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REVIEW ARTICLE

Clinical toxicology of newer recreational drugs

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Introduction. Novel synthetic 'designer' drugs with stimulant, ecstasy-like (entactogenic) and/or hallucinogenic properties have become increasingly popular among recreational drug users in recent years. The substances used change frequently in response to market trends and legislative controls and it is an important challenge for poisons centres and clinical toxicologists to remain updated on the pharmacological and toxicological effects of these emerging agents. *Aims.* To review the available information on newer synthetic stimulant, entactogenic and hallucinogenic drugs, provide a framework for classification of these drugs based on chemical structure and describe their pharmacology and clinical toxicology. *Methods.* A comprehensive review of the published literature was performed using PUBMED and Medline databases, together with additional non-peer reviewed information sources, including books, media reports, government publications and internet resources, including drug user web forums. *Epidemiology*. Novel synthetic stimulant, entactogenic or hallucinogenic designer drugs are increasingly available to users as demonstrated by user surveys, poisons centre calls, activity on internet drug forums, hospital attendance data and mortality data. Some population sub groups such as younger adults who attend dance music clubs are more likely to use these substances. The internet plays an important role in determining the awareness of and availability of these newer drugs of abuse. *Classification.* Most novel synthetic stimulant, entactogenic or hallucinogenic drugs of abuse can be classified according to chemical structure as piperazines (e.g. benzylpiperazine (BZP), trifluoromethylphenylpiperazine), phenethylamines (e.g. 2C or D-series of ring-substituted amfetamines, benzodifurans, cathinones, aminoindans), tryptamines (e.g. dimethyltryptamine, alpha-methyltryptamine, ethyltryptamine, 5-methoxy-alphamethyltryptamine) or piperidines and related substances (e.g. desoxypipradrol, diphenylprolinol). Alternatively classification may be based on clinical effects as either primarily stimulant, entactogenic or hallucinogenic, although most drugs have a combination of such effects. *Clinical toxicology*. Piperazines, phenethylamines, tryptamines and piperidines have actions at multiple central nervous system (CNS) receptor sites, with patterns of effects varying between agents. Predominantly stimulant drugs (e.g. benzylpiperazine, mephedrone, naphyrone, diphenylprolinol) inhibit monoamine (especially dopamine) reuptake and are characteristically associated with a sympathomimetic toxidrome. Entactogenic drugs (e.g. phenylpiperazines, methylone) provoke central serotonin release, while newer hallucinogens (e.g. 5-methoxy-N,N-diisopropyltryptamine (5-MeO-DiPT), 2,5-dimethoxy-4-bromoamfetamine (DOB)) are serotonin receptor agonists. As a result, serotoninergic effects predominate in toxicity. *Conclusions.* There are limited reliable data to guide clinicians managing patients with toxicity due to these substances. The harms associated with emerging recreational drugs are not fully documented, although it is clear that they are not without risk. Management of users with acute toxic effects is pragmatic and primarily extrapolated from experience with longer established stimulant or hallucinogenic drugs such as amfetamines, 3,4-methylenedioxymethamfetamine (MDMA) and lysergic acid diethylamide (LSD).

Keywords Designer drug; Research chemical; Stimulant; Hallucination; Entactogen; Piperazine; Phenethylamine; Tryptamine; Piperidine.

Introduction

Recreational use of stimulant, entactogenic (ecstasy-like) or psychoactive drugs is an important health issue. Until recently, the most frequently used substances by far have been cocaine and amfetamines, including the related substances 3,4-methylenedioxymethamfetamine (MDMA, ecstasy) and metamfetamine. In Europe it is estimated that 12 million people or 3.5% of the population have taken amfetamines at some point in their lives and in 2 million this was within the last year alone.[1] Data from the USA suggest a lifetime prevalence of use of 5% for ecstasy and a similar figure for metamfetamine.[2] Recreational drug use is more prevalent amongst younger adults than other age groups[1] and there are other population sub groups with higher prevalence such as young adults frequently attending night clubs[3,4] and men who have sex with men.[5,6]

The illegal status of the classical recreational substances has encouraged users to seek newer options that offer the advantages of being either legal, less expensive, less contaminated with adulterants, more readily available or having more desirable pharmacological effects.[7,8] The term, 'designer drug' refers to chemicals created for recreational use to evade drug legislation, usually by modification of the

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molecular structures of existing drugs (or less commonly, by finding new drug classes), to produce similar subjective effects from established illegal recreational drugs. Newer recreational drugs with stimulant, entactogenic and/or hallucinogenic effects that are not subject to legislative control are sometimes referred to as 'legal highs'. Considerable innovation is shown by illicit markets in development of new production processes, products and marketing opportunities.[1] The suppliers are able to adapt rapidly to control measures and to market legal alternatives to drugs subject to control.[1]

The internet allows effective marketing, sale and distribution of recreational drugs and is a major reason for the recent increase in availability of newer drugs.[1,9] Dissemination of information and drugs to users is much more rapid and presumably allows substantial profits to be made before the market can be limited by legal regulations. The International Narcotics Control Board regards the internet as, 'a growing source of on-line drug trafficking'.[10] The contents of internet purchased products may vary over time,[11] or involve chemicals not listed in marketing literature, meaning that users are often unaware of what or how much they are taking.[11,12]

It is important to acknowledge that reliable clinical and experimental data are not available for many of these substances.

Methods

A comprehensive review of the published literature was undertaken using PUBMED and Medline (1950 to present) databases. Search terms included drug names (including common names), drug family or group names, neurotransmitter related terms such as 'serotonin release' and more general terms such as 'designer drug', 'entactogen', 'hallucinogen', 'stimulant', 'legal high' and 'party pill'. Substances not covered in this review, due to their substantially different clinical toxicology to the drugs described include the synthetic cannabinoids[13] and gamma butyrolactone (GBL)/gamma hydroxybutyric acid (GHB)/1,4-butanediol.[14] Synthetic cocaines are also not included.[15] Bibliographies of identified articles were screened for additional relevant studies including non-indexed reports. Additional non peer-reviewed sources were also studied including books, media reports, governmental publications and internet resources, particularly drug user web forums. Identified material was then collated and inserted into the manuscript based on relevance and interest.

Epidemiology

Data on use of newer recreational drugs are usually not collected routinely and it is very difficult to establish trends in use for these substances. Some indication of the substances of interest to drug users can be inferred from activity on drug-related websites,[9] while illegal activity can be quantified in terms of arrests and seizures by law enforcement agencies. Toxicity relating to recreational agents may be reflected by numbers of enquiries to poisons centres,[16] attendances at emergency departments or admissions to hospital, although poor coding of these episodes may mean these data under report the problem.[17] Statistics on deaths associated with newer recreational drugs may also be available, although often after some delay. A common theme is a lack of, or delay in, analytical confirmation of the agents involved. This is important as drug users may not be aware of the constituents of substances that they have purchased.[11,12]

Obtainable information suggests that newer recreational drugs are increasingly available.[9,18] For example, during 2008 there were 11 new synthetic drugs notified in the EU including one phenethylamine, two tryptamines and six cathinones.[1] Similarly, the United Kingdom National Poisons Information Service reported that between March 2009 and February 2010 there were 2900 web based database accesses and 188 telephone enquiries related to cathinones from a baseline of virtually none.[16]

A recent dance music magazine survey in the UK reported that 41% of 2295 dance music nightclub attendees had ever used the synthetic cathinone mephedrone, 33% within the last month; another synthetic cathinone, methylone, had been used by 10% at some time in their lives and by 7% in the last month.[19] In the same study 90% had used ecstasy, 70% amfetamine and 26% BZP at some point in their lives. Surveys from 2003 to 2008 had not identified any mephedrone use,[3] illustrating the rapid recent increase in use and the marked variability in substances used across time. A questionnaire survey of pupils in schools (35%), colleges and universities in Scotland revealed that 20% had used mephedrone with more than half reporting adverse effects from its use.[20]

Legal status

The United Nations International Convention on Psychotropic Substances (1971) is the basis for worldwide control of psychotropic drug use. The legislative interpretation of this treaty and hence control of recreational drugs varies between countries with some able to control any chemical with a chemical structure (generic) or pharmacology (analogue) that is similar to a known scheduled drug. Other countries need to control each new drug (specific) as it becomes available. The latter allows new chemicals to be created to evade legislation.

The legal status of individual agents varies from country to country and changes with time and, therefore, a detailed review is outside the scope of this article. However, the changing nature of drugs being supplied to users in response to evolving legislation presents a difficult problem to clinical toxicologists and poisons centres as often the information available on the pharmacology and toxicology of newer unregulated chemicals is very limited.

Classification

Most newer recreational drugs can be considered members of one of the four distinct chemical families; the piperazines, phenethylamines, tryptamines or piperidines and related substances (Fig. 1). Each family is reviewed separately below with pharmacological, toxicological and clinical information, and presented where they are available.

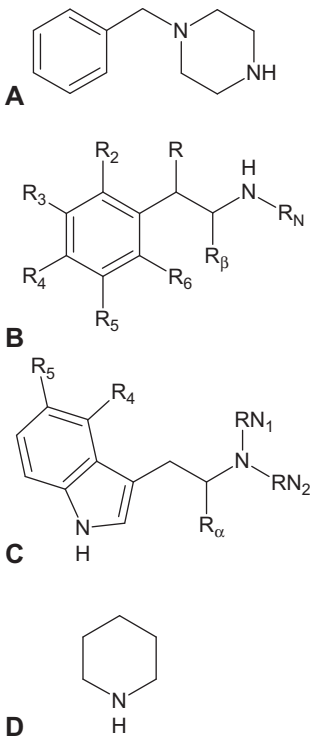

Fig. 1. Basic chemical structures of the piperazines (A), phenethylamines (B), tryptamines (C) and Piperidine (D).

Recreational drugs can also be classified by their clinical effects as predominantly stimulant, ecstasy-like (entactogenic), or hallucinogenic. These features can, to a large extent, be predicted from the structural chemistry of each compound or chemical family. However, many designer drugs have combined stimulant and psychoactive effects due to action at multiple CNSreceptor sites with varying affinity.[21–23] As discussed below, common patterns of pharmacodynamic and clinical effects may be identified within each chemical family group.

Pharmacodynamic actions

The pharmacodynamic principles underlying our understanding of classical recreational drugs such as amfetamine, methylenedioxymethamfetamine and LSD, and the differences between them, hold true for the newer designer drugs. Therefore new stimulants such as BZP, mephedrone, naphyrone or diphenylprolinol inhibit presynaptic reuptake of monoamines, particularly dopamine; newer drugs with entactogenic action such as phenylpiperazines or methylone tend to release of serotonin from central axon boutons and newer hallucinogens such as 5-MeO-DiPT are serotonin receptor agonists. In reality most drugs have actions at multiple CNS receptor sites. These actions, where demonstrated, are reported in the individual drug sections below.

Piperazines

The piperazines are not closely chemically related to any of the more familiar recreational drugs. Although sometimes marketed as 'herbal' or 'natural' preparations, members of this family of drugs are fully synthetic in the sense that, unlike tryptamines or phenethylamines, there are no examples found in nature. Piperazines may be sub-classified into 2 groups; the 1-benzylpiperazines and the 1-phenylpiperazines (Fig. 2), both of which include compounds reported to have been used recreationally.

Piperazines were developed as anti-helminthic agents in the 1950s and BZP was evaluated as an anti-depressant in the 1970s. This development was terminated once amfetamine like effects were noted. There are, however, non-stimulant piperazine compounds with legitimate medicinal uses, for example cyclizine (1-diphenyl-methyl-4-methylpiperazine) and precursors of trazodone.

Recreational use of piperazines was first reported in California in the 1990s and subsequently these agents have become widely used, particularly since 2004.[24] Only in more recent times have they become subject to widespread control measures. Piperazines are often constituents of tablets sold as 'ecstasy', often with more than one piperazine type in each tablet.[25,26]

Benzylpiperazines

The vast majority of recreational BZP use has been with 1-benzylpiperazine, usually as the dihydrochloride salt. This is presented as a loose white powder which is often placed in capsules or pressed into tablets. The free base is available as a pale yellow liquid which is alkaline and corrosive.[21]

Pharmacology

1-Benzylpiperazine is a sympathomimetic stimulant with similar actions to amfetamine sulphate. In fact, users of amfetamine were unable to distinguish the effects of

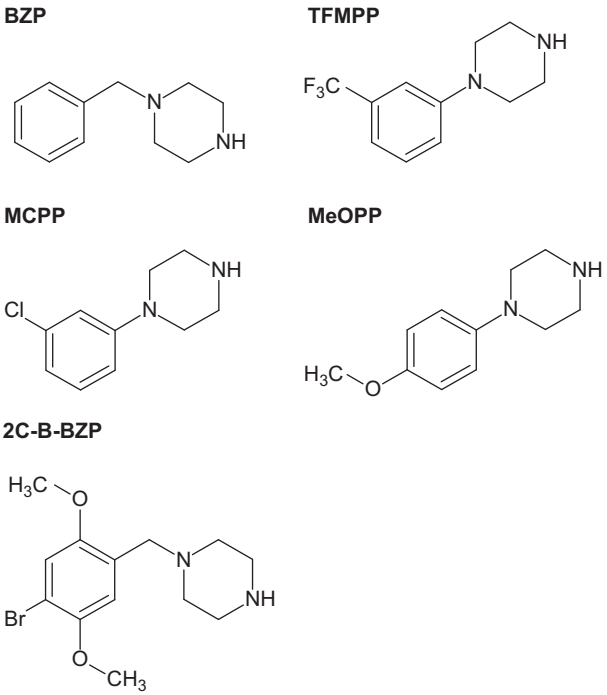

Fig. 2. Skeletal formulae of piperazines.

equipotent intravenous doses of BZP from dexamfetamine in one study,[27] while the subjective effects of BZP were also 'dexamfetamine like' in a volunteer study.[28] Pharmacodynamic studies in animals have shown that BZP increases extracellular CNS dopamine, serotonin and noradrenaline concentrations by both enhanced neurotransmitter release and reuptake inhibition.[29]

The human pharmacokinetics of BZP have recently been investigated in 7 healthy volunteers, each receiving a 200 mg oral dose.[30] Mean maximum plasma concentration was 262 ng/ml 75 min after ingestion. The major plasma metabolites were 3 hydroxy-BZP and 4 hydroxy-BZP, while urinary O- and N- sulphated conjugates accounted for 80% of excreted BZP. In contrast to earlier studies,[31] glucuronidated conjugates were not identified. Elimination half life was reported as 5.5 h and detection of BZP in plasma was possible for up to 30 h after ingestion. Bioavailability, assuming minimal biliary excretion or protein and tissue binding, was low at 12.5%.

Acute toxicity

Animal and human data support user accounts describing BZP as a stimulant with effects similar to dextroamfetamine (albeit with approximately one-tenth of the potency) and other sympathomimetics and it is likely to have similar abuse liability.[32,33] A typical dose would be about 100–250 mg.[24,34]

The clinical features associated with BZP use have recently been reviewed in detail.[35] High doses of BZP are usually associated with a sympathomimetic toxidrome.[35] More serious adverse effects have been reported such as metabolic acidosis, seizures, prolongation of ventricular repolarisation (as determined by the rate corrected QT interval), and possibly also toxic paranoid psychosis[36] and hyponatraemia.[37] More recently, two severe cases of BZP poisoning associated with multi-organ failure were reported.[38] Death from the confirmed sole use of 1-BZP has not been reported, although the combination of MDMA and BZP has been linked to fatalities in Sweden and Switzerland.[34,39] Post mortem samples following road traffic accidents or a fall have detected BZP in association with other substances, including phenylpiperazines.[40]

There are no specific data regarding the management of BZP toxicity, rather management is extrapolated from stimulant toxicity in general. This consists of early gastric decontamination with charcoal and control of agitation, seizures, hyperthermia and hypertension.[41]

Phenylpiperazines

The phenylpiperazines include trifluoromethylphenylpiperazine (TFMPP), m-chlorophenylpiperazine (mCPP) and paramethoxyphenylpiperazine (MeOPP).[42]

Pharmacology

In contrast with benzylpiperazines, the phenylpiperazines are active directly (post-synaptically) at serotonin receptors and, additionally, indirectly (pre-synaptically) by release of serotonin via reversal of the serotonin reuptake transporter (SERT).[29] They appear to have little, if any, effect on dopamine and noradrenaline transport.[29] The lack of dopaminergic effects means that reinforcement, and hence addictiveness, is probably low.[43] Clinical effects in volunteers include dysphoria, 'dexamfetamine-like effects', tension or anxiety and confusion or bewilderment.[44]

The combination of a phenylpiperazine and BZP provides equivalent pharmacodynamic responses in terms of dopamine and serotonin release in rat synapses to MDMA,[29,45] and their co-ingestion by users has been reported.[26]

The elimination half life of mCPP taken orally is 2.6–6.1 h with marked inter-individual variation in bioavailability and peak concentration.[46] Metabolism of mCPP and TFMPP primarily involves hydroxylation via CYP2D6 with subsequent phase 2 metabolism by glucuronidation, sulfation and acetylation.[47,48]

Acute toxicity

Users report clinical effects that begin about 2 h after oral use and last about 6 h.[49] Serotoninergic features predominate in toxicity associated with phenylpiperazines, with nausea, migranous headache and anxiety attacks being common; serotonin syndrome has also been reported after single doses.[50] One healthy volunteer study showed MDMA-like effects of TFMPP and BZP when taken in combination.[28] Dissociative symptoms (for example 'feeling like being in another world') have been attributed to phenylpiperazines, albeit in the context of mixed BZP/TFMPP ingestions.[51] A possible synergism between BZP and TFMPP leading to an increased risk of seizures has been suggested from animal model data.[29] A healthy volunteer study in which subjects were given TFMPP and BZP or placebo with or without alcohol was terminated early due to a high number of serious adverse events (agitation, anxiety, hallucinations, vomiting, insomnia and migraine) in the TFMPP/BZP groups (41%).[52] No deaths confirmed as associated with the sole use of a phenylpiperazine have been reported.

Phenethylamines

The phenethylamines are a large family of monoamine alkaloids that includes the familiar drugs of abuse amfetamine, metamfetamine and MDMA (see Figs. 3 and 4), although these longer established examples are not considered in detail in this review. Most phenethylamines have stimulant properties, although 'designer' substitutions have created substances with additional or alternative psychoactive properties. Tolerance to repeated doses of phenethylamines is reported across the group.[53,54]

Pharmacology

The phenethylamine structure is based on that of the amino acid phenylalanine and consists of an aromatic ring with a 2 carbon side chain leading to a terminal amine group (Fig. 1). Surprisingly little modification of this structure is required to elicit significant alterations in neurochemical and behavioural actions.[55] The optimal structure for psychostimulant actions appears to be amfetamine-like, that is, an unmodified ring, an alpha carbon with a methyl group attached and an amino

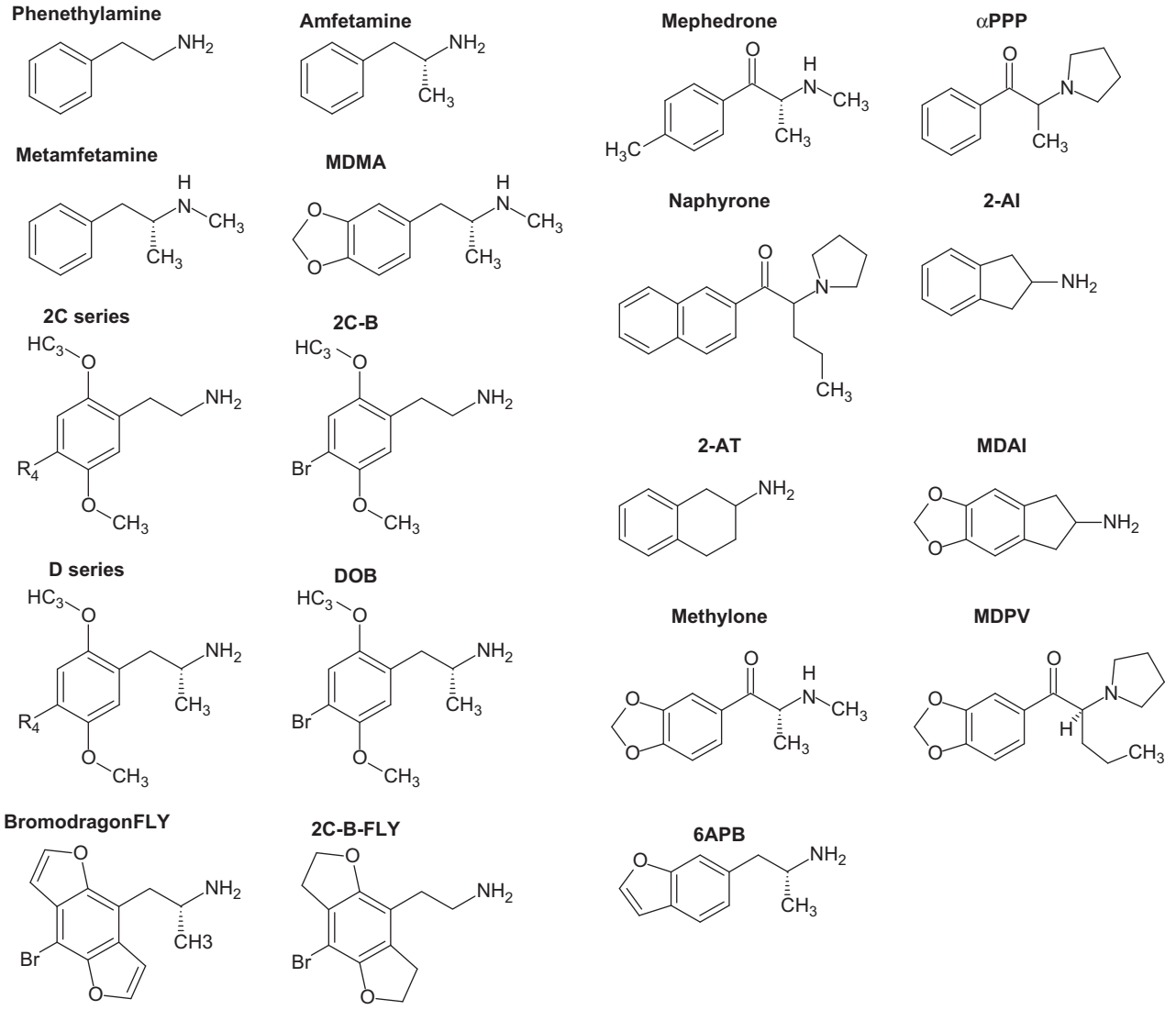

Fig. 3. Skeletal formulae for phenethylamines (note all are presented as the d stereoisomer irrespective of activity for ease of comparison).

group which is unsubstituted or has an N-methyl substitution.[55] The latter gives metamfetamine which is about twice as potent as amfetamine according to Nichols[55] (see Fig. 3). The methyl group on the alpha carbon protects the molecule from breakdown by the enzyme monoamine oxidase (MAO), while some phenethylamines also have MAO inhibiting properties.[55] Extension of either the side chain or amino group substitutions or any aromatic ring substitution dramatically attenuates stimulant properties or substantially alters neuropharmacology.

'Designer' substitutions to the aromatic ring lead to compounds that are psychoactive via either serotonin release (e.g. parachloroampfetamine, paramethyoxyamfetamine, MDMA)[55] or serotonin receptor agonism (2C and D series)[56] while stimulant effects are reduced. Hallucinogenic activity appears to be conferred particularly by methoxy groups at the 2nd and 5th positions with a hydrophobic substitution at the 4th position (Figs. 1 and 3). Iodine and bromine substituted phenethylamines are relatively more hallucinogenic than the hydrogen and nitrogen equivalents.[57]

The presence of a methyl group on the alpha carbon of such substituted phenethylamines increases hallucinogenic potency 210 fold as a result of greater 5HT2a agonism.[57] Such agents are sometimes termed 'hallucinogenic amfetamines'. In contrast, substitution at the amino group appears to attenuate hallucinogenic actions,[55] except for N-benzyl substitution which dramatically increases potency at 5HT-2a receptors.[58] The cathinones, which are amfetamine analogues oxidized at the benzylic carbon, retain psychostimulant activity and it seems likely that β-methoxy-substituted phenethylamines are also active.[55]

Ring substituted amfetamine derivatives

D series

The D series of substituted amfetamines are characterised by the presence of methoxy groups at positions 2 and 5 of the benzene ring with variable substitutions at the 4th position of the benzene ring (Fig. 3). This substitution pattern confers hallucinogenic properties probably via 5HT2a agonism.[57] In a cat model both dopaminergic and serotoninergic stimulation have been implicated in their mechanism of action.[59] Onset of action is relatively slow, being usually longer than 1 h,

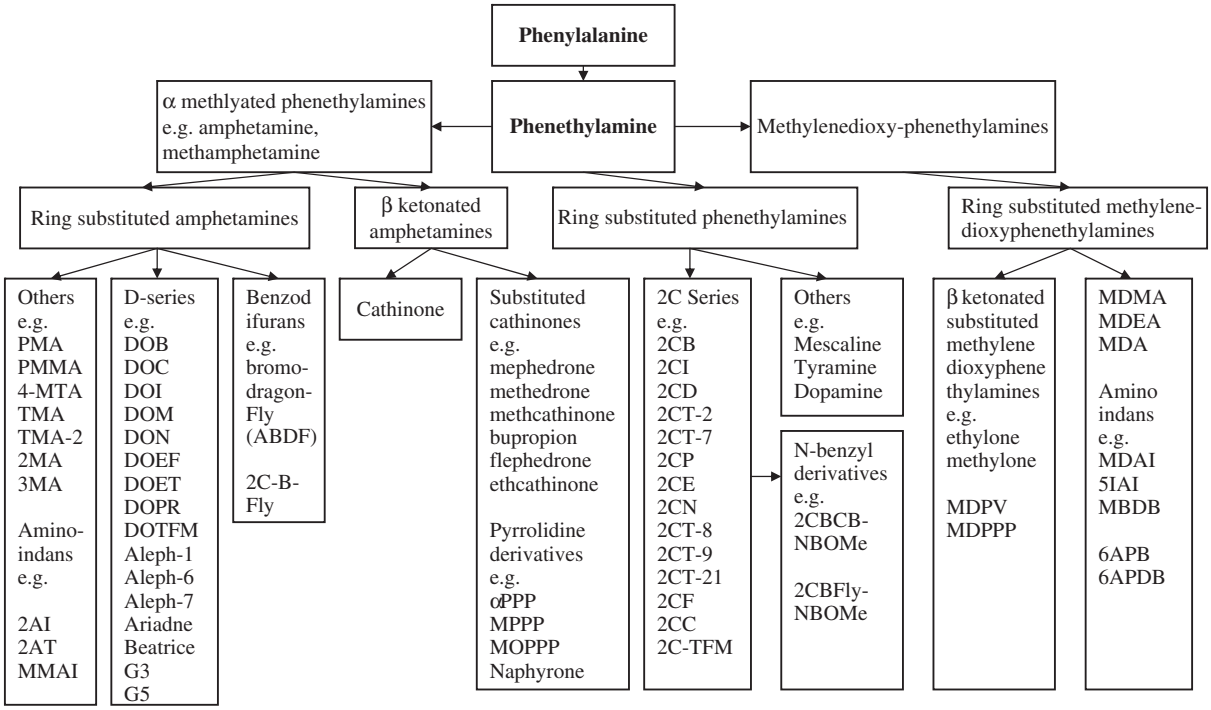

Fig. 4. Classification of the phenthylamines.

increasing the risk of early repeat dosing by inexperienced users.[60] D series agents are also longer lasting (1530 h), more potent (typical dose 1–3 mg for DOB), probably have less stimulant action and are more liable to induce vasoconstriction, when compared to other members of the phenethylamine family.[60] The latter action appears to account for the significant morbidity and mortality associated with this group. DOB and 2,5-dimethoxy-4-methylamfetamine (DOM) induce vasoconstriction in dog vasculature via serotonin receptor activation.[61] Two cases of DOB overdose characterised by agitation, seizures, metabolic acidosis, reduced consciousness and, in one case, death, are reported.[62] Diffuse vascular spasm associated with DOB exposure that responded to an intra-arterial alpha adrenoreceptor antagonist and sodium nitroprusside has been reported.[63]

Benzodifurans

Tetrahydrobenzodifuranyl and benzodifuranyl aminoalkanes, known by the street names 'FLY' and 'DragonFLY' are potent hallucinogens due to their characteristic dihydrofuran or difuran rings, respectively (see Fig. 3) which confer high potency as 5HT2a receptor agonists.[64,65]

BromodragonFLY (DOB-Dragonfly, 1-(8-bromobenzo[1,2-b;4,5-b']difuran-4-yl)-2-aminopropane) is the archetypal member of this uncommon sub group of phenethylamines with an apparently greater potency and adverse effect profile than other sub groups. Its name apparently arises from the chemical structure resembling an insect (Fig. 3). According to user websites, a typical BromodragonFLY dose is 0.2–1 mg with an onset of action of up to 6 h and duration of action of 2 or 3 days (Psychonaut web mapping 2010).[66] This chemical has been linked to a number of deaths, particularly in Scandinavia,[67,68] apparently resulting from severe and prolonged arteriolar vasoconstriction mediated by very potent agonism at $5HT_2$ and alpha adreno-receptors, which may persist for days. It has been suggested that cases of sudden death may be due to coronary arterial vasoconstriction.[68] As for D-series drugs, treatment of vasospasm with intra-arterial vasodilators seems logical. In addition, agitation, tachycardia, mydriasis, hallucinations, severe limb ischaemia, seizures, liver and renal failure have been reported, with toxicity seemingly dose-related.[66,69]

2C-B-Fly (1-(8-bromo-2,3,6,7-tetrahydrobenzo[1,2-b;4,5-b´] difuran-4-yl)-2-aminoethane), the tetrahydrodifuran equivalent of 2C-B, is apparently less potent than BromodragonFLY.[70] At least one death may have occurred due to confusion between these two substances, resulting in inadvertent overdosing with BromodragonFLY.[71]

Others

Some ring substituted amfetamine derivatives including paramethoxyamfetamine (PMA, 'Death'), Paramethoxymethamfetamine (PMMA) and 4-methyltrioamfetamine (4-MTA, 'Flatliner') have resulted in apparently greater morbidity and mortality rates than for other phenethylamines. Clinical features are often characterized by severe hyperthermia[72–76] and probably result from severe serotonin toxicity arising from the combined effects of marked serotonin release and strong monoamine oxidase inhibition.[76] Animal data suggests that CYP2D6 rapid metabolisers may be at increased risk of toxicity from 4-MTA, although the mechanism is unclear.[77]

Beta ketonated amfetamines (cathinones)

The increasing use of synthetic cathinones, especially mephedrone, has been the major change in the pattern

of drug misuse in the UK during 2009 and early 2010, as evidenced by substantial increases in poisons centre enquiries,[16] user surveys,[19,20] seizures by law enforcement agencies and identification in biological samples.[78] Cathinone use has also been widely reported across Europe,[79,80] but is apparently less prevalent elsewhere, although use outside Europe may be increasing.[81–83] Since April 2010 the cathinones have been controlled in the UK.[84] Mephedrone is also currently specifically controlled in a number of US states and across much of Europe, and covered by analogue laws in Australia, New Zealand and Canada.[85] Following the UK legislative changes, poisons centre calls relating to cathinones have reduced substantially,[86] although user surveys have not shown compelling evidence of any reduction in usage.[87,88]

The cathinones are defined by the presence of a ketone group on the beta carbon (Figs. 1 and 3), which increases polarity and leads to a reduction in CNS penetration and, hence, potency when compared to non-ketone molecules.[89] However, this may lead to higher dosing and perhaps more marked peripheral adverse effects. The parent chemical, cathinone, is a constituent of Khat (Catha Edulis), the leaves of which are chewed in certain communities for their stimulant effects. Synthesis of methcathinone from psudoephedrine using permanganate is reported and has been associated with manganese toxicity in users.[90,91] There are limited pharmacokinetic data available for the cathinones but their metabolism is primarily by N-demethylation and subsequently reduction of the ketone group.[92]

Methcathinone and methylone have been shown to inhibit plasma membrane catecholamine uptake transporters (Dopamine Active Transporter (DAT), Serotonin Transporter (SERT), Norepinephrine Transporter (NET)) but not vesicular monoamine transporters (VMAT2) in cell lines.[93] This contrasts with the actions of metamfetamine and MDMA, where VMAT2 is also inhibited.[94] Methcathinone and methylone are about one third less potent for the SERT when compared with metamfetamine and MDMA respectively. Methylone, unsurprisingly, demonstrated greater potency at SERT inhibition than methcathinone.[93] Methylone releases serotonin in rat brain synaptosomes.[22]

N-Alkylated cathinones

Mephedrone

Twelve months prior to the introduction of legislation to control synthetic cathinones, mephedrone (4 methylmethcathinone, 'Meow-Meow', 'Bubbles') made up 88% of cathinones seized in the UK.[78] Between March 2009 and February 2010 the United Kingdom National Poisons Information Service received calls from health care professionals for advice on 188 cathinone exposures of which 157 involved mephedrone, in 131 cases without other substances, other than ethanol.[16] Use was most commonly by ingestion (53%) or insufflation (32%). In 12% of the cases the route was unknown. The median reported dose used was 1 g. Common clinical features reported included agitation (24%), tachycardia (22%), anxiety (15%), confusion (14%), chest pain (13%) and nausea (11%). Other less common effects included palpitations, fever, breathlessness, peripheral vasoconstriction, mydriasis, reduced level of consciousness and abdominal pain. Four people had convulsions while one person died following a cardiac arrest, although this appeared unrelated to the drug. Symptoms persisted for more than 24 h in 45% and more than 48 h in 30% of cases. Thus the clinical picture is chiefly of prolonged sympathomimetic action, although some features could be consistent with added serotonin toxicity.

These clinical data correspond with those from others, including smaller series with analytical confirmation of mephedrone exposure.[95–97] There are no data on management of mephedrone toxicity and in practice[95] this has been based on recommendations for other stimulants.[35,41]

There have been several reports of serious toxicity associated with synthetic cathinones, including fatalities.[98–105] The National Programme on Substance Abuse Deaths report that by October 2010 there had been 48 deaths in the UK where mephedrone has been detected post mortem, although causality has not been established in many of these.[106]

Other N-Alkyl cathinones

These include methcathinone, ethcathinone, buphedrone, flephedrone, methedrone and brephedrone. There are no clinical data available relating to these agents, but stimulant and entactogenic effects might be expected based on structure. Note that me*the*drone (4-methoxymethcathinone) is not equivalent to me*phe*drone (4-methylmethcathinone) and indeed the para (4) methoxy substitution may confer increased toxicity.[107] There have been 2 deaths reported from Sweden associated with methedrone,[108] both characterized by hyperthermia and multi-organ failure. These features resemble those of PMA and PMMA toxicity, perhaps arising from the para-methoxy group. Recently, 4-fluromethcathinone (flephedrone), has been detected increasingly frequently in 'legal high' capsules.[12,109]

Pyrrolidine derivatives

Pyrrolidinyl derivatives of the cathinones, such as alpha-pyrrolidinopropiophenone (α-PPP), 4-methyl-pyrrolidinopropiophenone (MPPP) and 4-methoxy- pyrrolidinopropiophenone (MOPPP) are a sub-group with assumed primarily stimulant effects.[110] The napthyl derivative of pyrovalerone (napthylpyrovalerone, naphyrone, 1-naphthalen-2-yl-2-pyrrolidin-1-yl-pentan-1-one, sold sometimes as 'NRG-1'), is a noradrenaline, dopamine and serotonin reuptake inhibitor. It appears to be a more potent monoamine uptake inhibitor than many other stimulants.[111] User accounts report an almost pure stimulant effect lasting hours.[112] There were concerns that it might become the next designer drug trend in the UK, with a surge in popularity following legal controls to mephedrone and related cathinones[113] that did not affect naphyrone, however, this agent was also subsequently controlled in the UK from July 2010.[114]

Ring substituted phenethylamines

2C series

The 2C series are a large group of chemicals characterised by methoxy groups at positions 2 and 5 of the benzene ring (Fig. 3). They differ from the D series of substituted amfetamines only by the absence of a methyl group on the alpha carbon of the side chain. Within this family there are differences in the substitution at the 4th position on the benzene ring, for example 2C-B (2,5-dimethoxy-4-bromophenethylamine) has bromine at this position while 2C-I has iodine (Fig. 2).

In Xenopus laevis oocytes, 2C series chemicals had little or no efficacy at 5HT2a receptors but were active at 5HT2c receptors.[57] User accounts report typical doses of 12–24 mg for 2C-B,[115] although doses of up to 100 mg have apparently been tolerated.[115] The pharmacokinetic properties of the drug are not well characterized but the onset of clinical effects occurs after a few minutes when insufflated and after about 1 h when taken orally. Effects appear to peak at about 2 h and last about 5 h.[115] Metabolism is hepatic via oxidative deamination[116] and/or O-demethylation.[117] There appears to be a wide variation in human hepatocyte susceptibility to 2C-B *in vitro*, suggesting that certain individuals may be at higher risk of toxicity than others.[116]

Clinically the 2C series are primarily stimulant at lower doses, e.g. $<$10 mg for 2C-B, but the dose response curve is reported to be steep and has substantial inter-individual variability.[115] In a rat model, locomotion was inhibited by 2C-B.[118] Doses of more than 10 mg tend to be psychoactive with hallucinogenic and entactogenic effects, while doses of 30 mg or more may cause intense hallucinations or psychosis[119] prompting some users to present to medical services. 2C-T-4 has also reportedly led to psychotic reactions.[120] Deaths have been associated with the 2C chemicals; for example 2C-T-7 has been implicated in 3 deaths in the US, one as the sole substance involved (35 mg insufflated), with analytical confirmation of exposure post mortem. Vomiting, agitated behaviour and possible seizures were reported in these cases.[121] One case of diffuse cerebral vasculopathy has been reported after use of 2C-B.[122]

Aminoindan and aminotetran derivatives

The side chain of phenethylamines may be incorporated into carbocyclic rings such as indan or tetralin rings (Fig. 3). These appear to substitute for the parent compound from which they are derived, but at a lower potency, with tetralin rings being generally more potent than indan rings. As examples, in rat discrimination paradigms 2-aminotetralin (2-AT) substitutes completely and 2-aminoindan (2-AI) substitutes partially for d-amfetamine, but with reduced potency.[123] 5,6-dihydroxy-substituted aminoindans are dopamine agonists[124] and indeed form a fragment of the apomorphine molecule. Users report a short lived stimulant effect[125] but there is little other clinical information available.

Substituted methylenedioxyphenethylamines

MDMA, 3,4-Methylenedioxyamfetamine (MDA), methylbenzodioxolylbutanamine (MBDB), benzodioxolylbutanamine (BDB) and 3,4-methylenedioxy-N-ethylamfetamine (MDE) have been well described in the literature[126] and so are not discussed further, except to note that MDMA is the most widely used designer drug in most countries.

Aminoindan methylenedioxyphenethylamines

5,6-Methylenedioxy-2-aminoindan (MDAI) has been detected in legal high products recently[12] and substitutes for MDMA but not LSD or amfetamine in animal discrimination models.[123,127] There are some data to suggest that, in comparison to MDMA, MDA and MDE, the aminoindan derivatives are less neurotoxic, as demonstrated by preservation of serotonin levels and serotonin receptor sites.[127] This is attractive to sophisticated drug users who seek to minimise the potential longer term risks of their drug use. 5-iodo-2-aminoindane (5-IAI) is another similar drug of interest to drug user forums as an alternative to MDMA with possible reduced neurotoxicity.[128] Again, reliable data describing clinical effects are not available and management is extrapolated from other methylenedioxyphenethylamines such as MDMA.

Beta ketonated methylenedioxyphenethylamines (methylenedioxy-cathinones)

This sub-group of methylenedioxyphenethylamines are characterised by a ketone group on the beta carbon of the side chain and therefore may also be classified as cathinones (Fig. 3). Methylone (3,4-methylenedioxymethcathinone, or bk-MDMA or M1), for example, is the beta ketonated analogue of MDMA. Methylone is metabolized either via N-demethylation to MDC and subsequently conjugation or via demethylenation followed by O-methylation and then conjugation.[129] It has lower affinity for the serotonin reuptake transporter and the vesicular monoamine transporter when compared to MDMA.[93] Methylone inhibits dopamine, noradrenaline and serotonin reuptake.[22,130] In rat drug discrimination models, methylone substituted fully for MDMA, albeit with reduced potency, but did not substitute for DOM. It substituted for amfetamine at a lower potency than MDMA.[131] The clinical effects of methylone are similar, although according to users not identical to those of MDMA.[132] There is a report of toxicity when used in combination with 5-MeO-MiPT,[133] featuring psychomotor excitement and a stimulant toxidrome.

Other members of the group include ethylone (3,4 methylenedioxy-N-ethylcathinone) and butylone (beta-keto-N-methylbenzodioxylpropylamine, bk-MBDB). The clinical features associated with these are apparently broadly similar to those of methylone, according to user accounts, but that are probably of lower potency.[134]

Pyrrolidine derivatives of beta-ketonated methylenedioxyphenethylamines

Methylenedioxypyrovalerone (MDPV), and 3,4-methylenedioxy-α-pyrrolidinopropiophenone (MDPPP) have no entactogenic action but are purely stimulant according to collated internet user accounts;[135] this is perhaps surprising

given their chemical structure (Fig. 3). Reports suggest a duration of action of about 48 h.[135] Clinical features are of a typical stimulant toxidrome, including vasoconstriction and agitation or panic attacks.[135–137] Metabolism of MDPPP is by demethylenation.[138]

Other substituted methylenedioxyamfetamines

Removal of either the 3rd or 4th position methoxy groups and replacement with methylene groups leads to chemicals such as the unsaturated compound 6-(2-aminopropyl)benzofuran (6-APB or 'benzofury') or the saturated compound 6-(2-Aminopropyl)-2,3-dihydrobenzofuran (6-APDB) for MDA (Fig. 3). These are probably stimulant and entactogenic in effects, based on animal models where they substitute for entactogens such as (MBDB) and 5-Methoxy-6-methyl-2-aminoindane (MMAI),[139] but clinical information is lacking and even user websites reports are scarce.

The UK National Poisons Information Service received 32 telephone enquiries relating to cases of apparent (analytically unconfirmed) 'benzofury' toxicity.[140] They described a prolonged stimulant toxidrome characterized by hypertension, tachycardia and agitation. More than half of these cases had symptoms lasting longer than 48 h after ingestion.

Tryptamines

Natural tryptamines are derived from the amino acid tryptophan by a variety of biosynthetic pathways. These include serotonin and melatonin as well as others with a long history of use for their hallucinogenic properties, such as psilocybin in 'magic mushrooms' and dimethyltryptamine (DMT) in Ayahuasca brews. Sumatriptan, the anti-migraine medication, is a synthetic tryptamine without psychoactive properties. Given that many natural tryptamines are hallucinogenic, it is unsurprising that designer synthetic tryptamines have been developed and found their way into recreational drug cultures.

Tryptamines have an indole ring structure; a bicyclical combination of a benzene ring and pyrrole ring, joined to an amino group by a 2 carbon side chain (Figs. 1 and 5). Clearly there are some similarities to the phenethylamine structure. Designer chemical substitutions occur at the amino group, side chain and aromatic ring. Modification of the indole ring at positions 6 and 7 leads to marked reductions in hallucinogenic activity and so most designer substitutions have been made at positions 4 or 5 (see Fig. 5).

Nichols[21] sub-classified the tryptamines into the simple tryptamines and the ergolines. Fantegrossi et al.[141] suggested subdivision of the simple tryptamine group based upon the site of modification of the indole ring into unsubstituted, 4th position substituted and 5th position substituted rings (Fig. 6).

The tryptamines are agonists at a wide range of serotonin and other receptors and ion channels.[22,23] In general they are less selective for and of lower affinity at the 5HT2a receptor than the hallucinogenic phenethylamines. In addition to 5HT2a agonism, tryptamine induced hallucinations are also partly mediated by agonism at 5HT1a receptors.[141] The

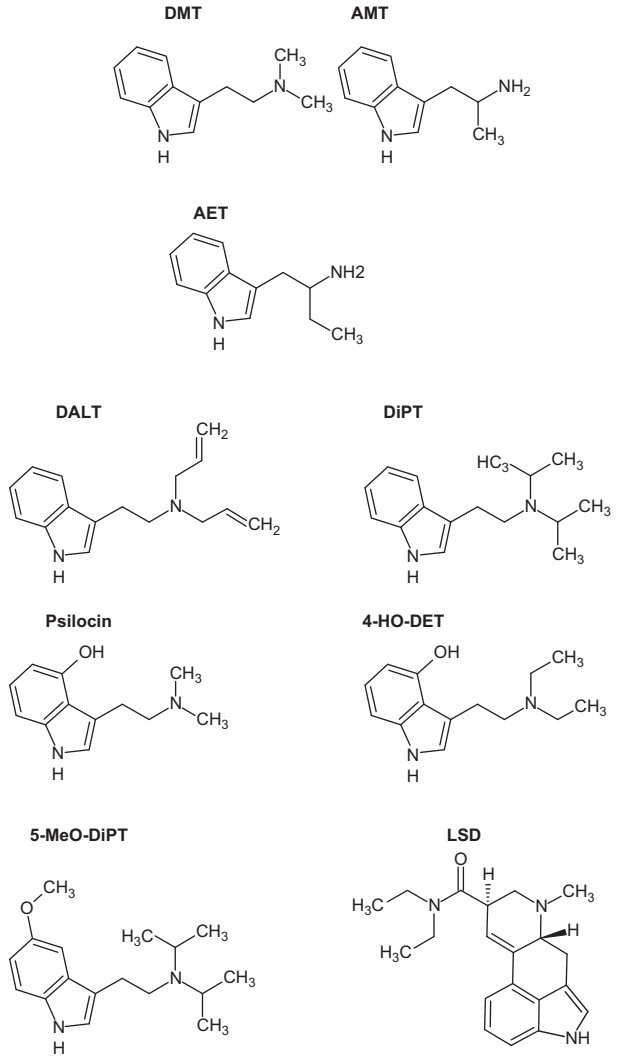

Fig. 5. Skeletal formulae of the tryptamines.

mechanism of tryptamine induced psychoactivity is complex and a number of tryptamines are also substrates for SERT, VMAT2 and other receptors.[22,142]

The tryptamines have primarily hallucinogenic rather than entactogenic or stimulant properties, although many, particularly the alpha methylated tryptamines (AMT and 5-MeO-AMT), have stimulant activity. This is especially related to the presence of the alpha carbon methyl group, a feature shared with amphetamine.[143]

LSD is the archetypal member of the synthetic ergolines, a group named following their original synthesis from an ergot fungus that grows on certain grains. It has a more complex structure than the simple tryptamines (Fig. 5) with an indole system and a tetracyclic ring, and has been used for its hallucinatory effects since the 1940s.[144] Indeed it remains the most potent of all hallucinogens.[141]

Tryptamines are generally considered 'not to cause life-threatening changes in cardiovascular, renal, or hepatic function because of their lack of affinity for the relevant receptors and targets'.[21] There are, however, data to contradict this view. For example, AMT and/or 5-MeO-AMT have been associated with deaths in the US,

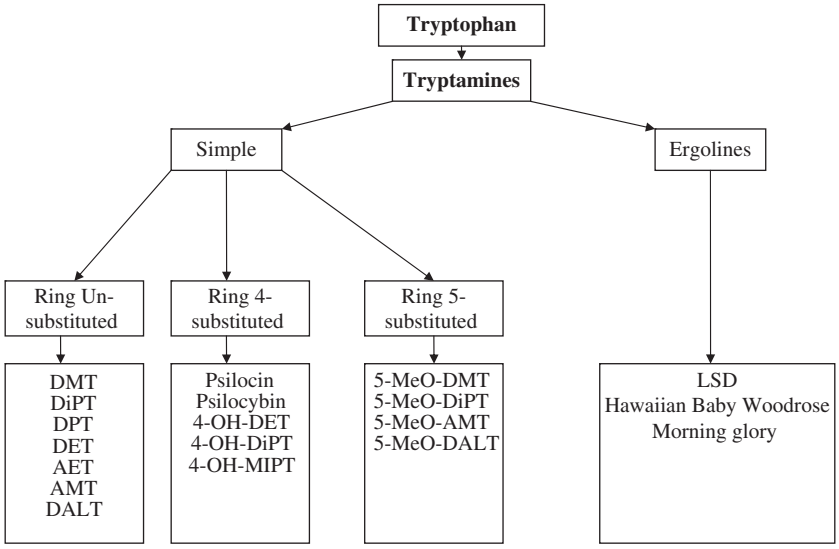

Fig. 6. Classification of the tryptamines.

although apparently these were not confirmed by post mortem analysis.[145] In addition, massive overdoses of LSD have caused psychosis, tachycardia, hyperthermia, mydriasis, CNS depression and respiratory depression as well as possible platelet dysfunction with bleeding.[146] Hallucinogenic effects may be associated with life threatening behavioural disturbances.[147]

Simple unsubstituted synthetic tryptamines

AMT and alpha ethyltryptamine (AET) have stimulant properties as well as hallucinatory effects.[143] This is unsurprising given that AMT is a strong re-uptake inhibitor and releaser of dopamine, noradrenaline and serotonin.[22] It is active after oral ingestion as the alpha methyl group protects from monoamine oxidases (MAO) degradation.[143] Like other serotonin releasing agents, AMT has been shown to be neurotoxic[148] and may also cause serotonin syndrome. Users report dose-dependent effects, with lower doses leading mainly to stimulation, while increasing doses cause more psychoactive effects.

Most information on the pharmacology of simple tryptamines relates to DMT obtained from natural sources rather than synthetic forms; there is little information available for other synthetic tryptamines. DMT is ring-unsubstituted with two methyl groups added to the amino group (Fig. 5). It is not active after oral ingestion due to extensive first pass metabolism, probably via the rapid action of MAO. This provides a rationale for the co-ingestion of MAO inhibitors in Ayahuascan brews, as well as the use of insufflation, inhalation, intramuscular or intravenous routes by users. When smoked, a typical dose of DMT is 60100 mg[149] with onset of action in less than 1 min. Blood concentrations peak at 10–15 min following intramuscular injection but may be delayed to more than 1 h following oral ingestion, corresponding to peak clinical effects,[150] although there is wide human inter-individual variability in both peak plasma concentrations and time to peak.[150] The duration of clinical effects is dose dependent, but is usually less than 1 h.[149]

The metabolism in humans is rapid following intramuscular administration with almost no DMT detectable in plasma after 1 h.[151] The primary metabolite of DMT is 3-indoleacetic acid and no unmetabolised DMT is detectable in urine.[151] It is probable that oxidative deamination of the side chain by MAO is largely responsible for the metabolism of DMT, although N-oxidation or N-demethylation may represent additional, probably minor, metabolic pathways.[152]

Clinical effects of DMT include intense visual hallucinations and some sympathomimetic features.[149,152] As with other simple tryptamines, stimulant effects predominate at lower doses, while at higher doses visual hallucinations became more prominent.[153]

Other unsubstituted simple synthetic tryptamines are N,N-diallyltryptamine (DALT), diethyltryptamine (DET), di-isopropyltryptamine (DiPT) and dipropyltryptamine (DPT) (see Fig. 5). Each is active after ingestion, with serotonin-mediated visual hallucinations the main clinical effect. DiPT is unusual in that it produces primarily auditory hallucinations, with tinnitus as a side effect.[154]

4-Substituted tryptamines

Psilocin (4-hydroxy-N,N-dimethyltryptamine) and Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) are the active constituents of Psilocybe hallucinogenic mushrooms. These are not designer synthetic drugs as such but provide insight into the clinical toxicology of four substituted chemicals. Psilocybin is converted *in vivo* by dephosphorylation to psilocin, which is a DMT analogue with a hydroxyl group substitution on the 4th position of the ring. Metabolism is via hepatic glucuronidation.[155] Typical psilocin doses are in the range 6–20 mg. The onset of action occurs 20–30 min after ingestion and effects last 4–8 h.[156] Psilocin is a partial 5HT2a agonist but is also agonistic at other serotonin receptors, with little dopaminergic or noradrenergic action. There is some sympathetic stimulation with tachycardia, hypertension and mydriasis, although visual hallucinatory effects predominate.[147]

Designer synthetic 4- substituted tryptamines include 4-hydroxy-N,N-diethyltryptamine (4-HO-DET), 4-hydroxy-N,N-diisopropyltryptamine (4-HO-DiPT), 4-hydroxy-N-isopropyl,N-methyltryptamine (4-HO-MiPT) and their acetic acid derivatives (e.g. 4-acetoxy-N,N-diethyltryptamine, 4-acetoxy-N,N-diisopropyltryptamine). Each appears to have similar actions to psilocin according to users,[157] but very little clinical information on these drugs is available.

5-Substituted tryptamines

The addition of a methoxyl (or hydroxyl) group at position 5 of the tryptamine ring appears to be associated with similar clinical effects but increased potency when compared with the unsubstituted molecule.[158] Examples include 5-methoxy-N,N-diisopropyltryptamine (5-MeO-DIPT, 'foxymethoxy'), 5-methoxy-N,N-methylisopropyltryptamine (5-MeO-MIPT) and 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT). These agents inhibit monoamine re-uptake, but have limited effects on monoamine release.[22] Metabolism is by hepatic cytochrome P450 via O-demethylation, 6-hydroxylation or N-dealkylation followed by conjugation with glucuronide or sulphide.[155]

There is a case report of a fatality due to 5-MeO-DiPT in a person with known polyarteritis nodosa. Post mortem detected 5-MeO-DiPT and the reported cause of death was acute cardiac failure due to neurotoxicity resulting from overdose of 5-MeO-DiPT.[159] One case report of tactile hallucinations and paranoia also exists[160] with another of rhabdomyolysis and probable serotonin syndrome.[161] A 15 month review of the American Association of Poison Control Centers' Total Exposures Surveillance System database revealed 41 exposures with tachycardia, hypertension, agitation and hallucinations as the main clinical features.[160]

5-MeO-AMT has reportedly been sold as LSD in the United States, leading to concerns regarding repeat dosing because, relative to LSD, it has a steep dose-adverse effect relationship and indeed one death has been reported.[162] A case of serotonin syndrome following ingestion of 5-MeO-DMT together with a monoamine oxidase inhibitor has also been reported.[163]

Piperidines and related substances

Pipradrol and desoxypipradrol (2-diphenylmethylpiperidine, 2-DPMP) are piperidines and are therefore structurally related to methylphenidate (Fig. 7). In the spring of 2010, the National Poisons Information Centre in Ireland reported experience of the toxic effects of a legal high termed 'whack'. This was associated with extreme agitation and psychotic reactions lasting several days in some users.[164] The product was found to contain flourotropacocaine, a synthetic cocaine, together with desoxypipradol; the latter was considered responsible for the prolonged psychotic effects.[164]

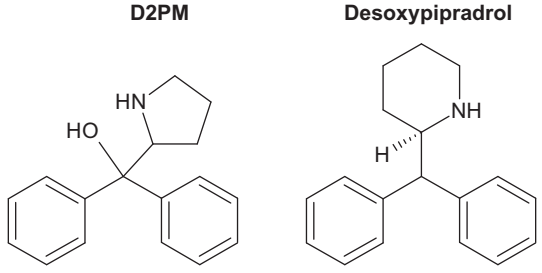

Fig. 7. Skeletal formulae of the piperidines and related drugs.

A preparation referred to as 'Ivory Wave' has recently been used by drug users in the United Kingdom. Analysis of Ivory Wave samples obtained in 2009 and 2010 revealed the presence of the cathinone MDPV in earlier cases, but desoxypipradol has been found in more recent samples, and these have been associated with similar extreme psychiatric effects reported previously in Ireland.[165]

Diphenylprolinol (D2PM, diphenyl-2-pyrrolidinyl-methanol) has a structure similar to that of pipradrol and is reported to be a stimulant with a mechanism of action that probably involves inhibition of the dopamine reuptake transporter.[166,167] A single case report exists of confirmed and isolated D2PM toxicity associated with a sympathomimetic toxidrome of agitation, mydriasis, chest pain, tachycardia and hypertension.[166] Diphenylprolinol has been shown to be cytotoxic in cell lines and suggested to inhibit neuronal development.[167]

Some designer drugs may be classified as belonging to more than one of the major drug groups. For example 4-Bromo-2,5-dimethoxy-1-benzylpiperazine, recently seized in Germany, has both phenethylamine and BZP structures.[168] However, user reports suggest it acts clinically as a BZP and stimulant rather than having hallucinogenic activity keeping with the 2C series structure.[169]

Conclusions

A large number of new designer drugs have become available to recreational users; the demand has been driven by a desire for physically and legally safer options, improved drug experiences or perhaps due to the control of more established drugs. The internet has facilitated the international marketing and supply of these compounds. Many are primarily stimulant in effect, while others are predominantly hallucinogenic or entactogenic although combinations of these effects are common. The harms associated with these substances are not fully documented, although it is clear that they are not without risk. Serious clinical effects have occurred and fatalities are reported, although analytical confirmation is often not available. The management of users with acute toxic effects is pragmatic and, in general, as for poisoning with longer established stimulant or hallucinogenic drugs such as amfetamines and MDMA.

Declaration of interest

The authors declare no conflicts of interests and the authors alone are responsible for the content and writing of the article.

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