The Use and Abuse of Psychostimulants

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ABBREVIATIONS: DAWN = Drug Abuse Warning Network; ED = emergency department; MDA = methylenedioxyamphetamine; MDMA = methylenedioxymethamphetamine; OTC = over the counter.

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Drug use has become a significant medical and social problem in the United States. Toxicological analysis of biological specimens from individuals is generally accepted to be the most objective method for determining drug use and abuse. As a science, forensic toxicology deals with the medico-legal implications of drug use, misuse, and abuse. This may include the following: criminal penalties imposed for the distribution, possession, and use of illicit drugs; assessment of drug impairment in human performance (behavioral) toxicology; assessment of drug toxicity as a contributing factor in the cause and manner of death in postmortem forensic toxicology cases; or detection of drug use in workplace drug testing programs.

Psychostimulants include a diverse class of drugs exhibiting central nervous system stimulant properties, and have a high abuse potential. Drugs in this class include illicit drugs, prescription medications, over the counter (OTC) preparations, and dietary supplements. Clinical indications for therapeutic use include treatment of narcolepsy, attention deficit disorder, and as an appetite suppressant in the treatment of obesity. Pharmacological effects of psychostimulant drugs include the ability to increase alertness, relieve fatigue, decrease appetite, elevate mood, increase confidence, and produce euphoria. Abuse of psychostimulant drugs may lead to tolerance that is exhibited by the need of higher doses of the drug to produce the same desired effects. Consequently, users may try to intensify the drug's positive effects by increasing the drug dosage, taking it more frequently, or changing the route of administration leading to the possibility of drug abuse, misuse, or toxicity. The most common psychostimulant drugs of forensic interest with documented abuse potential are listed in Table 1. These drugs are characterized as either sympathomimetic or hallucinogenic amines with psychostimulant effects. Phentermine, fenfluramine, and diethylproprion are related prescription medications used as appetite suppressants. There is little epidemiological evidence to support the abuse of these three psychostimulant drugs. However, their use is not recommended for individuals with current or past drug abuse problems.

TRENDS IN PSYCHOSTIMULANT ABUSE

Statistics released by the Drug Abuse Warning Network (DAWN) reflect the reporting of specific illicit, prescription, and OTC drugs that are linked to drug abuse in visits to hospital emergency departments (EDs). The data are presented in two issues of The Dawn Report.[1,2] In 2002, there were an estimated 670,307 ED visits related to drug abuse in the continental U.S. This translates to 0.7% of all visits. Over the past nine years, reports of drug-related ED visits associated with drugs grew at roughly twice the rate of total ED visits. From 1994 to 2002, ED visits related to drug abuse rose 29%, while total ED visits rose only 15%. In 2002, about half (54%) of all visits related to drug abuse involved multiple drugs. Four illicit drugs including cocaine, marijuana, heroin, and methamphetamine accounted for 36% of the drugs involved in these visits.

Cocaine continues to be the most frequently mentioned illicit substance reported to DAWN by hospital EDs nationwide.[2]

Illicit use of psychostimulant drugs reported in 2002 included 199,198 cases for cocaine; 17,696 cases for methamphetamine; and 4,026 cases for methylenedioxymethamphetamine (MDMA). From 1995 to 2002, the rate of cocaine-related ED visits increased 33% whereas the rate of methamphetamine-related visits remained stable. Visits involving cocaine exceeded the number of visits for any other illicit drug in 18 of the 21 metropolitan areas monitored by DAWN. Western metropolitan areas including San Francisco, Seattle, San Diego, Los Angeles, and Phoenix had the highest rates of methamphetamine ED visits. According to the National Drug Threat Assessment 2003, prepared by the National Drug Intelligence Center, cocaine is the primary drug threat in the U.S. because of its high demand and availability, expanding distribution to new markets, high rate of associated toxicity issues, and relation to violence.[3]

According to 2002 estimates from DAWN, there were almost 39,000 ED visits related to drug abuse involving amphetamines and methamphetamine. In more than half of these visits the age of the patient was 18 to 34.[1,4] In the report, the category of amphetamines included dextroamphetamine, methcatinone, and methylenedioxyamphetamine (MDA). Visits involving the amphetamines and methamphetamine increased 54% between 1995 and 2002.[4] Data also show that methamphetamine abuse, which was predominately located on the west coast of the U.S. may be spreading eastward. This was demonstrated by an increase in ED visits for amphetamines and methamphetamine in several metropolitan areas in the Midwest, South, and Northeast. However, even though there was an increase, the overall numbers of related visits in these areas remained low. More than 60% of the amphetamine and methamphetamine visits also involved other drugs. Marijuana, alcohol, cocaine, benzodiazepines, opioid pain relievers, and heroin were the most frequently reported substances in combination with amphetamines and methamphetamine.

The term 'club drugs' is used to describe illicit recreational drugs that have gained popularity in recent years at nightclubs or large dance parties called 'raves'.[5,6] Club or rave drugs include stimulants, depressants, and hallucinogenic substances frequently taken for their psychedelic and/or euphoric effects to enhance dancing, auditory, and visual perceptions. Drugs in this class include the following: lysergic acid diethylamide (LSD), gamma-hydroxybutyrate (GHB), ketamine, flunitrazepam (Rohypnol), and MDMA or ecstasy. For the year 2002, club or rave drugs were implicated in approximately 1.2% of all ED visits related to drug abuse that were reported to DAWN.[6] Some of these visits involved multiple club drugs, that were frequently used in combination with alcohol, marijuana, cocaine, and heroin. The incidence of ED visits involving MDMA is increasing based on data provided to DAWN.[1,6] In 1994 MDMA was mentioned 253 times. In 2001 the number of times MDMA was mentioned increased to 5,542 and then subsequently declined to 4,026 in 2002. In 2002, MDMA was the most common club drug detected in drug related ED visits, with 75% of these visits involving patients 26 years or younger.

Methylphenidate (Ritalin®), a schedule II substance, is associated with patterns of abuse similar to other psychostimulants.[7,8] Since it produces many of the same pharmacological effects as cocaine or the amphetamines, a high potential for abuse of this drug also exists. The primary legitimate medicinal use of methylphenidate is for the treatment of attention deficit hyperactivity disorder (ADHD) in children. The increased therapeutic use of this drug for treatment of ADHD is paralleled by an increase in the abuse of the drug among adolescents and young adults due to its increased availability. A recent survey of Wisconsin schools found that most schools did not control how Ritalin was stored or dispensed on school property, making it easy to steal, give away, or sell the drug.[9] Approximately 16% of the students surveyed reported that they had been asked to sell, give, or trade their Ritalin to other students. This pattern of abuse is characterized by increasing

Table 1. Common psychostimulant drugs of forensic interest

Drug	Type
Amphetamine	Sympathomimetic stimulant
Cocaine	Sympathomimetic stimulant
Ephedrine	Sympathomimetic stimulant
Methamphetamine	Sympathomimetic stimulant
Methylenedioxyamphetamine (MDA)	Hallucinogen
Methylenedioxymethamphetamine (MDMA)	Hallucinogen
Methylphenidate	Sympathomimetic stimulant

doses, frequent episodes of binge use followed by depression, and the desire to continue the use of the drug despite medical and social consequences. The abuser may change the route of administration of the drug from oral to snorting or intravenous injection to intensify the effects.

Recent years have seen an increase in the use of dietary supplements, not only to promote good health, but also as a means of obtaining a 'natural' legal high.[10] Stimulants are the most commonly abused dietary supplements used for this purpose. Manufacturers of stimulant dietary supplements market them as natural and safe alternatives for enhanced mental alertness, weight loss, bodybuilding, and athletic performance enhancement. See the table in reference 10 for information on common dietary supplements. Most stimulant dietary supplements contain one or a combination of the following ingredients: ephedrine, pseudoephedrine, synephrine, caffeine, or yohimbine. Herbal Ecstacy®, Metabolife®, and Xenadrine® are examples of OTC dietary supplements containing ephedrine as the selected stimulant. Even though these products are probably safe in most cases when used as directed, a potential for abuse and toxicity still exists as with the other illicit, prescription, and OTC psychostimulants. According to the Toxic Exposure Surveillance System of the American Association of Poison Control Centers, ephedrine products accounted for 77% of the cases of abused or misused dietary supplements in 2002.[10] Due to the increased abuse of stimulant dietary supplements with potential risk of serious adverse events including arrhythmias, seizures, heart attacks, and strokes, the FDA prohibited the sale of all dietary supplements containing ephedrine as of April 12, 2004.

PHARMACOKINETICS OF ILLICIT PSYCHOSTIMULANTS

Cocaine, an alkaloid, is a naturally occurring central nervous system stimulant found in the South American plant *Erythroxylon coca.* For medicinal use as a local anesthetic, cocaine is administered topically as a hydrochloride in 10% to 20% solutions for the membranes of the throat and nose or in 1% to 4% solutions for ophthalmologic procedures.[11] Street forms of cocaine are sold as either hydrochloride salt or crack. Crack is cocaine that has been processed from cocaine hydrochloride to a free base for smoking. Common routes of administration include intranasal, intravenous, or smoked. Oral is not the preferred route of administration because, when taken orally, the first-pass effects result in low drug bioavailability and reduced euphoric effects due to inefficient delivery to the brain.[12] The intravenous route of administration produces 100% drug bioavailability whereas bioavailability by the intranasal and smoked routes can be quite variable. Due to the convenience of administration, and the rapid, intense onset of effects from the smoked route, intranasal and smoked routes are most commonly used for cocaine self-administration.

Cocaine is metabolized to benzoylecgonine and ecgonine methyl ester, the two major metabolites, by different mechanisms.[12,13] Cocaine is metabolized in the blood to benzoylecgonine via spontaneous hydrolysis at a physiological and alkaline pH and metabolized to ecgonine methyl ester via enzymatic hydrolysis by pseudocholinesterase and liver esterases with the reaction rate being dependent on drug concentration. Both benzoylecgonine and ecgonine methyl ester are further metabolized to ecgonine. When cocaine is used in combination with ethyl alcohol, a pharmacologically active metabolite, cocaethylene (ethylcocaine), is produced by the transesterification of cocaine with ethyl alcohol. Therefore, in cases of simultaneous alcohol and cocaine use, cocaethylene concentrations should also be considered when interpreting results for assessment of toxicity. Anhydroecgonine methyl ester has been identified as a unique metabolite in the postmortem blood and urine specimens of persons after smoking cocaine.[14] Benzoylecgonine can be detected in blood within 15 to 30 minutes after intravenous, intranasal, and smoking routes of administration. Detection of benzoylecgonine in the urine can provide a means of estimating an approximate window of time of the use of cocaine. Benzoylecgonine can be detected in urine for two to four days after use of cocaine depending on dose, frequency of use, urine pH, and clearance. Detection has been reported seven to sixteen days after chronic compulsive cocaine use.[12,13]

Ecstasy or MDMA is the most prominent member of the methylenedioxy-substituted amphetamines (hallucinogenic amines) to gain popularity for illicit recreational drug use.[5,6] At normal doses, the effects include mild to moderate central nervous system stimulating effects as well as enhanced feelings of empathy, closeness, and response to intimate touch, which is why it is also classified as an empathogen-entactogen.[13,15] Currently, there is no legitimate approved therapeutic use for MDMA in the U.S. The manufacture of MDMA is typically in clandestine laboratories, primarily in Western Europe where it is easier to obtain the precursor chemicals. It is estimated that 80% of the MDMA consumed worldwide is produced in Belgium, Luxembourg, and the Netherlands. The drug is typically supplied in tablet form with an embossed logo, usually white but also available in a variety of colors. Most frequently, MDMA is administered orally in tablet or capsule form in doses of 100 mg to 150

mg. A popular variation on oral ingestion is 'parachuting', in which a tablet is crushed, wrapped in tissue paper, and swallowed for more rapid absorption.[15] This is sometimes supplemented with an uncrushed tablet to achieve both rapid onset as well as a sustained effect.

The onset of action following oral administration is 30 to 60 minutes.[5] MDMA has a half-life of approximately seven hours and undergoes N-demethylation to the active metabolite MDA, which is the metabolite usually detected in blood. Illicitly produced MDMA is a racemic mixture. The enantiomers exhibit differences in pharmacological activity as well as affinity for the enzyme responsible for their metabolism.[15] MDMA also exhibits nonlinear pharmacokinetics suggesting that beyond a certain threshold, small increases in dose may result in larger increases in blood concentrations with greater risk of toxicity.[15] About 65% of the dose is eliminated in the urine as parent drug and 7% as MDA.[11] Mono- and di-hydroxy metabolites are excreted in the urine as conjugates.

Amphetamine and methamphetamine have limited legitimate pharmacologic use. Methamphetamine is the more potent of these two drugs, producing greater central nervous system effects and having a longer duration of action, most likely due to its greater ability to penetrate the central nervous system (CNS). Current therapeutic uses of these drugs are for the treatment of narcolepsy, obesity, and ADHD. Amphetamine can also be detected as a metabolite of other drugs including fenethylline, fenproporex, and methamphetamine. Illicit preparations of amphetamine usually contain a racemic mixture.[11] Clandestine laboratories use phenylpropanolamine as a precursor to amphetamine manufacture. Because of its ease of manufacture and ready availability, methamphetamine has become the sympathomimetic amine of choice among stimulant abusers. In the U.S., methamphetamine is the most frequently encountered clandestinely produced controlled substance.[13] Methamphetamine is easily synthesized from ephedrine. In the U.S., l-methamphetamine (under the label l-deoxyephedrine) is the active constituent of the OTC decongestant Vicks Inhaler containing approximately 50 mg of drug.[11, 16] This isomer is reported to have less CNS activity and greater peripheral sympathomimetic activity than the d-enantiomer. l-methamphetamine can also be detected as a metabolite of selegiline. d-methamphetamine is a legal prescription drug (Desoxyn®) and a prominent form in many illicit methamphetamine drug preparations available as a water soluble, white, crystalline powder (methamphetamine hydrochloride). Determination of the enantiometric ratio can be useful in determining drug source as illicit, diverted, or licit.[13,16]

Common routes of administration include oral, intranasal, and intravenous. Smoking remains a minor route of administration compared to the others.[16] Methamphetamine users feel a short yet intense 'rush' when the drug is initially administered. In abuse, there is a progression following the start of use, from oral or intranasal routes to intravenous use of the drug. At higher doses, particularly following intravenous use, users typically report intense exhilaration and euphoria, elevated self-esteem, extreme wakefulness, rapid flow of ideas, and increased physical and mental capacity. These effects are perceived as positive and generally encourage repeated administration and produce a binge-type pattern of use.[16] In the binge-type pattern of use, the initial positive effects may be followed by restlessness, irritability, and possibly paranoid psychoses that reinforce the continued use of the drug to maintain the 'high' which eventually will lead to tolerance and psychological dependence.

Methamphetamine undergoes phase I metabolism by N-demethylation to amphetamine, its major active metabolite via the cytochrome P450 2D6 isoenzyme system. Amphetamine is metabolized to a variety of metabolites, including norephedrine and p-hydroxyamphetamine, both of which are pharmacologically active and may contribute to the effects of the drug, especially during chronic usage. Accumulated hydroxylated metabolites have been implicated in the development of amphetamine psychosis.[13] Under normal conditions, up to 43% of a dose of methamphetamine is eliminated unchanged in the 24-hour urine, with about 4% to 7% as amphetamine.[11] Elimination of the sympathomimetic amines is highly pH dependent. Urinary acidification to a pH less than 5.6 decreases the plasma half-life from 11 to 12 hours to 7 to 8 hours whereas alkalinization increases the half-life to 18 to 34 hours.

PSYCHOSTIMULANT TOXICITY

In toxic doses, the psychostimulants begin to produce unpleasant CNS symptoms including anxiety, agitation, hallucinations, delirium, seizures, and death.[13] High-dose, long-term use of stimulants can induce an acute psychotic state in previously healthy individuals. CNS-induced abnormalities, seizures, or muscular hyperactivity may induce hyperthermia. Secondary rhabdomyolysis may also be seen. Cardiovascular manifestations include hypertension, tachycardia, arrhythmias, and myocardial ischemia. Cerebrovascular accidents are precipitated by elevated blood pressure or drug-induced vasospasms.

The clinical picture of stimulant intoxication also includes a wide array of psychiatric symptoms including schizophrenic symptoms, manic-like states, psychoses, depressions (especially during withdrawal), and various types of anxiety conditions including panic states.[8] Psychotic symptoms usually arise with chronic abuse but may also appear acutely with large doses of stimulants. With high doses of stimulants, symptoms of extreme anger in conjunction with aggressive behavior can also be a catalyst for both violence and murder and is especially seen in cases of methamphetamine and cocaine intoxication.[12,16]

Many factors must be considered when interpreting psychostimulant concentrations in blood for an assessment of toxicity since clinical and postmortem studies clearly show that therapeutic, toxic, and lethal concentrations overlap. Tolerance, sensitization, and specimen stability problems are factors complicating the correlation of blood concentrations with assessment of toxicity. Many pathological conditions may predispose an individual to toxicity and possibly death at lower than expected blood concentrations.[17] Sudden death that is attributed to the complications of methamphetamine and cocaine abuse is most commonly associated with cardiovascular effects (disturbances in heart rhythm, heart attacks), but may also be associated with respiratory failure, and neurological effects (strokes, seizure). Seizures are often associated with stimulant abuse but tend to occur only at higher doses. Convulsions are a common sequel to long-term and high dose use that is associated with typical abuse patterns.

Cocaine-induced excited or agitated delirium is an example of a toxic response to cocaine that is frequently associated with death. This syndrome is associated with severe hyperthermia, extreme agitation and delirium, respiratory arrest, and sudden death. These individuals exhibit extreme strength in combination with bizarre and/or violent behavior.[12]

Use of methamphetamine can cause damage to the brain that is detectable months after the use of the drug. The damage to the brain is similar to damage caused by Alzheimer's disease, stroke, or epilepsy.[18]

Rave party attendees who ingest MDMA are at risk of dehydration, hyperthermia, and heart or kidney failure. These risks are due to a combination of the drug's stimulant effect that allows the user to dance for long periods of time in the hot and crowded environment of rave parties. The combination of crowded all-night dance parties and MDMA use has been reported to cause fatalities.[5,15]

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