Drugs of abuse (amfetamines, BZP, cannabis, cocaine, GHB, LSD)

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Abstract

The features of amfetamine poisoning are related predominantly to stimulation of central and peripheral adrenergic receptors, and in severe cases, excitability, agitation, paranoid delusions, hallucinations with violent behaviour, hypertonia and hyperreflexia develop. Convulsions, rhabdomyolysis, hyperthermia, intracerebral haemorrhage and cardiac arrhythmias are less common. In addition, hyperthermia and hyponatraemia are features of severe MDMA toxicity.

Benzylpiperazine (BZP) has stimulant and amfetamine-like properties. Those severely poisoned may develop seizures, collapse, hyperthermia, myoclonic jerks, extrapyramidal features and respiratory failure.

Features of cannabis use include euphoria, distorted and heightened images, colours and sounds, altered tactile sensations, impairment of memory, sinus tachycardia, hypotension and ataxia. Visual and auditory hallucinations, depersonalization and acute psychosis are particularly likely to occur after substantial ingestion in naive cannabis users. Heavy chronic users suffer impairment of memory and attention, and have an increased risk of psychotic episodes and later schizophrenia.

Cocaine is a psychomotor stimulant that inhibits re-uptake of monoamines into presynaptic terminals, thereby prolonging and augmenting their effects. Cocaine is also a powerful local anaesthetic and vasoconstrictor. In addition to euphoria, ventricular arrhythmias, acute myocardial infarction, stroke, acute dissection of the aorta, renal and intestinal infarction occur. Chronic intranasal use may cause perforation of the nasal septum and cerebrospinal rhinorrhoea as a result of thinning of the cribriform plate.

After ingestion of a substantial amount of GHB, bradycardia, hypotension, myoclonus, respiratory depression and deep coma occur rapidly but usually resolve spontaneously within 12 hours, though deaths have been reported.

Lysergic acid diethylamide (LSD) acts as an antagonist at peripheral 5-HT receptor subtypes, but as a 5-HT_{2A} receptor agonist in the CNS. In severe poisoning, hyperreflexia, tremor, muscle twitching, coma, seizures, hypotension and respiratory arrest have been reported. In addition, changes in perception, mood and behaviour, panic, agitation and excitement, visual hallucinations, delusions and psychosis are observed. Hallucinogen persisting perception disorder ('flashbacks') may persist for several years after exposure has ceased.

Keywords amfetamines; benzylpiperazine; BZP; cannabinoids; cannabis; cocaine; dexamfetamine; ecstasy; GHB, gamma-hydroxybutyric acid; hallucinations; LSD; lysergic acid diethylamide; MDMA; metamfetamine; psychosis

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Amfetamines

Amfetamine was first synthesized in 1887 and the medicinal product is usually the dextro-isomer, dexamfetamine. The *N*-methylated derivative, metamfetamine, is now abused widely, and the crystalline form of this salt is known as 'crystal meth' or 'ice'. Since the 1980s, the so-called 'designer amfetamine', 3,4-methylenedioxymethamfetamine (MDMA), commonly known as ecstasy, has been abused worldwide.

Mechanisms of toxicity

Amfetamines cause the release of serotonin, dopamine and noradrenaline from presynaptic terminals in the central nervous system and peripherally. They also bind and inhibit their reuptake transporters at the synapse, principally serotonin. Thus, there is an acute increase in the intra-synaptic concentration of these transmitters, followed by a period of depletion. In addition, there is an increase in blood concentrations of cortisol, prolactin, adrenocorticotropic hormone (ACTH) and antidiuretic hormone.[1] MDMA increases core body temperature regardless of ambient temperature.[2]

Features

Dexamfetamine and metamfetamine: intoxication is characterized by increased alertness and self-confidence, euphoria, extrovert behaviour, talkativeness, rapid speech, loss of desire to eat or sleep, tremor, dilated pupils, tachycardia and hypertension.[3] In severe cases, excitability, agitation, paranoid delusion, hallucinations with violent behaviour, hypertonia and hyperreflexia may occur. Convulsions, rhabdomyolysis, hyperthermia, intracerebral haemorrhage and cardiac arrhythmias are uncommon.

Sequelae particularly from chronic abuse have been reported, including necrotizing vasculitis, cardiomyopathy, pulmonary hypertension and long-term neuronal damage in abstinent metamfetamine users. These neuronal changes are commonly associated with persistent forms of cognitive impairment, including deficits in attention, memory and executive function.

MDMA: typical features include agitation, tachycardia, hypertension, widely dilated pupils, trismus (contraction of the muscles of mastication), bruxism (clenching or grinding of the teeth) and sweating. In more severe cases, hyperthermia, hyponatraemia, cerebral oedema, seizures, disseminated intravascular coagulation, rhabdomyolysis, severe hepatic damage, including fulminant hepatic failure (experimentally, hyperthermia potentiates ecstasy-induced hepatotoxicity), and acute renal failure predominate. The serotonin syndrome has been described and sudden death has been reported.

MDMA can cause life-threatening hyponatraemia due to inappropriate secretion of antidiuretic hormone,[1] particularly when accompanied by excessive fluid ingestion. Death occurred in two of 17 patients with serum sodium concentrations of 107–128 mmol/L.[4] Their clinical course was remarkably similar; initial vomiting and disturbed behaviour was followed by seizures, drowsiness, a mute state and disorientation.

Repeated use of ecstasy is associated with sleep and mood disturbances, anxiety, increased impulsiveness, memory deficits

and attention problems, which may persist for up to 2 years after cessation of abuse.

Management

Activated charcoal, 50–100 g may be considered if the patient presents within 1 hour of a substantial overdose, but no clinical trial has confirmed the efficacy of this procedure. Intravenous fluids should be given for dehydration. Diazepam, 10–20 mg intravenously or haloperidol, 2.5–5.0 mg intramuscularly or intravenously are effective in controlling agitation. The peripheral sympathomimetic actions of amfetamines may be antagonized by β-adrenergic blocking drugs (e.g. propranolol, 40–80 mg orally). Although, theoretically, acidification of the urine increases renal elimination of amfetamines, sedation is usually all that is required. Dantrolene, 1 mg/kg intravenously, could be administered for hyperthermia not responsive to sedation with adequate doses of diazepam. In most cases, hyponatraemia responds to fluid restriction alone.

Benzylpiperazine (BZP)

Benzylpiperazine is a synthetic phenylpiperazine analogue that has been used as a substitute for amfetamine-derived designer drugs. It was legally available in a number of countries, particularly in New Zealand, and was marketed as party pills, but is now more heavily regulated.[5] BZP is often ingested with other drugs such as ethanol, cannabis, MDMA, and/or other stimulants; ethanol appears to be an especially common co-ingestant.

Mechanisms of toxicity

BZP has stimulant and amfetamine-like properties. It enhances the release of catecholamines, particularly dopamine, from sympathetic nerve terminals, increasing intra-synaptic concentrations. The resulting elevated intra-synaptic monoamine concentrations cause increased activation of both central and peripheral α- and β-adrenergic postsynaptic receptors. BZP has primarily dopaminergic and noradrenergic actions.

Features

Toxicity is unpredictable with some patients developing severe symptoms after ingestion of 'recommended' doses. The most commonly reported effects include palpitations, tachycardia, hypertension, chest pain, agitation, anxiety, confusion, dizziness, headache, tremor, mydriasis, insomnia, urine retention, and gastrointestinal upset including nausea, vomiting and abdominal pain. More severe toxicity may include seizures, collapse, hyperthermia, myoclonic jerks, extrapyramidal features (such as choreoathetoid movements and/or dystonic reactions), hyperventilation, and respiratory failure.

Prolonged, excessive motor activity and/or hyperthermia may lead (or contribute) to effects such as rhabdomyolysis, renal impairment or failure, respiratory or metabolic acidosis, hypoglycaemia, hepatic injury, and disseminated intravascular coagulation.

Management

Supportive care including the termination of seizures is paramount, with relief of symptoms by benzodiazepines alone.

Cannabis

Cannabis is obtained from the plant *Cannabis sativa*, which contains over 400 compounds including over 60 cannabinoids.[6] The most potent cannabinoid is Δ^9-tetrahydrocannabinol (Δ^9THC), which is responsible for the psychoactive effects seen with cannabis use; other cannabinoids include Δ^8THC, cannabinol and cannabidiol.[6] Over the last 20 years sophisticated cultivation techniques have greatly increased the potency of cannabis products.

Smoking is the usual route of use, but cannabis is occasionally ingested as a 'cake', made into a 'tea' or injected intravenously. Cannabis use is often a group activity.

Toxicokinetics

Absorption by inhalation is rapid; smoking produces effects in seconds, which are fully apparent in a few minutes. Bioavailability after oral ingestion is much less; not only is the onset of effects delayed but also the duration is prolonged because of slow absorption from the gut.[6] Following absorption, distribution is rapid to all tissues including the brain. Cannabinoids are metabolized in the liver; the major metabolite is Δ^{11}THC, which is probably more potent than Δ^9THC and may explain some of the observed effects. Cannabinoids accumulate in fatty tissues, so the elimination half-life of Δ^9THC is approximately 7 days.

Mechanisms of toxicity

Cannabinoids exert their effect by interaction with specific endogenous cannabinoid receptors: CB_1 receptors are found in the central nervous system and peripheral nerves, and CB_2 receptors in the spleen and other immune cells. In animals, Δ^9THC enhances dopaminergic neurotransmission in brain regions known to be implicated in psychosis.

Features

Acute intoxication: features include euphoria, distorted and heightened images, colours and sounds, altered tactile sensations, sinus tachycardia, hypotension and ataxia.[7] Visual and auditory hallucinations, depersonalization and acute psychosis are particularly likely to occur after substantial ingestion in naive cannabis users. Cannabis impairs all stages of memory including encoding, consolidation and retrieval.[8] Memory impairment following acute use may persist for months following abstinence.

Cannabis infusions injected intravenously may cause nausea, vomiting and chills within minutes; after about 1 hour, profuse watery diarrhoea, tachycardia, hypotension and arthralgia may develop. Marked neutrophil leucocytosis is often present, and hypoglycaemia has been reported occasionally.

Chronic use: heavy users suffer impairment of memory[7] and attention, and poor academic performance. There is an increased risk of anxiety and depression.[9] Regular users are at risk of dependence.[10] Cannabis use results in an overall increase in the relative risk for later schizophrenia[11] and psychotic episodes.[12]

Cannabis smoke is probably carcinogenic **and** may contribute to the development of chronic obstructive pulmonary disease, pneumothorax and respiratory infections, including tuberculosis.[13]

Management

Most acutely intoxicated patients require no more than reassurance and supportive care. Patients who are disruptive or distressed should be sedated with diazepam (10 mg intravenously,

repeated as necessary). Haloperidol (2.5–5 mg intramuscularly, repeated as necessary) is occasionally required.

Cocaine

Cocaine hydrochloride ('street' cocaine, 'coke') is a water-soluble powder or granule that can be taken orally, intravenously or intranasally. 'Freebase' or 'crack' cocaine comprises crystals of relatively pure cocaine without the hydrochloride moiety. It is more suitable for smoking and can also be heated on foil and the vapour inhaled.

Users, body-packers and those who swallow the drug to avoid being found in possession of it ('stuffers') are at risk of poisoning. Other drugs (e.g. cannabis, conventional hypnotics and sedatives) are often taken with cocaine to reduce the intensity of its less pleasant effects. Heroin and cocaine may be injected together as a 'speedball'.

Cocaine is metabolized to methylecgonine, bebzoylecgonine and, in the presence of ethanol, cocaethylene.

Mechanism of toxicity

Cocaine is a psychomotor stimulant that inhibits re-uptake of monoamines into presynaptic terminals, thereby prolonging and augmenting their effects. Inhibition of dopamine re-uptake is believed to be the principal mechanism of euphoria. Cocaine is also a powerful local anaesthetic and vasoconstrictor.

The aetiology of cocaine-induced myocardial ischaemia is complex. It appears to result from coronary artery vasoconstriction, intracoronary thrombosis and accelerated atherosclerosis.[14,15]

Cocaine impairs sweating and cutaneous vasodilatation (the autonomic adjustments to thermal stress) and heat perception (trigger for behavioural adjustments).[16] Thus, cocaine impairs thermoregulatory adjustments that mediate heat dissipation.

Features

Acute intoxication: it produces euphoria, agitation, sinus tachycardia, hypertension, sweating, hallucinations, prolonged convulsions, hyperthermia and rhabdomyolysis. Ventricular arrhythmias, acute myocardial infarction, acute myocarditis, stroke (about 50% from cerebral haemorrhage, 30% from subarachnoid haemorrhage[17] and 20% ischaemic), acute dissection of the aorta, renal or intestinal infarction, retinal vascular occlusion and cardiorespiratory arrest may complicate severe poisoning.

Various unusual complications associated with the route of abuse of cocaine have been described, including pulmonary oedema after intravenous injection, and pneumomediastinum and pneumothorax after snorting.

Chronic abuse: this may lead to depression, memory loss, mania or paranoid psychosis. Myocardial fibrosis, cardiomyopathy, cerebral vasculitis, facial dystonic movements, preterm labour and fetal death have also been reported. Chronic intranasal use may cause perforation of the nasal septum and cerebrospinal fluid (CSF) rhinorrhoea as a result of thinning of the cribriform plate.

Management

Sedation with diazepam (10 mg i.v., repeated as necessary) is effective in controlling agitation and convulsions. Active external cooling is required when the patient's temperature exceeds 41°C. Hypertension and tachycardia usually respond to sedation and cooling. β-adrenoceptor-blocking drugs are contraindicated because of the risk of paradoxical hypertension via unopposed α-receptor stimulation. Phentolamine (2–5 mg i.v.) or another vasodilator can be used if necessary.

Early use of a benzodiazepine, aspirin and nitrates is effective in relieving cocaine-associated chest pain.[18] β-adrenoceptor blocking drugs are contraindicated because they may exacerbate cocaine-induced coronary artery vasoconstriction. Thrombolytic therapy should be restricted to those patients who have continued evidence of evolving myocardial infarction despite the administration of first-line treatment. Accelerated idioventricular rhythm should not usually require treatment, but ventricular fibrillation and asystole should be managed conventionally.

Gamma-hydroxybutyric acid (GHB)

Gamma-hydroxybutyric acid (GHB; liquid ecstasy) is used increasingly recreationally and, due to its amnesic properties, has been implicated in cases of 'date rape'. Gamma-butyrolactone (GBL) and 1,4-butanediol (1,4BD) are chemically very similar to GHB and are rapidly broken down *in vivo* to GHB. GHB is a precursor of GABA and acts predominantly as an agonist at $GABA_B$ receptors but also at a separate, GHB-specific receptor.[19] The effects of GHB are potentiated by ethanol and opiates. [20]

Features

Acute ingestion: after ingestion of a substantial amount of GHB liquid, rapid onset of bradycardia, hypotension, myoclonus, respiratory depression and deep coma occurs, resolving spontaneously usually within 12 hours, [19] though deaths have been reported from GHB alone. [20] In less severe cases, drowsiness, confusion, euphoria, amnesia, urinary incontinence, tremor, hypotonia, and hypothermia may be present. Pupils may be small or dilated. Paradoxical agitation and aggressive behaviour occur. Metabolic acidosis, hypernatraemia, hypokalaemia and hyperglycaemia have been reported.

GHB withdrawal syndrome: it can occur in patients using GHB chronically.[19] Early features, which may commence within 6 hours of the last dose, particularly in those using GHB every 1–3 hours, include anxiety, insomnia, tremor, confusion, tachycardia and hypertension; agitation and hallucinations may develop over the next 48 hours. Death can occur due to pulmonary oedema.[21]

Management

Treatment is supportive, though in severe cases transient assisted ventilation may be required. Atropine may be given intravenously for persistent bradycardia. There is no role for naloxone or flumazenil unless opiates and benzodiazepines have also been taken in substantial amounts and coma is present.

LSD

LSD is usually taken orally, but may be snorted or injected. LSD and MDMA are sometimes combined ('XL'; 'candyflipping') to increase the response to MDMA. Dependence is psychosocial in origin, with no physical or withdrawal syndrome.

Mechanisms of toxicity

LSD acts as an antagonist at various peripheral 5-HT receptor subtypes, but as a 5-HT_{2A} receptor agonist in the CNS. LSD alters perception leading to distorted sounds, smells and visual images. Hallucinations are probably a manifestation of this effect. Confusion and illogical actions follow on from alteration in thought processes.

Features

In the absence of a history of LSD use, the diagnosis should be considered in any patient who is confused, agitated and hallucinating. The initial effects usually occur within one hour and include sinus tachycardia, dilated pupils, hypertension, hyperthermia[22–24] and piloerection. In severe cases, hyperreflexia, tremor, muscle twitching, coma, seizures, respiratory arrest, hypotension,[24] coagulation disturbances and platelet dysfunction have been reported in those who have snorted large amounts of pure LSD.[25] Vasoconstriction of the internal carotid artery leading to stroke has been observed.[26]

The psychoactive effects (changes in perception, mood and behaviour, panic, agitation and excitement, visual hallucinations, delusions and psychosis) can last for 48 hours. Panic attacks are relatively common; frank psychotic episodes are not, but may result in homicide. Auditory hallucinations are rare.

The ability of LSD to distort reality is well recognized. Perception may be heightened and distorted. Time appears to pass slowly for affected individuals and their behaviour may become disturbed, with paranoid delusions. Users often exaggerate their mental and emotional capacities, attributing to themselves extraordinary powers; meaningfulness and a sense of universal union often predominate.

Episodic visual disturbances can occur ('flashbacks'; hallucinogenic persisting perception disorder) in which the effects of LSD are re-experienced without further exposure to the drug.[27] The symptoms include false fleeting perceptions in the peripheral fields, flashes of colour, geometric pseudohallucinations and positive afterimages. These disturbances may persist for several years but are often treatable with benzodiazepines and exacerbated by phenothiazines.

Management

Most patients need only reassurance and sedation. Those who are paranoid require chlorpromazine (50–100 mg intramuscularly) or haloperidol (2.5—5 mg intramuscularly or intravenously), repeated as necessary. There is no specific treatment for 'flashbacks'. ◆

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