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Social, policy, and public health perspectives on new psychoactive substances

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New psychoactive substances pose a particular challenge to those formulating drugs policy and related public health responses. This paper outlines some of the main issues arising from their use, with a particular focus on user perspectives. Such substances are often (at least initially) produced and distributed for different reasons than controlled drugs. They emerge in users' repertoires undetected by most monitoring systems and general population drug surveys. While reasons for use by innovators and early adopters are often in the spirit of self-experimentation, such substances may rapidly diffuse to the recreational arena as a result of enthusiastic user propagation where they act as substitutes or complements to controlled drugs. The majority of substances are believed to be sourced, albeit not exclusively, from manufacturers based in China. They are retailed to consumers through the Internet and physical shops (such as 'head' and 'smart' shops), as well as traditional 'street dealers' (although data on the significance of this latter route of supply are limited). The data required for risk assessment of the harms such substances may pose, as well as information required for accurate user-derived harm reduction advice, are often limited. Moreover, some involved in the commercial supply have deliberately misbranded products, including substituting the active substance, in apparent attempts to circumvent regulatory frameworks. This leaves users susceptible to both health and criminal justice harms. Despite various attempts to restrict the supply, they often continue to be available through the illicit market, although it is not yet possible to predict whether they will join other drugs such as MDMA and LSD as mainstays of the recreational pharmacopeia.

Keywords: new psychoactives; drug policy; legal highs; entactogens; hallucinogens

Accounts of psychoactive drug use in the twentieth century illustrate distinct phases of activity that come to define popular associations and understanding of drugs. While often focused on youth subcultures (such as in the the case of amphetamine use or global dance music and ecstasy),[1] the drugs that emerged to define these eras have intricate histories, which for synthetic substances, includes the route taken from laboratory to emergence on the street as new psychoactives.[2–6]

Briefly, Lysergic Acid Diethylamide (lysergide, LSD), for example, is still closely associated with the sociocultural and political changes of the 1960s,[7,8] although epidemiologically and sociologically it was more important in the UK in the 1970s and 1980s.[9] The drug entered the recreational arena through a variety of pathways,[10] but originated from the work of Hoffman *et al*. in Zurich, Switzerland in the 1940s and 1950s.[11] Clinical studies into potential uses for a range of developmental, psychological, and dependence disorders,[5] and problem-solving sessions[12] brought LSD to the attention of both the general public and military agencies.[11] Simultaneous popularization on the east and west coasts of the United States inspired use in most other countries of the Western world, and currently whereas only a small minority of the European population reports a lifetime use of LSD,[13] a far greater number have learned to recognize and understand its effects through representations in popular culture. Similarly, 3,4-methylenedioxymethamphetamine (MDMA), was created as a potential pharmaceutical product, and despite unrevealing military testing in the 1950s,[14,15] the first street seizures (around 1970[16]) coincided with interest in its potential psychotherapeutic uses – a use which has recently been granted Investigational New Drug status by the United States Food and Drug Administration.[17] As with LSD, a pathway can be drawn from the first discovery of MDMA, to it becoming an integral part of recreational life for some groups of young people in the late 1980s and early 1990s.[14,15,18]

At the beginning of the twenty-first century, we are encountering another new range of era-defining substances. Unlike previous drug 'movements' and fashions though, the number of new substances on offer, their utility and function of use, and their availability and routes of access, means that writing their history is likely to be more difficult. Here we briefly present a number of perspectives that illustrate the challenges faced by, among others, researchers, practitioners, policy-makers, and the users themselves in understanding the role that these substances play, and how this might impact on the formulation of effective and efficient policy, particularly in relation to public health responses.

In this paper, new psychoactives refers to those emerging substances that are used for psychotropic[19] effects that are not subject to control under the United Nations Single Convention on Narcotic Drugs 1961[20] and the United Nations Convention on Psychotropic Drugs 1971[21] (although it is important to recognize that Nation States may act unilaterally and regulate them under their national controlled drug frameworks).

As the scientific data on human use of these substances is sparse, 4-methylmethcathinone (mephedrone) is often used as the exemplar substance. Mephedrone is perhaps the most well-known substance to recently emerge in the UK (at least to the general population), despite its synthesis being first described

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in 1929,[22] and a body of scientific evidence is now beginning to develop around it.[23] Its emergence and rise in popularity in some areas and some groups typifies the new pharmacopoeia, and provides a useful reference point from which to discuss many of the issues relevant to these substances in general. Widespread recreational interest in mephedrone began with the academic publication of one 'simple' two-step synthesis in 2003.[24] This was soon followed by a similar, albeit not identical, method distributed on an Internet discussion forum, The Hive. Such websites can provide relatively unmonitored and anonymous forums where chemists with varying degrees of legitimacy and expertise are able to discuss new synthesis pathways and describe preliminary dose finding self-titration 'bioassays', much in the same way as Shulgin's popular titles PIHKAL[25] and TIHKAL[26] did in the printed form (both titles are now available online without copyright restriction). In contrast to the history of drugs such as LSD or MDMA (which were first synthesised by pharmaceutical companies), most of these new substances are perhaps not of interest to these chemists because of their potential clinical utility, but because of the challenges faced in synthesizing them, the possibility of synthesizing a substance that is not subject to controlled drug frameworks, and the desire for new subjective experiences. It is interesting to speculate whether the desire for the same level of recognition and respect afforded to Albert Hoffman and Alexander Shulgin – who are (inadvertently) important cultural figures respected by many hundreds of thousands of people as much for their culture-defining chemistry as their lives and opinions* – are also motivators for many of these 'opinion leader' chemists.[28]

Some of the syntheses undertaken by this group mirror previously published work, but as with the case of mephedrone, alternative pathways are proposed, and putative new substances are also discussed (Brandt, pers. comm.). Other less specialized forums (e.g. bluelight.ru) allow more general discussion of drug effects, subjective experiences, dosage, and availability. It is through these sites that new substances begin to become better known in the general population of users, much like 'word-of-mouth' marketing of consumer products can be driven by 'early adopters'.[28,29]

Although use in established drug-using populations is to be expected, new substances that are not subject to controlled drug frameworks are also attractive to many individuals because they do not necessarily lead to being associated with a 'drug user identity',[30] with all of the perceived criminality and stigma this brings.[31] While differing conclusions have been presented as to whether users view new psychoactives as 'safer' than their controlled counterparts,[32–34] it is clear that the attraction of some of these substances lies in the fact that they are 'legal' and the (mis)perception that the quality and purity is subsequently superior[35,36] to those controlled drugs available on the illicit market.[37] However, if an individual continues to use such new substances after they have been brought under controlled drug frameworks, then they may also have to adopt a new set of behaviours if they are to avoid being identified as a drug user, including the avoidance of formal help with drug-related problems. As new substances are not subject to a body of scientific investigation into adverse drug reactions or sensationalizing media accounts (at least not in their early stages of diffusion[38,39]), innovators may also view them as non-problematic, instrumental to specific activities, and bringing psychological and physical benefits. This is a hypothesis that requires further investigation. The development of informal harm-reduction practices and understanding of some drug effects through (shared) experiential learning – 'ethno-scientific knowledge'[40] or 'e-commons' – also means that early adopters may also have a distrust of 'experts' and 'authorities' that provide official medical and drug information, whom they may perceive as lacking the specialist knowledge that they possess. This, of course, is not necessarily problematic in itself, as some of this advice may be sensible and of practical use to early adopters, but it does become problematic when the user-derived body of knowledge is incorrect[41] or is based upon a misinterpretation of scientific evidence (e.g. the belief that water was an 'antidote' to ecstasy intoxication[42]).

Once use becomes more popular, diffusing to larger groups, those that become involved in the commercial supply of such substances may engage in creative strategies[43] in an attempt to circumvent regulatory frameworks.[39,44] Principally these include the deliberate misbranding of products[35] that aims to disguise the fact that they are intended for use in humans (widely believed to circumvent the regulatory framework for medicinal products[44]), as well as the identity of the active substance. Some suppliers also resort to substituting the active substances. In the former cases such strategies include the use of vague product descriptions and invented names;† and/or, marketing them as 'plant food', 'bath salts', 'room deodorizers', 'not for human consumption', and 'research chemicals'. Moreover, the use of similar-sounding invented/trivial names, such as mephedrone, methylone, and methedrone, may result in users inadvertently purchasing a different type of product than intended.[45] Overall, such strategies are likely to exclude many users[46] from both formal and informal bodies of drugs advice and information.

The Internet has become a key source of information and communication[47] for many individuals, especially young people.[48,49] For information on drugs, user-orientated sites can often be rated as more useful and trustworthy than official sources.[50] Moreover, these sites are often ranked higher in search engine results than official sources.[51] Objective analysis of some popular sites reveals that they often contain incorrect or misleading information,[52,53] a failure which they share with some sites providing information on prescription medicines.[54,55] Online retailers of new psychoactives sometimes offer 'safety advice', but these have been assessed as being sparse and of questionable quality.[56] The accuracy of the warnings that did appear often consisted of broad disclaimers, sometimes apparently part of the creative strategies (e.g. marketing them as 'not for human consumption'), and could not be evaluated further without forensic analysis of the active substance(s), which may often differ from that advertised.[57] There can also be discordance between some of these warnings and the description of products as fun recreational pursuits. One site, for example, instructs potential consumers that 'Salvia is a truly unique visionary herb and when treated with respect can reward you and guide you towards greater self-knowledge and harmony' but then asserts 'Salvia is fun and bouncy; effects are unlike anything you will have experienced; Salvia seldom produces adverse side-effects or hangover'.[58]

Despite the huge media, professional, and political interest in new psychoactives over the last few years, we have limited data on measures of incidence and prevalence, motivations for use, and patterns of use, as well as (objectively measured) adverse drug reactions and other harms. Moreover, fear and panic, often fuelled by sections of the popular media, have often become

* For example, after suffering a stroke in December 2010, Shulgin received substantial donations to help with his medical costs.[27]

† "Groove-E gets you in the fun, free spirit of the 60's. It gives a happy warm buzz that comes around you like a big hug - you'll be feeling the love in no time" (http://www.herbalhighs.com, accessed January 2011).

the dominant forces framing the problem. This is likely to limit the ability to collect data required for risk assessments in a valid and precise manner, which may bias both the subsequent policy measures chosen, as well as the evaluation of their effectiveness and efficiency in preventing and reducing harm.[44]

Presentations at specialized harm-reduction services, including needle and syringe programmes, can play an instrumental role in identifying emerging substances and trends. Recently, these have included synthetic peptides such as the melanocortin receptor agonists melanotan I and melanotan II (largely used to increase skin pigmentation in order to obtain a cosmetic 'skin tan')[59] and the synthetic growth-hormone-releasing peptide GHRP-6 (that is used as part of the performance-enhancing pharmacopeia[60]). However, presentations of new psychoactives are rarely recorded at these and related drug-treatment services or are too infrequently reported to include in routine monitoring reports and therefore may not come to the attention of relevant stakeholders. Some prevalence data does exist for mephedrone, although these are taken from convenience samples. Dargan *et al*.[34] surveyed educational establishments in the Tayside area of Scotland (UK) before mephedrone became a controlled drug. Of the 1006 students that completed the survey, 20.3% reported use of mephedrone on at least one occasion, while 4.4% reported daily use (mean ages of the samples ranged from 14–20 years). Although the accuracy of these data are uncertain, especially in the context of intense media reporting on mephedrone at the time of survey,[60] of note was the increasing tendency of respondents to report purchasing the drug on the Internet. In a more targeted population, the 2009 Mixmag drugs survey reported that 41.3% of 2295 readers of the dance music magazine had ever used mephedrone (again, not a controlled drug at the time of survey), and it was the sixth most frequently used drug in the previous month[62], with 12.6% also reporting use of 'Spice' smoking mixtures (containing cannabinoid receptor agonists), and 25.9% BZP (1-benzylpiperazine) or other 'party drugs'. The accuracy of some of these findings should be viewed with caution as they rely on self-report, and forensic data suggest, for example, that a large proportion of recent ecstasy tablets obtained from submissions at a large dance music event in the north west of England in the UK were in fact BZP not MDMA (Brandt, in preparation). Mephedrone was included for the first time in the 2010/2011 British Crime Survey (BCS),[63] but general population surveys tend to underestimate use of all types of drug, exclude key groups such as university students (although the BCS often includes a young people's booster sample drawn from 16–24-year-olds), have poor representation of young people in high crime areas (who would be more likely to report drug use), and can only provide data on those drugs that have already reached a threshold level of use which warrants the attention of policy-makers. Furthermore, there is a lack of evidence that such drugs are being sold in appreciable quantities by street dealers, so no conclusion can be made about street availability and prevalence of use. In contrast to the high levels of use reported in the Mixmag survey, the 2009/2010 BCS estimated that 1.2% of adults aged 16–24 reported last year use of Spice smoking mixtures and 1.4% BZP (compared with 0.2% of adults aged 25–59).[63] So while these data are of some use in policy monitoring, with the margin of error present in most general population surveys,[65] such low prevalences are not of great use in designing policy and related service responses, or in assessing patterns of use (particularly concomitant poly-substance use). As the prevalence of use of most new or recently controlled psychoactives will initially be low, it is important that, in addition to seizure reports from law enforcement agencies or web monitoring projects (e.g. the European Union's early-warning system[66,67] and Psychonaut Web Mapping Reseach Project[68]), spontaneous reporting systems are made available to services in regular contact with drug users, particular young people. Although these systems would not help with population incidence and prevalence estimates, they would allow relevant stakeholders to become more rapidly aware of substances that have moved from just being of intellectual curiosity or being used by small coteries of individuals with access to chemists or materials, to more widespread diffusion in general populations of drug users.

The availability of drugs, including supply, cost, psychological attractiveness, and social acceptance within peer groups (i.e. injunctive norms are favourable within both drug and non-drug using peers), is strongly associated with the initiation and maintenance of all types of substance use.[69] New psychoactives are readily available to those who wish to buy them. Simple Internet searches using terms such as 'buy legal high + UK' conducted in 2009 revealed 39 unique online retailers based in the UK that offered a wide range of products, mostly herbal and plant materials including Salvia divinorum, kratom (Mitragyna speciosa), Hawaiian Baby Woodrose seeds (Argyreia nervosa), and fly agaric mushrooms (Amanita muscaria), but also poorly described powder and tablet preparations.[56] A brief subjective review by us of some Internet shops (presumably based in the UK) that offered mephedrone for sale before it became a controlled drug (using the search term 'buy mephedrone UK' on google.co.uk, 28 March 2010) suggests that the marketing strategy may be pitched as 'quality, value, convenience': '99.8% pure ... best quality cheap Mephedrone on the market ... buy ... online securely with us ... and we will have it delivered to your door step tomorrow' (ordermephedrone.co.uk, 28 March 2010) in 'discreet packaging' (4-mmcshop.co.uk, 28 March 2010). While some sites only accepted payment by bank transfer or Internet payment accounts, others offered a range of payment options, including credit and debit cards as well as postal orders. Some shops offered refunds that appeared to be in accordance with the UK's distance selling regulations.[70] Overall what role such strategies play in the diffusion of new psychoactives – particularly towards the adoption by the 'early majority' – by legitimating such shops as engaged in the lawful sale of 'ordinary commodities', requires further research.

As informal surveys suggest that the street price of many illicit drugs is increasing,[71] behavioural economic theories would suggest that above certain price increases, new psychoactives may act as substitutes,[72] particularly those which are marketed to mimic the effects of stimulants, entactogens, and cannabis. Whether these substitutes are acceptable to users (e.g. produce similar effects with the same degree of intensity) is another matter, but many Internet retailers offer discounts on individual or bulk purchases of products (which may also be used for local distribution by street-dealers, increasing the availability of the product), and most behavioural active doses sell at around £10,[56] making them very affordable for initial experimentation.

Manufacturers and wholesalers based in China have come to prominence as a suspected wholesale source of many of the precursors and bulk active substances for synthetic products;[73,74] indeed, a cursory Internet search conducted by us produced links to sites such as made-in-china.com – 'Connecting buyers with China suppliers' – which at the time of writing provided links to three companies offering 200 kg drums of the mephedrone precursor 4-methylpropiophenone. (Another listed company offered vials

of the synthetic melanocortin analogue melanotan II,[59] which was sold alongside foodstuffs such as potatoes; either suggesting unusual stock diversity, or of more concern, a lack of specialization that would not be tolerated in the mainstream pharmaceutical industry.) Although relatively easily available for purchase, in common with illicitly supplied controlled drugs,[37] concerns exist about the quality of some of the wholesaled precursor and bulk active substances, as well as finished dosage forms originating from the middle-income countries such as China where regulatory oversight and enforcement can be limited.[75]

Investigations of the source of counterfeit medicines may provide a model for identifying and constructing international multiagency responses to manufacturers and wholesalers if offences under international and national laws have been committed. In the case of investigations into counterfeit sources of the socially and economically important anti-malarial drug artesunate, for example, the Chinese government, it was noted, was quick to respond to intelligence with arrests and seizures.[76]

Early reports on the availability of mephedrone before and after it became a controlled drug in the UK have concluded that prohibition had not worked as the substance was still available.[77,78] Such studies also implied that harms would increase as a result of such legislative action, and that such approaches were not an effective form of regulating new psychoactives. Other commentators have also suggested, without direct evidence, that the presence of mephedrone in the UK market was responsible for the reduction in cocaine-related deaths in the UK in 2010.[79,80] These assertions may be correct, but small-scale studies with such short follow-up times are not appropriate to assess the impact of policy on incidence, prevalence, and behaviours.[81] As we have shown in our own studies, after mephedrone was controlled, it and other substituted cathinones were being sold under different brand names (e.g. NRG1), suggesting that wholesalers and retailers (including 'street dealers') had stockpiles of these drugs,[57] thus accounting for its continued availability. Furthermore, as there is currently no published evidence to suggest that mephedrone and related drugs are still being imported into the UK, we believe that it is not possible at the time of writing to discount or support the effects of these policy measures. It is also difficult to assess what the levels of mephedrone-related harm might have been if it had not been regulated as a controlled drug. Recent months (as a result of the intrinsic delays of scientific publication) have led to the availability of an increased body of data on toxicity that wasn't available at the time that mephedrone became a controlled drug. The number of fatalities appears to be small;[82] however, caution should be taken in interpreting these data due to the limited information on pharmacoepidemiology and pharmacovigilance, (including exposure to this substance).[83–85]

Users (and unsuspecting retailers) also face other risks as a result of misbranding of newly controlled drugs as 'new', 'legal' products (e.g. NRG-1[57]). It might be argued, for example, that the adverse effects of criminalization of the user is more likely[86–90] and associated with more severe outcomes (e.g. loss of employment and travel opportunities, stigma) than the probability of experiencing a serious adverse drug reaction. Such misbranding means that users and (some) retailers will be unaware that they may have committed an offence under controlled drug frameworks, and most, unless they have access to suitable analytical equipment, are unlikely to be able to accurately identify the active substance(s) in the products they have bought or are selling – although in the UK, section 28 of the Misuse of Drugs Act 1971 (the principal body of legislation concerning controlled drugs) may provide such individuals with a defence.[91–93]

In their critiques of the policy response to mephedrone, McElrath *et al*.[77] and Measham *et al*.[61] argue that in the absence of 'legal' mephedrone, users may revert to previously used controlled drugs; a pertinent social harm that is a consequence of policy, albeit one that was unintended. These are interesting hypotheses that are in need of testing, but such critiques are not without fault. First, with regard to acute medical harms, they seem to assume that mephedrone use is preferable to that of drugs such as MDMA as toxicity is less pronounced, for which there is currently insufficient evidence to conclude.[83–85] Secondly, such arguments also assume that the most pertinent adverse drug effects are related to user engagement in criminal behaviour rather than toxicity (which may be true), but that toxic effects might be ameliorated through regulation outside of controlled drug frameworks. Although forms of regulation that allow new psychoactive substances to be lawfully placed on the market may improve product quality, experience has shown that even with highly restrictive regulatory frameworks – such as those that regulate medicinal products – minimizing the risk of toxicity posed by an active substance can be difficult.[83–85]

One recent Internet survey has examined the effect of mephedrone control in the UK on self-reported user behaviour. Here the authors report that 49% of self-identified mephedrone users ($n = 1265$) stated that they would use more MDMA after mephedrone was controlled.[94] However, this paper provided an incomplete assessment as no data were presented that MDMA use had ever been reduced in response to the availability of mephedrone in the first place, or that MDMA use would increase beyond levels usually taken (as suggested by the interpretation). There was also inconsistency in reporting as this figure was also interpreted to indicate that making mephedrone a controlled drug would make respondents more likely to take MDMA, which in the case of existing MDMA users would be unsurprising as they were already initiates; secondly, no data breakdown was provided as to the likelihood of MDMA use in MDMA-naive individuals. Furthermore, 73% reported that they preferred the effects of MDMA anyway, suggesting that for regular drug users at least, mephedrone would not be a suitable substitute for MDMA.

Regulating new and emerging psychoactives substances as controlled drugs will likely have the effect of preventing and reducing use in some types of user (thus suggesting the need for research to construct profile analyses of new psychoactive users), but most experienced users will either look on the Internet or to friends and dealers for the next new substance (novelty and sensation seeking are in themselves risk factors for substance misuse[95]) or continue to seek out the drug illegally (e.g. data from the 2011 Mixmag drug survey on self-reported use of mephedrone suggests that some individuals are using it after it became a controlled drug,[78,96] although given the potential for misbranding the actual substance that they are using is unknown[57]). As noted above though, the general population prevalence of recently controlled drugs is low, and so law enforcement efforts are unlikely to produce significant population-level health savings.

At the policy level, it is difficult to know how to respond to new and emerging substances, but in a field where there is so little evidence available to policy-makers,[44,97] or where they are often unaware of the subtle nuances of evidence[98,99] it is important that any policy measures are not discounted prematurely. While detailed discussion of such measures is beyond the scope of this paper, a range of approaches have been proposed.[39,44,100–104]

These should be subject to rigorous research and evaluation to determine effectiveness and efficiency in preventing and reducing harm.[68,105]

The challenge to researchers, practitioners, and policy-makers alike, is to predict what new substances will next emerge after mephedrone (and to a lesser extent naphthylpyrovalerone (NRG-1[106]), 3,4-methylenedioxypyrovalerone (MDPV, sometimes sold as Ivory Wave, and NRG-1,[107] and 6-(2-aminopropyl)benzofuran, sometimes sold as BenzoFury[108]). Within the European Union, Council Decision 2005/387/JHA provides a legal framework for defining new psychoactive substances, as well as an early-warning system for reporting such substances that have been identified within member states, a mechanism for formal risk-assessment of selected substances and, if required, eventual EU-wide control[66,67,109] (although this framework does not prevent member states acting unilaterally to control such substances). The early-warning system is somewhat reactive as it relies on formal submission by partner organizations, but a recent report from the EMCDDA noted that 41 new psychoactive compounds were identified in the EU in 2011.[110] This figure is supported by the findings of the more dynamic Psychonaut web-monitoring project which identified 412 new substances (151 Chemical, 121 Herbal) and combinations (140) being discussed or sold online over a two year period (2008–2010).[111]

In a recent editorial in Nature,[112] Professor David Nichols, a medicinal chemist specializing in the development of putative therapeutic serotonergic agents, lamented what he perceived as misuse of scientific data for commercial gain in the recreational arena. Referring specifically to 4-methylthioamphetamine (4-MTA), a substituted amphetamine with some MDMA-like behavioural properties that he had developed in the early 1990s, he described how he was alerted to press interviews with 'opinion leader' chemists who had specifically referred to his work as a source of inspiration for new commercial synthesis routes. Nichols was particularly concerned that this compound, and by extension others he had published on, had been incompletely tested and had been implicated in several fatalities. Public discussions focused on the responsibilities of the medicinal chemist to understand the implications of working in a field with legally and often socially proscribed outcomes (e.g. Radio 4, Material World 6/1/11). However, perhaps of greater interest in the current discussion was that other compounds such as 5,6-methylenedioxy-2-aminoindan (MDAI), another compound from Nichols' group, which has similar (behavioural) pharmacology to MDMA, but not its serotonergic neurotoxicity in rodents,[113] have rarely appeared in published seizures or street drug monitoring systems,[114] and are infrequently reported by users in online forums. It is interesting to speculate why one compound, and not the other was made available in appreciable quantities. This was, of course, not the first example of scientific data mining by enterprising chemists and new psychoactives enthusiasts. The benzylpiperazine, meta-chlorophenylpiperazine (m-CPP) briefly came to prominence as an MDMA substitute after human drug discrimination studies showed it produced similar subjective effects to MDMA.[115,116] A metabolite of the antidepressant trazodone, and available as a research tool, perhaps it was the greater body of literature or the more certain legal status of mCPP compared with MDAI that meant that the former gained popularity and not the latter. Shulgin's PIHKAL[25] and TIHKAL[26] describe synthesis routes and basic human psychopharmacology of many potential hallucinogenic and entactogenic compounds; many of which have subsequently found an audience of both 'research chemical' enthusiasts (for example see the discussions at the erowid.org 'Psychoactive Vaults' http://www.erowid.org/psychoactives/psychoactives.shtml) and more casual recreational users. Jonathon Ott's Pharmacotheon[117] provides a similarly comprehensive overview of plant hallucinogens, many of which are unknown to law enforcement agencies, and are not controlled drugs in Europe and North America. Shulgin (and Perry's) less well known The Simple Plant Isoquinolines[118] exhaustively details another class of potentially psychoactive alkaloids, the isoquinolines found in, amongst other materials, cacti such as Lophophora williamsii and Papaver somniferum, better known as the opium poppy. The Shulgin Index Volume 1, Psychedelic Phenethylamines and Related Compounds (to be followed by a similar volume on tryptamines) was published in 2011,[119] providing a focused, fully referenced examination of the chemistry and pharmacology of 126 compounds, many of them new. Considering the popularity of PIHKAL it is likely that 'research chemical' manufacturers will be taking particular note of this new title. What distinguishes the collection though, apart from similarities in chemical structure, is that almost none of the materials mentioned have undergone even basic toxicological profiling.

King and Kicman[120] note that many new psychoactives fail to become popular because of their lack of oral availability or hallucinogenic rather than entactogenic and psychostimulant effects. Alongside those discussed above, here we suggest some additional features which explain why some substances become popular and remain so despite measures to regulate them as controlled drugs: (1) the substance can be administered easily (oral, insufflation, sublingual or smoked); (2) its perceived quality and price is comparable or superior to more established drugs;[121] (3) the perception that the individual level of risk associated with use is not greater than that of other comparable drugs[122] – in addition, as individuals tend to discount individual level harm, population harms associated with use must also be low; (4) the culture associated with use does not drastically alter (e.g. use of the substance is associated with a particular form of music or recreational pastime which becomes unfashionable; (5) it does not have to compete (economically or psychopharmacologically) with other new substances; and, (6) it can be relatively easily obtained (i.e. availability, which in itself is determined by the willingness of manufacturers to continue production, the availability of precursors, the profits resulting from producing illicit compound versus producing a new substance that is not controlled (that in itself is determined by the number of users prepared to break the law to continue to purchase the drug)).

Discussions of 4-MTA are noteworthy in other ways. For the scientific researcher interested in helping to prepare legal and public health responses to new psychoactives, an uncomfortable move away from evidence-based investigation is often required. For example, we conducted a very brief literature search for 4-MTA using Web of Knowledge in January 2011. This is a relatively well-known drug for which we expected there to be an appreciable body of literature. The earliest paper from 1992[123] concerned in vitro pharmacology, while later papers focus on forensic detection, illicit synthesis, and toxicity (mainly assessment of hepatotoxicity in rodents). Ignoring control, classification and scheduling under controlled drug frameworks on structural reasons, the limited behavioural pharmacology (e.g. in vivo 5-HT release, drug discrimination) and lack of qualification of the human toxicity data available for 4-MTA would be, we believe, insufficient to make a formal risk assessment of the harmfulness of this drug if it emerged today (4-MTA was also subject to a risk assessment by the European Monitoring Centre for Drugs and Drug Addiction in 1999

from which limited conclusions could be drawn;[124] see also Nutt *et al*.[97] for a discussion on the classification of drug harms and the difficulties in objectively defining these). The UK Government has recently proposed to insert a 'holding category', known as temporary class drug orders, for new psychoactives by amending the Misuse of Drugs Act 1971 (section 152, Schedule 17 of the Police Reform and Social Responsibility Bill).[125] after consultation with the Advisory Council on the Misuse of Drugs (ACMD), the independent statutory body in the UK that was established under the Misuse of Drugs Act 1971 to advise government 'on the control of dangerous or otherwise harmful drugs', new substances can be 'temporarily controlled' for up to a period of 12 months. During this period, the production, possession with intent to supply, and supply of such substances without authority would be an offence and subject to Class B penalties (i.e. up to 14 years' imprisonment and an unlimited fine on indictment). Users would not be prosecuted for simple possession; police would have the power to seize and dispose of named substances (although without power of warrant). It is presumed that this period would be used to more fully assess the harms of new substances in order to mitigate potential adverse population effects, and subsequently, to allow the ACMD time to make a recommendation on whether it should be brought under 'permanent' control of the 1971 Act, and if so, classification and scheduling.[91,126] In this respect, it's important to note that the duty of the ACMD goes beyond such advice to include measures that may not involve alterations of the law 'which . . . ought to be taken for preventing the misuse of such drugs or dealing with social problems connected with their misuse'.[88]

It is unclear whether this amendment will work as intended. However, 'inaction' on this issue is not an option politically. We have recently suggested that, in the UK, the existing medicine regulatory framework may be a pragmatic compromise, allowing a proportionate and legitimate response where public health may be at risk.[44] Here, should a new psychoactive substance be classed as a medicinal product by the Medicines and Healthcare products Regulatory Agency (the UK's national medicine regulatory authority), then it would be an offence to manufacture or import, market, or advertise it without authority. If this framework were to be used, a synergy between compliance and deterrence through responsive regulation will need to be found. The principal aim of this approach would be to prevent harm (through compliance), rather than punishment post hoc (deterrence). This will require, among other things, engagement with stakeholders to provide education and advice (including what is meant by the broad term 'medicinal product'), along with persuasion and negotiation as necessary. Better use of the pharmacovigilance system, including spontaneous reporting systems, may also help identify and reduce harms. Importantly, this approach will not compromise the UK's obligations to international treaties,[20,21] the European Union,[66] or, if necessary, the control of such substances under the Misuse of Drugs Act 1971.[91] (Again, if such an approach were to be used, it should be subject to rigorous research and evaluation to determine effectiveness and efficiency in preventing and reducing harm.[68,105])

Referring to 4-MTA, a substance which was first described in the scientific literature over 20 years ago,[123] but subject to little investigation, it is perhaps reasonable to conclude that bodies such as the ACMD would be unable to provide comprehensive advice on the (social) harms of many new and emerging substances. There has certainly been no discussion at the time of writing on whether this assessment period will be associated with research funding beyond basic chemical and pharmacological characterisation, and in reality, it is unlikely that it will be forthcoming or sufficient time provided between the announcement of temporary control and formal risk assessment for such research to take place. While risk assessments may be made on the structural and pharmacological similarity of new substances to those that are more well known (e.g. mephedrone and MDMA[63]) it is less often recognized by policy-makers (at least in public) that the harm resulting from substance use also results from contextual and environmental factors which are difficult to generalize.[97,127] The ACMD risk assessment on substituted cathinones[63] provides a case in point. While comprehensive information was reported on chemistry, pharmacology, and seizures by law enforcement agencies, data on their effects in humans and use behaviours were limited to a small number of self-report data. Although case report data were later published,[128] only one (Swedish language) forensic report was included in the review.[129] Researchers may face a situation whereby users themselves have greater knowledge about certain aspects of a particular substance, obtained through shared experiential discussion and learning, than those experts tasked to make judgements on behalf of government.[23]

Competing interests

HRS was appointed to the Advisory Council on the Misuse of Drugs (ACMD) in January 2011 and receives expenses payments to attend Council meetings. The views expressed here are personal and do not represent those of the ACMD. ME-B is contracted by the Department of Health to coordinate the early-warning system on new psychoactive substances for the UK National Focal Point, reporting to the European Monitoring Centre for Drugs and Drug Addiction under the terms of European Union Council Decision 2005/387/JHA. The views expressed here are personal and do not represent those of the UK Focal Point nor the Department of Health. ME-B and JM have provided advice to the ACMD and received expenses payments for travel to attend ACMD meetings. ME-B has provided advice to the Independent Scientific Committee on Drugs (ISCD) and received expenses payments for travel to attend ISCD meetings. All authors declare no other relationships or activities that could appear to have influenced the submitted work.

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