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CORE TRAINING FOR DOCTORS

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Novel psychoactive substances or 'legal highs'

The last few years have seen a new challenge for clinical toxicologists and those in front-line medicine with the emergence of novel (new) psychoactive substances, sometimes colloquially referred to as 'legal highs' (European Monitoring Centre for Drugs and Drug Addiction, 2014). Currently in Europe novel psychoactive substances are detected at a rate of at least one new substance per week (European Monitoring Centre for Drugs and Drug Addiction, 2014; United Nations Office on Drugs and Crime, 2014). This is a challenge for legislative processes as it takes time to gather the necessary information on the frequency of their use and/or significant acute harm to institute potential control for an individual or class of new novel psychoactive substances (European Monitoring Centre for Drugs and Drug Addiction, 2014).

It appears that most novel psychoactive substances are manufactured in China and other areas of east and south east Asia. Novel psychoactive substances are available to users through street level drug dealers, through high street 'head' shops or from internet sites (a study in 2012 revealed 693 internet sites selling novel psychoactive substances) (European Monitoring Centre for Drugs and Drug Addiction, 2013). They are often marketed as 'research chemicals' or under names such as 'plant food' or 'bath salts' and labelled as 'not for human consumption'. The expanse of the so-called 'dark web', a virtual marketplace that is concealed and therefore hidden from usual search mechanisms, has offered another route of supply for novel psychoactive substances and other recreational drugs. The impact of the temporary closure of the 'Silk Road' site on the dark web on the sale of novel psychoactive substances and other recreational drugs is unknown (United Nations Office on Drugs and Crime, 2014).

The number of recorded novel psychoactive substances continues to increase and in 2013 81 new substances were identified and reported to the European Union Early Warning System based at the European Monitoring Centre for Drugs and Drug Addiction (*Figure 1*) (European Monitoring Centre for Drugs and Drug Addiction, 2014). The UK National Poisons Information Service Annual Report 2012/13 reported that telephone calls to the National Poisons Information Service and accesses of the online TOXBASE Internet site increased by 49% and 128% respectively from the previous year (Gordon and Eddleston, 2013).

The rapid emergence of novel psychoactive substances can make it difficult for front-line clinicians to manage patients presenting with acute toxicity related to the use of novel psychoactive substances. For the purposes of this article a novel psychoactive substance is a drug that has become available over the last 10 years; however, as time goes on it will be important to differentiate newer novel psychoactive substances and the term 'recently emerged novel psychoactive substances' is often used in this regard. This article provides a practical overview of some of the novel psychoactive substances that have emerged in the last 5–7 years to help front-line staff in hospitals as well as paramedics and GPs in the community.

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Classification of novel psychoactive substances and patterns of acute toxicity associated with their use

As shown in *Figure 1*, there has been a year on year increase in the detection and

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reporting of novel psychoactive substances in Europe over the last 5 years. Most novel psychoactive substances fall into one of five main groups:

1. Synthetic cannabinoid receptor agonists
2. Synthetic cathinones
3. Piperazines
4. Phenylethylamines
5. Tryptamines.

In addition to these five main classes of novel psychoactive substances, there has been an increase in novel psychoactive substances from other classes. The 2014 European Drug Report demonstrates the diversity in agents identified: there were 29 synthetic cannabinoid receptor agonists, 13 phenethylamines, seven synthetic cathinones, one piperazine and one tryptamine. In addition, there were 30 compounds reported from drug classes outside these five main novel psychoactive substances classes, including arylcyclohexamines and synthetic opioids (European Monitoring Centre for Drugs and Drug Addiction, 2014).

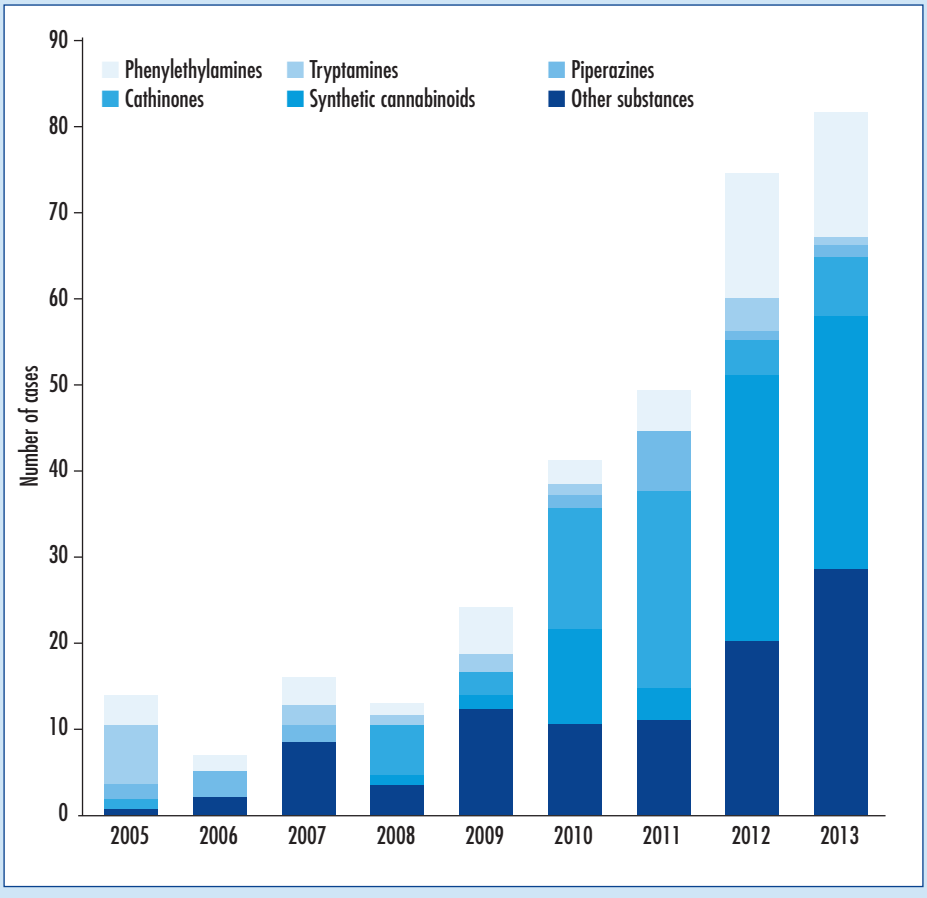
The content of novel psychoactive substances is highly variable with many products containing additional ingredients to those advertised, a different novel psychoactive substance, a controlled recreational drug, another substance such as caffeine, or no active ingredient (Wood and Dargan, 2012a, b). This may result in unexpected clinical effects or increased potency, and the user might not be aware of the presence of illicit substances that carry a risk of criminalization.

When new psychoactive substances first emerge onto the drug scene, there are often few data available on their pharmacology or potential for acute toxicity. Current hospital coding systems are also not suitable to allow identification of presentations related to acute toxicity caused by novel psychoactive substances and therefore document the pattern of toxicity seen in presentations. Therefore a process known as data triangulation is often used to combine data from multiple sources including the published scientific literature and grey information sources (Wood and Dargan, 2012a, b). Data sources for this process include internet drug user forums, in situ and other drug user surveys, poisons information services and published case reports/series (based on self-reported or analytically confirmed acute novel psychoactive substance toxicity).

Generally the pattern of toxicity associated with the use of novel psychoactive substances is similar to classical recreational drugs and can be divided into stimulant, hallucinogenic and depressant effects. However, with some novel psychoactive substances there have been reports of overlap between these effects and/or additional toxicity not typically seen with classical, established recreational drugs such as cocaine and MDMA (3,4-methylenedioxymethamphetamine). To complicate this matter further, little is known about the risks of poly-drug use either of novel psychoactive substances together or of novel psychoactive substances with classical recreational or prescription medications.

Despite the significant time lag between substances arriving on the scene and legislative change, this remains the key strategy for minimizing drug-related harm. An example of this includes the documented fall in mephedrone presentations associated with the control of the drug in 2010 (Wood et al, 2013) and also the drop in poison information centre calls in the same period (Wood et al, 2014).

Figure 1. Number and main groups of novel psychoactive substances notified to the EU early warning system 2005–13 (adapted from European Monitoring Centre for Drugs and Drug Addiction, 2014).



Synthetic cannabinoid receptor agonists

These drugs, often sold under the name 'spice' in Europe and 'K2' in the USA, were first seen in Europe in 2005–6. They are commonly sold as 'herbal incense' or smoking mixtures with the synthetic cannabinoid receptor agonists sprayed onto herbal matter. There are dozens of different chemicals classes and over 200 different synthetic cannabinoid receptor agonists have been characterized (Auwärter et al, 2009).

Some users report that 'spice' has a greater psychotropic effect than cannabis, but the desired effects appear similar in nature to cannabis with alterations of mood, hallucinations and wakefulness. (Wood and Dargan, 2012b). There are increasing reports that synthetic cannabinoids may precipitate or worsen psychosis in those who are already susceptible (Papanti et al, 2013). In addition to cannabis-like toxicity additional features are reported in some with acute synthetic can-

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nabinoid toxicity, in particular stimulant features including seizures, agitation, hypertension and tachycardia (Simmons et al, 2011; Wood and Dargan, 2012a). There have also been reports of acute kidney injury associated with the use of synthetic cannabinoids (Thornton et al, 2013).

Synthetic cathinones

The cathinones are beta-keto derivatives of amphetamine (Gibbons, 2012). Cathinone is a mild stimulant that is found naturally in the khat plant, but in the last 5–6 years numerous synthetic cathinones have emerged onto the recreational drug market as novel psychoactive substances. Mephedrone is the commonest cathinone taken in the UK: in the 2014 Crime Survey for England and Wales 0.6% of adults (aged 16–59 years) had used mephedrone in the last year – by comparison, 1.6% had used ecstasy, 0.8% amphetamines and 0.6% ketamine (Home Office, 2014). Other cathinones include methylone, methedrone and methylenedioxypyrovalerone.

Most of the data available on the pattern of acute toxicity associated with the synthetic cathinones are for mephedrone – these show that it is associated with stimulant toxicity similar in nature to MDMA and cocaine. Commonly reported features include agitation (38%), palpitations (20–43%), nausea/vomiting (17–37%), chest pain (12%), headache (7–50%) and seizures (7%) (Dargan et al, 2011). Methylenedioxypyrovalerone appears more likely to be associated with significant neuropsychiatric effects such as psychosis (Spiller et al, 2011).

Piperazines

The piperazines which have emerged as novel psychoactive substances include 1-benzylpiperazine, trifluromethylphenylpiperazine, (methoxyphenyl)piperazine and meta-chlorophenylpiperazine. The piperazines were commonly encountered in New Zealand and the UK/Europe in 2008–10, but, based on the limited data that are available, they appear to be less widely available and less commonly used in the UK more recently (Schep et al, 2011).

Generally the piperazines are associated with stimulant toxicity, but some have additional features – in particular trifluromethylphenylpiperazine is more likely to be associated with hallucinogenic effects (Gee et al, 2005; Wilkins et al, 2008). Clinical features seen in those with toxicity include insomnia (54%), headaches (26%), nausea (21%), palpitations (18%), dizziness (15%), vomiting (13%), chest pain (4%) and seizures (0.4%) (Wood and Dargan, 2012a).

Other agents

Phenylethylamines and tryptamines are very broad categories of illicit substances with a very long history that include MDMA and mescaline (phenylethylamines) and lysergic acid diethylamide (LSD) and psilocybin, also known as magic mushrooms (tryptamines). Other agents include the pipradrols, diphenylprolinol (D2PM) and desoxypipradol (2-DPMP), are noradrenaline-dopamine reuptake inhibitors. In addition to typical stimulant toxicity (bruxism, sweating, insomnia, hypertension, chest pain and seizures), the pipradrols have been reported to be associated with prolonged neuropsychiatric features such as euphoria, paranoia, hallucinations and psychosis that may last for a few days after use (Wood and Dargan, 2012c).

There are numerous arylcyclohexamines that have emerged as novel psychoactive substances; these include ketamine derivatives such as methoxetamine which has been marketed as a 'bladder safe' alternative to ketamine. However, evidence from animal studies suggests that chronic methoxetamine use has a similar potential for bladder and urinary tract toxicity to chronic ketamine use (Dargan et al, 2014). Acute methoxetamine toxicity is associated with dissociative states similar to those seen with acute ketamine toxicity; however, in addition to this there are reports of additional features associated with acute methoxetamine toxicity including significant cerebellar features (e.g. ataxia, nystagmus) and stimulant features (e.g. severe hypertension, agitation and tachycardia) (Shields et al, 2012; Wood and Dargan, 2012a).

Another class of phenylethylamine novel psychoactive substances are the 'NBOMes' (containing the group N-methoxybenzyl group) that have been reported during 2012–14. These drugs have potent serotonergic effects and are active in microgram quantities. They are generally sold as 'blotters' (similar to LSD) but are also available in powder form and many of the reports of acute NBOMe toxicity have occurred in individuals who have used NBOMe powder and taken it in milligram rather than microgram doses. A case series described severe toxicity associated with 25I-NBOMe in seven patients, with features of tachycardia (n=7), rhabdomyolysis (7), agitation (6), visual and auditory hallucinations (6), hypertension (4), hyperpyrexia (3), metabolic acidosis (3), seizures (3), clonus (2) and acute kidney injury (1) (Hill et al, 2013).

KEY POINTS

- Novel psychoactive substances are increasingly popular synthetic agents designed for recreational use.
- The toxicity of novel psychoactive substances can broadly be divided into stimulant, sedative and hallucinogenic effects. In addition, some novel psychoactive substances appear to be associated with additional, unexpected and/or prolonged toxicity.
- The contents of any novel psychoactive substance may not be in fact be legal and may contain many substances instead of and/or in addition to those advertised.
- A lack of analytical standards presents problems in the detection of novel psychoactive substances. In most cases identification of the precise contents of what has been taken, either from the analysis of the drug samples or biological samples, is not possible in most hospital laboratories.
- The management of most novel psychoactive substances is largely supportive and similar to the current management strategies of classical recreational drug-related acute toxicity.
- Where there are additional/unexpected acute toxicity features, then this should be managed appropriately (with advice from the National Poisons Information Service or local clinical toxicologists if available).

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Management of acute novel psychoactive substance toxicity

The management of acute novel psychoactive substance toxicity is based on the clinical pattern of toxicity together with the drug(s) reported to be used by the patient. Analytical screening results for novel psychoactive substances are not widely available, particularly for newer novel psychoactive substances and results will not be available in a time-frame that will be able to inform patient management. The management of patients with acute novel psychoactive substance toxicity is supportive and similar to the management of acute toxicity related to established classical recreational drugs. There are a few practical tips for clinicians managing these patients:

Safe sedation

Agitation is common and similar to the management of any drug-induced agitation, these patients should be managed in a quiet, non-stimulating environment. If pharmacological treatment is needed, benzodiazepines are recommended as first-line treatments rather than antipsychotic agents because of the risk of cardiac toxicity and seizures associated with the latter drug classes.

Watch out for hyperpyrexia

Hyperpyrexia requires aggressive treatment as it can be associated with rapid deterioration including rhabdomyolysis, acute kidney injury, disseminated intravascular coagulation and acute liver failure. If the core body temperature is >39°C then aggressive and rapid cooling is required. This includes cold intravenous fluid alongside other active cooling techniques. If this is ineffective then the patient should be paralysed, intubated and ventilation and specific agents such as cyproheptadine should be considered (along with the advice from the National Poisons Information Service and/or a clinical toxicologist if available locally).

Measure blood sugar

Although novel psychoactive substances have not been reported to alter glucose homeostasis to any significant extent, since this is one of the most easily correctable causes of altered consciousness, it is imperative that hypoglycaemia (and hyperglycaemia) are not missed.

Consideration of fluid status

Often patients who are have been dancing or have been sweating owing to the effects of recreational drugs are dehydrated and may require oral or intravenous rehydration. Clinicians are often concerned about hyponatraemia in acute recreational drug toxicity, which can occur as a result of both excess fluid ingestion and/or syndrome of inappropriate antidiuretic hormone. This is uncommon, although it is important to ensure that serum sodium concentration is measured early to further guide fluid management.

Conclusions

Novel psychoactive substances are a new challenge facing our emergency departments and while our knowledge regarding some of these drugs is quite limited, it is important that we equip ourselves as well as possible to enable us to manage patients effectively. **BJHM**

Conflict of interest: Dr K Bonnici: none; Professor PI Dargan is a member of the UK Advisory Council on the Misuse of Drugs and European Monitoring Centre for Drugs and Drug Addiction Scientific Committee; Dr DM Wood is an expert adviser to Advisory Council on the Misuse of Drugs and European Monitoring Centre for Drugs and Drug Addiction.

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TOP TIPS

- Try to obtain a history from the patient, friends and/or relatives regarding what has been taken, from where it was obtained and the estimated quantity.
- Nurse in a calm, quiet environment, away from stimuli.
- Avoid antipsychotics and use benzodiazepines if pharmacological agents are required for treatment of agitation.
- Monitor the patient's temperature, blood sugar and fluid assess regularly.
- Contact the National Poisons Information Service (see further information) if the patient is not improving.

FURTHER INFORMATION

- National Poisons Information Service and TOXBASE (www.toxbase.org)
- Useful contacts for users and their friends/relatives www.talktofrank.com or 0300 123 6600
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