Management of stimulant drug overdose

Substance abuse is one of the most pervasive problems in modern culture.

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The impact of substance abuse in terms of lost or ineffective working hours, lost or damaged property, the overall loss of productive life and the resultant socio-economic drain upon individuals, communities and society as a whole, is poorly quantified but nevertheless appreciated to be of great magnitude and steadily increasing. The emergency doctor is often first in the line of fire in dealing with the medical, surgical and psychiatric consequences of chemical substance abuse – the first person called upon to manage the acute overdose situation.

The increasing popularity of rave music events, where masses gather, is having a significant impact on the number of drug-related cases presenting to the emergency medical services and to casualty departments, enhancing the awareness that special emergency medical knowledge and skills are needed to handle these cases correctly.

This review looks at illicit stimulant use and abuse and focuses on the initial diagnosis and management of medically dangerous chemical substance use with reference to common South African examples. Illicit refers to illegal substances as well as legal or prescription medication used for medically unacceptable purposes.

Amphetamines

Background

Although used in folk medicine for thousands of years as the herb Ma Huang, ephedrine was not isolated until 1885. Amphetamine was synthesised in 1887 and methamphetamine in 1914. D-amphetamine (first used in Benzedrine inhalers in 1932) was initially a treatment for narcolepsy before gaining rapid popularity as a stimulant. Amphetamines were made available to World War II soldiers to counteract fatigue. The subsequent steady increase in abuse climaxed in the so-called 'speed epidemic' in the USA in the 1960s. 'Speed kills' was the motto promoted by the Food and Drug Administration (FDA) and gradually the use of pure amphetamines has tapered off, only to be accelerated again by the introduction of forms of methamphetamine that can be smoked. The ready availability of these substances (e.g. in diet control medication) and their long half-life (amphetamine 3 - 6 hours, methamphetamine 12 - 36 hours) in comparison to other pure stimulants such as cocaine, ensures their popularity. 'Crystal meth' is known uniquely in SA as 'tik'.

Pharmacology

Amphetamines are a group of sympathomimetic compounds structurally related to phenylisopropylamine, and to the neurotransmitters dopamine and noradrenaline (norepinephrine). They produce their effects by increasing the synaptic concentrations of noradrenaline and dopamine by inducing the release of neurotransmitters from storage granules, by inhibiting reuptake or by acting as a false neurotransmitter. They have variable peripheral and central alpha- and beta-adrenergic effects. They raise systolic and diastolic blood pressure and initially slow the heart rate; higher doses result in tachycardia, palpitations and a variety of arrhythmias. Other signs of sympathetic stimulation may also occur (see clinical features below).

Amphetamines are taken orally, intranasally, intravenously, subcutaneously (skin popping) or are inhaled. They are often mixed with contaminants such as chalk or flour (by as much as 90%) which, being insoluble, can cause venous thrombo-embolism.

Symptoms and signs of amphetamine usage

Amphetamines are used as stimulants, to increase alertness, confidence and energy, and to create a sense of euphoria. Other symptoms and signs are listed in Table I.

Differential diagnosis

CNS infections, thyrotoxicosis, other psychedelic agents (e.g. phencyclidine, 'magic mushrooms'), hypoxia, and sedative/hypnotic/alcohol withdrawal. Also consider toxicities of carbon monoxide, carbamazepine, theophylline, tricyclic antidepressants, anticholinergics, organochlorine compounds, monoamine oxidase inhibitor (MAOI) drug interactions, isoniazid, cyanide, ergot compounds, lithium, hydrocarbons and salicylates.

Management

- General resuscitative and subsequent supportive measures are the most crucial aspects. Ensure adequate airway protection, facilitate breathing with supplemental oxygen, and gain control of the circulation with intravenous crystalloid (e.g. normal saline 0.9%).
- Initiate cardiac monitoring and electrocardiographic studies. Gastric decontamination should be attempted with gastric lavage and activated charcoal if the agent was taken orally within the last 1 - 2 hours, or if delayed gastric emptying is present.

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- Seizures should be actively managed with benzodiazepines (e.g. diazepam 0.1 mg/kg IV bolus). Check blood glucose and manage accordingly. If status epilepticus supervenes, early aggressive management may be necessary to prevent hyperthermia, rhabdomyolysis, acidosis and renal failure.
- Severe hypertension (> 180/110 mmHg) needs to be controlled to avert intracerebral catastrophes such as haemorrhage and encephalopathy. One can use nifedipine 5 mg po stat or, if appropriate, sodium nitroprusside 0.25 - 10 mg/kg/min via a central line in an ICU. Nonspecific beta-blockers such as propranolol are not recommended because the subsequently unopposed alpha-stimulation with the blockade of beta$_2$-mediated vasodilation may in fact worsen the hypertension and its attendant complications. Labetalol (10 - 20 mg IV) may be useful, particularly in the presence of tachycardia.
- Arrhythmias should be managed on an individual basis and we would usually only advocate pharmacological intervention for the unstable patient. For supraventricular tachycardias one can use verapamil 5 mg IV slowly (0.075 - 0.15 mg/kg), or consider cardioversion if the patient is profoundly unstable. For ventricular tachycardias consider lignocaine (lidocaine) 1 mg/kg IV bolus followed by an infusion of 2 - 4 mg/min (maximum total dose 3 mg/kg).
- Agitation (often with seizures) can be controlled with benzodiazepines (e.g. diazepam or midazolam 0.1 mg/kg IV); this may subsequently control both tachycardias and hypertension. In the past, neuroleptics were advocated for the acute management of agitation and psychosis. This is no longer recommended because neuroleptics impair heat dissipation and may lower the seizure threshold. Neuroleptics may be useful if psychosis persists after the acute toxicity has resolved.
- Cardiac chest pain will be dealt with in the section on cocaine. It is managed like any other case of acute cardiac chest pain and responds similarly to standard therapy.
- Hyperthermia can be life threatening and should be treated actively. Minimise excessive activity with benzodiazepines (even consider paralysis) and institute cooling measures. Pharmacological therapy with antipyretics, bromocriptine or dantrolene is not usually required or recommended.
- Urinary acidification to increase the elimination of amphetamines, although pharmacologically effective, is not indicated. The duration of toxicity is usually limited (except methamphetamine, 'ice'). Urinary acidification could exacerbate renal failure due to rhabdomyolysis. Extracorporeal drug removal is also not likely to be effective (except caffeine) as most sympathomimetics have large volumes of distribution or are highly lipophilic.

Table I. Symptoms and signs of amphetamine usage

System, symptoms and signs	Frequency
Central nervous system	
Anxiety/agitation	Listed in decreasing order of frequency per organ system
Confusion	
Delusions/hallucinations	
Loss of appetite	
Paranoia/aggression	
Seizures	
Nausea and vomiting	
CVA – thrombotic	
haemorrhagic (2° to acute hypertension)	
Encephalopathy	
Focal neurological signs	
Hyperreflexia	
Cardiovascular system	
Sinus tachycardia	
Bradycardia	
A-V block	
Cardiac ischaemia	
Tachyarrhythmias	
Mesenteric ischaemia	
Vasculitis	
Other	
Tremor	
Mydriasis	
Rhabdomyolysis	
Muscle rigidity	

Ecstasy

Background

Ecstasy is the common street name for a modified synthetic amphetamine known as 3,4 methylenedioxymethamphetamine (MDMA). It is used as an illicit designer drug for its stimulant and hallucinogenic properties, and was first patented by a German pharmaceutical company in 1913 as an appetite suppressant. It was also used as an unapproved adjunct to psychotherapy in the late 1970s and early 1980s. The widely held opinion that ecstasy is a safe recreational substance is the probable basis for the vast number of people who claim to use or have used MDMA. Studies in the UK reported that as many as 6 - 9% of 15 - 25-year-olds have tried MDMA. Anecdotal accounts suggest that approximately 500 000 people use MDMA

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for weekend recreation in England. Two studies at American universities showed, respectively, that 39% and 24% of students randomly polled had used MDMA at least once. Unpublished data from our experience at rave music events in South Africa have shown that more than 95% of 15 - 25-year-old rave-goers have tried MDMA.

Ecstasy is illegal and as such there is no pharmacological quality control. Doses per tablet vary considerably, and partial substitutes and adulterants are commonplace – seldom other expensive drugs (heroin is frequently rumoured but not substantiated), but rather other designer amphetamine-like substances such as paramethoxyamphetamine (PMA) and 3,4 methylenedioxyethamphetamine (MDEA), and countless other products including caffeine, sugar, calcium gluconate, lignocaine, ephedrine, paracetamol, etc. MDMA is a drug which has no bona fide medical application and has been documented as being fatal after single normal recreational use. We feel this merits its broad classification with other illicit stimulants like amphetamines and cocaine. Its use, therefore, cannot be condoned nor recommended as safe or non-addictive.

Pharmacology

MDMA has about one tenth the central nervous system stimulant effect of amphetamine. Onset of action is within 30 minutes of ingestion with peak effects occurring at 60 - 90 minutes and the duration of psychic effects being 3 - 4 hours. The stimulation is presumed to be on a similar basis to that of amphetamines. However, unlike amphetamines, MDMA is also a potent releaser of serotonin from presynaptic vesicles and also inhibits its uptake. Serotonin (5 hydroxytryptamine) can function as a neurotransmitter influencing pain pathway inhibition, mood control and sleep induction. It can cause rapid vasoconstriction or vasodilation in localised areas, and can also interfere with thermoregulation. These are all seen in the clinical picture of MDMA toxicity.

Symptoms and signs of ecstasy usage

Ecstasy is used as a stimulant and to cause subsequent relaxation, euphoria and feelings of enhanced emotional insight. Other symptoms and signs are listed in Table II.

Differential diagnosis

CNS infections, thyrotoxicosis, other psychedelic agents (e.g. phencyclidine, 'magic mushrooms'), hypoxia, and sedative/hypnotic/alcohol withdrawal. Also consider toxicities of carbon monoxide, carbamazepine, theophylline, tricyclic antidepressants, anticholinergics, organochlorine compounds, MAOI drug interaction, isoniazid, cyanide, ergot compounds, lithium, hydrocarbons and salicylates. Also consider serotonin syndrome – defined as at least three of the following: mental state changes/behavioural changes (confusion, agitation, hypomania, coma), alteration in muscle tone or neuromuscular activity (incoordination, shivering, tremor, hyperreflexia, myoclonus, rigidity), autonomic instability (diaphoresis, tachycardia, hypertension, hypotension), hyperpyrexia and diarrhoea. Many of these features have been documented in patients dying from MDMA toxicity.

The differential diagnosis of the serotonin syndrome in turn includes malignant neuroleptic syndrome (MNS), MAOI overdose, tyramine reaction, strychnine ingestion, and the use of cocaine, amphetamines or other sympathomimetic drugs. With regard to MNS, clinical findings are similar but the patient has a

Table II. Symptoms and signs of ecstasy usage (listed in decreasing incidence)

Symptoms
Feel strange/dizzy/unwell
Nausea
Anxiety/panic
Palpitations
Thirst
Feverish
Headache
Visual disturbances
Chest pain
Difficulty breathing
Myalgia
Menstrual disturbances (with repeated use)
Clinical signs
Tachycardia
Mydriasis
Hyperventilation
Anxiety/agitation
Hyperthermia
Hypertension
Decreased level of consciousness
Dehydration
Sweating
Shivering
Nystagmus
Seizures (focal and generalised)
Supraventricular tachycardia
Rhabdomyolysis
Disseminated intravascular coagulopathy
Keto-acidosis
Renal failure
Hepatitis

Cocaine-related stroke was first documented in 1977, and is now most common in the third decade of life of cocaine users, with haemorrhage far outweighing infarction as the pathophysiological cause.

history of taking a neuroleptic agent that antagonises dopamine receptors, and 'lead pipe' muscle rigidity may be seen. CNS infections and metabolic disturbances (e.g. thyroid storm; phaeochromocytoma) should also be excluded.

Management

- As for amphetamines – general resuscitative and subsequent supportive measures are the most critical elements. Secure ABC as per level of consciousness and vital signs; administer supplemental oxygen and IV normal saline if indicated.
- NB: Remove the patient to a safe, quiet, non-stimulating environment, and provide psychological support.
- Check blood glucose (with regard to metabolic disturbances and prolonged physical exertion) and supplement if necessary.
- Control agitation and seizures with benzodiazepines (as for amphetamine toxicity), e.g. midazolam or diazepam 0.1 mg/kg IV.
- If the patient is clinically dehydrated, initiate isotonic rehydration and evaluate blood urea and electrolytes as soon as possible.
- Check temperature and initiate cooling measures if the patient is hyperthermic. If concomitant with serotonin syndrome, one can consider dantrolene (although there is no local experience with its use in MDMA toxicity).

Cocaine

Background

The history of cocaine use dates back to 1500 BC when Peruvian Incas chewed the leaves of *Erythroxylon coca* to increase their endurance and ability to work at high altitudes. Scores of famous personalities from Sigmund Freud to Sherlock Holmes have sung praises to its amazing powers. It was used for, among other things, opioid withdrawal and treating depression. It is only within the last 30 years that its true status as a powerfully addictive, dangerous and potentially lethal illicit drug has been recognised. In 1985, when crack cocaine hit the streets, cocaine diversified into a drug accessible to all as opposed to an indulgence of the wealthy. Prices dropped from well over R1 000 per gram to less than R250 per gram, with individual rocks selling for as little as R5.

Pharmacology

Cocaine may be obtained as the water-soluble crystalline salt, cocaine hydrochloride (can be used medicinally as a local anaesthetic), or as the free cocaine base in powder or pellet (crack) form. Cocaine hydrochloride melts at 195°C and decomposes with heat while the freebase alkaloid is insoluble in water, melts at 98°C and vaporises at higher temperatures – therefore it can be smoked. Cocaine hydrochloride can be converted to freebase via alkaline dissolution and solvent (e.g. ether) extraction, or as is done on the streets simply with baking soda and water.

Its half-life averages 60 - 90 minutes after inhalation, mucous membrane absorption, gastrointestinal absorption or intravenous dosing. The major neurochemical actions of cocaine include:

- central nervous system stimulation with dopamine release
- generalised sympathetic nervous system stimulation from the inhibition of neuronal catecholamine uptake
- release of serotonin or blockade re-uptake
- local anaesthesia from the inhibition of sodium channels in neural tissue.

Symptoms and signs (in decreasing incidence per organ system)

The desired effects of cocaine use are euphoria, mental and physical stimulation. Other clinical features are listed in Table III.

Some explanatory notes

- The cardiovascular effects are predominantly a hyper-sympathetic phenomenon. Arrhythmias are relatively common compared with the other illicit drugs, the most frequently encountered being sinus tachycardia. Of particular note is that the electrocardiogram may well depict a wide complex tachycardia, which is in fact sinus in origin but with impaired cardiac conduction due to the local anaesthetic effect of cocaine. (Cocaine can prolong PR, QRS and QT intervals.)

Organ ischaemia is thought to be largely due to intense arterial vasospasm. Myocardial infarcts, for example, are frequently precipitated by a combination of coronary artery vasospasm (which can be induced by very small doses of cocaine), increased myocardial work load, and coronary thrombosis. Cocaine has been shown to increase platelet aggregation and subsequent thrombus formation.

Ischaemic limbs have occurred after accidental intra-arterial injection of cocaine.

- The convulsant effects of cocaine are probably related to its local anaesthetic properties (similar to seizures occurring with lignocaine toxicity), while hyperthermia and acidosis may also contribute to a lowered seizure threshold. Cocaine-related stroke was first documented in 1977, and is now most common in the third decade of life of cocaine users, with haemorrhage far outweighing infarction as the pathophysiological cause. The strokes themselves may be secondary to acute hypertension or cerebral vasospasm.
- 'Crack lung' is a syndrome of transient fever, pulmonary infiltrates, bronchospasm and eosinophilia.

Differential diagnosis

The usual spectrum of medical illnesses such as meningo-encephalitis, epilepsy and thyrotoxicosis need to be excluded. So too does the ingestion of other drugs such as amphetamines (no local anaesthetic properties though), phencyclidine (usually has normal pupils and multidirectional nystagmus), anticholinergic drugs and poisons (check for flushed, dry skin), and the delirium tremens of ethanol or sedative-hypnotic withdrawal.

Management

- Ensure adequate control of ABC, i.e. assess airway; position patient appropriately or intubate if necessary. Administer supplemental oxygen and establish an IV line with 0.9% normal saline. Evaluate vital signs, including temperature, and obtain ECG.
- Agitation – benzodiazepine sedation is the safest and most predictable (e.g. midazolam 0.1 mg/kg IM or IV). One

Table III. Symptoms and signs of cocaine use

System	Symptoms and signs
Cardiovascular	Hypertension
	Intracranial haemorrhage
	Aortic dissection/rupture
	Arrhythmias
	Sinus tachycardia
	Ventricular fibrillation
	Organ ischaemia
	Angina/chest pain
	Myocardial infarction
	Renal infarction
	Intestinal infarction
	Limb ischaemia
	Myocarditis
	Cardiogenic shock
Central nervous system	Headache
	Restless/agitation
	Depression – typically with withdrawal
	Seizures
	Transient focal neurological deficits
	Stroke
	Encephalopathy
	Coma
Respiratory	Chronic cough (often black sputum)
	Pneumothorax/pneumomediastinum (due to cough)
	Pulmonary oedema
	'Crack' lung
	Respiratory arrest
Metabolic/other	Hyperthermia
	Rhabdomyolysis
	Wound infections/tetanus

can also consider haloperidol 5 - 10 mg IM or IV.

- Gastrointestinal decontamination is indicated if the patient has clinical features of toxicity and ingestion (especially 'body packers'). Use activated charcoal 50 - 100 g orally or via nasogastric tube if the patient has a decreased level of consciousness and the airway has been secured. If necessary, consider whole-bowel irrigation.
- Seizures are usually self-limiting. If sustained, use diazepam 0.1 mg/kg IV and phenytoin 15 mg/kg IV by slow infusion.
- Hypertension – treat as for amphetamines.
- Cardiac tachyarrhythmias – manage on an individual basis. If associated with hypertension, consider labetalol 10 - 20 mg IV slowly; if unstable, treat as for amphetamines.
- Cardiac chest pain – treat as for standard suspected acute myocardial infarction (although the actual risk is relatively low):
  - tachycardias – benzodiazepines, labetalol,
  - hypertension – benzodiazepines, labetalol, sodium nitroprusside
  - ischaemia – nitrates
  - thrombosis - aspirin, heparin, thrombolytics.
- Concentrate on decreasing the sympathomimetic effects of cocaine.
- Chronic users are at increased risk for coronary artery disease, cardiomyopathies and ventricular dysfunction, although ischaemia can even occur on first exposure.
- Hyperthermia requires aggressive external cooling – consider active cooling or decreased heat generation if temperature > 40°C with neuromuscular paralysis.
- Rhabdomyolysis – ICU fluid monitoring; increase IV fluids. Urinary acidification may improve cocaine excretion while urinary alkalinisation can decrease the toxicity of myoglobin. Generally manipulating urinary pH is avoided. Treat individually as per electrolyte and acid-base evaluations.

Summary

The emergency doctor and other health care workers involved in the initial management of patients suffering from the toxic effects of illicit substances need to have a special understanding of the use and effects of these drugs. Common confounding variables to the well-delineated clinical pictures described above include polypharmacy and alcohol. Many patients will have used a variety of substances, and as each spectrum of effects wears off or is treated, others may be exposed.

Supportive management will adequately deal with the bulk of illicit substance overdoses, with meticulous attention to the ABCs. A common drug user's maxim is: 'What goes up, must come down!'. Once the 'trip' is over, or once the acute toxicity has been managed, what then?

We recommend that emergency personnel establish lines of referral, particularly to facilities with the capabilities to handle serious toxicities, and to social rehabilitation programmes that are both appropriate and effective.

Table IV gives the common street names of some illicit drugs.

Table IV. Common street names of some illicit drugs

Drug name	Common street names
Amphetamine	Benzy; white crosses; black beauties; Bennies; uppers; speed
Ephedrine (if used with caffeine)	Herbal ecstasy; cloud 9
Dextroamphetamine	Dexies
Methamphetamine	Speed; crystal meth; ice; glass; tik
4-methyl-2-5-dimethoxyamphetamine	Dom; STP (serenity/ tranquility/peace)
3,4 methylenedioxymethamphetamine (MDMA)	Ecstasy; Adam; M & M; Doves; x-men
3,4 methylenedioxyethamphetamine (MDEA)	Eve
3-methyl fentanyl	China white
Cocaine	Crack; coke; rock; nose candy; snow; shnaaf; white lady; she flake; blow; Bernice
Marijuana/cannabis	Dope; zol; weed; ganja; grass; doob
Lysergic acid diethylamide (LSD)	Acid; dots; blotter; caps; purple ohms; geminis; strawberries; cubes; liquid A
Phencyclidine (PCP)	Angel dust; monkey dust; animal tranquiliser; hog; dust

In a nutshell

- The emergency doctor is often first in the line of fire in dealing with the medical, surgical and psychiatric consequences of chemical substance abuse.
- Supportive management will adequately deal with the bulk of illicit substance overdoses, with meticulous attention to the ABCs.
- Common confounding variables to the well-delineated clinical pictures described include polypharmacy and alcohol.
- Management should include referral to appropriate rehabilitation agencies once the patient is stable.

single suture

Obesity paradox and heart disease

We all know that obesity is a risk factor for developing heart disease. But if you are too fat and your heart is already failing, your fat could save your life. Gregg Fonarow and colleagues, publishing in the *American Heart Journal*, found that the fatter a person admited to hospital with worsening heart failure, the less likely they were to die during a week-long hospital stay. The study included 100 000 patients admited to hospital because their heart failure was deteriorating. The researchers suggest that fat people may cope better with heart failure because they have more metabolic reserves to draw on when the heart isn't pumping blood fast enough to meet the body's needs.

Fonarow GC, *et al. Am Heart J* 2007; 153: 74-82.