Problem Based Reviews

Legal Highs, Lethal Lows

B Shah & T Heaps

Abstract

Novel Psychoactive Substances (NPS), sometimes referred to as Legal Highs, are newly available drugs with psychoactive properties that are not currently prohibited by United Nations Drug Conventions. Despite many of these compounds still being 'legal' and readily available via online mail-order companies and high-street 'headshops', their rapid emergence in the UK has been associated with increasing hospital admissions, enquiries on TOXBASE® and fatalities. It is therefore vital that Acute Physicians have a good understanding of the issues in recognizing, investigating and managing patients presenting to the AMU with toxicity due to legal highs. This article outlines the classification and effects of various novel psychoactive substances and presents a strategy for management according to the prevailing toxidrome.

Key learning points

- 'Legal highs' or novel psychoactive substances are a rapidly growing public health concern in the UK
- 'Legal' does not mean safe and there are increasing numbers of fatalities reported in association with the use of novel psychoactive substances
- Current legislation is unable to keep pace with the rate at which new psychoactive compounds are emerging
- Legal highs may be classified according to their effects; synthetic cannabinoids, stimulants and hallucinogens are most commonly encountered in clinical practice
- In patients presenting with toxicity due to legal highs, attempts to determine the exact substance responsible are fraught with difficulties and are not usually necessary
- The best approach to management is to identify the predominant toxidrome and provide supportive care accordingly

Introduction

Novel Psychoactive Substances (NPS) or 'Legal Highs' contain chemical compounds that produce similar effects to illegal drugs such as cannabis, ecstasy and cocaine. A NPS Expert Review Panel report in 2014[1] defined legal highs as *'Psychoactive drugs, newly available in the UK, which are not prohibited by the United Nations Drug Conventions but which may pose a public health threat comparable to that posed by substances listed in these conventions'*. Many of these substances are not currently covered by the Misuse of Drugs Act; they are not licensed for legal use and are not regulated under the Medicines Act 1968. They therefore cannot be marketed for human consumption so are often sold as bath salts, research chemicals, incense or plant foods with labelling which states 'strictly not for human consumption' to circumvent the law.

Consumers of legal highs may erroneously think that because a substance is currently legal, it must be safe to use. These compounds have not been rigorously tested for safety in human subjects and it is the unwitting consumer who becomes the 'guinea pig'. Legal highs are usually cheaply manufactured in underground laboratories in China and are sold on the internet (see www.iceheadshop.co.uk as an example) or in high-street 'headshops'. As a result of how they are manufactured, there is no quality control or guarantee of purity and they are often adulterated or 'cut' with illicit drugs or other toxic substances e.g. caffeine, benzocaine, detergents. The actual constituents of a legal high often differs markedly from the 'ingredients' listed on the packaging. Furthermore, products with the same brand name and similar packaging may contain completely different compounds on chemical analysis.

The International Narcotics Control Board Annual Report in 2013[2] stated that the UK has the 5th largest market for legal highs in the world and that there was a 56% increase in UK hospital admissions associated with the use of legal highs from 2009-2012. The EMCDDA European Drugs report 2015[3] showed that 10% of all 15-24 year olds in the UK admit to having taken legal highs and the Republic of Ireland has the highest prevalence of use in this age group in Europe at 22%.

The number of novel psychoactive substances emerging each year is increasing at an alarming rate; the EMCDDA[3] detected 106 newly designed drugs on the market in 2014, compared with 71 in 2012 and 41 novel substances in 2010. As soon as legislation is introduced to criminalize a specific compound or family of compounds, chemists modify key aspects of the molecular structure to produce a drug with similar effects that is not subject to current legislation. Synthetic Cannabinoid Receptor Antagonists (SCRAs) and other types of legal high were ranked 2nd and 3rd respectively in the top 10 drugs of misuse for telephone enquiries to the National Poisons Information Service (NPIS) in 2013/14.[4] In the same year, TOXBASE® accesses

Bhavini Shah
(ST3 in Acute Medicine)

Tom Heaps
(Consultant Acute Physician)

Correspondence
Tom Heaps
Consultant and Clinical Lead for Acute Medicine, AMU (Ward 20), Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS
Email: tom.heaps@heartofengland.nhs.uk

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for SCRAs increased by 253% and for other legal highs by 66% compared with 2012/13.[4] 97 deaths in the UK were directly attributed to NPS in 2014 compared with only 9 deaths in 2007.[5]

In recognition of the scale of this problem, the Home Secretary (Theresa May) drafted a bill in May 2015 which will criminalize the production, supply and import / export of any psychoactive substance which is not specifically named on an official list of exempted substances. At the time of writing, this Psychoactive Substances Bill: 2015-2016 has just passed its second reading in the House of Commons (for more information visit http://services.parliament.uk/bills/2015-16/psychoactivesubstances.html).

Clinical Case

A 24-year-old male is admitted to AMU with a 12-hour history of agitation, sweating and vomiting. The ED clerking states that he had taken a 'legal high' the night before at a party. There is no significant past medical history, he does not take any regular medications and there are no documented drug allergies.

How should you proceed?

As with all cases of suspected poisoning, it is important to approach this scenario with an open mind and first carry out a comprehensive ABCDE survey. Regular physiological observations should be carried out to screen for tachycardia and hyperpyrexia together with neurological observations for reductions in the Glasgow Coma Score (GCS). A 12-lead ECG is essential to assess for prolongation of the QRS and / or QTC intervals and continuous cardiac monitoring is advisable due to the potential risk of arrhythmia. Capillary blood glucose checks are important, especially if there is co-ingestion of alcohol. Baseline blood tests including FBC, U&E, LFT, CK and coagulation screen plus paracetamol levels are always useful. A venous blood gas (VBG) should be performed at the same time to provide a rapid assessment of acid-base status and other important biochemical parameters.

Although it may seem important to identify the chemical compound or group responsible for causing toxicity, in practice this can be very difficult. Attempting to get as much history from the patient and collateral history (where possible) regarding the substance/s ingested and route of ingestion can be helpful. In the case of legal highs, the patient will often know the brand name of the product ingested and may be able to produce the packaging which can provide additional useful information.

If the brand name of the substance/drug can be identified, there are several resources available on the internet to help determine the likely chemical constituents, adverse effects and their management. TOXBASE®, the online database of the National Poisons Information Service (NPIS), allows you to search by either brand/street name (e.g. 'Black Mamba') or by the name of the chemical compound / type of drug ingested, if this is known (e.g. 'synthetic cannabinoid receptor antagonist'). However, the database of brand/street names on TOXBASE® is limited and if the only information you have is the brand name of a relatively new or less commonly used legal high, the TOXBASE® search engine will often fail to return any results.

The Welsh Emerging Drugs and Identification of NOvel Substances (WEDINOS) harm-reduction project was set up by Public Health Wales and provides a free service whereby users of drugs (and clinicians) can anonymously submit samples of substances for analysis. The chemical profile of the submitted substance is published online within several days of receiving the sample at http://www.wedinos.org/db/samples/. Searching this database of sample results by keyword (e.g. using the brand name of a legal high) allows the clinician to determine the potential psychoactive compounds ingested for any given product.

Other useful online resources providing information, drug facts and educational materials relating to novel psychoactive substances are KFX http://www.kfx.org.uk/index.php and Erowid https://www.erowid.org/psychoactives/psychoactives.shtml.

Clinical Case Continued

On examination, the patient is sweating and anxious, pupils are symmetrically dilated and there is no obvious delirium or confusion. Blood pressure is 160/90mmHg and pulse is 120/min with sinus tachycardia on ECG and no QRS/QTC prolongation. VBG shows a mild metabolic acidosis (pH 7.31, BE -4.2) with a raised lactate (3.1mmol/L). Baseline bloods reveal a slightly raised creatinine kinase (302 iU/L) and neutrophilia (WCC 13.9 x 109/L) but were otherwise unremarkable.

What is the most likely class of drug responsible for this presentation?

Newer models for the classification of psychoactive substances categorize drugs based on their predominant effects i.e. stimulants, empathogens, cannabinoids, psychedelics, dissociatives, depressants and opioids. Legal highs containing substances in the first three of these classes are most commonly encountered on the AMU and are discussed in detail below. The Drugs Wheel is a regularly updated visual model for classifying psychoactive substances and separates drugs in each class based on their current legal status in the UK. The wheel can be

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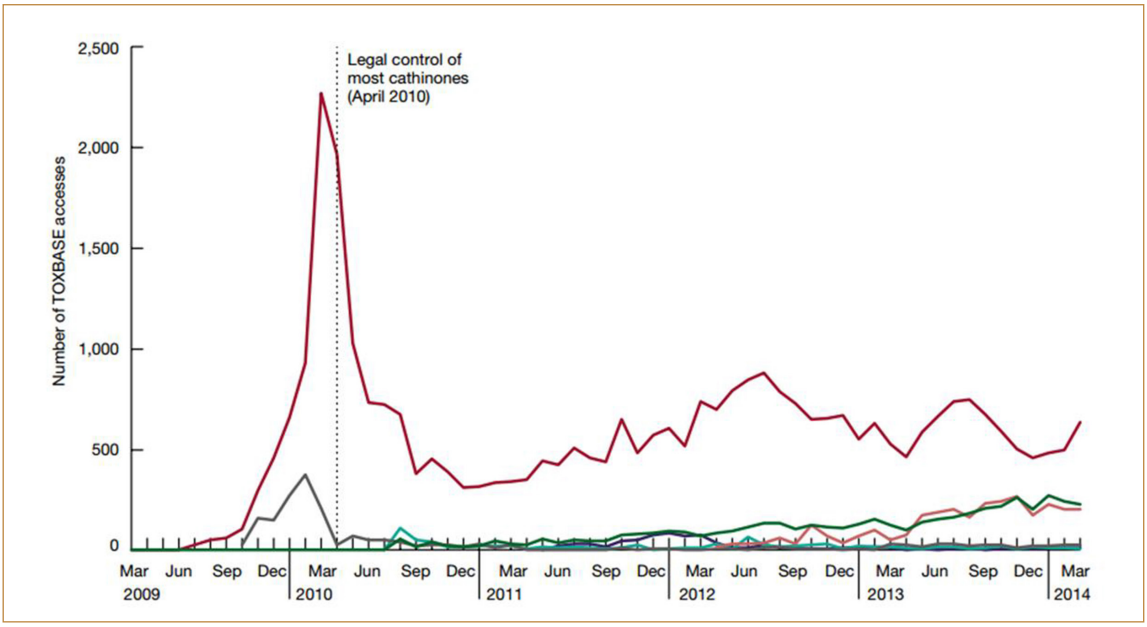


Figure 1. Monthly trends in telephone enquiries to the NPIS and TOXBASE® accesses for mephedrone and related cathinones

freely downloaded in PDF format or as PowerPoint slides for training at http://www.thedrugswheel.com/?page=wheels.

Stimulants

Stimulants are drugs with similar properties to cocaine and amphetamines which increase levels of adrenaline, noradrenaline and dopamine. They are usually produced as white powders and can be nasally insufflated ('snorted'), swallowed ('bombed') or less commonly injected intravenously.

Examples of stimulants include the synthetic cathinones (e.g. mephedrone), paramethoxyamphetamine (PMA) / paramethoxymethamphetamine (PMMA), benzylpiperazine (BZP), methylenedioxypyrovalerone (MDPV, a frequent constituent of 'bath salts'), ethylphenidate (EPH) and methiopropamine (MPA).

Brand names of legal highs containing various combinations of these stimulants include *Gogaine, Ching, Chang, Charles, Charly Sheen, China White, Schniff, Hooter*.

Signs and symptoms of toxicity associated with stimulants include tachycardia / tachyarrhythmias, hypertension, dilated pupils, sweating, agitation, delirium, seizures and the risk of developing serotonin syndrome with malignant hyperpyrexia, rhabdomyolysis and multi-organ failure in severe cases.

Mephedrone (4-methylmethcathinone, 4-MMC, MCAT, Meow-Meow, Drone, Bubbles) is a stimulant cathinone which occurs naturally in the plant Catha edulis ('Khat'), native to parts of Africa and the Arabian Peninsula. Mephedrone was the forerunner of today's legal high market, first synthesized in 1929 from pseudoephedrine, with recreational use not reaching prominence until 2007. Its popularity in the UK grew rapidly between 2009 and 2010 due to its high availability and 'legal' status at that time. It is usually purchased as an off-white powder which is 'snorted', smoked or 'bombed' and more recently injected with high rates of soft tissue and vascular complications. Chronic heavy use has been associated with drug dependency and psychosis. By 2010, mephedrone was allegedly involved in 52 fatalities in the UK leading to the recommendation that all synthetic cathinone derivatives, including mephedrone, should be brought under the control of the Misuse of Drugs Act 1971 as Class B drugs. The use of mephedrone in the UK has declined significantly since this legislation came into force in April 2010, but it has not been eliminated (Figure 1.)

Empathogens

Empathogens (sometimes referred to as entactogens) are drugs similar to ecstasy (MDMA, 3-4 methylenedioxy-n-methylamphetamine) which produce elevated mood and feelings of emotional-relatedness amongst users by increasing levels of serotonin and dopamine.

Examples of newer empathogens include methylenedioxyamphetamine (MDA), 6-(2-aminopropyl)benzofuran (6-APB), butylone, ethylone, 5-iodo-2-aminoindane (5-IAI) and methylenedioxyaminoindane (MDAI). Brand

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Table 1. commonly encountered features of toxicity due to NPS and their management

Symptom / Sign	Management
Anxiety / agitiation / delirium	Benzodiazepines
Hyperthermia	Benzodiazepines, active cooling, IV dantrolene, neuromuscular paralysis
Hypotension	IV fluids, vasopressors, inotropes
Hypertension	Benzodiaepines, IV GTN, IV labetolol
Metabolic acidosis	Oxygen, IV fluids, IV sodium bicarbonate
Seizures	Benzodiazepines, phenytoin, thiopental / propofol
QTc prolongation	IV sodium bicarbonate, IV magnesium
Respiratory depression	Naloxone, (flumazenil), airway and respiratory support
Serotonin syndrome	Benzodiazepines, cyproheptadine / chlorpromazine, treatment for hyperthermia as above

names of legal highs containing empathogens include *Benzo fury, Sparkle, Mindy, Adam, X-Tacy, Yin Yang*.

Toxicity is similar to ecstasy with stimulant / sympathomimetic effects and risk of severe serotonergic syndrome.

Cannabinoids / Synthetic Cannabinoid Receptor Agonists (SCRAs)

Synthetic cannabinoids are often sprayed onto dried herbs, marketed as 'incense', 'herbal blends' or 'spice' and are usually smoked or vaporized. Desired psychoactive effects are mediated through agonism at the endogenous cannabinoid-1 (CB-1) receptor. They are up to 100x more potent than the active ingredient in cannabis, delta-9-tetrahydrocannabinol (Δ9-THC), and will not give a positive urine toxicology screen for cannabis.

Synthetic cannabinoid compunds are often named using the initials of the chemist/s responsible for first synthesizing them e.g. JWH-018 (John W. Huffman) and AM-1220 (Alexandros Makriyannis). Street/brand names include *Spice, K2, Black Mamba, Blue Cheese, Psyclone, Exodus Damnation, Joker, Clockwork Orange, Pandora's Box, Whitey, Happy Rasta*.

Toxicity may manifest as anxiety, agitation, hallucinations and delirium with mild stimulant effects. In severe cases, seizures, hypokalaemia, rhabdomyolysis, acute kidney injury, myocardial infarction and persistent psychosis have been reported.

What are the difficulties in managing patients presenting with toxicity due to legal highs?

Patients may be extremely agitated, delirious and uncooperative which poses risks to both their safety and the safety of other patients and staff on the AMU. In such situations, the Mental Capacity Act may be used to provide pharmacological (and occasionally physical) restraint.

Often, users of these drugs do not know exactly what they have taken and not uncommonly, multiple different substances have been co-ingested with alcohol. Even if the patient can provide the name or packaging of the legal high used, it is not possible to confirm with any certainty what compounds were ingested; different mixtures of drugs may be sold under the same brand name in similar, if not identical packaging; ingredients listed on packaging frequently bear no resemblance to the actual contents on chemical analysis and drugs may be cut with other substances which are not listed on the packet. Furthermore, it is never possible to ascertain the purity and dose of the drug ingested at the bedside.

This is all compounded by the fact that toxicological databases and the accumulation of evidence regarding the toxicity of a particular substance simply cannot keep pace with the number of novel compounds being released onto the legal high market.

So what is the best approach to managing these patients?

Most legal highs have no specific antidote and therefore, in consideration of the inherent difficulties outlined above, the best strategy for managing toxicity is to determine the predominant *toxidrome* (collection of clinical features due to toxicity) and provide supportive treatment accordingly. Enquiries regarding the method of drug ingestion may also assist in identifying the likely toxidrome e.g. a powder that is insufflated or 'bombed' may be associated with a stimulant toxidrome whereas a herbal mixture that is smoked is more likely to result in a synthetic cannabinoid toxidrome. Table 1 summarizes the commonly encountered features of toxicity due to NPS and their management.

Typing 'legal high' into the TOXBASE® search box will bring up a page titled 'Drug of Abuse (Unknown) – Legal Highs' (available at https://www.TOXBASE.org/Poisons-Index-A-Z/L-Products/Legal-Highs) which lists the commonly encountered

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toxidromes (Stimulant, Synthetic cannabinoid, Sedative, Serotonin toxicity, Hallucinogenic, Dissociative) and their characteristic associated clinical features. A link is provided for each toxidrome which takes the clinician to a page detailing typical products, their expected toxicity and management in more depth e.g. *'Stimulant – typical features include tachycardia, hypertension, dilated pupils, sweating, seizures and agitation. Follow the entry for Amfetamines and cathinones features and management'*.

It is important to remember that more than one toxidrome may need to be considered as some chemicals have mixed toxic features or the patient may have ingested multiple different chemicals, either intentionally or unintentionally.

Case Conclusion

Based on our patient's case history, method of ingestion (nasal insufflation) and presenting clinical features, it was highly likely that he had taken a stimulant drug. This was later identified as Ching, containing methiopropamine (MPA), which his friend had purchased from an online retailer. Identification of the predominant toxidrome at the time of presentation enabled us to administer appropriate supportive treatment. He was given IV diazepam for his agitation and fluid resuscitation which corrected his lactate and metabolic acidosis. His symptoms settled within 24h and he was discharged with advice to refrain from using legal highs in the future.

Conflicts of Interest

Nothing to declare

Further Reading / Resources

1. Online learning module 'Club Drugs and Legal Highs' via BMJ Learning accessible at http://learning.bmj.com/learning/module-intro/.html?moduleId=10043909
2. Drug Fact Sheet 'Newer Unregulated Drugs' from KFX: Learning of Substance accessible at http://www.kfx.org.uk/drug_facts/drug_facts_images_and_pdfs/researchchemicals_4.2015.pdf
3. Review Article 'Designer drugs: update on the management of novel psychoactive substance misuse in the acute care setting' in the RCP journal Clinical Medicine accessible at http://www.clinmed.rcpjournal.org/content/14/4/409.full.pdf+html

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