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The new drug phenomenon

Introduction

This special issue provides a multidisciplinary snapshot of recent developments of the broader, arguably phenomenal, changes to the drug market that have occurred in the past decade related to the rise of the new drug phenomenon. This change is largely a result of the growing commodification by entrepreneurs, and increasingly, by criminal groups, of a huge range of psychoactive substances not controlled under drug laws and fuelled by their sale on an open market.

The issue includes papers that were presented at the Third International Forum on New Drugs, organized by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and held in Lisbon in June 2013. The aim of the forum was to bring together experts from around the world to exchange experiences, identify information gaps and research needs, as well as anticipate future developments and challenges related to the emergence of new drugs. The issue builds on and provides an update to the papers published in the special issue on new psychoactive substances published in *Drug Testing and Analysis* in 2011 (Vol. 3, issues 7–8). Other issues dedicated to psychoactive substances ('illicit drugs' and 'psychedelic substances') were also published in 2011 (Vol. 3, issue 9) and 2012 (Vol. 4 issues 7–8), respectively.

The search for new experiences is part of the human condition and for many, this includes the exploration of psychoactive substances.[1,2] In some cases, the use of these substances may be just for experimentation by an individual or by small groups of like-minded people (what some term 'psychonauts'), while in other cases, there may be a drive to exploit substances commercially.[3–6] The success of this latter strategy is largely based on the acceptability of the substance to users, particularly in terms of its psychopharmacological effects and its side effects.[3] In 1975, when reflecting on 'drugs of abuse in the future', Dr Alexander T. Shulgin noted:

> *In every issue of the journals in the fields of pharmacology, medicinal chemistry, the botanical sciences, and biochemistry, articles appear that advertise the isolation, synthesis, or evaluation of materials which have some pharmacologic action. Any article describing a new family of compounds ('Potential Centrally Active Stimulants Evaluated in Experimental Animals', for example) will encourage an unknown number of synthetic repetitions by underground researchers and manufacturers (with immediate pharmacologic evaluation in man). These studies follow none of the recognized guidelines for clinical investigation and are not responsible to any regulatory agency. If the results are undesirable or unacceptable, the matter is forgotten. If the results are considered virtuous or marketable, a new product appears briefly, under some popularly recognizable name and achieves, de facto, a broadly based "clinical" evaluation. When the product survives this initial marketing experiment, a new drug problem has made its appearance on the drug-abuse scene. However, if the product proves unacceptable (dysphoric, debilitating, lethal), the inquiry is dropped. Such explorations continue outside of the awareness of the social body politic.*[7]

Keeping Dr Shulgin's observations in mind, one cannot help but think that little has changed. Over the past few years, the new drug phenomenon has become largely defined by both the growing number of substances being detected from increasingly broader chemical and pharmacological families, and the open sale of many of these substances as 'legal highs', 'bath salts', or 'research chemicals' from bricks and mortar and online shops that specialize in the sale of such substances and/or cannabis seeds and drug paraphernalia (so-called head shops or smart shops), but they are also sold by street-level drug dealers.[5,6] Others have emerged as a result of their diversion and misuse as medicines,[5,6,8] while to a lesser degree, new drugs continue to emerge as a result of their production in either hobbyist or clandestine laboratories. In the latter case, this includes new drugs, which emerge either deliberately or unintentionally as a result of the use of unlisted precursors, such as 4-methylamphetamine synthesized from 4-methylphenyl-2-propanone.[9]

Most new substances first emerged as a result of chemical curiosity either from formal or informal study, and were commodified by entrepreneurs who saw the potential value of the substance based on initial human experimentation. From a historical point of view, perhaps only a comparatively small number have emerged on the drug market and gained a foothold beyond experimental use by psychonauts and diffused to broader sections of the population. Ketamine, 3,4-methylenedioxymethamphetamine (MDMA) or γ-hydroxybutyrate (GHB) may serve as prominent examples.[3,4,10] In some cases the diffusion of these substances appeared to be a rather slow process compared to how they may be presented in the media. For example, experimental use of MDMA began, if not in the late 1960s, then certainly by the early 1970s, with broader use only occurring from the 1980s onwards. Of note is that ketamine, MDMA and GHB did not emerge as 'legal' replacements to controlled drugs, although it seems reasonable to assume that their non-controlled status under drug laws in some countries ultimately helped their diffusion: during the early 1980s, MDMA tablets, for example, were sold by entrepreneurs in Texas as 'Sassyfras' in bottles, mislabeled as a health food product while mainstream marketing techniques of mail order using a toll-free phone number and payment by credit card were used as well as sale in bars which were subject to sales tax.[3]

Nomenclature and definitions of new substances

The appearance of new psychoactive substances (NPS) on the drugs market that are not controlled under international and national drug control laws is not a new phenomenon; many of the substances themselves were first synthesized years ago.

The 'cat and mouse game', whereby there is a continuous circumvention of existing legislation as new substances appear, can be traced back to the early years of the twentieth century with international attempts to control esters of morphine.[11]

In recent years, however, there has been an increasing commodification of the market in new substances. This has been fuelled by entrepreneurs, and increasingly organized crime groups, who have exploited a growing manufacturing capacity in countries such as China and India and globalized trade. Here, the Internet has played a key role in both the advertisement and sale allowing an open market to develop. This is reflected in the rapid rate of appearance of NPS, which in Europe over the past few years has averaged one new substance every 5–6 days. Indeed in 2013, 81 NPS were detected on the European drug market compared to 74 in 2012, 49 in 2011, and 41 in 2010. In the first five months in 2014, 37 were detected.[6] Similarly, monitoring of Internet shops typically selling new substances as 'legal highs' and 'research chemicals' to European consumers by the EMCDDA identified 651 shops in 2013, similar to the 693 identified in 2012 and vastly higher than the 314 and 170 shops identified in 2011 and 2010, respectively.[6]

Though a number of ring-substituted phenethylamines, such as 2,5-dimethoxy-4-methylamphetamine (STP)[12,13] began to appear in the 1960s, a major shift began in the late 1970s, and particularly in the 1980s with the emergence of the proliferation of uncontrolled derivatives of α-prodine and fentanyl (e.g. α-methylfentanyl and 3-methylfentanyl) which were given the nickname 'designer drugs' by Gary Henderson.[14] The term was pointing towards *analogs of compounds with proven pharmacological activity manufactured by underground chemists for sale on the street* which meant, for example, that MDMA and its analogues were originally not considered as such.[14] It has been estimated, however, that in 1984 the concept of designer drugs appeared only four times in the US print media while it rose to about 400 times in 1985/1986, which also included increasing association with MDMA.[15] Table 1 provides some representative examples of designer drug definitions.

Although many substances had been deliberately created to evade drugs legislation, some, such as desmethylprodine or 3,4-methylenedioxypyrovalerone (MDPV), provided examples of what might be termed 'failed pharmaceuticals', namely substances originally developed by the pharmaceutical industry as potential therapeutic agents, but which, largely for unknown reasons, were never commercialized as licensed medicines. Indeed, an increasingly important feature of the new drug phenomenon in more recent years has been the re-discovery of these agents as a potential source for commercial distribution on the drug market.

Table 1. Various definitions of newly-emerging psychoactive substances

Term	Definition	Reference
'Designer drug'	'*…analogs of compounds with proven pharmacological activity manufactured by underground chemists for sale on the street*'	Baum[14]
'Designer drug'	'*…(1) synthesized from common chemicals, (2) exempt from control by the Drug Enforcement Administration because of their unique chemical structure, and (3) skillfully marketed under attractive, often exotic names*'.	Henderson[109]
'Designer drug'	'*…analogs, or chemical cousins, of controlled substances that are designed to produce effects similar to the controlled substances they mimick*'.	Redda *et al.*[110]
'Designer drug'	'*…substances that have been developed especially to avoid existing drug control measures… "Designer drugs" are manufactured by making a minor modification to the molecular structure of controlled substances, resulting in new substances with pharmacological effects similar to those of the controlled substances.*'	INCB[111]
'New Synthetic Drugs' (NSD)	'*…new synthetic drugs which are not currently listed in any of the Schedules to the 1971 United Nations Convention on Psychotropic Substances, and which pose a comparable serious threat to public health as the substances listed in Schedules I or II thereto and which have a limited therapeutic value.*'	EU[19]
'New Psychoactive Substances' (NPS)	*(a) "new psychoactive substance' means a new narcotic drug or a new psychotropic drug in pure form or in a preparation; (b) 'new narcotic drug' means a substance in pure form or in a preparation, that has not been scheduled under the 1961 United Nations Single Convention on Narcotic Drugs, and that may pose a threat to public health comparable to the substances listed in Schedule I, II or IV; (c) 'new psychotropic drug' means a substance in pure form or in a preparation that has not been scheduled under the 1971 United Nations Convention on Psychotropic Substances, and that may pose a threat to public health comparable to the substances listed in Schedule I, II, III or IV.*'	EU[20]
'Novel Psychoactive Substances' (NPS)	'*…psychoactive drugs which are not prohibited by the United Nations Single Convention on Narcotic Drugs or by the Misuse of Drugs Act 1971, and which people in the UK are seeking for intoxicant use*'.	ACMD[22]
'New Psychoactive Substances' (NPS)	'*New psychoactive substances are substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat.*'	UNODC[21]

INCB: International Narcotics Control Board; EU: European Commission; ACMD: Advisory Council on the Misuse of Drugs (UK); UNODC: United Nations Office on Drugs and Crime.

There is little doubt that the publication of PiHKAL in 1991[16] and TiHKAL in 1997[17] provided the next stimulus for novel substances. During the 1990s, many new substances on the illicit market were ring-substituted phenethylamines, almost all of which had been described in PiHKAL and have been classified as designer drugs. The impact of TiHKAL was less marked; although many novel tryptamines appeared, they have been of minor significance and never became widespread or were ever seen in large quantities, perhaps reflecting the smaller market for hallucinogens compared to stimulant and entactogenic substances. Throughout this period, illicit drugs were manufactured in clandestine laboratories, mostly located in Europe and the United States, and produced as tablets bearing characteristic logos or as powders. They were sold directly on the illicit drug market, often surreptitiously as amphetamine and MDMA (or more commonly as 'ecstasy') by criminal networks; sometimes they were sold as a 'new type' of ecstasy or as drugs in their own right. In the European Union (EU), concern about new substances was focused on possible health risks and the problems that could arise, particularly in terms of law enforcement and judicial cooperation if such substances were controlled in some member states, but not in others.[18] It was agreed that progress could be made by sharing information and by establishing a risk-assessment procedure and a mechanism for their eventual control across the EU. This led, in 1997, to the 'Joint Action concerning the information exchange, risk assessment and control of new synthetic drugs' (NSDs) (Table 1).[19]

By the early years of the twenty-first century, however, there began a diversification into new drug families; a process that in the past few years has taken on an unprecedented pace.[5,6] Some of these substances fitted the description of designer drugs, some were NSDs, some 'failed pharmaceuticals', while others were plants or plant products. Even a few licensed medicines became drawn into the net. The EU Joint Action of 1997 was replaced in 2005 with a strengthened mechanism based on Council Decision 2005/387/JHA.[20] Thus, NSD was replaced with 'new psychoactive substance' (NPS), which encompassed a broader definition (Table 1). The United Nations Office for Drugs and Crime has subsequently adopted an essentially similar definition but also introduced the legally contentious concept of abuse.[21] In the UK in 2011, the Home Office Advisory Council on the Misuse of Drugs (ACMD)[22] created a definition of what it called 'novel psychoactive substances' which contained a modified definition with reference to 'seeking for intoxicant use' (Table 1). In 2013, the European Commission proposed new legislative measures that would replace the Council Decision with the aim of strengthening the response to new psychoactive substances in the EU; the proposals are currently being examined by the Council of the European Union and the European Parliament.[23–25]

Alongside these many definitions, many less formal names have been used including 'research chemical' and 'plant food', while synthetic cannabinoids frequently became known and marketed as 'incense' or 'herbal smoking blends', such as 'Spice' and 'K2'.[26] In New Zealand, piperazine derivatives were known as 'party pills' and in the United States cathinone derivatives became 'bath salts'. Some of these names were selected as attempts to circumvent regulatory systems by hiding the fact that they were intended for human consumption. Table 2 shows how a selected group of substances may be captured by these various definitions. Although the term 'legal high' had been used since at least the 1950s, it gained more common currency during the 1970s, largely to describe herbal products.[27,28] Since the emergence of substances such as the synthetic cathinone mephedrone in the late 2000s, it has become a widely used term, often by the media and subsequently the public, to refer to the entire group of largely synthetic new substances. Today, a 'legal high' is frequently perceived as a psychoactive substance not covered by existing domestic drugs legislation but this is often not the case, with the media frequently referring to now controlled drugs, such as mephedrone and synthetic cannabinoids, as 'legal highs' which confuses the issue. There is a need to consider this carefully, for example, when collecting data related to public health, which may be destined to inform policymaking, as highlighted by King and Nutt.[29,30]

Understandably these developments, particularly those related to the open sale of 'legal highs' and 'research chemicals', have caused concern in policymakers, drug professionals, the media, and general public that society is exposed to hundreds of 'legal' pharmacological replacements for cannabis, MDMA, amphetamine, cocaine, and heroin. While many new substances will not gain a foothold as drugs in their own right and spread to broader groups of users, they may still be capable of causing serious harm. The largely unknown pharmacology, their routes of administration, and their potential potency, can pose serious risks to users. This is compounded by both the growing range of substances and the generally high availability; problems that are especially apparent when

Table 2. Various definitions as applied to a selected group of psychoactive substances.

Definition	MDMA	Phenazepam	Mephedrone	Diamorphine	*Salvia divinorum*	Khat	Cannabis	BZP	MDPV
Designer drug	○	○	●	○	○	○	○	○	○
NPS	○	●	●	○	●	●	○	●	●
MDAct	●	●	●	●	○	●	●	●	●
Medicinal product[a]	○	●	○	●	○	○	●[b]	○[c]	○
Plant/plant extract	○	○	○	○	●	●	●	○	○
Failed pharmaceutical	●	○	○	○	○	○	○	●	●

MDMA: 3,4-Methylenedioxymethamphetamine; BZP: 1-benzylpiperazine; MDPV: 3,4-methylenedioxypyrovaerone; NPS = new psychoactive substance; MDAct = Misuse of Drugs Act 1971 (UK).

[a]Medicinal product in any country (i.e. not Schedule I in UN Conventions);

[b]as e.g. Sativex;

[c]BZP was designated by the UK Medicines and Healthcare Products Regulatory Agency as a 'medicinal product' for the purposes of the Medicines Act 1968, notwithstanding that BZP is not used in any licensed proprietary medicinal product in any country.

they are sold as 'legal highs' with no information provided to the user of the actual substance(s) and dose present, and as a result of an increasing number finding their way to the black market where they are sold as ecstasy, cocaine, ketamine, heroin, or LSD to unsuspecting users.[6]

The need for synthetic and analytical chemistry

The emergence of new drugs has created a need for access to reference material in order to verify their identification. Structural elucidation of newly encountered substances requires the availability of sufficient amounts of material, which is normally not an issue when bulk powders or pellet-type formulations are encountered. A more critical issue is their detection in biological fluids related to serious adverse events, such as deaths,[6] as well as for drug testing required by the criminal justice system. Here the concentration values are much smaller and implementation of techniques such as liquid chromatography nuclear magnetic resonance (LC-NMR) is normally not available in routine laboratories. Various forms of mass spectral detection methods are often involved in the analysis of newly emerging substances, which may offer first clues about their identity. It has been increasingly recognized in recent years, however, that the presence of isomers has to be considered as well, which can place obvious limitations on the reliance on mass spectral analysis alone. The time lag between compound identification and its availability from commercial suppliers has decreased, thanks to the increasing speed of dissemination regarding the detection of newly identified substances (e.g. through drug monitoring systems such as the European Union 'Early Warning System on New Psychoactive Substances' (EU Early Warning System),[6] publications in scientific journals, and discussions available on the Internet, etc.). Practical difficulties can arise, for example, when the attempt to purchase certified reference material results in exceedingly long delays. In cases where such standards fall under legislative control, commercial suppliers have to comply accordingly, for example in the form of applying for an import licence. One alternative, presumably also used by commercial suppliers of reference material, is the purchase of uncontrolled material from Internet vendors followed by purification and certification. Ideally, compound identification of a suspected new compound is supported by targeted organic synthesis. Clearly, some compounds may be more challenging to prepare than others but a range of advantages are frequently observed: (1) the analyte in question may not be commercially available; (2) a targeted synthesis of its isomers enables unambiguous identification; (3) independence from commercial suppliers; (4) ability to observe synthesis-related impurities which may be relevant when characterizing a newly emerging substance, thus, gaining potential insights into how this substance may have been manufactured; (5) extending the synthesis of a currently emerging substance to a range of analogs and derivatives allows for the ability to disseminate analytical data to the forensic, law enforcement and clinical community at the same time. The preparation of target analytes and impurities can also form an important basis for further studies beyond analytical characterization, such as exploration of pharmacological features and metabolism. The articles presented in this special issue provide examples where a number of these angles have been explored.

Dr Albert Hofmann, the famous natural product chemist and discoverer of LSD, psilocybin, and many other biologically relevant substances, had an extraordinary track record in terms of published and patented research when working at Sandoz.[31] An important body of work included an extensive exploration of tryptamine chemistry and one example that became relevant in 2012 was 5-(2-aminopropyl)indole (5-IT) which was associated with 24 deaths in Europe that were reported to the EU Early Warning System.[32] In 2013, this resulted in a decision by the Council of the European Union to subject the substance to control measures across the EU following a risk assessment conducted by the Scientific Committee of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).[33] 5-IT, and five of its isomers, including α-methyltryptamine (AMT, 3-IT), which indicated some bioactive properties, had been prepared by Hofmann and Troxler in the early 1960s.[34] The need for re-investigating the synthesis of such examples often stems from the fact that a range of analytical data considered important from a contemporary perspective, for example MS and NMR, were often not available in those earlier days. In the present issue, Scott *et al.* have re-investigated the synthesis and characterization of all six isomers and demonstrated the ability to differentiate between the isomers at the same time.[35] An important observation made during the preparation of 2-IT was that the solvent commonly used during the final reduction step (tetrahydrofuran) led to the formation of a tricyclic by-product. The implementation of an HPLC-based method was described by Herraiz and Brandt who demonstrated that 5-IT was a selective, competitive and reversible inhibitor of the monoamine oxidase A isozyme (MAO-A) with IC_{50} and K_i values of 1.6 μM and 0.25 μM, respectively.[36] It was also demonstrated that 5-IT was less potent than clorgyline and harmaline but more potent than toloxatone and moclobemide under the *in vitro* conditions studied.

Another range of psychoactive materials that emerged in recent years was based on the 1-(1-phenylcyclohexyl)piperidine (PCP) and 1-(1-phenylcyclohexyl)pyrrolidine (PCPy) template. In a carefully researched investigation, which included interviews with contributors from online discussion forums, Morris and Wallach trace the history of non-medical use of dissociative agents. The authors skillfully guide the reader from the beginnings of non-medical use of PCP starting to be recognized in the late 1960s to recent inventions made by recreational users themselves as exemplified by methoxetamine and beyond.[37] The preparation and full characterization of three PCP derivatives (3-MeO, 4-MeO and 3-Me) and their PCPy counterparts have been provided by Wallach *et al.* who demonstrated that differentiation between the isomeric candidates was feasible. Interestingly, a GC-MS induced degradation following the analysis of 4-MeO substituted analytes was observed (HCl salts) which led to the detection of 1-(1-cyclohexen-1-yl)-4-methoxybenzene.[38]

The availability of cathinone-based products has caught the attention of extensive research in recent years and the range of products commercially available tends to differ around the world. Christie *et al.* provided an exciting example of how non-invasive analysis can be effectively employed when analyzing cathinone products that used to be commercially available. The authors demonstrated the powerful combination of organic synthesis of cathinone isomers with analysis by Raman and infrared spectroscopy.[39]

The exploration of rigidified conformers based on a range of 2,4,5-trisubstituted phenethylamines, which eventually became known as FLY and DFLY analogues, has yielded potent 5-HT_{2A}

receptor agonists[40] and a number of them have briefly appeared on the recreational market although it is currently unclear how prevalent these particular analogues are at this stage. As is the case with many other phenethylamines, a commonly used method of synthesis includes the preparation of ketone precursors that are then subject to reductive amination procedures. Following this approach, O'Connor and Keating explored the preparation and characterization of four ketone intermediates to set the scene for their future conversion to 3C-B-FLY and bromo-dragonFLY, respectively. The other two ketones were represented by their dehalogenated counterparts.[41]

The synthesis and characterization of nitracaine (3-(diethylamino)-2,2-dimethylpropyl 4-nitrobenzoate), methoxypiperamide (4-methoxyphenyl) (4-methylpiperazin-1-yl)methanone) and mephtetramine (2-((methylamino)methyl)-3,4-dihydronaphthalen-1(2*H*)-one) was described by Power *et al.* who encountered these substances as 'research chemicals' from online vendors in 2013. The authors extended the work to the incubation with pooled human liver microsomes to assess their transformation by LC-MS.[42] The presence of nitracaine was also confirmed in a test purchase. Nitracaine is the 4-nitrobenzoate analogue of dimethocaine (4-aminobenzoate nucleus), which has also appeared on the market. While dimethocaine has been shown to display cocaine-like properties,[43] further work is warranted to assess whether nitracaine shows a similar profile.

The synthesis of *N*-methyl-1-(thiophen-2-yl)propan-2-amine (methiopropamine, MPA) was first published in 1942[44] and represents a thiophene bioisostere of methamphetamine. It appears to be considered as a psychostimulant although detailed studies are unavailable. However, it has been marketed as an individual substance or in combination with others in a range of branded products. The pyrolysis of MPA, i.e., mimicking conditions encountered during smoking, was investigated by Bouso *et al.* who observed the formation of 13 products. Ten analytes were confirmed by synthesis and the authors could show that the pyrolysis products were formed in analogy to those observed with methamphetamine. In addition, it was also confirmed that β-keto MPA and a bicyclic tetrahydropyridine compound were formed.[45]

Aminorex (5-phenyl-4,5-dihydrooxazol-2-amine), originally described in the early 1960s as a potential anorexigen, commercialized as such, and later withdrawn from the market as a result of it causing an epidemic of pulmonary hypertension,[46,47] forms a template that can give rise to a range of analogues with anorectic properties in animals.[48] One of the analogues described at the time, i.e., 4-methylaminorex (4-MAR), appeared briefly as a recreational psychostimulant in the late 1980s[49] but aminorex-type substances have generally not been encountered to a large extent. However, 27 deaths have been reported in Hungary and the United Kingdom to the EU Early Warning System in the past year, which were associated with the detection of the previously unknown analogue *para*-methyl-4-methylaminorex (4,4′-DMAR, or 'Serotoni'). Brandt *et al.* describe a comprehensive investigation that included the preparation and analytical characterization of the (±)-*cis*- and (±)-*trans*- racemates. A test purchase from an Internet shop confirmed that (±)-*cis*-4,4′-DMAR was available for sale as a 'research chemical'. Finally, studies with rat brain synaptosomes, which included the comparison with *d*-amphetamine, aminorex and (±)-*cis*-4-MAR showed that (±)-*cis*-4,4′-DMAR was a potent, efficacious substrate-type releaser at transporters for dopamine, norepinephrine and serotonin with EC_{50} values of 8.6 ± 1.1 nM (DAT), 26.9 ± 5.9 nM (NET) and 18.5 ± 2.8 nM (SERT), respectively.[50] Non-clinical studies such as that provided by Brandt *et al.*, which characterize the chemical, pharmacological, and toxicological properties of new psychoactive substances provide critical data in our understanding of the potential harms posed by such substances in order to understand the data reported through early warning systems.

The impact of degradation on analysis has to be taken into account as well when dealing with the detection of drugs in biofluids as it is not always clear whether the presence of certain analytes is the consequence of degradation or metabolism. External factors of relevance include temperature, pH, exposure to light, type of matrix and duration of storage. Soh and Elliott investigated the stability of 13 new drugs in blood and plasma at room temperature using LC-based UV and Q-TOF methods of detection. Two substances that were shown to suffer particularly from instability under the conditions used were 4-methyl-*N*-ethylcathinone (4-MEC) and AMT. While the former became undetectable in blood within 14 days, with a corresponding loss of 54% in plasma, the latter was observed to result in a variety of breakdown products. The remaining eleven new drugs remained stable in blood and plasma for at least 21 days. Casework data have also been presented. For example, in the case of 4-MEC, dihydro-4-MEC was detected as a metabolite but also as a degradation product during storage.[51] Emilia Fornal reported the electrospray ionization Q-TOF product spectra for thirty-nine substituted cathinones. The high resolution approach enabled the identification of dissociation pathways due to the ability to determine the molecular formulae associated with the particular product ions.[52]

The nature of immunoassay screening kits requires time for development when new substances appear on the market and a number of challenges have to be overcome if these are to be employed under routine conditions. Swortwood *et al.*[53] and Ellefsen *et al.*[54] have taken on the challenge of evaluating a range of kits and compounds. In the former case, sixteen immunoassay kits were obtained and tested with 24 phenylethylamines (including 8 substituted cathinones), 3 piperazines, and 3 tryptamines. In the latter case, the authors tested commercialized anti-mephedrone and anti-MDPV antibodies, which included method development, validation and analysis of authentic urine samples followed by confirmatory screening by LC-MS, and in both studies, both potential for high-throughput analysis and opportunities for improvements have been highlighted.

Bioactive properties: pharmacodynamics, pharmacokinetics, and toxicity

Given the diverse nature and background of newly emerging substances, available data on their bioactive properties can vary quite dramatically and perhaps in the majority of cases, very little is known without further study. An extra dimension in the debate has been set against the backdrop of the situation in New Zealand where the Psychoactive Substances Act 2013 has been introduced, which has laid the foundation for a pre-marketing regulatory framework associated with new drugs. An important key feature includes the need for establishing low risk of harm, and while exact details remain to be determined in more detail, there is little doubt that the implementation of established rules, guidelines and procedures commonly encountered in the medicine regulatory system will be important.[55–58] The recently

enacted Psychoactive Substances Amendment Act, offered further clarification that, as a principle, animal tests obtained from experimentation within New Zealand should not form the basis for decisions regarding product approval.[59] Whether this might raise occasional deviation from procedures commonly accepted as industrial standards remains to be seen.

In any event, the challenges remain in cases where little data may be available about a particular substance, which includes questions about the extent of toxicity and whether a new drug is psychoactive in the first place. The perspective article provided by Andrew Leach touches on a range of methods used in the pharmaceutical industry to assess whether a given substance shows desired (efficacy) and/or undesired effects (toxicity) within the field of central nervous system-targeted development. It is also pointed out that although computational results do not form part of the submission of a regulatory package, a range of both two- and three-dimensional predictive tools are commonly explored to inform drug development. The range of *in vitro*, *in vivo,* and supporting experimental and computational approaches is vast and yet, the failure rate of clinical trials is far over 90%, which highlights the difficulties when attempting to evaluate and predict central nervous system (CNS) related properties.[60]

Major challenges remain for the development of new CNS-targeted medicines based on the knowledge of primary targets alone and the same may apply when attempting to assess abuse potential. There is a tendency to apply some form of post-rationalization of the off-target effects of known compounds when interpreting adverse events associated with new drugs, for example, when pointing towards similarities in binding targets, which also includes the use of computational methods. While the concept of substitution pharmacotherapy has been applied to nicotine or heroin addition, similar principles have been of interest to research for treatment strategies associated with cocaine and amphetamine-type psychostimulant dependence. This gives rise to the idea of evaluating psychostimulant-like substances for their treatment potential and the concept of agonist therapy has formed the basis for important research in this area[61,62] and further examples may also include the evaluation of bupropion and methylphenidate as potential candidates for treatment.[63]

A range of centrally active cathinone psychostimulants, carrying the 3,4-methylenedioxyphenyl template was prepared in the 1960s by Boehringer Ingelheim,[64,65] when it was attempted to search for alternatives to pyrovalerone-based analogues that were patented previously by others.[66] Various per oral and parenteral formulations have been considered and suggested dosage levels ranged between 2 and 40 mg but preferably between 10 and 20 mg.[67,68] A variety of analogues were featured in those studies including MDPV. Another substance that appeared on the market was the α-ethyl analogue 1-(3,4-methylenedioxyphenyl)-2-(1-pyrrolidinyl)-1-butanone (MDPBP). Meyer *et al.* have provided a detailed description of the formation of *in vivo* and *in vitro* phase I and II metabolites in human and rat urine using a GC-MS- and LC-MS-based implementation of their standard urine screening approaches (SUSA). The authors identified extensive transformations and observed five metabolic pathways. In addition, it was observed that CYP2C19 and CYP2D6 were crucial for demethylenation of the parent molecule.[69]

The muscle relaxant, sedative, and anti-convulsant properties of many benzodiazepines form the basis of important medicinal applications. While the use of benzodiazepines outside the confines of medical supervision has always been an area of attention, it has recently become clear that several analogues have become available as 'research chemicals' over the Internet as well. Current examples include phenazepam, etizolam, pyrazolam, and flubromazepam and not all of those substances have been found to have marketing authorization as medicines in the countries of their detection. Another example presented in this special issue is diclazepam (Ro 5-3448), i.e., the 2'-chlorodiazepam analogue of diazepam which was originally developed by Hoffman-La Roche.[70] Moosman *et al.* present preliminary data on pharmacokinetic properties and metabolism in humans as well as information about the window of detection in serum and urine. What makes this particular study so valuable is the fact that it was based on self-administration, which included ingestion of one diclazepam tablet. As is commonly the case with such products obtained from Internet retailers, dosage uniformity was not confirmed when the authors observed that the amount of diclazepam per tablet ranged from 0.59 to 1.39 mg (median: 0.95 mg, mean: 0.94 mg, SD: 0.23). Diclazepam was found to show an approximate elimination half-life of 42 h with formation of the pharmacologically active benzodiazepine metabolites delorazepam, lorazepam, and lormetazepam, which were detectable in urine for 6, 19, and 11 days, respectively. In serum, consumption could be confirmed up to 99 h post-intake targeting the parent compound and up to 10 days targeting the metabolite delorazepam.[71]

The need for analytical clarification within the context of case work is demonstrated by two reports provided by Poklis *et al.*[72] and Rojek *et al.*[73] In the former case, the detection of 2-(4-bromo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethan-1-amine (25B-NBOMe) is described and how this substance was associated with precipitation of severe intoxication in a 19-year-old male. Serum urine concentrations were determined at the 180 pg/mL and 1900 pg/mL level.[72] Rojek *et al.* reported two fatal cases which were associated with the detection of mephedrone, methcathinone and ethanol in one (blood levels: 210 ng/mL, 1300 ng/mL and 2.80 ‰) and 4-MEC and amphetamine in the other case (blood levels: 1200 ng/mL and 230 ng/mL).[73]

Medicinal products and dietary supplements

The misuse of medicines in their various adaptations forms an increasingly important part of the new drugs phenomenon, thus, showing increasing interest from a public health and drug policy perspective. Marie Claire Van Hout has provided the reader with a scoping review that followed a narrative review design. The author offers an insightful reminder that the misuse, diversion, tampering, home manufacture, and injecting use of over-the-counter and prescribed medicine are an emerging issue of global importance.[74]

Adding to the complexity of the market in 'legal highs' and 'research chemicals' is the sale of new substances as 'dietary supplements'.[5,6] These products are often widely available on popular e-commerce sites, online health food shops, as well as in fitness equipment shops. In some cases they are marketed as 'natural' exploiting the general belief that they are safe and healthy options for consumers. The availability of these products is of particular concern because the retailers and products are typically not covered by existing drug monitoring systems, effectively creating a blind spot for public health agencies.[6,75] 4-Methylhexan-2-amine (1,3-dimethylamylamine, DMAA, 'geranamine') is one such an example. DMAA, originally described as a nasal

decongestant[76] with pressor activity,[77,78] found its way into a range of sport supplements as well as 'party pills'.[79,80] Lesiak *et al.* demonstrated the applicability of DART-TOF-MS. This direct analysis using a real time mass spectrometry ionization method was successfully applied to the analysis of DMAA-containing supplements and the direct detection of DMAA present in a urine sample following ingestion of one of those products. The implementation of in-source collision-induced dissociation revealed that differential fragmentation was observed with the DMAA isomer heptan-2-amine.[81] The report submitted by Austin *et al.* employed a UPLC-ESI-MS/MS method for the quantitative determination of DMAA in a range of commercially available dietary supplements. In addition, the authors convincingly demonstrated that *Pelargonium* and *Geranium* plant species, or commercial pelargonium and geranium oils, were devoid of naturally containing DMAA, thus, helping to dispel this myth of natural origins.[82] More recently, Cohen *et al.* identified and characterized the methamphetamine homolog *N*,α-diethylphenylethylamine (*N*-ethyl-1-phenylbutan-2-amine) which has also been sold as a 'dietary supplement' aimed at the gym/sport market.[83]

Prevalence of use and epidemiological perspectives

The growth in the number of new substances is likely to continue and while this phenomenon is considered by some to have reached epidemic proportions, it seems more likely that the engagement with new drugs on a recreational basis may be a comparatively low prevalence behavior if one considers the use of psychoactive substances in the general population. Nevertheless, the crucial questions about the reality of new drug use, e.g. the harms associated with their use and the number of regular users, remains to be explored. If one considers the number of substances available, combined with the range of caveats associated with this phenomenon (e.g. uncertainty about the identity of the substance or products, limited availability of funding to carry out appropriate household surveys), it seems clear that there is a need for further developments.[84]

The multidisciplinary nature of new drug-related subjects offers exciting opportunities for many levels of exploration in terms of information gathering and monitoring. Key contributions come from detection and chemical identification of new drugs, followed by their notification and dissemination. In Europe, EMCDDA and Europol, with their partners, operate the EU Early Warning System, which lies at the heart of information exchange across the member states, Turkey, and Norway. The perspective article written by Les King provides an overview of the phenethylamines that have been notified within the EU Early Warning System since 1997. Between 1997 and early September 2013, and excluding those not at the time listed in the UN 1971 Convention, a total number of 77 phenethylamines have been reported to the EU Early Warning System. In recent years, the repertoire of classic PiHKAL compounds[16] has been extended to include benzofurans, indanylalkylamines, dibenzofurans and *N*-benzylated phenethylamines. Interestingly, King notes that in the past 20 years, more than one-third have been notified on only one occasion and a number of 2C compounds are still among the most reported representatives.[85]

A number of drug testing services have been established in some European countries with the aim of obtaining and providing information about the drug market with regard to music festivals, clubs, and other environments associated with recreational drug use. Drug users are encouraged to submit their substances for analysis followed by communication of the results linked with harm reduction advice. One example from a Spanish non-governmental organization called Energy Control is presented by Giné *et al.* who provide an overview of the presence of new drugs in samples believed by drug users to be MDMA, amphetamine, ketamine, LSD, cocaine, methamphetamine or mescaline. Between 2009 and 2012, NPS were identified in 173 submitted samples, acting as adulterants. The majority of NPS were encountered in MDMA samples and a total number of 24 NPS were detected. Interestingly, 2C-B (although controlled under international law, and therefore perhaps not considered a 'new drug') was the most abundant constituent in the submitted MDMA products. Other NPS frequently encountered included 4-fluoroamphetamine, mephedrone, methylone and methoxetamine.[86]

While much focus has been given on the use of new substances by recreational users, they are also being used by high risk drug users, including those who inject drugs. This is likely to present challenges for service providers, including low threshold services such as needle and syringe programs that often have limited experience of these drugs and their effects.[6] Péterfi *et al.* provide a perspective on this from Hungary, where a shift to new substances, particularly synthetic cathinones, by individuals injecting heroin and amphetamine has been observed since 2010. The authors point out that additional factors may have been relevant to account for this change of use patterns, including differences in price, decreasing purity of heroin and amphetamine, and legal status of the new substances.[87]

Another fascinating perspective is given by Kikura-Hanajiri *et al.* who explain that the Japanese Pharmaceutical Affairs Law had to be amended in 2006 in an attempt to find a suitable category that would offer an effective approach to the control of new drugs. A newly introduced category, known as 'Designated Substances', was created in order to capture a range of non-pharmaceutical products. As of 1 September 2013, the total number of 'Designated Substances' was 881 and one plant. The authors have monitored the identification of new drugs on the Japanese market since 2004 and this perspective places an important focus on the work related to synthetic cannabinoids. Given their structural diversity encountered with these substances, a particular challenge includes the need for refining an update of definitions and control measures and this perspective article illustrates provides a very valuable insight into the phenomenon.[88]

The strengthening of epidemiological methods and indicators that allow for the development of increasing insights into the use of new substances is a critical priority in the response. Monitoring through general population surveys and targeted surveys forms an important basis for understanding trends and some of the harms arising from the use of new psychoactive substances.[84] In the overview given by Burns *et al.,* the reader learns about the monitoring systems in Australia ranging from 'National Drug Strategy Household Survey' (NDSHS) to the 'Ecstasy and Related Drugs Reporting System' (EDRS). In addition, web search results obtained for the period September 2012–February 2013 showed that the most commonly-encountered substances on offer to the Australian market included 6-APB, ethylphenidate, AMT, MPA and MDAI; while searches of the now defunct Silk Road marketplace showed that 2C-X and NBOMe compounds were common new drugs that were offered.[89] Furthermore, an additional contribution provided by Burns *et al.* reports on an investigation of new drug use in regular ecstasy users. These data were obtained from the EDRS

and compared ecstasy users who use new drugs and those who did not. Interestingly, 2C-based compounds were among the most popular substances used, which coincided with declining popularity of mephedrone and methylone. The authors also report on a range of characteristic differences observed between the two user groups.[90]

Information on serious adverse events, such as non-fatal intoxications that require treatment at hospital and deaths, play an essential role in identifying, understanding, monitoring and responding to the harms caused by new drugs through a toxicovigilance system within early warning systems. An important source of this information may be obtained from emergency presentations and poison information services. The opportunity to gain insights from such systems is discussed by Wood *et al.*[91] who review international literature to offer examples from data obtained from poison information services and how clinically-relevant data or information about the number of calls or enquiries can play a helpful role in toxicovigilance. In this particular case, a focus is placed on synthetic cannabinoids and selected cathinones.

While estimating the prevalence of use of new psychoactive substances continues to present challenges, other indicators are being explored. One more recently-applied approach is the extension of work based on the detection of medicines and illicit substances in wastewater. The idea of analyzing influent wastewater samples is to assess the potential to obtain data related to substance use within a given population associated with a catchment area. A tandem mass spectrometry screening method was developed by van Nuijs *et al.* who demonstrated the quantitative detection of ketamine and THC-COOH in influent wastewater samples that were taken from three wastewater treatment plants in Belgium. Method development included the separation and detection of mephedrone and MDPV but these remained unconfirmed in the water samples.[92]

Law and regulatory perspectives

The problem of whether and how to control the availability of many new drugs now occupies the minds of policymakers in many countries, and a number of different approaches have already started to appear. Some countries have introduced generic controls, analogue controls or temporary legislation, while others have enacted specific legislation aimed solely at psychoactive substances, which can raise important questions about the nature of psychoactivity, particularly when trying to provide legal definitions. On the other hand, some have introduced import controls and other restrictions on their trade. It is beyond the scope of this editorial and perspective to examine these methods in detail, partly because they have recently been reviewed[93] and partly because the international situation is changing rapidly. The subject was also addressed by a seminar on 1 May 2014 organized by DrugScience[94] and the Criminal Justice Centre at Queen Mary's College, London.[95] The current concern with new substances is also reflected by the increasing levels of activity by the World Health Organization (WHO) and United Nations agencies. For example, the WHO Expert Committee on Drug Dependence has now reviewed the status of a range of new substances for its 36th meeting in June 2014.[96]

There is no doubt that the pre-market approval regulatory approach currently pursued in New Zealand has attracted a great deal of global interest. The article provided by Chris Wilkins[97] offers valuable insights into important features associated with the step-wise development of the Psychoactive Substances Act 2013 and elements of secondary regulation that are currently being developed. A key example for the fast pace environment with regards to the new drug phenomenon can be seen with this particular article. It also informs the reader about the details related to the concept of interim product licenses but also hints towards mixed perceptions and responses from the public. With the introduction of the Psychoactive Substances Amendment Act, however, all interim product approvals and interim retail and wholesale licences have been revoked.[59]

A German law enforcement perspective is offered by Anna Duffert[98] who describes some of the challenges encountered when dealing with the difficulties of finding approaches to legislation of new drugs. For example, since new drugs cannot be easily captured by the German Narcotics Act (Betäubungsmittelgesetz, BtMG), alternative approaches, such as employment of the German Medicinal Products Act (AMG), have been considered and applied. However, recent uncertainties have arisen with regards to the question whether new drugs should be classified as a medicinal product by function within the definition set out by the Directive 2001/83/EC (as amended). This in turn, has been referred to the European Court of Justice to seek clarification on the matter. Indeed, a closely related example may also be found in the world of drugs legislation that employs seemingly simple terminology that, upon close inspection, may not be as clear cut as originally anticipated. King *et al.* exemplify this by discussing the chemical term 'derivative' and the potential for uncertainty that arises from a range of definitions that may be applicable to this particular term. Correspondingly, the authors recommend avoiding the term 'derivative' in future legislation unless qualified in order to reduce the issue of unnecessary ambiguity.[99]

Kavanagh and Power offer a two-fold perspective: first, an overview is given about the evolution of new drug legislation in Ireland, which is then followed by a reflection about the practical issues encountered from an academic research institution. The authors make a convincing point when highlighting the contributions made by academic chemistry research including the ability to provide support to forensic providers who can face increasing pressures due to high numbers of sample submissions. A key element of academic research is the interest in exploring complex avenues of chemistry and chemical analysis related to new drugs and dissemination to relevant stakeholders. Correspondingly, the authors point to the need for providing a legislative framework that allows such a fruitful area of work to continue while minimizing practical difficulties related to perhaps unintended consequences of drugs legislation,[100] which have raised concerns previously.[101,102]

When reflecting on the new drug phenomenon within our globalized world, one cannot help but wonder about a variety of overlapping mechanisms and forces that may play a part. Modern-day psychoactive drug use in its various manifestations may perhaps be, at least in part, a reflection of the growing medicalization of society, which is permeating deeply into the debate about the concepts of health, enhancement, recreation and consumerism.[103–105] The new drug phenomenon has clearly expanded beyond the so-called designer-drugs of the 1980s and 1990s, into a commodified open market comprised of 'legal highs' and 'research chemicals'. Yet still a common thread remains to this market through a direct and indirect link to medicines, whether they are substances marketed as a result of a 'failed' medicine or diversion of licensed medicine. One is reminded here of the similarities with the 'look-alike' drug market in the United States that appeared in the 1970s and continued until the 1980s offering replacements for controlled

substances such as amphetamine which were effectively mixtures of over-the-counter active ingredients. These look-alikes apparently gained some popularity in the United States after increased enforcement activities to prevent the diversion of psychoactive medicines such as amphetamine were introduced after the Controlled Substances Act came into force.[106,107] Interestingly, the marketing began to evolve into products that are more akin to the modern 'legal highs' market seen today with products such as 'Supercaine', 'Ultracaine', and 'Toot' advertised as legal replacements to cocaine. So-called 'drugs of deception' were also encountered in the 1980s, for example, in the form of counterfeit methaqualone tablets found to contain high dosage levels of diazepam. Their 'look-alike' versions, on the other hand, were mostly believed to contain doxylamine succinate and salicylamide.[112]

There may be a variety of reasons for the use of new drugs. These may include: (1) dissatisfaction with current drug(s) of choice and their effects (perhaps due to low dose or presence of adulterants; (2) curiosity about a new substance; (3) an inducement to move from current controlled drug(s) to a 'legal' new substance; (4) availability of new or substitute substances, often making claims of superior performance or benefit ('clean high', 'guaranteed', 'legal' = 'safer'); (5) a move to the new substance for reasons of variety, risk management, price consciousness, or simple indifference; and, (6) price, strength and availability of the new substance may be better than the current drug of choice. In terms of being unknowingly exposed to a new psychoactive substance, drug users may also be surreptitiously sold another substance when trying to purchase their drug of choice.

The increasing structural diversity of new drugs encountered in recent years also demonstrated that the development of new substances has not been limited to modifications of similar structural templates but also included the identification of primary binding targets commonly associated with a particular drug property as a starting point. It is anticipated that the existing patent and medicinal chemistry literature will continue to serve as an important source of ideas and information. It is also clear that the exploration of psychoactive materials allowed modern psychopharmacology to flourish while the need for further developments that might lead to new medicines continues to exist. A key topic for discussion since the occurrence of the 'designer drug' phenomenon in the 1980s has always included concerns about potential impact on research within the context of legislation related to drug abuse. Differences in terminology and classification (see above) seem context-dependent which can manifest in a range of interesting debates within the new drug phenomenon when substances that have been explored within legitimate pharmaceutical drug discovery reappear in high purity as 'research chemicals'. For example, the psychostimulant-type properties of methylphenidate (before being controlled internationally) and bupropion might have led to their classification as a new drug if they had appeared on the market and if they had not found their applications as medicines. Indeed, a range of bupropion analogues have been explored to aid understanding of its mechanism of action in smoking cessation[108] and if one of those were to appear on the streets, it seems conceivable that they would have been classified as new drugs as well. On the one hand, this appears to be a trivial example, and this applies to increasing numbers of substances labeled as new drugs or so-called designer drugs, but it underlines the complexity involved in the new drug phenomenon and how to approach this. There is no doubt that the nature of drug use, the potential for harm and potential areas of intervention and harm reduction are complex and it also appears that these issues can perhaps not be easily reduced to individual substances alone. There is also a need to be mindful about a potential shift of perception once a substance, or a group of substances, is associated with a certain terminology.

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