Amphetamines

Information for Health Professionals

Introduction

Amphetamines belong to the class of drugs known as stimulants. Stimulants, which also include caffeine, cocaine, and nicotine, have the common property of increasing activity in the central nervous system (CNS). Some stimulants are produced naturally by plants, while others are the result of chemical syntheses. The amphetamine family of compounds include amphetamine, methamphetamine, and others.

Amphetamine is the original drug of this group and was first synthesized in Germany in 1887; however, its stimulant properties were unknown at that time. Amphetamines were first used for medical purposes in the 1920s. It was discovered that amphetamine had both vasoconstricting and broncodilating effects and could help those who suffer from asthma or allergies breathe easier. Amphetamine was marketed as Benzedrine, a non-prescription inhaler to treat nasal congestion.

In the mid to late 1930s, amphetamine was also used in the treatment of depression, obesity, and narcolepsy; however, early enthusiasm for medical use quickly weakened as it was discovered that the therapeutic benefits of amphetamines were short-lived. Harmful effects of chronic use, including physical and psychological dependence, sleep disorders, psychological disturbances, and unwanted appetite suppression also led to a decrease in the medical use of amphetamines.

The ability of amphetamines to reduce the need for sleep and increase alertness led to their use by military personnel during 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 drugs became more widespread. Severe addiction and serious medical side effects prompted government intervention. In Canada, the sale of amphetamines over the counter was banned and prescriptions became regulated.

Amphetamines can be swallowed, snorted, or injected. Many users begin taking the drug orally, but because of the slow onset of action (30 to 60 minutes) and the development of tolerance, some may move to intravenous use. Intravenous injection will produce greater effects for the same dose of drug and the effects occur much more rapidly, usually within minutes. The normal dose for a new user may be from 10 to 20 mg, with regular users consuming 25 to 50 mg taken orally. Some intravenous users are reported to inject several hundred milligrams at a time and those who have built up a tolerance may

take as much as 5 grams per day. Some types of amphetamines have the ability to create stimulant effects that last up to 12 hours.

The therapeutic uses of amphetamines and related drugs are limited to situations requiring CNS stimulation, like in 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); however, at therapeutic doses there is no association between serious cardiovascular events and amphetamine use.

How amphetamines work

Amphetamines have a chemical structure that mimics the structure of the neurotransmitters adrenaline (epinephrine), noradrenaline (norepinephrine), and dopamine. When amphetamines are synthesized, two mirror image molecules are formed, designated a "D" form (D-amphetamine or dextroamphetamine) and an "L" form (L-amphetamine or levoamphetamine). D-Amphetamine is generally more potent than L-amphetamine, though both forms appear to have biological activity. Upon ingestion of amphetamines, many of the biological processes controlled by adrenaline, noradrenaline, and dopamine are enhanced.

Because amphetamine is not metabolized rapidly, it 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. Amphetamine is well-absorbed from the gut and penetrates freely into the brain. Approximately 30-40% is excreted unchanged into the urine. The plasma half-life can range from 6 to 12 hours, but varies widely depending on urine pH. Amphetamine is usually fully eliminated within 2 days of the last oral dose.

Amphetamines affect the brain by a mechanism similar to that of cocaine. Amphetamines affect the binding of neurotransmitters to the adrenergic receptors, which are part of the sympathetic nervous system responsible for the "fight or flight" response. Normally, neurotransmitters are released from one neuron to interact with adrenergic receptors on another neuron to increase activity of the organ serviced by that nerve. This initiates processes like vasoconstriction and increased heart rate associated with "fight or flight". Amphetamines are indirect-acting agonists of the adrenergic receptors. Amphetamines work to increase the overall concentrations of neurotransmitters available to activate these receptors by increasing neurotransmitter release and/or stopping processes that remove the neurotransmitters (reuptake and metabolism). This results in prolonged stimulant responses, even when the body should be in a resting state. This differs slightly from cocaine, which only blocks neurotransmitter reuptake.

Amphetamines target the dopamine-signaling pathways by a similar mechanism. Amphetamines enhance dopamine concentrations, which results in prolonged activation of the dopamine receptors to activate the reward system. This contributes to dependence on amphetamines. Amphetamines also have a similar, though less pronounced, effect on serotonin pathways.

Nerves do not commonly synthesize new neurotransmitter after their release. Instead, under normal conditions, a nerve will reuptake neurotransmitters after their release to recycle their use. Since amphetamines inhibit the reuptake process, high doses of amphetamines taken over an extended period can deplete the nerve terminal of neurotransmitters. After long periods of amphetamine use, recovery cannot occur until neurotransmitter levels are restored in nerve terminals.

Short-term effects of amphetamines

Amphetamines enhance the actions of adrenaline, noradrenaline, and dopamine in the brain and the rest of the body. Amphetamines affect the body by increasing adrenaline and noradrenaline from nerve endings to activate various organ systems. The effects on the heart are significant, causing an increase of heart rate and blood pressure. Neurotransmitter release also causes veins to contract (vasoconstriction), which can further increase blood pressure levels. The increases in heart rate and blood pressure are dose-dependent and may be very high, causing palpitations and chest pain. Amphetamines can cause urinary retention by contracting the sphincter and relaxing the bladder; it can also affect the gastrointestinal system, causing nausea, vomiting, diarrhea, abdominal cramps, loss of appetite, and weight loss.

The effects of amphetamines on the brain result from the release of adrenaline, noradrenaline, and dopamine. 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 not interest them. This effect makes these drugs popular among post-secondary students and truck drivers, as they are able to continue studying or driving without distraction or fatigue.

The euphoria, appetite suppression, thirst suppression, and reduced need for sleep are likely mediated by the dopamine “reward pathway” in the brain. Overlying all of these effects is a sense of excitement caused by noradrenaline. Euphoria occurs with most doses of the drug and with most routes of administration. A “rush” is an intense sudden feeling of extreme pleasure, which may occur if the drug is taken intravenously, but not as likely if the drug is taken orally. Many users cannot describe the sensation except to profess that it is very pleasant.

Long-term effects of amphetamines

Chronic amphetamine users are likely to build tolerance to the drug, meaning they need greater amounts to achieve the same effect. Prolonged use of amphetamines can promote episodes of psychosis, resembling the paranoid form of schizophrenia. Amphetamines reduce the need for sleep and sleep can be postponed for several days, leading to exhaustion. Because amphetamines negatively affect appetite, long-term users may suffer from malnutrition, pale complexion, and rotting teeth.

Thinking patterns are often altered by high doses and extended use of amphetamines, and social contacts can become strained due to secretive behaviour. Paranoid behaviour can occur and, coupled with increased aggression, may lead to violence. Mood swings and mental instability may also occur.

Other effects of long-term amphetamine use may include trouble breathing, rapid heart rate, seizures, coma, loss of coordination, and ulcers. 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.

Extremely high doses of amphetamines can cause rupture of blood vessels in the brain (brain hemorrhage), heart failure, hyperpyrexia (extremely high body temperature), seizures, and coma. Symptoms of overdose can include kidney failure, acute psychosis accompanied by paranoia and delusions, as well as fluid build-up in the lungs.

Amphetamine misuse is significantly associated with death from 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.

Specific amphetamines

MDA (methylenedioxyamphetamine)

MDA is classified as both an amphetamine and a hallucinogen. The structure of MDA is similar to both mescaline and the amphetamine MDMA. As a typically brown or white powder, MDA is sold loose, in capsules, or as an amber liquid. The common dose is 100 mg, which is usually swallowed. Other drugs, such as PCP (phencyclidine), are frequently sold as MDA.

The effects of MDA occur in 30 to 60 minutes and last about eight hours. Users report a sense of well-being along with heightened tactile sensations and emotions. Higher doses produce effects that include dilated pupils, high blood pressure, and dry nose and throat. Overdoses can cause death.

MDMA (3,4-methylenedioxymethamphetamine "molly", "M", "ecstasy,", "X","XTC")

MDMA is classified as both an amphetamine and a hallucinogen. MDMA is similar in structure to MDA and is sold as white or off-white powder. It is usually taken orally in doses of 75 mg to 100 mg. MDA and MDMA have both stimulant and psychedelic effects.

The effects of MDMA are similar to MDA, but are somewhat milder and of shorter duration. Long-term effects of MDMA use including sleeping difficulties, high blood pressure, jaundice, liver problems, panic attacks, as well as memory and attention deficits.

DOM (2,5-dimethoxy-4 methlyamphetamine, "STP")

DOM is classified as both an amphetamine and a hallucinogen. DOM is similar to MDA but is more potent (usual dose 3 to 10 mg) and longer lasting (16 to 24 hours). Because it has a reputation for creating "bad trips", use of DOM is now rare compared to use of other hallucinogenic amphetamines.

PMA (paramethoxyamphetamine, "death", "Dr. Death") & PMMA (paramethoxymethamphetamine)

PMA and PMMA are classified as both amphetamines and hallucinogens. Although rare, PMA and PMMA are two of the most dangerous stimulants. Sold as beige, white or pink powder and taken orally, these drugs are often misrepresented as MDA. Doses that may be considered safe for MDA are highly toxic when the same amount of PMA or PMMA is ingested.

The hallucinogenic effects of PMA and PMMA are similar to those of LSD; physical effects of PMA and PMMA resemble MDMA and includes racing pulse, high blood pressure, increased and labored breathing, high fever, erratic eye movements, muscle spasm, and vomiting. At high doses, convulsions, coma and death can result. Between 2011 and 2012, there were 27 deaths in Alberta and British Columbia related to ecstasy containing PMMA.

Methylphenidate

Paradoxically, CNS stimulants (dextroamphetamine, methylphenidate) are used in the treatment of attention deficit/hyperactivity disorder (ADHD), and narcolepsy. One of the most common brand names of methylphenidate is Ritalin®. Methylphenidate is a piperidine derivative that is structurally related to amphetamines. New formulations contain both immediate-release and extended-release methylphenidates which allow for once-daily dosing, as the dose is released over 8 to 10 hours. Use of methylphenidate for ADHD is associated with predictable side effects: appetite loss, insomnia, headache, abdominal pain, and anxiety.

Methamphetamine

Methamphetamine is a derivative of amphetamine that was first synthesized from ephedrine in Japan in 1893. 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.

Methamphetamine can be taken the same ways as amphetamine: orally, by snorting, or by intravenous injection. Methamphetamine is also often smoked; the drug is vaporized and the fumes are inhaled. Inhaling gets the drug into the bloodstream very rapidly. Transport of the drug to the brain occurs in about eight seconds, which is faster than intravenous injection. It is possible to feel a very powerful rush after smoking methamphetamine.

The initial high from smoking or injecting methamphetamine usually lasts only a few minutes, but is very intense. Snorting or orally ingesting methamphetamine leads to a longer, but less intense, high. Some people may repeatedly use amphetamines and methamphetamine for several days in order to stay high. Methamphetamine for smoking is re-crystallized to form large crystals known as "ice" or "crystal meth".

Methamphetamine is synthesized in illegal laboratories using amphetamine produced by reducing ephedrine or pseudoephedrine, a common ingredient in over-the-counter cold medications. While much of the methamphetamine on the streets comes from underground labs, a significant amount is now being imported from Mexico and other countries. In 2016, Canada seized 547.7 kilograms of

methamphetamine, an increase of approximately 330% from 2015. In Alberta, the Alberta Law Enforcement Response Team (ALERT) reported that methamphetamine accounted for 40% of the drugs they seized in 2017-2018. In 2017, Edmonton had the highest methamphetamine possession rates among major Canadian cities.

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 or toxic chemicals.

Methamphetamine is often made with commonly available and inexpensive chemicals, and can differ in composition and strength between batches. Methamphetamine has also been found mixed with other dangerous drugs, such as MDMA and fentanyl. In Alberta, around 42% of all 2017 fentanyl-poisoning deaths had methamphetamine listed as a contributing factor. Between 2014 and 2016, methamphetamine had the second largest increase (500%) after cocaine in fentanyl deaths involving other substances and rose 2.6 times from 2015 to 2017.

Methamphetamine is not available legally in Canada. It is available in the United States by prescription only for treatment of ADHD; however, many doctors no longer prescribe it due to the high potential for abuse and addiction.

How methamphetamine works

Compared to amphetamine, methamphetamine has a greater impact on CNS activity; it is stronger and acts more quickly. 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 effects in the CNS. Although anecdotal stories attribute more CNS effects to methamphetamine than amphetamine, studies fail to show any difference between the two when comparing subjective effects and peripheral effects.

Like amphetamine, methamphetamine is chemically similar to adrenaline, noradrenaline, and dopamine and. Methamphetamines also follow a similar mechanism of action to amphetamine by increasing neurotransmitter release leading to prolonged activation of receptors. The excess of dopamine in the brain causes feelings of pleasure and euphoria, whereas the excess of adrenaline and noradrenaline in the brain are responsible for causing the user to feel more alert. This results in strong, prolonged effects.

Short-term effects of methamphetamine

Methamphetamine can have an array of mental and physical short-term effects. People who use this drug usually experience a temporary rush of well-being, as well as higher energy, increased alertness, a rapid flow of ideas and speech, a sense of inflated confidence, and decreased appetite. Short-term effects can also include dry mouth, dizziness, stomach ache, muscle twitching or teeth grinding, shortness of breath, increased blood pressure, anxiety, fainting, and fast or irregular heartbeat. These effects have been known to increase as dosages become greater and can last up to 12 hours.

At high doses, aggressive thoughts/behaviours, tachycardia, and hypertension have been shown to occur. Methamphetamine can also increase body temperature which can be lethal in overdose situations.

Long-term effects of methamphetamine

Long-term methamphetamine use has been associated to an increased risk of dental caries, teeth grinding, and tooth fractures. Due to suppressed appetite, users may become unhealthily thin and undernourished, impacting the strength of bones. Skin infections, as well as skin-picking may result from meth use as tactile hallucinations are common features, especially among those with methamphetamine psychosis. Continual amphetamine or methamphetamine use can also lead to cardiovascular complications, including heart disease, cardiomyopathy, and stroke.

Research studies using magnetic resonance imaging (MRI) technologies have shown that methamphetamine use is also associated with abnormalities in some parts of the brain, which are known to be associated with depressive and generalized psychiatric symptoms (e.g., right prefrontal cortex, corpus callosum). Repeated use of methamphetamine can lead to neurocognitive impairment, impacting one's ability to learn, remember, and focus. Some studies have suggested that methamphetamine use increases the likelihood of Parkinson's disease, which is a neurodegenerative disorder.

Regular methamphetamine use is associated with a high incidence of chronic psychotic symptoms, including hallucinations, delusions, and odd speech. The length to which these symptoms occur varies among users and dosages; however, approximately 50% of cases do not require long-term antipsychotic medication and psychotic symptoms usually disappear following abstinence. With this being said, meth use also decreases impulse control, which can make it difficult for users to remain abstinent.

Methamphetamine produces the same effects of amphetamine and the mechanism of action is the same (i.e., increases dopamine); however, it appears that methamphetamine may be more toxic in long-term use than amphetamine. Studies of chronic methamphetamine users have shown that changes in the dopamine system can occur, which is associated with impaired verbal learning and reduced motor speed. Support cells in the brain called microglia are also damaged by methamphetamine use, causing the microglial cells to attack healthy neurons. 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 are at risk of contracting infectious diseases, such as hepatitis and HIV/AIDS.

Amphetamines and pregnancy

Amphetamines used during pregnancy can impact unborn children, as the drug can pass from the mother's circulatory system to the infant's circulatory system, and end up in the umbilical cord, placenta and amniotic fluid. Maternal vasoconstriction and hypertension from amphetamine use can lead to fetal hypoxia, an increased risk for placental hemorrhage, obstetric complications, preterm labour, and low

birth weight. Adverse effects on the newborn child can include abnormal sleep patterns, tremors, poor feeding, hypotonia (low muscle tone known as “floppy baby syndrome”), fever and vomiting. Amphetamine also accumulates in breast milk, causing irritability, and poor sleep patterns. Use of amphetamine should be avoided during pregnancy and lactation.

Tolerance and dependence

Amphetamines and methamphetamine are highly addictive and tolerance to these drugs can build up quickly in regular users. This means that more of the drug needs to be used to create the desired effect. Dependent users may transition from smoking to injecting the drug so they can achieve the high that satisfies them and reduces withdrawal symptoms.

Because these drugs interact with the body’s “reward system” and decrease one’s impulse control, dependence on the drug can occur rapidly and be hard to overcome.

Withdrawal and Treatment

People who stop using amphetamines, including methamphetamine, will likely experience symptoms of withdrawal. Many will feel extremely fatigued and will have a strong desire to sleep. They may become depressed, especially if they were chronic or heavy users.

In some cases, cessation may induce a syndrome called “amphetamine-type stimulant withdrawal syndrome”, which can cause disrupted sleep, depressed mood, anxiety, cognitive impairment, excessive hunger, and reduced energy. Sudden abstinence of the drug may also lead to agitation, suicidal ideation, and severe anxiety.

Treatment for withdrawal may include the use of very mild stimulants, medications for depression, as well as medications for psychotic symptoms or seizures.

Who uses amphetamines?

According to the 2015 Canadian Tobacco, Alcohol and Drug Survey (CTADS), it was estimated that there were roughly 59,000 methamphetamine users in Canada. Data from the 2017 Canadian Student Tobacco, Alcohol and Drugs Survey (CSTADS) reported that 1.2% of Canadian grade 7-12 students had used methamphetamine in the past year. Alberta Health Services reported that between 2016 and 2017, 7,475 people sought treatment for methamphetamine use in the past 12 months. Between 2012 and 2017, Ontario reported a 5.4% increase in the number of individuals seeking treatment for methamphetamine use.

National survey data estimates that 0.2% of the general population used non-medical prescription stimulants. In 2016–2017, 3% of Canadian students in grades 7 to 12 reported using stimulants, including medications used to treat attention deficit hyperactivity disorder (ADHD). Data drawn from 41 Canadian post-secondary institutions indicated that 4.5% of post-secondary students had used

stimulants that were not prescribed to them in the past 12 months. Other studies conducted on post-secondary campuses have indicated rates as high as 5.9%.

According to the 2015 Canadian Tobacco Alcohol and Drugs Survey (CTADS), the prevalence of ecstasy use among Canadian youth aged 15 to 24 had risen 0.4% since 2013. Among grade 7 to 12 students in Canada, past year use was reported to be 2.4%, and 4.0% in grade 10 to 12 students.

Amphetamines and the law

Amphetamine and methamphetamine are Schedule I drugs under Canada's Controlled Drugs and Substances Act. It is illegal to possess, produce, sell, or import amphetamines or their derivatives.

If caught in possession of a Schedule I drug, first time offenders may face a fine of up to $1,000 and/or imprisonment for up to six months. For subsequent offences, the penalty is a fine of up to $2,000 and/or imprisonment for up to one year. For more serious indictable offences, the penalty is imprisonment for up to 7 years.

Trafficking, possession for the purpose of trafficking, production, and importing and exporting amphetamines are serious offences and are punishable up to life imprisonment. In 2012, Bill C-10 introduced mandatory minimum sentences for trafficking ecstasy when violence (one year) or proximity to a school (two years) are present.

Driving while impaired by methamphetamine is also a criminal offence and oral drug screening devices can be used to test for the presence of methamphetamine.

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