Recognition and management of complications of new recreational drug use

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Use of illicit drugs in clubs and large dance parties (so-called raves) is a burgeoning cultural trend. Such recreational drug use is associated with several medical complications, both acute and longstanding. Although few, if any, of the drugs currently used in recreational venues are truly new, their patterns and context of use have changed (a great deal in some instances). For some of these substances, this cultural repackaging of the drug experience has resulted in various medical disorders that have previously gone undocumented. This review aims to help treating physicians recognise and manage complications associated with the use of new drugs in clubs, including methylenedioxymethamphetamine, ephedrine, γ-hydroxybutyrate; γ-butyrolactone, 1,4-butanediol, flunitrazepam, ketamine, and nitrates. We also alert researchers to specific toxic effects of club-drugs on which more basic information is needed.

Diagnosis and treatment of toxic effects from recreational club-drugs, acute or long-term, can be very challenging, both in the emergency department and in the community. In view of the illicit nature of most club drugs, patients may not be forthcoming about a history of recent drug ingestion, and by the time they reach medical attention, they could be incapable of providing lucid information. Most of these drugs are illegal in many developed countries, and therefore users generally obtain their supplies from the black market or the grey market in diverted pharmaceuticals. Even if patients are able and willing to recount a drug history, they are seldom aware of the exact formulation of the substance ingested. Moreover, polysubstance use is common, which often makes the offending drug difficult to pinpoint. Therefore, medical practitioners should be vigilant for potential drug interactions, combined drug effects, and emerging toxic effects during the course of treatment. Further, because therapy for a drug-related toxic effect can be at direct odds with that for another, physicians need to carefully prioritise medical issues.

Additional challenges exist for clinicians in an outpatient setting, because they are less likely to encounter acute toxic effects of club drugs but could face the substantial task of identifying delayed effects related to previous club-drug use. For example, as discussed later, persistent neuropsychiatric syndromes have been reported after exposure to methylene-dioxymethamphetamine (MDMA) including psychosis, mood disturbance, anxiety disorders, and cognitive deficits. These syndromes, which can first become apparent well after the drug has been cleared from the blood and urine, could be related to drug-induced injury and misdiagnosed as idiopathic neuropsychiatric illnesses.

Despite these immense challenges, some common strategies have been proposed to deal with suspected, acute, recreational club-drug intoxication. These approaches are detailed later, followed by a consideration of individual drugs (table) and their major toxic effects, and management strategies. Overall, these strategies have unavoidable uncertainties associated with the management of complications from drug use, and treatment of illicit-drug effects is rarely straightforward or definitive. We do not include some older, psychoactive drugs of abuse (eg, metamfetamine, cocaine, lysergic acid, alcohol) on which reviews are already available, as well as some emerging drugs (eg, α-methyltryptamine; α-ethyltryptamine; 2,5-dimethoxy-4-bromophenethylamine) about which little is known. Drugs were selected for review on the basis of several considerations, including their prevalence of use in the context of clubs and large dance parties, their potential to cause harm, and the availability of sufficient information to comment reliably on issues related to the recognition and management of drug-related complications.

Common strategies
Club-drug toxic effects should be considered in the differential diagnosis when a previously healthy individual (typically a young adult) has a history of acute change in mental status, especially if they have come from or recently attended a social event. Agitation and raised heart rate, blood pressure, or temperature might suggest recent use of stimulants or

Search strategies and selection criteria
Archival articles and reviews were identified through a computerised search of Medline from 1966, to May, 2004, with "methylene-dioxymethamphetamine", "ephedrine", "gamma-hydroxybutyrate", "gamma butyrolactone", "1,4-butanediol", "flunitrazepam", "ketamine", and "nitrates" as index terms. We selected reports dealing with acute and long-term adverse effects of these drugs and their management. Reports were reviewed by the authors who have expertise in neurology, psychiatry, pharmacology, and toxicology, and assessed for appropriateness for inclusion in the present review.
ketamine, whereas lethargy, bradycardia, and respiratory depression could indicate recent ingestion of a sedative-hypnotic drug such as γ-hydroxybutyrate. Information from friends could help pinpoint the drug type and timeline. Irrespective of which substance is suspected, treating physicians should bear in mind that in recreational settings, polydrug use is frequently the rule rather than the exception. Also, routine urine drug screens are often insufficiently sensitive or specific (or both). Sophisticated toxicological tests that use gas chromatography or mass spectroscopy are preferable, although management decisions often have to be made in the absence of such information. Moreover, physical dependence, which could develop with chronic use of some club drugs (table), can lead to withdrawal that will need additional treatment.

Thus, initial steps in patient assessment (panel) should be taken in an effort to cover various contingencies. Additionally, competing management approaches are not uncommon in the context of club-drug intoxication. For example, rhabdomyolysis typically needs liberal hydration with alkalinisation of urine. However, the alkalinising of urine in a patient with rhabdomyolysis secondary to MDMA or ephedrine intoxication will slow rather than promote drug excretion. Thus, in the treatment of acute toxic effects of drugs, successful management needs not only thorough understanding of the physiological or metabolic derangement taking place, but also of the pharmacology and toxicology of the offending compounds.

### MDMA (ecstasy)

Structurally related to the psychostimulant metampetamine and the hallucinogen mescaline (figure 1), MDMA produces a mixture of stimulant and mild psychedelic effects. In the developed world, use of the compound is increasing at a rate higher than that of most other recreational drugs. With college students and young adults in the USA, MDMA has become very popular, and lifetime prevalence rates range from 10% to 15%. Like other sympathomimetic drugs that readily cross the blood-brain barrier, MDMA stimulates both the CNS and sympathetic nervous system mainly by releasing serotonin, dopamine, and norepinephrine, and blocking their reuptake inactivation.

MDMA is generally taken orally, in tablet or capsule form. Individuals often take one or more booster doses

**Panel: Common measures for initial assessment of patients with altered mental status and suspected drug- ingestion**

- Measure vital signs and, if possible, check for orthostasis.
- Ensure airway patency and check blood gases (if indicated).
- Establish vascular access and send blood samples for complete blood count and chemistry panel including serum creatine kinase, osmolality, myoglobin, and lactic acid.
- Check electrocardiogram.
- Send blood and urine samples for drug toxicology screen; extra samples need to be obtained and stored (not all drugs are detected by routine drug screens; a growing number of methods based on gas chromatography or mass spectrometry are now available).
- Send urine samples for routine studies and check urine sodium, osmolality, and creatine kinase.
- Assess for possible infection, including meningitis (lumbar puncture).
- Give glucose, thiamine, and naloxone in usually recommended (ie, no need to adjust) doses.
- Check head CT or MRI for space-occupying lesions or evidence of raised intracranial pressure.
- Use activated charcoal if drug ingestion is recent.
- Consider possibility of physical dependence and potential for withdrawal (table).

**Table: Common names and salient features of new club drugs used recreationally**

<table>
<thead>
<tr>
<th>MDMA</th>
<th>Ephedrine</th>
<th>γ-hydroxybutyrate</th>
<th>γ-butyrolactone</th>
<th>1,4-butanediol</th>
<th>Ketamine</th>
<th>Flunitrazepam</th>
<th>Nitrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common name</td>
<td>Ecstasy, XTC, E, X, adam, hug drug</td>
<td>Herbal ecstasy, herbal fuel, zest</td>
<td>Liquid ecstasy, goop soap, georgia homeboy, grievous bodily harm</td>
<td>Blue nitro, longevity, revivitar, G H revitaliser, gamma G, nitro, insom-X, remforce, firewater, invogurate</td>
<td>Thunder nectar, serenity, pine needle extract, zen, enliven, revivalse plus, lemon drops</td>
<td>K, special K, vitamin K, ket, kat</td>
<td>Roofies, circles, rophies, nb, roche, roaches forget pill, R2, mexican valium, roopies, ruffies</td>
</tr>
<tr>
<td>Duration of action</td>
<td>4–6 h</td>
<td>4–6 h</td>
<td>1·5–3·5 h</td>
<td>1·5–3·5 h</td>
<td>1·5–3·5 h</td>
<td>1·5–3·5 h</td>
<td>1·5–3·5 h</td>
</tr>
<tr>
<td>Elimination half-life</td>
<td>8–9 h</td>
<td>5–7 h</td>
<td>27 min</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>2 h</td>
</tr>
<tr>
<td>Peak plasma concentration</td>
<td>1–3 h</td>
<td>2–3 h</td>
<td>20–60 min†</td>
<td>15–45 min</td>
<td>15–45 min</td>
<td>20 min</td>
<td>20 min</td>
</tr>
<tr>
<td>Physical dependence</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Antidote</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>DEA schedule</td>
<td>I</td>
<td>None</td>
<td>III</td>
<td>None</td>
<td>None</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>Detection with routine drug screen</td>
<td>Yes†</td>
<td>Yes†</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Best detection method (timetable)</td>
<td>GC/MS (4 h–2 days)</td>
<td>GC/MS (4 h–2 days)</td>
<td>GC/MS (1–12 h)</td>
<td>GC/MS (1–12 h)</td>
<td>GC/MS (1–12 h)</td>
<td>GC/MS (1–12 h)</td>
<td>GC/MS (1–12 h)</td>
</tr>
</tbody>
</table>

ND—not determined in human beings. DEA=US Drug Enforcement Agency; currently reviewing possibility of flunitrazepam being placed into schedule I of the US Controlled Substance Act. GC/MS=gas chromatography/mass spectrometry. Duration, half-life, and peak plasma are probably different after high or sequential doses because of non-linear pharmacokinetics. Cross reactions: †Flunitrazepam can give positive results for benzodiazepines; ketamine can give positive results for phencyclidine; ephedrine can give positive results for phentermine; liquid ecstasy, liquid e, liquid amfetamine because of cross reactions. ‡Flunitrazepam can give positive results for benzodiazepines; ketamine can give positive results for phencyclidine.
4–6 h afterwards. This dose regimen is noteworthy because MDMA shows non-linear kinetics, and high or closely spaced doses lead to disproportionate rises in plasma MDMA concentrations that, in turn, produce additional effects.\textsuperscript{1,2}

MDMA ingestion should be suspected if a patient exhibits mydriasis, tachycardia, increased blood pressure or temperature, nystagmus, or bruxism.\textsuperscript{7–9} Acute adverse effects of the drug largely represent exaggerations of its pharmacological actions and thus are most referable to overactivation of the CNS and sympathetic nervous system. Changes in mental status most often lead to anxiety, agitation, confusion, and occasionally psychosis. Other uncommon adverse effects include cardiac dysrhythmias, myocardial infarction, severe hypertension, seizures, strokes (both ischaemic and haemorrhagic), stupor, coma, or sudden death.\textsuperscript{8–10} These toxic effects could occur even after commonly used doses. Chronic use is not known to be associated with physical dependence. Although data are scarce regarding the management of these complications, available reports indicate that treatment should be the same as that for neuropsychiatric illnesses without known cause. For example, in the case of MDMA-induced anxiety or panic, oral, intramuscular, or intravenous benzo diazepine treatment (eg, lorazepam, 1–2 mg) would be appropriate if verbal reassurance and emotional support are ineffective.

In addition to adverse effects probably related to sudden stimulation of the CNS and sympathetic nervous system, MDMA produces several major adverse effects that are less well understood. Most notable of these effects are pronounced hyperthermia, hyponatraemia, large rises in serum creatine-kinase concentrations, hepatotoxicity, and persistent neuropsychiatric syndromes.

**Hyperpyrexia**

Severe, potentially fatal hyperthermia has been described after MDMA use, especially following excessive exertion in warm, crowded settings such as dance clubs or raves.\textsuperscript{11,12} The possibility of MDMA ingestion should be aggressively pursued in any young adult who presents with an acutely altered mental status and a raised temperature because this disorder can result in several serious complications if left untreated, including disseminated intravascular coagulation, rhabdomyolysis, hepatic and renal failure, and death. The best treatment for MDMA-induced hyperthermia is akin to that used to treat other types of heat stroke; urgent fluid replacement enables thermoregulation and is followed by cooling and support of organ system function.\textsuperscript{13} Paralysis and intubation might be needed to reduce muscular thermogenesis.

-Benzodiazepines are the first-line drugs used to reduce agitation. Antipsychotic substances should be avoided because their use can cause clinical complications and introduce the possibility of neuroleptic malignant syndrome, lower seizure threshold, or produce hypotension. Toxicology screens are often (but not always) helpful, since false positives and negatives are common. Although dantrolene use is controversial, some doctors recommend such treatment if the core temperature exceeds 39°C.\textsuperscript{14} Urine acidification, which can increase urinary excretion of amphetamines, is not recommended if serum concentrations of creatine kinase are raised because it can promote renal myoglobin precipitation. The potential role for serotonin antagonists (eg, cyproheptadine) and selective serotonin reuptake inhibitors has not been sufficiently tested, and could worsen complications (eg, induce serotonin syndrome).

**Hyponatraemia**

Pronounced hyponatraemia is another life-threatening complication of MDMA. It is thought to be caused by MDMA-induced secretion of antidiuretic hormone or by excessive water consumption (due to overzealous efforts to ward off dehydration).\textsuperscript{15,16} The disorder should be considered in all patients with suspected recent exposure of MDMA and with psychiatric or neurological symptoms. Initial symptoms can include nausea, drowsiness, vomiting, headache, muscle cramps, and weakness, which can progress to obtundation, seizures, and coma, possibly secondary to cerebral oedema. In the initial assessment, physicians should measure serum concentrations of sodium to yield the diagnosis. Volume status should also be determined, along with urine osmolality and electrolytes to assess fractional excretion of sodium. In the absence of other complications, management of symptomatic hyponatraemia suspected to be MDMA-related mainly includes fluid restriction and cautious

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**Figure 1: Chemical structure of MDMA and related drugs**

Parmethoxyamphetamine has been implicated in many deaths.\textsuperscript{7} Ephedrine is either synthetic or derived from the Chinese herb ma huang, which until recently was readily available as a dietary supplement. Ephedrine has been implicated in various cardiovascular and neurologic adverse events.\textsuperscript{4}
infusion of normal saline. If deemed necessary, hypertonic saline may be used.15-27 Correction of serum sodium concentrations should be gradual to keep the possibility of central pontine myelinolysis to a minimum. In patients with life-threatening cerebral oedema, intravenous mannitol or use of a loop diuretic is appropriate.16,17

**Rhabdomyolysis**

Rare, substantial rises in the amounts of serum creatine kinase (>25 000 IU/L) have also been noted after MDMA use.18 These increases are usually due to rhabdomyolysis (secondary to hyperthermia, prolonged dancing, or seizures) but can take place in the absence of muscular damage. Presentation varies but could include diarrhoea and general muscle aches. Urinalysis shows dark urine, proteinuria, and no evidence of pronounced haematuria (although a urine test for haemoglobin could cross-react with myoglobin). Attention should be given to life-threatening hyperkalaemia and associated arrhythmias. Treatment should include vigorous hydration and forced diuresis, with careful attention to fluid and electrolyte status and renal function. Alkalisation of the urine is not recommended acutely on a routine basis, since it can slow MDMA excretion. However, in patients with pronounced rhabdomyolysis, alkalisation should take precedence.

Although patients with raised amounts of serum creatine kinase and concomitant hyponatraemia are rare, they pose unique challenges because of competing management strategies. In such individuals, physicians must first determine the volume status by seeking a history of water intake, by examining patients for evidence of volume depletion, and also by checking serum electrolytes and urine sodium concentrations. In those who are volume-depleted, careful hydration with normal saline is indicated to slowly correct the hyponatraemia and promote diuresis. In those with healthy or expanded intravascular volumes, hypertonic saline can be used to help curb hyponatraemia and promote diuresis, thus guarding against acute renal failure when creatine-kinase concentrations are raised.

**Hepatotoxicity**

Hepatotoxicity due to MDMA is rare and can range from mild, self-limited episodes to fulminant hepatotoxicity needing transplantation.19,23 Some cases seem to be related to necrosis, secondary to hyperthermia. Others seem to result from a direct action of MDMA on hepatic tissue. Most patients present with progressive jaundice and weight loss that could recur if exposed to MDMA again. Some individuals present the disorder in acute crisis within hours of MDMA ingestion. Treatment should be tailored individually and ranges from nutritional support and careful longitudinal assessment of liver function to liver biopsy and transplantation.

**Neuropsychiatric dysfunction**

Occasionally, MDMA can also produce severe, longlasting neuropsychiatric complications including atypical psychosis, depression, and anxiety disorders.8,18,20 Some neuropsychiatric complications can develop acutely or shortly after MDMA ingestion, whereas other symptoms can emerge weeks or months afterwards and be longlasting. For example, many but not all research studies have shown that MDMA users with no overt psychiatric diagnoses have subtle cognitive deficits that persist with prolonged abstinence.21 These deficits seem to be unrelated to polydrug use (including use of marijuana) and rather could be specifically associated with previous MDMA exposure.

The most consistently reported deficit in MDMA users has been in short-term and working verbal memory, although other cognitive impairments have also been reported. Because MDMA-related cognitive deficits are subtle, formal neuropsychiatric testing might be needed for their detection. Cognitive and other lasting sequelae of MDMA use could be related to neurotoxic effects on brain serotonin (damage of serotonergic axons and axon terminals), which has been convincingly shown in animals (including primates);22 additionally, it also seems to occur in people.20,21 Evidence that indicated possible dopaminergic neurotoxic potential of MDMA in non-human primates was retracted when the animals in the study were discovered to have been treated with a drug from a mislabelled bottle.24

**Ephedrine**

Ephedrine is another amphetamine analogue that is sometimes used recreationally. Until recently, the compound was widely promoted for weight loss, bodybuilding, and increased energy.4,25 In clubs and parties, ephedrine-containing products are sometimes sold as herbal ecstasy. Both synthetically and botanically derived formulations of ephedrine are readily available (table). As with MDMA, adverse effects of ephedrine-containing products generally are overstimulation of the CNS and sympathetic nervous system. Common symptoms include hyperactivity, tremulousness, agitation, anxiety, and palpitations. Serious but rare adverse cardiovascular events such as strokes, seizures, myocardial infarction, hepatitis, psychosis, and sudden death have also been reported.24,25 Recognition and management of ephedrine intoxication parallels that of MDMA and other amphetamine-type stimulants such as metamfetamine.26 Ephedrine could give rise to a positive drug screen for amphetamine.

**γ-hydroxybutyrate**

γ-hydroxybutyrate and its precursors, γ-butyrolactone and 1,4-butanediol (figure 2), are CNS-suppressant drugs that are analogues of γ-aminobutyric acid (GABA), the major inhibitory transmitter in the CNS.27 In addition to binding to GABA receptors,
γ-hydroxybutyrate affects endogenous opioid, dopamine, and serotonin systems. 29-31 γ-hydroxybutyrate, γ-butyrolactone, and 1,4-butanediol are pharmacologically related and probably act via similar CNS mechanisms. γ-hydroxybutyrate is endogenously present in the brain and probably has its own receptor. 32

γ-hydroxybutyrate is used for its euphoric and sedative effects, and in some instances for its putative anabolic effects. 33 At dance parties, γ-hydroxybutyrate is sometimes referred to as liquid ecstasy, 34 even though it has a different pharmacological profile than MDMA. In clubs, γ-hydroxybutyrate has been used to facilitate sexual assault (date rape). Use of this drug in conjunction with MDMA is not uncommon. 35,36 Effects of γ-hydroxybutyrate taken orally in liquid form are discernable within minutes and typically last 1-4 h.

Acute adverse effects of γ-hydroxybutyrate are generally related to dosage. Low doses can cause nausea, vomiting, drowsiness, lightheadedness, and visual disturbance. 37-39 High-dose effects include confusion, abnormal involuntary movements, seizures, respiratory depression and hypoxia, respiratory arrest, and coma, in the order of increasing dose and gravity. Bradycardia and hypothermia could arise. Complications are likely if γ-hydroxybutyrate is mixed with other CNS-depressant drugs, such as alcohol.

The most serious risk of γ-hydroxybutyrate overdose is respiratory arrest and coma. Treatment is mainly supportive. In addition to standard measures for the treatment of potential polydrug overdose, other approaches that could be needed include blood pressure and fluid support, endotracheal intubation, and mechanical ventilation. If intubation is needed, post-intubation sedation is often useful (with a short-acting benzodiazepine), since patients can rapidly emerge from sedation and become very agitated. γ-hydroxybutyrate-induced CNS and respiratory depression typically resolves in 2-6 h. Sudden awakening is a characteristic of overdose. Cardiac depression induced by γ-hydroxybutyrate rarely needs aggressive treatment. Gastric lavage is rarely useful because γ-hydroxybutyrate is quickly absorbed.

Notably, physical dependence and a withdrawal syndrome could arise in individuals such as bodybuilders who use γ-hydroxybutyrate or its precursors chronically (several times every day) and stop use abruptly. 40-42 Although the withdrawal syndrome of the drug is not fully characterised, it is similar to that of ethanol and can include symptoms of anxiety, tremulousness, irritability, chills, autonomic dysfunction (diaphoresis, increased heart rate and blood pressure), and insomnia. γ-hydroxybutyrate withdrawal can last 3-12 days and could progress to profound disorientation, paranoid psychosis, respiratory difficulties, tremulousness, and seizures. Concomitant ethanol withdrawal often exists. Management of γ-hydroxybutyrate withdrawal is mainly supportive and should include psychological reassurance and (if indicated) a benzodiazepine or pentobarbital taper. 43 Large benzodiazepine doses might be necessary. Use of antipsychotic treatment for severe psychosis is reasonable, with attention to possible complications such as hypotension. Clinicians should be vigilant for the emergence of a withdrawal syndrome during γ-hydroxybutyrate detoxification and should inform patients that a syndrome could develop after discharge.

**γ-butyrolactone**

γ-butyrolactone, a precursor of γ-hydroxybutyrate (figure 2), is readily converted into γ-hydroxybutyrate without sophisticated laboratory methods or equipment. Also, once ingested, γ-butyrolactone is metabolised into γ-hydroxybutyrate by a peripheral lactonase. 44 γ-butyrolactone has also been marketed as a health supplement, under various brand names (table). Pharmacological and toxic effects of γ-butyrolactone resemble those of γ-hydroxybutyrate; 45,46,47 thus the precursor is also touted for its ability to increase muscle mass, increase sexual potency, and burn fat. γ-butyrolactone has approximately 85% oral bioavailability (higher than γ-hydroxybutyrate) and a slightly different biodistribution. These factors are believed to account for its extended duration of action. Chronic use of γ-butyrolactone can also lead to physical dependence and a withdrawal syndrome at acute discontinuation. 48 Acute toxic effects or withdrawal of γ-butyrolactone should be managed much the same as that for γ-hydroxybutyrate.

**1,4-butanediol**

1,4-butanediol (table) is an aliphatic alcohol that, similar to γ-hydroxybutyrate, occurs endogenously in trace amounts. 49 Once ingested, it is converted to γ-hydroxybutyrate by dehydrogenase enzymes
(figure 2). 1,4-butanediol is used in industrial solvents and, as mentioned earlier, in various health supplements. Subjective and toxic effects of 1,4-butanediol are similar to those of γ-hydroxybutyrate and γ-butyrolactone. Features of 1,4-butanediol overdose that could be more prominent than those for γ-hydroxybutyrate and γ-butyrolactone are urinary and faecal incontinence. After acute overdose of 1,4-butanediol, individuals present with bradycardia, altered mental status, abnormal movements, and respiratory depression that can progress to respiratory arrest, coma, and sometimes death. Treatment for 1,4-butanediol overdose and withdrawal is the same as that for γ-hydroxybutyrate. Typically, use of drugs such as benzodiazepines is best reserved for individuals with a history of chronic 1,4-butanediol or γ-hydroxybutyrate use in which physical dependence is a distinct possibility.

**Flunitrazepam**

Flunitrazepam (table) is abused for its intoxicant and relaxant effects, and has become known as a date-rape drug because sexual predators use it to chemically incapacitate their victims. Flunitrazepam is a highly effective benzodiazepine-GABA-receptor-complex agonist with pharmacology similar to other benzodiazepines. It has excellent oral bioavailability, and is highly lipophilic. The benzodiazepine-GABA-receptor complex is thought to mediate the muscle relaxant, anxiolytic, sedative, amnestic, and anticonvulsant activities of flunitrazepam. The drug is available in tablets or capsules, at doses ranging 0.5–1.0 mg.

Adverse and toxic effects of flunitrazepam are dose-related, and can be potentiated by other central depressants as well as nitrous oxide and ketamine. Similar to those of other benzodiazepines, adverse effects are related to CNS depression. Toxic effects of flunitrazepam include somnolence, impaired psychomotor behaviour, confusion, and amnesia. Depressions of the respiratory drive can be seen, especially when flunitrazepam is used in conjunction with other CNS depressants. Other adverse CNS effects reported in association with flunitrazepam include: visual disturbances, hallucinations, and paradoxical reactions consisting of excitement, stimulation, and hyperactivity. Benzodiazepine overdose is characterised by slurred speech and ataxia when mild and by respiratory depression, bradycardia, hypotension, and stupor or coma when severe. These symptoms are rarely fatal unless other CNS-active drugs are used. Intravenous flumazenil, a selective and competitive benzodiazepine antagonist, can be used in certain cases of confirmed benzodiazepine overdose; although it might precipitate withdrawal in benzodiazepine-dependent patients. Notably, the pharmacological action of flumazenil is short; therefore the drug is more useful for diagnosis than treatment. Treatment for flunitrazepam withdrawal parallels that for ethanol and other benzodiazepines and uses replacement with a long-acting benzodiazepine (eg, diazepam), often followed by gradual taper.

**Ketamine**

Ketamine (table) is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist and therefore blocks the actions of the excitatory aminoacids, glutamate and aspartate. It was introduced as a general anaesthetic drug in the late 1960s to replace phencyclidine, which had developed a reputation for unpleasant, post-anaesthetic emergence reactions. In addition to the action of ketamine on NMDA receptors, the drug exerts mild to moderate sympathomimetic effects by blocking the reuptake of catecholamines.

Ketamine, like phencyclidine, can lead to post-anaesthetic reactions that include unpleasant vivid dreams and sometimes hallucinations. Ketamine abuse has been on the rise over the past decade, particularly in the dance or rave scene where the compound is sometimes misrepresented as MDMA. Ketamine is sold as a liquid or powder that can be injected, ingested, or added to materials for smoking. The psychedelic effects of the drug usually dissipate within 1 h, which leads to the common practice of sequential dose-taking.

Acute pharmacological effects of ketamine include: tachycardia, increased blood pressure, impaired memory and cognitive function, and visual alterations similar to those reported after dissociative anaesthetic drugs. High doses of ketamine are often reported as unpleasant, and can include out-of-body or near-death experiences. Toxic effects of ketamine and other NMDA receptor antagonists (phencyclidine, dextromethorphan) include: hyperexcitability, severe agitation, and paranoid psychoses. Treating physicians need to be watchful for potential dangers of usually benign supportive measures and for emerging complications such as hyperthermia, seizures, and rhabdomyolysis. Transient respiratory depression could also take place. Physical dependence has not been noted. In animals, including primates, ketamine destroys a specific group of brain cells in the limbic cortex. It is not known whether similar neurotoxic effects occur in human beings or whether there are clinical consequences.

Treatment of ketamine-induced toxic effects or overdose includes supportive care and, in instances of severe agitation or anxiety, one or several doses of a benzodiazepine or a high-potency antipsychotic drug. Great caution should be used if an antipsychotic substance with high potency is used, because such treatment can lower seizure threshold, aggravate dystonia, precipitate hypotension, and cause
neuroleptic malignant syndrome and myoglobinuria. Since high ketamine doses can induce vomiting, aspiration precautions should be taken in stuporous patients. If rhabdomyolysis takes place, it should be treated with liberal hydration; physicians should be aware that polydrug use is common and that concomitant complications due to other drugs are possible (eg, MDMA-induced hyponatraemia). As with MDMA, fluid and electrolyte management in ketamine-induced concomitant rhabdomyolysis and hyponatraemia should proceed after the patient’s volume status is determined and the severity of metabolic derangement is considered. Since the duration of ketamine pharmacological effects is less than 1 h, alternative diagnoses should be sought if symptoms of agitation or psychosis (or both) persist for extended periods. A persistent psychosis, perhaps related to the cortical neurotoxic effects described earlier, has been noted by some investigators in some individuals with a history of phencyclidine abuse.31

Nitrites

The nitrites (amyl, butyl, and isobutyl nitrite) are volatile, clear, amber-coloured liquids that have had a history of abuse for more than three decades, especially in gay and bisexual men.32,33 However, in the past few years, nitrites have gained popularity in dance clubs, where they are used alone or in combination with other drugs. Nitrites are used recreationally for the rapid onset of their psychoactive and physical effects, which include a so-called high feeling, a slowed sense of time, and a carefree sense of wellbeing. Nitrites are also thought to intensify sexual experiences.

Originally used for therapeutic purposes as an antiangina drug, amyl nitrite is a potent vasodilator.34 The substance was originally dispensed in small glass capsules (known as pearls) surrounded by cotton. These pearls were crushed by patients’ fingers, which caused a popping noise, and the amyl nitrite was then absorbed by the cotton and inhaled; hence nitrites became known as “poppers” (table). Nowadays, nitrites in the USA are typically sold in small glass ampules containing individual doses, whereas in Europe they are usually sold in small bottles containing multiple doses. They are usually inhaled.35 After inhalation, nitrites are rapidly absorbed into the bloodstream, with the onset of physiological and psychological effects developing in seconds. The compounds are rapidly metabolised, with effects dissipating within 3–5 min.

Acute adverse effects include headache, syncope, hypotension, tachycardia, postural hypotension, increased intraocular pressure, and flushing. Patients with pre-existing medical disorders are at additional risk and can develop life-threatening arrhythmias, loss of consciousness, and severe glaucoma. Some individuals develop respiratory irritation after nitrate inhalation and have coughing, wheezing, and dyspnoea.

Regular nitrite users develop tolerance, needing increased doses to achieve the same effects. These individuals can also have crusty skin lesions around exposure areas (eg, nose, mouth, lips). A serious complication that can develop is methaemoglobinemia, which is caused by the entry of nitrites into red blood cells, leading to oxidation of haemoglobin and forming methaemoglobin.34 Treatment of nitrite-induced adverse effects is largely supportive. In view of the short duration of action, adverse effects of nitrite that are presented to physicians are generally related to chronic use (eg, dermatitis, methaemoglobinemia), skin lesions (ie, chemical burns), or oral ingestion. In the case of methaemoglobinemia-induced cyanosis, oxygen therapy might not be sufficient, and the use of methylene blue (1%) could be needed with repeated doses (1–2 mg/kg) up to 7 mg/kg per day. Chemical burns should be treated with generous rinses of soap and water and with standard burn protocols. If oral ingestion of nitrates is suspected, activated charcoal should be given immediately.

Research priorities

Our review addresses a difficult and complex topic, in which requisite data are often not yet available. In future years, research is needed on pharmacological interactions in the development of club-drug toxic effects. Other research priorities include the possible role of previous club-drug use in the subsequent development of neuropsychiatric illness, effective treatment and better understanding of drug-induced heat stroke, improved knowledge of the characteristics that render some individuals more vulnerable than others to adverse effects of club-drug use, and ways to eliminate or keep to a minimum the potential adverse effects of recreational drug use. Also, with the changing patterns of club-drug use (alone and in combination), researchers and clinicians should be vigilant for the emergence of new toxic syndromes so that effective treatment regimens can be recognised and developed.

Conclusions

Recognition and treatment of complications of new recreational club-drugs can be very challenging. These difficulties notwithstanding, certain common strategies are helpful. In the emergency department, after instituting no-harm measures (panel), management should be guided by the assumption of polydrug intoxication, and treating physicians should be vigilant for emerging toxic effects due to either drug combination or incipient withdrawal. Additionally, if several complications coexist and treatment of one complication (eg, rhabdomyolysis) competes with that of another (eg, hyponatraemia), prioritisation according the severity and time course is crucial. In the
outpatient department, a complete and accurate drug history with a working knowledge of toxic effects of individual drugs (acute and long-term), are indispensable to recognise drug-related complications.

Although not the focus of this review, two of the recreational drugs we discuss here (MDMA and ketamine) have well-documented neurotoxic potential in animals (including non-human primates) at doses in the range of those frequently used by human beings. If such selective neurotoxic effects on the brain should take place in people, they could produce long-term or tardive adverse results that might be misdiagnosed when encountered months or years after drug ingestion. Awareness of the toxic effects associated with the use of new or emerging recreational drugs is essential to effectively confront the diagnostic and potential therapeutic challenges they pose.

Contributors
Both authors contributed to the conception and content of the review; analysis and interpretation of archived articles cited in the review; and the drafting and revising of the paper.

Conflict of interest statement
We declare that we have no conflict of interest.

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