

Clinical Features and Management of Intoxication Due to Hallucinogenic Drugs

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Summary

Hallucinogenic drugs are unique in that they produce the desired hallucinogenic effects at what are considered non-toxic doses. The hallucinogenic drugs can be categorised into 4 basic groups: indole alkaloid derivatives, piperidine derivatives, phenylethylamines and the cannabinols. The drugs reviewed include lysergic acid diethylamide (LSD), phency-

clidine (PCP), cocaine, amphetamines, opiates, marijuana, psilocybin, mescaline, and 'designer drugs.'

Particularly noteworthy is that each hallucinogen produces characteristic behavioural effects which are related to its serotonergic, dopaminergic or adrenergic activity. Cocaine produces simple hallucinations, PCP can produce complex hallucinations analogous to a paranoid psychosis, while LSD produces a combination of hallucinations, pseudohallucinations and illusions. Dose relationships with changes in the quality of the hallucinatory experience have been described with amphetamines and, to some extent, LSD. Flashbacks have been described with LSD and alcohol.

Management of the intoxicated patient is dependent on the specific behavioural manifestation elicited by the drug. The principles involve differentiating the patient's symptoms from organic (medical or toxicological) and psychiatric aetiologies and identifying the symptom complex associated with the particular drug. Panic reactions may require treatment with a benzodiazepine or haloperidol. Patients with LSD psychosis may require an antipsychotic. Patients exhibiting prolonged drug-induced psychosis may require a variety of treatments including ECT, lithium and l-5-hydroxytryptophan.

1. Terminology

The plethora of terms used to describe hallucinogenic drugs in the medical literature is indicative of how little is known about them. The diverse chemical structures, mechanisms of action and resultant effects compound the controversy. The term 'hallucinogen', derived from the Latin 'alucinari' or 'to wander in mind', is itself ambiguous, since agents in this class do not always cause hallucinations, and true hallucinations are rare. An hallucinogen may be defined as a compound that causes gross distortions in perception without loss of consciousness when taken in non-toxic doses (West 1975). Hallucinations are frequently a component of the distortions. Hallucinogens are also likely to exert profound effects on mood, thought and behaviour, which may mimic psychoses.

Strassman (1984) suggested that the terminology used by individual investigators is dependent on the individual's orientation. Researchers who use the terms 'hallucinogenic' or 'illusionogenic' are oriented primarily to the perceptual effects of these drugs. Others interested in the psychotic effects, have used the terms 'psychotomimetic' or 'psychotogens'. The term 'psychedelic' was coined by Osmond in 1957 in an attempt to find a non-judgemental term. Psychedelic may be defined as 'pertaining to or characterised by visual hallucinations, intensified perception, or behaviour sim-

ilar to psychosis' (Dorland's Illustrated Medical Dictionary 1988). To some, the use of 'psychedelic' has the connotation of being pro-drug, whereas 'hallucinogen' is associated with being anti-drug.

Other terms used include 'pseudohallucination', 'mysticomimetic', 'phantastica', 'psychotaxic', 'psycholeptic' and 'psychomystic'. Of these, only 'pseudohallucination' can be found in the medical dictionary, and is defined as 'an hallucination induced by the exercise of memory and imagination; the person experiencing it realises that it is not real' (Dorland's Illustrated Medical Dictionary 1988). The most recent term added to the armamentarium is 'entactogen', used specifically to describe MDMA and its α -ethyl homologue MBDB (Nichols 1988) which allow a patient to reach inside and deal with painful emotional issues.

Humans have been attempting to alter their level of consciousness throughout time. It is said that the Oracle of Delphi inhaled carbon dioxide emanating from a rock fissure to produce an altered state of consciousness. Cannabis and certain mushrooms were used at the time of the Vedas (Stafford 1977). It is postulated that at the time, abuse was rare because of cultural, religious and social prohibitions (Weil et al. 1972).

In 1845 a French psychiatrist published one of the first texts on hashish (Moreau 1845). He pro-

posed that mental illness should be studied by artificially inducing it by ingesting hashish, describing the hallucinations as being similar to dreams. Moreau believed that the hallucinatory state resulted from excitation of the brain enabling imagined thoughts and memories to become transformed into visions and sounds. Although Moreau was unsuccessful in convincing his medical associates to experiment with hashish, the Bohemian artists and writers in Paris at the time were willing to indulge.

Heinrich Kluver was the first to analyse the phenomenon of drug-induced visual imagery, finding that following ingestion of mescaline, visual hallucinations could be observed with either open or closed eyes (Kluver 1926). Drug-induced visual imagery is similar to that resulting from other physical conditions. Keeler (1970) noted that there are more aetiologies of hallucinations than mechanisms, which may explain the overlap in hallucinatory experiences secondary to different hallucinogens.

Siegel and Jarvik (1975) found from their extensive research in drug-induced hallucinations that the most apparent aspect is the presence of form, colour and movement constants in the visual imagery. The constants consist primarily of lattice-tunnel forms, red colours, and exploding and rotational movements. As one's drug experience progresses, more complex imagery, such as recognisable people and objects, can be experienced.

Although the most commonly experienced hallucination involves visual imagery, tactile, auditory, olfactory and gustatory hallucinations have also been reported (Siegel 1978). Auditory hallucinations are usually unformed and experienced as indistinct noises (Malitz et al. 1962). Tactile hallucinations, sometimes referred to as haptic hallucinations, may result from cocaine or amphetamine use (Ellinwood et al. 1973; Siegel 1978). They may occur in the form of insects crawling up the skin or, after hearing a loud noise, a patient may experience a colourful hallucination. This phenomenon is termed 'synaesthetic' hallucination, and is thought to be secondary to drug-induced cortical hypersensitivity.

There are numerous classification systems for hallucinogens, and few authors are consistent in their choice. According to West (1975), the 4 major classes of hallucinogens are the indole alkaloid derivatives, the piperidine derivatives, the phenylethylamines, and the cannabinoids (West 1975). The indole alkaloids include the tyramine derivatives, such as the *Psilocybe* species of the southern Mexican mushroom, the harmine/ibogaine derivatives, and lysergic acid diethylamide (LSD). Piperidine derivatives include the anticholinergics [atropine, hyoscine (scopolamine), hyoscyamine], cocaine, ditran, phencyclidine (PCP) and ketamine. The most significant phenylethylamine is mescaline, and the amphetamine derivatives should also be included here. A detailed description of the chemical classifications is found in table I.

2. Indole Alkylamines

The indole alkylamines include drugs such as tryptamine, dimethyltryptamine (DMT), 5-methoxydimethyltryptamine, bufotenine (5-hydroxydimethyltryptamine) and psilocin. Lysergic acid amides contain an indole structure and are often included in this group, although it is suggested that they be categorised separately (Domino 1986).

While the hallucinogenic use of tryptamine derivatives dates back to the pre-Columbian era, there has been little research focused on these entities (Glennon & Rosecrans 1982). Bufotenine appears to be one of the more active tryptamines, being able to produce visual hallucinations at doses of 10 to 12.5mg (Glennon & Rosecrans 1982). It appears that, as with LSD, the site of psychoactive action of these compounds is the serotonin (5-HT₂) receptors (Lyon et al. 1988).

2.1 Lysergic Acid Diethylamide (LSD)

LSD is one of the more common hallucinogens used in the US. Originally discovered by Hoffman in 1943, its use reached a peak in the Haight-Ashbury district of San Francisco in the mid to late 1960s, but it remains a popular hallucinogen with

Table I. Chemical classification of hallucinogens

Common name	Chemical name
Indole Alkaloid Derivatives	
Psilocin	Dimethyl-4-hydroxytryptamine
Psilocybin	Dimethyl-4-phosphoryltryptamine
Harmine	7-Methoxy-1-methyl-9H-pyridol-[3,4-b]-indole
Ibogaine	
LSD	D-Lysergic acid diethylamide Lysergic acid amide Isolysergic acid amide
DMT	Dimethyltryptamine
DPT	Dipropyltryptamine
AMT	α -Methyltryptamine
DET	Diethyltryptamine
	6-Hydroxymethyltryptamine
Bufotenine	Dimethyl-5-hydroxytryptamine
Piperidine derivatives	
Atropine	N-Ethyl-2-pyrrolidylmethylphenyl-cyclopentylglycolate
Hyoscyne (scopolamine)	
Hyoscyamine	
Cocaine	
Ditran	
Phencyclidine (PCP)	1-(1-Phencyclohexyl) piperidine
Ketamine	2-(O-Chlorophenyl)-2-(methylamino)-cyclohexanone
Phenylethylamine derivatives	
Mescaline	3,4,5-Trimethoxyphenylethylamine
STP/DOM	2,5-Dimethoxy-4-methylamphetamine
DOE	2,5-Dimethoxy-4-ethylamphetamine
DOB	2,5-Dimethoxy-4-bromoamphetamine
MDA	Methylenedioxyamphetamine
DOET	Dimethoxyethylamphetamine
MMDA	3-Methoxy-4,5-methylenedioxy-amphetamine
PMA	p-Methoxyamphetamine
TMA	3,4,5-Trimethoxyamphetamine
Cannabinols	
Marijuana	Δ^9 -Tetrahydrocannabinol

adolescents (Hoffman 1975). Several studies have shown a prevalence of use in high school students approaching 10% (National Institute on Drug Abuse 1982) and it was reportedly the drug of choice in 14% of the students who reported using drugs (Schwartz et al. 1987).

LSD can be obtained from several sources. The ergot-related alkaloid is found naturally in morning glory seeds (*Rivea corymbosa*). The embryo of the seed can contain up to 25 μ g of the alkaloid (Taber & Heacock 1962). Additionally, the odourless alkaloid is produced by the parasitic fungus *Claviceps purpurea* which is associated with rye and wheat (Hoffer 1965). Epidemics of ergotism from eating contaminated rye bread were once common. The gangrenous ergotism associated with feverish hallucinations was often referred to as the 'Holy Fire' or St Anthony's Fire (Siegel 1985).

Currently, LSD is primarily derived from synthetic sources. A usual oral ingestion ranges from 100 to 300 μ g (Cohen 1984) and it has been known to be impregnated in sugar cubes, gelatine squares, powder, crackers, chewing gum, blotting paper and postage stamps (Kulberg 1986; Litovitz 1983). Following oral, nasal or parenteral administration, absorption is rapid and complete. Plasma protein binding is over 80%. The elimination half-life is about 2.5 hours and approximately 0.01% crosses the blood-brain barrier (White 1986) [table II].

The onset of effect occurs within 5 to 10 minutes, and psychosis appears within 15 to 20 minutes. Peak effects are described 30 to 90 minutes after ingestion and wane after 4 to 6 hours. The duration of the effects may be 8 to 12 hours, but psychic numbness lasts for days.

LSD is concentrated within the visual brain areas, and the limbic and reticular activating systems which correlate perceived effects. The compound is also concentrated in the liver, spleen, lungs and salivary glands.

Metabolism involves both phase I and phase II processes, including hydroxylation and conjugation with glucuronic acid. Excretion into the bile accounts for 80% of the dose. The urine may be positive for LSD for up to 120 hours after a single exposure (Barkin 1986; Goodman & Gilman 1985).

The immediate effects of LSD are a function of the amount ingested and the degree of developed tolerance. Acute intoxicating effects are seen with doses from 20 to 50 μ g administered orally or parenterally. The pupils may be dilated, and both anisocoria (unequal size) and hippus (spasmodic

Table II. Principal pharmacological properties of hallucinogenic drugs

Drug; chemical structure	Duration of acute effect (h)	pKa	Route of metabolism/excretion	Half-life	Protein binding (%)	Vd (L/kg)	Urine screen positive for	Duration of psychotropic effects	Doses of abuse	Fatal dose
Phencyclidine (PCP); arylcyclohexylamine	4-6	8.5	Hepatic/urine	1h	65	6.2 to 0.3	2 weeks	Up to 1 month	1 to 9mg	1 mg/kg
Cocaine; tropane alkaloid	0.5	5.6	Plasma hydrolysis ^a	48-75 min	8.7	1.2-1.9	144 hours	≤ 5-7 days	20-200mg (intra-nasally)	1-1.2g
Cannabis; monoterpenoid	0.5-3	10.6	Hepatic hydroxylation	25-57h	97-99	10	Up to 6 days	≤ 6h	5-15mg THC	
LSD; indole alkylamine	0.7-8	7.8	Hepatic hydroxylation	2.5h		0.27	120h	May last for days	100-300μg	0.2 mg/kg
Psilocybin; tryptamine	0.5-6						Not detected	12h	20-100 mushrooms	5-15mg of psilocybin
Mescaline; phenylalkylamine	4.6	Not known	Hepatic/urine ^b	6h	None	Not known		12h	5 mg/kg	20 mg/kg
Morphine; alkaloid/derivative of opium	4-5	8.05	Glucuronidation/urine	1.9-3.1h	35	3.2	48h	≤ 6h	2-20mg	Variable – dependent on tolerance, non-tolerant fatal dose is 120mg orally or 30mg parenterally
Heroin; diacetylmorphine	3.4	7.6	Hepatic ^c	3 min	40	25	≈ 40h	≤ 6h	2.2mg	Variable – dependent on tolerance
Amphetamine; b-(phenylisopropyl)-amine	Variable	9.93	Hepatic ^d	12h ^e	16-20	3-6	2-4 days	Delusions may remain for months	100-1000mg daily	Variable – dependent of tolerance

a By serum cholinesterase.

b 60% excreted unchanged.

c Converted to morphine.

d Converted to phenylacetone.

e Urine pH-dependent.

rhythmical dilation and constriction) are noted. Sympathomimetic effects are common. The blood pressure is moderately elevated, accompanied by tachycardia. Body temperature is moderately elevated, often accompanied by facial flushing and piloerection. Hyper-reflexia and tremors with muscle weakness in the quadriceps following the CNS effects have been widely described. Euphoria with anxiety or panic episodes are frequently experienced. Polydrug users may ingest benzodiazepines to overcome the unwanted anxiety episodes and panic experience ('bad trip') [Ellenhorn 1988; Strassman 1984].

Biochemically, the hallucinatory mechanism of LSD has been postulated as a potentiation of the excitomodulatory effect of serotonin (5-hydroxytryptamine) in the facial motor nucleus and possibly in the nucleus accumbens. This activity was noted with its non-hallucinogenic congener lisuride hydrogen maleate (Titeler et al. 1988; White 1986). This action, together with inhibition of dorsal and medial raphe neurons, may play a role in propagating and sustaining hallucinatory-related effects (Mokler et al. 1986; White 1986). Furthermore, evidence exists that LSD hallucinations involve tryptamine through an endogenous neurotransmitter mechanism (Martin & Solan 1986).

LSD has traditionally been classified as an hallucinogen, yet it has been termed an 'illusionogenic' drug, because of its ability to create synaesthesias and distortion of existing environmental stimuli (Kulberg 1986). However, it does appear that a combination of visual hallucinations and illusions play an important role in LSD effects. Sudden appearance of Satan's face in space or on another person's body was reported by 18% of users, with an additional 12% reporting dramatic aging on friends or stranger's faces (Schwartz et al. 1987). Siegel and West administered LSD to subjects in a stimulus-deprived environment. The subjects reported pulsating imagery in geometric forms in a rapid flow (Siegel 1985). Multiple colours were reported, with the incidence of red increasing as the dose increased. Complex images followed with reports of recognisable scenes, people and objects, often against a background of geometric forms.

During peak periods of the hallucinatory experience, the subjects felt that they were part of the imagery.

Hoffer (1965) categorised the changes that LSD induced into 4 groups: perceptual, thought, mood and activity changes (table III). Aggernaes (1972) found that LSD actually promotes pseudohallucinations. His patients often reported that the LSD hallucinations were not real with actual perceptions or even schizophrenic hallucinations. As Siegel (1985) has stated, it appears that the hallucinations induced by LSD are mixtures of true hallucinations, pseudohallucinations and illusions.

Violent behaviour is often associated with 'bad trips', although homicide or suicide is relatively rare (Klepfisz et al. 1973; Schwartz et al. 1987).

2.1.1 Flashbacks

Flashbacks are a recurrence of imagery that had been associated with an hallucinogen, which occurs after the acute effects of the drug have worn off. They have primarily been associated with LSD use, although they have been reported with mescaline, phencyclidine (PCP) and marijuana use (Keeler et al. 1968; McGee 1984; Yajo et al. 1981). The incidence of flashbacks among LSD users ranges from 16% to 57%, with some episodes occurring as long as 4 years after drug ingestion (Schwartz et al. 1987).

Flashbacks were triggered during times of stress, illness and exercise, as well as with marijuana and alcohol use (Alarcon et al. 1982; Schwartz et al. 1987). Most of the flashbacks were a virtual recurrence of the previous hallucinations. Perceptual distortions, disorientation, increased susceptibility to spontaneous imagery and auditory hallucinations have been consistently mentioned by users (Horowitz 1969).

The aetiology of flashbacks is unknown. Theories have been proposed relating flashbacks to a 'visual seizure' phenomenon due to LSD effects on the lateral geniculate nucleus, and benzodiazepines (diazepam) and anticonvulsants (phenytoin), and psychotherapy have been used with some success (Abraham 1983; Alarcon et al. 1982; Horowitz 1969; McGee 1984; Thurlow 1971). However, McGee (1984) proposed that flashbacks are not a

Table III. Behavioural changes induced by LSD (Hoffer 1965)**Perceptual changes****Visual**

- blurring of vision
- imagery filling
- changes in 3-dimensional space
- changes in faces or objects
- colours and coloured objects
- illusions and formal hallucinations
- changes in intensity of light
- visual perseveration (after images)
- qualitative changes in objects

Auditory

- increased or decreased auditory acuity
- inability to localise source of sound
- inability to comprehend sounds
- qualitative changes
- mixed sensation of sound

Gustatory**Olfactory****Tactile****Kinaesthetic****Changes in body image****Somatic****Sense of time passing****Thought changes****Process**

- concentration span becomes shortened
- interposed thoughts
- mind wandering
- wavelike changes in thoughts
- unable to control thoughts
- memory changes

Content**Mental testing**

- general comprehension tests
- proverb association
- problem solving
- comprehension and similarities
- digit span memory
- word association test
- numerical test subtraction (serial 7s)
- learning
- performance test
- intellectual function
- Rorschach test

Mood changes**Euphoria****Transcendental****Flat****Fear****Activity changes**

pathological entity but a function of the normal memory process and this should be classified as an atypical dissociative disorder.

2.2 Psilocybin and Psilocin

Hallucinogenic mushrooms have been used by Mexican Indians in religious rites for centuries. The hallucinogens, psilocin and psilocybin, were first isolated from these ritualistic mushrooms in 1958 (Badham 1984). The 3 major genera of mushrooms which contain psilocybin are *Psilocyba*, *Panaeolus* and *Conocybe* (Schwartz & Smith 1988). The most popular hallucinogenic mushroom among mushroom users or 'shroomers' in the United States is *Psilocybe cubensis*, while in the United Kingdom it is *Psilocybe semilanceata*. In a 1986 survey of California high school students, the reported use of hallucinogenic mushrooms ranged from 3.4% in the seventh grade (12 to 13 years old) to 8.8% in the eleventh grade (16 to 17 years old). In a survey of 1500 American college students, 15% admitted mushroom abuse compared to 5% for LSD (Schwartz & Smith 1988). A review of 297 psilocybin-related calls to the London National Poison Information Service (NPIS) between 1978 and 1981 revealed peak usage in the 15 to 19 years age group, with males comprising 83% or more of the cases (Francis & Murray 1983).

Psilocybin (4-phosphoryloxy-N,N-dimethyl-tryptamine) and psilocin (4-hydroxyl-N,N-dimethyltryptamine) belong to the group of indole alkylamine hallucinogens derived from tryptophan (Aboul-Enein 1974). Psilocybin is more resistant to oxidation than psilocin and retains its activity in dried mushrooms (Lampe 1979). Psilocin is approximately 1.5 times as potent as psilocybin, but the 2 alkaloids are otherwise pharmacologically similar (Aboul-Enein 1974). The dose which produces hallucinogenic effects in non-tolerant adults is approximately 6 to 12mg, which may require a large number of mushrooms depending on species and growth conditions (Lampe 1979). Previous series have shown little correlation between the clinical effects and the number of mushrooms ingested (Francis & Murray 1983; Mills et al. 1979;

Peden et al. 1981). The hallucinogenic dose may vary from less than 10 up to 100 mushrooms. The behavioural response will be determined not only by dose, but also by the setting, mood, personality and tolerance of the patient. The mushrooms are eaten raw, dried, as a brew, or stewed. Less than 30% of street samples alleged to be psilocybin contained the alkaloid, with the remainder containing LSD, PCP or no psychoactive drugs (Schwartz & Smith 1988).

Pharmacokinetic studies of radiolabelled psilocybin in rodents have shown 50% gastrointestinal absorption; distribution throughout most tissues including brain; excretion of 65% of the dose in urine and 15 to 20% in bile and faeces, with most of the excretion occurring during the first 8 hours, and small amounts excreted for up to 7 days (Aboul-Enein 1974). The signs and symptoms develop within 1 hour of ingestion and last from 6 to 15 hours (Mills et al. 1979). Several respondents to a survey of psilocybin cases conducted by the London NPIS reported symptoms lasting for several days, although it is unclear whether these were pure psilocybin ingestions (Francis & Murray 1983). A few subjects reported flashbacks occurring up to 4 months after ingestion of the mushrooms.

The most commonly reported effects are perceptual disorders or hallucinations, which occurred in 36% of patients reported to the London NPIS (Francis & Murray 1983), and in 85% of patients presenting to hospitals in Tayside with 'magic mushroom' ingestion (Peden et al. 1981). The hallucinations are usually visual, but may also be auditory or tactile (Peden et al. 1981). Other signs and symptoms in this series included mydriasis (74%), dysphoria (48%), hyper-reflexia (44%), tachycardia (> 100 beats/min) [37%], drowsiness (26%), and euphoria (19%). Other symptoms reported in patients ingesting *Psilocybe semilanceata* have included nausea, cramping, abdominal pain, and a sensation of swelling of body parts. Mortality appears to be very rare. There were no deaths reported among the 318 cases reported to the London NPIS between 1978 and 1981. One death has been reported in a 6-year-old child who developed hyperthermia and status epilepticus following

ingestion of *Psilocybe baeocystis* (McCawley et al. 1962).

3. Piperidine Derivatives

3.1 Phencyclidine (PCP)

Phencyclidine [1-phenyl-cyclohexyl]-piperidine hydrochloride] was first marketed as a dissociative anaesthetic by Parke Davis Laboratories in 1958. It was withdrawn from the market in 1965 following reports of postanaesthetic dysphoria, delirium and psychosis (Sioris & Krenzelok 1978). A veterinary formulation was introduced in 1967, and within a year was a major drug of abuse in San Francisco, known as the 'peace pill'. Its popularity as a recreational drug increased over the succeeding years until it accounted for 25% of all psychoactive drugs in use (Sioris & Krenzelok 1978). By April 1979, all legal manufacture of the drug was stopped.

The pattern of use of PCP in the United States is well documented in the Drug Abuse Warning Network System (DAWN 1987) [table IV]. Nearly 61% of emergency department cases of PCP occurred in Los Angeles or Washington DC, with 64% of users stating that smoking was the primary administration route, often combined with marijuana and termed 'happy sticks' or 'joy sticks'. Almost 41% of users stated that they were PCP-dependent and it has been characterised as a drug of downward mobility (Giannini et al. 1987).

The pharmacokinetic profile of PCP is summarised in table II. While its effects may be virtually instantaneous when injected, it may take up to 5 minutes when smoked at a usual dosage of 1 to 5mg (Giannini et al. 1987; Young et al. 1987). Its behavioural effects are somewhat dose related (Thompson & Morschlbaechler 1984). At doses of 5 to 10mg, excitation with agitated behaviour may predominate. A free-floating dissociative reaction may develop (Giannini et al. 1987). As the dose is increased to 10 to 20mg, catatonia (either stuporous or excited) may develop, with dystonia, myoclonus and paranoid schizophrenia. Seizures may also be present. In overdose (at doses ranging from 20 to 500mg) the patient will become comatose,

Table IV. Demographic and drug use characteristics [from data in Drug Abuse Warning Network (1987)]

Characteristic	Amphetamine	Cocaine	Heroin/ morphine	LSD	Marijuana/ hashish	PCP	Methamphet- amine
Number of ER mentions	1200	46,331	18,556	1482	10,083	9545	1555
City which has most ER mentions (no.)	San Diego (608)	New York (10,899)	New York (4590)	Los Angeles (125)	Washington DC (1469)	Washington DC (4235)	San Diego (512)
Used alone (%)	32.2	47.3	44.6	35.8	17.3	45.9	42.1
Used in combination (%)	67.8	52.7	55.4	64.2	82.7	54.1	57.9
Drug use motive (%)							
Psychic effects	24.7	22.6	10.6	54.7	36.2	35.5	47.0
recreational use	20.7	20.8	9.5	52.4	33.5	33.9	43.4
other psychic effects	4.1	1.8	1.1	2.4	2.7	1.6	3.6
Dependence	40.1	57.8	76.6	23.4	37.4	40.8	38.8
Suicide attempt/gesture	14.6	4.8	2.7	6.8	5.0	3.1	7.3
Other	1.3	0.6	0.4	2.0	1.0	1.1	0.5
Unknown/no response	19.2	14.2	9.7	13.0	20.4	19.5	6.4
Administration route (%)							
Oral	40.6	0.8	0.7	55.9	0.9	3.7	7.1
Injected	16.6	26.1	81.3	2.0	0.3	0.9	34.0
Inhaled	0.3	1.8	0.3	0.5	1.0	0.8	2.6
Smoked	1.3	29.9	0.7	2.0	76.5	64.2	4.8
Sniffed	3.2	15.1	2.4	0.5	0.6	1.7	22.2
Other/multiple		0.1	0.1	0.5		0.1	0.1
Unknown/no response	38.0	26.2	14.4	38.3	20.7	28.6	29.3
Sex (%)							
Male	58.5	65.7	68.8	75.2	72.5	74.1	62.4
Female	40.9	33.3	30.2	23.3	26.7	25.1	36.5
Unknown/no response	0.6	1.0	1.0	1.0	0.9	0.7	1.0
Number of medical examiner mentions	62	1696	1572	4	146	249	141
City (excluding New York) with most medical mentions (no.)	San Diego (60)	Los Angeles (447)	Los Angeles (428)	Los Angeles (2)	Washington DC (48)	Washington DC (103)	San Francisco (51)

with seizures and respiratory depression (Giannini et al. 1987; Young et al. 1987).

The emergency department presentation of PCP intoxication is well described. Ahmad (1987) noted that from 1.6 to 5.8% of all patients with depressed sensorium and altered personality presenting to Riverside General Hospital from 1981 to 1985 tested positive for PCP. McCarron et al. (1981a), in their study of 1000 presentations of PCP intoxication, noted that while 45.9% were alert and oriented on initial examination, 36.9% had either acute

brain syndrome or CNS depression. Violent behaviour was noted in 35.4% and hallucinations were present in 18.5%. The hallmarks of PCP intoxication – horizontal, vertical or rotatory nystagmus or hypertension – were noted in 57% of patients. Tachycardia was noted in 30% of patients.

In a companion article, McCarron et al. (1981b) classified 4 major and 5 minor clinical patterns in acute PCP intoxication. The major patterns of intoxication (with percentage of PCP intoxication in parenthesis) were acute brain syndrome (26.6%),

toxic psychosis (16.8%), catatonic syndrome (14.6%) and coma (9.2%). Minor patterns included bizarre behaviour (10.6%), violent behaviour (9.7%), agitation (3.5%), euphoria (3%) or lethargy/stupor (2.3%). Similarly, in a retrospective review, Barton et al. (1981) noted that mental/behavioural abnormalities were present in 27 confirmed cases of PCP intoxication.

Although its exact mechanism of action is unknown, PCP appears to block acetylcholine at post-synaptic sites and inhibit reuptake of noradrenaline (norepinephrine), dopamine and serotonin (Smith et al. 1979). The psychotomimetic effects appear to be related to its anticholinergic effect (Maayani et al. 1974). The catecholamines are probably most responsible for stimulant-induced psychosis, while the serotonergic system may be related to the development of tolerance and aggressive behaviour (Domino 1986; Piacente 1986; Smith et al. 1981).

Smith et al. (1978) characterised the acute behavioural effects of PCP into 4 phases: acute PCP toxicity, PCP toxic psychosis, PCP-precipitated psychotic episodes and PCP-induced depression. The basis for this psychosis, which may persist for up to 1 month, has been ascribed to its involvement with the dopamine neurotransmitter system, μ and σ opioid receptors and/or a CNS-specific PCP receptor (Giannini et al. 1987). It does appear that PCP causes violent, often bizarre, behaviour patterns that may involve self-mutilation (Moskovitz & Byrd 1983). Wish (1986) noted that 12% of male arrestees in Manhattan and 30% of arrestees in Washington DC, had a urine test positive for PCP.

The PCP toxic psychosis usually manifests itself after the acute intoxication phase has passed. Seen in chronic abusers, the patient may display impaired judgement, paranoid delusions, agitation, violent or self-destructive behaviour and a flattened effect. Auditory and visual hallucinations may occur (Smith et al. 1978). PCP-precipitated psychotic episodes may mimic clinical schizophrenia, and can occur following a single dose of PCP (Smith et al. 1978). It is thought that individuals with psychotic or prepsychotic personalities are more prone to develop this disorder (Piacente 1986).

PCP-induced psychosis parallels acute schizophrenia in terms of loosening of association, waxing and waning thought disorder, depersonalisation, response to isolation, autistic dreamy states and overinclusive thought (Domino & Luby 1981). Acute schizophrenia is more likely to be intensified by amphetamines, and to cause feelings of influence than PCP-induced schizophrenia (Domino & Luby 1981).

PCP-induced depression may occur following the PCP-precipitated psychotic reaction and may be responsible for suicides occurring in these patients. Clinically, the patients may demonstrate prolonged cerebral dysfunction, and may use PCP in an attempt to relieve their depression (Smith 1981).

3.2 Cocaine

Unlike the other hallucinogens, cocaine use and abuse has shown a steady increase in the US (Vogel & Leikin 1986) and many other countries, over the past 15 years. We are obviously experiencing an epidemic in use, whose origins date back to the mid-nineteenth century. It is the most frequently cited drug in the Drug Abuse Warning Network (DAWN) emergency room mentions (DAWN 1987).

Cocaine is an alkaloid derived from the plant *Erythroxylon coca*. It is highly lipid soluble with a volume of distribution ranging from 1 to 2 L/kg and a plasma elimination half-life of 90 minutes with the peak euphoric effect occurring within 20 minutes. The urine drug screen (for the major inactive metabolite benzoylecgonine) may become positive within 1 hour of use and can stay positive for up to 144 hours after use (Ellenhorn 1988). Street cocaine is diluted to 30 to 75%, usually leaving a 5% mixture, with an average 'line' consisting of 25mg of cocaine. The average freebase dose is 85mg (range 50 to 120) [Siegel 1982]. Intravenous cocaine is administered in doses of 10 to 15mg, which is equivalent to 10mg of dextroamphetamine (Haddad 1983). The minimum lethal dose is approximately 500mg and it is the second-ranked drug in overall deaths (next to alcohol-in-combination) in the DAWN system (DAWN 1987; Haddad 1983) [table IV].

The usage of cocaine is in constant flux. According to the DAWN system, it is smoked in 30% of emergency room episodes, with injection occurring in 26% and sniffing in 15% (DAWN 1987). However, the use of cocaine (often termed 'speed-ball') in narcotic addicts is increasing. In Chicago, heroin and cocaine are the primary combination of drugs injected by intravenous drug users not in treatment – being mentioned in 62% of 619 users (Wiebal & Horan 1988). This combination is used to diminish cocaine-associated psychomotor agitation (Siegel 1982). Additionally, it was used at least once in the week prior to interview by 36% of 368 methadone maintenance clients, with 28% using it up to 6 times weekly (Hunt et al. 1984).

Although cocaine is a powerful stimulant with positive reinforcing actions, its overall mechanism of action relating to its hallucinatory effects are poorly understood. It blocks the presynaptic uptake of noradrenaline, serotonin and dopamine in a manner similar to that of amphetamine. Furthermore, repeated cocaine use is thought to decrease brain dopamine levels (Wyatt et al. 1988a). However, unlike amphetamine, it does not release presynaptically stored monoamine transmitters. Its actions on the serotonin pathway are primarily inhibitory (Taylor & Ho 1977).

The clinical behavioural spectrum of cocaine use can practically be divided into 3 syndromes: cocaine euphoria, cocaine dysphoria and cocaine schizophreniform psychosis (Post 1975).

3.2.1 Cocaine Euphoria

Euphoria is a nearly constant effect of cocaine use. It was described in 100% of 85 cocaine abusers (Siegel 1977) and is related to dopamine activation (Dackis & Gold 1988). It may occur with cocaine doses as small as 5mg (Post 1975). The alternation of dopamine activation in acute ingestion and dopamine depletion in chronic administration leads to craving. This dopaminergic alternation has been hypothesised as a cause of intense cocaine addiction (Dackis & Gold 1988; Wyatt et al. 1988b). Symptoms such as increased sexual arousal, anorexia, insomnia, hyperactivity, elation, loquacity, grandiosity and psychomotor agitation can occur

within 1 hour and the patient may appear manic (Post 1975; Siegel 1982). Approximately 20% of chronic abusers of cocaine meet the DSM III manic depressive criteria, while only 1% of opiate abusers meet these criteria (Wyatt et al. 1988a).

3.2.2 Cocaine Dysphoria and Nervousness

Dysphoria and nervousness appear to be more dose-related (Post 1975). The response rate to cocaine self-administration in rats decreases as the dose increases (Pickens & Thompson 1968). Depression was noted in 43% of 'crack' users, 53% of freebase users, 64% of intravenous users and 32% of intranasal users. Additionally, 33 of 75 patients presenting to San Francisco General Hospital were described as anxious, agitated or depressed (Lowenstein et al. 1987). Suicidal ideation was noted in 18 patients. This depression, characterised by inability to concentrate, painful delusions, apathy and decreased verbal behaviour is thought to be related more to the depression associated with cyclothymic disorders than endogenous depression (Post 1975).

3.2.3 Cocaine Psychosis

Cocaine psychosis usually follows the dysphoric phase in the chronic abuser. This psychosis may resemble acute paranoid schizophrenia and is analogous to that seen with amphetamines. The psychosis is characterised by paranoid ideation, stereotyped behaviour, delusions, loss of impulse control, hallucinations and violence. The psychosis and violence appear to correlate more with crack use than with any other form of cocaine (Honec et al. 1987; Siegel 1982). In a recent study of 137 patients presenting to a university medical centre emergency department as a result of cocaine use, 40 (31.2%) had altered mental status (consisting of hallucinations, paranoia, agitation, confusion and aggressive behaviour) as a chief complaint (Derlet & Albertson 1989). The correlation between this drug and aggressive behaviour was shown in Chicago, where arrestees for street crimes are more likely to have urine positive for cocaine than any other illicit substance (55% of males testing positive and 74% of females testing positive) [Wiebal & Horan 1988].

The biochemical basis for the psychosis (which

resembles amphetamine psychosis) is under investigation. It was suggested that the noradrenergic rather than the dopaminergic system is responsible for this effect (Wyatt et al. 1988b). However, a recent report correlated degree of focused suspicious behaviour approaching overt paranoia with amount of cocaine administered and baseline homovanillic acid levels (Sherer 1988).

The nature of cocaine-induced hallucinations has been better characterised. In Siegel's (1978) report of cocaine-induced hallucinations in 85 recreational cocaine users, 37 (43.5%) experienced perceptual phenomena (consisting of increased sensitivity to light, halos around bright lights, difficulty in focusing due to chronic mydriasis) and 15 users (17.7%) reported hallucinatory phenomena. These experiences were multisystem and characterised in the following manner:

1. Visual hallucinations (13 subjects or 15% of users) characterised initially by object movement in the periphery of the field, followed by geometric patterns located approximately 2 feet in front of the eyes. Four subjects experienced polyopia (duplication of objects).

2. Tactile hallucinations (11 subjects or 13% of users) occurring after several days of use; involved the sensation of 'moving itches' primarily of the hands.

3. Olfactory hallucinations (6 subjects), involving the perception of odours such as gasoline, faeces and urine. Four of these users had evidence of nasal damage.

4. Auditory hallucinations (3 subjects or 3.5% of users), usually characterised as 'whispering'.

5. Gustatory hallucinations (3 subjects or 3.5% of users), associated with olfactory changes as well as attentional dysfunction.

4. Phenylethylamine Derivatives

4.1 Mescaline

Mescaline (3,4,5-trimethoxyphenylethylamine) is the hallucinogenic alkaloid found in the North American peyote cactus and in several species of South American *Trichocereus* cacti. Peyote (*Lo-phophora williamsii*) is a small spineless grey-green

cactus native to the Rio Grande valley of Texas and northern and central parts of the Mexican plateau. The ritual use of peyote in central Mexico is documented from the sixteenth century and is preserved in the practices of the Native American Church (La Barre 1979). Mescaline was first isolated from peyote in 1896 and synthesised in 1918.

Peyote is commonly ingested in the form of brown discoid 'mescal buttons' which are the sundried crowns of the cactus (Mack 1986). Each button may contain 45 to 100mg of mescaline (Schwartz 1988). The hallucinogenic dose in humans is approximately 5 mg/kg, and users typically ingest 3 to 8 buttons. Mescaline tablets may be either synthetic mescaline or ground peyote which has been compressed into a tablet. Genuine peyote and mescaline are rare outside the southwestern United States and Mexico, and assays of street samples have shown that less than 17% of the samples actually contained mescaline (Schwartz 1988).

Mescaline is absorbed rapidly from the gastrointestinal tract, and 87% of radiolabelled mescaline is excreted in the first 24 hours, with an elimination half-life of 6 hours. The physiological and psychological effects usually appear within 30 minutes, peak at 4 hours, and last 8 to 14 hours (Hollister & Hartman 1962).

Ingestion or intravenous administration of mescaline causes initial symptoms of nausea, vomiting, sweating, generalised discomfort, dizziness and headache (Kapadia & Favez 1970). These symptoms are accompanied by autonomic signs including tachycardia, pupillary dilatation, and a small rise in body temperature and systolic blood pressure. Reflex bradycardia may sometimes be seen (Kapadia & Favez 1970) and larger doses can cause hypotension, bradycardia and respiratory depression (Ellenhorn et al. 1988).

The unpleasant symptoms resolve within 1 to 2 hours, although the autonomic signs persist during the psychic phase which begins several hours after ingestion. It consists of a general feeling of well-being, euphoria, a great sense of physical power and distortions of sensory perceptions (Mack 1986). Visual hallucinations are common and consist of intense visions with vivid colours and geometric

patterns (Mack 1986). Auditory, gustatory and olfactory hallucinations and synaesthesias also occur but are less frequent (Hollister & Hartman 1962). Users may experience paraesthesias, depersonalisation, a dreamlike feeling and disorientation of time or space. Euphoria with laughter occurs initially, which may give way to anxiety and depression (Kapadia & Favez 1970).

In an experimental setting, subjects given 5 mg/kg of mescaline orally showed a significantly increased perception of colour evoked by flicker, which is normally an inadequate stimulus for eliciting colour perception (Hollister & Hartman 1962). At the same time response to an adequate stimulus (the Farnsworth-Munsell colour discrimination test) was reduced. The authors felt that these findings support the hypothesis that unusual colour perception following psychotomimetics may result from the action of normally inadequate stimuli.

The psychic phase of mescaline intoxication lasts for approximately 6 hours, after which the user may fall asleep. Tolerance to the psychic, but not the vegetative, phase develops rapidly if mescaline is used on a daily basis. This tolerance regresses rapidly 3 to 4 days following withdrawal (Kapadia & Favez 1970). Physical dependence does not occur (Mack 1986).

4.2 Hallucinogenic Amphetamines

Amphetamine abuse is becoming increasingly prevalent in the US, especially in terms of illicit production. Methamphetamine laboratories accounted for 82% of all illicit laboratories seized in the US by the Drug Enforcement Agency in 1988 (DAWN Briefings 1989). Additionally, over the past 2 years, the number of emergency department cases involving methamphetamine have doubled and deaths have increased 80%. While most of this activity is in the western US, the National Institute on Drug Abuse warns that US-produced methamphetamine looms as a potential drug crisis for the 1990s (DAWN Briefings 1989).

Amphetamine abuse falls into 2 categories: (a) abuse in association with opiates to take advantage of its stimulant action; and (b) abuse singularly with

amphetamine and methamphetamine analogues (the 'designer drugs').

Up to 25% of the 20,000 heroin addicts in the Italian province of Liguria also use stimulants (Keup 1986). Furthermore, in West Germany fenethylamine was abused by 16.1% of 700 abusers, with a dependence rate of 64.4%, indicating a high abuse potential (Keup 1986). This CNS stimulant is a combination of xanthine and amphetamine (Harris 1986). Fenethylamine appears to have low potential as a primary drug of abuse, shown by its lack of reinforcing properties or euphoric effect in cocaine-dependent monkeys (Kristen & Schaefer 1986).

However, of interest is the use of amphetamine derivatives such as methylenedioxymphetamine (MDA) and its derivative 3,4-methylenedioxymphetamine (MDMA). These are included in the category of 'designer drugs', which also includes 2 opioid analogues, pethidine (meperidine) and fentanyl (Beck & Morgan 1986; Climko et al. 1986-7).

MDA, which was widely abused in the US between 1960 and 1973, primarily exhibits 3 mechanisms of action: the release of noradrenaline (nor-epinephrine) and blockade of its reuptake, MAO inhibition, and binding with 5-hydroxytryptamine receptors, which may account for its behavioural effects (Climko et al. 1986-7; Fellows & Bernheim 1950; Glennon & Young 1984). While its hallucinogenic effects appear confined to serotonergic actions, MDA does not produce visual or auditory hallucinations as does mescaline, but diminishes anxiety, enhances emotions and empathy and exhibits some aphrodisiac properties (Climko et al. 1986-7; Nichols 1986).

However, probably the prototype of designer drugs is MDMA. First synthesised in 1914 as an appetite suppressant, since 1982 MDMA has been a popular recreational drug, commonly known as 'Ecstasy', 'XTC' or 'Adam' (3,4-methylenedioxymphetamine or MDEA is known as 'Eve'). Street doses range from 16 to 150mg, with toxic effects appearing at doses greater than 100mg (Hayner McKinney 1986).

Whether MDMA should be classified as an hal-

lucinogenic amphetamine is controversial. Previous studies have suggested that addition of the *N*-methyl group to the structure of an amphetamine results in diminution of hallucinogenic activity (Shulgin 1978; Winter 1980). Due to its pronounced effects of increased intimacy, improved awareness and communicative properties, it has been advocated as having some use in psychotherapy (Greer & Tolbert 1986; Leverant 1986; Nichols 1986). Greer and Tolbert (1986) noted that after administration of 75 to 150mg of MDA there was improvement in 9 patients with DSM III psychiatric diagnoses, and a decrease in substance abuse was seen in 14 subjects. 16 subjects experienced undesirable emotional symptoms, and 4 subjects reported undesirable cognitive symptoms (Greer & Tolbert 1986). Nichols (1986) advocated that MDMA should not be considered as an hallucinogen or even an empathogen, but as an 'en-tactogen' (see section 1).

However, Siegel (1986) in his review of 44 users documented perceptual changes in 19 subjects (44%), consisting of attentional dysfunction, blurred vision and accommodation difficulties. Additionally, 9 subjects (20%) reported illusional experiences with pseudohallucinations. Nine subjects (20%) reported visual hallucinations, such as sensation of object movement in peripheral visual fields and following ingestion of more than 300mg, geometric patterns that became coloured.

Also of interest are the reports of polyopia (duplication of objects) and dysmegalopsia (distortion of size of objects), which can also occur with mes-caline or cocaine use (Kluver 1942; Siegel 1978, 1986). Doses of 500 to 700mg produced tactile sensations of lightness and floating in 3 subjects, and transient auditory sensations were also noted in 3 subjects.

Serious toxic effects are well documented. A case of severe hypertension, diaphoresis, decreased mental status and hypertonicity with opisthotonic movements was noted in a 50-year-old man taking MDMA concurrently with the monoamine oxidase (MAO) inhibitor phenelzine (Smilkstein et al. 1987). No immediate improvement occurred after intravenous administration of diphenhydramine 50mg,

but following supportive care mental status improved by about 7 hours after ingestion and blood pressure normalised 12 hours after ingestion. Five deaths have been reported associated with MDMA and DMEA use in young (18- to 32-year-old) users (Dowling et al. 1987). MDMA was thought to be the immediate cause of death in one 18-year-old female, who apparently took 150mg of MDMA (resulting in a blood concentration of 5.2 $\mu\text{mol/L}$) and subsequently developed ventricular fibrillation.

5. *Cannabinols*

Cannabis sativa, a hemp plant, may contain more than 60 cannabinoid compounds (Razdan 1986), the greatest concentration of psychoactive compounds occurring in the flowering top. The primary psychoactive cannabinoid is Δ^9 -tetrahydrocannabinol (Δ^9 -THC). Agents containing Δ^9 -THC include marijuana, hashish, hash oil and the prescription drugs dronabinol and nabilone (Goodman & Gilman 1985; Mechoulam & Feigenbaum 1987; Poster et al. 1981; Ward et al. 1985; Weintraub & Standish 1983). An increase in heart rate and cardiac output may be generally anticipated after smoking marijuana (Bloodworth 1985; Vieweg & Hillard 1986). Blood pressure upon standing is decreased, especially with larger doses. Prolonged use of moderate to higher doses may decrease heart rate and produce signs and symptoms of congestive heart failure. A dose-related increase in both systolic blood pressure and heart rate has been observed with acute doses. Body temperature may be slightly decreased (Clark 1987). CNS effects include drowsiness, euphoria (which appear within 30 to 120 minutes), heightened sensory awareness, paranoia (Ghodse 1986), hallucinations (Aghajanian 1977) and distortions of time and space. Seizures have been reported in users with or without a seizure history. An irritable cough may lead to a chronic respiratory syndrome (Goodman & Gilman 1985; Halikas et al. 1982; Institute of Medicine 1982; Jones 1983; Mendelson & Mello 1984; Perez-Reyes et al. 1981; Petersen 1980; Pet-
twee 1988; Tunving 1985).

Less than 50% of Δ^9 -THC is absorbed system-

ically into the circulation following inhalation. Onset of action and peak plasma concentrations occur in less than 10 to 12 minutes. The peak intensity of effect is reached within 30 minutes and lasts for 180 to 240 minutes (Hollister et al. 1981; Hunt & Jones 1980). Less than 10% is absorbed after oral ingestion. The effects begin within 1 hour and last for up to 6 hours. Peak plasma concentrations are reached within 2 to 3 hours.

Δ^9 -THC is highly (97 to 99%) bound to plasma protein and partitioned into lipid tissue sites. Upon depletion of lipid storage sites, prolonged excretion will produce detectable urine concentrations for up to 6 days (table II).

Δ^9 -THC undergoes extensive hepatic first-pass metabolism to the 11-hydroxy metabolite which has psychomimetic effects similar to the parent compound. Phase II oxidation produces inactive 11-nor- Δ^9 -THC-9-carboxylic acid, which comprises the major portion of the metabolites following inhalation and oral ingestion. Additionally, concentrations of this metabolite are detectable in the plasma for up to 6 days after smoking a marijuana cigarette. Excretion occurs within 72 hours, with 10 to 15% of a dose appearing in the urine and 1% excreted in the faeces (Caridland et al. 1983).

After 72 hours, about 15 to 20% of Δ^9 -THC is eliminated as acidic metabolites in the urine, and 30 to 35% is eliminated in the faeces. In chronic Δ^9 -THC users detectable cannabinoid metabolites may appear in the urine for 6 to 7 weeks after an exposure. The half-lives of the metabolites are about 3 to 8 days.

It is important to note that infrequent users may test positive for carboxy-THC, the major urinary metabolite, for up to 6 days after exposure, more frequent users may test positive for 3 to 4 weeks, while chronic users may test positive for up to 6 to 7 weeks (Baselt 1985; Morgan 1988; Morland et al. 1985; Perez-Reyes 1983). Thus, a positive urine test for cannabinoid metabolites only reflects marijuana exposure within weeks prior to urine collection, and is unrelated to time or degree of exposure, state of intoxication or task performance (Fehr & Kalant 1983; Finnegan & Fehr 1980; Law et al. 1984; Martin 1986). Prolonged secretion is a

function of the high lipid solubility and slow release into plasma tissue of Δ^9 -THC (King et al. 1987).

The primary effect of Δ^9 -THC within the CNS and cardiovascular system is a combination of serotonergic, cholinergic and catecholaminergic effects. Psychomimetic actions may involve the serotonergic pathways (Dewey 1986).

A 'joint' of marijuana leaf weighing 0.5 to 1.0g in the past produced an average Δ^9 -THC yield of 1 to 2% (5 to 20mg). During the late 1970s the content of active drug increased to 7 to 8% due to selective cultivation and more environmental control to produce higher yields. Hash oil contains 30 to 50% Δ^9 -THC and hashish contains 3 to 6% (Perez-Reyes et al. 1982).

Cannabis intoxication produces variable alterations in both physiological and psychological functioning, cognitive functioning or mood states. Such disruptive consequences are not uncommon following moderate to high level use (Jones 1987; Kandel 1984).

Mild cannabis intoxication (occasional users: 8 to 10g per month) produces a sense of well-being, relaxation, alteration in perceptual distortions of time and space and an increase in visual and auditory sensory awareness. The duration of euphoric effects is 3 to 4 hours and is often coupled with fatigue (Dewey 1986; Institute of Medicine 1982; Jones 1983).

Moderate cannabis intoxication (moderate users: 30g per month) produced mood swings, impaired recall and memory deficit and depersonalisation or distortions of self perception, a loss in identity in relation to others, and loss of feeling of reality and task performance impairment.

Excessive cannabis intoxication (chronic users: 60g per month) produces neurological effects: ataxia, speech slurring, decreased and impaired motor coordination, anxiety (which may progress to a panic episode), hallucinations, delusions, paranoid behaviour, a motivational syndrome and, rarely, stimulation (Tunving 1985; Ward & Holmes 1985; Wert & Raulin 1986).

Additional intoxicating effects include:

1. Injected conjunctiva due to congested blood

vessels from the low grade anaesthetic effect of Δ^9 -THC. Tolerance to 'red eyes' does not occur.

2. Respiratory bronchial and pulmonary irritation and coughing; bronchodilation with improved pulmonary toilet (acute effect), dose-related bronchoconstriction with compromised pulmonary function (chronic effect).

3. Tachycardia and increased cardiac output exacerbating angina pain; decreased exercise tolerance.

4. Increased hunger and appetite, urinary retention, diminished lower intestinal motility, xerostoma, dry throat.

5. Diminished cell-mediated immune response.

6. Impaired fertility with chronic use (in males may decrease plasma testosterone, decrease sperm counts, cause structural abnormalities in sperm and impair motility; in females abnormal menstruation and decreased ovulation) [Mendelson et al. 1984; Morishima 1984; Tennes 1984].

Perceptual alterations with characteristic synaesthesia are reported. Perception in one sensory system overflows into another sensory system and a sensory amalgamation develops. Frequently the user describes hearing colours and seeing strands of tastes. The affect is often inappropriate with illusions, hallucinations, time/vision distortions as a loss of feeling of reality. Depersonalisation is described as perceiving one's own body as unreal, with a loss of body boundary along with alteration of kinaesthetic sense (perception of the body position in space). The user-specific desirable effects ('good trip') are hypersuggestibility, intensified emotional-based perception, with a dreamy timelessness sensation and stimulus-induced sensitivity. Hallucinations are multisensory, including visual, auditory, tactile and lacking fantasy/reality discrimination. Tolerance to behavioural effects occurs with daily use and cross-tolerance to other hallucinogens is reported (Barkin 1986; Mendelson 1987).

6. Other Hallucinogens

6.1 Opiate Agonists

Central nervous system and gastrointestinal sites are the most prominent receptor sites for opiate-like substances. The highest concentrations of op-

Table V. Opiate receptor effects

Opiate receptor	Standard agonist	Effect
μ_1	Morphine	Supraspinal analgesia
μ_2	Morphine	Respiratory depression Chemical dependence Constipation Euphoria
κ	Nalbuphine Butorphanol Pentazocine	Spinal analgesia Sedation Miosis
σ	Pentazocine	Psychomimetic effects (dysphoria, hallucinations) Tachycardia, hypertension Respiratory and vasomotor stimulation
δ	Endogenous opioid peptides	Analgesia, affect alterations, limbic region

iate receptors are found in the limbic system, thalamus, hypothalamus, striatum, midbrain and spinal cord. Several types of opiate receptors have been identified: μ -receptors, localised in the CNS pain centre; κ -receptors localised in cerebral cortex deep layers; δ -receptors localised in limbic regions; and σ -receptors (AMA 1988; Clouet & Yonehara 1984; Manara & Bianchetti 1985; McFadden 1988; Pasternak 1988; Schulz & Herz 1984; Simon & Hiller 1978; Way 1986) [table V].

Morphine, the standard of comparison, has greater agonist activity at μ - than κ -receptors, some activity at δ -receptors and minimal activity at σ -receptors (Bozarth & Wise 1984; Chang & Cuatrecasas; Mazoit et al. 1987; Sicuteri 1978; Simon & Hiller 1978; Snyder 1978; Snyder et al. 1981, 1984).

Opiate agonists act at multiple sites to produce analgesia (Akil et al. 1984; Goldstein 1984; Gustafsson & Wiesenfeld-Hallin 1988; Johnson et al. 1985; Koob & Bloom 1988; Pasternak et al. 1980; Simon & Hiller 1978; Snyder, 1984). These effects include: (a) altered pain perception at spinal and supraspinal CNS levels; (b) altered emotional response to pain; and (c) altered central release of neurotransmitters from afferent nerves sensitive to noxious stimuli.

Opiate agonist non-analgesic CNS effects include drowsiness, sedation, insomnia, mood changes, euphoria, dysphoria, mental clouding, apathy, confusion, light-headedness, dizziness, agitation, fear, hallucinations and performance deficits (Dukes 1980). Nausea (stimulation of chemoreceptor trigger zone in medulla oblongata or from orthostatic hypotension) and vomiting (stimulation of chemoreceptor trigger zone initially produces vomiting; subsequent doses depress vomiting centre) are not infrequent in ambulatory patients. Vestibular sensitivity may also increase nausea and vomiting incidence. EEG changes and diaphoresis are reported with doses greater than those of analgesic doses; other events reported are anaesthesia, excitation, and seizures. A decrease in auditory and olfactory acuity has been noted (Jellema 1987; Pfau & Gurzalka 1987; Roth et al. 1985; Waller & Bailey 1987; Wise & Bozarth 1985).

Some opiates are well absorbed orally, others must be parenterally administered. Opiates are rapidly removed from the blood (Laitinen et al. 1975) and distributed, in decreasing order of concentration, into skeletal muscle, kidney, liver (Mazoit et al. 1987), intestinal tract, lungs, spleen, and brain. Morphine is metabolised through the hepatic microsomal enzymes in the endoplasmic reticulum and in other sites (Misra 1978), such as the CNS, kidney (Chan & Matzke 1987), lungs and placenta. Metabolic pathways include conjugation with glucuronic acid, hydrolysis, oxidation and/or *N*-dealkylation. Bioavailability is 20 to 30%, with excretion occurring in the urine (90% in 24 hours) in unchanged form and metabolites, in the bile (10%), and in the faeces in small amounts. The comparative pharmacology is shown in table VI (Dahlstrom et al. 1982; Dixon et al. 1983; Edwards et al. 1982; Glynn & Mather 1982; Gourlay et al. 1982; Inturrisi et al. 1982; Sawe et al. 1981; Swerolow & Holley 1987).

6.2 Synthetic Opioids: 'Designer Drugs'

A recent trend in street drug abuse is the use of 'designer' opioid drugs. Two major opioids constitute the foundation of this trend: the analogues

of fentanyl and pethidine (meperidine). It is of interest that both analogues originated in California: fentanyl being located in Southern California and pethidine in Northern California.

Fentanyl has a relatively short onset of action (30 minutes), and is used primarily as an analgesic which is 80 to 100 times as powerful as morphine. Its analogues were often called 'China White' from the street name of pure heroin processed in Southeast Asia (Ayres et al. 1981). These analogues, 3-methylfentanyl, α -methylfentanyl, *p*-fluorofentanyl and 2-methylfentanyl, were said to be 1000 to 2000 times more potent than morphine.

While it was estimated that up to 20% of California's addicts were regular users of these analogues, there appeared to be a difference between users of fentanyl and heroin (Beck & Morgan 1986). In one study, 88% of users stated they preferred the intoxication of heroin to fentanyl, and that the fentanyl rush was more subtle than that of heroin. However, the 'nod' related to fentanyl was longer (2 to 4 hours) and the 'come-down' was more gradual than with heroin (LaBarbera & Wolfe 1983).

The major problem associated with fentanyl analogues is that in novice users, respiratory depression and death may occur very rapidly. During 1 year, 19 deaths were ascribed to fentanyl analogues in San Diego. These deaths occurred with such rapidity that the needle was often found in the injection site (Manoguerra et al. 1985).

The pethidine derivatives MPPP (1-methyl-4-phenyl-4-propionoxypiperidine) and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) were found on the street in Northern California in the early 1980s (Buchanan & Brown 1988). Structurally similar to paraquat, these analogues have been shown to selectively destroy neuronal tracts in the substantia nigra (Fellman & Nutt 1985). Thus symptoms consistent with idiopathic Parkinson's disease persisting for as long as 18 months have been described in intranasal and intravenous users (Davis et al. 1979).

Table VI. Comparative pharmacology of narcotic agonists

Drug	Onset of effect (min)	Peak of effect (h)	Duration of effect (h)	$t_{1/2}$ (h)	Equianalgesic doses ^a	
					IM (mg)	oral (mg)
Morphine	15-60	0.5-1	3-7	2-4	10	60
Levorphanol	30-90	0.5-1	4-8	12-16	2	4
Hydromorphone	15-30	0.5-1	4-5	2-3	1.5	7.5
Oxymorphone	5-10	0.5-1	3-6	ND	1	6
Methadone	30-60	0.5-1	(4-6)	15-30	10	20
Pethidine (meperidine)	10-45	0.5-1	2-4	3-4	75	300
Codeine	15-30	0.5-1	3-6	3	130	200
Oxycodone (oral)	15-30	1	3-6	ND	ND	30
Propoxyphene (oral)	30-60	2-2.5	4-5	6-12		
Hydrocodone	30-60	0.5-2	4-8	3.3-4.5	ND	15-20

a Based on acute, long term use; during long term morphine therapy the oral : parenteral ratio decreases to 1.5-2.5 : 1.

Abbreviations: $t_{1/2}$ = elimination half-life; IM = intramuscular; ND = no data.

7. Management of Hallucinogenic Drug Toxicity

Simple hallucinations are rarely a presenting complaint among users of psychedelic drugs, since that is the pleasurable, desired effect of such drug use. However, hallucinogenic drugs may give rise to acute panic reactions, flashbacks, or acute or chronic psychoses. In the acutely anxious, hallucinating or psychotic patient presenting to the emergency department, the clinician must attempt to answer the following questions: (a) Are the patient's symptoms organic or psychiatric? (b) If organic, are they of a medical or toxicological aetiology? and (c) If toxicological, are there clues to a specific aetiology (in particular, adrenergic or anticholinergic)?

Failure to distinguish organic from psychiatric, medical from toxicological or adrenergic from anticholinergic syndromes may result in the improper management of a patient, with a potentially adverse outcome.

All patients presenting with acute psychiatric symptoms should be carefully evaluated for evidence of organic disease. A thorough history of the current symptoms, and of premorbid functioning, personal or family history of psychiatric disease, and recent or chronic drug ingestion, should be

sought from patient, family or friends. Accurate vital signs must be taken, and a careful physical examination, with particular attention to neurological function, must be done.

A reliable physical examination may initially be difficult in an uncontrollably agitated or potentially violent patient. Such circumstances do not lessen the need for such an examination. The use of neuroleptics, benzodiazepines and barbiturates in the emergency management of violent patients has recently been reviewed by Brizer (1988).

Laboratory investigations should include electrolytes, tests of renal and hepatic function, complete blood count, urinalysis, and toxicological screening of blood and urine for suspected drugs. In patients suspected of acute intoxication, an ECG and arterial blood gases may be required to uncover unsuspected drug toxicity or adverse effects on the cardiopulmonary system.

Fever, neck stiffness, neurological deficit, electrolyte abnormality or any other feature of the history, physical examination or laboratory evaluation which suggests an infectious, inflammatory, structural CNS or any other medical cause of the patient's illness should be vigorously pursued. Behavioural emergencies should be presumed to be of organic aetiology until proven otherwise. A toxic aetiology may be suggested by the history or physical exam, and may be supported by toxicological

screening (see table II). Therapeutic agents associated with hallucinations are listed in table VII.

Ingestion of LSD, sympathomimetics or cocaine, or an acute panic reaction from any cause, may give signs of adrenergic hyperactivity including tachycardia, mydriasis, diaphoresis and hyperactive reflexes. These findings are generally less prominent in LSD intoxication than in sympathomimetic intoxication. The hyperadrenergic state of PCP can be distinguished from the above by the characteristic small, fixed pupils, and the presence of lateral nystagmus. It is important to differentiate the hyperadrenergic state from that of anticholin-

ergic intoxication, which will also produce tachycardia, pupillary dilatation and general agitation. Careful examination in anticholinergic poisoning will show dry, flushed skin, fixed pupillary dilatation, dry mucous membranes and an absence of sweating, and evidence of gastrointestinal hypomotility and urinary retention. Δ^9 -THC causes dilatation of conjunctival vessels, giving the characteristic 'red eye'.

The management of PCP and anticholinergic poisonings are substantially different from that of the other major hallucinogenic drugs, and these are discussed separately.

Table VII. Therapeutic drugs associated with hallucinations^a

Drug	Type of hallucination	Drug	Type of hallucination
Acyclovir	V,T	Imiprimine	V
Amantidine	A,V	Indomethacin	V,O
Baclofen	A,V	Isosorbide	V
Benztropine	V	Levodopa	A,V
Biperiden	V	Lorazepam	V
Bromocryptine	A,V	Orciprenaline (metaproterenol)	V,G
Carbamazepine	V	Methyldopa	V
Chlordiazepoxide	V	Methylphenidate	V
Chlorpheniramine	A,V	Methylprednisolone	V
Chlorpromazine	A,V	Minocycline	V
Cimetidine	A,V	Pemoline	A,V,T
Clonazepam	A,V,T	Phenylzine	A,V
Clonidine	A,V	Phenylephrine	A,V
Cyclosporin	V	Pindolol	A
Dantrolene	A,V	Procainamide	V
Dextromethorphan	A,V	Propranolol	V
Diethylpropion	A	Quinidine	NS
Digoxin	A,V	Ranitidine	A,V
Dimenhydrinate	A,V	Streptokinase	N,S
Diphenhydramine	V	Sulphasalazine	V
Disopyramide	A,V	Timolol	NS
Ephedrine	A,V	Triazolam	A,V,T
Gentamicin	NS	Trihexphenidyl	A,V
Griseofulvin	A	Vidarabine	NS
Hyoscine (scopolamine)	NS		

^a This table was prepared from the following sources: Gelam & Rumack (1989), Brown et al. (1980), Black & Woollacott (1974), Darc et al. (1976), Davies (1976), Herridge & A'Brook (1968), Jeffrey & Whitfield (1974), Polchert & Morse (1985), Tomson et al. (1985), AMA Drug Evaluations (1983), White et al. (1983).

Abbreviations: A = auditory; V = visual; T = tactile; G = gustatory; O = olfactory; NS = not specified.

7.1 Acute Hallucinoses and Acute Panic Reactions

LSD is the prototypic drug which gives rise to acute panic disorders, psychoses and flashbacks, although mescaline, psilocybin and psilocin can have similar effects. The acute panic disorder is characterised by frightening illusions or hallucinations, tremendous anxiety, apprehension and a terrifying sense of loss of self-control (Taylor et al. 1970). Patients lose insight that their symptoms are drug-induced, and become terrified that they are losing their minds. Treatment should be directed at relieving the patient's overwhelming anxiety (Ungerleider & Frank 1976). They should be treated in a quiet room, with a soothing, reassuring and non-judgemental approach, and should not be left alone. The majority of patients can be 'talked down' by repeated orientation (who, and where they are), explaining that they are experiencing drug-related symptoms, and they are not 'going crazy'.

More severe agitation may require the use of a benzodiazepine or haloperidol. Diazepam 5mg orally or intravenously may be given every 1 to 2 hours as needed. The dose may be titrated up according to patient response. When benzodiazepines are inadequate to control agitation, haloperidol 5 to 10mg intramuscularly or 10 to 20mg orally may be administered hourly, as necessary (Strassman 1984).

Phenothiazines have been advocated in the past (Solursh & Clement 1968a; Taylor et al. 1970). However, phenothiazines have been associated with fatal outcomes when given to patients with 4-methyl-25-dimethoxyamphetamine [DOM; also known as 'serenity, tranquility, peace' (STP)] ingestions, and they may potentiate the toxicity of an unsuspected anticholinergic poisoning. Thus phenothiazines are contraindicated in acute hallucinosis (Haddad 1976).

Although hospitalisation should be available, it is rarely necessary in the acute panic reaction. When the perceptual disorganisation and anxiety have resolved, the patient can be discharged to the care of a responsible friend or relative for the next 24 hours (Taylor et al. 1970). The patient should be en-

couraged to return for a follow-up visit, when assessment of the need for further therapy and of any psychosocial problems related to drug use may be made (Taylor et al. 1970).

Overnight hospitalisation is recommended if the patient does not regain insight or control of his or her thoughts or impulses. Patients detoxifying from amphetamines ('speed') may develop severe depression with increased suicidal risk, and may need hospitalisation (Taylor et al. 1970). DOM psychosis may be prolonged, also requiring hospitalisation with intensive psychotherapy (Solursh & Clement 1968a).

7.2 Psychosis

LSD psychosis requires treatment with neuroleptics. Lisansky et al. (1984) recommends drug-free observation for several days, using only minor tranquilisers if necessary, and then treating any clinical symptoms which develop. Haloperidol or phenothiazines are the recommended therapy for prolonged drug-induced psychosis (Haddad 1976; Litovitz 1983); ECT (Muller, 1971), lithium (Horowitz 1975) and *l*-5-hydroxytryptophan (Abraham 1983) have also been employed. The prognosis for hallucinogen-induced psychosis is variable. One follow-up study involving 15 patients showed that half did relatively well, and half did poorly (including 2 suicides). There was a general, but not strong correlation between poor outcome and lower pretreatment prognostic scores (Bowers 1973).

Cannabis-induced psychosis has resolved spontaneously with discontinuation of the drug (Drummond 1986) and with haloperidol 10mg four times daily for 1 week (Onayango 1986).

7.3 Flashbacks

The treatment of flashbacks, like that of the acute panic reaction, requires reassurance that the experience is drug related and that the patient is not losing his or her mind. The patient should also be reassured that, with time, the flashbacks will probably diminish in frequency, intensity and duration (Ungerleider & Frank 1976). Intense panic

or anxiety can be treated with diazepam, and the patient may be instructed to take one 5mg tablet of diazepam at the first sign of a recurrence (Ungerleider & Frank 1976). Haloperidol has been used successfully, although the flashbacks transiently increased during the first week of therapy (Moskowitz 1971). Chlorpromazine has not been useful (Moskowitz 1971) but a single case was successfully treated with phenytoin (Thurlow & Girven 1971). Patients should be instructed to avoid stress, antihistamines, marijuana and fatigue, which all may precipitate flashbacks (Cohen 1984).

7.4 Anticholinergic Toxicity

Treatment for the anticholinergic toxicity of *Datura stramonium* includes gastric emptying, supportive care as needed, and physostigmine. Severe hallucinations were the indication for physostigmine administration in 23 of 59 young patients with Jimsonweed ingestion requiring a hospital visit (Klein-Schwartz & Oderda 1984). Response was usually seen shortly after the dose was given, although one-third of patients required additional doses. No adverse effects were reported in this series. Physostigmine may cause sinus bradycardia, cardiac arrest and bronchoconstriction and should be used only in severe cases and, then, only with extreme caution. The dose is 1 to 2mg intravenously slowly over 2 to 5 minutes, and may be repeated in 20 minutes if reversal of anticholinergic effects has not occurred and there are no cholinergic signs.

7.5 Phencyclidine

Management of PCP intoxication is supportive and symptomatic, with attention to cardiovascular, respiratory, renal and neurological function. Patients should be cared for in a quiet, darkened environment, with a calm and reassuring manner, minimising external stimuli (Aronow et al. 1980). Gastric emptying by lavage (but not emesis induction) and elimination enhancement by multiple-dose activated charcoal or intermittent gastric suction may be necessary in moderately to severely

poisoned patients. However, in an effort to diminish all external stimuli in the agitated patient, nasogastric intubation should be avoided when possible.

Hyperthermia, hypertensive crisis, seizures and rhabdomyolysis with myoglobinuria should be treated aggressively with standard measures (Aronow et al. 1980; Becker 1989). Although much has been written about urinary acidification and forced diuresis, these measures do not have a place in current management of PCP intoxication (Becker 1989).

General hyperactivity, agitation and combativeness may be treated with slow intravenous administration of diazepam 10mg. The use of restraints may increase the risk of rhabdomyolysis, and should be avoided unless necessary to maintain the physical safety of the patient or staff.

There is no single, specific antidote for the central actions of PCP. Haloperidol, chlorpromazine (Castellani et al. 1982; Luisada & Brown 1976), physostigmine, and pethidine (meperidine) have been used to treat the hallucinations, delusions and often acute psychotic effects of PCP intoxication (Castellani et al. 1982; Luisada & Brown 1976). The rationales for haloperidol and chlorpromazine, and for physostigmine, therapy derive from the dopaminergic and cholinergic effects, respectively, of PCP. The use of pethidine relates to the reported interactions between PCP and the σ -opiate receptors.

Although there are no randomised trials of the therapy of PCP-induced psychosis, 2 non-randomised studies provided valuable information on the efficacy of the above modalities. Castellani et al. (1982) found that physostigmine therapy resulted in a significant decrease in anxiety, suspicion and conceptual disorganisation, as measured by the Brief Psychiatric Rating Scale (BPRS). Patients with delusions or hallucinations received haloperidol following an initial dose of physostigmine, and showed further improvement in unusual thought content, conceptual disorganisation and hallucinations.

In a similar study (Castellani et al. 1982b) patients with PCP intoxication received either physostigmine, pethidine or hydroxyzine initially, and

subsequent injections of haloperidol if delusions or hallucinations persisted. It was found that physostigmine, pethidine and haloperidol noticeably reduced hyperexcitability, suspiciousness and conceptual disorganisation, as measured by the BPRS. Haloperidol and pethidine, but not physostigmine, reduced hallucinations and unusual thought content. Control patients receiving hydroxyzine showed antianxiety but not antipsychotic responses, thus supporting the pharmacological specificity of the treatment drugs.

Although no adverse drug reactions were seen in the preceding studies, physostigmine may result in bronchial constriction, seizures and cardiac arrest. Its use in PCP intoxication should be avoided, given the existence of other effective therapy with less serious side effects. Phenothiazine administration in PCP intoxication has resulted in significant hypotension, and is contraindicated in known or suspected PCP-induced psychosis (Burns & Lerner 1976).

Phencyclidine-induced cerebral artery vasospasm has been also implicated in some of the drug's central effects (Altura & Altura 1981). Such vasospasm can be reversed *in vitro* with the calcium antagonist verapamil, and thus verapamil has been suggested as a pharmacological antagonist to PCP (Altura & Altura 1981). In addition, verapamil has been found to have some antimanic (Gianini et al. 1985) and antipsychotic (Price et al. 1985) properties. Several case reports describe an apparent clearing of PCP-induced confusion, bizarre thoughts and altered mental status in response to verapamil (Price et al. 1986; Montgomery & Mueller 1985). However, McCann et al. (1986) found that verapamil potentiated PCP effects in rats, and cautioned against its use in PCP intoxication. This remains an area for further study.

The chronic psychosis induced by phencyclidine is not typically responsive to standard antipsychotic therapy. Haloperidol was felt to be generally ineffective in 9 patients with subacute or chronic psychosis (Allen & Young 1978). ECT has been used successfully in a few patients (Allen & Young 1978; Grover et al. 1986) as has reserpine,

either alone or in combination with a phenothiazine (Berlant 1985).

Finally, a potentially promising form of therapy is the use of antigen-binding (Fab) fragments directed at the PCP molecule. High affinity phencyclidine-specific Fab raised in goats has been shown to dramatically decrease the volume of distribution of PCP in dogs, while decreasing the serum free fraction (Owens & Mayersohn 1986). Whether this redistribution of PCP from its peripheral receptor sites corresponds to a clinical response in PCP intoxication has yet to be shown. Although still in the experimental stages, this application of immunotherapy may eventually prove effective in PCP intoxication.

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