responsible for methamphetamine entering the brain rapidly and producing more CNS effects. Although anecdotal sto-

ries attribute more CNS effects to methamphetamine than amphetamine, studies fail to show any difference between the two when comparing subjective effects and peripheral effects. Methamphetamine is not available legally in Canada, although it is available in the United States by prescription only. Methamphetamine is considered a drug with a very high potential for abuse and addiction.

Illegal production

Methamphetamine is synthesized in illegal laboratories using amphetamine produced by reducing ephedrine or pseudoephedrine obtained from legitimate sources. While much of the methamphetamine on the streets comes from underground labs, a significant amount is now being imported from Mexico and other places. Laboratories for production of methamphetamine can be set up in virtually any location—small sheds, basements, and even mobile labs in semi-trailer trucks have been utilized. These laboratories are dangerous due to the presence of flammable liquids and corrosive chemicals.

Methamphetamine use

Methamphetamine can be taken the same way as amphetamine: orally, by snorting, or by intravenous injection. In addition, methamphetamine is often smoked. The drug is vapourized and the fumes are inhaled. Inhaling the drug gets it into the blood very rapidly. Transport of the drug to the brain occurs in about eight seconds, which is even faster than intravenous injection. It is possible to feel a very powerful “rush” after smoking methamphetamine.

Methamphetamine for smoking is re-crystallized to form large crystals known as “ice” or “crystal meth.”

Drug effects

Methamphetamine produces the same effects as amphetamine and the mechanism of action is the same. However, it appears that methamphetamine may be more toxic in long-term use than amphetamine. Some studies report the breaking and truncation of nerve fibres following heavy methamphetamine use. Recovery and re-growth of these terminals appears to be slow. Although methamphetamine use

can cause personality and psychological disorders in users, there is little evidence to suggest that the damage is permanent. Individuals who inject methamphetamine intravenously run the same risks as other intravenous drug users of contracting infectious diseases such as hepatitis and HIV/AIDS.

Amphetamines and the law

Under Canada's Controlled Drugs and Substances Act, possession of amphetamines or their derivatives is a criminal offence. For less serious charges tried by summary conviction, the penalty for a first offence is a fine of up to \$1,000 or imprisonment for up to six months, or both. For subsequent offences, the penalty is a fine of up to \$2,000 or imprisonment for up to one year, or both. For more serious indictable offences, the penalty is imprisonment for up to three years.

Trafficking in, possession for the purpose of trafficking in, production of, and importing and exporting amphetamines are serious offences and are punishable on summary conviction by imprisonment for up to 18 months or on indictment by imprisonment for up to 10 years.

ADDITIONAL READING

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