Chapter 33

Abuse of Magic Mushroom, Peyote Cactus, LSD, Khat, and Volatiles

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INTRODUCTION

Magic mushroom is a common name given to various species of psychedelic fungi, which are used for recreational purpose. Hallucinogenic mushroom, cactus such as peyote cactus, and plants were used to induce altered state of consciousness in healing ritual and religious ceremonies during ancient pre-Columbian Mesoamerican culture. Maya and Aztec people used magic mushroom peyote cactus and other psychedelic plants/fungus in group ceremonies to achieve intoxication. Archeological evidences indicated use of magic mushroom even in 3000 BC and use of peyote cactus in 5000 BC. Today local shamans and healers still use these psychoactive compounds during healing and or religious ceremonies [1]. Under the influence of magic mushroom and peyote cactus, people see images and feel sensations that are unreal. Emotional mood swings and feeling of spiritual energy may also occur under the influence of hallucinogens. These agents produce their biochemical effect by disrupting the interaction of nerve cells and the neurotransmitter serotonin. Despite abuse, hallucinogens are not routinely tested in workplace drug testing. Khat abuse is common among certain ethnic population. Lysergic acid diethylamide (LSD) was a popular drug of abuse in 1960s and is still abused today. Solvent and glue sniffing are also of significant concerns especially among younger people. Death may result from such abuse. Street names of magic mushroom, peyote cactus, LSD, and khat are listed in Table 33.1.

MAGIC MUSHROOM

Magic mushrooms (psychoactive fungi) that grow in the United States, Mexico, South America, and many other parts of the world contain the hallucinogenic compounds psilocybin and psilocin. Psilocybin and psilocin are tryptamines because they have an indole ring structure, a fused double ring consisting of a pyrrole ring and a benzene ring joined to an amino group by two carbon side chains [2]. Active ingredients of magic mushroom are classified under Schedule I controlled substances with no known medical use but these agents have a high abuse potential. Unlawful possession of a Schedule I controlled substance is a felony by law in the United States. In 2005 the UK government changed the law and included dried or cooked psychoactive mushrooms under Class A drugs which are similar to Schedule I drugs in the United States.

In general most species of magic mushrooms appear as brown or dark tan in color. Magic mushrooms are eaten raw, cooked with food or as dried. These mushrooms can be mistaken for other nonhallucinogenic mushrooms or even poisonous mushrooms such as Amanita class. Death from ingestion of Amanita mushroom due to mistaken identity as magic mushroom has been reported [3]. It is dangerous practice to eat wild mushrooms because there are other reports of severe toxicity due to ingestion of toxic wild mushroom as a result of misidentification [4].

Prevalence of Magic Mushroom Abuse

Magic mushrooms were widely abused in the United States during 1960s when LSD was very popular. However, magic mushroom is very popular in rave parties and college parties even today. Hallock et al. based on a survey of 409 college

TABLE 33.1 Street Names of Magic Mushrooms, Peyote Cactus, LSD, and Khat

Abused Agent	Common Street Names
Magic mushroom	Magic mushroom, sacred mushroom, musk, Mexican mushroom, fly-agaric, God's flesh
Peyote cactus	Buttons, mesc, peyote, cactus
LSD (lysergic acid diethylamide)	Acid, blotter, doses, trip
Khat	Chat, khat kat, kafta, qat, qaad, quaadka ghat, mirra, Abyssinian tea, Somali tea, Arabian tea

students reported that 29.5% of responded experimented with psilocybin-containing hallucinogenic magic mushrooms. The number one cause of using magic mushroom was to achieve mystical experience. Interestingly, users did not believe that abuse magic mushroom may negatively impact their academic performance, physical well-being, as well as mental health because they did not believe that magic mushroom use may cause addiction. Magic mushroom users were also prone to abuse other drugs including cocaine, ecstasy, opiates, prescription drugs, and LSD [5]. Another study indicated that an estimated 21 million people in the United States used magic mushrooms in the past while an estimated 11 million people experimented with mescaline. The authors commented that psychedelics continue to be widely used in the United States. Common reasons for such uses include curiosity, mystical experiences, and introspection. Rates of use of psychalics are higher in men than women. Interestingly, psilocybin (magic mushroom) use is more common in younger adults while use of LSD and mescaline are more common among older adults [6].

Riley and Blackman surveyed 174 participants from United Kingdom in 2004 when the sale of magic mushroom was not prohibited. Participants reported infrequent but heavy consumption of magic mushroom (47% used magic mushroom 4−12 times in a year) and the average consumption in one setting was about 12 g. Although hallucinations were experienced by majority of participants, feeling of altering perceptive (41%−74%) and experiencing closer to nature (49%) were also common. However, a significant number of participants also felt negative experience including paranoia (35%) and anxiety (32%) [7].

Active Ingredients of Magic Mushroom

Psilocybin and psilocin are found in over 150 species of mushrooms. The structures of psilocybin and psilocin are given in Fig. 33.1. The group of psychoactive mushrooms includes species of the genera of *Conocybe*, *Gymnopilus*, *Panaeolus*, *Pluteus*, *Psilocybe*, and *Stropharia* [8]. *Panaeolus cyanescecens* usually contains the high amounts of psilocybin and psilocin, while the most common type of magic mushroom in Germany is *Psilocybe semilanceata*, which contains highly variable amounts of psilocybin (<0.003%−1.15%) and psilocin (0.01%−0.90%) [9]. The psilocybin contents in *Psilocybe cubeneis* was 0.44%−1.35% in the cap of the mushroom and 0.05%−1.27% in the stem while the corresponding psilocin concentrations were 0.17%−0.78% and 0.09%−0.30%, respectively, according to a published report. In general hallucinogenic alkaloids are found more in the cap of the mushroom than the stem [10]. Active ingredients and duration of action of magic mushroom are given in Table 33.2.

Pharmacology and Toxicology of Psilocybin

After oral administration, psilocybin, the major active ingredient of magic mushroom (*O*-phosphoryl-4-hydroxy-*N*,*N*-dimethyl-tryptamine), is rapidly dephosphorylated into psilocin (*N*,*N*-dimethyl-tryptamine), an active metabolite under acidic environment of the stomach and in the intestinal mucosa by alkaline phosphatase (and other nonspecific esterases). Conversion of psilocybin into psilocin also occurs during hepatic first-pass metabolism. Psilocybin could therefore be considered as a "prodrug" where most pharmacological activities are due to active metabolite psilocin. Both psilocybin and psilocin are structurally related to neurotransmitter serotonin. Psilocybin and psilocin in their pure form are white crystalline powders. While psilocybin is water soluble, and psilocin is more soluble in lipids. As a result psilocin readily crosses the blood−brain barrier where it exerts psychedelic effect which is similar to LSD [11].

Psychedelic effect of magic mushroom requires ingestion of over 15 mg of psilocybin which produces plasma psilocin levels of 4−6 ng/mL. The onset of psychedelic effect after ingestion of magic mushroom is 20−40 min and maximum effect is observed within 60−90 min. The duration of effect is 4−6 h after oral ingestion while most effects

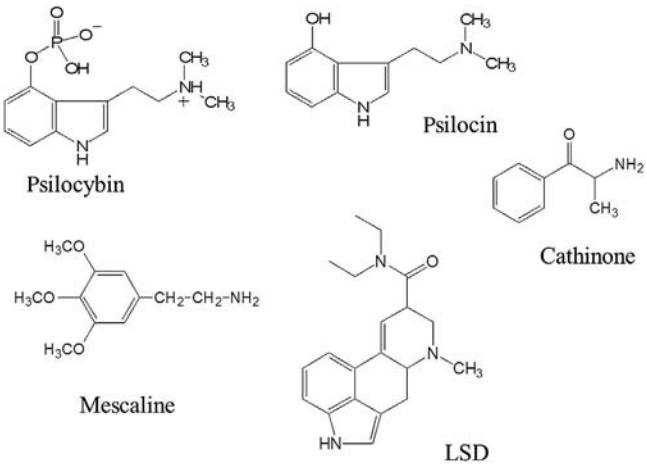

FIGURE 33.1 Chemical structures of psilocybin, psilocin, mescaline, cathinone, and LSD.

TABLE 33.2 Active Ingredients and Duration of Action of Magic Mushrooms, Peyote Cactus, LSD, and Khat

Abused Agent	Active Ingredient	Duration of Action
Magic mushroom	Psilocybin and psilocin, but psilocin is also the active metabolite of psilocybin and is responsible for most psychedelic effects	The duration of effect is 4–6 h after oral ingestion while most effects disappear within 6–8 h.
Peyote cactus	Mescaline	The highest psychedelic effect may be achieved within 2 h of ingestion but the effect may last as long as 8 h.
LSD (lysergic acid diethylamide)	LSD	The duration of effects: 9–10 h.
Khat	Cathinone (major active ingredient)	The stimulatory effects appear approximately 30 min after initiation of chewing khat plant and the effects may last up to 3 h.

disappear within 6–8 h. In general no effect is observed after 24 h [12]. In another study when healthy subjects ingested 0.224 mg/kg body weight of psilocybin (10–20 mg), peak plasma level of psilocin was observed at 105 min (the mean value), and average plasma concentration was 8.2 ng/mL. The average bioavailability of psilocin was 52.7% after oral administration of psilocybin according to this study [13].

Passie et al. detected psilocin in human plasma 30 min after oral administration of psilocybin. Maximum plasma levels were observed between 80 and 105 min while detection window was approximately 6 h. The full psychedelic effects occurred with oral dosage of psilocybin between 8 and 25 mg. The average half-life of psilocin in plasma after oral administration of psilocybin was 2.5 h [14]. In another report the concentration of psilocin in serum was 52 ng/mL and psilocin concentration in urine was 1760 ng/mL in one person who consumed magic mushroom [15].

Psilocin is conjugated in the liver by the action of UDP-glucuronosyltransferase into psilocin-*O*-glucuronide and in this form 80% of psilocin is excreted from the body in urine. In addition, psilocin is also subjected to metabolism through methylation and deamination of into 4-hydroxyindole-3-yl-acetaldehyde. Further oxidation of this metabolite produces 4-hydroxyindol-3-acetic acid and 4-hydroxytryptofol. These minor metabolites account for approximately 4% metabolism of psilocin. Both psilocin (90%–97%) and psilocybin (3%–10%) are detected in human urine mostly conjugated with glucuronic acid. Only 3%–10% psilocin and psilocybin are detected in unmodified form in urine. The majority of pharmacologically active compounds are excreted from the body (mostly urine but also bile and feces) within 3 h after oral administration of magic mushroom. Although these compounds are almost completely eliminated from the body within 24 h, trace amount may be detected in urine even after a week [16].

Poisoning as well as organ damage from use of magic mushroom is common but fatality is less common. Satora et al. reported that in the autumn of 2004 several people were admitted in the hospital after ingesting magic mushroom to experience hallucinatory sensations. Three people had visual hallucination while the fourth person had both visual and auditory hallucinations followed by psychosis [17]. Borowiak et al. described a case where an 18-year-old man suffered from Wolff−Parkinson−White syndrome, arrhythmia, and myocardial infarction as a result of magic mushroom poisoning (*P. semilanceata*) [18]. Raff et al. reported renal failure in a 20-year-old woman who consumed magic mushroom [19]. Bickel et al. reported severe rhabdomyolysis, acute renal failure, and posterior encephalopathy after abuse of magic mushroom (*Psilocybe cubensis*) [20].

There are several reports of fatality due to ingestion of magic mushroom. One person died 6−8 h after ingestion of unknown quantity of magic mushroom. Postmortem toxicology analysis showed very high plasma concentration of psilocin (4000 ng/mL). Another person who was a heart transplant recipient died after consumption of magic mushroom. This individual showed a much lower psilocin concentration of 30 ng/mL in postmortem plasma. However, tetrahydrocannabinol level of 4 ng/mL was also reported in plasma although no other drug or alcohol was present [21]. A fatal case of magic mushroom poisoning in a 27-year-old male has also been reported from Japan [22].

Some of the species of magic mushroom contain phenylethylamine which may cause cardiac toxicity. Beck et al. reported that the amount of phenylethylamine may vary much more than psilocybin in magic mushrooms. Three young men were hospitalized due to adverse reaction from using magic mushroom. The highest amount of phenylethylamine found in the mushroom (*P. semilanceata*) was 146 μg/g wet weights [23].

Mechanism of Action of Active Ingredients of Magic Mushroom

Psilocin, the major metabolite of psilocybin, and psilocybin have predominant agonist activity on serotonin (5-hydroxytryptamine: 5-HT) receptors located within and beyond the central nervous system (CNS) as well as several transporters (serotonin and norepinephrine). Psilocybin and psilocin bind with high affinity to 5-HT_{2A} receptor and such activation occurs in several brain network hubs where cells become more sensitive through depolarization. However, these compounds also bind with 5-HT_{2C}, 5-HT_{1A}, and 5-HT_{1D} receptors with lower affinity. Although these compounds exhibit no apparent affinity for dopamine D_2 receptor, administration of haloperidol, a D_2 receptor antagonist, reduces psilocybin-induced psychotomimesis, raising the possibility of a dopaminergic neuronal transmission involvement [24].

In vitro studies indicate that ketanserin, a 5-HT_{2A} agonist, prevents most psychotic symptoms associated with magic mushroom ingestion indicating that serotonergic system is responsible for psychedelic effect of magic mushroom mediated through activation of 5-HT_{2A} receptor [25]. Study with rat model indicated that effect of psilocin was more intense in male rats than female rats indicating that there may be sex difference in serotonergic response after ingestion of magic mushroom [26].

Therapeutic Potential of Psilocybin

Dysregulations in the serotonin system are associated with alteration in stress hormones, such as cortisol, and mood disorders. Psilocybin has structural similarity with serotonin, and after administration of psilocybin in a clinically controlled situation, executive control network of the brain is activated with subsequent increased control over emotional process and relief of persistent negative emotion. Preliminary data indicates potential therapeutic use of psilocybin in treating drug and alcohol addictions. Psilocybin also has a low risk of dependence [27]. Studies have shown that single oral doses of psilocybin reduced anxious depressed mood, existential distress, and improved quality of life in test subjects [28]. Preliminary results also show that psilocybin may be effective in treating drug-resistant depression [29].

Analysis of Active Ingredients of Magic Mushroom

Psilocin is not routinely tested in urine or blood and as a result toxicology report may be negative in a person who is exposed to magic mushroom. A 28-year-old man with a history of drug and alcohol abuse presented multiple times to the hospital over a period of 2 months (three emergency department visits, two medical flood admission and one intensive care admission), but his toxicology results in urine conducted using gas chromatography/mass spectrometry (GC/MS) were always negative. His symptoms included altered mental status, vomiting, diaphoresis, and mydriasis. The patient later admitted to the nurse that he used magic mushroom. The authors concluded that in the absence of confirmatory tests, but supported by exclusionary and anecdotal data, most likely symptoms of the patient was consistent with magic mushroom toxicity [30].

However, psilocin has a low cross-reactivity with the fluorescence polarization immunoassay (FPIA) of amphetamine for application the AxSYM analyzer (Abbott Laboratories, Abbott Park, IL). Tiscione and Miller described a case of a 20-year-old male driver who drove of the road and struck a light pole and was taken into the hospital. The subject indicated to the emergency personnel that he recently consumed mushroom. Suspecting a case of driving under influence, urine specimen was collected for toxicological analysis. The initial screening with immunoassay showed positive result with amphetamine/methamphetamine FPIA assay. However, analysis of urine specimen using GC/MS did not show the presence of amphetamine, methamphetamine, or related drugs, such as MDMA (3,4-methylenedioxymethamphetamine) or MDA (3,4-methylenedioxy amphetamine). Further investigation identified the presence of psilocin. Using psilocin standard, the authors determined that at a concentration of 50 μg/mL, the cross-reactivity of psilocin with the amphetamine immunoassay was 1.3%. The urine concentration of psilocin decreased rapidly despite the fact that the specimen was stored at 4°C indicating that psilocin is unstable in urine specimen [31].

In general, high-performance liquid chromatography or GC/MS is used for identification and quantification of psilocybin and psilocin in biological specimens. Because psilocin is found mostly in the conjugated form, hydrolysis of the glucuronide derivative prior to extraction is recommended. In one report the authors performed enzymatic hydrolysis using beta-glucuronidase to liberate free psilocin from its conjugated form in urine and then used MSTFA (*N*-methyl-*N*-trimethylsilyltrifluoroacetamide) for derivatization of psilocin to its trimethylsilyl derivative in order to determine the concentration of psilocin by GC/MS [32]. Psilocin can also be analyzed by GC/MS after derivatization with BSTFA reagent (*N*,*O*-bis-trimethylsilyl-acetamide containing 1% trimethylchlorosilane) to covert psilocin to its trimethylsilyl ester (psilocin-1,4-di-trimethylsilyl) (Paul DB unpublished data). The mass spectrum of derivatized psilocin is given in Fig. 33.2. In the mass spectrum, a distinct molecular ion peak at *m/z* 348 was observed. The base peak at *m/z* 290 ($M^+ - 58$) was due to loss of $N(CH_3)_2CH_2$ group from the side chain of the derivatized psilocin.

Psilocin and psilocybin can also be determined using liquid chromatography combined with tandem mass spectrometry (LC-MS/MS). For LC-MS/MS method derivatization prior to analysis is not required. Kamata et al. used LC-MS/MS for analysis of psilocin and psilocybin in magic mushroom samples. The authors used octadecysilyl (ODS) column for liquid chromatographic analysis. The authors observed wide variation in psilocybin (0.18−3.8 mg/g of dry weight) and psilocin (0.60−1.4 mg/g of dry weight) content in four samples of magic mushrooms analyzed [33]. Anastos et al. also used high-performance liquid chromatography for analysis of psilocin and psilocybin in magic mushroom samples. The authors used 4-hydroxyindole as the internal standard [34].

Martin et al. developed a valid method for quantitation of psilocin in plasma using a liquid chromatography−electrospray ionization/tandem mass spectrometry method. The authors used solid-phase extraction using ascorbic acid and nitrogen for drying to protect unstable analyte. A reverse phase C-18 which was heated to 40°C during analysis and 10 μL of the specimen was injected in the column. Separation was achieved with a 10% mobile phase A (methanol with 0.1% formic acid) 90% mobile phase B (2 mM ammonium acetate buffer with 0.1% formic acid, pH 3) at a flow rate of 0.2 mL/min for 7 min, switching to 90% mobile phase A for 4 min to remove lipophilic impurities. The

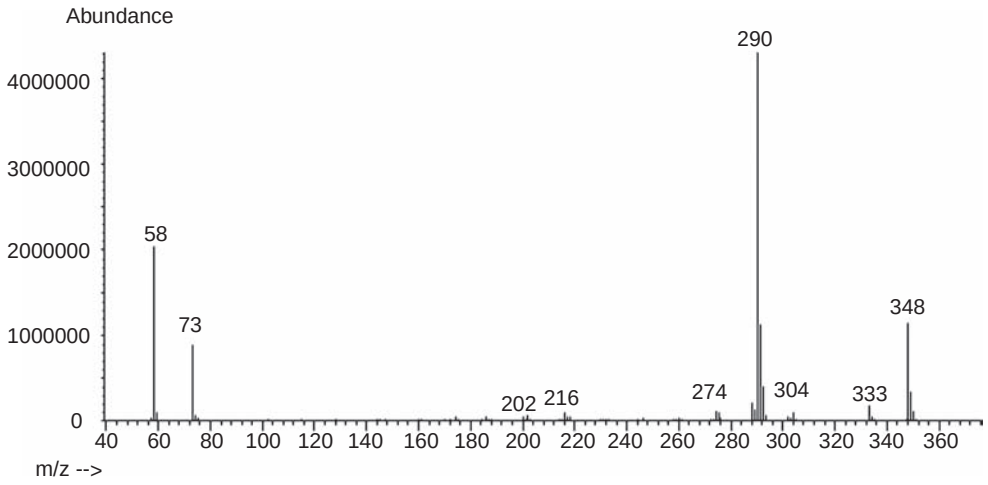

FIGURE 33.2 Mass spectrum of psilocin-1,4-di-trimethylsilyl (trimethylsilyl derivative of psilocin). *Figure courtesy of Dr. Buddha D. Paul, OAFME-Forensic toxicology division of Armed Forces Institute of Pathology, Rockville, MD (now retired).*

TABLE 33.3 Analytical Methods for Analysis of Active Ingredients of Magic Mushrooms, Peyote Cactus, LSD, and Khat

Abused Agent	Analytical Methods
Magic mushroom	Although psilocin at high concentration cross-reacts with antibody of FPIA amphetamine immunoassay, this assay is not sensitive enough for screening of psilocin in urine. In general, both GC/MS- and LC-MS/MS-based assays are used for detection and confirmation of psilocin and psilocybin in biological matrix.
Peyote cactus	Mescaline, the active ingredient of peyote cactus can be detected in urine using a biochip array immunoassays. However, both GC/MS- and LC-MS/MS-based assays are used for detection and confirmation of psilocin and psilocybin in biological matrix.
LSD	Various immunoassays are commercially available (CEDIA, EMIT, KIMS, etc.) for screening in urine. However, both GC/MS- and LC-MS/MS-based assays are used for detection and confirmation of psilocin and psilocybin in biological matrix.
Khat	Cathinone cross-reacts with one antibody used in biochip array immunoassays and also can be analyzed by both GC/MS and LC-MS/MS. However, abuse of bath salts (synthetic cathinones) is significantly more widespread than khat abuse . In some published protocol for detection and confirmation of bath salts in urine, cathinone can also be measured.

column was equilibrated for 10 min and as a result total run time was 21 min. The retention time of psilocin was 6 min. The mass spectrometer was operated in multiple reaction monitoring mode. The authors used deuterated psilocin (psilocin-d_{10}) as the internal standard. The ions monitored were m/z 205 > 58 (quantifier) and m/z 205 > 160 (qualifier) for psilocin. The ions monitored for the internal standard were m/z 215 > 66 (quantifier) and m/z 215 > 164 (qualifier). The limit of detection was 0.1 ng/mL and the limit of quantitation was 0.34 ng/mL. Processed samples were stable in the auto-sampler (cooled at 12°C) for at least 26 h. However, specimens stored at room temperature showed a continuous decline in psilocin concentration leading to loss of 90% in 1 week. Storage in a refrigerator at 4°C improved specimen stability almost for 7 days if fluoride was added as a preservative but freezing of blood samples lead to a not reproducible loss of psilocin. The authors suggested that enzymes involved in psilocin degradation are released from hemolysis that may occur during freezing [35].

Martin et al. also reported a valid method for quantitation of psilocin, bufotenine (a compounds secreted from glands present on skin of toad; genus *Bufo* which has hallucinogenic activity), LSD and its metabolites in serum and urine using a liquid chromatography−electrospray ionization/tandem mass spectrometry method after solid-phase extraction [36]. Analysis of psilocin, bufotenine, LSD, and its metabolites in hair has also been reported [37]. Analytical methods for analysis of active ingredients of magic mushroom are listed in Table 33.3.

USE OF PEYOTE CACTUS

Peyote cactus (*Lophophora williamsii*) is a small spineless cactus that grows in the Southwestern part of the United States and Mexico. Peyote cactus is small and round without sharp spines and the top of the cactus which is above ground is called “crown.” The crown consists of disc-shaped buttons which contain the psychoactive compound mescaline (3,4,5-trimethoxyphenethylamine). Chemical structure of mescaline is given in Fig. 33.1. Mescaline can be extracted from the peyote cactus or buttons can be chewed or soaked in water to produce psychoactive liquid. Native North American Indian recognized the psychotropic properties of peyote as long as 5700 years ago. El-Seedi et al. analyzed two archeological specimens of peyote buttons from the collection of the White Museum in San Antonio using carbon dating and reported that the buttons dated back to 3780−3660 BC. The authors also extracted alkaloids from the buttons and demonstrated the presence of mescaline the active ingredient of peyote [38]. Mescaline is classified as a Schedule I controlled substance but approximately 300,000 members of Native Americans Church can ingest peyote cactus legally as a religious sacrament during all night prayer in the Native American Church based on 1994 the American Indian Religious Freedom Act. The members can attend the prayer ceremonies as regularly as 2−3 times a week or infrequently as once a year. Based on a study of three groups of Navajo Native American Indians, age 18−45 (group 1: 61 Native American Indian church members who regularly ingested peyote, group 2: 36 individuals with pattern of alcohol dependence, and group 3: 79 individuals reporting minimal use of peyote, alcohol, or other substances), the authors found no evidence of psychological or cognitive deficits among Native American Indians using peyote regularly in a religious setting [39].

Native Americans not only used peyote for centuries and for its hallucinogenic effects but also for its medicinal properties. It can be used for treating snake bites, burns, wounds, and rheumatism, as well as for toothache, fever, and scorpion stings [40].

Prevalence of Peyote Cactus Abuse

In general use of peyote cactus is low in the United States. According to a survey completed by 886,088 individuals (surveyed for most years 1995−2010), peyote use among American Indian and general US population remained stable between 1% and 2% [41]. Exposure to peyote is rarely reported to poison control centers. In 2007 a total of 116 peyote/mescaline exposures were reported to US poison control centers out of more than 2.8 million total reported exposures. Therefore exposure to peyote cactus represented only 0.004% of all exposures reported. Out of these 116 exposures, only 32 patients (28%) were treated in health care facilities but no major toxicity or death was reported [42]. Interestingly among youths aged 12−17 years, lifetime use of peyote has been reported to be significantly less (0.4%) compared to other hallucinogens such as ecstasy (3.2%), LSD (3.1%), or psilocybin-containing mushrooms (2.1%) [40].

Based on the review of California Poison Control System database for years 1997−2008, Carstairs and Cantrell identified 31 cases of single substance abuse involving peyote cactus. The majority of these individuals were male (84%) and ages ranged from 14 to 59 years. Thirty (97%) exposures were through oral route: 23 ingested plant material, 6 boiled peyote buttons and drank the resulting tea, and 1 ingested a tablet containing mescaline. The commonly reported symptoms included hallucination, tachycardia, agitation, and mydriasis. One subject reported vomiting. Although five subjects were managed at home, others received medical attention in health care facilities indicating dangers of peyote cactus abuse [40].

Pharmacology and Toxicology of Mescaline

Mescaline [2-(3,4,5-trimethoxyphenyl) ethanamine], a natural alkaloid present in peyote cactus, is a hallucinogen with psychoactive properties. It can be ingested orally for hallucinogenic effects similar to LSD which include deeply mystical feelings, but LSD is approximately 4000 times more potent than mescaline in producing altered state of consciousness [43]. Although mescaline has the lowest potency among naturally occurring hallucinogens (30 times less potent than psilocybin), a full dose (200−400 mg) has a long duration of action. Mescaline is rapidly absorbed from the gastrointestinal tract and onset of effect may be observed within 30 min of ingestion. The highest psychedelic effect may be achieved within 2 h of ingestion but the effect may last as long as 8 h. The plasma half-life of mescaline is approximately 6 h [44]. Higher dosage of mescaline is needed to produce the psychedelic effect not only due to weak potency of mescaline as a hallucinogen but also due to polar nature of the mescaline molecule. Because of poor lipid solubility, mescaline does not easily pass the blood−brain barrier [45]. Active ingredient and duration of action after abuse of peyote cactus are given in Table 33.2.

Although mescaline is metabolized by the liver enzymes, approximately 87% of ingested dosage is excreted in urine within 24 h while 92% is excreted within 48 h [46]. A small amount of mescaline is oxidatively deaminated into 3,4,5-trimethoxyphenyacetic acid [47]. Another minor metabolite of mescaline in human is 3,4-dimethoxy-5-hydroxyphenyethylamine.

After ingestion, mescaline can be detected in blood, urine, and hair. A mother found her boy of 17 years in his bedroom along with a plastic glass containing dark green liquid (tea) with strong bitter odor. The analysis of the liquid by GC/MS showed mescaline concentration of 1.3 mg/L. However, no other drug was detected indicating that the tea was prepared from peyote cactus. No mescaline was detected in the urine specimen but the analysis of hair showed the presence of mescaline at a concentration of 1 ng/mg of hair in the portion of the hair nearest to the scalp. Based on these results, the authors confirmed abuse of peyote cactus in this boy [48].

Mescaline, the active ingredient of peyote, may cause fetal abnormalities [49]. Although rare, severe toxicity, and even death may occur from mescaline overdose. One person who died under the influence of mescaline showed 9.7 μg/mL of mescaline concentration in blood and 1163 μg/mL in urine [50]. Henry et al. described distribution of mescaline in postmortem tissue in an individual who died due to multiple gunshot wounds. The concentrations of mescaline were 2.95 μg/mL in blood, 2.36 μg/mL in vitreous, 8.2 mg/kg in the liver, and 2.2 mg/kg in the brain [51].

Botulism causes skeletal muscle weakness due to bacterial exotoxin that irreversibly blocks the release of acetylcholine from presynaptic motor neurons. Thirteen church members ingested peyote from a communal jar during a ceremony and 2−4 days afterward, three men developed severe clinical symptoms due to botulism. The peyote recovered from the jar containing water was analyzed by the Center of Disease Control and Prevention, Botulism Laboratory,

Atlanta, Georgia, and type B botulinum toxin was identified in the peyote cactus. Fortunately no patient died [52]. Food-borne botulism is due to toxin produced by harmful bacteria *Clostridium botulism* and such bacteria grow in anaerobic condition. Storing peyote cactus with water in a closed jar may provide such condition for bacteria to grow.

Nolte and Zumwalt reported a case where a 32-year-old Native American man with a history of alcohol abuse ingested peyote tea. Later he developed respiratory distress and suddenly collapsed. His antemortem blood specimen showed the presence of mescaline (0.48 μg/mL) and the concentration of mescaline in urine was 61 μg/mL. Other than a trace amount of chlordiazepoxide, no other drug or ethanol was detected in postmortem blood [53].

Mechanism of Action of Mescaline

Although weaker than LSD and MDMA in potency, mescaline is also a serotonin receptor agonist with affinity for 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors [54,55]. However, mescaline is a nonselective serotonin receptor agonist. Interestingly, biochemical and neural patterns are common to both mescaline and morphine. The study has indicated an association between mescaline-induced aggression and abnormal electrical activities in amygdale [56].

Laboratory Determination of Mescaline

The sole active ingredient of peyote cactus is mescaline. Currently there is one commercially available biochip array immunoassay (drugs of abuse array V assay by Randox Corporation) capable of detecting the presence of mescaline in urine specimens. This assay has 11 different antibodies capable of detecting various bath salts (two antibodies), benzylpiperazines, mescaline, various phenylpiperazine (two antibodies), salvinorin, and various synthetic cannabinoids (four antibodies targeted to different compounds). These antibodies are polyclonal antibodies which are immobilized on a chemically modified biochip. This is a competitive immunoassay where drugs if present in the urine specimen compete with horseradish peroxidase-labeled analyte (conjugate) for binding sites on the immobilized polyclonal antibody specific for the drug. After incubation, a single reagent containing 1:1 mixture of luminol/enhancer and peroxide solution is added and chemiluminescent signal is detected (horseradish peroxidase-labeled analyte bound to antibody provides the signal).

Battle et al. evaluated performance of this assay to detect the presence of mescaline in urine by analyzing 526 presumptive positive and 198 randomly selected negative specimens (source of specimens department of defense). The authors also used GC/MS method for confirmation of mescaline if present in the urine specimen. The cutoff level of the immunoassay as suggested by the manufacturer is 6 ng/mL. For GC/M analysis, mescaline was extracted from 1 mL of urine after addition of the internal standard (deuterated mescaline: mescaline-d_9) using solid-phase extraction. The drug along with the internal standard was eluted using 3 mL methylene chloride/2-propanol/ammonium hydroxide (78:20:2 by vol). Then mescaline along with the internal standard was derivatized using pentafluoropropionic anhydride. The mass spectrometer was operated using selected ion monitoring mode scanning *m/z* 181.1, 194.1, and 357.1 for mescaline and *m/z* 190.1, 203.1, and 366.1 for the internal standard. For quantification, *m/z* 181.1 was used for mescaline and *m/z* 190.1 for the internal standard. The limit of quantification was 1 ng/mL. Using GC/MS the authors were unable to confirm the presence of mescaline in any urine specimen presumptive positive by the immunoassays. The authors concluded mescaline use among US military personnels is rare. Therefore routine monitoring of mescaline during drug of abuse testing is not warranted at this time [57].

There are other reports of GC/MS analysis of mescaline in biological matrix without derivatization. Henry et al. used a GC with nitrogen phosphorus detector as well as GC/MS for analysis of mescaline in postmortem blood and tissue. The authors extracted mescaline from blood or tissue specimens using butyl chloride. For identification and qualitative analysis of mescaline, the authors operated mass spectrometer in the selected ion monitoring mode. The primary ion used for positive identification was *m/z* 182 with secondary ions at *m/z* 167 and 181. For quantitative analysis, the authors used GC combined with nitrogen phosphorus detector [51]. The electron impact mass spectrum of mescaline is shown in Fig. 33.3. A distinct molecular ion peak was observed at *m/z* 211.

Mescaline can also be analyzed by LC-MS/MS. In one study the authors developed a protocol for analysis of mescaline in urine using LC-MS/MS. The authors used reverse phase C-18 column (5-μm particle size) and methanol gradient in ammonium acetate buffer for the mobile phase. The authors also used deuterated mescaline as the internal standard. Among 462 urine samples collected from young people with alcohol or drug problem, 32% specimens were positive for illicit drugs but none for mescaline [58]. Analytical methods available for analysis of active ingredient of peyote cactus are given in Table 33.3.

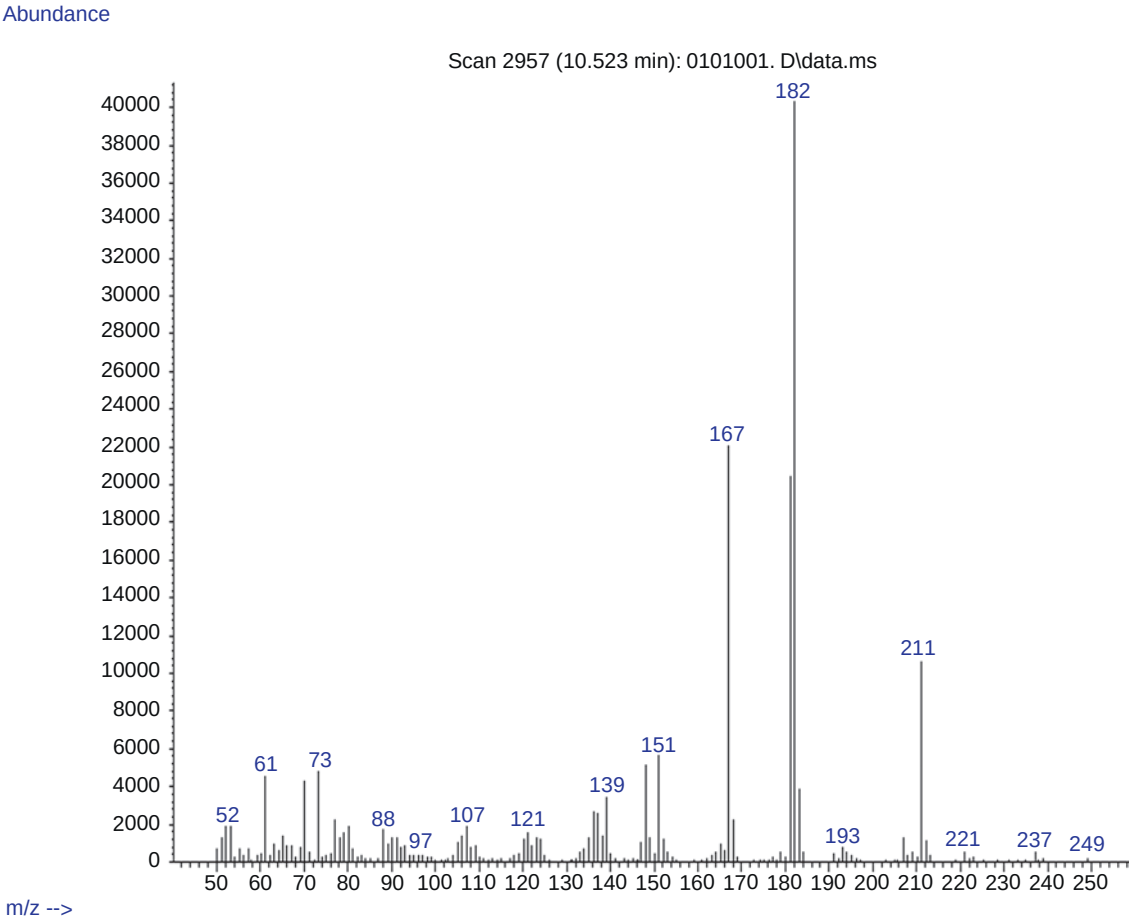

FIGURE 33.3 Mass spectrum of mescaline. *Figure courtesy of Dr. Buddha D. Paul, OAFME-Forensic toxicology division of Armed Forces Institute of Pathology, Rockville, MD (now retired).*

ABUSE OF LYSERGIC ACID DIETHYLAMIDE

LSD is a semisynthetic substance derived from lysergic acid, a natural product found in parasitic rye fungus (*Claviceps purpurea*). The molecule consists of an indole system with a tetracycline ring. LSD was first synthesized by Albert Hofmann, a scientist at the Sandoz AG Pharmaceutical Company (Basel, Switzerland) in 1938, while searching for pharmacologically active derivative of lysergic acid. He accidentally discovered dramatic psychological effect of LSD in 1943. Toward the end of 1960s, people used LSD for recreational and spiritual purposes leading to a "psychedelic movement." Although use of LSD has declined after that, it is still abused today. LSD is a very potent hallucinogen (D-isomer) where an oral dose of 75−150 μg can produce altered state of consciousness. The optimum dosage was suggested being 100−200 μg [59]. The chemical structure of LSD is given in Fig. 33.1.

After oral administration, LSD is absorbed and effects are observed 30−45 after ingestion. In one study, the authors showed lower blood level of LSD if ingested (160 μg) after meal. The peak plasma concentration was reached after 60 min (mean value: 2.75 ng/mL) in subjects who ingested LSD after full meal. The peak concentration was also reached after 60 min in subjects who ingested LSD without meal but the peak LSD level was significantly higher (mean value: 4.9 ng/mL). The duration of effects was 9−10 h [60]. Dolder et al. studied pharmacokinetics of LSD after oral administration using 16 healthy subjects (8 males and 8 females). The oral bioavailability of LSD was determined to be 71%. After ingestion of LSD, maximum plasma concentrations of LSD (mean: 4.5 ng/mL) were reached 1.5 h (median value) after administration (range: 0.5−4 h). Then LSD concentration declined following the first-order kinetics with a mean half-life of 3.6 h for first 12 h. Only 1% LSD excreted in urine was unchanged while the major metabolite detected in urine was 2-oxo-3-hydroxy-lysergic acid diethylamide. The authors also observed a close relationship between plasma LSD level and its psychotropic effects [61].

In another study involving 24 subjects who ingested 100 μg LSD and 16 subjects who ingested 200 μg LSD, the authors observed maximum plasma concentration values (range:1.2−1.9 ng/mL) 1.4 h after administration of 100 μgof LSD. Interestingly peak plasma concentrations (range: 2.6−4.0 ng/mL) was also reached 1.5 h after ingestion of 200 μg LSD by volunteers. The mean plasma half-life was 2.6 h. The subjective psychotropic effects lasted for 8.2 h (mean value) after ingestion of 100 μg LSD but such effects lasted for 11.6 h (mean value) after ingestion of 200 μg of LSD. Subjective peak effects were reached 2.8 and 2.5 h after administration of 100 and 200 μg of LSD, respectively [62].

Similar to active ingredients of magic mushroom and peyote cactus, LSD also binds to serotonin receptor. Studies have shown that serotonin 2A receptor (5-HT_{2A}) is critically involved in the formation of visual hallucinations and cognitive impairment in LSD-induced states. Moreover activation of 5-HT_{2A} receptor by LSD leads to a hippocampal-prefrontal cortex-mediated breakdown of inhibitory processing, which might subsequently promote the formation of LSD-induced visual imageries [63]. Duration of action of LSD is given in Table 33.2.

Analysis of Lysergic Acid Diethylamide and Its Metabolite

Immunoassays are commercially available as screening tests for the presence of LSD in urine. For example, cloned enzyme donor immunoassay (CEDIA) for LSD assay utilizes a monoclonal antibody capable of detecting LSD and the assay has a cutoff concentration of 0.5 ng/mL. CEDIA for LSD can be used either as a positive/negative screening mode or for obtaining semiquantitative values. Other immunoassays such as enzyme multiplied immunoassay technique (EMIT), kinetic interaction of micro-particles in solution (KIMS) are also commercially available. These assays can be easily adopted on automated analyzers commonly used in clinical laboratories. However, initial screening results must be confirmed by another analytical method such as LC-MS/MS or GC/MS because LSD immunoassays are subjected to interferences. Ritter et al. observed a high rate (4.2%) of positive results for LSD using EMIT assay in 1898 urine specimens that were submitted primarily from psychiatric patients for drugs of abuse testing. Specimens that tested positive by EMIT subsequently tested negative by two radioimmunoassays designed for detecting LSD in urine. In addition, randomly selected EMIT positive LSD urine specimens also tested negative when tested by GC/MS [64].

Several drugs such as ambroxol, fentanyl, and sertraline are known to cross-react with CEDIA assay for screening of LSD in urine [65]. In one report, the authors observed significant discrepancy between KIMS and CEDIA assay (cutoff concentration: 5 ng/mL LSD for both assays) for screening of the presence of LSD in urine specimens. However, the CEDIA assay showed overall a satisfactory total concordance of 92.3% with LC-MS assay. Two specimens which were positive for LSD in the CEDIA assay but negative using LC-MS assay contained fentanyl [66].

It is important to confirm initial positive test result for LSD by a chromatography-based confirmation method. Moreover chromatographic methods are also capable of detecting various LSD metabolites in urine. Iso-LSD, a diastereomer of LSD, is formed as an impurity during synthesis of LSD under basic condition. This compound can be used as a biomarker of LSD abuse. The main metabolite of LSD is 2-oxo-3-hydroxy-lysergic acid diethylamide (O-H-LSD) which is usually measured in urine for documentation of LSD abuse. Another metabolite *N*-desmethyl-LSD (nor-LSD) is also measured in urine. Minor metabolites present in urine after LSD abuse include nor-iso-LSD, lysergic acid ethylamide (LAE), lysergic acid ethyl-2-hydroxyethylamide (LEO), trioxylated-LSD, di-hydroxy-LSD, and glucuronides of 13- and 14-hydroxy-LSD [67].

Francom et al. described a protocol for analysis of LSD in urine at a concentration as low as 0.5 ng/mL using GC/MS. After addition of deuterated LSD as the internal standard to the urine, LSD if present along with the internal standard were extracted using *n*-butyl chloride at pH 8 followed by derivatization using *N*,*O*-bis(trimethylsilyl) trifluoroacetamide. The trimethyl silyl derivative of LSD as well as the internal standard was analyzed using a fused silica capillary column and electron impact ionization mass spectrometry operated in selected ion monitoring mode. The ions monitored for LSD were *m*/*z* 395.2 (the molecular ion of *N*-trimethylsilyl derivative of LSD), 293.2, and 268.2. The molecular ion of tri-deuterated LSD trimethylsilyl derivative (*m*/*z* 398.3) was also monitored. After administration of 7.5 μg of LSD in two human volunteers, in the urine of subject A, LSD was detected up to 8 h and in subject B up to 10 h after which that the LSD level was below the detection limit (0.5 ng/mL) of the assay. The maximum concentration of LSD detected in subject A was 0.9 ng/mL but in subject B maximum value was 1.6 ng/mL [68]. Paul et al. also described a protocol for analysis of LSD after converting LSD into trimethylsilyl derivative. The authors used LSD analog lysergic acid *N*-methyl-*N*-propylamide (LAMPA) as the internal standard. The procedure allowed detection of LSD concentrations as low as 20 pg/mL. Quantitation of LSD was linear over the concentration range 50−2000 pg/mL [69]. Sklerov et al. reported analysis of underivatized LSD in urine by gas chromatography−ion trap tandem mass spectrometry following a single-step solid-phase extraction of 5 mL urine [70].

LSD and its metabolites can be analyzed in both blood and urine. Cheung et al. developed a protocol for analysis of LSD and its metabolites (iso-LSD, nor-LSD, and O-H-LSD) in blood and urine using ultra-performance LC/MS/MS. The limit of detection in blood was 5 pg/mL (LSD and iso-LSD) or 10 ng/mL (nor-LSD and O-H-LSD). In urine, detection limit was 10 pg/mL for all analytes [71]. An LC-MS/MS method has also been developed for the simultaneous determination of LSD, iso-LSD, nor-LSD, and O-H-LSD in blood, urine, and vitreous humor samples. The limit of quantification was 20 pg/mL for both LSD and nor-LSD in blood, urine, and vitreous humor. No significant interfering substance or ion suppression was observed for LSD, iso-LSD, and nor-LSD analysis. The method was successfully applied to the forensic determination of postmortem LSD levels in the biological fluids of a multidrug abuser where LSD could be detected in vitreous humor [72].

Jang et al. described an LC-MS/MS method for analysis of LSD and its major metabolite O-H-LSD in both urine and hair using deuterated LSD (LSD-d_3) as the internal standard. The target analyte was extracted from hair using methanol at 38°C for 15 h while for urine (100 μL urine supplemented with 50 μL of 1 ng/mL LSD-d_3 and 300 μL of distilled water and 300 μL of 0.1 M sodium carbonate buffer; pH: 9.5) liquid−liquid extraction was performed using dichloromethane/isopropyl alcohol (1:1 by vol). The chromatographic separation was achieved by using a C-18 reverse phase column (2.1 × 100 mm, particle size 1.8 μm). The mass spectrometer was operated in electrospray ionization positive ion mode. The precursor ion monitored for LSD was *m/z* 324.1 and the product ions were *m/z* 229.9 and 226.0. For the O-H-LSD, the precursor ion monitored was *m/z* 356.2 while product ions were *m/z* 236.8 and 222.1. The precursor ion monitored for LSD-d_3 was *m/z* 327.3 while product ion was *m/z* 226. The limit of detection in hair was 0.25 pg/mg for LSD and 0.5 pg/mg for O-H-LSD. The detection limits in urine were 0.01 and 0.025 ng/mL for LSD and O-H-LSD, respectively. The authors applied this method to detect LSD in two legal cases of LSD ingestion. In these two cases, LSD concentrations in hair were 1.27 pg/mg and 0.95 pg/mg, respectively. No LSD metabolite in hair was detected in subject 2, but the concentration was below the limit of quantitation in subject 1. In urine sample collected 8 h after LSD ingestion in subject 1, the concentrations of LSD and O-H-LSD were 0.48 and 4.19 ng/Ml, respectively. For subject 2, urine specimen collected 3 h after ingestion showed LSD and O-H-LSD concentrations of 2.70 and 25.2 ng/mL. As expected, concentrations of O-H-LSD were significantly higher than LSD in urine [73]. There are other chromatography-based published methods for analysis of LSD and its metabolites in blood and urine. Analytical methods for analysis of LSD in biological matrix are given in Table 33.3.

ABUSE OF KHAT

Khat (*Catha edulis*) is a flowering evergreen shrub cultivated as a bush or small tree which is native to Ethiopia, East Africa, and the Southern Arabian Peninsula. The leaves of khat tree have an aromatic odor and slight sweet taste. Its young bud and tender leaves contain amphetamine-like psychoactive substance which upon chewing produces stimulation and euphoria. Historical evidences indicate that khat use existed in ancient Ethiopia (Abyssinia) as early as 13th century and khat leaves were introduced in Yemen in early 15th century. Therefore cultivation of khat plant started earlier than cultivation of coffee plants. Khat leaves can be chewed or leaves may be dried and powdered to make tea known as Abyssinia, African, or Arabian tea. The dried powder can also be consumed as a paste with honey [74]. Moreover, alcoholic extracts of khat are sold as "herbal high."

Khat use is a part of Yemen culture where approximately 90% males and 50% females chew khat leaves on a regular basis. Even 15%−20% children below the age of 12 chew khat plants. Global distribution of khat has increased significantly in last three decades where khat is available in both European and US market. Although in the past most consumers of khat in the Western countries were immigrants from East Africa or Middle-East, in last 10 years khat has emerged in illicit drug markets of the United States, Canada, New Zealand, Norway, and Hong Kong [75]. The World Health Organization considers khat as a drug of abuse. Khat is banned in European countries, United States, and Canada while it is lawful in Yemen, Somalia, and Ethiopia [76].

The fresh khat leaves contain many compounds including alkaloids, tannins, flavonoids, terpenoids, sterols, glycosides, amino acids, vitamins, and minerals. Of these chemicals, the most important group of compounds responsible for stimulating activity is phenyl-alkylamines which constituent cathinone (S(-)-alpha-aminopropiophenone), norpseudoephedrine, and norephedrine. Cathinone is a sympathomimetic amine and has structural similarity with amphetamine. Besides phenyl-alkylamines, the other major alkaloids found in khat leaves include cathedulins (62 compounds known in this calls isolated from fresh khat leaves) [77]. Chemical structure of cathinone is given in Fig. 33.1. Khat is known as "Herbal Ecstasy" because of its CNS stimulant effects similar to amphetamine.

Khat: Pharmacology and Toxicology

The active ingredients of khat are released during chewing. However, cathinone due to higher lipid solubility is more psychoactive than other components after khat abuse. Cathinone is degraded with time to cathine (inactive metabolite) and norephedrine by enzymatic actions. The degradation of cathinone is accelerated due to exposure to sunlight and heat. As a result after cultivation, khat plants are wrapped with banana leaves to reduce degradation. Usually 100−200 g of fresh leaves wrapped in banana leaves are chewed for getting stimulatory effect of cathinone present in khat leaves [78].

Cathinone is present in varying amounts (78−343 mg) in 100 g of khat leaves. The stimulatory effects of khat appear approximately 30 min after initiation of chewing khat plant and the effect may last up to 3 h. Approximately 90% of active compound present in leaves are released during chewing. The main route of absorption of cathinone is through oral mucosa (approximately 60% of absorption) and the rest of cathinone is absorbed through the gastrointestinal tract [79]. A typical session of khat chewing is similar to the effect of 5 mg amphetamine [80].

Halket et al. studied plasma concentration of cathinone after consuming khat (0.8 mg/kg). The mean peak cathinone level of 83 ng/mL was observed 1.5−3.5 h after chewing khat leaves [81]. Cathinone is extensively metabolized into cathine and norephedrine while only 7% of dose is excreted unchanged in urine [82]. Cardiovascular complications from cathinone use are similar to the complications observed with amphetamine abuse [83]. Moreover, increased blood pressure and increased heart rates are also observed in individuals abusing khat [84]. Ali et al., based on a study involving 934 patients who were khat chewers, concluded that khat chewing is associated with increased risk of stroke and death [85]. In general effects of khat on peripheral nervous system could include constipation, urine retention, and acute cardiovascular effects while effects on CNS could include increased alertness, dependence, and psychiatric symptoms [86].

Cathinone, the active ingredient of khat, is also sold in form of capsules and are also abused. Hagigat capsules (containing 200 mg cathinone produced illicitly) have been available in streets in Israel as a natural stimulant and aphrodisiac. Bentur et al. studied data of 34 consecutive patients (age 16−54) who consumed half to six Hagigat capsules. The major complications of use of cathinone were myocardial ischemia, pulmonary edema, and intracerebral hemorrhage. The authors concluded that exposure to illicitly synthesized cathinone may cause serious cardiovascular and neurological toxicity even in young subjects [87]. Active ingredient and duration of action of khat are listed in Table 33.2.

Mechanism of Action

Cathinone has similar CNS stimulatory and sympathomimetic effects characterized by increased blood pressure, heart rate, mydriasis, and hyperthermia similar to amphetamine [88]. All cathinones including natural cathinone and its synthetic derivatives (bath salts) are inhibitors of monoamine transporters, but their selectivity for serotonin receptors, norepinephrine transporter, and dopamine transporters vary substantially. The mechanism of cathinone on neurotransmission is to trigger presynaptic dopamine release and reduce the reuptake of dopamine which is similar to mechanism by which amphetamine exerts its pharmacological effects. Cathinone although binds to dopamine and serotonin receptors, it has the highest affinity for norepinephrine receptors. Moreover, cathinone has also been shown to induce serotonin release and inhibits its reuptake [89].

Laboratory Analysis of Cathinone

Abuse of bath salts (synthetic cathinone) is more widespread than khat abuse. Although cathinone cross-reacts with one antibody used in biochip array immunoassays (Randox Corporation), some of the chormatographic methods for analysis of bath salts also include cathinone as an analyte. Chromatographic-based assays offer more sensitivity and specificity than biochip array immunoassays for detection of bath salts in urine. In general three synthetic cathinone, methylone, mephedrone, and 3,4-methylenedioxy pyrovalerone (MDPV) currently make up approximately 98% of all bath salts abuse. In one published report, the authors developed a GC/MS protocol for analysis of seven amphetamine-type stimulants and 22 cathinones including three metabolites in urine. Using this protocol, cathinone if present in the urine specimen can also be analyzed [90]. Abuse of synthetic cathinones is a serious public health issue because fatalities have been reported in the literature due to abuse of bath salts. The death was attributed to hyperthermia, hypertension, cardiac arrest, and more in general to the classical serotonin syndrome [91]. For in-depth coverage of this topic please see Chapter 21: Review of bath salts on illicit drug market. Analytical methods for analysis of active ingredients of khat in biological fluids are listed in Table 33.3.

ABUSE OF VOLATILES AND GLUE

The general populations are exposed to many volatile compounds which are used in common household products including cleaning agents, adhesives, paints, and cosmetic products. The occupational exposures to various solvents are also troublesome but in most developed countries, such exposures are limited due to stringent regulations. However, there are certain volatile compounds which are listed under drug class of abused inhalants. These compounds usually have low vapor pressure and high volatility at room temperature that enables use of these solvents as euphorigenic inhaled agents. These volatiles classified as abused inhalants include aromatic hydrocarbons, aliphatic hydrocarbons, halocarbons, halogenated ethers, nitrous oxide, and alkyl nitrites [92].

Prevalence of Solvent Abuse

Various readily available household and office products are abused including glue, adhesives, nail polish, nail polish remover, cigarette lighter fluid, butane gas, air fresheners, deodorant, hair spray, pain relieving spray, typewriter correction fluid, paint thinners, paint removers, and a variety of other agents. These household and office products contain toxic solvent such as toluene (paint, spray paint, adhesives, paint thinner, shoe polish), acetone (nail polish remover, typewriter correction fluid, and markers), hexane (glue, rubber cement), chlorinated hydrocarbon (spot and grease removers), xylene (permanent markers), propane gas (gas to light the grill, spray paints), butane gas (lighter fluid, spray paint), and fluorocarbons (hair spray, analgesic spray, refrigerator coolant such as Freon). However, toluene is found in many household products such as glues and thinners which are widely abused due to psychoactive property of toluene. Chemical compositions of commonly abused inhalants are summarized in Table 33.4.

Although solvent (inhalant) abuse is common among adolescents not only in the United States but also worldwide, this problem is often overlooked. In the United States, approximately 20% of adolescents have tried inhalants at least once by the time they had reached eighth grade. Analysis of data from the US Poison Control Centers from 1993 to

TABLE 33.4 List of Commonly Abused Inhalants and Their Composition

Product	Solvent Found
Spray paint	Propane, butane, toluene, hydrocarbon, fluorocarbons
Hair spray	Propane, butane, fluorocarbons
Analgesic spray	Fluorocarbons, isopropyl alcohol
Paint thinner	Toluene, methyl chloride, methanol
Shoe polish	Toluene
Cleaner, disinfect	Xylene
Nail polish remover,	Acetone, toluene
Lighter fluid	Butane
Domestic fuel	Propane, butane, isooctane
Film cleaner, correction fluid	1,1,1-Trichloroethane, acetone
Adhesive glue	Toluene, xylene, ethylbenzene, hexane
Air freshener	Fluorocarbons
Rubber cement, marker	Toluene, hexane, methyl chloride, acetone
Spot remover, degreasers	Chlorinated hydrocarbons
Gasoline	Combination of aliphatic and aromatic hydrocarbons and other volatile organic compounds
Refrigerator fluid	Trichlorofluoromethane (Freon)
Metal cleaner	*n*-Propyl bromide

2008 showed 35,453 cases of toxicity due to abuse of inhalants. Prevalence was highest among children 12−17 years and peaked in 14 years old. Inhalant abuse was more common in boys (73.5%) than girls indicating that boys may pursue riskier usage behavior. More than 3400 different products were involved in inhalant abuses. Propellants, gasoline, and paint were the most frequent product categories. Butane, propane, and air fresheners had the highest fatality rates [93]. Although solvent abuse is common among adolescents, solvent abuse by pregnant woman has also been reported. Such abuse in pregnancy is associated with severe maternal and neonatal sequela [94].

Although drug abuse has been known for over 2000 years, abuse of solvents is a relatively new phenomenon. The first documented case was in 1946 when a boy being treated for psychotic symptoms at a hospital admitted to the attending physician that he chronically and uncontrollably inhaled gasoline for its intoxicating effect. A decade later the press from major American cities started reporting on intentional glue sniffing among youths. At that point medical professionals started to become aware that solvents may have euphorigenic properties and could possibly produce dependence. Solvent abuse may induce psychotic symptoms including hallucination and delusion [92].

Pharmacology and Toxicology of Abused Solvents

Inhalants are abused either by breathing directly from a container or by soaking a rag with the solvent and then placing it over the nose and mouth. Moreover abusers also pour the solvent in a plastic bag and then breathe fumes. Abuse of inhalant can produce euphoria like other abused drugs. When an abuser becomes hypoxic by rebreathing from a bag, the euphoric effect may even intensify. In general one of the commonly abused volatile toluene can be detected by humans at a very low concentration of 11 ppm (parts per million) and low-detectable concentration is also likely for other abused solvents. However, solvent abusers who intentionally inhale volatiles for intoxication usually expose themselves for approximately 15 min to extremely high vapor concentrations up to 15,000 ppm [92].

Toluene has the well-documented pharmacological and toxicological profile of all solvents studied. Inhalation of toluene vapor causes euphoria followed by CNS depression. Toluene is metabolized by the liver cytochrome P-450 mixed function oxidase into benzoic acid and hippuric acid which are excreted in urine. The most common clinical presentation of toluene intoxication is muscular weakness due to hypokalemia which may cause respiratory depression and may be life-threatening. Renal tubular acidosis may also occur due to toluene poisoning. Liver injury and rhabdomyolysis is also common feature of toluene poisoning [95].

Toluene is an aromatic hydrocarbon found in gasoline, acrylic paints, varnishes, paint thinners, adhesive, and shoe polish. Fatalities due to abuse of products containing toluene have been reported. A middle-aged man was found dead in his house after varnish application by spray. The blood test revealed the presence of toluene and the cause of death was established as cardiopulmonary failure caused by toluene [96]. The toluene concentration over 2000 ppm is considered dangerous to life and health. Argo et al. reported death of a 15-year-old boy due to ingestion of varnishes diluting solvent after failing an examination. Volatile organic compounds such as toluene and xylene were detected in gastric content, blood, liver, and kidney [97]. In another report, the authors described two cases of fatal intoxication with toluene due to glue sniffing. Using gas chromatography with flame ionization detector and GC/MS with headspace method, toluene was detected in biological specimens. Highest concentrations were observed in liver and brain in both cases (13.82−20.97 μg/g). Based on this data, the cause of death in both cases was determined to be due to toluene poisoning [98].

In one study the authors investigated 318, 939 exposures and concluded that exposure to hydrocarbons which are systematically absorbed and have low viscosity such as benzene, toluene, xylene, halogenated hydrocarbon, kerosene, and lamp oil caused the highest hazard values. Moreover, the risk associated with hydrocarbon exposure is greater among children and adolescents [99]. Fatalities may occur from abusing any solvent. Seetohul reported a case of death from abusing diethyl ether [100]. Sugie et al. reported three cases of sudden death due to inhalation of portable cooking stove fuel (case 1), cigarette lighter (case 2), and liquefied petroleum gas (case 3). Butane was found in tissues of cases 1 and 2 while propane was the major compound present in case 3 [101]. Alunni et al. reported death from butane abuse in two teenagers. An 11-year-old boy died after inhaling deodorant aerosol. The toxicological analysis detected the presence of butane at concentrations of 22 mg/L in the peripheral blood, 97 mg/L in the gastric fluid, and 8 mg/kg in the lung. The authors also detected limonene (gastric fluid) and decamethylcyclopentasiloxane (gastric fluid and fatty tissue). Identification of these chemicals may help in identifying particular brand of deodorant because these compounds are not present in all brands. A 16-year-old girl with unregulated type 1 diabetes also died after deodorant abuse. Butane was identified in postmortem peripheral blood at a concentration of 18.1 and 27.3 mg/L in the gastric fluid. One limonene was identified in gastric fluid. It emerged that the victim has suffered the seizure after inhaling from a tissue soaked in deodorant [102].

Solvent abusers often present themselves with nonspecific symptoms, but long-term abusers may come to the hospital with a wide range of neuropsychiatric symptoms. The exact mechanism of action for the volatiles and inhalants has

TABLE 33.5 Adverse Effects of Solvent and Inhalant Abuse

Toxicity	Agents
Cardiotoxicity	Inhalants such as fluorocarbons, gasoline, benzene, toluene, butane, propane (acute effect of inhalants on the heart may be fatal) are cardiotoxic.
Pulmonary	Some hydrocarbons may cause chemical pneumonitis.
Renal	Toluene, hydrocarbons.
Hepatic	Halogenated hydrocarbons such as carbon tetrachloride, trichloroethane, toluene are liver toxins.
Teratogenic	Inhalants due to lipophilic nature cross the placenta.
Neurologic	Various inhalants such as toluene, hexane, methyl isobutyl ketone.

not been completely understood yet. It is possible that volatiles in general produce a slowing of axonal ion channel transport by increasing fluidity of membranes. Another possibility is that volatiles potentiate hyperpolarization of gamma-aminobutyric acid receptors (GABA receptors). At the primary site of action of inhalants due to their lipophilic nature can quickly produce CNS depression which results in slurred speech, diplopia, ataxia, visual hallucination, and disorientation. Further CNS depression can cause respiratory arrest, seizures, and coma. The most serious consequence of solvent abuse is death which may occur secondary to aspiration or asphyxia. Nearly 50% of deaths from solvent abuse are due to sudden sniffing death syndrome. When an acutely intoxicated abuser is startled, a burst of catecholamines may trigger ventricular fibrillation [103]. Adverse effects of solvent abuse are listed in Table 33.5.

Laboratory Detection of Solvent Abuse

Laboratory tests are helpful for diagnosis of solvent abuse in a suspected patient. As a result, diagnosis is based on clinical presentation and high index of suspicion. In general complete blood count, electrolyte, acid−base assessment, and hepatic and renal chemistry profiles are ordered. Blood alcohol should be ordered as many solvent abusers also abuse alcohol. Urine drug screen should also be ordered as illicit drugs are often detected in solvent abusers. Treatment is mostly supportive. For forensic investigation, headspace gas chromatography is useful to identify individual solvent. Detection can be carried out using flame ionization detector or mass spectrometry [104]. Antonucci et al. described a protocol for analysis of 10 volatile compounds (benzene, toluene, ethylbenzene, ortho-xylene, meta-xylene, para-xylene, methyl tert-butyl ether, ethyl tert-butyl ether, 2-methyl-2-butyl methyl ether, and diisopropyl ether) in urine of children using headspace gas chromatography/mass spectrometry [105].

CONCLUSIONS

Abuse of magic mushroom, peyote cactus, khat, LSD, and solvent are problematic. Psilocybin and psilocin are active components of magic mushroom which can be identified by various chromatographic methods including GC/MS and LC-MS/MS. The active component of peyote cactus is mescaline which cross-reacts with some amphetamine/methamphetamine immunoassay. A specialized immunoassay marketed by the Randox Corporation (drugs of abuse array V biochip immunoassay) is also useful to detect the presence of mescaline in urine because a specific antibody is immobilized on the biochip capable of detecting mescaline. Chromatographic methods are also available for detection of mescaline in various biological matrixes. The active component of khat plant is cathinone which cross-reacts with various amphetamine/methamphetamine immunoassays. Synthetic derivatives of cathinone are sold as bath salts and some of these compounds can be detected by the drugs of abuse array V biochip immunoassay. Chromatographic methods are also available. Although immunoassays are available for screening of the presence of LSD in urine, false-positive tests may occur. Therefore chromatographic methods must be used to confirm the presence of LSD in urine specimens tested positive for LSD using an immunoassay. Moreover, chromatographic methods are also applicable for analysis of LSD in blood and other body fluids. For detecting solvent abuse, headspace gas chromatography coupled with flame ionization detector or mass spectrometry is the preferred analytical method.

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