**The public health evidence-base on novel psychoactive substance use: scoping review with narrative synthesis of selected bodies of evidence**

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**Abstract**

Background: This review aimed to address what was known about the public health burden associated with novel psychoactive substances (NPS) use, and the effectiveness of responses targeting NPS use and/or associated problems.

Methods: Relevant literature was identified through a range of searches covering the period from January 2006 to June 2016. Data synthesis was undertaken in three stages. Firstly we mapped the evidence available in order to characterise the literature according to a set of analytic categories developed a priori. Secondly, we identified evidence gaps from a set of a priori research questions. Finally, we then undertook a narrative synthesis of selected bodies of evidence, interpreting data using a conceptual framework specifically designed for use in this review.

Results: 995 articles were included in the scoping review with the majority being case reports/ series on individual level adverse effects due to NPS use. We synthesised UK data from 29 surveys and 7 qualitative studies, and international data in 10 systematic reviews on harms associated with NPS use, and 17 evaluations of policy responses. We found little data on risk factors, harms associated with long term NPS use, and interventions.

Conclusion: In all cases we found the available evidence to be at an early stage of development.

**Background**

Novel psychoactive substances (NPS) are defined as psychoactive drugs not prohibited by the United Nations conventions on drugs.1 This definition constitutes a diverse category of drug classes (e.g. synthetic cannabinoids, synthetic cathinones, phenethylamines).2 3 Most NPS are the result of minor changes to molecular structure of well-known legal or illegal drugs (such as cannabis, opioids, ecstasy).

There is debate on the scale of challenges posed by NPS. For example, general population surveys suggest the prevalence of NPS use is relatively low.4 However, the speed of technological innovation and ease of synthesising NPS present substantial challenges to regulatory authorities.2 3 5 6 For example, in 2014, 101 newly identified NPS were reported to the EU early warning system.5 The rapidly evolving nature of NPS makes it difficult to assess both current and future harms associated with their use. There are also substantial innovations in global marketing and supply of NPS through the internet that provides a potential platform for growth in NPS use.

Uncertainties associated with the current and future public health burden of NPS suggest the importance of synthesising available data to inform national and international responses, including for research agenda setting. There is need to estimate the scale of the problem and potential health inequalities; for example, if use is more common in particular subgroups, or if subgroups experience greater harms due to NPS use. Secondly, it is currently unclear what is known about the problems (any acute or chronic health-specific, social or wider harm due to NPS use, experienced by the user or others) associated with NPS, including risks associated with particular substances, in order to inform interventions. Thirdly, there are issues to do with the availability of interventions for NPS users (including whether some sub-groups have lower levels of access to, or engagement in, treatment than other users with problems) and whether there are intervention effectiveness data. Current guidance (e.g. Novel Psychoactive Treatment UK Network (NEPTUNE)7) recommends the adaptation of generic psychosocial interventions for illegal drugs, and therefore we were interested in whether subsequent studies have investigated the effectiveness of these interventions in NPS users. Given the high number of newly identified substances by early warning systems in the UK and the EU, and uncertainties regarding the current and future public health burden of NPS in the UK, we were commissioned to conduct a review to address these challenges and to identify research priorities for NPS in the UK.

**Objectives**

The study objectives were to:

1. Conduct a scoping review of the international literature on NPS use, related health and social harms (any acute or chronic health-specific, social or wider harm due to NPS use, experienced by the user or others) and public health responses (any intervention at policy, health or other service, or clinical levels, aimed at addressing NPS use and/or related problems).
2. Identify key gaps and more developed areas of the NPS literature, judged most relevant to UK public health research, which may benefit from further exploration through narrative synthesis.
3. Conduct narrative syntheses of selected areas of the NPS literature

To inform these objectives we developed the following research questions *a priori* to identify key gaps and literature that warranted further narrative synthesis:

1. What are the prevalence and patterns of NPS use in the UK general population and do they differ in particular subgroups of the population?
2. How do existing patterns of both legal and illegal drug use and social and other risk factors influence NPS use?
3. Which other population-level risk factors influence NPS use?
4. Which acute intoxication problems are associated with NPS use?
5. What problems are associated with long-term regular NPS use?
6. In addition to intoxication, long-term regular use and dependence problems, are there other types of NPS-specific problems or other problems associated with NPS use?
7. Are there dedicated primary or secondary prevention interventions in the UK, and if so what is known about their outcomes?
8. Which generic interventions (early in life and early in drug using careers) target NPS?
9. How extensively does current generic UK drug prevention practice cover NPS?
10. How good are treatment outcomes for NPS?
11. What promising approaches are currently available, or can be made available, in the UK for intervening with NPS use?
12. What are the population-level or social structural factors limiting the effects of individual-level interventions?
13. What is the nature of the current early warning systems (EWS) provision?
14. Are there sentinel populations capable of being monitored to provide early warnings of new trends?
15. What are the issues raised by uncertainties about the identities of substances being used?

**Methods**

**Scoping review work**

Briefly, we outline below the methods used in our review (for further details, see appendix 1 and also Mdege et al8). Literature search strategies are summarised in Box 1.

***Inclusion criteria***

Participants/ population

We included studies on novel psychoactive substance use, problems and responses (for definitions see appendix 1). Studies on animals only were excluded.

Context

There were no restrictions on context or location for the scoping review, but some narrative syntheses (see later) were restricted to UK studies.

Study design

No restrictions on study design were applied. Commentaries and letters were included if presenting new primary or secondary data. Non-English language publications were excluded.

***Article selection***

Screening of titles and abstracts were conducted by two authors (NM and NDM) using selection criteria described above, discrepancies resolved through discussion with third author (JM).

***Data extraction***

The data extraction form was designed and piloted by two authors (NM and NDM). The following data were extracted:

• General characteristics: location, setting, study design, publication type.

• Population characteristics: age, gender, ethnicity, sample size, novel psychoactive use status.

• Novel psychoactive substance type

• Principal focus (use, problems, responses)

Data from each article were extracted by one author and checked by another, with discrepancies resolved by a third author. Authors were contacted for missing or unclear data.

***Risk of bias (quality) assessment***

No risk of bias assessment was conducted, for further discussion of this decision see evidence map section below.

***Evidence mapping and narrative synthesis***

We conducted a scoping review of all relevant material to map the available evidence (see Appendix 1 for further details). The extracted data was utilized by one researcher to map the literature according to principal focus (use, problems/harms or responses), NPS type, study design, region, setting, year of publication and publication type. This was checked by another researcher.

We used these data to conduct an evidence gap analysis based on our *a priori* research questions (see above). The literature was judged to be at an early stage of development such that the benefits of conducting detailed risk of bias assessments were not justified. Selected areas were pragmatically judged to be most promising in terms of having sufficient data to synthesise and likely value in informing thinking about the development of UK public health research priorities.

**Results**

A total of 13,772 records were identified through electronic databases searches. A further 3,260 were obtained through other sources including contacting key researchers and policy experts (Appendix 3). Results are summarised according to three stages of the review: initial evidence mapping of all studies (i.e. scoping review), gap-analysis, and narrative synthesis of selected areas of the literature.

***Scoping review***

General characteristics of the 995 included articles are briefly summarized (Appendix 4). Majority of articles reported on problems. Synthetic cannabinoids and synthetic cathinones were most reported on. Most studies were conducted in general hospital settings, followed by specialist settings. Within hospital settings, most articles were in emergency departments (236 reports), whilst for specialist settings most articles were in poison centres (65 reports). 252 of the included reports were not specific to a particular setting.

*Year of publication*

Appendix 5 plots number of included records per year from 2006 to 2015. From 2006 to 2009 there were few publications on NPS, however published records increased sharply from 2010 onwards. While there is a slight dip in 2015, this is most likely explained by a time lag between date of publication and date added to bibliographic databases. We further investigated whether the increase in publications on NPS from 2009 onwards was a general trend or limited to a particular issue within the NPS literature, and found publications across the literature as a whole.

*Geographical location*

The largest number of studies were conducted in Europe (n=385), followed by North America (n=294) and Australia/New Zealand (n=58). Within Europe, the largest number were conducted in the UK (n=185). However, it should be noted the grey literature search particularly reflected UK data sources therefore UK research may have been over-represented. In addition searches were limited to English language only.

*Study design and principal focus*

Most common study designs were case reports/case series (n=367), followed by evidence syntheses (n=211), largely of case reports. There appears a large volume of early preliminary data, as well as a concerted effort to grapple with challenges of researching this topic.

Unsurprisingly, the literature is dominated by studies investigating problems associated with NPS (773/995 records). There is also a growing literature on the prevalence of NPS use, with 130 records presenting survey data internationally. While there were a number of policy discussion papers (n=84), studies are only beginning to quantitatively evaluate policy interventions (n=17). There were also a growing number of case reports and reviews discussing the clinical management of NPS, although these were largely focused on managing an emergency.

*Type of NPS*

The most commonly investigated type of NPS were synthetic cannabinoids (n=310), followed by synthetic cathinones (n=271), and then the more generic category of any NPS (n=259).

We also examined regional variations in studies of NPS type. Synthetic cannabinoids, synthetic cathinones and phenythylamines were most commonly investigated in North America. Research on piperazines was more commonly investigated in Australia or New Zealand. In the UK and the rest of Europe there was more of a focus on generic NPS use.

**Evidence gap analysis**

We used the findings of the scoping review to identify major gaps in the literature in respect of our *a priori* research questions i.e. those that we deemed needed to be addressed from a public health perspective. This exercise enabled us to identify emerging data that were suitable for more detailed narrative syntheses, as presented below.

*Use*

Although we identified a large number of relevant reports, the evidence base is at an early stage of development. We identified a number of studies on prevalence and patterns of NPS use. Given the UK focus of the research funding we decided to conduct narrative syntheses on UK populations only. We found little data on sociodemographic or other risk factors, other than age or gender, that influence NPS use prevalence.

*Problems*

The majority of data on problems associated with NPS use were based on case studies or case series of people presenting to emergency departments, and elsewhere with similar acute presentations. This is a large literature (over 300 reports) but given the limitations of these data (i.e. they mainly consisted of case reports) we judged it would be more appropriate to summarise the findings of systematic reviews that synthesise this literature. However, data on long term regular NPS use and the associated social/health harms (e.g. dependence) have received less research attention. There is almost no epidemiological data on long term harms but there is a small qualitative literature,19 34 36 38-42 from which UK studies were synthesised.

*Responses*

Data on responses to NPS use and related problems were very limited. We did not find any data specifically investigating the effectiveness of interventions (either specifically developed for NPS users or generic interventions adapted for NPS users) for improving outcomes in NPS users. However, there is an emerging evidence base in policy responses to NPS which we judged warranted further evidence synthesis.

**Narrative synthesis**

*UK survey data*

We identified 29 studies reporting survey data on NPS use in UK (see Table 2).9-37 Strongest evidence (from nationally representative samples) was for mephedrone, where the Crime Survey for England and Wales (CSEW) and the Scottish Crime and Justice Survey (SCJS) have been conducting national surveys since 2010-2011. Lifetime mephedrone use is uncommon in adults in the general population (approximately 1-2%) but is about two to three times more prevalent in men than women, and also among young adults compared with older adults. Prevalence rates of recent mephedrone use are declining substantially. For example, past year prevalence of mephedrone use declined from 1.3% in 2010-2011 to 0.5% in 2014-2015 (CSEW, 2015).13

Nationally representative data on NPS use as a whole and on particular NPS other than mephedrone are less developed. While SCJS have been collecting data on generic NPS use since 2010/2011 specific substances included in this category have changed over time (for example, mephedrone is no longer considered a ‘new drug’ in the survey) which makes comparisons of prevalence estimates across years difficult. In addition, CSEW and the All Ireland Prevalence Survey (AIPS) only began collecting data on generic NPS in 2014/2015.

Therefore, considerable uncertainties persist about basic monitoring data. Nationally representative surveys of school children found similar low prevalence for mephedrone use and NPS as a whole. Data on sentinel populations are growing. For example several studies of attendees of gay-friendly night-clubs suggest the trend in reduction of mephedrone witnessed nationally may also be occurring in this subgroup too.24 26 37

*Qualitative studies of novel psychoactive substance in the UK*

Qualitative studies of NPS use in the UK19 34 36 38-42 are at an early stage of development. Existing studies show potential benefits of collecting qualitative data to inform understanding about long term effects of NPS use (such as impact on relationships, and risk of violence). In addition, there is potential to further investigate reasons for and patterns of use, and harms. As the evidence base deepens, these data may help to inform targets for behavioural epidemiological studies. Studies assessing aspects of drug market functioning and the effects of mass and social media (including internet forums) have promise to inform future responses including early identification of increases in NPS use or related harms and preventive interventions.

*Systematic reviews*

Systematic reviews43-52mainly summarised clinical presentation data (see Table 3) on problems associated with NPS. One review was on all NPS use among people with severe mental illnesses, five on synthetic cannabinoids, two on synthetic cathinones, and two on NBOMe.

Most commonly reported side effects of NPS were psychiatric,45 46 49 52 48 51cardiovascular44 45 49 52 51renal52 45and gastrointestinal symptoms. 52 Treatment of these effects appears to mostly involve observation and supportive care, and in severe cases hospitalization. Treatment of intoxication with synthetic opioids was predominantly through opioid antagonists such as naloxone. We did not find population-level data on acute health harms with dedicated attention to prevalence and policy issues, or data on chronic health or social harms in a longitudinal context.

*Responses to novel psychoactive substance use and problems/harms*

Quantitative studies53-68 evaluated effects of legislative prohibitions of NPS use or supply on outcomes including access, use, healthcare utilization and self-reported exposure and toxicity (see Table 4). Reductions in use, presentations or other outcomes were generally observed, though not always. 58 67Studies typically utilized simple counts of routinely collected data, particularly poison centre and hospital admissions data. Study designs were mainly before and after comparisons, which clearly limits attribution of effects as such studies are not designed to address the impact of residual confounding and the regression to the mean phenomenon.

**Discussion**

***Summary of principal findings***

A comprehensive search of peer-reviewed and grey literature on NPS identified 995 relevant records. We then developed an evidence map and identified evidence gaps based on a priori developed research questions. We identified a number of areas (UK prevalence surveys and qualitative studies, policy evaluation studies and systematic reviews of problems associated with NPS use) where more detailed synthesis were appropriate. However, we judged there was not yet sufficient basis for a full systematic review based on the extensive scoping review and evidence gap analysis. Evidence mapping suggested limited benefits of risk of bias assessments since most studies were unlikely to be of sufficient quality. Study designs, in most cases, were such that it is difficult to establish the nature of relationships between NPS use and problems/ harms, or responses to NPS use and outcomes. The more detailed narrative syntheses, taken together with broader evidence mapping, led us to conclude that the literature on NPS is at an early stage of development in its capacity to inform strategic public health responses.

Use

Preliminary findings suggest that NPS use is rare if viewed only in a general population UK context. While it appears that young people, particularly males, are more likely to engage in NPS use there is little other data regarding social or other risk factors. While data on sentinel populations are growing (e.g. attendees of gay-friendly night-clubs)24 26 37 the main limitations of these studies regard generalisability of findings across the UK and beyond.

Problems

There is now a large literature of case reports and case series reporting acute toxic effects or emergency room attendances related to NPS. The most common side effects reported were psychiatric, cardiovascular, renal and gastrointestinal symptoms. However, due to the limitations of the data it is somewhat challenging to differentiate harms associated with NPS as a whole, and how harms differ between specific types of NPS, both within and between drug classes (such as synthetic cannabinoids, synthetic cathinones etc). In addition,

 data on other harms (e.g. social harms such as impact on relationships, work and family) are currently lacking.

Responses

No data were identified on effectiveness of preventive interventions or interventions for current NPS users. There was limited literature on regulation of NPS which generally showed reductions in incidence, however, limitations in reporting and quality of data limit conclusions that can be drawn from these studies.58 67 Examination of the utility of routinely collected NPS data in different settings is needed, incorporating attention to sources of information bias that will facilitate more rigorous assessments of the impacts of major policy changes on NPS use and harms.

***Strengths and weaknesses of the current review***

*Strengths*

We conducted evidence mapping of a large and diverse literature (995 studies) and constructed an evidence gap analysis to help prioritise topic material for more detailed narrative syntheses. We aimed to minimize error and bias through the use of two researchers to independently select articles and extract data.

*Limitations*

Scoping reviews are not designed to provide in-depth interrogation of the content of the evidence. Although the scoping review assessed all literature, our narrative syntheses of nationally representative surveys were limited to studies conducted in the UK. It is therefore innappropriate to generalise the prevalence findings beyond the UK. In addition, much of the data on NPS use is self-report and therefore refers to what substance was thought to have been used. However, it is not possible to know with certainty what substance was taken without confirmation with laboratory tests.

A further limitation was that although we identified a large quantity of grey literature, our search methods were weighted to sources in the UK and USA and therefore not necessarily representative of grey literature outside these countries.

***Conclusion***

The burden associated with NPS is unclear, as is the shape of any evolving public health responses. These findings suggest directions for research needed to address NPS, though not separately from investigation of other licit and illicit drugs. For further detail on possible priorities for future research indicated by this study, see Mdege et al. 8) Although the literature appears large and to have grown quickly, it will need to develop further if it is to inform policy and practice.

**Box 1: *Literature searches***

|  |
| --- |
| Electronic databases were searched between 1st January 2006 and 29th June 2016 inclusive: MEDLINE, Embase, PsycINFO and Science Citation Index. The search strategies also included trade or brand names for a number of NPS products. These names were selected by examining the websites of three popular NPS online headshops (i.e. globalweekends.co.uk, www.iceheadshop.co.uk, and www.legalhighsworld.co.uk) and selecting those that appeared in all three for inclusion. Searches for grey literature included a google search, hand searching of relevant UK Government websites (https://www.gov.uk/ (which includes Department of Health, Home Office, Public Health England), NHS Evidence, Office of National Statistics, National Drug Treatment Monitoring System (NDTMS), Scottish Government, National Assembly for Wales, Public Health Wales, Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS), Information Services Division Scotland, and the Department of Health Northern Ireland), EU (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)), and US websites (Centers for Disease Control and Prevention (CDC), National Institute on Drug Abuse (NIDA), Substance Abuse and Mental Health Services Administration (SAMHSA), and contacting experts. Relevant online drug forums were identified from published literature as well as through contacting experts in the field. We searched the following online forums: BlueLight, Erowid, Drugs Forum, and Talk Drug Abuse. For a full search strategy please see appendix 2. |

**Table 1 Summary study characteristics of nationally representative surveys of NPS use in the UK**

|  |  |  |  |
| --- | --- | --- | --- |
| **Author** | **Population** | **Drug** | **Sampling** |
| Department of Health, Northern Ireland9 | General population (15-67 years) | NPS | N=2,535, nationally representative sample of Ireland,  |
| European Commission10 | European Youth (15-24 years) | NPS | N=13,128 (UK: N=501), nationally representative samples for member states |
| Health and Social Care Information Centre11 | 11-15 year olds | NPS | N=6,173, nationally representative sample of schools in England |
| NHS National Services Scotland12 | 13 and 15 year olds | NPS | N=33,685, nationally representative sample of schools in Scotland |
| Office for National Statistics13 | General population (16 years and over) | NPS | N=35,000, nationally representative sample of England and Wales (Crime Survey for England and Wales) |
| Robertson14 | General population (16 years and over) | NPS | N=12,035, nationally representative sample of Scotland (Scottish Crime and Justice Survey) |
| Corazza *et al*.15 | Pupils and students | NPS | N=446; Online survey (The Study Room forum), gender: 50% male, mean age: 19 years (range 13-30) |
| Dargan *et al*.16 | Pupils and students | Mephedrone | N=1,006; Tayside area of UK, gender: 50% male, mean age school children: 14 years, mean age university students: 21 years |
| Penney *et al*.17 | School children (15-18 years) | NPS | N=533; Greater London, gender:55% male, age range: 15-18 years, ethnicity: 14% White, 26% Black, 9% Mixed, 23% Asian |
| Mounsey *et al*.18 | School children (15-18 years) | NPS | N=917; Greater London (four private schools, and four state schools), gender: not reported, age range 15-18 years ethnicity: not reported |

NPS: novel psychoactive substances, NHS: national health service, N=sample size

**Table 2 Surveys of NPS use in sentinel and drug user populations**

| **Author** | **Setting /Population** | **Drug** | **Participant characteristics** |
| --- | --- | --- | --- |
| Baker19 | Prison in Rochester  | Synthetic cannabinoids | N=101, gender: 100% male, mean age: 32 years (range 18-59),ethnicity: 72% white, 12% black, 6% Asian, 6% mixed ethnicity, Offences convicted for: 30% violent offences, 21% robbery, 26% drugs, 5% motoring related, 9% acquisitive |
| Homeless Link20 | Day centres for homeless people | NPS | N=56, gender: 59% male, mean age: 29 years |
| Chung *et al*.21 | HIV outpatient clinic | NPS | N=223, all were MSM and HIV positive |
| Daskalopoulou *et al*.22 | HIV outpatient clinic HIV positive MSM | Mephedrone | N=2,248, all were MSM and HIV positive, median age: 46 years, ethnicity: 89% White |
| Thurtle *et al*.23 | Two sexual health clinics in London  | NPS | N=1,472, gender: 53% male, mean age: 30 years |
| Lovett *et al.*37 | Gay friendly night clubs | Mephedrone, Methiopropamine | N=397, Gender: 89% male, mean age:30 years |
| Measham *et al*.24 | Gay friendly night club (2010) | NPS, mephedrone | N=308, gender: 82% male, 17% female, 1% trans-gender; mean age: 30 years, ethnicity: 75% White, 10% Black, 10% Mixed race, 4% Asian; Sexuality: Homosexual 70%, Bisexual 9%, Heterosexual 17% |
| Measham *et al*.25 | Night clubs in Lancashire | NPS | N=343, gender: 48% male, mean age: 23 years, ethnicity: 96% White |
| Wood *et al.*26 | Gay friendly night clubs in London (2011) | NPS, mephedrone | N=315, gender: 82% male, 15% female, 1% transgender, mean age:30 years |
| Roche and Huke27 | Eating Disorders outpatient clinics  | NPS | N=72, no further data on study characteristics reported |
| Moore and Lesser28 | Acute mental health services in Devon | NPS | N=100, no further data on study characteristics reported |
| Stanley *et al.*29 | General adult psychiatric wards in a Scottish city | NPS | N=388, gender: 49% male; mean age: NPS users 36 years, non-NPS users 43 years; ethnicity: not reported |
| Winstock *et al*.30 | NPS users recruited through dance music and clubbing website | Mephedrone | N=947, gender: 60% male, mean age: 24 years |
| Winstock *et al*.31 | NPS users recruited through involvement in the dance music scene (subsample of study above) | Mephedrone | N=100, gender: 77% male, mean age: 25 years |
| Winstock *et al.*32 | Online survey of UK-based polydrug users | Methoxetamine | N=5,367, gender: 82% were male, mean age: 25 years, ethnicity: 91% white, sexuality: 78% were heterosexual, 9% homosexual, 7% bisexual |
| Fletcher *et al*.33 | NPS users in Tayside area | NPS | N=687, gender: ratio of female to male participants was approx. 5:2, age: most respondents were 20-64 years |
| O’Brien *et al.*34 | NPS users in online survey | NPS | N=183, gender: 78% men, Age: majority aged 16-29 years |
| NHS Lothian Substance Misuse Directorate35 | Opportunistic sampling by outreach workers of NPS users | NPS | N=100, gender: 77% male, age range: 21-59 years, approximately half were homeless, 76% had been in prison, almost all unemployed |
| Brookman36 | Agencies in South Wales: Criminal justice, charities working with offenders, drug users or those with broad range of needs | Mephedrone | N=67, gender: 73% male, age range (15-55 years), 12% under 18 years, 48% were aged 18-29, 40% were over 30 years |

NPS: novel psychoactive substances, N:sample size, MSM: men who have sex with men

**Table 3: Study characteristics of included systematic reviews on NPS**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Principal Focus** | **Population** | **NPS type** | **Types of included studies** |
| Brewer and Collins43 | Harms associated with NPS | Adolescents and adults (12-67 years) | Synthetic cannabinoids | Case reports |
| Busardo *et al*.44 | Fatalities associated with NPS | Cases with analytically confirmed presence of mephedrone | Synthetic cathinone: mephedrone | Case reports |
| Castaneto *et al*.45 | NPS use and harms | Not specified | Synthetic cannabinoids | Surveys, case reports, case series  |
| Gray *et al*.46 | Mental and physical health effects and fatalities associated with NPS | Adults (aged 18 years or over) with a diagnosis of SMI and a history of NPS use. | All NPS | Case reports/ series, qualitative interviews, questionnaires  |
| Gunderson *et al*.47 | Harms associated with NPS | Not specified | Synthetic cannabinoids | Case reports; semi-structures interviews; toxicology laboratory studies |
| Kyriakou *et al*.48 | Harms associated with NPS | Not specified | NBOMe | Not specified |
| Miotto *et al*.49 | Harms associated with NPS | Not specified | Synthetic cathinones: bath salts | Retrospective studies, toxicology data, chemical analyses studies, and case reports |
| Papanti *et al*.50 | Harms associated with NPS | Psychiatric treatment patients; accident and emergency patients; general public calls, toxicology/ poison centres | Synthetic cannabinoids | Retrospective toxicology surveys; case reports/ series; human laboratory studies; interviews/ surveys with synthetic cannabinoids users |
| Suzuki *et al*.51 | Harms associated with NPS | Not specified | NBOMe | Case reports |
| Tait *et al.*52 | Harms associated with NPS and clinical management of these adverse effects | Hospital presentations and poison centre data | Synthetic cannabinoids | Case series (≥10 cases)Case reports (≤10 cases) |

NPS: novel psychoactive substance use

**Table 4: Characteristics of and results from quantitative policy evaluation studies**

| **Study** **Country** | **Setting** **Publication type** | **Intervention** | **NPS type** | **Study design** |
| --- | --- | --- | --- | --- |
| Brown *et al*.53Australia | Poisons CentreConference abstract | 9 June 2013 legislation and enforcement by state and federal governments to restrict the sale of synthetic cannabinoids. | Cannabinoids | Before and after comparison through retrospective review of Poisons Information Centre Data (5 months prior and five months after ban) |
| Christie and MacFarlane 54New Zealand | Addiction treatment settingLetter to Editor | May 2014: Ban of NPS under the Psychoactive Substances Act | Cannabinoids | Before and after comparisons (12 month before and 12 months after) |
| Dargan *et al*.55UK | Community settingPeer reviewed journal article | December 2009: The classification of synthetic cannabinoid receptor agonist constituents of Spice were as Class B in the UK | Cannabinoids | Before and after comparison using product purchased from legal high websites |
| Kriikku *et al.*56Finland | Police custody: driving under the influence of drugs; toxicology unit: autopsy casesPeer reviewed journal article | Ban of 3,4-methylenedioxypyrovalerone (MDPV) in June 2010 | Cathinone: MDPV | Before and after comparison  |
| Loeffler *et al*.57USA and UK | Poison centreLetter to the Editor | The 21 October 2011 temporary federalban on a number of bath salt compounds-USAApril 2010 mephedrone ban in the UKApril 2012 ban on methoxetamine in the UK | Cathinones: bath salts; mephedroneMethoxetamine | Before and after comparison using data from national poison control centers (PCC) |
| Pettie *et al*.58UK | General hospital inpatient settingConference abstract | 10 April 2015 control of methylphenidate-based NPS by the UK government under the Misuse of Drugs Act 1971 (Temporary Class Drug) Order | methylphenidate-based NPS | Before and after comparison using hospital admissions data  |
| Plumb *et al*.59USA | Poison centreConference abstract | A state law making spice illegal | Cannabinoids | A retrospective chart review: Before and after comparison |
| Reuter60USA | Setting: not applicablePhD thesis | 2011 legislation criminalising the possession of ingredients used in the production of synthetic drugs  | Cathinones: bath salts | Before and after comparison. |
| Ryan and Arnold61USA | Poison centreConference abstract | Control of six cathinones under Schedule I in Louisiana on January 6, 2011 | Cathinones | Before and after comparison through secondary analysis of the National Poison Data System (December 2010 - month prior; and February 2011- month after ban) |
| Sheridan *et al*.62New Zealand | InternetPeer reviewed journal article | Prohibition of BZP-containingparty pills and related substances from 1st April 2008(provided for a six-monthamnesty period in which possession of small quantities for personal use was permitted) | Piperazines: Benzylpiperazine (BZP) and related substances | Before and after comparison through an internet based survey among adults aged 18–30 years |
| Smyth *et al*.63Republic of Ireland  | Specialist alcohol treatment service: Youth Drug and Alcohol servicePeer reviewed journal article | 2010 legislative changes in Ireland- adding over 100 NPS onto the Misuse of Drugs Act, and restrictions on sell of psychoactive substances. | All NPS | Before and after comparisons (before: six months prior 10 May 2010; after: six months prior 10 May 2011) using data from the National Drug Treatment Report System |
| Wahl and Theobold64USA | Poison centreConference abstract | A multi-pronged approach of surveillance, reporting, law enforcement partnership and legislative changes  | All NPS | Before and after comparison with national averages |
| Winstock *et al.*65UK | Internet surveyLetter to editor | April 2010 classification of mephedrone and similar compounds as Class B substances in the UK under the Misuse of Drugs Act | Cathinone: Mephedrone | Before and after comparison: Findings from an online survey conducted in June 2010 compared with those from one in November,2009, and another telephone survey in 2010 before the legislation |
| Wood *et al*.66UK | Emergency Department (ED)Conference abstract | Control of cathinones under the UK Misuse of Drugs Act, 1971 on the 16th April 2010 | Cathinones: mephedrone | Before and after comparison through secondary analysis of ED data. (eight months each side) |
| Wood *et al.*67UK | EDPeer reviewed journal article | Control of cathinones under the UK Misuse of Drugs Act, 1971 on the 16th April 2010 | Cathinones: mephedrone | Before and after comparison through secondary analysis of ED data. (12 months each side) |
| Wood *et al*.68UK | Nightclubs (gay-friendly)Conference abstract | Control of methoxetamine under the Temporary Class Drug Order (TCDO) legislation in March 2012. | Methoxetamine | Before and after survey comparison (July 2011 and July 2012) |

**Appendix 1 Expanded methods section**

*Electronic database searches*

The following electronic databases were searched via the OVID platform for articles published between 1st January 2006 and16th November 2015 inclusive: MEDLINE, Embase, PsycINFO and Science Citation Index(see Appendix 2 for the search strategies used in each database). The database searches were updated on 29 June 2016. The search strategies also included trade or brand names for a number of NPS products. These names were selected by perusing through the websites of three popular NPS online headshops (i.e. globalweekends.co.uk, www.iceheadshop.co.uk, and www.legalhighsworld.co.uk) and selecting those that appeared in all three for inclusion.

*Google search for grey literature*

A google search was conducted using the following key phrases: “novel psychoactive substances”, “new psychoactive substances”, and “legal highs”. The file type was restricted to pdf, and the searches were conducted on 17th March 2016.

*Hand search of websites relating to the UK and USA*

Websites of the following institutions and organizations were hand searched on 13th May 2016 to identify national and international surveys, monitoring systems and early warning systems: gov.uk (which includes Department of Health, Home Office, Public Health England), NHS Evidence, Office of National Statistics, National Drug Treatment Monitoring System (NDTMS), European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Scottish Government, National Assembly for Wales, Public Health Wales, Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS), Information Services Division Scotland, and the Department of Health Northern Ireland, Centers for Disease Control and Prevention (CDC), National Institute on Drug Abuse (NIDA), Substance Abuse and Mental Health Services Administration (SAMHSA).

*Search for relevant online drug forums*

Relevant online drug forums were identified from published literature as well as from contacting experts in the field. We searched the following online forums: BlueLight, Erowid, Drugs Forum, and Talk Drug Abuse.

*Contacting experts*

Calls for information were sent to Public Health England and forwarded to the NPS Clinical Network Working Group and the Novel Psychoactive Treatment UK Network (NEPTUNE). Nineteen researchers were also contacted for any unpublished relevant literature, or literature not identified by the searches.

***Inclusion/ Exclusion criteria***

Participants/ population

Articles were included if reporting on humans. In addition, articles were included if they were on novel psychoactive substance use, problems and responses. The following definitions were used for use, problems and responses:

Use: Any use of a novel psychoactive substance.

Problems: Any acute or chronic health-specific, social or wider harm due to NPS use, experienced by the user or others.

Responses: Any intervention at policy, health or other service, or clinical levels, aimed at addressing novel psychoactive substance use and/or related problems

Context

There were no restrictions on context or location.

Study design

Articles were included if they were either primary studies (i.e. involving the collection of original primary data through directly measuring the outcome of interest within the relevant population), secondary studies involving the analysis and interpretation of primary research, or discussion papers. Commentaries and letters were only included if they presented new primary or secondary data. Non-English language publications were excluded.

We distinguished generic literature reviews and systematic reviews based on the following criteria:

• Search of at least two electronic databases, or one electronic database and reference checking of included studies or some other source of obtaining further studies

• Explicitly stated inclusion/exclusion criteria

• List of included studies

• Risk of bias assessment of included studies conducted by authors or sufficiently reported study characteristics of included studies that would enable others to make judgements on risk of bias of individual studies

• Narrative or quantitative synthesis of data from included studies

Any review that did not meet these criteria was classified as a literature review.

***Article selection***

The screening of titles and abstracts and the selection of articles from retrieved potentially relevant full manuscripts was conducted by two reviewers (NM and NDM) using the selection criteria described above. The reviewers independently classified the articles as “include”, “unclear”, or “exclude”, with discrepancies being resolved by discussion or referral to a third reviewer (JM). Full manuscripts that did not fulfil all of the criteria were excluded with documented reasons for their exclusion.

***Data extraction***

Data extraction was performed using EPPI-Reviewer 4 software. The data extraction form was designed by two researchers (NM and NDM), piloted on a small selection of articles and adjusted as necessary. The following data was extracted:

• Include/exclude decision, with reasons for exclusion where applicable.

• General characteristics for included studies: author, year, location, setting, study design, publication type.

• Population characteristics: age, gender, ethnicity, sample size, novel psychoactive use status.

• Novel psychoactive substance type:

• Principal focus (use, problems, responses)

• Research recommendations in the case of reviews, systematic reviews, qualitative studies, surveys and articles on responses.

Data from each article were extracted by one researcher and checked by another, with discrepancies being resolved by consensus or recourse to a third researcher if necessary. Where necessary, authors were contacted for missing or unclear data.

***Risk of bias (quality) assessment***

No risk of bias assessment was conducted. This decision was made after developing the evidence map, for further discussion of this decision see evidence map section below.

***Strategy for data synthesis***

The framework for data synthesis was the conceptual framework specifically designed for use in data analysis and interpretation for the current scoping review and narrative synthesis, to which the research questions listed above contribute. Data synthesis was done in three stages: evidence mapping, identification of evidence gaps, and then a narrative synthesis of selected research areas.

*Evidence map*

For reviews addressing complex topic areas, evidence mapping is a well-established tool to explore relevant literature before progressing to more advanced research design decision making. The extracted data was utilized by one researcher to map the literature according to principal focus (use, problems/harms or responses), NPS type, study design, region, setting, year of publication and publication type. This was checked by another researcher. The aim of the map was to provide a comprehensive yet concise descriptive map of the nature and breadth of research on NPS, and identify obvious research gaps.

*Identification and evaluation of evidence gaps*

After the mapping, an a priori developed set of research questions were then utilised to identify and evaluate evidence gaps, and to make decisions about narrative syntheses. In addition, the conceptual framework guided our evaluation of what was missing from the literature.

This process, based on the evidence map, facilitated discussions about categories of evidence where it was feasible to conduct narrative syntheses (in consultation with the project steering group). We initially considered whether it would be possible to restrict the inclusion criteria to a small number of narrowly focused research questions for the purposes of conducting a full systematic review (i.e. including detailed risk of bias assessment).

However, in discussion with the project steering group, we concluded that given the early stage of development for all areas of the literature this would not be the best use of the time and resources of the project. Therefore, we developed broader inclusion criteria that enabled us to conduct narrative syntheses where there was judged to be a sufficient evidence base.

The steering group supported this decision. We were also necessarily pragmatic in our decision-making addressing questions of primary relevance to the UK as the data allowed, in ways which were manageable within the time and resources allocated to the project, bearing in mind the large size of the literature included in the scoping review and the short duration of the project (14 months).

*Narrative synthesis*

In addition to the evidence map, and evidence gap analysis, a narrative descriptive synthesis was conducted for the following categories of articles and data:

• Systematic reviews

• UK survey data on NPS use

• UK based qualitative studies

• Articles on responses, including policy evaluation studies and studies of individual level interventions

**Appendix 2 Search strategy**

**MEDLINE via OVID**

**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>**

1 exp designer drug/

2 psychotropic drugs/

3 drug abuse/

4 2 and 3

5 (designer adj (drug$ or stimulat$ or amphetamine$)).ti,ab.

6 legal high$.ti,ab.

7 ((club or street) adj drug$).ti,ab.

8 ((new or novel or emerg$ or illicit$ or illegal) adj psychoactive drug$).ti,ab.

9 ((new or novel or emerg$ or illicit$ or illegal) adj psychoactive agent$).ti,ab.

10 ((new or novel or emerg$ or illicit$ or illegal) adj psychoactive substance$).ti,ab.

11 ((new or novel or emerg) adj (cannabinoid$ or phenethylamine$ or arylalkylamaine$ or cathinone$ or opioid$ or benzodiazepine$ or piperidine$ or pyrolidine$ or piperazine$ or arylcyclohexylamine$ or aminoindane$ or tryptamine$)).ti,ab.

12 (synthetic adj (cannabinoid$ or phenethylamine$ or arylalkylamaine$ or cathinone$ or opioid$ or benzodiazepine$ or piperidine$ or pyrolidine$ or piperazine$ or arylcyclohexylamine$ or aminoindane$ or tryptamin)).ti,ab.

13 (psychotropic adj (drug$ or substance$ or agent$)).ti,ab.

14 13 and 3

15 ((psychotropic adj2 (drug$ or substance$ or agent$)) and (abuse or misuse)).ti,ab.

16 (herbal adj (blend$ or high$ or incense$)).ti,ab.

17 (party pill$ or research chemical$ or smoking mixture$).ti,ab.

18 1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 14 or 15 or 16 or 17

19 benzylpiperazine$.ti,ab.

20 cannabimimetic$.ti,ab.

21 diclazepam.ti,ab.

22 gamma butyrolact$.ti,ab.

23 mephedrone.ti,ab.

24 methiopropamine.ti,ab.

25 methoxetamine.ti,ab.

26 naphyrone.ti,ab.

27 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28 Drug abuse/ or (drug abuse or "drug use" or drug misuse).ti,ab.

29 27 and 28

30 BZP.ti,ab.

31 MPVD.ti,ab.

32 NRG-1.ti,ab.

33 MDAI.ti,ab.

34 25i-NBOMe.ti,ab.

35 30 or 31 or 32 or 33 or 34

36 Drug abuse/ or (drug abuse or "drug use" or drug misuse).ti,ab.

37 35 and 36

38 (Annihilation or Armageddon).ti,ab.

39 (bamboo or bathsalt$ or bath salt$ or benzofury or benzo fury or berry bomb or black mamba or bromo-dragonfly or bullet or bumpin).ti,ab.

40 (charly sheen or cherry bomb or chillout or china white or ching or c-liquid or clockwork orange).ti,ab.

41 (disco biscuits or doves ultra).ti,ab.

42 (exodus damnation or exodus nightshade).ti,ab.

43 focus.ti,ab.

44 (gogaine or green beans).ti,ab.

45 (happy joker blueberry or happy joker juice fruit or happy rasta or head trip or hipster or hooter).ti,ab.

46 insane joker.ti,ab.

47 jammin joker.ti,ab.

48 (K2 or king joker or kronic).ti,ab.

49 lotus.ti,ab.

50 (Mexecat or mcat or m-cat or mind melt).ti,ab.

51 (pandora$ box or pink panthers or plant feeder$ or plant food$ or pond cleaner$ or psyclone).ti,ab.

52 (salvia or sensate or sexy v or spice or super lemon haze or synthacaine).ti,ab.

53 timeless.ti,ab.

54 voodoo.ti,ab.

55 (White MM or white widow or wicked).ti,ab.

56 38 or 39 or 40 or 41 or 42 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55

57 Drug abuse/ or (drug abuse or "drug use" or drug misuse).ti,ab.

58 56 and 57

59 18 or 29 or 37 or 58

60 exp animals/ not humans/

61 59 not 60

62 limit 61 to yr="2006 -Current"

**Appendix 3: Flow of articles for the evidence mapping**



**Appendix 4:** **General characteristics of included articles**

| **Characteristics** |  | **Distribution, n (%)** |
| --- | --- | --- |
| *Principal focus* |
|  | Use | 385 (39%) |
|  | Problems/ Harms | 773 (78%) |
|  | Responses | 148 (15%) |
| *Novel Psychoactive Substance (NPS) type* |
|  | All NPS | 259 (26%) |
|  | Synthetic cannabinoids | 310 (31%) |
|  | Synthetic cathinones | 271 (27%) |
|  | Phenethylamines | 69 (7%) |
|  | Piperazines | 29 (3%) |
|  | Other | 114 (11%) |
| *Setting* |
|  | Specialist settings (addiction treatment, psychiatric treatment, forensic and rehabilitation, poison centres, needle exchange, other similar settings) | 134 (13%) |
|  | General Hospital (inpatient, emergency department, outpatient settings) | 294 (30%) |
|  | Primary care setting | 3 (0.3%) |
|  | Educational Setting (school, higher educational institutions- University/ College) | 32 (3%) |
|  | Criminal justice | 9 (1%) |
|  | Police | 27 (3%) |
|  | Defence forces (Airforce, Army, Navy) | 9 (1%) |
|  | Community setting | 64 (6%) |
|  | Home | 27 (3%) |
|  | Club/ disco/ dance scene | 14 (1%) |
|  | Internet | 59 (6%) |
|  | Data registry | 13 (1%) |
|  | Early warning systems | 9 (1%) |
|  | Research setting | 22 (2%) |
|  | Other | 21 (2%) |
|  | Not applicable | 252 25%) |
|  | Nor reported | 24 (2%) |
| *Study design* |
|  | Systematic review | 10 (1%) |
|  | Literature review | 243 (24%) |
|  | Randomised controlled trial | 13 (1%) |
|  | Survey | 130 (13%) |
|  | Laboratory sample analysis | 58 (6%) |
|  | Secondary quantitative data analysis | 99 (10%) |
|  | Prospective cohort studies | 6 (0.6%) |
|  | Case-control | 1 (0.1%) |
|  | Qualitative study | 47 (5%) |
|  | Case series/ reports | 367 (37%) |
|  | Other | 64 (6%) |
| *Publication type* |
|  | Peer reviewed journal article | 654 (66%) |
|  | Peer reviewed report | 1 (0.1%) |
|  | Non-peer reviewed article/ report | 119 (12%) |
|  | Conference abstracts | 205 (21%) |
|  | Book | 4 (0.4%) |
|  | Dissertation | 1 (0.1%) |
|  | Online discussion forum | 4 (0.4%) |
|  |  |  |

**Appendix 5: 2 Number of records by year of publication**



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