RECREATIONAL DRUGS

Current Trends in the 90s

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Recreational drug use in the 1990s continues to be widespread, infiltrating all social strata to some degree. Drug abuse has become commonplace within many social settings as a consequence of individuals' desire to feel elation, escape life's troubles, or conform to peer pressure. With the inception of trends such as all-night dance raves and gang-banging, newer illicit drugs have gained tremendous popularity. These recreational drugs allegedly enhance sociability and liberate inhibitions, allowing users to experience feelings of euphoria. In any setting, these drugs, alone or taken in combination with other drugs, such as alcohol, are dangerous and may have devastating effects that include acute toxic reactions and death.

A more sinister trend occurring with recreational drug use is its close association with criminal acts. Several drugs have been dubbed "date-rape" drugs because of their use in facilitating nonconsensual sex. Social predators use these drugs with the intent to render their victim incoherent or even unconscious before committing their heinous crime. McKissick has reported that female victims as young as 13-years-old have been incapacitated in this way.[40]

This article reviews recreational drugs that have gained notoriety in the 1990s. These include gamma-hydroxybutyrate (GHB, γ-hydroxybutyric acid, sodium oxybate), flunitrazepam (Rohypnol), and amphetamine analogues, such as 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxymethamphetamine (MDMA), and 3,4-methylenedioxyethylamphetamine (MDEA).

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GAMMA-HYDROXYBUTYRATE

Gamma-hydroxybutyrate (GHB) was synthesized in 1960 by French physician Henry Laborit, as an alternative anesthetic to aid in surgery. Acknowledging its unpredictable nature and associated adversities, the medical community quickly discarded GHB use in surgical procedures.[17]

In the past, GHB had two other notable uses: (1) body-builders used GHB to promote muscle mass and maintain weight; and (2) the health food industry promoted GHB as a replacement over-the-counter (OTC) sedative agent after the 1989 Food and Drug Administration (FDA) ban of *L*-tryptophan.[19] Between June and November, 1990, however, at least 57 cases of illness attributed to GHB were reported from 9 states.[17] Because of this multistate outbreak of poisonings, the FDA issued a warning on the use of GHB and banned its OTC sale. Moreover, in the past 2 years at least six deaths have been attributed to GHB ingestion.[33]

The FDA classifies GHB as an investigative new drug for use exclusively in FDA–approved clinical research projects. This includes the ongoing clinical research of the treatment of sleep disorders, including narcolepsy. Although possession of GHB is legal in most states, manufacture and distribution, other than by FDA–approved drug companies, is a federal offense and prosecuted under FDA laws. Several states, including California, Rhode Island, and Georgia, however, have passed laws classifying GHB as a state-controlled illicit substance.[2, 33] The Drug Enforcement Administration (DEA) is currently reviewing the status of GHB to determine if it should become a Schedule I controlled substance.

Any person possessing a little knowledge of chemistry can synthesize GHB in a clandestine laboratory from limited, readily obtained materials. GHB is produced by ester hydrolysis of γ-butyrolactone (GBL), a compound commonly used as a wood cleaner, paint remover, or textile aid, in the presence of sodium hydroxide or lye. The hydrolysis product is a clear solution with a chemical composition consisting of approximately 70% yield of the GBL weight.[2] The manufacture of GHB can be a lucrative business; a producer can invest $800 to synthesize 15 to 18 gallons of concentrated GHB, which has a comparative street value of approximately $92,000.[21] Table 1 lists common street names attributed to GHB.

Use and Misuse

Gamma-hydroxybutyrate has been purported to be an effective antinarcoleptic, anesthetic, anorectic, sedative, inducer of rapid eye movement sleep, and agent for the treatment of ischemic conditions and alcohol and opiate withdrawal. Other desirable effects of GHB include its quick "high" and associated heightened sexual desire. Users have also compared it to other central nervous system (CNS) depressants like marijuana, alcohol, and diazepam.[22, 34]

Gamma-hydroxybutyrate is distributed as a liquid, crystalline pow-

Table 1. COMMON STREET NAMES OF RECREATIONAL DRUGS

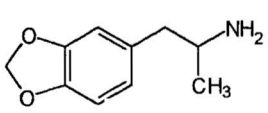
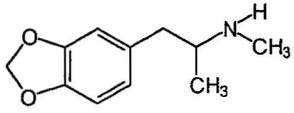
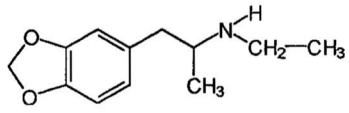
MDMA	MDA	MDEA	Gamma-Hydroxybutyrate	Flunitrazepam
Ecstasy	Love Drug	Eve	GHB	Rohypnol
XTC	Love Pills		γ-OH	Rophies
Adam			Easy Lay	Circles
California Sunrise			Everclear	Darkene
E			Georgia Home Boy	Forget Pill
Hug Drug			Great Hormones at Bedtime	La Roche
Love Doves			Grievious Bodily Harm	Mexican Valium
M & M			Goops	Mind Erasers
			Liquid X	Rib
			Liquid Ecstasy	Roaches
			Nature's Quaalude	Roachies
			Oxy-sleep	Roche
			Poor Man's Heroin	Roofies
			Salt Water	Rope
			Scoop	Ropies
			Soap	Roples
			Somatomax PM	Row-shay
			Somsanit	Ruffies
			Vita-G	R05-4200
			Water	R-2
			Wolfies	Trip & Fall
			Zonked	The "Drop Drug"
				Wolfies

Data from References 18, 19, 21, 23, 30, 33, 34, 41, 43, 48, 50.

der, or in a gel form of the sodium salt. Its general properties are listed in Figure 1. The liquid form of GHB is clear and oily and has a slightly solvent or salty taste. To make it more palatable, GHB is sometimes mixed with cinnamon or food dye. If undiluted, the liquid consistency of GHB is slightly thicker than water. A common street dose is prepared by mixing 2 tsp of the hygroscopic GHB powder with 8 oz of water, fruit juice, carbonated drink, or alcohol.[21] GHB is usually given orally in doses of 2.5 to 3.0 g (35 mg/kg).[3]

Pharmacology

Gamma-hydroxybutyrate occurs naturally in the mammalian brain as a catabolite of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter. Cyclic biochemical pathways of the brain oxidize succinate semialdehyde, an intermediate of succinic acid and GABA, to GHB, which can revert to succinate semialdehyde. GHB readily crosses the blood-brain barrier to depress the CNS. GHB influences dopamine release in the substantia nigra, producing pleasurable effects such as euphoria, hallucinations, and smooth muscle relaxation. It may also exert effects through endogenous opioid and currently unidentified receptors. Not

	MDA	MDMA	MDEA
			
NOMENCLATURE:	3,4-methylenedioxyamphetamine	3,4-methylenedioxymethamphetamine	*N*-ethyl-3,4-methylenedioxyamphetamine
MOLECULAR WEIGHT:	179.22	193.25	207.27
MOLECULAR STRUCTURE:	$C_{10}H_{13}NO_2$	$C_{11}H_{15}NO_2$	$C_{12}H_{17}NO_2$
APPEARANCE:	nearly colorless oil	oil	viscous, colorless oil
MELTING POINT:	181-188°C	147-153°C	197-202°C
SOLUBILITY (HCl Salt):	easily in water and alcohol	easily in water and alcohol	easily in water and alcohol

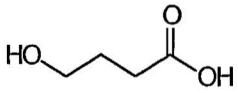
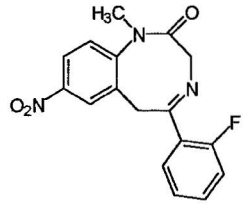
	GHB	Flunitrazepam
		
NOMENCLATURE:	4-Hydroxybutyrate	5-2(2-Fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-2H-1,4-benzodiazepin-2-one
MOLECULAR WEIGHT:	104.11	313.29
MOLECULAR STRUCTURE:	$C_4H_8O_3$	$C_{16}H_{12}FN_3O_3$
APPEARANCE:	crystalline HCl salt	crystalline HCl salt or yellowish, needle-like crystals from methylene chloride-hexane
MELTING POINT:	146-149°C	166-172°C
SOLUBILITY (HCl Salt):	easily in water and methanol	easily in water and methanol

Figure 1. General properties of recreational drugs. (Data from Budavari S, O'Neil MJ, Smith A, et al (eds): The Merck Index, ed 2. Whitehouse Station, New Jersey, Merck Research Laboratories, 1996; and Radian International, Inc. 4-Hydroxybutyric acid sodium salt: Standard Certificate of Analysis. Compound Lot No. 31544-31A.

only has GHB been identified in the brain, but non-neuronal tissues, such as kidney, heart, and skeletal muscle, contain GHB. The peripheral tissues may have 15 to 20 times higher GHB concentrations than the CNS. In the brain, GHB receptor sites and a GHB antagonist have also been identified.[10, 19]

Gamma-hydroxybutyrate is metabolized to γ-butyrolactone and carbon dioxide by oxidizing enzymes in the peripheral tissues. GHB is also metabolized through the tricarboxylic acid cycle to carbon dioxide, which is subsequently expired during breathing.[10]

Peak GHB concentrations are observed in the urine within the first 4 hours postingestion, and GHB is usually not detectable in urine by 12 hours. Also, approximately 2% to 5% of GHB is excreted in the urine unchanged.[16]

Gamma-hydroxybutyrate demonstrates rapid absorption kinetics with the onset of effects occurring within 15 to 30 minutes following the oral ingestion of a 2 to 3 g dose. Its duration of action is approximately 3 hours. GHB's time to peak varies with the dose and ranges from 25 to 45 minutes following doses of 12.5 mg/kg and 50 mg/kg, respectively. A study of 60 patients demonstrated the duration of action for GHB's clinical effects, such as sedation, ranged from 75 to 225 minutes following a 50 to 60 mg/kg dose. Given a higher dose of 75 to 100 mg/kg, peak plasma concentrations were reached in 1.5 to 2 hours.[16] GHB's plasma elimination half-life ranges from 20 min to 1 hour depending on the dose.[3]

In a recent report, the concentration range of GHB in blood obtained from six fatalities ranged from 98 to 596 mg/L. In four other fatalities, the concentration range was 20 to 52 mg/L. These lower concentrations are consistent with endogenous GHB blood concentrations.[33]

Clinical Presentation and Treatment

Gamma-hydroxybutyrate has many adverse effects, ranging in severity from minor to life-threatening. These effects are listed in Table 2. Many of the effects are dose-dependent; smaller doses of 10 mg/kg are associated with amnesia and hypotonia, whereas larger doses of 50–70 mg/kg lead to anesthesia, coma, seizures, and respiratory depression.[3] Acute symptoms usually resolve within 7 hours, but dizziness has been reported for up to 14 days.[19]

Adverse effects are highly variable among individuals, typically requiring experimentation to obtain an optimal dose. This variability, in addition to variability inherent in street manufacturing, makes GHB a dangerous drug to consume. Moreover, combining GHB with other CNS depressants leads to synergistic actions, which can intensify its effects.[19, 21]

There have been several cases of GHB addiction reported.[21] Treatment of GHB overdose includes supportive care and enhanced elimination using gastric lavage or activated charcoal.[19, 34]

Table 2. PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF RECREATIONAL DRUGS

Drug	Desired Effects	Toxic or Undesired Effects	
MDMA	euphoria	hypertension	insomnia
	empathy	tachycardia	hot/cold flashes
	talkativeness	muscular hypertonicity	nystagmus
	elevated self-esteem	jaw clenching	tremor
	enhanced sociability	nausea	anxiety
	fear dissolution	ataxia	paranoia
	visual hallucinations	seizure	poor concentration
	appetite suppression	hyperpyrexia	
	increased energy level		
	enhanced sensory perception		
MDA	similar to MDMA	hyperactivity	seizures
		tachycardia	mydriasis
		hypertension	vasoconstriction
		hyperpyrexia	agitation
		hyperventilation	tremor
MDEA	similar to MDMA	hypotension	muscular hypertonicity
		tachycardia	
GHB	euphoria	absence-like seizure	bradycardia
	mood elevation	hypotension	respiratory depression
	hallucinations	coma	incontinence
	muscle growth	anxiety	nausea
	intensify effects of other drugs	hypotonia	vomiting
	hypnotic tendencies	dizziness	vertigo
	amnesia	excessive salivation	unconsciousness
		amnesia	
		tremors	
Flunitrazepam	euphoria	drowsiness	cough
	hallucinations	tachycardia	nausea
	disinhibition	dizziness	diarrhea
	skeletal muscle relaxation	apnea	visual disturbances
	sedation	ataxia	confusion
	reduced trepidation	hypotension	urinary retention tremors
	light and sound sensitivity	headache seizures	hiccups
	memory impairment (criminal uses)		

Data from 3, 7, 18, 19, 21, 23, 30, 41, 48, 50.

Laboratory Analysis

The identification of GHB by crime laboratories is achieved using techniques such as Fourier transform infrared spectroscopy, high pressure liquid chromatography (HPLC), and gas chromatography (GC).[2] HPLC and GC are the most commonly used techniques.

The analysis of GHB typically requires its conversion to GBL, a less soluble form of GHB, by acidic hydrolysis. Once hydrolyzed, the GBL is extracted into an organic solvent such as chloroform, ether, or methylene chloride. Although GBL can be successfully analyzed in its underivatized form, improved gas chromatographic separation and sensitivity are generally achieved following derivatization. Common derivatizing reagents include heptafluorobutyric anhydride and bis(trimethylsilyl)-trifluoroacetamide (BSTFA) with 1% trimethylchlorosilane (TMCS).

Several compounds have been used as internal standards for GHB

analysis. These include δ-valerolactone, n-undecane, deuterated analogues of GHB and GBL, and δ-hydroxy-valeric acid.[22, 28, 33]

For HPLC analysis, refractive index or ultraviolet detection is used. Again, derivatization may enhance HPLC detection of GHB. GHB is usually quantitated using GC coupled to an electron capture detector (ECD), flame ionization detector (FID), or mass spectrometer (MS).[15, 22] When a GC-MS is used, operation in the selected ion monitoring mode provides enhanced sensitivity.

Historically, GBL has been the target analyte, but given GHB's recent controlled status, it is imperative that laboratory techniques identify GHB itself rather than its hydrolytic product. The US FDA laboratory recently developed an assay for the direct analysis of GHB.[28] The method uses a GC coupled to an FID and employs derivatization with BSTFA with 1% TMCS. A modified version of this method has been used to successfully detect GHB by GC-MS. For quantitation by GC-MS, the prominent mass spectral ions of the trimethylsilyl derivative of GHB are *m/z* 233, 204, and 147. If derivatization is not used, a lower GC injection port temperature (e.g., 140°C) must be used to prevent the conversion of GHB to GBL.[2]

Alternatively, Kuwahara et al[33] reported a procedure in which the specimen is split into two fractions before analysis. One fraction is assayed directly (free GBL) to measure any GBL formed in vivo by chemical or enzymatic processes. The other fraction is hydrolyzed (total GBL) to convert GHB to GBL. Using this technique, the GHB concentration in the specimen is estimated by subtracting the free GBL concentration from the total GBL concentration. This study corroborated results from past studies, in that, no measurable amounts of free GBL are present in post mortem tissue.[22] Interpretation of results should always take into account the endogenous GHB concentrations.

FLUNITRAZEPAM (ROOFIES)

Flunitrazepam is a benzodiazepine manufactured by the Swiss-based pharmaceutical company Hoffman-LaRoche. Flunitrazepam is legally distributed in 80 countries throughout the world; however, it has never been approved for medicinal use in the United States.[42] In Europe, flunitrazepam is used as a hypnotic, sleep-inducing, or pre-anesthetic agent.

In 1983, flunitrazepam was classified a Schedule IV drug according to the United Nations Convention on Psychotropic Substances. In compliance, the DEA scheduled flunitrazepam as a Schedule IV compound in the Controlled Substance Act (CSA) of the United States.[23, 52]

Noticeable abuse of flunitrazepam in the United States was first reported in southern Florida in 1993. Its popularity has led to many street names, summarized in Table 1.[49] With its overwhelming popularity and reports of overdoses and associated crimes, many states have begun legislation to move flunitrazepam to a Schedule I class. As of March

1997, the states of Florida and Oklahoma successfully rescheduled flunitrazepam to Schedule I status. The federal government has also introduced legislation that proposes to reschedule flunitrazepam to a Schedule I drug of the CSA. Internationally, the World Health Organization moved flunitrazepam to a Schedule III in March 1995, requiring additional record keeping for its distribution.[52]

Pharmaceutically manufactured flunitrazepam gains access to the United States by illegal routes of passage across the Mexican border or from South American countries by way of Miami. The DEA has intercepted and seized overnight express packages mailed to the United States originating from South America or Mexico.

Use and Misuse

Flunitrazepam is abused primarily for its euphoric, hallucinogenic, and disinhibiting effects. In addition, drug abusers use flunitrazepam to enhance the effects of low-grade heroin or to ameliorate the adverse effects associated with cocaine or crack binges. Its general properties are summarized in Figure 1.

Flunitrazepam is administered intravenously (IV), intranasally (IN), intramuscularly (IM), or orally (PO). For anesthetic purposes, doses of 0.015 to 0.03 mg/kg are administered IV for induction and one third of the dose is given for maintenance. For anesthetic premedication, IM injections are given in doses of 0.015 to 0.03 mg/kg. Oral administration, given in doses of 0.5 to 2.0 mg, is the most common route.[34]

In Germany, the Substance Abuse Warning Network reported oral use of flunitrazepam prior to 1990, but by 1994, their reports indicated that as much as 36% of flunitrazepam users were injecting the drug. Most of these IV drug users coadminister flunitrazepam and heroin to augment and prolong the effects of the heroin. For illicit use, a dose of 2 mg/mL is commonly given by IV injection. Moreover, studies have shown that flunitrazepam tablets can be pulverized, and subsequently, inhaled to produce subjective effects in 5 minutes.[52]

Recently, in response to reported cases of sexual assaults involving the use of flunitrazepam, Hoffman-LaRoche now markets a new formulation. This new formulation takes approximately 20 minutes to dissolve, turns a bright blue in lightly colored liquids and a murky color in darker liquids, and forms a buoyant precipitant in solution.[26, 42]

Hoffman-LaRoche also offers toxicologic analysis of specimens from suspected drug-related sexual assault cases at no charge to law enforcement agencies, rape crisis centers, or hospitals. As of October 1997, only 5 (1%) out of 410 samples analyzed were positive for flunitrazepam. Ten other drugs were identified in these specimens, including alcohol (34%), cannabinoids (14%), and GHB (7%).[26, 42]

Pharmaceutically manufactured flunitrazepam tablets are white with a single-scoring or cross-scoring on one side and markings of "Roche" and an encircled "1" or "2" on the opposite side. Other mark-

ings are used and depend on the manufacturing plant's geographic location. Other colorations, such as a brownish-pink tint, usually indicate counterfeit products.[41]

Flunitrazepam is relatively inexpensive ($1 to $5 per tablet) and easily accessible, contributing to its growing abuse in Europe, Asia, South America, and the United States.[41, 49] Many users falsely believe flunitrazepam is a safer drug to consume because the tablets come in tamper-evident bubble packs distributed by the manufacturer; thus, adulteration is less likely to occur. Their appearance also makes it easier to conceal their identity from authorities. Flunitrazepam tablets are often substituted with other benzodiazepines, such as nitrazepam.

Pharmacology

Flunitrazepam depresses the CNS by acting on the benzodiazepine receptor within the γ-aminobutyric acid$_A$ ($GABA_A$) complex. The affinity and efficacy at the benzodiazepine receptor largely determines the differences in pharmacodynamics among the benzodiazepines. Flunitrazepam has a greater affinity for the benzodiazepine receptor than clobazam, diazepam, oxazepam, and alprazolam, but less affinity than midazolam and triazolam.[52] On a weight basis, flunitrazepam is approximately 10 times more potent than diazepam in its sedative/hypnotic effects.[49]

Flunitrazepam is a fluorinated 7-nitrobenzodiazepine analogue of nitrazepam. Flunitrazepam is relatively lipid soluble allowing it to quickly cross the blood-brain barrier and produce its CNS effects.

When given orally, absorption occurs rapidly, producing effects within 15 to 20 minutes. Flunitrazepam is an intermediate-acting benzodiazepine having a duration of action between 6 and 12 hours, with residual psychomotor effects persisting for up to 24 hours. Its elimination half-life varies from 9 to 25 hours.[3, 34] Pharmacokinetically, flunitrazepam demonstrates a rate of plasma concentration increase and rate of distribution similar to diazepam. Given in a 2 mg oral dose, a peak blood concentration of 6 ng/mL was measured in one subject. The same dose injected IV in two subjects demonstrated peak blood concentrations of 28 to 52 ng/mL, which declined to less than 10 ng/mL within 10 minutes.[9] Plasma proteins bind approximately 80% to 90% of a flunitrazepam dose.[34] Flunitrazepam's major metabolites, 7-aminoflunitrazepam, norflunitrazepam, and 7-aminonorflunitrazepam, can be detected in the plasma following chronic, frequent IV injections.[51]

Hepatic metabolism occurs by several metabolic pathways including *N*-demethylation, 3-hydroxylation, and glucuronidation. In addition, the nitro group can be reduced to an amine that is subsequently acetylated.[29] At least 11 flunitrazepam metabolites have been identified in urine. The primary metabolites are 7-amino-flunitrazepam, 3-hydroxyflunitrazepam, 7-acetamidonorflunitrazepam, and 3-hydroxy-7-acetamidonorflunitrazepam. Less than 0.2% of the dose remains as the parent drug in the urine.[3]

Clinical Presentation and Treatment

Flunitrazepam shares several adverse effects with GHB in addition to having other unique effects. Its adverse effects are summarized in Table 2. Blackouts and sedation, lasting as long as 8 to 24 hours, have also been reported. Oral doses of 28 mg have been associated with fatalities.[34]

Treatment of flunitrazepam overdose includes supportive care, enhanced elimination measures, such as gastric lavage or activated charcoal used in combination with a cathartic, and administration of a benzodiazepine antagonist, flumazenil (Romazicon, Mazicon).[34]

Prolonged use of flunitrazepam can cause physical dependence. Abrupt withdrawal from flunitrazepam can precipitate symptoms including headache, muscle pain, extreme anxiety, confusion, irritability, numbness, and tingling of extremities. Reports of more serious withdrawal signs include hallucinations, delirium, convulsions, shock, cardiovascular collapse, and seizures. Treatment of flunitrazepam dependence, including administration of phenobarbital or other benzodiazepines, should follow a gradual protocol to minimize adverse reactions.[23]

Laboratory Analysis

There are several commercial immunoassays available for the screening of benzodiazepines and their metabolites in urine. These techniques include enzyme immunoassay (EIA), fluorescence polarization immunoassay (FPIA), and radioimmunoassay (RIA).[4, 20, 46] These immunoassays are class-specific and are designed to detect a large variety of benzodiazepines and their metabolites, including 1,4-, 7-nitro-, triazolo-, and other structurally related benzodiazepines.

The most sensitive immunoassays for the detection of flunitrazepam and its metabolites in urine are the kinetic interaction of microparticles in solution (KIMS, Roche Diagnostic, Indianapolis, IN) and cloned enzyme donor immunoassay (CEDIA, Boehringer Mannheim Corporation, BMC, Indianapolis, IN) techniques. These assays demonstrate sufficient cross-reactivity to flunitrazepam and its metabolites at typical dosing levels, whereas the other immunoassay techniques offer limited sensitivity. The less sensitive immunoassays also demonstrate a diminished immunoreactivity for the 7-nitro-metabolites.[27]

To improve benzodiazepine immunoassay sensitivity, enzymatic hydrolysis can be used to deconjugate the glucuronidated metabolites before screening. A study by Beck[4] demonstrated that although pretreatment of urine specimens with β-glucuronidase effectively increases the sensitivity of the FPIA system for several benzodiazepines that are present in urine in highly conjugated form, flunitrazepam detection is not improved. In contrast, β-glucuronidase pretreatment does not significantly improve the sensitivity of the enzyme multiplied immunoassay technique (Emit, Dade Behring Diagnostics, Inc., Atlanta, GA).[4]

Moreover, the CEDIA immunoassay methodology has recently been modified to incorporate on-line hydrolysis for improved sensitivity.[5, 47]

There are several methods for the confirmation and quantification of flunitrazepam and its metabolites in biologic specimens. Boukhabza[6] investigated the simultaneous analysis of flunitrazepam, nitrazepam, estazolam, and triazolam using reverse-phase HPLC with ultraviolet detection following liquid-liquid extraction of plasma specimens with diethyl ether-methylene chloride (2:1;*v/v*).[6] Sumirtapura[51] also used reverse-phase HPLC with fluorescence detection following a multistep diethyl ether liquid extraction to identify picogram concentrations of the major flunitrazepam plasma metabolites.[51]

Although the parent compound has been successfully quantitated by GC-ECD, acid hydrolysis conversion to a detectable amino-benzophenone derivative is more commonly performed.[9, 20] Again, GC-MS offers the greatest specificity and sensitivity for the identification of flunitrazepam analytes.

AMPHETAMINE ANALOGUES

Amphetamine analogues are categorized as designer drugs because street chemists design and synthesize them to mimic the effects of other illicit drugs. In the past, changes to the chemical structure would allow the newly synthesized drug to escape regulation until the legal authorities discovered its existence. Now, the DEA can take immediate action and schedule related substances. Many times, these chemically modified versions of pharmaceutically manufactured drugs have greater potencies than the pre-existing drugs from which they are modeled. For example, a ring substitution of either phenethylamine, amphetamine, or methamphetamine forms amphetamine analogues such as MDA, MDMA, and MDEA. All of these substituted alkoxyphenethylamines have enhanced CNS and hallucinogenic effects making them popular drugs of abuse.[43] Common names and general properties of these analogues are listed in Table 1 and Figure 1, respectively.

MDMA (ECSTASY)

3,4-methylenedioxyamphetamine (MDMA) was first patented in 1914 as an appetite suppressant for soldiers in World War I. It was later evaluated in the 1970s and 1980s as an adjunct to psychotherapy because of its ability to augment self-esteem and self-insight and to enhance empathy, communication, and interpersonal relations. During the 1980s, MDMA became a prevalent recreational drug and was subsequently classified by the DEA as a Schedule I drug in 1985 after no acceptable therapeutic use could be determined. In 1994 however, the FDA formally approved human research to investigate the usefulness of MDMA in psychotherapy.[18]

Use and Misuse

Most noted therapeutically in the United States as an appetite suppressant and psychotherapy aid, other countries have used MDMA for many additional medicinal purposes. Terminal cancer patients have been treated with MDMA to relieve pain and emotional stress. It has also been used to treat patients suffering from post-traumatic stress disorder, anxiety, depression, and schizophrenia.[18]

MDMA is abused for its psychoactive and hallucinogenic effects. The hallucinogenic effects of MDMA are less intense than LSD or mescaline with visual, auditory, and tactile hallucinations reported only 20% of the time.[13, 18] Desired effects of MDMA are summarized in Table 2. MDMA users report an enhanced sociability, affability, and a feeling of closeness to friends and loved ones. Frequent or successive doses have been associated with a reduction in desired effects accompanied by an augmentation of unpleasant effects. As a consequence, many recreational users take MDMA sporadically.

MDMA can be manufactured illicitly by a relatively simple process using safrole, an active ingredient of oils from nutmeg, dill, vanilla beans, and other natural sources.[18, 48] The end product, MDMA, is a white, foul-smelling powder that is distributed as a pill or capsule.[18] The common oral dose of MDMA is 75 to 150 mg.[3, 48] Street samples of MDMA vary in content and dosage depending on the presence of adulterants and other drugs. Other less common routes of administration include IV and subcutaneous (SC) injections (IN), smoking (SM), and as a suppository.[18]

Electrolyte and energy replenishing drinks or fruit juices are commonly ingested by MDMA users at dance clubs because of the physical exertion and the potential for hyperthermia and dehydration.[7] Unlike other drugs, MDMA is not usually combined with alcohol consumption for these reasons.[18]

Pharmacology

Much of the pharmacology and toxicity of MDMA was elucidated in the 1950s by a study funded by the United States Army. MDMA acts on the CNS as an indirect sympathomimetic by releasing and preventing the reuptake of catecholamines, such as serotonin. It acts as an α- and β-adrenergic agonist leading to symptoms such as urinary retention, smooth muscle relaxation, increased heart rate, dry mouth, and appetite suppression. At low doses MDMA does not apparently have significant sympathomimetic and hallucinogenic effects, but at high doses dysphoria and amphetamine-like cardiovascular effects may occur.[12, 19]

Animal studies suggest that its chronic action on the CNS can lead to damage of the brain serotonin 5-hydroxytryptamine (5-HT) neurons resulting in mood and appetite disturbances, cognition, anxiety, and sleep disorders.[1, 43] Other studies indicate that MDMA may stimulate

dopamine release contributing to behavioral toxicity, such as rage, agitation, and psychosis.[18] Thus, the mechanism of MDMA neurotoxicity has not been fully elucidated.

MDMA undergoes *O*-dealkylation and *N*-dealkylation to form more polar metabolites. The major metabolite of MDMA, MDA, is derived by *N*-demethylation by hepatic metabolic pathways. Further metabolism by phase II metabolic pathways produce glucuronic acid and sulfate conjugates.[3, 35]

Average peak plasma concentrations of MDMA administered as a 105-mg dose approached 0.30 mg/L and were reached in approximately 2 hours.[3] MDMA's duration of action ranges from 4 to 6 hours.[12] The elimination half-life of MDMA is approximately 8 hours. Sixty-five percent of MDMA remains unchanged in the urine, whereas MDA accounts for 7% of the urinary excretion.[3]

Recreational blood concentrations of MDMA range from 0.05 to 0.34 mg/L, whereas toxic blood concentrations range from 0.11 to 1.26 mg/L. The considerable overlap between recreational and toxic blood concentrations of individuals demonstrates the danger associated with ingestion of MDMA.[12, 30] Lethal doses vary with route of administration and coadministration of other drugs.

Clinical Presentation and Treatment

MDMA intoxication can lead to tachycardia, fever, hypertension, coma, and death. Individuals with Wolff-Parkinson-White syndrome seem to be at a higher risk for sudden cardiac death from taking MDMA.[13] Table 2 summarizes adverse effects associated with MDMA toxicity. Symptoms of fatal overdose include hyponatremia, rhabdomyolysis, disseminated intravascular coagulation (DIC), and renal failure. Hepatotoxicity has also been reported. There have also been two reports of aplastic anemia; however, the source of this adversity, whether MDMA or a contaminant of the production process, remains unknown. Reports of MDMA use also describe rare intracranial hemorrhaging, subarachnoid hemorrhaging, and ruptured berry aneurysm in some fatal cases.[13, 30]

Reports of persistent neurobehavioral symptoms have been associated with single and chronic dosing of MDMA and withdrawal from MDMA. Recurrent acute paranoid psychosis, depression with suicidal intentions, panic disorder, and anxiety are some of the psychiatric symptoms.[36–39]

Treatment of MDMA overdose follows the same procedures used to treat amphetamine and methamphetamine overdose. Decontamination with either lavage or activated charcoal with cathartic techniques and enhanced renal elimination by acidification of urine are important therapeutic measures.[19] The use of pharmaceutical agents, including nitroprusside for hypertension, benzodiazepines for agitation, and haloperidol for hallucinations may also be needed.[34]

MDA (LOVE DRUG)

3,4-methylenedioxyamphetamine (MDA) is a sympathomimetic-hallucinogenic agent that was first synthesized in 1910 by Mannich and Jacobsohn of Merck Pharmaceutical Company. MDA was originally investigated as a potential psychotherapy aid and was later patented as an anorectic and antitussive agent in the late 1970s. It was never commercially distributed in the United States, however, for any of these therapeutic applications. MDA first appeared on the streets as a drug of abuse in the 1960s; its use waned until the 1980s, and its current popularity continues to increase.[30] The principal desired effects of MDA are euphoria and enhanced sociability, but others have been reported (Table 2). Presently, MDA has no medicinal use in the United States and is scheduled as a Class I drug.

MDA can be synthesized from several starting compounds, including MDP-2, a once commercially available ketone that has been subsequently regulated, or from safrole, an oil found in nutmeg, and other plants.[30]

Use and Misuse

MDA is manufactured as a racemic mixture of *d*- and *l*-isomers. The *l*-isomer is responsible for its amphetamine-like actions, including vasoconstriction, tachycardia, and mydriasis, whereas the *d*-isomer produces hallucinogenic actions. The more toxic effects are attributed to the *l*-isomer. Variations in the proportion of each isomer exist with street production; thus, the true potency is unknown to the user.[30]

Doses of 40 to 150 mg were used during therapeutic investigations of MDA. For illicit use, MDA is administered orally or intravenously in doses of 50 to 250 mg. The minimal lethal dose is 500 mg, whereas blood concentrations in fatalities ranged from 1.8 to 26 mg/L.[3, 12]

MDA is sold as a powder or liquid form of the hydrochloride salt. Like other illicit drugs, MDA purity varies depending on the addition of adulterants and other drugs. Illicit MDA has been known to contain phencyclidine or other amphetamine analogues such as MDMA and MDEA.[43]

Pharmacology

MDA and its metabolites act on the CNS by releasing norepinephrine and blocking its reuptake. Animal studies indicate that MDA metabolites do not deplete brain serotonin to mediate its toxic effects but rather another metabolite or alternative mechanism is responsible.[36] Animal studies further indicate that MDA and MDMA act on the CNS differently and demonstrate a lack of cross-reactivity. MDA has hallucinogenic effects and equipotent adrenergic actions as amphetamine.[12]

Its onset of action ranges from 30 to 60 minutes postingestion, and

the duration of its action is 6 to 10 hours.[50] Blood and plasma concentrations following a typical dose have not been determined, but predictions based on amphetamine data indicate that the concentrations should not exceed 0.4 mg/L.[3]

A limited number of studies have investigated the metabolism and excretion of MDA. Animal studies indicate that O-dealkylation, deamination, and conjugative pathways metabolize MDA to less polar forms. The two major metabolites of MDA are α-methyldopamine and 3-*O*-methyl-α-methyldopamine.[3, 36] Large urinary concentrations of MDA found in fatalities suggest that a high percentage of the drug is excreted unchanged.

Clinical Presentation and Treatment

MDA intoxication can lead to tachycardia, hyperthermia, hypertension, and death. Table 2 summarizes adverse effects associated with MDA use. In cases of acute toxicity, rhabdomyolysis, DIC, and respiratory arrest may exist. In many of the MDA deaths, extreme physical exertion and dehydration were contributing factors to the acute reaction to the drug.[30, 50] Treatment of MDA overdose follows the same procedures used for other amphetamines.

MDEA (EVE)

3,4-Methylenedioxyethylamphetamine (MDEA) is an *N*-ethyl analogue of MDA introduced about the same time as MDMA. MDEA has a lower potency than MDMA, although they are structurally and pharmacologically similar. Like MDMA, MDEA has hallucinogenic effects.[7, 43]

Use and Misuse

MDEA is listed, along with MDMA, by the DEA as a Schedule I drug because of its associated toxicity and abuse liability.[32] A common oral dose for MDEA ranges from 100 to 200 mg.[12] MDEA is sold as a "pure" form and in combination with other amphetamine analogues. Sometimes it is sold under the guise of its more familiar relative MDMA.

Pharmacology

MDEA is a sympathomimetic stimulant having peripheral and central α- and β-adrenergic effects. Its actions result in strong cardiovascular, CNS, and anorectic activity.[12]

MDEA is readily detected in urine as unchanged drug and as its *N*-

deethylation metabolite, MDA. Furthermore, conjugates of MDEA are formed by metabolism of phase II hepatic enzymes.[35]

Clinical Presentation and Treatment

There are few reported deaths directly attributed to MDEA alone. Dowling[14] summarized five cases associated with the use of MDEA and MDMA. Postmortem blood concentrations ranged from 1.0 to 1.1 mg/L for MDMA and 0.95 to 2.0 mg/L for MDEA.[14] Similarly, Cox[12] reported a death having the following postmortem amphetamine concentrations: amphetamine, negative; MDA, 0.25 mg/L; MDMA, 0.43 mg/L; and MDEA, 0.30 mg/L.[12] Anecdotal evidence from the case suggested that the individual consumed MDEA during the earlier evening hours and subsequently ingested MDMA. The MDA present was likely a metabolite of MDEA or MDMA rather than a directly ingested drug. The results, along with previously reported amphetamine data, suggest that MDEA was the primary toxic agent. In a patient surviving an MDEA overdose for a period before death, significant blood concentrations of MDA should persist.[24]

Symptoms associated with MDEA acute toxicity and overdose are summarized in Table 2. Overdose treatment of MDEA follows the same procedures used to treat amphetamine and its analogues.

OTHER AMPHETAMINE ANALOGUES

2,4,5-Trimethoxyamphetamine

In 1947, 2,4,5-Trimethoxyamphetamine (TMA) was the first designer amphetamine analogue to be synthesized. It was structured after mescaline, a psychoactive and hallucinogenic agent. The potency of TMA is twice that of mescaline. The dose required for desired effects approaches the dose responsible for toxic effects; thus, TMA is a less commonly used analogue.[30, 43]

Methyl-2,5-dimethoxyamphetamine

Methyl-2,5-dimethoxyamphetamine (DOM) was introduced in 1963. It quickly became an abused drug producing effects for which it was dubbed "serenity, tranquility, and peace" or "STP." DOM's effects are similar to mescaline in a dose of 3 mg or less. At higher doses adverse effects, including nausea, tremor, and diaphoresis occur, in addition to hallucinations. The duration of action for DOM is approximately 8 hours.[30, 43]

4-Bromo-2,5-dimethoxyamphetamine

4-Bromo-2,5-dimethoxyamphetamine (DOB) is a potent hallucinogenic and sympathomimetic agent. Compared with other amphetamine analogues, it is fairly long acting, taking 3 to 4 hours for symptoms to manifest and up to 24 hours for some residual effects to clear. An effective dose of DOB is between 2 to 3 mg. DOB can be impregnated onto blotter paper similar to lysergic acid diethylamine (LSD). In this form, it is commonly distributed in 1-cm squares that vary in dose depending on its migration on the sheet of blotter paper. DOB is a potent amphetamine analogue with many reported cases of morbidity.[30]

R, S-1-1(3′,4′-methylenedioxyphenyl)-2-butanamine

R, S-1-1(3′,4′-methylenedioxyphenyl)-2-butanamine (MBDB) is another "entactogenic" amphetamine analogue that has the ability to enhance understanding, communicativeness, and empathy without showing significant hallucinogenic effects.[35] Based on case reports, MBDB has neurotoxic potency slightly less than MDMA. Metabolic studies for MBDB are lacking in the literature and many of its pharmacologic properties have not been elucidated.

Urinary metabolites of MBDB include its desmethylated metabolite, 3,4-(methylenedioxyphenyl)-2-butanamine (BDB), and *O*-dealkylated compounds. Recently, Kintz reported the simultaneous identification of MBDB and BDB in urine, saliva, and sweat following a single oral dose of 100 mg of MBDB. Peak urine concentration occurred at 4 hours and the drug remained in the urine for 36 hours.[31]

Laboratory Analysis of Amphetamine Analogues

The analysis of amphetamine analogues is similar to the analysis of other sympathomimetic amines including amphetamine and methamphetamine. Typically, these compounds are present in fluids and tissues in high concentration.

Commercial immunoassays such as EIA, FPIA, and RIA have been used for preliminary identification of specimens containing amphetamine analogues.[11, 32, 43, 44] Polyclonal assays such as the Emit amphetamine assays, however, are relatively insensitive, having cross-reactivity to MDMA and MDEA only at high concentrations.[32] Specific immunoassay cutoff concentrations for amphetamine analogues have not been established.

Specimen preparation includes either liquid-liquid or solid-phase extraction. Before the extraction of urine specimens, hydrolysis with enzymes such as glucuronidase and arylsulfatase may be used to release conjugated metabolites that would otherwise go undetected.[35] Subse-

quent derivatization is not usually necessary to obtain acceptable chromatography; however, derivatization is used by many laboratories.

Confirmatory techniques include HPLC, GC, and GC-MS.[3, 25, 35] Chromatographically, the amphetamine analogues elute near other sympathomimetic amines, such as amphetamine and methamphetamine. Because of the potential for coelution and similarity of mass spectra, all laboratories should verify the specificity of their assays to ensure accurate identification of amphetamine analogues.

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