Profile, effects and toxicity of novel psychoactive substances: A systematic review of quantitative studies

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Running head: Profile, effects and toxicity of novel psychoactive substances

Keywords Novel psychoactive substances, legal highs, cathinones, profile, effects, toxicity

Abstract

Objective To investigate the profile, effects and toxicity of novel psychoactive substances (NPS).

Methods A systematic literature review was conducted between May 2015 and February 2016 and included 19 databases. Search terms included: 'novel psychoactive substance(s)', 'effect(s)' and 'toxicity' and their synonyms. Studies included were those from any country, in any language and between January 2007 and April 2015. Studies published before 2007 and those regarding the synthesis of NPS were excluded. Data was extracted by evaluating the titles, abstract and full text respectively. Consequently, the extraction yielded 20 studies.

Results A total of 43 NPS derivatives of eight main pharmacological classes were identified. NPS were mostly used among young adults and adults within the age range of 16-64 years old. Cathinones and synthetic cannabinoids were the most prevalent amongst the aforementioned classes. The main desired effects of NPS use were empathy and increased ability to socialise. Reported toxicity associated with the use of NPS included cardiovascular, neurological and psychoactive adverse reactions.

Conclusions Despite the unique subjective effects associated with the use of NPS, harmful effects could be severe and/or lethal. Therefore, there is a need to develop research in the area of NPS and promote awareness among healthcare professionals.

Keywords Novel psychoactive substances, legal highs, cathinones, profile, effects, toxicity

Introduction

Novel psychoactive substances (NPS) have emerged over the last decade as alternatives to classical drugs of abuse in order to surpass the regulations surrounding them (EMCDDA, 2016a). These drugs have been continuously emerging at a rate of approximately twice a week (EMCDDA, 2016b). The European Monitoring Centre for Drugs and Drug Addiction EMCDDA reported more than 500 NPS derivatives available on the market in 2015 (EMCDDA, 2016b).

The increased number and diversity of NPS products imposed a burden on regulatory authorities and policy makers. With limited evidence on NPS health risks, it was difficult to introduce controls and new laws. Yet, once a law regarding an NPS derivative was introduced, another derivative was ready on the market. Hence, the UK introduced the New Psychoactive Substances Act (2016) which did not require the name of the NPS derivative in order to control it.

NPS represent a major challenge in relation to their chemistry, pharmacology and toxicity. Though the general pharmacological classes of NPS were known; information regarding specific associated effects and toxicity is still limited (Patterson, Young & Vaccarino, 2017). This is mainly associated with the fact that most NPS were modifications of famous drugs that were not subject to clinical trials and/or drugs which failed clinical trials and withdrawn from the market. Other types of NPS included were medicines licenced in few countries only. For instance, phenazepam is licenced in Russia but not in the UK where it is sold (Corkery et al., 2012).

The general effects reported from the use of NPS were stimulant (euphoria), hallucinogen (dissociative or psychedelics) and depressant effects (CNS inhibition) (Tracey, Wood & Baumeister, 2017). Yet, many specific effects were still underreported and this is partly due to the diversity of NPS users. NPS use is not limited to party scenes but could be encountered in users' homes, individuals in custody and among psychonauts.

Likewise, toxic effects associated with the use of NPS are underrepresented with only symptoms reported relating to agitation, aggression, cardiovascular toxicity, hyperthermia, palpitations, paranoia, psychotic symptoms and seizures (Tracey, Wood & Baumeister, 2017). Some specific symptoms are underreported. For instance, bladder toxicity associated with the use of methoxetamine (an NPS hallucinogen) was only identified in 2012 from users' reports (Corazza et al. 2013). There is a growing concern over the harm associated with the use of NPS with increased emergency department admissions and demands for drug treatment (EMCDDA, 2016b).

Subsequently, we have conducted a comprehensive systematic review of the profile, effects and toxicity of NPS from the literature. We have provided analysis of studies which met the inclusion criteria. We then critically discussed our findings and summarised the evidence for the effects and toxicity of NPS.

Methods

Search strategy

We searched the following 19 databases between May 2015 and February 2016: British Nursing Index, CINAHL, Cochrane Library, EBSCO, Embase, Global Health, Google, Google Scholar, International Pharmaceutical Abstracts, ISI Web of Science, JSTOR, Medline,

National Electronic Library for Medicine (NeLM), PsychExtra, PsychInfo, PubMed, ScienceDirect and Scopus. The search strategy evaluated articles retrieved predominantly through databases. We also retrieved bibliographic lists from published reviews where relevant.

We used the following search terms: 'novel psychoactive substances', 'effects' and 'toxicity'. The search strategy involved use of the three terms in each database as follows: 'novel psychoactive substance(s)' OR 'legal high(s)' OR 'designer drug(s)' OR 'bath salt(s)' OR 'herbal high(s)' OR 'novel recreational drugs' OR 'party drugs' AND 'effect(s)' OR 'effectiveness' OR 'efficacy' AND 'toxicity' OR 'harm' OR 'side effect(s)' OR 'adverse effect(s)' OR 'adverse reaction(s)' OR 'overdose' OR 'drug interaction(s)'.

Inclusion criteria

Studies were included in the systematic review if they investigated the effects and toxicity associated with NPS, published from 2007 onwards and had explicit data on young adult- and/or adult-population (above 15 years).

Exclusion criteria

Three types of studies were excluded from the review. The first type were studies that encompassed information regarding the synthesis and analytical characterisation of NPS. The second type were studies that investigated NPS among children < 15 years old. The third type were studies that investigated receptor pharmacology through animal models.

List of definitions

An adverse drug reaction (ADR) is defined as " any noxious, undesired and unintended drug effect that occurs at doses used in human for therapy, diagnosis or prophylaxis" (WHO, 1972). Oral intake of a drug involves direct swallowing of the formulation as a tablet, powder dissolved in a liquid, or powder wrapped in a cigarette paper (bombing). Intravenous (IV) and intramuscular (IM) intake of a drug comprises the injection of the drug solution into a vein or muscle respectively. Nasal insufflation involves the snorting of the NPS powder.

Data extraction

Data extraction was conducted by the authors and included the following information: study type (case report, user report, interview, survey), country, study settings, population age, study aim, duration and sample size. Articles were scanned independently and systematically by two reviewers (SA and NG), and the screening process included titles, abstracts and full articles. Disagreement among reviewers was resolved by discussion. When the inclusion and exclusion criteria were applied, a third reviewer (DO) verified the data.

Results

In total, 11,550 studies were retrieved (Figure 1) before applying the limitation of time (beyond 2007) and age (≥ 15 years old) limits. When applying inclusion/exclusion criteria and removing duplicates, 648 studies were obtained. Upon inspection of titles 386 studies remained. Out of the 386, 333 were excluded because they did not consider NPS. The abstracts of the remaining 53 studies were evaluated and 33 were found not relevant. The search resulted in 20 studies which investigated effects and toxicities associated with NPS.

Study characteristics

Studies extracted in this review were from 10 countries (Table 1) including Australia (Goggin, Gately & Bridle, 2015), France (Eiden et al., 2013), Italy (Gerace et al., 2014), Netherland (Hondebrink et al.,2015), Norway (Karinen et al., 2014), Poland (Kulhawik & Waleski, 2015; Rojek et al., 2012), Singapore (Winslow & Mahedran, 2014), Spain (Gonzalez et al., 2013; Papaseit et al., 2013), the UK (Arora, Kumar & Raza, 2013; Dargan & Wood, 2012; Winstock et al., 2011) and the USA (Antonowicz et al., 2011; Belton et al. 2012; Borek, Christopher & Holstege, 2012; Kelly, 2011; Spiller et al., 2011; Stogner & Miller, 2013; Lajoie & Rich, 2012). The majority of the studies were retrospective and fewer were prospective. Retrospective studies included audit (n = 2) (Hondebrink et al., 2015; Spiller et al., 2011) and case report (n = 11) (Antonowicz et al., 2011; Arora, Kumar & Raza, 2013; Belton et al. 2012; Borek, Christopher & Holstege, 2012; Eiden et al., 2013; Gerace et al., 2014; Karinen et al., 2014; Kulhawik and Walecki, 2015; Rojek et al., 2012; Lajoie & Rich, 2012; Winslow & Mahedran, 2014). Prospective studies included interview/telephone interview (n = 2) (Kelly, 2011; Winstock et al., 2011), observational (n = 1) (Papaseit et al., 2013) and survey (n = 4) (Goggin, Gately & Bridle, 2015; Gonzalez et al., 2013; Kelly et al., 2013; Stogner & Miller, 2013). The age groups reported in the 24 studies included mainly young adults and adults (range 15-64 years old). The sample size investigated had a minimum of 1-2 (for case reports) and a maximum of 42,243 (for retrospective audit). The duration of the studies ranged between few hours to few years.

NPS class, formulation and modality of intake

A total of 43 NPS derivatives were reported in the studies and were used as cognitive enhancers, empactogenic or euphoric agents, hallucinogens and/or stimulants (Table 2). The NPS derivatives were of the following pharmacological classes: cathinones (n=18) (Antonowicz et al., 2011; Belton et al., 2013; Eiden et al., 2013; Gerace et al., 2014; Gonzales

et al., 2013; Hondebrink et al, 2015; Kelly et al., 2013; Papaseit et al., 2013; Stogner & Miller, 2013; Winslow & Mahedran, 2014), kratom (n = 1) (Karinen et al., 2014); opioids (n = 1) (Karinen et al., 2014), ketamines/phenethylamines/piperidine (n = 9) (Gonzales et al., 2013; Hondebrink et al., 2015), Salvia (n = 2) (Kelly, 2011; Winslow & Mahedran, 2014), synthetic cannabinoids (n = 6) (Antonowicz et al., 2011; Arora, Kumar & Raza, 2013; Goggin, Gately & Bridle, 2015; Hondenbrink et al., 2015; Kelly et al., 2013) and tryptamines (n = 2) (Hondebrink et al., 2015).

For the formulation of NPS used, 15 (62.5%) studies described the use of powder NPS products, six (25%) reported tablets, four (16.7%) reported herbal material and one (4.16%) reported liquids. Regarding the modality of intake of NPS, oral route was reported by 12 (50%) of studies and comprised both direct swallowing or bombing of the substance. Other routes used for intake of NPS were smoking, nasal insufflation, IV, IM and rectal and were reported by 10 (41.6%), eight (3.33%), seven (2.92%), two (8.33%) and one (4.16%) study respectively. The frequency of intake was mainly acute (among 14 studies) and only six studies reported chronic use.

Most of the NPS products were used in conjunction with alcohol (n = 10), energy drinks/caffeine (n = 2), tobacco (n = 1) and or classical drugs (n = 11). The aforementioned classical drugs were: amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, ecstasy, lysergic acid diethylamide (LSD), marijuana, methylenedioxymethamphetamine (MDMA), magic mushrooms, methadone, oxazepam, opiates, oxycodone and oxymorphone.

NPS effects

Users from seven (29.1%) studies reported achieving the desired effects as a result of the recreational use of NPS. The aforementioned desired effects encompassed four categories: empathogenic, hallucinogen or stimulant effects. Empathogenic effects included "being compassionate" and "feeling of social intimacy". Hallucinogen effects were extracampine hallucinations, vivid auditory and visual hallucinations, and a change of time perception. Stimulant effects included euphoria, increased alertness, increased sexual desire, enhanced cognitive skills and prosocial effects.

NPS toxicity

Toxicity of NPS derivatives included two main categories: ADR and drug overdose. ADRs were reported in 14 studies and were associated with newer amfetamine analogues, cathinones, ketamine derivatives and herbal highs. Newer amfetamine analogues and cathinones were associated with cardiovascular, neurological, psychotic, renal and respiratory effects (Antonowicz et al., 2011; Borek, Christopher & Holstege, 2012; Eiden et al. 2013; Gonzalez et al. 2013; Hondebrink et al., 2015; Lajoie & Rich, 2012; Papaseit et al. 2013; Spiller, 2011; Winstock et al., 2011). Reported cardiovascular ADRs associated with cathinones included cardiac arrest, chest pain, hypertension, palpitations, tachycardia and vasoconstriction. Nervous system ADRs included coma, confusion, drowsiness, fatigue, headache, hyperthermia, hypothermia, increased muscle tone, insomnia, loss of appetite, loss of concentration, mydriasis, nausea, numbness, seizures, tremors, vertigo, vomiting and weakness. Psychotic ADRs included agitation, anxiety, confusion, depression, irritability, paranoia, psychosis, psychotic breakdown, self-harming and suicidal thoughts. Only two ADRs were reported for each of the renal and respiratory systems and were urinary tract infection and pulmonary edema respectively. Novel ketamine analogues (methoxetamine) and herbal highs (artificial hashish, Kratom, Salvia) were associated mainly with psychotic ADRs

such as vivid, visual and auditory hallucinations (Hondebrink et al. 2015; Kelly, 2011; Winslow & Mahedran, 2014). Additionally, a case of hypoxemic respiratory insufficiency due to artificial hashish was reported (Kulhawik & Waleski, 2015).

Only three studies reported lethal overdose associated with the use of NPS, and included both accidental (Gerace et al., 2014; Karinen et al., 2014) and deliberate overdose (Rojek et al., 2012). The above mentioned three cases involved the use of kratom, butylone and mephedrone respectively.

Discussion

To our knowledge, this is the first systematic review to investigate the profile, effects and toxicity involving NPS within an adult population. Three other reviews were reported in the literature in relation to NPS. A recent systematic review investigated the prevalence of NPS in non-clinical population (Khaled et al. 2016). Yet, it did not examine in depth the toxicities associated with NPS. A second review investigated the effects of NPS but was limited to population with severe mental illness (Gray et al. 2016). Another systematic review has been published regarding the effects and risks associated with NPS (Hohmann, Mikus & Czock, 2014). However, the scope of the latter review was limited to publications between 2010 and 2012 years. Our review considered all studies since 2007 (marked as the year of emergence of NPS) up to 2015.

Our findings suggested that NPS were highly prevalent among young adults and adult populations. Cathinones were the most prevalent NPS derivatives followed by synthetic cannabinoids. This result confirmed the outcomes of other studies which showed that

cathinones and synthetic cannabinoids were the most reported substances to the EMCDDA (Hohmann, Mikus & Czock, 2014; Martinotti et al. 2015; Stephenson and Richardson 2014).

Powdered NPS-formulations were preferred over tablet/capsules. This could be attributed to the increased availability of powder formulations, ease of use and ability to be used in multiple routes (either directly or via mixing with a liquid). The main routes for NPS intake were oral (by swallowing) and IV (by injecting) routes. This finding was supported by Schmidt et al. (2011) who identified that around 60% of NPS derivatives were designed to be swallowed. NPS were often mixed with alcohol and classical drugs of abuse (such as cocaine). This finding confirmed previous studies where poly drug use was witnessed among NPS and other psychoactive substances/alcohol (Davey et al., 2012; Corbo et al. 2015). Poly drug use could attribute to unpredictable drug interactions that depend to a degree on the purity of the NPS present.

Little information regarding the effects of NPS was extracted in this review. This could be attributed to the fact that the majority of the included studies were case reports of toxicity. Where reported, users were interested in the unique subjective experience achieved upon intake of NPS. Among other effects, users experienced empathy and increased socialising ability when taking stimulants (Newcombe, 2009). Likewise, users taking phencyclidine derivatives had vivid/auditory hallucinations and near-death experience (Corazza et al., 2012; Corazza, Assi & Schifano, 2013).

Despite achieving the desired effects, numerous ADRs were associated with the use of NPS and included both physical and neuropsychiatric symptoms. Common cases involved psychotic breakdown. In severe cases, ADRs led to respiratory depression, cardiac arrest or multiple

organ failure. Lethal effects were also seen with both accidental and deliberate overdose of NPS. This could be critical in the current changing scenario of drug abuse where multiple factors play a role in the efficacy/safety of drugs. These factors include polydrug use, different routes of intake and different dosing intervals of drugs (Corazza et al., 2013). Henceforth, further research and healthcare education is needed in order to tackle issues associated with NPS.

Strength and limitations

This systematic review involved investigating data from previous studies by two independent reviewers. The studies included in the review were further verified by a third independent reviewer in order to avoid bias. For each study, the inclusion/exclusion criteria were applied to achieve the research objectives, to identify the profile, effects and toxicity associated with the use of NPS. Nonetheless, the systematic review had some limitations. Due to the limited number of studies available, it was not possible to get the profile of NPS per country. Moreover, information extracted from this review was restricted mainly to case reports/emergency department admissions. Major information was missing regarding demography of participants, first time exposure to drug, time of intake of drugs and scene where the drug was taken. This influenced the understanding of the effects and toxicity associated with drugs. It was not possible to identify drug interactions associated with polydrug use. Furthermore, it was not possible to correlate the exact effects associated per specific NPS derivative. This was because when subjects were reported to the emergency department no confirmatory testing was undertaken on blood or urine to correlate the signs and symptoms with what was actually consumed. Instead, physicians treat the symptoms and then discharge patients when the symptoms have worn off. Moreover, it was not possible to obtain conclusive data regarding severity and preventability, which were not reported in any of the studies. The heterogeneity

of the data in this review was mainly attributed to differences between countries, study settings, sample size and duration. Hence, it was not possible to make a conclusive judgement for all countries.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Antonowicz, J.L., Metzger, M.D., Sai, L., Ramanujan, M.D., 2011. Paranoid psychosis induced by consumption of methylenedioxypyrovalerone: two cases. *General Hospital Psychiatry* [online], 33, 640.

Arora, A., Kumar, A., Raza, M.N., 2013. *'Legal high' associated Wallenberg Syndrome: Case Report*. Gloucestershire: British Medical Journal.

Baumann, M. H., Solis, E., Watterson, L. R., Marusich, J. A., Fantegrossi, W. E., & Wiley, J. L. (2014). Baths salts, spice, and related designer drugs: the science behind the headlines. The Journal of neuroscience, 34(46), 15150-15158.

Baumeister, D., Tojo, L.M. & Tracy, D.K. (2015). Legal highs: staying on top of the flood of novel psychoactive substances. Therapeutic advances in psychopharmacology, 5(2), 97-132.

Belton, P., Sharngoe, T., Maguire, F.M. & Polhemus, M., 2013. Cardiac Infection and Sepsis in three intravenous Bath Salts Drug Users. *Clinical Infectious Diseases*, 56 (11), 102-104.

Borek, H.A., Christopher, M.D., Holstege, P., 2012. Hyperthermia and multiorgan failure after abuse of "Bath Salts" containing 3,4- Methylenedioxypyrovalerone. *Annals of Emergency Medicine* [online], 60 (1).

Corazza, O., Schifano, F., Simonato, P., Fergus, S., Assi, S., Stair, J., Corkery, J., Trincas, G., Deluca, P., Davey, Z. and Blaszko, U., 2012. Phenomenon of new drugs on the Internet: the case of ketamine derivative methoxetamine. *Human Psychopharmacology: Clinical and Experimental*, *27*(2), pp.145-149.

Corazza, O., Assi, S., Simonato, P., Corkery, J., Bersani, F.S., Demetrovics, Z., Stair, J., Fergus, S., Pezzolesi, C., Pasinetti, M. and Deluca, P., 2013. Promoting innovation and excellence to face the rapid diffusion of novel psychoactive substances in the EU: the outcomes of the ReDNet project. *Human Psychopharmacology: Clinical and Experimental*, *28*(4), pp.317-323.

Corazza, O., Assi, S. and Schifano, F., 2013. From "Special K" to "Special M": the evolution of the recreational use of ketamine and methoxetamine. *CNS neuroscience & therapeutics*, *19*(6), pp.454-460.

Corbo, M., Santacroce, R., Cinosi, E., Sarchione, F., Acciavatti, T., Lupi, M., Marini, S., Fiori, F., Di Tizio, L., Dezi, S. and D'ascanio, G., 2015. Polydrug Use in a Population of Young Italian Adults. *European Psychiatry*, *30*, p.479.

Corkery, J. M., Schifano, F., & Ghodse, A. H. (2012). Phenazepam abuse in the UK: an emerging problem causing serious adverse health problems, including death. *Human Psychopharmacology: Clinical and Experimental*, *27*(3), 254-261.

Dargan, P. and Wood, D., 2003. *Novel Psychoactive Substances: Classification, Pharmacology and Toxicology*. 1st edition. Amsterdam: Academic Press

Davey, Z., Schifano, F. Corazza, O., Deluca, P., 2012. E-Psychonauts: Conducting research in online drug forum communities. *Journal of Mental Health*, 21 (4), 386-394.

Davies, S., Wood, D. M., Smith, G., Button, J., Ramsey, J., Archer, R., ... & Dargan, P. I. (2010). Purchasing 'legal highs' on the Internet—is there consistency in what you get?. *Qjm*, *103*(7), 489-493.

Dawson, P., & Moffatt, J. D. (2012). Cardiovascular toxicity of novel psychoactive drugs: lessons from the past. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *39*(2), 244-252.

Eiden, C., Mathieu, O., Cathala, P., Debruyne, D., Baccino, E., Petit, P., Peyriere, H., 2013. Toxicity and death following recreational use of 2-pyrrolidinovalerophenone. Clinical Toxicology, 51, 899-903.

European Monitoring Centre for Drug and Drug Addiction (EMCDDA), (2016a). European Drug Report: Trends and Developments: http://www.emcdda.europa.eu/edr2016 accessed 28 November 2016.

European Monitoring Centre for Drug and Drug Addiction (EMCDDA), (2016b). News release from the EU drugs agency Lisbon 26 June international day against drug abuse and illicit trafficking: http://www.emcdda.europa.eu/news/2016/7/nps-responses accessed 15 February 2017.

Gerace, E., Petrarulo, M. Bison, F., Salomone, A., Vincenti, M., 2014. Toxicological findings in a fatal multidrug intoxication involving mephedrone. Forensic Science International, 243, 68-73.

Gilani, F. (2016). Novel psychoactive substances: the rising wave of 'legal highs'. British Journal of General Practice, 66(642), 8-9.

Global Drug Survey (GDS). (2016). The Global Drug Survey 2016 findings. https://www.globaldrugsurvey.com/past-findings/the-global-drug-survey-2016-findings/ Accessed 28 November 2016

Goggin, L.S., Gately, N. & Bridle, R., 2015. Novel Psychoactive Substance and Other Drug Use by Young Adults in Western Australia. *Journal of Psychoactive Drugs* [online], 47 (2), 140-148.

Gonzalez, D., Ventura, M., Caudevilla, F., Torrens, M., Farre, M., 2013. Consumption of new psychoactive substances in a Spanish sample of research chemical users. *Human Psychopharmacology: Clinical and Experimental*, 28, 332-340.

Gray, R., Bressington, D., Hughes, E., & Ivanecka, A. (2016). A systematic review of the effects of novel psychoactive substances 'legal highs' on people with severe mental illness. *Journal of psychiatric and mental health nursing*, *23*(5), 267-281.

Hohmann, N., Mikus, G., Czock, D., 2014. Effects and Risks Associated with Novel Psychoactive Substances. *Deutsches Ärzteblatt International*, 111 (9), 139-147.

Home Office (HO). (2014). Home office. Drug Misuse: Findings from the 2013/14 Crime Survey for England and Wales. N. statistic. GOV.UK website available at https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/335989/drug_misuse_201314.pdf. Accessed 15 December 2016

Hondebrink, L., Nugteren-van Lonkhuyze, J.J., Van Der Gouwe, D., Brunt, T.M., 2015. Monitoring new psychoactive substances (NPS) in The Netherlands: Data from the drug market and the Poison Information Centre. *Drug and Alcohol Dependence*, 147, 109-115.

Karinen, R., Fosen, J.T., Rogde, S., Vindenes, V., 2014. An accidental poisoning with mitragynine. *Forensic Science International*, 245, 29-32.

Khaled, S. M., Hughes, E., Bressington, D., Zolezzi, M., Radwan, A., Badnapurkar, A., & Gray, R. (2016). The prevalence of novel psychoactive substances (NPS) use in non-clinical populations: a systematic review protocol. *Systematic Reviews*, *5*(1), 195.

Kelly, B.C., 2011. Legally Tripping: A Qualitative Profile of Salvia Divinorum Use Among Young Adults. *Journal of Psychoactive Drugs*, 43 (1), 46-54.

Kelly, B.C., Wells, B.E., Pawson, M., Leclair, A., Parsons, J.T., Golub, S.A., 2013. Novel psychoactive drug use among younger adults involved in US nightlife scenes. *Drug and Alcohol Review*, 32, 588-593.

Kulhawik, D. and Waleski, J., 2015. Toxic Lung Injury in a Patient Addicted to "Legal Highs"-Case Study. *Polish Journal of Radiology*, 80, 62-66.

Lajoie, T.M. and Rich, A., 2012. "Bath Salts": A New Drug Epidemic—A Case Report. *The American Journal on addictions*, *21*(6), pp.572-573.

Lindsay, L. and White, M. L., 2012. Herbal Marijuana Alternatives and Bath Salts- 'Barely Legal' Toxic Highs. *Clinical Pediatric Emergency Medicine* [online], 13 (4), 283-291.

Martinotti, G., Lupi, M., Carlucci, L., Cinosi, E., Santacroce, R., Acciavatti, T., Chillemi, E., Bonifaci, L., Janiri, L. and Di Giannantonio, M., 2015. Novel psychoactive substances: use and knowledge among adolescents and young adults in urban and rural areas. *Human Psychopharmacology: Clinical and Experimental*, *30*(4), pp.295-301.

Newcombe, R. (2009). The use of mephedrone (M-cat, Meow) in Middlesbrough.

Papaseit, E., Perez-Mana, C., Meyono, E., Perx, M., Gilbert, C., Pujadas, M., Fonseca, F., de la Torre, R., Farre, M., 2013. Pharmacology of Mephedrone in Humans: A Pilot Dosefinding Study. *Basic and Clinical Pharmacology and Toxicology*, 113 (2), 16-37.

Patterson, Z. R., Young, M. M., & Vaccarino, F. J. (2016). Novel psychoactive substances: What educators need to know. *Clinical Pharmacology & Therapeutics*.

Psychoactive Substances Act (2016). http://www.legislation.gov.uk/ukpga/2016/2/contents/enacted accessed 15 December 2016.

Public Health England (PHE). (2014). New psychoactive substances: A toolkit for substance misuse commissioners. P. H. England. London: 1-16.

Ratnapalan, S. (2013). Legal substances and their abuse: legal highs. *Journal of Paramedic Practice, 5*(1), 40-51.

Rojek, S., Klys, M., Strona, M., Maciow, M., Kula, K., 2012. "Legal Highs"- Toxicity in the clinical and medico-legal aspect as exemplified by suicide with bk-MBDB administration. *Forensic Science International*, 222, 1-6.

Royal College of Psychiatrists (RCP). (2014). The Royal College of Psychiatrists One new drug a week: Why novel psychoactive substances and club drugs need a different response from UK treatment providers. Faculty of Addictions Psychiatry and R. C. o. Psychiatrists. UK: 1-19.

Salomone, A., Gazzilli, G., Di Corcia, D., Gerace, E., & Vincenti, M. (2016). Determination of cathinones and other stimulant, psychedelic, and dissociative designer drugs in real hair samples. Analytical and bioanalytical chemistry, 408(8), 2035-2042.

Spiller, H.A., Ryan, M.L., Weston, R.G., Jansen, J., 2011. Clinical experience with analytical confirmation of "bath salts" and "legal highs" (synthetic cathinones) in the United States. *Clinical Toxicology*, 49, 499-505.

Stephenson, G., & Richardson, A. (2014). New psychoactive substances in England: a review of the evidence.

Stogner, J. M., & Miller, B. L. (2013). Investigating the 'bath salt'panic: the rarity of synthetic cathinone use among students in the United States. Drug and alcohol review, 32(5), 545-549.

Tracy, D. K., Wood, D. M., & Baumeister, D. (2017). Novel psychoactive substances: types, mechanisms of action, and effects. *Bmj*, *356*, i6848.

UNODC. (2016). United Nations Office on Drugs and Crime; World Drug Report. U.N.O.O.D.A.Crime.Vienna, Available from: http://www.unodc.org/doc/wdr2016/WORLD_DRUG_REPORT_2016_web.pdf accessed 28 November 2016.

Watson, L., 2014. Doctor warns of the horrific effects of legal high drugs. *The Herald*, 23 April 2014. Available from: http://go.galegroup.com Accessed 07 November 2016.

Werse, B., & Morgenstern, C. (2012). How to handle legal highs? Findings from a German online survey and considerations on drug policy issues. Drugs and Alcohol Today, 12(4), 222-231.

Winslow, M. & Mahedran, R., 2014. From divination to madness: features of acute intoxication with Salvia use. *Singapore Medical Journal*, 55 (4), 52-53.

Winstock, A., Mitcheson, J.R., Davies, S., Puchnarewicz, M. Marsden, J., 2011. Meohedrone: use, subjective effects and health risks. *Addiction* [online], 106, 1991-1996.

World Health Organisation (WHO). (1972). International drug monitoring: the role of national centres. Tech Rep Ser WHO, no 498: apps.who.int/iris/bitstream/10665/40968/1/WHO_TRS_498.pdf accessed 29 November 2016

Figure legend

Figure 1. Data extraction and the study selection process

List of tables

Table 1. Characteristics of the studies that investigated novel psychoactive substances

Study	Year	Country	Study type	Study settings	Age	Aim	Duration	Sample size
Prospective studies								
Goggin et al 2015	2013	Australia	Questionnaire survey	Young Adults participated in the survey	18-35 years old	To obtain data on prevalence of NPS and other drug use by young Western Australians.	6 months	682
Gonzalez et al 2013	2010-2011	Spain	Questionnaire survey	Music festivals and online drug forums	adults average age 27 years old	To know the pattern of use of NPS in a Spanish sample of RC users and to deepen the RC user profile and risk reduction strategies	10 months	230
Kelly, 2011	2008-2009	USA	Interview	Users' homes, parks, bars and parties.	19-29 years old	To present data from an ethnographic project to provide a qualitative profile of Salvia use among young adults.	1 year	25
Kelly et al 2013	2012	USA	Questionnaire survey	Nightclub venues in New York City	18-40 years old	To gain an indication of the prevalence and understanding of demographic factors associated with mephedrone and synthetic cannabinoid use	6 months	1740
Papaseit et al 2013	2013	Spain	Observational	outpatient clinic	NR	To obtain preliminary data regarding mephedrone effects	3 days	9
Stogner et al 2013	2012	USA	Questionnaire survey	Southeastern US university	adults of mean age 20.06 years old	Gain understanding about the prevalence of synthetic cathinones	3 months	2349
Winstock et al 2011	2009	UK	Telephone interview	Telephone questionnaires 20-25 minutes each	adults of mean age of 25.1 for males and 23 for females	To describe initiation to mephedrone and patterns of use, assess acute and withdrawal effects, and assess the prevalence of dependence symptoms	3 months	100

Retrospective studies

Antonowicz et al 2011	2011	USA	Case report	General hospital	27 years old and 32 years old	To investigate two cases of a paranoid psychosis in individuals consuming MDPV	4 days	2
Arora et al 2013	2013	UK	Case report	A 56-year-old male attending A&E after inhaling unknown quantity of synthetic cannabinoid called 'herbal haze' few hours before.	56 years old male	To present the first described case of a 'legal high' intake linked to a posterior circulation stroke.	4 days	1
Belton et al 2013	2012	USA	Case report	Hospital	34 , 39 and 38 years old	To report three different cases regarding MRSA secondary to intravenous bath salts use.	55, 42 and 14 days	3
Borek & Holstege 2012	2011	USA	Case report	Hospital emergency department	25 years old	Toxicity resulting from injecting bath salts.	1 month	1
Eiden et al 2013	2012	France	Case report	Hospital	32 and 21 years old	To investigate death associated with 2-PVP	30 minutes and 1 day	2
Gerace et al 2014	2014	Italy	Case report	Apartment	25 years old	To investigate the cause of death	2 days	1
Hondebrink et al 2015	2007-2013	Nertherlands	Audit	DIMS drug testing facilities	15-41 years old	To obtain data regarding NPS-related intoxications from drug users in Netherlands	6 years	42,243
Karinen et al 2014	2013	Norway	Case report	Home	Middle aged	To investigate the cause of death	3 days	1
Kulhawik & Waleski 2015	2014	Poland	Case report	Hospital lung disease department	20 years old	To investigate the lung injury associated with the use of artificial hashish	5 weeks	1
Lajoie & Rich 2012	2011	USA	Case report	Hospital	50 years old	To investigate MDPV intoxication	15 days	1
Rojek et al 2012	2012	Poland	Case report	Hospital	21 years old	to investigate methylone deliberate overdose	4 hours	1
Spiller et al 2011	2010-2011	USA	Audit	Two poison centres	16-64 years old	To report the experience of synthetic cathinones in two regional poison centers	13 months	236
Winslow & Mahedran 2014	2014	Singapore	Case report	Home	30 years old	To investigate acute Salvia intoxication	45 minutes	1

2-PVP: 2-pyrrolidinovalerophenone, A&E: accident and emergency, DIMS: Drug Information and Monitoring System, MDPV: methylenedioxypyrovalerone, MRSA: methicillin resistance staphylococcus aureus, NPS: novel psychoactive substances, NR: not reported, RC: research chemical

Table 2. Modalities of intake of novel psychoactive substances

Study	NPS(s) used	Formulation	Modality of intake	Combination of drugs
Antonowicz et al 2011	MDPV, herbal incense	solution, powder	oral and insufflation	energy drink; case and Suboxone
Arora et al 2013	synthetic cannabinoids	plant	smoking	tobacco, alcohol and cannabis
Belton et al 2013	mephedrone and methylone	liquid	IV	none
Borek & Holstege 2012	MDPV	liquid	IV	none
Eiden et al 2013	2-PVP	powder	insufflation	cannabis and alcohol
Gerace et al 2014	mephedrone	powder	oral ingestion	alcohol and cocaine
Goggin et al 2015	synthetic cannabinoids	plant	smoking	alcohol, energy drinks and tobacco
Gonzalez et al 2013	mephedrone, methylone and PEA	powder	oral and insufflation	cannabis, alcohol and MDMA
Hendebrink et al 2015	2C-B, 4-FA, 6-APB, mephedrone and MXE	powder and tablet	insufflation, IV, oral and smoking	MDMA, amphetamine, alcohol and cocaine
Karinen et al 2014	kratom	powder	oral	none
Kelly et al 2013	mephedrone and synthetic cannabinoids	powder and plant	smoking and insufflation	alcohol and other drugs
Kelly, C.B., 2011	Salvia divinorum	plant	smoking	LSD, psilocybin
Kulhawik & Waleski 2015	artificial hashish	plant	smoking	marijuana, alcohol and tobacco
Papseit et al 2013	mephedrone	powder	oral	MDMA
Rojek et al 2012	methylone	tablet	oral	none
Spiller et al 2011	cathinones and MDPV	powder	insufflation, IV and oral	amphetamines, barbiturates, benzodiazepines, caffeine, cannabinoids, cocaine, MDMA, methadone, opiates, oxycodone and oxymorphone
Stogner et al 2013	cathinones and MDPV	powder	oral and insufflation	alcohol
Lajoie a& Rich 2012	MDPV	powder	IV	none
Winslow & Mahedran 2014	Salvia	plant	smoking	none
Winstock et al. 2011	mephedrone	powder	oral and insufflation	alcohol, cannabis, cocaine and ecstasy

2-CB: 2,5-dimethoxy-4-bromophenethylamine, 2-PVP: 2-pyrrolidinovalerophenone, 4-FA: 4-fluoroamphetamine, 6-APB: 6-2aminopropylbenzofuran, IV: intravenous injection, LSD: lysergic acid diethylamide, MDMA: methylenedioxymethamphetamine, MDPV: methylenedioxypyrovalerone, MXE: methoxetamine, PEA: phenethylamine.