'Designer drugs': update on the management of novel psychoactive substance misuse in the acute care setting

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ABSTRACT

The use of novel psychoactive substances ('legal highs' or 'designer drugs') is increasing worldwide. Patients misusing such substances have been reported to experience severe or prolonged side effects requiring admission to acute or critical care wards. These complications can be life threatening if misdiagnosed or mismanaged. As physicians have traditionally had less involvement with the management of such patients compared with their colleagues in emergency departments an update in the management of such patients is indicated. Here we present a summary of the management of those novel substances with the potential for serious complications based on a review of current literature.

KEYWORDS: Complications, designer drugs, legal highs, management, novel psychoactive substances

Box 1. Case study.

A 26-year-old male office worker is admitted to your acute care ward on a Friday evening presenting with suddenly reduced Glasgow Coma Scale (GCS) score. A friend reports that he had repeatedly ingested a clear substance from a water bottle prior to this. Following a period of reduced GCS score in the emergency department, which required simple airway adjuncts and observation, he regained full consciousness and was due to be discharged after a period of observation. However, during this time he became increasingly agitated and delirious in the emergency department, with tachycardia and resting tremor. He was referred to the medical team for further investigation and management.

- What are the differential diagnoses and likely diagnosis?
- How would you manage this patient?
- What are the possible complications?

Introduction

Novel psychoactive substances, often erroneously referred to as 'legal' or 'herbal' highs, are substances that are used recreationally and that simulate the effects of traditional substances of misuse – for example, amphetamine ('speed') and 3,4-methylenedioxy-N-methylamphetamine (MDMA or 'ecstasy').

The use of these substances has increased markedly in the last decade; 2009 represents the beginning of a surge in media and internet search interest related to novel psychoactive substances.[1] Data from the National Crime Survey for England and Wales in 2012 shows that 3.3% of adults aged 18–24 years had used mephedrone (a novel synthetic cathinone) within the previous year.[2] On an international level, data from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)'s early warning system currently receives a report relating to a newly identified substance about once every week. An increase in the use of novel psychoactive substances has also been seen in the USA.[3,4] This increase in popularity has a number of potential triggers. However, it predominantly relates to the availability of these substances via anonymous internet retailers, a belief that substances sold as 'legal highs' (despite many actually containing controlled substances) may be less harmful, decreased purity and availability of traditional club drugs, and the ease in which new psychoactive substances can be engineered to evade existing regulation.[5–7]

An increase in use would not necessarily be relevant to acute healthcare professionals if these substances were not harmful. However, existing data shows that this is not the case. In 2012 alone, 52 deaths in England and Wales were directly attributable to novel psychoactive substances, with no other drugs listed on the death certificate.[8] Many more deaths reference co-ingestion of these substances. These deaths primarily relate to ingestion of synthetic cathinones, piperazine compounds and gamma-hydroxybutyric acid (GHB)/gamma-butyrolactone (GBL).

Given that most patients presenting with complications of novel psychoactive substance ingestion will present directly to the emergency department, it is unsurprising that emergency department physicians are, on the whole, aware of these substances and the potential for complications. However, such complications are increasingly resulting in admissions to acute medical wards and critical care or high dependency units. In a case series of emergency department admissions for cathinone exposure, 51% of patients were not discharged home from the emergency department, with 21% of these admitted to critical

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Box 2. Learning points.

- Use of novel psychoactive substances is increasing worldwide
- Many of these substances result in complications that require input from acute physicians or intensivists
- There is a current gap in knowledge relating to the identification and management of such substances and awareness of possible complications, particularly among physicians who have less contact with them compared with their emergency medicine colleagues
- Although management of some substances is much like that for more commonly known drugs of misuse, eg mephedrone and MDMA, other substances present unique challenges – for example, the risk of withdrawal in users presenting with overdose of GHB/GBL
- Front-line clinicians should ensure toxicological identification and reporting of suspected complications in order to build on the limited body of knowledge in this area

care.[9,10] Given that acute care physicians and intensivists have so far had less exposure to such substances and their potential for complications, and that undergraduate and postgraduate medical education has not traditionally covered such drugs of abuse, an update aimed at acute and critical care physicians is indicated to fill this gap in knowledge.

Methods

A literature search was carried out using Medline, Embase, Google Scholar and Cochrane databases. Where possible, medical subject heading (MeSH) search terms were used: 'designer drugs'/to (toxicity)/po (poisoning)/ae (adverse effects) and keywords (for non-Medline databases) including 'legal high*' and 'novel psychoactive substance*' AND substance-related disorders/psychoses, substance-induced/substance withdrawal syndrome. There were a total of 274 relevant results.

Results

The terms 'novel psychoactive substances', 'designer drugs' (the MeSH heading) and 'legal highs' cover a range of classes of drugs. An awareness of the broad categories of substances is necessary for all clinicians in order to pre-empt possible side effects, complications and drug interactions. Short-acting highs, such as those generated by inhalation of nitrates ('poppers') or nitrous oxide ('laughing gas'), remain commonly used but rarely result in admission to hospital and are not, therefore, discussed further. However, novel stimulants such as the cathinone derivatives (eg mephedrone, 'meow-meow' or 'm-cat') and piperazines (benzylpiperazine [BZP]) have been directly attributed to death and serious complications and will be discussed in detail. Novel depressants primarily include GHB/GBL and ketamine-like substances (methoxetamone [MXE] or 'mexxy'). These substances can cause life-threatening complications initially; however, both have medium-to-long-term effects that can present problems to acute physicians. Hallucinogens such as 'salvia' (*Salvia divinorum*) are commonly ingested for their psychedelic properties; however, patients rarely present to acute medical services unless they develop anxiety or altered behaviour resulting in trauma. Finally, synthetic cannabinoids (eg 'spice') can present with acute complications of altered behaviour (falls and arson) or psychiatric complications (psychosis) in addition to single or multi-system organ failure.

Synthetic cathinones

Synthetic cathinones are artificially engineered derivatives of a psychoactive chemical (2-amino-1–phenylpropanone) that occurs naturally in the *Catha edulis* (khat) plant. They exert psychoactive effects through binding of monoamine transporters for noradrenaline, dopamine and serotonin. By promoting release of these substances in varying amounts synthetic cathinones result in increased autonomic stimulation and an enhanced sensation of euphoria and empathy.[11] They are therefore used in place of more traditional 'club drugs' such as MDMA and amphetamine. Although some synthetic cathinones have medicinal uses – for example, bupropion is a cathinone licensed for smoking cessation – those discussed here have no medicinal uses.[12] These substances are sometimes described as 'first generation' or 'second generation', which is largely related to an original class ban of the rapidly popular first-generation 'designer drug' mephedrone (4'-methyl-methcathinone, known as 'meow-meow' or 'm-cat') and should not be confused with the opiate methadone or the beta-keto analogue methedrone. The ban on mephedrone in the UK occurred in 2009 but was quickly circumvented with the production of 'second-generation' naphthyl derivatives (napthylpyrovalerone, naphyrone or 'NRG-1') and methylenedioxypyrovalerone (MDPV), before legislation was amended to cover these second-generation derivatives.[12] Synthetic cathinones are predominantly ingested but can also be snorted or injected.[13] They are often labelled as 'bath salts' or 'plant food', with a message such as 'not for ingestion' in an attempt to avoid regulations regarding the sale of medicinal products. Adding to the confusion relating to terminology, the brand name (eg NRG-1) is recognised to correlate poorly with the active substance(s) and should not be relied upon to inform about the active agent.[1]

Most cathinones have sympathomimetic effects. Symptoms and signs therefore include sweating, palpitations, restlessness, tachycardia, nausea, chest pain, confusion, headache and psychosis. Skin changes (rash and blue discolouration) and changes in body odour have also been reported.[14,15] Self-limiting seizures have also been described in a number of patients.

Many patients who present to the emergency department do not require admission and are treated with observation with or without medication for symptom control, such as benzodiazepines for anxiety. In patients requiring hospital admission, the most common complications are cardiovascular, including tachycardia and hypertension, and neurological, including extreme or prolonged agitation.[11] These symptoms alone can usually be managed supportively with anxiolytics and observation. Although successful use of antidopaminergic drugs such as droperidol has been reported in patients with significant hallucinations and psychosis, benzodiazepines should remain the mainstay of treatment due to the risk of precipitating neuroleptic malignant syndrome.[16]

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The possibility of more serious complications, including hyperpyrexia, serotonin syndrome and hyponatraemia, should be carefully considered, as described below, especially in patients who have concomitant neurological or psychiatric conditions or are taking other medications.[17]

Hyperpyrexia is a life-threatening complication, with one death attributable to mephedrone in a patient with a temperature recorded at 42°C on arrival at the emergency department.[18] Hyperpyrexia can present as part of serotonin syndrome, with tremor and increased tone, hyperreflexia, diaphoresis, and inducible or spontaneous clonus. It should be suspected particularly in patients taking other serotonergic medications, which include monoamine oxidase inhibitors, serotonin-releasing agents such as serotonin reuptake inhibitors, and the opioid analgesics tramadol and pethidine. In addition to cooling and benzodiazepines, management includes administration of a 5-hydroxytryptamine receptor 2A (5-HT2A) antagonist such as ciproheptadine or chlorpromazine in consultation with local toxicology services.[19] In patients who are critically unwell (ie temperature >41°C), immediate paralysis with a non-depolarising muscle relaxant and tracheal intubation and ventilation should be considered. In addition, as previously reported with use of MDMA, mephedrone can cause hyperthermia without other serotonergic substances and is associated with rhabdomyolysis.[1,20,21] The mechanism is thought to be associated with uncoupling of oxidative phosphorylation in skeletal muscle mitochondria and activation of β-3- and α-1-adrenoreceptors, inducing vasoconstriction at cutaneous blood vessels.[22] In such cases, aggressive cooling should be instituted, benzodiazepines should be used to reduce muscle activity, and paralysis and intubation should be considered, as described above. Antipyretics have no role in reducing temperature due to muscular activity, and the role of dantrolene used outside of anaesthetic-related malignant hyperthermia remains unclear.[23] These agents therefore should not be part of routine management of cathinone-induced hyperthermia. Rhabdomyolysis should always be considered in cases of cathinone toxicity, and creatine kinase and renal function should be monitored in these patients.

Hyponatraemia, a well-recognised complication of MDMA, has also been reported in patients taking synthetic cathinones and has been associated with multiple fatalities.[11] Currently few data have been published regarding treatment of cathinone-induced hyponatraemia; however, given similarities with MDMA, a similar approach should be taken, namely fluid restriction for asymptomatic patients or sodium correction using hypertonic saline if neurological deficits are present. In severely hyponatraemic patients, rapid correction of sodium can cause central pontine myelinosis. However, this risk is reduced if the initial fall in sodium is acute (<48 hours), and the risks of rapid correction must be weighed against the risk of neurological complications if left untreated. If the patient has severe neurological signs, it therefore seems preferable to correct sodium levels rapidly to a level where neurological symptoms subside (ie 1 ml/kg/hour of 3% sodium chloride), with further reversal aimed at a rate of <10–12 mmol/l in the first 24 hours and <18 mmol/l in 48 hours.[24] The use of hypertonic saline is preferred over 0.9% saline.[25] It is evident that patients presenting with these complications should be treated by a multiprofessional team, with early discussion with intensivists, toxicologists and psychiatry services.

There are reports of dependence syndromes and psychosis associated with cathinones in patients who are frequently using such substances. This should be managed in consultation with psychiatry colleagues.[26]

Piperazine compounds

Piperazine compounds are synthetic substances with no naturally occurring form (despite frequent spurious marketing as 'herbal' highs).[27] Piperazine was originally produced as a veterinary anti-helminthic drug and was licensed in the 1950s with no noted psychoactive properties. Diphenylmethylpiperazines such as cyclizine are currently used in routine medical practice as antiemetics.[12] However, the 1-benzylpiperazines (eg BZP and 1-(3,4-methylenedioxybenzyl) piperazine [MDBP]) and phenylpiperazine derivatives (eg 1-(m-chlorophenyl) piperazine [mCPP], 1-(m-trifluoromethylphenyl) piperazine [TFMPP] and 1-(4-methoxyphenyl)piperazine [MeOPP]) produce stimulant effects similar to that of MDMA and amphetamines, with varying levels of hallucinogenic activity. As such, they are predominantly used as 'club drugs'. They have no current recognised medicinal use, having been withdrawn as potential antidepressants due to adverse stimulant properties.[28] Benzylpiperazine, which is one of the more commonly encountered piperazines, is known to inhibit reuptake of dopamine and stimulate release of noradrenaline, resulting in an amphetamine-type response. 1-(m-trifluoromethylphenyl) piperazine has more direct serotonergic activity, binding selectively to 5-hydroxytryptamine receptor 1 (5-HT1) and 2 (5-HT2). In combination, they produce an MDMA-type effect. These substances are typically supplied as capsules ('party pills') or, more rarely, loose powders and are sometimes mixed with other substances, such as MDMA, amphetamine and ketamine.[29] Intravenous injection has been reported.[30] Common names include 'Rapture', 'Legal X', 'Legal E', 'Frenzy' and 'Charge', and they are occasionally mis-sold as ecstasy.

Toxicological data relating to piperazines predominantly originates from New Zealand, where BZP and related compounds were 'Class D' substances for a number of years in the early 2000s, making them widely available to the population and therefore widely studied. Adverse effects include anxiety, agitation, palpitations, vomiting, confusion, dizziness, seizures, hyperventilation, headache, collapse, sweating and chest pain. Symptoms are reported to persist beyond 24 hours, making BZP a substance directly relevant to acute and intensive care physicians.

Presentation with seizures is a common complication of BZP. Without concomitant ingestion of ethanol, the propensity to seizure activity increases with plasma levels of BZP; however, this linear relationship does not hold true in patients who co-ingest ethanol. In addition, plasma levels of BZP recorded in patients with seizure activity are widely variable, suggesting that the drug concentrations that induce seizure activity vary considerably between patients. Although ethanol reduces the proconvulsant effect of BZP, it does increase the incidence of other symptoms such as anxiety, agitation and confusion.[31] Serious and prolonged adverse effects reported include metabolic acidosis, hyponatraemia,

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hyperthermia, psychosis and multi-organ failure.[32] It is worth noting that cross-reactivity with assays for amphetamine can result in false-positive toxicology screens for amphetamine.

Side-effects of BZP seen so far are similar to those associated with other stimulants, including novel cathinones. They should be managed as previously described. Given the lack of reports of complications with BZP, it is important for clinicians to report complications to local toxicology services to improve the existing knowledge base for this substance.

Gamma-hydroxybutyric acid/gamma-butyrolactone

Gamma-hydroxybutyric acid (GHB) is a colourless oily liquid. Following government legislation limiting the supply of GHB in the UK, gamma-butyrolactone (GBL), a chemical used extensively in the plastics and chemical industry, and its derivative 1,4-butandiole (1,4-BD), which are both metabolised to GHB *in vivo*, have become increasingly popular. These substances are administered as liquids diluted in bottles of water and are described as tasting like burnt plastic or stale water.[33] Ingestion results in rapid intoxication and euphoria, similar to that seen with ingestion of ethanol, and is associated with sedation, bradycardia, hypothermia and coma in overdose. Accidental overdose is common given that the therapeutic dose is within millilitres of a potentially toxic dose, and at least 96 deaths associated with GHB/GBL have been reported in the UK.[12]

Although commonly reported in the media as 'date-rape' drugs, these substances are frequently used voluntarily as club drugs. They have also increasingly been associated with dependence, with users ingesting the drug 'around the clock' (the elimination half-life of GHB is about 20 minutes) for over 2 years.[34] Such regular use was predominantly reported within the community of men who have sex with men in the UK; however, this subgroup is described as being at the 'vanguard' of changing drug trends, so more widespread use and dependence within other subgroups should not be discounted based on these initial data.[35]

Unwanted side effects of GHB/GBL ingestion at lower doses include aggression, nausea and urinary incontinence. At higher doses, it is not uncommon for patients to require intubation and mechanical ventilation; however, recovery is typically rapid and without further sequelae. Unfortunately, a growing problem among users of GHB/GBL who present with acute toxicity is inadvertent withdrawal, as exemplified by the short introductory case described in Box 1. Pharmacological studies show a role in activation of the gamma-aminobutyric acid class B (GABA(B)) inhibitory receptor system, as seen with ethanol, and, as such, withdrawal in patients with a history of chronic use can result in seizures and death. The significant difference compared with ethanol withdrawal is the timeframe, as severe withdrawal syndromes present initially within 1–6 hours with insomnia, anxiety, extreme restlessness and nausea/vomiting. This progresses over a period of days to include confusion, delirium and hallucinations and wanes over a period of 1–2 weeks.[36]

Initial management of GHB/GBL overdose involves supportive measures, including airway management where necessary. Renal function and creatine kinase should be checked, given reports of rhabdomyolysis. When withdrawal syndromes are not present, recovery is usually rapid and without complication. However, it is imperative that signs of withdrawal are recognised and that withdrawal symptoms are treated promptly, as death can result. The treatment of choice includes high doses of diazepam titrated to avoid oversedation (the mean daily dose in one study was found to be 75 [range 40–110] mg) and the GABA(B) agonist baclofen (10 mg three times daily, as tolerated). This regimen should be continued and titrated down over at least 5–7 days.[34]

The difficulty in diagnosing GHB/GBL withdrawal is compounded by a lack of awareness from physicians and often leads to confusion as to the cause of ongoing altered consciousness. Affected patients often undergo invasive procedures – for example, lumbar punctures – and ionising radiation in an attempt to identify the cause.[37] For this reason, it is essential that physicians are aware of this condition and the importance of establishing (if possible) a history of chronic use of GHB/GBL.

Methoxetamine

Methoxetamine (MXE or 'mexxy') is a dissociative anaesthetic with similar properties to the controlled but commonly misused substance ketamine (an N-methyl-D-aspartate [NMDA] receptor antagonist used for procedural sedation and rapid sequence induction of anaesthesia). Methoxetamine is reported to have longer-lasting effects than ketamine due to the presence of an N-ethyl group and additional affinity for serotonin receptors.[38] As seen with recreational use of ketamine, users report a feeling of derealisation and dissociation at high doses and mild euphoria, sensory intensification and 'cosiness' at lower doses. The substance is usually insufflated; however, it is occasionally taken intramuscularly. The onset of action has been reported to be longer than with ketamine – up to 90 minutes when insufflated – leading to users accidentally overdosing through cumulative dosing.[39] Clinical features include hypertension, confusion, dizziness, euphoria, somnolence and catatonia or hypertonia. Of note, cerebellar features seem to occur with methoxetamine (unlike with many other novel psychoactive substances and ketamine), which may be help to identify use of this drug.[38] Whether the chronic complications associated with ketamine misuse (predominantly bladder and other urinary tract pathology) are seen with chronic methoxetamine use is unclear.

Synthetic cannabinoid receptor agonists

Synthetic cannabinoid receptor aganists (CRAs) act like delta-9-tetrahydrocannabinol (Δ9-THC), the active substance in cannabis, producing a desired psychoactive effect, or 'high', through agonism at the cannabinoid 1 (CB1)-cannabinoid receptor.[40] There are a variety of structural groups; however, with the exception of nabilone (a synthetic cannabinoid licensed for use as an antiemetic), there are no current medicinal uses for these substances in the UK. Products are commonly sold as herbs or incense, with names such as 'spice' or 'K-2' and are usually smoked or vaporised. The active substance can be hundreds of times more potent than cannabis and can therefore be used to lace herbal mixtures, making their detection extremely difficult.[12] There is a scarcity of data relating to their pharmacology and long-term side effects; however, reports

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indicate that synthetic cannabinoids may have a longer half-life than cannabis and so users may experience prolonged psychotropic effects.[41]

Acute effects from synthetic cannabinoids are similar to those of cannabis and include changes in mood, perception, thinking and attention.[42] Reported adverse effects include agitation, paranoia and anxiety. These presentations will rarely be seen outside of the emergency department; however, there have also been reports of rhabdomyolysis and acute kidney injury, myocardial infarction, seizures and ongoing psychosis associated with use of synthetic cannabis.[43–46] Although it is not uncommon for patients to require psychiatric admission after their medical admission, physicians should be aware of synthetic cannabinoids as a potential cause for organ failure and tailor their investigations accordingly before referring to psychiatry colleagues.[47]

Summary

Novel psychoactive substances present a new challenge to acute care physicians. The combination of an ever-expanding range of substances, increased use among the population and the current gap in medical undergraduate and postgraduate education in this emerging field presents the possibility of adverse effects being inadvertently misdiagnosed or mismanaged. This review provides a broad overview of the management of some of the more commonly encountered and most dangerous substances, which are summarised in Table 1. There are, of course, many more substances and as yet undocumented complications and interactions. Clinicians are therefore invited to be vigilant and publicise novel substances and side effects where found for the benefit of patients and colleagues. ■

Table 1. Summary of management of novel psychoactive substances.

Substance	Serious complications	Treatment
Cathinones > Mephedrone (meow-meow, m-cat) > Naphyrone (NRG-1) > MDPV	> Sympathomimetic complications/agitation	> Benzodiazepines
	> Hyperpyrexia and neuroleptic malignant syndrome	> Cooling (active and/or passive) > Benzodiazepines > 5-HT antagonists, eg ciproheptadine/chlorpromazine (under specialist advice) > If severe hyperthermia (ie >41°C), immediate paralysis with non-depolarising muscle relaxant and intubation/ventilation and active cooling to normothermia on ICU > No role for antipyretics or dantrolene
	> Hyponatraemia	> If patient is asymptomatic and clinically euvolaemic, restrict fluids > If patient is symptomatic: hypertonic saline (3% NaCl) at 1 ml/kg/hour until neurological symptoms subside and then correction aimed at <10–12 mmol/l in the first 24 hours
Piperazines > BZP > MDBP > mCPP > TFMPP > MeOPP	> Sympathomimetic complications/agitation	> Benzodiazepines
GHB/GBL	> Sedation/respiratory suppression	> Supportive airway management as required
	> Acute withdrawal symptoms	> High-dose benzodiazepines (titrated to avoid oversedation, eg 40–100 mg/day diazepam in divided doses) with baclofen 10 mg three times daily
Ketamine derivatives > Methoxetamine ('mexxy')	> Agitation/cognitive impairment/motor disturbance	> Observation/symptomatic treatment (eg benzodiazepines) as required
Cannabinoid receptor agonists > 'Spice, herbal incense'	> Multi-organ failure > Acute delirium/psychosis	> Supportive care as required > Managed with psychiatric input

5-HT = 5-hydroxytryptamine; BZP = benzylpiperazine; GBL = gamma-butyrolactone; GHB = gamma-hydroxybutyric acid; ICU = intensive care unit; mCPP = 1-(m-chlorophenyl) piperazine; MDBP = 1-(3,4-methylenedioxybenzyl) piperazine; MDPV = methylenedioxypyrovalerone; MeOPP = 1-(4-methoxyphenyl)piperazine; NaCl = sodium chloride; TFMPP = 1-(m-trifluoromethylphenyl) piperazine.

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