

Graylands Hospital Drug Bulletin

Emerging Psychoactive Substances - Spotlight on 'legal-highs'

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Introduction

There has been increasing availability and use of a range of emerging psychoactive substances (EPS), commonly known as 'legal highs' or 'research chemicals' worldwide over the last few years. They include a wide range of synthetic and/or plant-derived substances intended to elicit a psychoactive response (e.g. stimulant, hallucinogenic, sedative or mood altering).¹

These products are available in a variety of formulations (powders, crystals, tablets, capsules, liquids, pre-rolled joints, smoking blends, herbal mixtures) and can be purchased both online and from high street retailers known as 'head shops'. EPS are frequently sold under the disguise of innocuous products like herbal blends, incense, or air fresheners and sold for purposes other than human consumption.¹

However, EPS are far from innocuous with increasing case reports of a broad range of physical and psychiatric adverse effects. Also, with the number of intoxicated people presenting to emergency departments dramatically increasing, EPS have become a burning media issue across the world. This Bulletin aims to provide an overview of what we currently understand about EPS, including a description of what they are, how they exert their effects and adverse effects.

Emerging Psychoactive Substances (EPS) - an umbrella term

Within the umbrella term EPS; there is a broad range of substances with different chemical and pharmacological properties. The main chemical groups discussed in this bulletin include: Synthetic cannabinoids, cathinones, piperazine-derivatives and hallucinogens.

Synthetic cannabinoids

Synthetic cannabinoids are dry herbs that have been sprayed or soaked in one or more synthetic chemical compound. Although these psychoactive compounds mimic the effects of cannabis, anecdotal evidence suggest the similarities and differences in the experience of synthetic cannabinoids compared to cannabis can vary widely.² While anecdotal reports of synthetic cannabinoid use in Australia date back

to 2005, it was in 2011 when synthetic cannabis emerged as a drug of concern. In April 2011, the media first began reporting on the use of *Kronic* at Western Australian (WA) mine sites. This was following the results of a large survey of WA mining workers, that found at least one in ten urine samples testing positive for *Kronic*.³

Pharmacology

Cannabinoids are chemicals found in cannabis that are unique to the plant.⁴ The most well known and researched of these, delta-9-tetrahydrocannabinol (THC), is the substance primarily responsible for the psychoactive effects of cannabis.⁴ Synthetic cannabinoids are functionally similar to THC. Like THC, they bind to the same cannabinoid receptors (CB1, CB2) in the brain and other organs.⁴

Synthetic cannabinoids encompass a large family of chemically unrelated structures. Hudson and Ramsey⁵ have classified them into 8 groups. These include: dibenzopyrans or 'classical' THC-like cannabinoids (e.g. HU-210), cyclohexylphenols or non-classical cannabinoids (e.g. 47 497), benzoylindoles (e.g. AM-694), phenylacetylindoles (e.g. JWH-250), naphthoylindoles (e.g. JWH-018), naphthylmethylindoles (e.g. JWH-185), naphthoylpyrroles (e.g. JWH-369) and naphthylmethylindenes (e.g. JWH-176).

Since the 1960s, many analogues of THC have been developed, including HU-210, which is reported to have 100 times the potency of THC. In 1994, J.W. Huffman and colleagues synthesised a large series of synthetic exogenous cannabinoid receptor agonists including a number of what are now known as JWH compounds, after the name of their inventor. These included JWH-015, JWH-018, JWH-073 and JWH-398.

Adverse effects

All of the synthetic cannabinoids currently being marketed are much stronger cannabinoid receptor agonists than THC. Some of the products on sale combine more than one synthetic cannabinoid, each of which acts in a slightly different way. These products contain no equivalent to the natural cannabinoid, cannabidiol (CBD), which has both antipsychotic and anxiolytic properties that ameliorates many of the potentially negative effects of THC.⁶ This makes 'greening-out', increased blood

pressure, heart palpitations, nausea, anxiety attacks and transient psychosis far more likely.⁷

Emerging evidence from recent case-histories document psychiatric adverse effects including anxiety, agitation, and psychosis. Commonly described physical manifestations include nausea, emesis, hypokalaemia, tachycardia, hypertension and seizures.⁸ Forrester and colleagues found that hallucinations, delusions and other psychotic symptoms were more common in cases of synthetic cannabis poisonings (11.2%) than in those involving 'plant' cannabis (2%).⁹

Hermanns-Clausen & colleagues⁸ report on a retrospective study of 29 patients who were hospitalized for *Spice*-related toxicity. *Spice* is one of the popular brands of synthetic cannabis available in the US. Individuals presented with agitation, hallucinations, acute psychosis, vomiting, tachycardia, hypertension and seizures. These cases involved nine synthetic cannabinoids belonging to different classes. They observed that the cannabinoids present in *Spice* changed over time.

Synthetic cathinones

Cathinone ((S)-2-amino-1-phenyl-1-propane) is a naturally occurring beta-ketone amphetamine analogue found in the leaves of the *Catha edulis* (khat) plant. Chewing the leaves of this plant for stimulant effects is popular in certain Middle Eastern countries, particularly Yemen. Synthetic cathinones are derivatives of the cathinones molecule.¹⁰

Mephedrone (4-methylmethcathinone) is one of the most popular cathinone derivatives. The drug has several brand names, for example; *4-MMC*, *MMCat*, *Meow/Miaow Miaow and Bubbles*.¹¹ The drug is usually sold as a white crystalline powder or as capsules and usually taken via snorting intranasally (insufflation) or by oral ingestion by either swallowing capsules, 'bombing' (wrapping powder in cigarette papers and swallowing) or dissolving it in liquid.

Users of mephedrone compare its effects to those exerted by cocaine, amphetamine and ecstasy.¹¹ Subjective effects most often described include euphoria, increased sociability, intensification of sensory experiences, sexual arousal and craving for re-dose. In the largest user survey to date, canvassing 947 mephedrone users who had also previously used cocaine, 20.4% felt the 'high' from mephedrone was as rewarding as cocaine and 54.6% reported the experience was better.¹¹

Methylenedioxypropylvalerone (MDPV) is currently being innocuously marketed as Bath salts under names such as *Ivory Wave*, *Vanilla Sky*, *Pure Ivory* and *Purple Wave*. Nasal insufflation, inhalation, and ingestion are the most commonly reported methods of intake; users report effects similar to ecstasy (increased energy, sociability, euphoria, mental stimulation, sexual

stimulation and empathy).¹²

Pharmacology

Synthetic cathinones are β -ketophenethylamines, which are structurally similar to amphetamine. These compounds have all been shown to strongly inhibit reuptake of dopamine, serotonin and noradrenaline.¹³ The substances also increase presynaptic release of the same monoamines, but to a lesser extent.¹³ Both mephedrone and MDPV increase dopamine levels, but via different mechanisms.¹⁴ This makes the combination of these two compounds (which are detected in some samples of 'Bath salts') particularly dangerous.

Adverse effects

Cardiac, psychiatric, and neurological signs and symptoms are the most common adverse effects reported in synthetic cathinone users who require medical care. Some of the most common adverse effects include agitation, palpitations, headache, chest pain, trismus, bruxism, tremor, insomnia and paranoia.¹² Retrospective data from the United Kingdom (UK) Poisons Information service, detailing telephone caller and internet reports of presumed cathinone exposures, noted that 28% of cases had agitation and aggression.¹⁵

Case reports of significant hyponatraemia have been reported with mephedrone use.¹² This is likely to be due to a combination of increased sweating, electrolyte loss, and substance-induced secretion of antidiuretic hormone.¹² A single case of mephedrone induced myocarditis has also been reported. Mephedrone has been implicated in several deaths in the US and Europe.¹² However, the extent to which mephedrone contributed to each fatality is contested. Multiple cases of mephedrone dependence have been described in the medical literature.¹²

Undesirable adverse effects of MDPV include fatigue, insomnia, tachycardia, nausea, muscle twitching, increased body temperature, difficulty breathing, paranoia and an intense desire to re-dose. There have been overdoses reported in Australia and Europe, including one death linked to MDPV use. Case reports of psychosis, hallucinatory delirium, significant injection site damage and hepatic failure have also been published.¹²

Piperazine derivatives

In recent years, benzylpiperazines (BZP) and trifluoromethylphenylpiperazine (TFMPP) have been used recreationally as substitutes for amphetamine-derived designer drugs. BZP produces a stimulant effect similar, although milder, to that of methamphetamine and when combined with TFMPP it produces euphoria similar to ecstasy (MDMA).

Table 1: Summary of EPS

Class	Chemical name	Product names	Subjective user effects	Undesirable effects
Synthetic Cathinone	Mephedrone (4-methylmethcathinone) Methylenedioxypropylammonium (MDPV)	4-MMC, MMCat, Meow/Miaow, Miaow, Bubbles, Bath salts, Ivory Wave, Vanilla Sky	Euphoria, increased sociability, intensification of sensory experiences	Agitation, palpitations, headache, chest pain, trismus, bruxism, tremor, insomnia and paranoia
Synthetic Cannabinoids	HU-210, JWH-015, JWH-018, JWH-073, JWH-398	Kronic, Skunk, Purple Haze, Black Label, Spice, K2	Relaxation, euphoria	Anxiety, agitation, psychosis, nausea, hypokalaemia, tachycardia, hypertension, seizures
Piperazines	Benzyloxypropylpiperazine (BZP); trifluoromethylphenylpiperazine (TFMPP)	Benzo Fury, MDAI, Head Rush, XXX Strong as Hell, Doves Original	Euphoria, stimulant	Hypertension, agitation, anxiety, confusion, tremor, mydriasis, insomnia, vomiting, seizures, hyperthermia
Hallucinogens	NBOMe series	25I-NBOMe (25I) and 25C-NBOMe (25B), N-Bomb, Smiley Paper	Powerful psychedelic effects	Agitation, seizures, hyperthermia, metabolic acidosis, organ failure

Although being popular in different countries, the drug has been the most prevalent in New Zealand (NZ). One large survey from NZ conducted in over 2000 people aged 13-45 years, found that 20% of respondents reported having tried BZP with 38% of respondents aged 20-24 years having consumed BZP in the previous 12 months.¹⁶

Besides recreational purposes, the drug is also used to increase alertness and overcome sleepiness by shift workers, truck drivers and students.¹⁷ BZP is predominantly consumed in a capsule or tablet, with a typical dose between 50 and 200 mg per tablet. Other reported routes of administration include snorting, injecting, ingesting powder-which is wrapped in a cigarette paper and swallowed (so called 'hammer'). BZP is often mixed with TFMPP ('Bliss' 100mg BZP and 50mg TFMPP).¹⁷

Pharmacology

BZP has central serotonergic effects caused by inhibition of serotonin reuptake and receptor agonism. BZP also causes serotonin transporter inhibition. Additional in vitro studies have demonstrated that TFMPP acts on the serotonin transporter (SERT) to release endogenous stores of serotonin from neurones, in a manner similar to MDMA and other amphetamines.¹⁷

Adverse effects

The majority of information on adverse effects

comes from studies performed in NZ, which appear mainly to involve BZP. The most commonly reported effects include palpitations, tachycardia, hypertension, chest pain, agitation, anxiety, confusion, dizziness, headache, tremor, mydriasis, insomnia, urine retention and gastrointestinal upset including nausea, vomiting and abdominal pain.¹⁸

More severe toxicity may include seizures, collapse, hyperthermia, myoclonic jerking, extrapyramidal features (such as choreoathetoid movements and/or dystonic reactions), hyperventilation and respiratory failure. There have also been several published reports of fatalities involving the ingestion of BZP. In most cases, the BZP was taken in combination with MDMA.¹⁸

BZP and TFMPP both have serotonergic effects, and possible serotonin toxicity has been reported following BZP ingestion. It has also been reported with the related piperazine, Meta Chlorophenylpiperazine (mCPP). Thus, there may be a risk of serotonin toxicity following BZP and/or TFMPP use, especially if used in association with other serotonergic agents either therapeutically or recreationally.¹⁸

Hallucinogens

The NBOMe series are currently the most common novel synthetic hallucinogens in Australia. These drugs were the most commonly discussed group of substances amongst web based drug forums in 2013.

They are typically sold on blotters and have sometimes been misrepresented as LSD, but they are more potent long-acting hallucinogens. The most popular of the NBOMs are 25I-NBOMe (25I) and 25C-NBOMe (25B).¹⁹

Pharmacology

The NBOMe series are analogues of the 2C series of psychedelic phenethylamine drugs that include an N-methoxybenzyl (hence NBOMe) substituent that has significant effects on their pharmacological activity. NBOMe drugs have been characterised in in-vitro receptor studies as potent agonists of the 5-HT_{2a} and 5-HT_{2c} receptors, which may account for the powerful psychedelic effects at very low doses that have been reported by users.

Doses of 750-1000 mcg of 25I or 25C can cause a strong psychedelic experience with effects comparable to LSD. Most descriptions indicate that NBOMs trigger less complex introspection than LSD, but produce strong visual and sensory effects.¹⁹

Adverse effects

The potential for toxicity is very high (much more likely than with LSD). Individuals presenting to emergency department with acute NBOMe toxicity might experience cardiovascular complications, agitation, seizures, hyperthermia, metabolic acidosis and organ failure.²⁰

As NBOMe drugs have a comparatively delayed onset of action (60-90 mins) it is likely that poorly informed consumers may engage in toxic 're-dosing' before the full effects of an initial dose have been felt. There are several media reports describing four Americans and one Australian who have died after reported 25I-NBOMe use.²⁰

EPS and the law

In Australia, the Poisons Standard (or Standard of Uniform Scheduling of Medicines and Poisons (SUSMP)) is the federal legislative instrument, but each state and territory has its own laws that determine what substances are subject to criminal control. Therefore, the legal status of EPS is variable among states and territories, and is changing rapidly.

A key challenge to government is that while states are legislating to ban the latest EPS from becoming available, manufacturers have responded with a cat-and-mouse game of creating new compounds with alleged similar effects in place of each previous one banned. In June 2011, WA implemented a ban via state-specific legislation on seven synthetic cannabinoids. Within several days of the release of the intent to ban these substances, an alternative synthetic cannabinoid was being marketed claiming to circumvent these controls.

According to the United Nations Office on Drugs and Crime's World Drug Report 2013, 'No sooner is one substance scheduled, than another one replaces it, thus making it difficult to study the long-term impact of a substance on usage and its health effects.'²¹

At present, Australian authorities claim to be detecting an entirely new legal high every week. So it is likely that in the foreseeable future, we are going to be faced with the challenge of new synthetic products, about which we know little, marketed in a manner that creates new challenges.

Looking ahead...

Information from web-based drug discussion forums is a valuable source for identifying, which substances are 'in vogue' and which ones are likely to be popular in the near future. The ten most commonly discussed EPS (in descending order) on drug forums in 2013 include the following:

NBOMe series, 2C series, Methoxetamine, DMT, Benzofury/benzofurans, ketamine, Ethylphenidate, Synthetic cannabinoids, Kratom/Kryptom, Poppy seed/Poppy pod tea.²²

Conclusion

In the past few years, we have witnessed an unprecedented increase in the popularity of EPS. These substances are readily available and may markedly differ in terms of ingredients and potency. In addition, there is a misconception that they are safe particularly as they are advertised as legal or natural alternatives.

However, as we have shown, EPS are not safe with serious adverse psychiatric and physical consequences. As the adverse psychiatric consequences are now emerging, little is still known about their impact on pre-existing mental health problems, and even less about the potential interaction with prescribed medications.

It is therefore imperative that health professionals are aware of these risks and should always enquire about EPS as part of routine drug and alcohol assessment. Healthcare provider awareness and patient education will remain cornerstones of public health initiatives in tackling the new challenges presented by these substances.

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