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‘Legal Highs’ – novel and emerging psychoactive drugs: a chemical overview for the toxicologist

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Introduction. ‘Legal highs’ are psychoactive chemicals which are sold from ‘head shops’, the internet and from street suppliers and may be possessed without legal restriction. An increase in the marketing of these materials has resulted in a corresponding increase in published reports of their adverse effects. However, a lack of primary literature pertaining to their chemistry, pharmacology and toxicology, makes an evaluation of their harm difficult. This review covers the basic chemistry of these novel psychoactive compounds and relates them to endogenous neurotransmitters and existing drugs of abuse.

Methods. A survey of the internet was used to identify websites that are marketing ‘legal highs’ in the UK. Trivial and systematic chemical compound names, for example methoxetamine, 4-methoxyphencycline, 4-fluorotropacocaine and ethyl phenidate were entered into PubMed to retrieve data on these compounds. This search elicited no citations. Other search terms which were more fruitful included desoxypipradrol, diphenylprolinol, methylenedioxy-2-amino-indane and methylenedioxy-2-amino-tetralin, alpha-methyltryptamine and 5-methoxy-N,N-diallyl-tryptamine.

Results. ‘Legal highs’ from the phenylethylamine, cocaine, tryptamine and phencyclidine classes are increasingly being marketed and, in the majority of cases, little is cited in the literature on their true chemical identity, pharmacology or toxicology.

Conclusions. ‘Legal highs’ are gaining in popularity and present clear challenges to toxicologists and society as a whole. Whilst improved use of existing legislation and development of new legislation can be used to reduce the supply of these materials, investment in better education for young people on the harms associated with ‘legal highs’ is needed.

Keywords Amphetamines; Cathinones; Cocaine; Herbal highs; Mephedrone; Neurotransmitters; PCP; Phenylethylamines; Tryptamines

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This review will describe the various sources of psychoactive compounds in nature and show that many of the ‘legal highs’ currently emerging (and our existing controlled drugs of abuse) have a high degree of structural similarity with endogenous neurotransmitters. Examples of naturally occurring phenylethylamines and their synthetic derivatives will be described and compounds that are related to the natural product cocaine and the dissociative anaesthetics ketamine and phencyclidine will also be highlighted. Some of the new synthetic tryptamine analogues will also be mentioned and their structural similarity to serotonin and the older psychedelic drugs such as LSD-25 will be demonstrated. Herbal and fungal ‘legal highs’ will also be described and their structural similarity to neurotransmitters demonstrated.

Methods

A survey of the internet was used to identify websites that are marketing ‘legal highs’ in the United Kingdom. Trivial and systematic chemical compound names such as methoxetamine, 4-methoxy-phencyclidine and 3-methoxy-phencycline were also entered into PubMed in an attempt to retrieve data on these compounds. This search elicited no citations. Other search terms which were more fruitful included desoxypipradrol, diphenylprolinol, methylenedioxy-2-amino-indane and methylenedioxy-2-amino-tetralin, alpha-methyltryptamine and 5-methoxy-N,N-diallyl-tryptamine.

Nature as a source of psychoactive compounds

Nature is an astounding chemist and has the ability to produce compounds that have profound effects on the Central Nervous System (CNS). Examples range in severity and toxicity from the Opium poppy (Papaver somniferum) which produces morphine,7 the precursor of heroin, to Cannabis (Cannabis sativa), producing tetrahydrocannabinol,8 to drugs of limited ethnic usage such as the South African plant Kanna (Sceletium tortuosum), which produces the phenylethylamine alkaloid mesembrine (Fig. 1).9

More exotic sources of psychoactive compounds include the fungal natural products muscimol and ibotenic acid from Amanita muscaria10 (Fly Agaric), which are analogues of γ-aminobutyric acid (GABA) and show structural and electronic similarity with the drugs γ-hydroxybutyric acid (GHB),11 its lactone, γ-butyrolactone (GBL)12 and the related butane-1,4-diol (1,4-BD) (Fig. 2).13

Magic mushrooms of the genera Psilocybe, Conocybe and Hygrocybe are still marketed as ‘legal highs’, notably the spores and mycelia of Psilocybe cubensis, which are sold with sand as ‘specimens for microscopy’; the addition of water allows fruiting of the mushrooms after a few days. These species contain the phosphate ester psilocybin which is hydrolysed in vivo to psilocin, which shows marked similarity with serotonin (Fig. 3).14

More exotic psychoactive compounds originate in the skins of poison arrow frogs from Central and South America. Epibatidine15 (Fig. 4) from Epipedobatides tricolor is a highly potent analgesic compound which binds to the nicotinic acetylcholine receptor.16

Structural similarity of many ‘legal highs’ and endogenous neurotransmitters

Many of the synthetic and natural psychoactive substances not only bind to receptors and exert their effects, but also are analogues of endogenous neurotransmitters and have the ability to bind to the dedicated transport systems for these
neurotransmitters and inhibit their reuptake. The similarity that exists between the psychoactive substance phenylethylamine, amphetamine (amfetamine) and tryptamine and dopamine, norepinephrine (noradrenaline) and serotonin can be seen readily (Fig. 5). The simple structural motif of phenylethylamine exists in dopamine and norepinephrine, as it does in amphetamine (α-methyl phenylethylamine). The methyl group of amphetamine is in the alpha position next to the nitrogen atom. One can also see how similar tryptamine is to serotonin, differing only in the absence of a hydroxyl group on the aromatic ring. These similarities undoubtedly contribute to the ability of phenylethylamine, amphetamine and tryptamine-related compounds to elicit psychoactivity.

Further examples include the hallucinogen, mescaline, from the psychoactive cactus Peyote17 (Lophophora williamsii) and cathinone from Khat (Catha edulis).18 Peyote is widely available in the United Kingdom as a house plant and Khat is flown in daily from East Africa, and the leaves are chewed by members of the Somali and Yemeni communities in the United Kingdom in a social setting.19 Both of these psychoactive natural products have the structural motif that resembles phenylethylamine, amphetamine and tryptamine-related compounds to elicit psychoactivity. Common horticultural plants and trees, particularly those of the pea family (Fabaceae) also contain psychoactive phenylethylamines such as hordenine20 and surprisingly even food plants such as the peel of bitter orange (Citrus aurantium) have small amounts of compounds such as synephrine,21 a phenylethylamine related to ephedrine (Fig. 6). Weight-loss preparations are being marketed globally through the internet and contain extracts of bitter orange peel, presumably because of the stimulant properties of synephrine, but there are the same risks of tachycardia, hypertension and palpitations associated with this compound as there are with phenylethylamines in general.22

Mephedrone and the cathinones
In 2009 there was an ‘explosion’ in the marketing of mephedrone23 and very similar compounds broadly termed cathinones due to their similarity to cathinone itself (Fig. 7). Mephedrone is the 4′-methyl-N-methyl analogue of cathinone and was marketed as Miaow-Miaow and MCAT and sold through many internet websites as ‘plant food’, ‘pond cleaner’ and even ‘bath salts’. This compound has clear similarity to the amphetamines, but having a ketone group beta to the nitrogen atom and directly next to the aromatic ring (Fig. 7). Other cathinone analogues that were appearing at the same time included methylone,24 which is similar to Ecstasy.

Fig. 5. Many drugs of abuse share structural similarity with our endogenous neurotransmitters.
(methylenedioxy-methylamphetamine; MDMA), having only a carbonyl group in place of a methylene moiety. As these compounds are similar chemically to MDMA and methamphetamine, the concern was that they might not only exhibit the same psychoactivity but also the same neurotoxicity as these compounds. Mephedrone was either insufflated or taken orally in capsules, whereas users of methylone preferred the oral route due to the high nasal irritancy of this compound. Users reported stimulation and cocaine-like effects and mephedrone was (and still is) highly popular.\textsuperscript{25} Recent data has shown that mephedrone increases dopamine and serotonin concentrations in the nucleus accumbens of rats.\textsuperscript{26}

The widespread appearance of mephedrone and related compounds was also possibly due to the ease of synthesis of this compound (Fig. 8). Starting with the solvent toluene, Friedel–Crafts acylation with propanoyl chloride in the presence of aluminium chloride as a catalyst, yielded a mixture of isomers but predominantly the \textit{para} isomer due to steric hindrance at the \textit{ortho} position. Simple addition of bromine in a solvent to the product would yield the alpha-bromo adduct which with the addition of an excess of methylamine would yield mephedrone in high yield and purity. The beauty of this synthesis is that the volatile methylamine can be removed very easily and the steps provide high purity and yield. Coupled with the ability to start with many different aromatic substrates, acylating groups (butanoyl, pentanoyl, hexanoyl) and even the final amines (ethylamine, pyrrolidine, piperidine), hundreds of cathinone analogues could potentially be produced.

The ease of production of many analogues was cause for concern and, coupled with the similarity of these compounds with existing phenylethylamines, the cathinones
were controlled by the UK Misuse of Drugs Act\textsuperscript{27} in April 2010. Before the ban, we acquired samples of mephedrone (Fig. 9) that were labelled specifically ‘not for human consumption’ but had the structure (correctly drawn). Anyone with a rudimentary chemical knowledge would realise how similar and close this compound is to the existing and controlled amphetamines. Our analysis showed that this material was of high-purity and, in this particular case, the hydrochloride salt (Fig. 10).

Following the control of these cathinones, another analogue appeared which was outside of the generic classification and possessed a naphthylene ring system rather than a benzene ring (Fig. 11). This compound, naphthylpyrovalerone (naphyrone; NRG-1), is related to the previously used fatigue medicine pyrovalerone.\textsuperscript{28} However, naphthylpyrovalerone is a highly potent triple reuptake inhibitor of nanomolar potency releasing dopamine, norepinephrine and serotonin at very low concentrations.\textsuperscript{29} Websites were offering to sell kilograms of this material packaged up in bags ready for distribution and given that an effective dose was as low as a few milligrams, the ability to titrate this low dose could have led to many cases of poisoning. Naphyrone was finally controlled by an amendment of the classification in July 2010,\textsuperscript{30} but it is possible that users avoided naphyrone due to concerns over its potency which was discussed on various internet drugs fora, and thankfully this material was never as popular as mephedrone was and is currently.\textsuperscript{25}

\textbf{New synthetic phenylethylamines}

Other ‘legal highs’ of the phenylethylamine class have also appeared on the internet and notably these are of the indane and tetralin groups (Fig. 12).\textsuperscript{31–33} Some of these compounds, such as methylenedioxy-2-amino-indane (MDAI), are selective serotonin releasers and are said to be ‘entactogens’ or ‘empathogens’, which are terms used to show that a compound causes social cohesion and empathy amongst users. This drug lacks the neurotoxicity\textsuperscript{31} seen with MDMA and is being marketed as a substitute for MDMA and the cathinone methylone.

Related compounds include the 5-iodo derivative being sold as NRG-2 and methoxy-methyl-2-amino-indane (MMAI) (Fig. 12). Amino-tetralin stimulants have an additional methylene group making a six-membered ring rather than the five-membered ring seen in the amino-indanes.\textsuperscript{31,32} These include methylenedioxy-2-amino-tetralin (MDAT) and methylenedioxy-2-methylamino-tetralin (MDMAT). Both the indane and tetralin classes are still phenylethylamines but are in effect, ‘masked amphetamines’. MDAT and MDMAT are commonly available and like the indanes are seen as substitutes for MDMA, though are purported to lack serotonin neurotoxicity.\textsuperscript{31} It should be noted, however, that whilst these early data suggest a lack of neurotoxicity of both these groups of compound, an in-depth evaluation of the general toxicity has yet to be conducted.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{mephedrone_nmr.png}
\caption{\textsuperscript{1}H NMR spectrum of mephedrone (See colour version of this figure online).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{naphyrone_pyrovalerone.png}
\caption{Structures of naphyrone and pyrovalerone showing re-uptake inhibition IC\textsubscript{50} values in nM for dopamine (DA), serotonin (SER) and norepinephrine (NE).\textsuperscript{29}}
\end{figure}
Other cyclic derivatives are typified by diphenylprolinol (D2PM) and diphenylmethyl-pyrrolidine, which possess a five-membered pyrrolidine ring system and are dopamine and norepinephrine reuptake inhibitors. Diphenylprolinol is used as a catalyst in organic synthesis (Fig. 13). Six-membered analogues include pipradrol, a previously licensed medicine used for obesity, that is no longer used widely due to its potential for abuse. Pipradrol is classified under the UK Misuse of Drugs Act as a Class C substance being a dopamine and norepinephrine reuptake inhibitor.

The desoxy form, desoxypipradrol (Fig. 13), was developed by Ciba Geigy in the 1950s as a preparation to wake patients from anaesthesia and hence its German name ‘Weckamine’. Several reports of patients presenting in a highly agitated state with hallucinations, paranoia and classical amphetamine-like overdose symptoms, such as ‘formication’, after consuming ‘Ivory Wave’, which was later shown to contain desoxypipradrol, have been published. The long half-life of this compound, coupled with its low dose, show that it has significant potential toxicity, and the Advisory Council on Misuse of Drugs advised that an Open General Important Licence (OGIL) for this material be revoked at the end of 2010. Both of these classes of compound are structurally related to methylphenidate (Ritalin®; Fig. 13). Other methylphenidate derivatives include the ethyl analogue currently marketed as ‘nopaine’ (ethylenphenidate). In the body, this compound can be formed by ingestion of methylphenidate and ethanol, presumably by trans-esterification. It is a dopamine and norepinephrine reuptake inhibitor.

Cocaine derivatives

Synthetic derivatives of cocaine also have their representatives on the ‘legal high’ scene. These include the anaesthetic dimethocaine (larocaine) (Fig. 14), which has been shown to substitute for cocaine in trained rats, and 4-fluorotropacocaine. To date there are no published data on 4-fluorotropacocaine, whereas dimethocaine is a mild dopamine releasing agent compared to cocaine. Both of these compounds show structural similarity in terms of the number of bonds between the ester group and the nitrogen atom and 4-fluorotropacocaine possesses a tropane ring system like cocaine.
Ketamine and phencyclidine derivatives

Other marketed ‘legal highs’ include derivatives of the dissociative anaesthetics ketamine and phencyclidine. These compounds are antagonists of the NMDA receptor and are members of the phenyl cyclohexylamine class. Ketamine is used as a veterinary anaesthetic and in the military where rapid anaesthesia is required. Ketamine use is on the increase, particularly in Hong Kong, where it is currently the drug of choice, despite the risks of urinary and bladder dysfunction inherent in its use. A close analogue, methoxetamine (Fig. 15), has different substitution of the phenyl ring and amine functionality compared to ketamine. Very little is known about the chemistry, pharmacology and toxicology of this material. Given the close structural similarity of this compound with ketamine, it is highly likely that similar effects would be seen in humans.

Phencyclidine (PCP; Phenyl-Cyclohexyl-Piperidine), also known as ‘Angel Dust’ is controlled globally and is Class A in the United Kingdom. Analogues of phencyclidine are appearing, notably the 3- and 4-methoxy derivatives, which possess an additional methoxy group on the phenyl ring (Fig. 15). As with methoxetamine, there is a dearth of data on these close structural analogues of phencyclidine. We conducted one test purchase of the 4-methoxy analogue, which was a pure sample and of the correct chemical identity.

Synthetic and natural tryptamines

The ‘legal high’ scene is also seeing examples of tryptamine-derived drugs of abuse. Tryptamine (Fig. 16) bears close structural similarity with serotonin as do a number of ‘classical’ controlled drugs of abuse including psilocin, the alcoholic hydrolysis product of psilocybin from the ‘magic mushrooms’ of the genus Psilocybe and other closely related genera. Other examples include bufotenin, (a positional isomer of psilocin), which occurs in the skins of various species of toad of the genus Bufo.

Tryptamines in general have a history of being associated with the psychedelic movement, and these compounds are hallucinogenic and inhibit the reuptake and increase the release of serotonin. Other examples include more complex chemicals such as the well known LSD-25, with very strong effects on awareness and perception of the environment when doses of 20 μg are used. Two synthetic tryptamines related to these compounds are alpha-methyltryptamine (α-MT, AMT) and 5-methoxy-N,N-diallyl-tryptamine (5-MeO-DALT) (Fig. 16). There is more primary literature on these materials which release serotonin and dopamine and have structural similarity to serotonin which partially explains their effects. We conducted a test purchase of
both materials, and structure elucidation has shown that they were of high-purity and correct identity. Compounds of this class can greatly alter perception, and this is highlighted by the tragic case of a 26-year-old man, who was killed after walking on to a motorway in Cambridgeshire in 2010. The Coroner recorded a ‘narrative verdict of death from injuries sustained when he was in collision with a lorry while under the influence of 5-MeO-DALT’ (http://www.cambridgenews.co.uk/Home/Familys-vow-over-legal-highs-drugs-danger.htm).

Many analogues of tryptamine can be made by substitution on the nitrogen atom or the aromatic ring, and the chemistry to reach these compounds is relatively simple, unfortunately giving ease of access to many potential ‘legal highs’. There has also been an increase in the marketing of plant extract that contain psychoactive compounds of the tryptamine class. These include leaf material itself or extracts of the SE Asian tree, Mitragyna speciosa, which is sold in various concentrated strengths according to the extraction method used. This material is known as Kratom in Thailand or Biak-Biak in Malaysia and is a controlled substance in both countries. In Europe, samples bought from the internet can arrive as ‘buttons’ of dried extract, which is ingested orally and made up as a tea which has a bitter taste. Extracts have been confirmed to contain the alkaloid, mitragynine, (Fig. 17) and its analogues, and this compound is a mu-opioid receptor agonist, which was investigated for its potential as an analgesic. Extracts are typically sold as ‘not for human consumption’ and as incense for burning (not to be inhaled!) and are often labelled as Mitragyna speciosa Thai resin × 20, clearly indicating the correct botanical nomenclature, origin and strength.

Obviously, the strength of × 20 is unimportant for incense but would give users the false impression of the concentration of the material in the packaging for ingestion. This is fraught with danger, as little is known on the effects of Kratom resin and only full analytical chemistry would give rise to the concentration of psychoactive compounds present or even the presence of adulterant psychoactives. This highlights the problems associated with herbal and natural product ‘legal highs’ in general as their chemical analysis is highly complex, and there is, of course, the possibility that suppliers could add other psychoactive compounds to these materials which can cause even further problems in terms of polypharmacology and toxicology.

Seeds from members of the morning glory family, Convolvulaceae, have a long history of usage as psychoactive materials. The seeds from species of this family include Hawaiian Baby Woodrose (Argyreia nervosa), Ipomoea sp. and Convolvulus sp which are marketed through the internet as ‘ethnobotanicals’ to enhance memory. These seeds contain alkaloids of the ergot type such as ergine (Fig. 18), also known as lysergamide or lysergic acid amide, which has a close chemical structure to LSD-25, but lacking just two ethyl groups on the nitrogen atom. A whole range of these natural products are present in the seeds from this family, and their ability to cause psychosis are demonstrated by two cases of human consumption of the seeds of Hawaiian Baby Woodrose resulting in one fatality from jumping from a building; ergine was present in the blood and urine of this individual.

It is the ability of these ‘reality-distorting’ materials to cause such accidents that makes these materials potential dangerous as ‘legal highs’. They are, however, not as popular as stimulants such as the now controlled mephedrone, and it is possible that the majority of ‘legal high’ users avoid them because of the possibility of accidents following ingestion.

Salvia divinorum
As with Kratom, herbal material and extracts of the psychoactive sage (Salvia divinorum, Lamiaceae), which is a member of the mint family, can be readily purchased through the internet and is still legal in many countries, including the United Kingdom. Live plants and leaf cuttings can be obtained; the plant is very easy to cultivate as is the closely related culinary sage, Salvia officinalis. The extracts and plants contain a series of clerodane diterpenes, typified by salvinorin A (Fig. 19), which is a potent kappa-opioid receptor agonist with activity at doses as low as 200 \( \mu g \).

Fig. 18. Ergine and LSD are highly similar and both have the serotonin moiety.
Extracts and leaves are typically smoked, although the traditional ethnomedical usage of this plant involved the chewing of the leaves as a ‘quid’ to elicit an effect. A variety of extract strengths are available through internet suppliers, for example, 10 × extract, although as with the case of Kratom, no realistic interpretation of the true concentration of salvinorin A can be made without proper analysis. Users report that they have tried the material once, and have no desire to re-dose as the experience was not particularly pleasant.

**Conclusion**

There are many chemical similarities between ‘legal highs’ and endogenous neurotransmitters, specifically serotonin, norepinephrine and dopamine. Several classes of ‘legal highs’ have been modelled on existing and controlled drugs of abuse, particularly from the phenylethylamine (amphetamine), cocaine, phencyclidine and tryptamine classes. The reason for this is the ease in synthesising these compounds; chemists can readily identify those compounds that fall outside of legislation and are therefore legal, and the routes to these compounds are easily accessible from the literature. The amino-indanes and amino-tetralins (MDAI, MDAT), psychedelic drugs (tryptamines) and anaesthetics (4-MeO-PCP/methoxetamine) are examples that fall outside of existing legislation. There are considerable potential harms associated with taking these ‘legal highs’ as they often have insufficient supporting biological and toxicological data.

**Declaration of interest**

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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