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Chapter 9: Synthetic cathinones – prevalence and motivations for use

John M. Corkery, Amira Guirguis, Duccio G. Papanti, Laura Orsolini, Fabrizio Schifano.

Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit
School of Life and Medical Sciences
University of Hertfordshire, Hatfield, UK

Contact: j.corkery@herts.ac.uk

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Abstract

This chapter considers the prevalence of and motivations for use of synthetic cathinones. As part of the scene-setting, the availability, legal status, numbers of cathinones, number and quantities confiscated are reviewed. This leads to the first substantive section of the chapter - an epidemiological investigation of the nature and extent of what is known about the use of these molecules. The second major section is more qualitative in its approach to understanding motivations for the use of any drug, Novel Psychoactive Substances (NPS), and then natural cathinones and synthetic cathinones. An examination is conducted of how cathinones may be compared to other stimulants and why particular cathinones may be preferred to others. The converse situation is then examined, what might be the motivations and reasons for ceasing to take cathinones and why this may not be rational decision. A brief examination of the consequences of ceasing versus continued use is presented. As it is very likely that further synthetic cathinones will continue to emerge, it is important to gain a much fuller insight into what motivates or causes individuals to use or cease using these molecules, so that communities and societies can respond in appropriate ways to the varying challenges that face them and their citizens.

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9.1: Introduction and Background

Despite the continuing increase in the emergence of Novel Psychoactive Substances (NPS), a core group of over 80 NPS have become established as attractive recreational drugs, supplementing traditional drugs of abuse and becoming part of the repertoire of substances available for consumption (UNODC, 2017a; Moore et al., 2013). This group has been reported every year from 2009 to 2016, including mephedrone and derivatives. In Central Asia, this group accounts for 42% of all new NPS notifications in 2013-6 compared to 16% of NPS notified from the Near and Middle East since 2008 (UNODC, 2017b). It is important, therefore, to understand the prevalence and motivations for use of the largest NPS groups, including synthetic cathinones (EMCDDA, 2016a; EMCDDA, 2017; UNODC, 2016a), in order to appropriately understand the nature and extent of the problem. This will facilitate the design of better-informed data collection models, as well as the delivery of appropriately tailored harm-reduction techniques and initiatives.

Estimating demand for and supply of psychoactive substances is problematic even for traditional drugs of abuse, let alone for NPS (Corkery et al., in press). For example, the number of NPS confiscations or the amounts of NPS seized by law enforcement agencies only reflect operational priorities by such organisations. Furthermore, only very inaccurate estimates can be made as to what proportion of the total supply of specific substances is accounted for by such law enforcement agency interdictions. On the demand side, very little is known about the nature of NPS consumption, especially with regard to typical doses taken to achieve particular effects, accuracy of dose measurement, frequency of dosing, need to redose, tolerance, duration of effects, length of half-life, metabolism, toxic and fatal levels, etc.

However, international agencies such as the United Nations Office for Drugs and Crime (UNODC) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) have work programmes aiming to enhance the development of more timely and robust techniques to not only monitor the current situation with regard to the NPS phenomenon but also predict future evolutions. In the meantime, we have to deal with the limitations and vagaries of the established monitoring systems and the challenges which face them (Palamar et al., 2015; UNODC, 2017a). Whilst patterns can be observed in the number and type of NPS being reported to such international agencies, there are limitations in terms of the timeliness of detection, accurate identification and submission of reports by law enforcement, forensic and toxicological services. Furthermore, whilst we may have a good estimate through these indicators of the number of NPS in circulation, the actual numbers that have been created and held ready for sale are likely to be higher.

It is very challenging to accurately estimate the prevalence of specific NPS classes because most of the surveys conducted focus either on NPS as a whole or on specific NPS, although some progress has been made in recent years in improving survey instruments and tools (UNODC, 2017a). Other technical issues include: self-reporting surveys, such as the Global Drug Survey (Winstock et al., 2017) may not be representative of all users; there may be differences between respondents who

have internet access and chose to participate compared to those who lack such access or desire to take part (Ashrafioun et al., 2016). General household surveys which will not capture people living alone, in institutional settings (hospitals, penal establishments, student accommodation, sheltered housing, etc.) or those who are 'homeless' or 'roofless' resorting to 'sofa-surfing' – who often comprise individuals most at risk of using and/or dependent on psychoactive substances, including synthetic cathinones. It often takes a relatively long period to get specific questions on special topics included in regular surveys, such as the Crime Survey for England and Wales (Broadfield, 2017), so that by the time the survey is in the field the substances being asked about may have disappeared from the market. Palamar et al. (2017) argue that 'gate' questions, which adopt a 'skip-logic' approach in surveys such that "only a "yes" response to the use of specific drug class is followed by more extensive queries of drug use in that drug class", may impact the accuracy of collected data via self-reporting. Therefore, surveys on NPS use should explicitly include the NPS classes, the specific NPS within each class as well as the street names.

NPS users often have little knowledge about what molecules they are actually consuming; they may only be aware of a brand name or a 'street' name, and almost certainly will not have had it analysed. That said, often products purchased as 'research chemicals' are indeed what they purport to be (Guirguis et al., 2017).

In this chapter we focus on the second largest group of NPS – synthetic cathinones. As noted elsewhere in this book, these substances are synthetic derivatives of the natural amphetamine-like substances 9cathine and cathinone) present in the leaves and stalks of the khat plant (*Catha edulis*), which produce mild stimulant and other psychoactive effects (Corkery, 2016).

9.2: Availability of synthetic cathinones

Before taking a closer look at the information available about the extent of use of synthetic cathinones, we will briefly review the situation regarding their availability. In Europe, by the end of 2016, some 629 NPS of all classes were being monitored by the EMCDDA, of which 66 were reported for the first time in 2016 (EMCDDA-Europol, 2017). By the end of 2016, 739 substances had been reported by 106 countries and territories through the global Synthetics Monitoring: Analysis, Reporting and Trends (SMART) programme to the UNODC (2017a); the number of NPS reported increased from 126 to 450 between 2009 and 2014.

9.2.1: Legal status of cathinones

Khat is regarded as "a particular NPS of concern" by the UNODC (2014). Although the plant itself is not under international control, at present, two of the principal psychoactive substances that are

present in it, cathine and cathinone are. This because in the early 1980s all amphetamine-like substances were placed group-wise under international control (ECCD, 1985). Cathinone was included in Schedule I of the UN Convention on Psychotropic Substances in 1988, and cathine was then included in Schedule III of this Convention. Cathinone and cathine are controlled substances under Class C of the UK Misuse of Drugs Act 1971 by virtue of Schedules 1 and 3 respectively of the Misuse of Drugs (Amendment) Regulations Act 1986.

A number of persistent NPS have been brought under international control, among them several cathinones: α-pyrrolidinovalerophenone (α-PVP) was placed under international control in 2016; 3,4-methylenedioxypyrovalerone (MDPV), mephedrone and methylone in 2015, all under Schedule II of the 1971 Convention on Psychotropic Substances (UNODC, 2017a). In March 2017, the Commission on Narcotic Drugs decided to add ethylone, pentedrone and 4-methylethcathinone (4-MEC) to the same Schedule. In the USA, MDPV, mephedrone and methylone come within the compass of Schedule I of the Controlled Substances Act 1970.

At the EU level, mephedrone was submitted to control measures in EU Member States by the European Council's decision of 2 December 2010 (2010/759/EU). Some cathinone derivatives are caught by drug control or equivalent legislation, for example: mephedrone (Belgium, Crotia, Denmark, Estonia, France, Germany, Ireland, Italy, Lithuania, Norway, Romania, and Sweden); methylone (Denmark, Ireland, Romania and Sweden); butylone (Denmark, Ireland, Norway, Romania, and Sweden); MDPV (Denmark, Ireland, Finland and Sweden); and flephedrone (Denmark, Ireland and Romania). Medicines' legislation is used in Finland and the Netherlands to control mephedrone. In the UK context, several generations/classes of synthetic cathinones and derivatives have been dealt with by means of generic definitions under the 1971 Act as Class B drugs and under Schedule 1 of the Misuse of Drugs Regulations (2003, as amended).

Some synthetic cathinones are licensed for medicinal use. For example, Bupropion (Zyban, Wellbutrin), primarily used as an antidepressant and smoking cessation aid, has been used recreationally (Vento et al., 2013). Pyrovalerone, developed in the late 1960s and structurally related to MDPV, has been used in the clinical treatment of chronic fatigue and lethargy due to its stimulant effects (Gardos and Cole, 1971), as well as an appetite suppressant and anorectic in countries such as France. However, it is not often prescribed these days because of issues with abuse and dependence (Deniker et al., 1975). The molecule is covered by Schedule IV of the 1971 UN Convention; it was controlled as a Class C drug under the Misuse of Drugs Act 1971 prior to the inclusion of other cathinones in April 2010.

In the past, synthetic cathinones could be purchased through a range of legal retail outlets, including convenience stores, gas/petrol stations, 'head'/'smart' shops, 'adult' stores, etc. (Meyers et al., 2015). Over the last decade, the Internet has become a major nexus for information on, and a leading market place for the purchase of NPS in general, but also for this group of psychoactive molecules. In fact, the

anonymity of the Internet has often been proposed as a reason for the growth in use of synthetic cathinones. However, the imposition of so-called 'blanket bans' by national governments, e.g. the Republic of Ireland and the UK, has not only led to the closure of retail outlets such as 'head'/'smart' shops and an open source of NPS, but has driven the market for NPS to the clandestine street market alongside traditional drugs such as amphetamine, cannabis, cocaine and heroin (Shapiro and Daly, 2017), as well as to the deeper recesses of the Internet. Wadsworth et al. (2017) report a possible shift of cathinone sales in the UK from the surface web to the deep web, following the coming into effect of the Psychoactive Substances Act 2016 on 26 May 2016.

9.2.2: Number of synthetic cathinones

At a global level, the UNODC reported that the number of synthetic cathinones identified/reported by member countries and territories rose from 7 in 2008 to 68 by the end of 2014, with about 55 in 2015 (provisional data) (UNODC, 2016b). Over the period 2005-16 the cumulative number of such molecules reported to the EMCDDA was 118, of which 14 were reported for the first time in 2016 (EMCDDA-Europol, 2017); at the time of writing, 31 October 2017, this total has increased to 128.

9.2.3: Number and quantities of cathinones confiscated

The fact that most NPS remain outside international drug control and cannot therefore be seized and reported to the UNODC as part of the regular data collection mechanisms, such as the Annual Report Questionnaire, means that is difficult to get an accurate picture of their movement and supply. To complicate matters further, confiscations of NPS are commonly only notified using a product name or at the substance group level, which prevents data from being linked to a specific substance.

Very few seizures of synthetic NPS were reported in 2010, but the UNODC (2017a) reports that in recent years 23-54 tons have been seized annually. Whilst global seizure amounts have been dominated since 2011 by synthetic cannabinoids, the amount of synthetic cathinones confiscated has risen greatly since they were first reported in 2010. In 2010 and 2011 less than 200 kg were seized, in 2012 and 2013 the quantities doubled to about 400 kg, but seizures trebled between 2013 and 2014, reaching a level of 1.3 tons (UNODC, 2016a). In 2014, most synthetic cathinones were seized in Eastern Europe (692 kg in the Russian Federation), in Western and Central Europe (312 kg in England and Wales) and in East and South-East Asia (226 kg in Hong Kong, China).

The most recent US figures indicate that the number of cathinone 'exhibits' submitted to the National Forensic Laboratory Information System (NFLIS) increased from 15,523 in 2014 to 19,490 in 2015, ethylone accounting for 47% of synthetic cathinone exhibits. (U.S. Department of State Drug Enforcement Agency (DEA), 2016). During 2016 most cathinone identifications conducted by the

DEA's Special Testing and Research Laboratory were for dibutylone (22%), followed by ethylone, N-ethylpentylone and α-PVP; these substances still appear to be most commonly identified in the first three quarters of 2017, although there is some variation from quarter to quarter (DEA 2016, 2017a, 2017b).

The EMCDDA (2017) reports that for the latest annual reporting year (2015) some 80,000 seizures of NPS were made through the EU Early Warning System (EWS). Synthetic cathinones accounted for the largest class of NPS, some one-third or 25,000+ seizures, an increase of more than 17,000 on 2014. The quantity of synthetic cathinones seized in 2015 was just over 1.8 tonnes (1.05 tonnes in 2014). According to the EU EWS, the five most commonly seized cathinones in 2015 were α-PVP, 3-MMC, ethylone, 4-CMC and pentedrone. Where information on country of origin is available, China accounted for more than 1.2 tonnes of the synthetic cathinones seized in 2015. Of these, 42% were 2-MMC (156 kg) and 3-MMC (616 kg). These molecules are chemically related to mephedrone (4-MMC), but are not internationally controlled. The EMCDDA (2017) consider it likely that supplies of these two molecules are being passed off as mephedrone.

The number of mephedrone seizures made by law enforcement agencies in England and Wales rose from 2,002 in 2010/1 (the first full year following control) to a peak of 3,850 in 2012/3 since when the number has steadily fallen to 1,031 in 2015/6. Over the same period, the amount of mephedrone confiscated has followed a similar trajectory: from 231 kg in 2010/1 to 716 kg in 2012/3, falling to 173 kg in 2015/6 (personal communication to first author by J. Hargreaves, Home Office Crime and Policing Analysis Unit, 24 November 2016). In Scotland the police made around 200 seizures of mephedrone each year between 2010/1 and 2012/3 but this has since fallen to only 11 in 2015/6. The amount seized rose from less than 6 kg in 2010/1 to 9 – 10 kg in the following two years, but reached a peak of about 67 kg in 2013/4 before falling to less than 1 kg in 2015/6 (personal communication to first author by H. Mackenzie, Justice Analytical Services, Scottish Government, 3 July 2017). In Northern Ireland the number of seizures of mephedrone powder fell steadily from 286 in 2010/1 to 46 in 2015/6. The amount of mephedrone seized in 2010/1 was 20.9 kg but fell to between 2.3 and 3.9 kg in 2011/2 to 2013/4 before falling to 0.4 kg in 2014/5 and 0.1 kg in 2015/6 (personal communication to first author by PSNI Statistics Branch, 2 December 2016).

9.3: Prevalence

Although mephedrone was first synthesised 90 years ago (Saem de Burnaga Sanchez, 1929), the first use of synthetic cathinones for recreational purposes seems to have been in the mid-2000s. The first wave or generation of synthetic cathinones to come to the attention of the general public, law enforcement and healthcare professionals was methylone in 2005 and mephedrone in 2007. This was at a time when the availability and purity of stimulants such as amphetamines, cocaine and ecstasy (MDMA) were falling and prices were going up, especially in the UK. Although synthesised in 1969

(http://catbull.com/alamut/Bibliothek/Boehringer_MDPV_Patent.htm), MDPV first emerged onto the recreational market in 2009; the number of pyrovalerone derivatives has increased greatly in recent years (Beck et al., 2017). The second generation of synthetic cathinones, such as naphyrone and 4-methyl-*N*-ethcathinone (4-MEC), emerged as replacements for mephedrone, methylone and MDPV when these became controlled in 2010. By this time, the so-called third-generation synthetic cathinones also began to emerge: 3,4-DMMC (3,4-dimethylmethcathinone), then pentedrone (α-methylaminovalerophenone) followed by α-PVP (α-pyrrolidinovalerophenone; α-pyrrolidinopentiophenone) (Valente et al., 2014).

Information on the availability of synthetic cathinones has provided some context against which we can examine the extent of their use. However, there are limitations in respect of the sources we can use to try and achieve this aim, especially with regard to trend data.

International sources

At the global level, the UNODC has not published any prevalence data for synthetic cathinones as a drug class or for individual molecules. However, some national data are available for a few countries.

In the USA little information has been collected on adult cathinone use (Stogner and Miller, 2013). However, the Monitoring the Future survey has been monitoring the drug use of college students and adults aged 19-55 years since 1975. Rather than looking at synthetic cathinones, they monitor 'bath salts'; however, questions were first introduced only in 2012. This was the first national survey in the USA to provide information on bath salts. Whilst the last year use rate was reported in 2012 at 0.8%, 0.6%, and 1.3% in grades 8, 10, and 12, respectively, by 2016 the levels had fallen to less than 1% in all three age groups (Schulenberg et al., 2017). Whilst 0.8% of high school seniors reported using bath salts in the previous year, the level amongst young adults (19-30 years) was typically 0.3%.
In 2012 the annual prevalence rate for males aged 19-22 years was 3.0% compared to 0.5% amongst females of the same age. However, this differential disappeared in 2013, at a time when there was a large rise in the perceived risk of harm from using bath salts; such a shift was also seen in older groups of young adults, as well as 12th graders (18 years). The fall in the use of bath salts and a rise in their perceived risk of causing harm echoes US National Poison Control Centers' data suggestive of a peak occurring in 2012 of their use, with the subsequent decline likely to be due to wide coverage of adverse effects in the media. There is currently little variation in last year use of baths salts across the different regions of the USA. In 2012 use of bath salts appears to have been higher in small towns and farm/country areas, particularly amongst young people, but now rates are very low (less than 1%) across all levels of population density. Use appears to be higher amongst non-college respondents (0.5%) than college students (< 0.05%) in 2016. A study (Stogner and Miller, 2013) of 2,349 students at a South Eastern university in early 2012 found that only 1.07% reported lifetime use of bath salts or MDPV; use was higher amongst men (1.7%) than women (0.5%). In terms of ethnicity, the highest

rates were for Hispanics (4.7%), followed by Native Americans (4.3%), Whites (0.9%), and Blacks (0.7%). Use was more common amongst athletes (4.0%) compared to non-athletes (0.9%).

In Australia, the The Ecstasy and Related Drugs Reporting System (EDRS) has been running since 2003. EDRS is a national monitoring system intended to identify emerging trends of local and national interest in the markets for such drugs. EDRS looks at the price, purity, availability and patterns of use of ecstasy, methamphetamine, cocaine, ketamine, GHB, MDA and LSD. However, it also captures some information on mephedrone. The 2010 sweep of regular ecstasy users, the first to record a synthetic cathinone, found that 21% reported lifetime use of the molecule and 17% had used it in the six months prior to interview (Matthews and Bruno, 2010). This was against a background of increased difficulty in obtaining ecstasy and lower purity levels. Recent use of synthetic cathinones fell from a peak of 18.5% in 2010 to 7.7% in 2015 (Sutherland et al., 2016). Recent use of mephedrone fell from 16% in 2010 to 13% in 2011 to 5% in 2012 and 6% in 2013, whilst use of MDPV increased from <1% to 1% between 2010 and 2011 before increasing to 2.5% in 2012 before falling to back to 15 in 2013; methylone use was 5% in 2011 and 2012, but fell to 3% in 2013 (Sindicich and Burns, 2011, 2013). Based on multivariable logistic regression analysis of the 2010-5 data, recent cathinone use was found to be associated with daily tobacco and poly-drug use. The combined intake of cathinones and cocaine was not statistically significant in the study by Sindicich and Burns (2011). Among poly-NPS users, in decreasing order to prevalence, recent cathinone use was associated with the intake of phenethylamines, tryptamines, synthetic cannabinoid receptor agonists (SCRAs), plants & extracts, arylcyclohexamines, piperazines and aminoindanes (Sutherland et al., 2016).

The EMCDDA has not yet collated any prevalence data for NPS; although whatever information that exists on specific molecules is presented in their Risk Assessment and EMCDDA-Europol Joint Report publication series. Available at: http://www.emcdda.europa.eu/activities/action-on-new-drugs, those currently available on synthetic cathinones only relate to mephedrone, MDPV, and α-PVP. It was estimated in 2012-3 that last year mephedrone use amongst European adults aged 16-59 years reached 0.5% (cited in Karila et al., 2016). Last year use of synthetic cathinones amongst young people aged 15-24 in Finland in 2014 was estimated to be about 0.2% (cited in Karila et al., 2017). In France MDPV and 4-MEC were in the top 10 NPS sold online in 2010-11 (cited in Karila et al., 2017). In 2012, methylone was the 11th most popular hallucinogen in the USA (DEA, 2012). In the Republic of Ireland, 3% of clients at a methadone maintenance clinic tested positive for methylone (McNamara et al., 2010). Past year use of injecting methylone was reported by 7% of male and 1% of female Irish prisoners in 2011 (Drummond et al., 2014).

In Europe, the Eurobarometer surveys on the attitudes of youth/young peoples' towards drugs only looked at "new substances that imitate the effects of illicit drugs" (http://ec.europa.eu/justice/anti-drugs/new-drugs/index_en.htm). Also at the European level, there are no international surveys, such as European School Survey Project on Alcohol and Other Drugs (http://espad.org/) and the Health

Behaviour in School-aged Children (http://www.hbsc.org/) capturing information on use of school-age children on either specific synthetic cathinones or these molecules as a drug class.

At the UK level, the Smoking, Drinking, Drug Use survey carried out on behalf of the Department of Health (England) has tackled this issue. The most recent sweep found that last year use of mephedrone fell from 0.7% in 2012 to 0.5% in 2013 and 2014, and then to 0.4% in 2016 for pupils aged 11-15 years; the rate starting off higher for boys (0.8%) compared to that for girls (0.6%) in 2012, but both having the same rate (0.5%) in 2014, before falling to 0.4% for boys and 0.1% for girls in 2016 (NHS Digital, 2017). In 2016, last year prevalence rates increased with age, as might be expected, for males from 0.0% for those aged 11 to 1.0% for 15 year-olds; for girls it rose from 0.0% aged 11 and 12 years to 0.5% at 15 years. Offers of mephedrone in the last 12 months also increased with age, with 1% boys aged 12 first experiencing offers compared to 4% of 15 year-old boys; for girls the age at when they were first offered mephedrone was 13 (1%), increasing to 3% by the age of 15 years. Whilst one-quarter (24%) of pupils aged 11 had ever tried mephedrone, by the age of 15 years this proportion had increased to 44% in 2016. In Scotland, a survey of students in high schools and tertiary educational institutions conducted a few years earlier found that lifetime use of mephedrone was 20.3%, 4.4% took it daily and 7.6% reported experiencing symptoms of dependence or addiction (Dargan et al., 2010).

Mixmag/Global Drug Survey

One of the longest running surveys of young people and their recreational drug use patterns is the UK Mixmag drug survey associated with the dance music scene, which in recent years has expanded to become the Global Drug Survey (GDS). Though international in reach, most respondents are from the USA or the UK. The most obvious limitation is that participants are self-selected, thus subject to response bias (i.e. those interested in a subject are more likely to respond than those who are not) and may not represent all those young people who use drugs recreationally. The GDS uses non-purposive, non-random, opportunistic sampling methods.

As with other surveys, mephedrone was the first synthetic cathinone to be reported by readers of the Mixmag clubbing magazine in its 2010 survey (conducted in 2009), being the fourth most popular drug; lifetime use was reported at 41.7% and last month use at 33.6%. It was the sixth most common substance used in the month prior to the survey, only bettered by tobacco, alcohol, cannabis, cocaine and MDMA. Mephedrone users tended to be younger and male compared to other respondents. Just over half (54.6%) of individuals who had also used cocaine reported that mephedrone high was of better quality; those using intranasally reported that mephedrone was more addictive and risky than cocaine (Winstock et al., 2011a). Lifetime use of mephedrone peaked in 2011 at 61%, as did last year use at 51%; these fell to 42.7% and 19.5& respectively in 2012, by which time last month use had fallen to 13%. However, last year use by regular UK clubbers was 30% (Winstock, 2012), mephedrone

use continued to decline in 2013: lifetime use was 36.1% and last year use was 13.8%. By 2014 last year use had fallen in the UK to 7.9%, compared to 1.2% in Hungary (Winstock, 2014). At present, there is no information available online regarding mephedrone for the 2015 and 2016 sweeps of the GDS; in 2017 lifetime use in the UK was down to 1.9%; no information is given for the UK in respect of last year use, but the lowest percentage given for any country was 0.7%, suggesting that the UK rate was lower than that (Winstock et al., 2017). Levels of mephedrone use in the USA appear to be much lower than in the UK. For example, in 2012 last year use was reported at only 2%, in 2013 lifetime use had risen to 5.3% with last year use at <5% (Winstock, 2012, 2013).

Other characteristics presented in the Mixmag/Global Drug Surveys include: MDPV first emerged in the 2011 sweep with lifetime use reported at 4.4% and last year use at 3.0%; a year later use in the previous 12 months had fallen to 0.5% (Winstock, 2012). In 2012, 70% reported snorting mephedrone, and 20% swallowed the substance. The following year the proportion snorting had increased to 86% and that swallowing had fallen to 12% (Winstock, 2012, 2013). Nearly half (49%) of respondents in 2012 thought the purity of mephedrone had fallen compared to the previous year; its value for money being rated 5.8 out of 10 in 2013 (Winstock, 2012, 2013). In 2013, the typical price for 1 g of mephedrone was £20, although 47% of UK respondents typically paid less; prior to mephedrone being controlled in April 2010 the price for 1 g was about £10. Over half of respondents (56%) typically used 0.25 to 1 g in a normal session; 10% reported normally using >2g, whilst one-third (33%) had consumed > 2g in a single session and 11% > 7g in a single session (Winstock, 2013).

Additional United Kingdom data

According to the 2016/7 sweep of the Crime Survey for England and Wales (CSEW), lifetime use of mephedrone by 16-59 year olds rose from 1.9% in 2012/3 to 2.3% the following year but has now fallen to 1.8%: rates for 16-24 year olds over the same period rose from 4.5% to 6.3% before declining to 3.3%. The rates for last year use have fallen for the wider age group from 1.3% in 2010/1 to 0.1% in 2016/7; amongst young people the fall was from 4.1% to 0.3% (Broadfield, 2017). These rates represent a fall from an estimated peak of 211,000 reporting use in the year prior to the survey in 2013/4 to only 48,000 in 2016/7. Combining the results from the 2013/4 and 2014/5 sweeps of the CSEW shows that mephedrone was the most likely drug to be used simultaneously with other drugs (68%), compared to ecstasy (57%) and amphetamines (50%) (Lader, 2015).

In Ireland and Northern Ireland, NPS use among persons aged 15-64 years dropped significantly between 2010/11 and 2014/15 according to the fourth drug prevalence survey of households in Ireland and Northern Ireland (National Advisory Committee on Drugs and Alcohol & Department of Health Northern Ireland, 2016). In Northern Ireland specifically, lifetime use of mephedrone rose from 2.0% to 2.5% between 2010/1 and 2014/5, whilst last year use fell from 1.1% to 0.5%, but last month use rose from 0.1% to 0.3% in the same period. Mephedrone usage rates were higher for males than for

females in both periods: lifetime 3.1% and 3.6% for males vs. 0.9% and 1.4%; last year 1.9% and 0.9% vs. 0.3% in both years; last month 0.1% and 0.5% vs. 0.0% and 0.1%. There were higher rates for those aged 15-34 years compared to those aged 35-64 years: lifetime 4.3% and 5.1% vs. 0.4% and 0.7%; last year 2.2% and 1.2% vs. 0.3% and 0.1%; last month 0.1% and 0.5% vs. 0.0% and 0.1%. The declines noted both for NPS and also for mephedrone in Northern Ireland occurred during a period during which national controls on NPS were introduced by both governments and government agencies were raising the awareness of drug users to the health risks associated with NPS.

Both the general household surveys and the Mixmag/Global Drug Surveys have demonstrated a fall in the use of mephedrone in recent years, although the timing is different according to the source, e.g. 2011 in the Mixmag/Global Drug Surveys but 2013/4 according to the CSEW, and 2014/5 in Northern Ireland. These patterns may represent a demonstration of how the diffusion of certain drugs may first appear and peak in specific sub-populations, such as the gay community, before spreading to the dance music scene and then spreading to the wider community.

It is noticeable, that levels of mephedrone use, in particular, were highest within the gay community, even after the UK government introduced controls. Mephedrone emerged from near obscurity to become the most popular illegal drug in a survey of 308 clients of two South London gay dance clubs in July 2010 (Measham et al., 2011). Just over half (52%) of respondents had used mephedrone in the last year, 41% had taken it in the past month and 27% had either taken and/or were planning to take it on the fieldwork nights. The second-generation cathinone “NRG-1” (naphyrone) had been taken by 11% of the sample in the past month and 3% had taken and/or planned to take it on the fieldwork night. Only cocaine was used more frequently than mephedrone; last year use was 59% and last month use was 44%. The majority (75-80% depending on the form) of last month ecstasy users had also used mephedrone during this period, as had two-thirds of cocaine users. Rather than displacing or replacing such stimulants, mephedrone became part of the club drug reportoire, reflecting the trend over recent years towards poly-substance use (Moore et al., 2013). These findings are replicated by another study looking at drug use in similar venues a year later: mephedrone had the highest prevalence of last month use (53.2%) and use on the night of the survey (41.0%); this compares with both cocaine (44.6% and 16.7% respectively) and MDMA/ecstasy (26.9% and 5.8% respectively). Other ‘legal highs’ were used ‘on the night’ to a more limited extent: methoxetamine (1.6%) and 1-benzylpiperazine (0.6%), Spice/K2 (0.6%) and pipradrols (0.6%) (Wood et al., 2012).

In France, research into the chemsex phenomenon found that across 13 Addictovigilance centres between 2008 and 2017, synthetic cathinones occupied 7 out of the 12 psychoactive substances used, in descending order: 4-MEC (61); 3-MMC (48); mephedrone (47); MDPV (17); methylone (4); 4-P (3); and α-PVP (2). This compares to cocaine (52), GHB/GBL (45), methylamphetamine (20), ketamine (11), and MDMA (6); most of these are stimulants. The relative proportions of cathinones in the Addictovigilance database for 2008-2017 were : 4-MEC (34%); 3-MMC (26%); mephedrone (26%); MDPV (9%); methylone (2%); 4-P (2%); α-PVP (1%). Mentions recorded by the national French

Helpline during 2014-7 were: 4-MMC/mephedrone (49%); 3-MMC (22%); 4-MEC (16%); MDPV (9%); methylone (2%); 2-MMC (2%); and α-PVP (1%) (Djezzar et al., 2017).

More generally, we can summarise that recent studies indicate that mephedrone, and most likely other synthetic cathinones, have been added to the established repertoires of psychostimulants instead of replacing or displacing ecstasy and cocaine (Schifano et al., 2017).

9.4: Investigating motivations for using psychoactive substances

Understanding motivations for drug use at an individual level helps to provide information on what factors might drive change(s) in the drug market(s) including the impact of policy changes (Reuter and Pardo, 2017). Such insight can facilitate effective harm-reduction initiatives, and help to anticipate what psychoactive substances may (re-)emerge in the future (Sutherland et al., 2017).

There are a number of ways in which we can gain an insight into the opinions, beliefs, desires and motivations of individuals. At a population level, we have exploited the use of various types of surveys, with a range of theoretical and practical challenges, to see what we can understand about the nature and extent of synthetic cathinone use. However, these patterns are an aggregation and cumulation of multiple and complex decisions by individual members of communities and societies. Reports from medical settings and poison information centres do not provide information about reasons for consumers starting use of these molecules (Ashrafioun et al., 2016).

For an insight into what factors may infuence and shape these decisions, as well as the *nexi* within which they are made, and thus try and understand such processes, it is necessary to consider individual experiences and lives. This could be done through a variety of ethnographic approaches: from individual interviews and focus groups, where access to the target population is straightforward, to using more indirect approaches as netnography (Kozinets, 1998). Here, methods such as conducting thematic analyses of discussions in online drug user *fora*, postings on social media resources such as YouTube, Facebook, Twitter, Instagram, etc., as well as experiences collated by databases such as Erowid (https://www.erowid.org/) can be employed (Davey et al., 2012; Deluca et al., 2012). For some at-risk groups, other types of survey have to be used e.g. online surveys advertised on user fora. These can also be used to find out about what people are using, how and when, why and where, effects (desired and unwanted) using a netnographic approach (Orsolini et al., 2015a). User fora on the open Web and the DeepWeb can not only be used to investigate such as aspects but also can be used to find out about prices, purity, availability, suppliers, etc. (Corkery et al., 2017).

Recently, more advanced techniques, such as social network analyis and analytic tools developed for ‘big data’, have been introduced from the related field of digital ethnography. For example, using

20,000+ drug experiences reported on Erowid, Krieg et al. (2017) argue for the integration of computational and digital data analyses with traditional ethnographic methods. The authors state that their study provided useful insights into the interconnections and relationships across several domains, e.g. drug phenomenology, consumption and harm reduction. This deeper understanding at the collective individual level helps researchers to make sense of developments at the wider social level (Kozinets, 2015; Krieg et al., 2017). Triangulation of information is important as this makes research findings more robust, reliable and generalisable.

Motivations for use of any drug

One can draw a distinction between motivations (which may include more subjective influences) and reasons (which may be more objective, logical, rational and determined, in part, by external influences) for the use of psychoactive substances.

The reasons for an individual using a psychoactive substance can be straightforward and singular or complex and multidimensional. To take alcohol as an example: on the surface, a consumer may consume an alcoholic drink just to enjoy its effects. However, if one starts to consider the context of its use, a wider range of possible influences may be seen as influencing its consumption, e.g. the effects may be more apparent in a specific setting, with certain other individuals, at a particular time, etc. In turn, these may be influenced by perceived needs to 'fit in' with or 'belong' to a particular social group (i.e. to have some sort of 'identity'), to socialise, to not feel isolated, etc.

Dimensions along which motivations (including desires, wants, and needs) for drug use can be described could include:

- Religious/spiritual – as part of a religious ritual (to celebrate 'sacraments' as in 'taking 'communion' using wine or marijuana); to be 'cleansed' or 'purified' (e.g. ayahuasca); to accompany reading a Holy Book; to enhance 'enlightenment', to commune more directly with deities or other spiritual forces;

- Exploratory/experimentation/curiosity – this can range from scientists (such as the late research chemist Alexander Shulgin) designing new molecules, self-experimenting with them and recording their effects, to 'e-Psychonauts' who intentionally experience drug-induced altered states of consciousness so as to try investigating their minds, and possibly address spiritual questions, through such direct experiences, through to 'creatives' such as artists, designers, musicians, writers, philosophers, thinkers and even academics using psychoactive substances to be more original, innovative and 'thinking outside the box' to achieve new insights or understandings of phenomena in the world(s) around them.

- Social/cultural – being part of a social (including religious) group will lead to expectations on the part of others that individuals will conform to particular norms, practices and customs (e.g. peer pressure), thereby confirming their allegiance or belonging to that group; symbolic evidence of this relationship may have to be demonstrated through the consumption of a psychoactive substance, such as at an initiation ceremony, a 'rite of passage', etc. Regular consumption, at regular intervals and settings, may help to reinforce this sense of belonging, e.g. "going out with the boys/girls" to the local bar or pub on a Friday or Saturday night. Loyalty to a group, a nation or its leader may be customary at formal occasions, e.g. 'toasting the bride and groom' or 'toasting the Queen'.

- Recreational – drug use is often associated with particular types of music scene, with specific drug classes being linked to individual genres of music, e.g. 'dance club' drugs; these scenes and their associated drug repertoires can be fluid and evolve;

- Employment/occupational – it may be necessary to taste psychoactive substances as part of one's occupation e.g. wine-taster, brewer, whisky-blender, law-enforcement agent, etc.; to consume it as a religious leader or practitioner (priest, shaman, etc.) during a religious service/rite, e.g. a 'sacrament' such as 'communion' or performing an exorcism; to facilitate business transactions;

- Therapeutic – this could be preventative or to cure (e.g. ibogaine to cure addiction to drugs), to deal with symptoms of a disease or mental health problem (whether prescribed by a health professional or self-medicated), to enhance the effects of another psychoactive substance, to ameliorate the side-effects of another psychoactive substance e.g. during 'come-down' or to facilitate withdrawal;

- Addiction/Dependence – physiological/chemical dependence as well as psychological dependence on, 'craving' for, etc. a substance may develop; the abrupt cessation of use may be potentially life-threatening in some extreme cases.

- Functional – searching for energy (Cadet-Taïrou, 2016); to be alert/stay awake; to stave off hunger, suppress appetite, and weight-loss; passing time/ avoiding boredom, etc. (Van Hout and Hearne, 2015).

These dimensions may well overlap, the boundaries can be blurred and intersect with one another, having different significances as the drug using career/history of an individual evolves. The themes above will be echoed in the following sections.

Motivations for using NPS

The reasons for using NPS and in what contexts are likely to reflect those for illegal drugs: socio-cultural, religious, and recreational use; therapetic/self-medication; functional goals; and exploratory/experimentation/curiosity. Typical reasons for using 'legal highs' include curiosity, pleasure and to get 'a better high than illegal drugs' (Norman et al., 2014). Initial experimentation and continued use may also be driven by such factors as boredom and peer socialisation (Van Hout and Hearne, 2015).

Factors specifically encouraging NPS use include: they are comparatively easier to source; their lower price; and (assumed) better quality and safety compared with traditional drugs. For individuals and groups subject to drug screening, such as prisoners, armed forces, law enforcement agencies, hospital in-patients, individuals undergoing drug treatment or detoxification, drivers of vehicles, trains, aircraft, etc. and the assumed, and actual, non-detectability in tests of NPS can be an important factor.

However, the creation and continual evolution of the Internet and social media appear to effect NPS use, especially 'legal highs', in additional ways and for additional reasons, including: no stigma being attached to their use; they are easily available; they can be purchased anonymously online; and there is no need to have a prescription for medications.

The development of the so-called 'Drugs 2.0' Internet has helped to facilitate a new drug 'scenario', where a new generation of users possessing quasi-expert pharmacological and chemical knowledge and ideas regarding NPS and/or combinations of NPS and known molecules to share information via virtual platforms (Power, 2013; Schifano et al., 2006). Such e-Psychonats also sell and buy NPS and other novel substances through this new cybermarket (Orsolini et al., 2015b; Power, 2013, Schifano et al., 2006). These self-experimenting psychonauts historically typically investigated the "*inner universe*"/"*Psychocosmos*" (Jünger, 1970), often through psychotropic ("*turning towards the psyche*") drugs (Labate and Jungaberle, 2011). These days, they could be referred to as pharmacological 'trippers' (Corkery et al., in press), since, as we saw earlier, they are individuals who deliberately experience states of altered consciousness, that are drug-induced to try and explore their minds, and find answers to spiritual questions via direct experiences (Power, 2013; Labate and Jungaberle, 2011; Carroll, 1987).

Drug use by psychonauts can be regarded as somewhat similar to ritual plant consumption by ancient and current shamans from an anthropological point of view, as they appear to favour mostly NPS with hallucinogenic/entheogenic properties (Orsolini et al., 2016, 2017). However, some consumers of NPS see a clear distinction between the neo-shamanic practices of psychonauts' mental exploration and genuine shaman practice that is healing focused (Power, 2013). Like shamans, e-Psychonauts may be conceived as a 'sub-cultural virtual group', and similarly their chief beliefs and goals often have more to do with the achievement of altered states of consciousness rather than with recreational

purposes (Psychonauts.com, 2017; Reddit.com, 2017). It could be argued (Corkery et al., in press) that the cultural reputation and attraction of NPS mainly derives from their use among e-Psychonauts (Deluca et al., 2012), whose extensive information and experience sharing on the Internet facilitates the difusion of the 'psychonaut cultural phenotype' (Psychonauts.com, 2017).

Earlier, we observed that the context or setting of drug use can influence what is taken. Taking the example of music, Cadet-Taïrou (2016) notes the association of phenethylamines with the 'electro' music scene in France. A range of external factors may influence NPS use in recreational night-life settings: the lower the age and educational level of users the more likely they were to consume NPS in a private setting (home of the user or a friend) rather than in a public setting such as a party or other event; occupational status and whether the consumer is the main salary earner in a household can also influence use of NPS.

As with traditional recreational drugs, temporal patterns can be observed in the consumption of NPS (Corkery et al., 2015). For example, α-PVP, BZP, mephedrone and methylone were mostly used at weekends, similarly to the pattern reported for cocaine and MDMA, whilst opioids and cannabis were used at a consistent level through the course of the week, in a study of waste-water samples analysed in Adelaide, Australia, between 2011 and 2015 (Tscharke et al., 2016).

It was noted earlier that NPS use is higher in some groups compared to the general population, including: young people; people in contact with mental health services; the homeless; people who inject drugs (PWID); and men who have sex with men (MSM) (UNODC, 2017a). A recent Scottish study found that amongst such groups, synthetic cannabinoids were used by 41% of subjects and mephedrone by 19% (MacLeod et al., 2016). Marginalised groups, including the young, socially disadvantaged and homeless with little disposable income, are more likely to be attracted to NPS as they are cheaper but have similar effects (MacLeod et al., 2016; NDEWS, 2016).

Economic factors (drivers, pushers) such as demand and supply, have been associated with the emergence of NPS in relation to the market for traditional recreational drugs, and the subsequent establishment and evolution of the NPS market (Tscharke et al., 2016; Van Hout and Hearne, 2015). Eight years ago the main drivers for NPS use were the poor quality of traditional drugs, especially cocaine, amphetamines and ecstasy/MDMA, and their lack of availability and high price (Corkery et al., in press; Guirguis et al., 2017); ease of access on line, 'value for money', rather than their apparent safety (assumed because of their 'quasi-legal' status) are now the impelling forces, as the quality of such traditional drugs has now recovered to (Winstock et al., 2016; MacLeod et al., 2016) or exceeded their former levels.

Reasons for using natural cathinones (khat)

Cathinone, one of the principal psychoactive constituents of khat (*Catha edulis*), a Central Nervous System stimulant acting on the dopaminergic and other pathways, was assessed in 1985 as being half as potent as amphetamine whilst cathine was assessed as being 7-10 less potent than amphetamine. In many countries the plant is still legal and available, although this situation is changing rapidly. These active ingredients, so-called 'natural amphetamines', can be extracted through chewing, but maximal plasma levels take a long time to achieve in order to give a 'buzz' or a 'high'; therefore, khat's reinforcing properties are far less than other stimulants, e.g. amphetamine and cocaine.

Traditional medicine has been a milieu within which khat has played a long-term role: as a treatment for depression, gastric ulcers, hunger, obesity and tiredness; to relieve vomiting, stomach ache, influenza ; to counter the effects of binge-drinking and hangovers; to treat asthma, coughs and other respiratory conditions; and as an aphrodisiac (Corkery, 2016). In recent decades, khat has been seen as a 'refuge', as a means to mediate stress and trauma occasioned by civil war and cultural dislocation, helping to 'kill time', and forget the troubles of the past. It may help young people deal with the frustrations of a lack of employment and boredom.

Within the male community, khat chewing helps individuals to socialise, facilitate business deals, and the venues where it is consumed provides a context for net-working, sharing information and social-bonding; for females it is mostly for social purposes. As khat-chewing is primarily culturally-bound, it help provides a sense of 'belonging' and social cohesion. Leaves are chewed whilst small groups gather to recite verses from the Koran.

Other functional aspects continue to be important: khat acts as an aid to concentration and prevents sleep whilst studying, thereby improving the chances of academic performance (not proven); helping drivers, night guards, etc. to remain alert and vigilant; provides energy, improved performance and thus increased productivity. These are the main benefits put forward for khat's use, along with it acting as an aid to rest and relaxation.

Why individuals use synthetic cathinones

There is considerable overlap between the reasons for using khat and for using synthetic cathinones. A range of reasons are reported, including: hallucinogenic experiences, euphoria, mood enhancement, openness in communication, empathy, mental clarity, increased alertness, insomnia, stimulation, intensification of sensory experiences, increased energy, reduced appetite, increased sociability, increased libido and sexual performance (Rosenbaum et al., 2012; Schifano et al., 2016), increased confidence (Brookman et al., 2017). 'Problem reduction' is also reported, e.g. mephedrone being taken to alleviate psychological problems and to help deal with emotional issues (Brookman et al., 2017).

Motivations for use of synthetic cathinones have varied over time, in different countries and amongst different user groups. These differences may be due, in part, to the varying patterns in the pace at which the knowledge of and use of synthetic cathinones have spread. For example, mephedrone use first emerged in 'sentinel' groups such as the 'gay' community in London before going mainstream in the UK and other European countries, before the bath salts craze hit the USA. By this time, MDPV was entering the scene and thus the North American experience was not identical to the European one. The highest number of calls to national poison information centres in the USA happened more than a year after the peak in the UK (Spyker et al., 2012).

Increased availability, ease of purchase via the Internet, perceived legality, assumed high purity, perceived better high, fewer side-effects, safer to use and short duration of action have all been cited as reasons for using synthetic cathinones by a sub-sample of ecstasy users in Australia in 2014 (Sutherland et al., 2017). In previous years, surveys of and interviews with users suggested that the increased popularity and convenience of purchasing mephedrone was associated with the unavailability, high price and impurity of several stimulants, chiefly amphetamine, cocaine and MDMA (ACMD, 2010; Carhart-Harris et al., 2011; Measham et al., 2010).

Data collected between April and September 2014 in Hungary from 198 opioid substitution therapy clients showed that these users substituted heroin for NPS, mainly cathinones, because of practical issues in obtaining and using the drugs rather than a preference of their psychopharmacological effects. In decreasing order of significance, these reasons included curiosity, replacing other drugs, increased availability, because their friends used it, more intense subjective effects, low price, legal status, poor detectability, exotic brand name, perceived safety, shorter effect duration and attractive packaging. Patients who shifted and substituted their opioid dependence to cathinones favoured mephedrone, methylone, 4-MEC and MDPV (Kapitány-Fövény et al., 2017; Brettville-Jensen et al., 2013). Brettville-Jensen et al. (2013) added that perceived lack of long- or short-term harm, good ratings from peers or on the Internet, good quality substitutes of low purity cocaine and ecstasy at the time, lack of detection, with an effect that mimics that of ecstasy and other club drugs, are other motivations for use of cathinones. Other practical reasons put forward by users include the range of methods by which they can be used (Brookman et al., 2017).

Medical practitioners, and users, report that the high from mephedrone lasts longer than that from heroin, requires fewer 'hits', can lessen the withdrawal effects of heroin, and may assist in harm-reduction through users migrating from heroin and crack cocaine (with their associated addiction and withdrawal problems) to mephedrone (Brookman et al., 2017).

In the context of chemsex, Djezzar et al. (2017) report the reasons for cathinone use, in descending order of importance, as: increasing sexual pleasure (> 80%); alter consciousness (c. 70%); hard sex (c. 70%); disinhibition (c. 60%); atypical sexual behaviour (c. 45%); prolonging erection (< 10%).

Consumption with other substances

Combining use of synthetic cathinnes with the other classes of psychoactive drugs, particularly stimulants, is very common and to be expected in today's poly-pharmacy recreational drug scene(s), as are counter-acting classes such as downers (sedatives, opiates/opioids, benzodiazepines, GHB/GBL and dissociatives). These drug classes can include prescription drugs, anaesthetic agents and alcohol (Valente et al., 2014).

Consumption of synthetic cathinones with other psychoactive substances may occur since, as with other drug types, they may counter-act the side-effects (e.g. taking alcohol after consuming mephedrone to reverse its side-effects) or prolong the desired-for effects of a molecule, or enhance it in some other way, e.g. make it more potent. Different combinations may be used in different settings and for different purposes For example, mephedrone may be consumed during partying alongside cocaine, MDMA, GBL (γ-butyrolactone) and ketamine (Kirby and Thornber-Dunwell, 2013), whereas in 'chem-sex' sessions MDMA, GBL and methamphetamine may be co-ingested with mephedrone (Bourne et al., 2015). Such combinations induce intensified sexual experiences and increased disinhibition (e.g. leading to risky behaviours, including not using protection during sex, and having multiple partners) (Batisse et al., 2016; Dargan et al., 2011; Karila et al., 2015).

Experiences shared on Bluelight and Drugs-Forum between 2010 and 2015 included: mephedrone being used with Viagra (Cialis) to boost libido and improve sexual perforamnce (e.g. prolonging erection); 4-MEC with 'weed' and GBL during 'chemsex' sessions (Drugs-Forum, 2010a, 2010b, 2015); MDPV with cocaine; amphetamines and methamphetamine for their entactogenic effects; MDPV with beta-blockers to counteract tachycardia; MDPV with GHB/GBL, and 5-MeO-MiPT (5-methoxy-N-methyl-N-isopropyltryptamine) to improve libido; MDPV with zopiclone to enhance visual hallucinations; caffeine for its stimulant effect; famotidine, omeprazole and domperidone to counteract stomach pain; and benzodiazepines for their anxiolytic effects (Coppola & Mondola, 2012; Katz et al., 2014).

Amphetamines, cocaine and ecstasy tablets may be singly or in combination with cathinones to maintain arousal and a state of alertness, since MDMA/serotonergic stimulant and entactogenic effects wear off after a few hours (Schifano, 2004). Theoretically, potential interactions occur between cathinones and prescribed medications. For example, the monoamine oxidase inhibitor moclobemide can be taken to enhance the effects of ecstasy-like stimulants (Vuori et al. 2003). These or selective serotonin reuptake inhibitors (SSRIs) could interact to induce Serotonin syndrome (Green et al., 1995), which can be fatal (Schifano, 2004). Such an outcome can occur when serotonergic release is intensified by parallel use of dopaminergic stimulants, such as cocaine and amphetamines (Huether et al., 1997; Schifano, 2004). Ketamine and/or LSD together with stimulants/cathinones can increase the likelihood of idiosyncratic/intoxicated 'behaviour', such as dangerous driving, with a consequent higher

risk of a lethal outcome. Concurrent use of sedatives could ameliorate excess sympathomimetic overactivity observed with stimulant use, including cathinones (Schifano, 2004).

Reasons for using certain psychoactive substances are arguably wider than purely intentional motivations, as in the sense of a desire, or more strongly a craving for consuming them. Use of synthetic cathinones may be symptomatic of wider influences at work. For example, a representative sample of 30,377 US adolescents from the 8th, 10th and 12th grade participating in the Monitoring the Future study from 2012-2014 showed that motivation for use of both SCRAs and synthetic cathinones was correlated with truancy, cigarette smoking, the use of alcohol and marijuana (Patrick et al., 2017).

Comparison of synthetic cathinones with other stimulants

Whilst some cathinones have behavioural effects, respectively, similar to amphetamine or methylamphetamine and cocaine, others produce effects that are closer to those of MDMA. Typically, four categories of synthetic cathinones are described (Guirguis et al., 2017):

- Cocaine-MDMA-mixed - e.g. mephedrone, 4-MEC, methylone, etylone, butylone and naphyrone. Such molecules are substrates for the dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET). When ingested orally these molecules are associated with an entactogenic, MDMA-like, effect, but when administered intranasally they have a psychostimulant cocaine-like effect (Liechti, 2015);

- Methamphetamine-like - e.g. cathinone, methcathinone, flephedrone, ethcathinone and 3-fluoromethcathinone. Such molecules are monoamine transporter substrates with DAT selective profiles, exhibit high inhibitory potencies at DAT and show lower inhibitory potencies at SERT (Simmler et al., 2013, 2014). Similar to methylamphetamine, they induce DA and NE release (Liechti, 2015);

- MDMA-like - e.g. methedrone and 4-trifluoromethylmethcathinone. Such molecules show a greater inhibitory potency at SERT compared to their inhibition of DAT, whilst inducing release of both NE and 5-HT like amphetamine analogues such as MDMA, paramethoxymethamphetamine (PMMA), paramethoxyamphetamine (PMA), 4-ethylthioamphetamine (4-MTA) (Simmler et al., 2014).

- Pyrovalerone - e.g. pyrovalerone, MDPV and α-PVP. Such molecules are non-substrate transporter inhibitors, exhibiting inhibitory potencies at DAT and NET equal or greater than cocaine (Baumann et al., 2013) or methylamphetamine (Aarde et al., 2013). Both MDPV and α-PVP are regarded as cocaine-like molecules (Smith et al., 2017). However, recent research

suggests that the pyrovalerone analogue α-PVT possesses rewarding and reinforcing effects akin to both cocaine and methylamphetamine (Cheong et al., 2017).

Some users reported that a cathinone-induced stimulant effect is comparable to methylphenidate at low doses or to a combined effect of both amphetamine and cocaine at high doses (Coppola and Mondola, 2012). Others consider cathinones to be pharmacologically similar to and as potent as amphetamine, cocaine, and MDMA (EMCDDA, 2012a).

The 'honeymoon' period for mephedrone lasted for a few years. It slowly became apparent that compared to cocaine and MDMA, mephedrone had some less favourable effects. Winstock (2012) reports that users ceased their 'love affair' with mephedrone, in part, due to its higher scores for extreme agitation, headaches, tremors, nausea and feeling depressed after use, and to a lesser extent paranoia and chest pain. In terms of positive effects of using drugs, mephedrone came second out of ten drugs for increased pleasure from social interactions, but had more negative effects, i.e. first for not being able to function normally in the days after use, negative effects on mental health; second for negative effects on ability to work/study/progress, negative effects on physical health; third for unpleasant physical and psychological effects when intoxicated (Winstock, 2013).

Use of specific types of synthetic cathinones

Typically, the literature classifies cathinones according to their pharmacological action and in comparison to more traditional stimulant drugs. However, there is no consensus on how to do this, or the categories to be used. Some approaches look at effects in terms of different substrates or non-substrate transporter inhibitors (Simmer et al., 2013). Others draw comparisons with certain 'classical' classes of traditional drugs of abuse, i.e. MDMA, amphetamine/methylamphetamine, cocaine (Concheiro et al., 2013), or even combinations such as MDMA/cocaine, together with chemical structure categories (Valente et al., 2014; Concheiro et al., 2013; Assi et al., 2017). Some of these approaches also single out pyrrolidines as a separate group. These approaches lead to overlapping of categories and blurred distinctions.

Attempting to establish a connection between different types of cathinones based on their DAT/SERT inhibition ratio, structural characteristics or other parameters and their similarity to traditional stimulants is difficult in the context of non-psychonaut consumers. An ideal solution in terms of categorising synthetic cathinones would be to employ a single criterion in terms of their similarity to the effects of 'classical' drugs of abuse. Therefore, a pragmatic approach has been adopted for a study being conducted by the lead author and colleagues into motivations for using specific types of synthetic cathinones, i.e. similarity to the effects of these classical drugs or combinations thereof, and the pyrrolidine group: amphetamine/methylamphetamine-like; cocaine-like; MDMA-like; MDMA- + cocaine-like; and pyrrolidines/pyrovalerone-type.

However, there are problems with ascribing particular effects to specific cathinone molecules or particular classes or families of cathinones.and asking users about them. The wording of questions has to be very clear as to which of these is actually being asked about. It is unlikely that a non-pyschonaut user will appreciate the distinction. It may even be the case that only very few psychonauts will feel it necessary to distinguish in this way what they consume.

The number of papers which have come closest to achieving this is very small, i.e.: Winstock et al. (2011a); Cahart-Harris et al. (2013); Johnson and Johnson (2014); and Ashrafioun et al. (2016). The first paper demonstrated that a web-based survey recruiting from an existing survey (Mixmag) could be employed to study users' experiences, but only contained a limited number of questions exploring motivations for use of particular types of synthetic cathinones. The second study also used a web-based survey, recruiting through advertisements on user fora, to ask about specific subject effects but did not investigate reasons for use. The third study followed a similar recruitment strategy to the second one and did get some information on reasons for using 'bath salts' as a generic class of drug: curiosity; mind/brain exploration; liking the effect; to remain alert/awake; to avoid failing drug tests; to enhance sexual experiences.

The fourth study listed above, set out to overcome the limitations of the previous three, using online recruitment through advertisements on specific websites; put a recruitment video in YouTube and purchased targeted advertsements on Facebook (Ashrafioun et al., 2016). The commonest reasons, in decreasing order for first trying synthetic cathinones were: curiosity, believing incorrectly that they were taking another substance; social pressure; having been offered 'bath salts'. The main reasons given for consuming 'bath salts' were: fun/enjoyment/euphoria/rush; curiosity/new experience; substitution for another drug; being at a party/event. The authors note that the effects and motivations echo those who use other illegal stimulants, and are similar to those of the previous three studies.

The co-consumption of several synthetic cathinones may occur. If a drug user consumes a branded product they may unintentionally take a number of different synthetic cathinones at the same time, as suppliers may seek to use up old stocks of molecules which have subsequently become regulated or controlled, to test the market with 'new' molecules, or to produce several different effects. Many of the structural pyrovalerone analogues that replaced MDPV in the cathinones market possess similar mechanisms of action and pharmacological effects. As these molecules were offered for sale with the same brand names, this fact was not evident to buyers or to consumers (Beck et al., 2016). During the period January 2011 to March 2016, the STRIDA project in Sweden recorded 11 pyrovalerone drugs in addition to MDPV and α-PVP across 114 intoxicated patients with 149 total pyrovalerne-type findings; only 8 patients had used a single cathinone, one patient had used 5 pyrovalerone molecules in combination. Co-administration of pyrovalerones and/or use in combination with amphetamines suggests that rather than using a specific pyrovalerone, patients were principally interested in obtaining a central stimulatory effect (Beck et al., 2017). Discussions on online user fora also suggest

that as well as suggesting particular combinations of cathinones, some suggest combining 4-MEC with the amphetamine-type 4-FA (Van Hout, 2014).

In addition to this, adulterants and cutting agents may be added to counter-act side-effects, or since they have a similar chemical structure to index molecules they may add to the complexity of the mixture, and have a stronger /masking detection signal hindering identification (Guirguis et al., 2017). On the other hand, some branded products may contain undisclosed synthetic cathinones; this could be very dangerous for consumers.

Reasons for the deliberate consumption of several cathinones may include, one could conjecture, a desire to self-harm or to attempt suicide (perhaps as 'a cry for help' or as a serious but unsuccessful attempt to kill oneself). Such a reason may be due to the panoia or depression induced by synthetic cathinones (Corkery et al., 2012). Another reason for co-adminstering cathinones, may be a belief that taking two or more synthetic cathinones simultaneously can cause a synergy between them, leading to an enhanced experience (Iversen et al., 2014). Rat studies suggest that the co-adminstration of MDPV, mephedrone, and methylone may intensify their associated neurochemical effects via a sustained increase in DA and 5-hydroxytryptamine (5-HT) in various brain regions through an additive effect (Allen-Campbell et al., 2016). Binary mixtures of common 'bath salts' constituents (i.e., MDPV, methylone, and caffeine) are generally additive in nature; however, both supra-additive (MDPV+caffeine and methylone+caffeine) and sub-additive interactions (MDPV+methylone) can be observed (Collins et al., 2017).

9.5: Stopping use of cathinones

As was the case with reasons for initiating and continuing consumption of synthetic cathinones, so with stopping use of them, in terms of drawing a distinction between motivations and reasons for doing so. Here again, the possibility of overlap and reinforcement does exist.

Dealing first with motivations, tolerance, dependence and withdrawal symptoms have been reported by many synthetic cathinone users. However, there is little published information to date on tolerance, craving, dependence/addiction and withdrawal in respect of these aspects (Prosser and Nelson, 2012). Ross and Peselow (2009) suggested that "the dopaminergic stimulation of the reward system could explain the development" of these consequences. These factors can create difficulties in ceasing cathinone use. In respect of mephedrone, users have reported tolerance, craving (being 'moreish'), need to re-dose, loss of control, addiction and stimulant withdrawal syndrome; echoing those found amongst amphetamine and cocaine dependent individuals (Bajaj et al., 2010; Carhart-Harris et al., 2011; Dargan et al., 2010; EMCDDA, 2011; Reed, 2010; Winstock et al., 2011b; Brookman et al., 2017). Evidence is lacking on these issues in respect of methylone (Karila et al., 2016). For MDPV there is some limited animal evidence for some of these features (tolerance,

craving, dependence and withdrawal syndrome) (Coppola and Mondola, 2012; Gannon et al., 2017). The structural parent of MDPV, α-PVP appears to give rise to extreme craving and risk of binge-consumption (EMCDDA, 2016b).

Unpleasant physical and mental symptoms may be experienced when going through withdrawal from synthetic cathinones. Feelings of depression and anxiety following use of mephedrone have been reported, but no physical withdrawal syndrome has been described (Dargan et al., 2011; Prosser and Nelson, 2012). Tiredness, insomnia, nasal congestion and impaired concentration have also been described as symptoms indicating mephedrone withdrawal (Winstock et al., 2011b). Pyschological dependency is possible in terms of mephedrone (Dargan et al., 2011). Following the abrupt stopping of chronic mephedrone, methcathinone and MDPV, some users have reported symptoms of anxiety and depression, craving, anhedonia, anergia and insomnia (Centers for Disease Control and Prevention (CDC), 2011; Winstock et al., 2011a).

Whilst Van Hout (2014) notes that 4-MEC users did not report withdrawal symptoms akin to those of mephedrone (i.e. depression, anergia, anhedonia, or insomnia), there is a case-report of neonatal withdrawal syndrome in a baby whose mother was a chronic 4-MEC user “The newborn presented with increased jitteriness and irritability, highpitched cry, hypertonia in the limbs and brisk tendon reflexes” (Pichini et al., 2014).

In terms of treatment for cathinone withdrawal, bupropion has been suggested (Coppola and Mondola, 2012; Lev-Ran, 2012).

Other motivations for cessation of use may include: previously experienced health harms, including negative impacts on physical and mental well-being, e.g. personality change, as well as not liking consuming NPS (MacLeod et al., 2016), including cathinones. The most common adverse reactions due to cathinones use are restlessness and anxiety, ranging from mild agitation to severe psychosis. Furthermore, tachycardia, hypertension, abdominal pain, chills, flushing, sweating, hyperthermia, renal failure, rhabdomyolysis, and seizures can also be observed (Schifano et al., 2017).

Reasons for discontinuing use can include social pressures, e.g. peer-pressure. Negative effects on relationships with family and friends could act as an incentive to change (Ashrafioun et al., 2016; Brookman and Bennett, 2017; Brookman et al., 2017). Additional experiences which may also influence change include: recognising that one has neglected responsibilities; missing school or work; feeling that use is a problem; realising that money spent on buying cathinones could have been used for other purposes; shame/embarrassment; avoidance by others (Ashrafioun et al., 2016).

Additional economic factors that could influence reduced consumption of synthetic cathinones or even cessation of use are the corollaries of those influnces which helped push their use in 2009-11:

increased price, reduced availability or reduced quality of cathinones; increased availability and quality of amphetamines, cocaine and ecstasy/MDMA.

Such external reasons or drivers such as those briefly outlined above are more lkely to be influenced by policy and treatment, thereby making individuals more receptive/susceptible to change.

Reasons to stop cathinone use

Major reasons for encouraging individuals to stop their use of synthetic cathinones include the potentially very serious physiological and psychiatric/psychological consequences that may occur. These, as a result of chronic use of both natural and synthetic cathinones, can include: suicidal ideation, attempted suicide, as well as completed suicide; paranoia, including audio and visual hallucinations; psychoses; depression; mood disturbances; sleep deprivation; loss of appetite leading to rapid weight-loss (Brookman et al., 2017).

Other reasons to stop can include: the avoidance of acquisitive crime to fund use; fear of acquiring a criminal record and/or being imprisoned; reducing the potential for violence when under the infuence; debt-avoidance; avoiding loss of employment and/or being made homeless (Brookman et al., 2017; Brookman and Bennett, 2017).

Injecting behaviours and blood-borne infections

The injecting of NPS is of increasing concern in Europe, the USA and elsewhere. There are several aspects to this issue, which will be briefly described, as the consequences of injecting synthetic cathinones can be very serious and injectors/users need to be aware of/educated about these in the hope that they will make rational decisions in relation to these risks.

Injecting drugs, especially powders or crushed pills (the commonest form of synthetic cathinones) diluted in a liquid, can cause damage to the injection sites, venous system and cause blockages such as thrombi – with associated risks of death. Injecting stimulant users are likely to inject more frequently due to their relatively short length of action, and share contaminated injecting equipment, thereby increasing health risks (Fischer et al., 2013; UNODC, 2017a).

At-risk populations include subgroups of Men having sex with Men (MSM), “long-term abstinent former opiate users, people who inject other drugs such as heroin and amphetamines, people who switch to injecting synthetic cathinones and people who have switched from snorting to injecting” (UNODC, 2017a). Such changes have occurred in Hungary during 2011-5 (Tarján et al., 2017). Typical synthetic cathinones injected by PWID in Hungary changed over time: 2010 mephedrone; 2011 MDPV and 4-

MEC; 2012-3 pentedrone; 2014 α-PVP; 2015 α-PHP (Rácz et al., 2015; Péterfi et al., 2014; Hungarian Focal Point, 2015).

Within the Chemsex context in the UK, synthetic cathinones/mephedrone misuse, either on their own or together with methamphetamine and/or GHB/GBL, especially in the MSM sub-population, has been associated with unprotected sex practices, sharing syringes, and highly elevated risk of the spread of blood-borne and sexually transmitted diseases including HIV and hepatitis C (Bourne et al., 2014, 2015; UNODC, 2017a). HIV rates amongst synthetic cathinone injectors appear to be higher than in 'traditional' drug injecting populations, e.g. Mephedrone, MDPV and methylone injectors in San Diego, California (Wagner et al., 2014), in Ireland amongst homeless α-PVP injectors who often reused syringes and shared filters (Giese et al., 2015); English mephedrone injectors (PHE, 2015); and pentedrone injectors in Hungary (Rácz et al., 2016).

Morbidity and mortality

A detailed description of the adverse medical consequences, including death, resulting from the use of synthetic cathinones is outside the scope of this chapter. However, it is important for (would-be) users of such molecules to be aware of the potential risks to which they may expose themselves. This may influence their decisions to use in the first place, make changes in their practice(s), or even stop.

Intoxications, hospital admissions

Cathinones are also characterised with increased presentations to emergency departments for both physical and mental health associated toxicity (UNODC, 2017a). For example, during 2011 there were 22,904 visits to US Emergency Departments (ED) recorded by the Drug Abuse Warning Network (DAWN) as caused by bath salts. This represented about 0.9% of all ED visits. One-third of cases involved solely bath salts, 15% were implicated with natural cannabis or synthetic cannabinoids, and 52% with combinations of other drugs (DAWN, 2013). In Florida between September 2014 and December 2015 an outbreak of α-PVP use was associated with 80 deaths and thousands of ED admissions, many from excited delirium syndrome - hyperstimulation, paranoia and hallucinations that can lead to violent aggression and self-injury (NDEWS, 2016).

The Euro-DEN project compiled information on 10,709 ED admissions across 16 centres in 10 European cities for the period 2014-5. NPS accounted for 7.3% of admissions; of which 61.2% were cathinones (mephedrone 73.9% of these). There were 9 deaths related to NPS out of a total of 67: all of these involved cathinones (Dargan, 2017).

A retrospective study conducted in Germany over a 6-year period between January 2010 and January 2016 on cathinone self-reported users presenting to emergency departments due to cathinone-related complications revealed that 64 % of patients (n = 81) were males with a median age of 34 years (Romanek et al., 2017). In this study, cathinones which related to higher rates of intoxications were MDPV, methylone and 3-MMC, in reducing order of frequency (Romanek et al., 2017).

Fatalities

A range of synthetic cathinones (including mephedrone, methylone and butylone, ethylone, α-PVP, MDPV, and methedrone) has been associated with fatalities (Schifano et al., 2017). This is especially true in the UK, where the number of synthetic cathinone-related poisoning deaths rose from 6 in 2010 to a peak of 49 in 2015, falling to 25 in 2016, with a cumulative total of 157. The majority (122) of these involved mephedrone (ONS, 2015, 2016a, 2016b, 2016c, 2017a, 2017b). In Scotland, the number of cathinone deaths registered rose from 1 in 2009 to 8 in 2010, falling to 6 in 2014 and 2015, and down to 1 in 2016, with a cumulative total of 32. The majority (17) of these involved mephedrone (NRS, 2017). In Northern Ireland, the number of cathinone deaths registered rose risen from 1 in 2010 to 3 before falling to 1 in 2016, with a cumulative total of 27. Only 6 of these involved mephedrone (NISRA, 2016; and personal communication to lead author for provisional 2016 data). In summary, since 2009 the cumulative total of synthetic cathinone-related poisoning deaths registered in the UK by the end of 2016 was 216, of which 145 involved mephedrone.

In a three-year review of NPS detected in 203 in-life or post-mortem blood and urine and in UK criminal case works, mephedrone and 4-MEC were the most common NPS identified. Interestingly, all fatalities related to cathinones in this review were hangings and mechanical suicides (Elliott & Evans, 2014). Another 3-year review conducted in Poland, from 2012-2014, for 112 cases, where NPS were identified in biological material from people driving under the influence of drugs, cathinones were prevalent in 88 % of the cases. In decreasing frequency, these were: 3-MMC, α-pyrrolidinopentiophenone (α-PVP), pentedrone, 3',4'-methylenedioxy-α-pyrrolidinobutyrophenone (MDPBP), ethcathinone, mephedrone, methylene- dioxypyrovalerone (MDPV), 4-methylethcathinone (4-MEC), buphedrone and methylone (Adamowicz et al., 2016).

9.6: What challenges might the future hold?

The different constituencies dealing with NPS are likely to continue facing challenges which may further compound the problem of getting a comprehensive understanding of synthetic cathinones.

Further new synthetic cathinone molecules are likely to appear, leading to not only intoxications but also to psychoses, paranoia and other psychiatric issues. Deaths are also likely to continue, especially against a background of polysubstance consumption.

There are reports of 'vaping' equipment being used to administer NPS/'legal highs' (Jones, 2016; Thurtle et al., 2017). There is some evidence of this occurring with mexedrone (Roberts et al., 2017), so it is conceivable that users of other cathinones could experiment with such a method of administration.

Following the introduction of 'blanket ban' legislation in countries such as Ireland and the UK, and disappearance of 'smart' or 'head' shops, it is likely that the Web (Surface and Deep) will increasingly utlised to source supplies of synthetic cathinones. NPS now being traded alongside traditional 'street' drugs such heroin, cocaine and cannabis in clandestine street drug markets (Shapiro and Daly, 2017).

9.7: Conclusions

This chapter has looked at the current and emerging knowledge and challenges of synthetic cathinones from epidemiological, anthropological and clinical pharmacological perspectives. With so much remaining unknown about a wide range of issues concerned with NPS, including synthetic cathinones, the need for inter-disciplinary approaches to the ever-evolving NPS phenomenon is clearly demonstrable. The need for timely, up to date information and the development of methods to understand the potential characteristics and properties of new molecules still remains. Forensic as well as socio-anthropological approaches are required to have a deeper understanding of synthetic cathinones and the implications of their use. This will help policy-makers, educationalists, health and other professionals, service providers and funders to develop responses including prevention and intervention initiatives. Furthermore, (would-be) psychoactive substance users can be assisted in making more rational decisions about synthetic cathinones.

The key dimensions that need documenting are the human ones of why people are looking for new synthetic cathinones, amongst other available NPS, what effects they are seeking, what they are actually taking (how, where and when), and what the consequences of their actions may be. Furthermore, external influences or factors which could may play a causative role in how these play out also need to be understood. The use of historic or traditional methods of epidemiology can play a part, but new and innovative approaches need to be continually improved and developed in a world of increasing reliance on rapid electronic exchange and dissemination of information.

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Some of this material has been presented as an oral presentation:
John M. Corkery (presenter), Amira Guirguis, Laura Orsolini, Duccio Papanti & Fabrizio Schifano (2017). Oral presentation. An investigation into the relationship(s) between the different chemical classes of synthetic cathinones and their effects: desired, adverse and toxic. Fifth international conference on novel psychoactive substances. United Nations Office On Drugs and Crime (UNODC) Vienna International Centre, Vienna 23-24 October 2017.

Conflicts of interest

The authors are unaware of any potential conflicts of interest. However, F.S. is a full member of the UK Advisory Council on the Misuse of Drugs (ACMD) and its NPS Committee; J.C. was a member of the ACMD's Working Groups on Drug-related deaths (1999-2000 and 2016-7), and is currently a co-opted member of the Technical Committee (2016 to date) and NPS Committee (2009 to date). JC was responsible for producing drug statistics for the Home Office (1994 - 2002), acted as the UK Focal Point on Drugs' expert on drug-related deaths and mortality related to drug use (2000 - 2015), and also contibuted to the UK Annual Report Questionnaire to the UNODC over the period 1994- 2013. The views expressed here reflect only the authors' views and not necessarily those of the Home Office or the ACMD.

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