

Legal Highs - Not so new and still growing in popularity

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Abstract

Designer or synthetic drugs which include legal highs and other “club drugs” are substances which have a propensity to cause euphoria, central nervous system stimulation, and hallucinations. Based on chemical formulae for opioids, mescaline, and cannabis, they are created in laboratories under lax conditions for no defined medical purposes. Because they vary in composition from batch to batch they are potentially dangerous for users. Furthermore, the chemical structure is continually changing in order to avoid legislation and therefore users can never be sure what they are taking.

For the purpose of this article readers should use the terms legal highs, designer drugs, bath salts, herbal highs, ‘research’ chemicals, and novel psychoactive substances, interchangeably. Their main purpose is to induce psychoactive effects that mimic amphetamines, cannabinoids or psychedelic drugs. The term ‘research’ only infers that very little is known about these substances and information on adverse effects is often sparse. The reader should also bear in mind that it is beyond the scope of this article to include many other agents.

Keywords: legal highs, bath salts, designer drugs

Overview

The term ‘designer drug’, coined in the 1980s, generally referred to various synthetic opioids based mostly on the fentanyl molecule (α -methylfentanyl) and MDMA (methylenedioxymethamphetamine) commonly known as ecstasy. Fentanyl is an extremely potent analgesic, some 100 times more potent than morphine. MDMA and fentanyl compounds were the most popular synthetic drugs initially. The terminology is confusing because although the description ‘designer drug’ seems to imply the creation of new drugs, many are not new. For example, cathinone derivatives have been reported since the late 1920s. MDMA was first synthesised in 1912, methcathinone in 1928, and mephedrone in 1929. Cathinone is chemically similar to ephedrine, cathine, methcathinone and other amphetamines.

Legal highs generally comprise cathinone stimulants and synthetic cannabinoids. Hallucinogenic agents such as salvia divinorum are also included, the latter sometimes described as herbal ecstasy. Synthetic amphetamines are not regarded as hallucinogenic, though hallucinations are experienced by some users.

Thus, the term ‘designer drugs’ covers an array of substances which are used recreationally, are not controlled under the Misuse of Drugs Act (1971), are not licensed for ‘legal’ use, and are not regulated under the Medicines Act (1968). They are chemicals produced by tweaking or altering the molecular structure of previous well-known psychoactive agents. By stating they are ‘not for human consumption’, or are just ‘bath salts’, they can be sold legally. Hundreds of such substances are now available, reflecting the ease at which chemists can produce them.

Availability and Consumption

The World Drug Report (available on the Internet) produced annually by the UN Office on Drugs and Crime (UNODC), provides information on the worldwide manufacture and marketing of illegal drugs. The 2013 report highlights a striking rise in the availability of new substances. Part of the challenge lies in their variety - some are derived from plants, for instance, the mint plant *Salvia divinorum*, native to Mexico, with synthetic cathinones and cannabinoids also being major contributors in other countries.

Ease of synthesis, low cost, and resourceful marketing have contributed to the problem. Information provided via the internet, combined with minimal difficulty in the manufacture and transport from distant regions, together with lax legal enforcement, creates an ideal opportunity for legal highs to flourish. The low cost is particularly attractive though ironically legal highs probably cost more these days: for example, 1g of mephedrone costs about £16.00 more than when legislation was introduced in 2010. On the other hand MDAI (methylenedioxy-2-aminoindane), a legal stimulant and club drug which is snorted or bombed, costs about half the price of cocaine (£20 per gm). It is sometimes cheaper to buy legal highs over the internet than from a drug dealer. Part of the increase in use of legal highs may be a result of decreasing purity of other ‘buzz’ drugs such as cocaine and MDMA. As with other illegal drugs regulatory measures drive the drugs ‘underground’ and into the hands of drug dealers and the price then varies with the purity of the drug and its ease of manufacture and availability.

Some users will revert to taking an illegal drug when the legal alternative is prohibited. There is also a certain curiosity to experiment with new drugs. Even so, to keep things in

perspective, consumption of more harmful familiar illegal drugs (for example, cocaine, amphetamines) has not abated, with over 315 million people worldwide thought to be using them. More worrying is that millions of individuals inject more harmful drugs such as opiates with resultant increased rates of HIV, hepatitis B and hepatitis C infection. Readers are also likely to be aware of the violence and deaths associated with drug manufacturing and supplying within countries such as Latin America.

Government Control

The Medicines Act 1968 (UK) governs the control of medicines for human and veterinary use. It defines three categories of medicines: a) prescription only medicines (POM), available solely from a pharmacist and requiring an appropriate practitioner to issue, b) pharmacy medicines (P), available only from a pharmacist, without the need for a prescription, and c) general sales list (GSL) meaning medicines bought without a prescription. The Medicines Act 1968 was set up to protect patients from unscrupulous suppliers of medicines. Safeguarding the public from illegal medicines or any inaccurate and misleading labelling of medicines is paramount. However, manufacturers have managed to sell legal highs by passing them off as bath salts or research chemicals.

Phenylalkylamines analogues such as amphetamine are widely misused and because of their simple structure hundreds of amphetamine analogues have been introduced for decades. This is the reason why so many legal highs are available. Amphetamine (phenylisopropylamine), a familiar central nervous system (CNS) stimulant, has effects which last for several hours after oral intake. Methamphetamine is closely related to amphetamine and ephedrine (a mixed-acting sympathomimetic). Ephedrine and pseudoephedrine (often used for relief of nasal congestion) undergo reduction to methamphetamine, or oxidation to methcathinone. As with methamphetamines, methcathinones can be readily 'cooked' in the laboratory and hence the term 'synthetic'.

Background biochemistry

Morphine, the most abundant opiate alkaloid found in the poppy plant, *papaver somniferum*, was first isolated in 1804. The actual term alkaloid is derived from "alkaloid" introduced in 1819 by the German chemist Carl Friedrich Wilhelm Meisner, from the Latin root '*alkali*', and the Arabic word '*al-qalwī*' meaning "*ashes of plants*".

Alkaloids are a group of naturally occurring organic nitrogen-containing bases, a base being a substance with a pH above 7 which turns red litmus paper blue. They include related compounds with neutral and even weakly acidic properties and more than 3,000 different types have been identified. In addition to nitrogen, hydrogen and carbon, most alkaloids contain oxygen, sulfur, and to a lesser extent, chlorine, bromine, and phosphorus. Generally, an alkaloid contains at least one

nitrogen atom in an amine-type structure, i.e. one derived from ammonia (NH₃) replacing the hydrogen atoms with hydrocarbons, for example, CH₃ or CH₂. Alkaloids generally are weak bases and some act as acid or base (amphoteric).

Alkaloids are produced primarily by flowering plants and organisms such as bacteria, fungi, and animals. Several alkaloids may be extracted from one plant. They can be purified from crude extracts by acid-base extraction and tend to have a bitter taste. Those containing a ring system are known as *indole* alkaloids (for example, terpenoids and steroids). Some are named after the biological species from which they are derived (morphine from the poppy plant *Papaver somniferum*, cocaine from *Erythroxylon coca*, and so on). Other common examples include psilocin, caffeine, nicotine, vincristine, reserpine, atropine, quinidine, ephedrine, strychnine and quinine. Atropine is the tropane alkaloid isolated from the deadly nightshade plant *Atropa belladonna*, and strychnine is derived from the seeds of the *Strychnos nux-vomica* tree. Caffeine, cocaine, codeine (methylnorphine) and nicotine are water-soluble alkaloids. Morphine and yohimbine are highly water-soluble. Other alkaloids dissolve poorly in water yet readily in organic solvents such as chloroform or ether. The biological precursors of most alkaloids are amino acids, such as phenylalanine, tyrosine, tryptophan, histidine, and aspartic acid, among others.¹

How are they used?

The synthetic cathinones (usually mephedrone and methylone, or M-Cats) are most commonly used intranasally (insufflated) or ingested. "Bombing" is a method of ingestion whereby mephedrone powder is wrapped in cigarette paper and swallowed. Because sniffing the drug may cause nasal burns users will often resort to 'bombing'. "Keying" is the practice of dipping a key into powder and then insufflating, with approximately five to eight "keys" per gram. Rectal administration, gingival delivery, inhalation, intramuscular and intravenous injection have also been described. Multiple concomitant routes of administration are reported. Self-reported doses range from a few milligrams to over 1 g of powder. A typical dose of mephedrone would be 100-200mg every 1-2 hours.

Users cannot be certain of the actual contents or indeed of the purity of the drug, therefore actual dosage and exposure is highly variable. For example, when MDAI (methylenedioxy-2-aminoindane) known as Sparkle (a granular, brownish powder) is snorted or bombed, it has an effect similar to ecstasy causing mood enhancement and hallucinations. Onset of action is usually within one hour and the effects are then almost immediate, perhaps a minute or so. The high lasts about six hours with a peak of two hours. It may cause hyperthermia, paranoid ideation and panic attacks.²

Cathinone is a naturally-occurring beta-ketone amphetamine analogue found in the leaves of the khat plant. Other synthetic cathinones such as methcathinone and MDVP (methylenedioxypropylvalerone) produce similar effects. Beta-ketone refers to the possession of a ketone group in the beta position of the aminoalkyl chain attached to the main molecular methylenedioxyphenyl ring.

Synthetic cannabinoids share some functional similarities with $\Delta 9$ -tetrahydrocannabinol (THC), the active principle of cannabis. Like THC, they can have sedative, depressant and hallucinogenic effects. They have been detected in herbal smoking mixtures such as 'Spice' as well as resins that mimic cannabis resin.

Khat (*Catha edulis*)

Some knowledge of this plant is necessary in order to explain the background to many of the synthetic designer drugs. Khat is an evergreen shrub the leaves of which are chewed for their stimulant properties. An understanding of its chemical composition helps to explain the use of its constituents in the formation of designer drugs. Khat contains more than 40 alkaloids as well as many other compounds. The khat phenylalkylamines consist of cathinone, cathine and norephedrine: these alkaloids are structurally related to amphetamine and noradrenaline. Although similar to methylamphetamine, methcathinone (variously known as *Cat*, *Kat*, *Qat*, *Ghat*, and *Chat*) possesses a chemical structure resembling cathinone; its side effects and addictive properties are more potent.

The plant is chewed into a ball and kept in the cheek for a while. When khat leaves dry, cathinone (benzoylethamphetamine) decomposes within 48 hours leaving behind the milder chemical, cathine (a phenethylamine compound). Therefore, to maintain the potency of the drug, harvesters transport khat by packaging the leaves and stems in plastic bags or wrapping them in banana leaves to preserve moisture. It is common to sprinkle the plant with water or use refrigeration during transportation. Khat is therefore best used within 12-48 hours when the leaves are still moist.

Catha edulis is a flowering plant (one that produces seeds) native to the Horn of Africa (Eritrea, Djibouti, Ethiopia and Somalia) and the Arabian Peninsula. In these countries chewing the leaves and stalks is a social custom dating back thousands of years. It may take 7-8 years for the shrub to reach its full height (6-12 feet or more). Globally it is estimated that some 10 million males (usually) use khat on a daily basis.

Catha edulis leaves contain a beta-ketone amphetamine analogue. Ketones contain a carbonyl group (C=O) bonded to two other carbon atoms. Phenylalkylamines (derived from *phenethylamine*) are often termed "bk-amphetamines" for the beta-ketone moiety.

The principal active components in khat are cathinone and cathine. By chewing khat these substances are secreted into saliva. The effects are similar to amphetamine though less potent. Psychological dependence does occur in some though generally khat is not addictive. It is freely available in many countries and its production, sale and consumption are legal, including the Horn of Africa. In the Arab Peninsula it is known as Arabian tea and in South Africa it is referred to as Bushman's tea.

Although its stimulant effect was originally attributed to cathine, extracts from fresh leaves of khat were shown to contain *cathinone*, isolated in 1975 and its properties recognized in 1978. Cathinone is not very stable and breaks down to produce cathine and norephedrine which belong to the phenylpropanolamine family, a subset of the phenethylamines and the catecholamines adrenaline and noradrenaline.

When the leaves are chewed the active ingredients are absorbed through the oral and gastric mucous membranes. The action of cathine and cathinone on the reuptake of adrenaline and noradrenaline results in the wakefulness associated with amphetamine derivatives. The effects of cathinone peak after 30 minutes, with nearly 98% of the substance metabolized by the liver into noradrenaline. Cathine has a half-life of about three hours in humans. Typically, an individual consumes 100-200 g of khat leaves (one bundle) in a session, and its effects last for several hours.

Symptoms are rather similar to the ingestion of strong coffee or amphetamines, for example, overtalkativeness and hyperactivity. The effects of oral cathinone occur more rapidly than those of amphetamine, 15 minutes compared to 30 minutes respectively. Khat causes constipation, dilated pupils (mydriasis), tachycardia and increased blood pressure, reflecting the sympathomimetic effects of the drug. Withdrawal symptoms, as would be expected, include mild depression and irritability, lethargy, rebound anxiety causing nightmares, tremulousness and loss of appetite. Long-term use may cause hepatic dysfunction, a permanent greenish tinge darkening of the teeth, and diminished libido. Rarely, dilated cardiomyopathy and myocardial infarction result from chronic use.³

Mephedrone

Mephedrone ('meow meow') is a synthetic stimulant chemically related to cathinone, the psychoactive substance present in the khat plant. It is usually sold as a white crystalline or off-white-yellow powder (as a hydrochloride salt) for about £10 per gram. Consumption is usually oral or intranasal and rarely, by injection. Sellers avoid attracting the attention of regulatory bodies by labelling the substance "not for human consumption," which means that no advice on safer use and dosing is provided.⁴

In one study the most commonly seen drug class were piperazines, followed by the cathinones, with significant

variation in the content in one quarter of these compounds. The authors stated that it was relatively easy to purchase a number of legal highs from different Internet suppliers, though there times when not all of the products were available leading to the problem of users buying different active drugs to those they are used to, raising the prospect of potential toxicity to unknown agents.⁵ A cross-sectional survey of 947 of mephedrone users found it to be the sixth most frequently used drug in the previous month after tobacco, alcohol, cannabis, cocaine and MDMA. Users typically were young males; 15% reported using weekly or more frequently; nearly 50% used between 0.5 and 1g during a typical session; intranasal use was the most common route of use (70%). Almost 55% of those who used cocaine reported that the 'high' obtained with mephedrone was better: intranasal use was also more likely addictive than oral use. Mephedrone appears to be the most widely abused synthetic cathinone in Europe, in contrast to the USA where MDVP and methylene are the most frequently abused.^{6,7}

Classification of mephedrone has had a limited effect on controlling its availability and use. Before the introduction of the legislation users generally obtained it via the internet. Now it is bought from street dealers, on average at double the price. Mephedrone was defined as a Class B drug under the Misuse of Drugs Act (1971) in the UK in April 2010.⁴

Mephedrone produces similar effects to ecstasy, amphetamines and cocaine. It is detected in 20% of ecstasy tablets. It simulates the release of and inhibits the reuptake of monoamine neurotransmitters. The onset of psychoactive effects after insufflation is usually 10–20 minutes with an expected duration of effect of 1–2 hours; after oral ingestion onset is about 15–45 minutes with duration of 2–4 hours, and intravenous users report symptoms peaking at 10–15 minutes with a 30-minute duration of the desired effect.

Mephedrone users report that it has a better quality high than cocaine. It is speculated that mephedrone's popularity reflects dissatisfaction with the purity and consistency of available cocaine and ecstasy. Concerns are also raised when it is considered that mephedrone is readily available from street dealers and may be taken by young people who have little previous experience of drug use.

Blood or plasma mephedrone concentrations are expected to be in a range of 50–100 µg/l in persons using the drug recreationally, >100 µg/l in intoxicated patients and >500 µg/l in victims of acute overdose.

Mephedrone induces a greater increase in dopamine than serotonin release whereas MDMA ('ecstasy') induces a huge increase in serotonin with an insignificant rise in dopamine. Amphetamine results in a surge in dopamine release with an insignificant increase in serotonin. Mephedrone, amphetamine, and MDMA have decay values of 25, 50 and 300 minutes

respectively. Therefore, the rapid rise and fall of dopamine levels could explain the addictive properties of mephedrone in some users. The effects are often described as somewhere between ecstasy and cocaine. As with cocaine, the 'high' generally lasts around an hour before wearing off. Furthermore, prolonged high-dose use of the substances can produce long-lasting neurotransmitter deficits in humans.^{8,9}

According to Mixmag (the online drug-use clubbing survey magazine for the UK) published in March 2012, 42% of clubbers had tried mephedrone the drug, and 34% had taken it in the last month. Some 30% of mephedrone users had reported using more ecstasy since the ban came into effect, while 19% reported using more cocaine. Blood or plasma mephedrone concentrations are expected to be in a range of 50–100 µg/l in persons using the drug recreationally, >100 µg/l in intoxicated patients and >500 µg/l in victims of acute overdose.

In 2011, Mixmag and the Guardian newspaper which draws on previous Mixmag surveys collected 15,500 responses from around the world, mostly the United Kingdom. In 2010/11, reported levels of use of mephedrone in the last year and last month were three times higher among clubbers (30 % and 13 %) than non-clubbers (10 % and 3 %).

Mephedrone predictably, causes increased alertness, restlessness, euphoria, excitement, the urge to talk, openness, time rushes, hot flushes, increased libido and elation. Hyperhidrosis, headache, palpitations, a Raynaud-type syndrome, and nausea are other relatively common unpleasant effects. Dizziness, hallucinations, panic attacks, and psychosis may occur. Other physical symptoms include dry mouth, blurred vision, and epistaxis. Symptoms of intoxication include agitation, aggression, violence, seizures and hyperthermia. Fatigue and insomnia are common residual effects. Mephedrone is generally used by nasal insufflation or ingestion of powder, liquid, capsule or tablets. The majority of users source mephedrone from street level dealers.¹⁰ Mephedrone induces strong feelings of craving in most users. If the unstable ecstasy market situation persists, the potential of mephedrone to substitute for MDMA might be substantial. Mephedrone, sold as ecstasy, is therefore more likely to be a cause for concern in the future.

Bath salts

This is the street name for substances which contain synthetic cathinone stimulants, such as methylenedioxypropylvalerone (MDPV) and mephedrone.¹¹ Bath salts components act synergistically at the dopamine transporter site and enhanced dopamine transmission may increase the potential for abuse. MDPV is consumed with other illicit drugs of abuse. It is the primary ingredient in "bath salts." Being a synthetic, cathinone-derivative it produces a high similar to cocaine or methamphetamine. It can be administered orally, by nasal insufflation, smoking, intravenously/intramuscularly, or per rectum, and intoxication lasts many hours.

MDPV may cause cardiac problems and disturbance of perception. During the withdrawal period after MDPV use, bone and muscle pain, and visual disturbances may occur. In the metabolism of MDPV, the most important catalyst is the CYP2C19 isoenzyme; the CYP1A2 and the CYP2D6 isoenzymes also play a role. The formed catechols are conjugated with either glucuronic acid or sulphate.

These compounds are not true bath salts in the traditional sense of household products. Cathinone is an amphetamine-like stimulant found naturally in the khat plant, described in more detail below. MDPV is much more potent than cocaine and its effect is longer lasting.¹²

Because of the sympathomimetic activity side effects are predictable and include cardiac arrhythmias, hypertension, arrhythmias, and hyperthermia. Chest pain, myocardial infarction, sweating, rhabdomyolysis, seizures, stroke, cerebral oedema, cardiorespiratory collapse, and rarely, death, have been reported. Psychiatric manifestations include hypersomnia, panic attacks, agitation, paranoia, suicidal ideation, self-mutilation, and aggressive behaviour.

The mode of action is thought to be the result of disruption and interference with central monoamine systems. In other words, synthetic cathinones increase extracellular monoamines by blocking transporter reuptake and increasing presynaptic neurotransmitter release. The dopamine (DA) transporter (DAT) and serotonin (5-HT) transporter (SERT) tightly regulate the amount of neurotransmitters within the synaptic cleft. Monoamine release also may be driven by presynaptic input from cholinergic or glutaminergic systems.^{12 7}

Psychoactive bath salts are sold as tablets, capsules, or powder and purchased in places such as tobacco and convenience stores, gas stations, head shops, and the Internet. Bath salts may mimic cocaine, lysergic acid diethylamide (LSD), methamphetamine, or MDMA. The most common bath salts are the cathinone derivatives MDPV, mephedrone and methylone. The drugs have the potential for addiction because they cause intense stimulation, euphoria, elevated mood, and a pleasurable "rush".^{13 14}

In the United Kingdom (UK) to avoid being controlled by the Medicines Act, legal highs are sometimes described as bath salts, fertilizer (plant food), or incense, even though they have never been used for these purposes. In other words, legal highs are not covered by current drugs laws yet are used by individuals in the same way as illegal drugs such as cocaine or cannabis. The easy availability of legal highs marketed as "bath salts", 'incense' and 'plant foods', with the added proviso that they are not to be consumed by humans allows the drugs to circumvent current legislation. When legislation is changed the molecular structure is easily altered to produce a new legal high.

Synthetic cannabinoids

Marketed as 'incense' and labeled "not for human consumption", these drugs were increasingly popular with students and young adults being initially legal and easily available from stores, online, head shops (outlets selling drug paraphernalia/counterculture magazines) and petrol stations. The structure of synthetic cannabinoids does not resemble that of tetrahydrocannabinol (THC) contained in marijuana or hashish, yet the drugs affect individuals in the same manner and are much more potent. Synthetic cannabinoids are sold under countless names such as 'Mr Nice Guy', 'Spice', 'Sabbaba' and 'Lemon Grass', to name a few. Spice is a designer drug derived from herbs sprayed with synthetic chemicals which mimic the effects of cannabis. The ingredients are thus similar to but not identical to THC. Synthetic cannabis can precipitate psychosis, especially in individuals with a previous history and a chronic psychotic disorder may persist in some vulnerable patients.

A great variety of synthetic cannabinoids, most often cannabicyclohexanol, are used in an attempt to avoid prosecution. Some are sold in 'herbal' smoking mixtures and the latter have been found on occasion not to contain any synthetic cannabinoids at all. Cannabicyclohexanol is a cannabinoid receptor agonist drug. It has been sold under various brands such as Black Mamba, Bombay Blue, Fake Weed, Genie, Bliss, Blaze, Yucatan Fire. Spice products sometimes sold as "incense," more closely resemble potpourri. Although Spice is usually smoked, sometimes individuals mix it with cannabis or prepare a herbal infusion for drinking.

Table 1: Side effects of mephedrone

<u>Common:</u>
Hyperhidrosis
Headache
Palpitations
Nausea
Raynaud-type syndrome
<u>Uncommon</u> < 10%
Dizziness
Hallucinations
Psychosis
Dry mouth
Increased sociability
Chest pain
Blurred vision
Agitation, aggression, violence,
Hyponatraemia
Seizures and hyperthermia
Fatigue and insomnia

To create the herbal products, synthetic cannabimimetics are dissolved in an organic solvent (e.g. acetone) and the resulting solution is sprayed on plant material. The doped plant material is then dried and smoked in a similar fashion to actual cannabis. Spice products typically have a pleasurable smell and taste. They are often referred to as herbal or legal highs because of their legal status and 'natural' herbal make-up. They are distributed in the form of dried leaves or resin, and powder, and are sold without age restriction in metal-foil sachets, usually containing

3 g of vegetable matter, to which one or more of the synthetic cannabinoids have been added. Spice is typically smoked, using a pipe or by rolling in a cigarette paper, and can also be ingested as an infusion, or inhaled.^{15 16}

Drugs of the 2C family (phenethylamines containing methoxy groups attached to a benzene ring) have hallucinogenic and stimulant effects. The term '2C' refers to the 2 carbon atoms between the benzene ring and the amino group in these compounds. The effects are a cross between MDMA and LSD. They are relatively new to the market and not widely available in the UK. An excited delirium presentation seems to be consistent in deaths attributed to 2C drugs and at least five deaths have been reported in the literature in patients intoxicated with 2C drugs. One agent known as 2C-1 or *Smiles*, which first appeared in 2003, has more potent effects than MDMA and LSD. Users report an intense energy with vivid visual and auditory hallucinations lasting hours to days. Patients may exhibit symptoms consistent with serotonin toxicity. Doctors need to be vigilant as synthetic drugs do not show up on routine testing. Treatment of 2C intoxication is primarily supportive.¹⁷

Despite widespread Internet availability, many of these drugs remain unfamiliar to doctors and yet 'bath salts', have resulted in nationwide emergency department visits for severe agitation, sympathomimetic toxicity, and death. As with other illicit substances designer drugs may compromise cardiac function causing hypertension and tachycardia and users who inject run the well-known risks of contracting hepatitis C or HIV, thrombophlebitis and embolus formation.

Methoxetamine

Methoxetamine (also known as 'mexxy') is available on the Internet and marketed as 'legal ketamine.' It is an arylcyclohexylamine chemically related to ketamine and PCP (phencyclidine). Methoxetamine is longer acting and more potent than ketamine. The drug, a white powder, is usually taken sublingually, snorted, 'bombed', or injected intramuscularly. Doses are typically between 5mg-90mg orally. After snorting the drug it may take 30-90 minutes for its effects to become apparent. When injected the onset of action is usually within five to ten minutes. The overall duration of effect is within the range of 1-3 hours, sometimes longer. The drug induces feelings of detachment (dissociative state), paranoid symptoms, visual hallucinations, restlessness and increased energy in some. Other reported symptoms include confusion, catatonia, depression, tachycardia and hypertension. Methoxetamine is now a Class B drug under the Misuse of Drugs Act.^{18 19}

Piperazine derivatives

The piperazine derivatives, a class of amphetamine-like compounds that includes BZP (benzylpiperazine) and TFMPP (trifluoromethylphenylpiperazine) are making a comeback as

"legal ecstasy." Often perceived as safe by the public, adverse effects may range from minimal to life-threatening. Co-ingestion of BZP and TFMPP causes increased action of dopamine and serotonin, similar to MDMA. Severe symptoms include seizures, hyperthermia, hyponatremia, dystonic reactions, rhabdomyolysis, renal failure, metabolic acidosis, DIC, and respiratory failure.²⁰ Over the last few years piperazine derivatives are being sold as ecstasy pills, or under the names of "Frenzy", "Bliss", "Charge", "Herbal ecstasy", "A2", "Legal X" and "Legal E". Although piperazine designer drugs enjoy a market reputation of being safe, they may cause distorted perceptions after ingestion. There are several reports of toxic symptoms experienced by users after drug intake. The piperazinic compounds are derived from piperazine, a cyclic molecule containing two opposite nitrogen atoms and four carbon atoms distributed between the two and were originally used as anti-helminthic agents in the 1950s. Designer drugs of this class can be divided into the benzylpiperazines such as benzylpiperazine (BZP) and its methylenedioxy analogue methylenedioxybenzylpiperazine (MDBP), and phenylpiperazines such as chlorophenylpiperazine (CPP), trifluoromethylphenylpiperazine (TFMPP), and methoxyphenylpiperazine (MeOPP). A third group includes the thienylmethylpiperazines. Chlorophenylpiperazine is an active metabolite of drugs such as trazodone, and nefazodone used as antidepressants. A survey in the UK found that piperazines are among the most common active drugs in tablets purchased from internet supplier sites. Piperazine-derived compounds are therefore emerging designer drugs, whose abuse has increased remarkably worldwide.²¹

Naphyrone

Naphyrone (*naphthylpyrovalerone*) or NRG-1 (or Energy1) is a cathinone derivative available to buy on a number of websites and is gaining popularity. It is sold as an alternative to mephedrone. Belonging to the designer drugs class, it is similar in structure to pyrovalerone, a monoamine uptake inhibitor and as it is somewhat similar to other cathinone derivatives it has the potential to produce anxiety, paranoia, and cardiovascular side effects. Two products, both sold as NRG-2 from different internet suppliers, were found to contain the banned substituted cathinones - 4-methylethcathinone (4-MEC) and 4-methylmethcathinone (4-MMC), the latter being present in much smaller quantities. Although sold as research chemicals and labelled 'not for human consumption', they are essentially legal highs and are available online.^{22 23}

Discussion

New designer drugs have increased in popularity over the past several years because of their euphoric effects. Understanding the pharmacology and toxicology of these agents is essential in order to provide the best medical care for patients. They are all potentially dangerous. For example, an excited delirium

presentation seems to be consistent amongst deaths attributed to 2C drugs.

Table 2: Some commonly used psychoactive substances

Drug	Mode of Action	How used
MDMA ('ecstasy') 'Molly' is the pure crystalline powder form	Releases and inhibits reuptake of dopamine, serotonin and noradrenaline	Tablet or capsules Sometimes one or more tablets taken at one time ('bumping')
Salvia divinorum	Partial dopamine receptor agonist; also works on kappa receptors	Smoked, inhaled, ingested, used sublingually
Mephedrone	Effects similar to MDMA, cocaine and amphetamines	Nasal insufflation, ingestion
MDVP (see text)	Related to cathinone. Effects similar to 'ecstasy'	Nasal insufflation, inhalation, ingestion
Spice	Similar to THC	Smoked; sometimes prepared as a herbal infusion for drinking
Naphyrone	Effects similar to mephedrone	Usually snorted, sometimes swallowed in paper wraps ('bombing')

From the above description it can be seen that synthetic drugs fall into three broad categories: synthetic cathinones (bath salts), synthetic cannabinoids (spice or incense), and amphetamine-like drugs (methamphetamine, ephedrine, MDMA). Cathinones being related to the amphetamine family will cause dilated pupils, hypertension, hyperventilation, paranoia, agitation, hyperthermia, tremors and seizures. Many countries have made certain cathinones illegal, for example, mephedrone, methylene and MDPV. Indeed, the robust stimulation of dopamine transmission by MDPV predicts serious potential for abuse and may provide a mechanism to explain the adverse effects observed in humans taking high doses of 'bath salts' preparations. Furthermore, pyrovalerone is much more potent than cocaine at inhibiting the uptake of dopamine and norepinephrine.

Methcathinone was previously used in Russia as an antidepressant, also known as "Cat" and "Jeff" when used recreationally. Nowadays the drugs are sold as bath salts, plant food, insecticides, chicken feed additives, or research chemicals with names such as like NRG (Energy) and meow, meow. Bath salts are water-soluble, usually inorganic, solid products designed to be added to water during bathing. Numerous nicknames are used to describe them including Ivory Wave, Purple Wave, Red Dove, Zoom, Bloom, Cloud Nine, Ocean

Snow, Lunar Wave, Vanilla Sky, White Lightning, and Hurricane Charlie.

Although 'legal highs' are commonly referred to as bath salts they are not Epsom salts (magnesium sulphate) or other water softeners within the usual meaning. In many cases the chemical ingredients are changed without the consumer knowing, making risks unpredictable. Some legal highs contain active ingredients controlled under the Misuse of Drugs Act 1971 (UK). Therefore any individual found in possession of these products would be liable to prosecution and the associated penalties, even if unaware that he/she has purchased a controlled drug. However, claiming a product to be "not intended for human consumption" can potentially circumvent the entire legal process. Drug designers are already showing skilful exploitation of the law and remain far ahead of criminalization efforts. Furthermore, the irony of prohibition is that the supply and slump in the market for cocaine and ecstasy in 2009 led to individuals resorting to untried and untested substances that are now easily available online.^{24 25}

Synthetic cathinones are mostly excreted via the urine and can be measured via gas or liquid chromatography-mass spectrometry in the blood, urine and stomach contents. They can also be analysed in hair. Unlike traditional cosmetic bath salts, which are packaged and sold for adding to bath water for soaking and cleaning, synthetic designer drugs sold as "bath salts" have no legitimate use for bathing and are intended for abuse. Bath salts contain one or more synthetic derivatives of the naturally-occurring stimulant cathinone. Low doses produce euphoria and increase alertness, but high doses or chronic use may cause serious adverse effects.²⁶

Treatment

Treatment should be tailored to the specific drug of abuse. Medical and psychological needs require examining. Generally, treatment uses a combination of counselling and medication to reduce the need or desire (craving) for the drug and give the person the skills to refrain from future drug use. Other treatments might include cognitive behavioural therapy, detox, and relapse prevention techniques.

Supportive care is the mainstay of treatment for untoward serious side effects. Sedation with benzodiazepines is indicated for agitation, seizures, tachycardia, and hypertension. Extreme hypertension that persists despite benzodiazepines may be treated with vasodilators. Beta blockers should be avoided due to the potential to cause unopposed alpha-adrenergic stimulation, worsening the hypertension. Significant hyperthermia may require passive or active cooling. All moderately to severe symptomatic patients should have an electrocardiogram (ECG), be placed on a cardiac monitor, and receive serial temperature checks. Electrolytes, liver function tests, cardiac enzymes creatine, and toxicology should be carried

out. Asymptomatic patients with no other suspected ingested drugs or psychiatric symptoms generally may be discharged.

Prevention

Banning legal highs is probably futile because it is impossible to keep up with newer drugs because they are synthesized as soon as the 'illegal' drug becomes banned. Some would argue that arresting users creates more harm for individuals, their families and society, as they are then caught up in the criminal system. Others may argue that 'legal highs' are not generally harmful and not as dangerous as opiates or their derivatives, or indeed alcohol. It might be more worthwhile making legal highs 'uncool', much in the same way that cigarette consumption is now frowned upon. However, it would require a great deal of public money to subsidise such an advertising venture.

Users of legal highs need to be made aware that such drugs purchased on-line may contain illegal substances and therefore may render them subject to prosecution if found in possession.²⁷

Pre-school family based programmes, and programmes involving the school and community, motivational interviewing for adolescents, and individual programmes, may be beneficial in reducing drug use and other harmful outcomes. Importantly, none of these approaches focus exclusively on particular substances or groups of substances, and although there have been relatively few investigations of intervention processes they most likely work by targeting a number of important precursors of drug use behaviour.²⁸

Preventing designer drug abuse begins with understanding the warning signs of addiction which in many respects are similar to alcohol or more common street drugs.

Club drugs are now widely available and their harmful effects are increasingly becoming more evident. Their effects are unpredictable as they are often 'contaminated' with other harmful substances. It is unlikely that legislation will have a meaningful impact. Increasing public awareness about these drugs is paramount, and medical and nursing staff should consider intoxication in those patients who present with agitation and psychosis who have no previous history of mental health problems.

Pharmacists are in a pivotal position to observe changes in patterns of drug use and report worrying trends to health care practitioners. Counselling for young people especially and prevention programmes based in schools could prove useful in pointing out the dangers of these drugs to teenagers. Health care professional too should endeavour to keep up with recent information on these substances by attending hospital-based lectures or conferences as part of continuing professional education.

Urine drug testing will generally be unhelpful as many club drugs are undetectable on standard urine drug screens.²⁹ Mental health staff should enquire about club drugs as part of routine drug and alcohol assessment and be aware that these patients may not fit the stereotype of a drug misuser.

Competing Interests

None declared

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