New ways of dealing with new psychoactive substances

MARK GREENER

In 2016, the Psychoactive Substances Act came into force to address increasing concerns about the use of new psychoactive substances (NPS), also known as designer drugs or ‘legal highs’. But how big is the problem, and what impact is the new Act likely to have?

In 1982, William Langston, then director of neurology at the Santa Clara Valley Medical Center in San Jose, California, examined a patient who presented with a putative diagnosis of catatonic schizophrenia. Langston recalls that the patient “was almost totally unresponsive yet eerily appeared to be alert… He was clearly awake, but had virtually no spontaneous movement, and exhibited ‘waxy flexibility’.”1 In other words, when doctors raised the patient’s arm, it remained in place for a prolonged time. The symptoms reminded Langston of advanced Parkinson’s disease before the advent of levodopa. But in contrast to Parkinson’s disease, the symptoms had emerged “literally overnight”.1

Langston and his team identified six similar cases, who had little in common except they had all used a synthetic heroin. The six patients showed almost all the motor features and some non-motor aspects – such as facial seborrhoea and mild cognitive deficits – characteristic of Parkinson’s disease. And all showed “a dramatic and near immediate response to L-DOPA”. Langston and colleagues traced the chemical responsible to a by-product generated during the manufacture of the synthetic heroin called MPTP.1

Although tragic for the “frozen addicts”, MPTP’s discovery offered important insights into the pathology of Parkinson’s disease and allowed researchers to develop animal models to investigate new treatments for this debilitating condition.2 And MPTP underscores the often unknown risks of chemically synthesised new (or novel) psychoactive substances (NPS), sometimes called designer drugs or, before the recent ban, ‘legal highs’.

New drugs, new problems
Several drugs covered by the UK’s drugs laws are synthetic chemicals, such as methamphetamine, ecstasy and ketamine. But NPS posed a novel challenge. As soon as legislators prohibited a specific drug, underground chemists synthesised an NPS that circumvented the ban. And some synthetic drugs are more potent and at least as dangerous as those derived from plants. The synthetic opioid fentanyl is 50 to 100 times more potent than morphine, for example.2
Another synthetic opioid called carfentanil (or carfentanyl) is about 10,000 more potent than morphine (www.drugbank.ca/drugs/DB01535). Heroin may be cut with synthetic opioids, which may increase the risk of overdose.

Synthetic cannabinoids seem to be the most widely used NPS and are responsible for most of the adverse events reported. Cannabinoid compounds, most notably tetrahydrocannabinol (THC), produce cannabis’ psychotropic effects. THC and other cannabinoids agonise CB1 receptors, which are expressed widely in the CNS. Synthetic cannabinoids, which often show markedly higher CB1 agonist activity than THC, are the basis of several NPS such as ‘Spice’, ‘Black Mamba’ and ‘Buzz’.3

“In our services, we find that the cannabinoids are the most commonly used NPS. However, the risks associated with NPS depend on the compound and how it is used. For example, injecting an NPS carries more risks than smoking or snorting,” says Roz Gittins, director of pharmacy for drug charity Addaction. However, “when adverse reactions occur, we typically never get to find what the person has actually taken,” she adds.

“There is a range of different NPS [see Table 1], each with different effects that mimic existing psychoactive drugs,” says Rosanna O’Connor, director of alcohol, drugs and tobacco at Public Health England (PHE). “The contents of NPS regularly change and their effects can be dangerous and unpredictable. It’s clear, however, that NPS can cause serious mental and physical health problems. Synthetic cannabinoids cause most of the adverse events associated with NPS that are reported to health services. The use of some synthetic opioids, such as fentanyl and carfentanil, is less frequently reported than synthetic cannabinoids. However, synthetic opioids cause concern due to the high risks to health associated with their potency.” Ms Gittins also stresses the importance of being “particularly mindful” of the risks associated with synthetic opioids.

**Growing concern**

Over recent years, healthcare professionals, the police and drug charities have expressed increasing concern about synthetic cannabinoids, opioids and other NPS especially among young people and vulnerable adults, such as prisoners and the homeless. Before the new legislation, NPS use peaked at 3.6% of men aged 16 to 24 years, according to the 2015 to 2016 Crime Survey for England and Wales (see Figure 1). Yet NPS still accounted for around half of all last-year users, which is around 147,000 people.4

The number of death certificates in England and Wales that mentioned NPS rose from 55 in 2012 to 123 in 2016, according to the Office for National Statistics. But being mentioned on a death certificate doesn’t mean the NPS killed the person. Many people who take NPS use a variety of other legal and illegal drugs, for instance. Indeed, the Advisory Council on the Misuse of Drugs noted that “only 27 of the 67 NPS-related deaths registered in 2014 did not also involve another substance.”5 And according to the Crime Survey, 84.9% of adults aged 16 to 59 years who took a NPS also took another drug in the same year, so teasing out attributable harm is difficult. A new initiative – the Report Illicit Drug Reaction (RIDR) system, discussed below – should help clarify the risks associated with NPS and other psychotropic drugs.

In the meantime, healthcare professionals need to keep the risks posed by NPS in perspective. Overall, NPS accounted for 2.1% and 3.3% of all deaths from drug poisoning in 2012 and 2016 respectively. Furthermore, as mentioned above, NPS (which included numerous individual chemicals) were mentioned on 123 death certificates in 2016. Paracetamol, tramadol and propranolol were mentioned on 219, 184 and 45 death certificates respectively.

Nevertheless, the government was sufficiently concerned to implement the Psychoactive Substances Act, which came into force on 26 May 2016. The Act covers substances that produce “a psychoactive effect in a person if, by stimulating or depressing the person’s central nervous system, it affects the person’s mental functioning or emotional state.” This led to concerns that the Act would ban incense, perfume and even flowers. This hasn’t happened and presumably wasn’t the intention. Rather, enforcement focuses on NPS that are “qualitatively identical” to a known controlled drug, such as chemicals that act on the same receptor as a conventional psychoactive.

**The Psychoactive Substances Act in action**

The Act commits the Home Office to review the legislation’s operation within 30 months of implementation, focusing on four key themes: enforcement, sales and availability, prevalence, and the health and social harms. The review will report in late 2018, but initial results are promising.

“NPS use is going down, according to the latest Crime Survey. The 2016/17 report estimates that 0.4% of 16 to 59 year olds in England and Wales had used an NPS in the last year [see Figure 1], which is around 147,000 people.6 Young people aged 16 to 24 accounted for around half of all last-year users, which is about 77,000. This is a statistically significant decrease from 2015/16,” says Ms

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**Table 1. New psychoactive substances: categories and examples (source: www.drugwise.org.uk)**

<table>
<thead>
<tr>
<th>Synthetic cannabinoids</th>
<th>Clockwork Orange</th>
<th>Black Mamba</th>
<th>Spice</th>
<th>Exodus Damnation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulant-type drugs</td>
<td>BZP</td>
<td>Mephedrone</td>
<td>MPDV</td>
<td>NRG-1</td>
</tr>
<tr>
<td></td>
<td>Benzo Fury</td>
<td>MDAI</td>
<td>Ethylphenidate</td>
<td></td>
</tr>
<tr>
<td>Tranquilliser-type drugs</td>
<td>Etizolam</td>
<td>Pyrazolam</td>
<td>Flubromazepam</td>
<td></td>
</tr>
<tr>
<td>Hallucinogenic drugs</td>
<td>25i-NBOMe</td>
<td>Bromo-Dragonfly</td>
<td>Methoxetamine</td>
<td></td>
</tr>
</tbody>
</table>

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4. “Only 27 of the 67 NPS-related deaths registered in 2014 did not also involve another substance.”5 And according to the Crime Survey, 84.9% of adults aged 16 to 59 years who took a NPS also took another drug in the same year, so teasing out attributable harm is difficult.
5. This led to concerns that the Act would ban incense, perfume and even flowers. This hasn’t happened and presumably wasn’t the intention. Rather, enforcement focuses on NPS that are “qualitatively identical” to a known controlled drug, such as chemicals that act on the same receptor as a conventional psychoactive.
6. “NPS use is going down, according to the latest Crime Survey. The 2016/17 report estimates that 0.4% of 16 to 59 year olds in England and Wales had used an NPS in the last year [see Figure 1], which is around 147,000 people.6 Young people aged 16 to 24 accounted for around half of all last-year users, which is about 77,000. This is a statistically significant decrease from 2015/16,” says Ms
O’Connor. “While the 2016 Psychoactive Substances Act seems to have helped reduce the easy availability of NPS, we are now seeing use becoming more concentrated in particular vulnerable groups, mainly homeless people and prisoners.”

The review will use several approaches to assess the Act’s effectiveness. In March 2017, PHE and the Medicines and Healthcare products Regulatory Agency (MHRA) launched the pilot RIDR system to improve monitoring of the negative effects of NPS and share best treatment practice across settings, including accident and emergency, sexual health clinics, mental health services, prison health services, drug treatment services and GP surgeries.

Using the RIDR system, frontline health staff can record anonymously information about a NPS and its effects using an online form (report-illicit-drug-reaction.phe.gov.uk). “The MHRA’s Yellow Card Scheme reporting rate in relation to prescription volume is among the best in Europe, according to the BMA’s Board of Science,” Ms O’Connor remarks. “We teamed up with MHRA to develop RIDR specifically because of their sound reputation among frontline health staff.”

Ms O’Connor comments that because the chemical content of NPS can change frequently, their effects can be unpredictable and dangerous, and the best way of treating the associated health problems may not yet be fully understood. “Data from RIDR will be analysed by clinical experts to identify patterns of symptoms and harms, which can then be used to inform treatment guidance and help staff deal more quickly with unknown substances to improve patient safety,” she adds. For example, increasing evidence suggests that CB₁ antagonists can reverse cannabinoid intoxication.³ If and when CB₁ antagonists are approved for this indication, RIDR could record the clinical circumstances in which they are used and the outcomes.

PHE told Prescriber that RIDR collected 204 reports of adverse side-effects to illicit drugs in its first six months of operation. “This provides reasonable evidence that collecting data about adverse reactions to drugs from the frontline is feasible,” Ms O’Connor says. “The response rate is also very encouraging, but it is too early to determine whether RIDR is a success.”

Addaction’s Roz Gittins also welcomes RIDR. “As with any new system, it takes time to embed,” Ms Gittins says. “We need to continue to raise the profile of this scheme and proactively encourage healthcare professionals to use RIDR.”

PHE uses several other sources to inform their advice on NPS and other drugs. For instance, sources that contribute to PHE’s NPS clinical network group include the Home Office Forensic Early Warning System (FEWS), European Drugs Early Warning System, National Poisons Information Service (NPIS), analysis of prison drug seizures and PHE regional teams’ alerting systems. “RIDR’s significance lies in the fact that it is a tailor-made additional source of information, specifically targeted to pick up adverse reactions to NPS and other drugs presenting to frontline workers in health and care services,” Ms O’Connor says. “We are confident that the RIDR pilot will demonstrate the value of its contribution to reducing the harm caused by NPS.”

**Treating NPS use**

Hopefully, greater awareness of the risks will increase the numbers of people treated for NPS use. “Despite the Act, we continue to see people presenting to our services as a result of developing a problem with NPS, though it is not always their primary substance of use,” says Ms Gittins. “However, we know that plenty of people who use NPS do not choose to access treatment services. We provide support to a wide variety of people. Some have a history of using substances, including the more traditional drugs, such as heroin and cocaine. Others present solely due to problems with NPS. Men who have sex with men, for example, are a particular group that we are mindful may be more likely to use an NPS.”

“The numbers of people receiving treatment for NPS problems are relatively low,” Ms O’Connor adds. “Only 2042 people mentioned NPS use when starting treatment for drug abuse in 2015/16, the most recent figures. While this was a 77% increase on the previous year, it is still only 1.5% of the total number of people entering drug and alcohol treatment that year. Just over a quarter of these also used other illicit drugs.”

Of course, if someone wants to get high, they’ll find a way. As I’ve discussed in Prescriber previously, prescription and over-the-counter opiates can be misused by polydrug users as a high, or used by people in chronic pain to blunt emotional trauma.⁷ Myristicin, a volatile oil in nutmeg, undergoes metabolism to a hallucinogenic amphetamine derivative,⁸ and nutmeg has been used in prisons since at the 1940s. Excessive nutmeg use can cause tachycardia, nausea, vomiting and agitation."
More than a decade ago, researchers recognised that smoking the anti-spasmodic drug hyoscine butylbromide (Buscopan) converts it to hyoscine (scopolamine), a naturally occurring hallucinogenic alkaloid contained in the Solanaceae family of plants (eg deadly nightshade). In 2015, NHS England wrote to prison services warning of the risks when prisoners crushed and smoked Buscopan. Hopefully, RIDR and the other sources used by PHE will offer an early warning if such abuse becomes more widespread in the community.

So, overcoming the problem posed by drugs such as NPS will need more than new databases and legislation. The government’s 2017 Drug Strategy envisages “a smarter, more coordinated approach” that engages a wide range of partners, including education, health, criminal justice, housing and employment. In her foreword, Home Secretary Amber Rudd suggests that “By working together, we can achieve a society... in which every individual is supported to live a life free from drugs, fulfil their potential and enjoy a brighter future for themselves and their families.”

The success of the Psychoactive Substances Act and the RIDR pilot will offer an initial indication of our progress towards this laudable ambition.

References

Declaration of interests
Mark Greener is a full-time medical writer and, as such, regularly provides editorial and consultancy services to numerous pharmaceutical, biotechnology and device companies and their agencies. He has no shares or financial interests.

Mark Greener is a freelance medical writer