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A systematic review of the effects of novel psychoactive substances “legal highs” on people with severe mental illness

Short title: NPS effects on people with SMI: A systematic review.

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Relevance Statement

People with severe mental illness (SMI) are more likely than the general population to use novel psychoactive substances (NPS). Unlike the effects of illicit drugs such as cannabis, the effects of NPS on people with SMI are unknown. In order to provide the best support and care to people with SMI, mental health nurses need to understand the potential effects of NPS and the circumstances of their use. This systematic review aimed to synthesise the state of knowledge about the effects of NPS on people with SMI.

A systematic review of the effects of novel psychoactive substances “legal highs” on people with severe mental illness

Abstract

Introduction: Novel psychoactive substances (NPS) are synthetic substances that have been developed to produce altered states of consciousness and perceptions. People with severe mental illness (SMI) are more likely to use NPS than people without mental illness, but the short and long-term effects of NPS are largely unknown.

Method: We systematically reviewed the literature about the effects of NPS on people with SMI.

Results: We included 12 case reports, 1 cross-sectional survey and 1 qualitative study. Participants included mostly males aged between 20 and 35 years. A variety of NPS were used, including synthetic cathinones and herbs such as salvia. The most commonly reported effects of NPS were psychotic symptoms (in some cases novel in form and content to the patients’ usual symptoms) and significant changes in behaviour, including agitation, aggression and violence. Patients’ vital signs; blood pressure, pulse rate and temperature were also commonly affected.

Conclusion: NPS potentially have serious effects on people with severe mental illness but our findings have limited generalisability due to a reliance on case studies. There is a paucity of evidence about the long-term effects of these substances. Further research is required to provide a better understanding about how different NPS affect patients’ mental and physical health.

PROSPERO Identifier: CRD42015026944

Keywords: legal highs, novel psychoactive substances, psychotic disorders, severe mental illness, schizophrenia, systematic review

Accessible summary

What is known on the subject?

- Novel psychoactive substances (NPS) include synthetic drugs mimicking the effects of illicit drugs, e.g. synthetic cannabinoids, and herbs such as salvia divinorum. NPS are substances that can trigger hallucinations and other effects altering the mind, and are currently uncontrolled by the United Nations' 1961 Narcotic Drugs/1971 Psychotropic Substances Conventions.
- NPS affect brain chemistry that induces the psychoactive effects, such as hallucinations and feeling 'high'. It is unknown what effects such drugs have on people with severe mental illness (i.e. psychotic illnesses).

What this paper adds to existing knowledge?

- Our review demonstrates that little is known about the effects of various NPS on people with severe mental illness. Almost nothing is known about the long-term consequences of NPS use on the mental and physical health of SMI patients.
- Patients may lack understanding that NPS are psychoactive drugs that can impact on their mental and physical wellbeing.

What are the implications for practice?

- Some patients might be reluctant or do not think it is relevant to disclose NPS use. Commonly used illicit drug-screening is unlikely to detect the presence of NPS, therefore health and mental health professionals should directly enquire about NPS and actively encourage patients with severe mental illness to disclose any substance use.

Background

People with severe mental illness (SMI) such as schizophrenia and bipolar disorder are at increased risk of suffering comorbid conditions including substance misuse (Merikangas et al 2008). For example, a study based on Danish national data showed that between 28-35% of people with psychotic disorders also have a coexisting substance use disorder (Toftdahl et al 2015). At the same time, substance misuse, especially cannabis use, is a known risk factor for developing psychosis (Arseneault et al 2002). There is also evidence that people with a dual diagnosis (substance use and SMI) have worse clinical outcomes in terms of symptom control, adherence to treatment and rates of violence and aggression (Soyka, 2000).

In recent years, new drugs and drug substitutes have emerged, possibly in response to the increased control of illicit drugs (EMCDDA, 2014). The use of so called 'legal highs' or novel psychoactive substances (NPS) is becoming increasingly common and NPS have been tried by at least 5% of young people aged 15-24 in the EU (Flash Eurobarometer, 2011). There is some evidence of considerable variation in the prevalence of use between countries, for example 1% of young people in Italy and 16% in Ireland are reported to have tried NPS (Flash Eurobarometer, 2011).

The UK government has introduced the Novel Psychoactive Substances 2015 bill in an attempt to ban all new and future substances with psychoactive effects intended for humans (excluding nicotine, caffeine, alcohol, food and medicines) in an attempt to keep up to date with new and emerging substances.

NPS are defined as narcotic or psychotropic drugs that are not currently controlled by the United Nations' 1961 Narcotic Drugs/1971 Psychotropic Substances Conventions, but which might pose a public health threat comparable to that posed by substances listed in these conventions (EMCDDA, 2006). Examples include synthetic cannabimimetics containing molecules that bind to cannabinoid

receptors, synthetic cathinones that are similar to amphetamines such as “bath salts” or methylenedioxypyrovalerone (MDPV) , new drugs mimicking the effects of MDMA (“Ecstasy”) and other substances including herbs like salvia divinorum, which can cause state of delirium and hallucinations (Schifano et al, 2015). Such substances are currently uncontrolled but hundreds of drugs with variable ingredients and untested effects/risks are available for purchase on the internet (Nelson et al, 2014). Within the general population, intoxication with novel psychoactive substances can pose significant health and mental health risks to their users, including but not limited to hallucinations, agitation, tachycardia, hypertension, vomiting, seizures, stroke, rhabdomyolysis (uncontrolled breakdown of muscle), kidney injuries and death (Schifano et al, 2015). The effects of NPS on people with existing severe mental illness are largely unknown.

The use of NPS appears to be significantly more common in people with psychiatric illnesses compared to healthy people (Martinotti et al 2014). It is therefore imperative to understand what effects NPS have on health and mental health, and specifically on people with co-existing mental illnesses.

Dopamine is a neurotransmitter with an established role in psychosis (Howes and Kapur, 2009). Studies involving PET scans of acutely psychotic patients show increased presynaptic levels of dopamine (Lindstrom et al, 1999). Dopamine is a neurotransmitter involved in controlling behaviours and thought processes (Cools, 2008). In a review of the literature, Schifano et al (2015) reported that dopamine function is disturbed when certain NPS (e.g. synthetic cathinones, synthetic cocaine substitutes and some novel stimulants such as methiopropamine) are used, triggering their psychoactive effects. It might be hypothesised that NPS use in people with severe mental illness could have stronger and more severe effects. However, the link between psychosis and NPS has not been examined. While various mental health complications have been described in people who have taken NPS (Schifano et al, 2015), to the best of our knowledge there has not been a systematic review that has examined the effects of NPS on patients with severe mental illness.

Review question

The aim of this systematic review is to explore the effects of novel psychoactive substances (NPS) on the mental and physical health of people with SMI.

Methodology

We have followed the PRISMA guideline for reporting systematic reviews (Moher et al, 2009). The protocol is registered on Prospero International Prospective Register of Systematic Reviews (<http://www.crd.york.ac.uk/PROSPERO/:2015> registration number: CRD42015026944

1.1 Search strategy

We used a broad sensitive search strategy to identify the relevant studies from the following electronic databases:

- EMBASE/OVID (1947-2015).
- MEDLINE/OVID (1961-2015);
- Cumulative Index to Nursing and Allied Health (CINAHL with Full Text) (1904-2015);
- The Cochrane Library (1900-2015);
- Scopus
- Pubmed

We also reviewed the reference lists of important articles in order to identify further potentially relevant papers, and we included papers identified serendipitously.

Our search string consisted of two main concepts. We searched the following keywords or key concept terms (as appropriate) related to novel psychoactive substances: “new psychoactive substances” OR “novel psychoactive substances” OR “legal highs” OR “designer drugs” OR “research chemicals” OR “smart drugs” OR “emerging drugs of abuse”. They were subsequently combined using ‘AND’ with the search terms related to the concept of severe mental illness: “schizophrenia” OR “manic depressive psychosis” OR “bipolar disorder” OR “psychosis” OR “psychotic disorders” OR “schizoaffective psychosis” OR “mania” OR “mixed mania and depression” OR “bipolar mania” OR “bipolar affective disorder” OR “depressive psychosis” OR “affective psychosis”. The search strategy was adapted accordingly for each database.

1.2 Inclusion criteria

This review is concerned with adults (aged 18 years or over) with a diagnosis of SMI and a history of NPS use. We included studies using any research design, reporting on how exposure to NPS affects mental and physical health of people with a current diagnosis of SMI. We included studies published in English with no restriction of context (i.e. any country, inpatients or outpatients), published in peer-

reviewed professional journals (including conference proceedings) before or electronically available in October 2015.

Participants

Studies were included if the participant(s) are described in the publication as being diagnosed with a SMI. Severe mental illness is defined as a documented diagnosis of schizophrenia or delusional/psychotic illness (ICD 10 F20.9 & F22 or DSM-equivalent) or bipolar disorder (ICD F31 or DSM-equivalent). The SMI-inclusive diagnosis was established by either a gold-standard structured clinical interview for establishing a DSM-IV/DSM-V or ICD-10 diagnosis (e.g. Structured Clinical Interview for DSM-IV/DSM-V), or made by a mental health professional and documented in the medical record.

Exposure

We included studies where participants were reported to have used novel psychoactive substances, which are narcotic or psychotropic drugs that are not currently controlled by the United Nations' 1961 Narcotic Drugs/ 1971 Psychotropic Substances Conventions but might pose a public health threat, as defined by the European Monitoring Centre for Drugs and Drug Addiction (EMCCDA, 2006). No comparator was defined for this review.

Outcomes

The primary outcome was change in psychiatric symptomatology of an existing SMI diagnosis in relation to recent use of NPS. Secondary outcomes were any other health-related effects caused by the use of NPS in people with SMI.

1.3 Study selection and data extraction

Articles identified in the literature searches were exported into reference management software (Endnote™). Duplicate records were excluded (using Endnote and manually) and the titles and abstracts of the individual articles were screened for eligibility based on inclusion criteria. We developed a data extraction tool for this review and piloted it on a sample of studies to check its utility. The relevant information about each study was recorded by two reviewers independently (AI and DB). We recorded the study characteristics, information about the study design and methodology,

participant characteristics (including the demographic and clinical characteristics) and the outcomes of the NPS exposure (i.e. the effects of NPS on health and mental health of the participants).

1.4 Risk of bias and quality assessment

We anticipated inclusion of studies using various designs. Their risk of bias (ROB) and methodological quality were therefore assessed using different validated ROB assessment tools, as appropriate. Qualitative research articles were assessed using a Critical Appraisal Skills Programme (CASP) tool (CASPa, 2014), case studies were assessed using a Newcastle-Ottawa quality assessment scale for case control studies (Wells et al, 2013) and other observational studies were assessed using a CASP tool for cohort studies (CASP, 2014b). The assessment of the risk of bias or quality of studies was not used to decide eligibility or inclusion of the relevant papers. Instead, the assessed risk of bias/quality will be reported to inform the interpretation of the findings.

1.5 Data synthesis

Information gathered from the included studies was synthesised according to the main principles of narrative synthesis (Popay, 2006).

Results

Figure 1 shows the flow of the articles through the review process. In the electronic database search and through other sources, we identified a total of 550 papers. After removing duplicates and non-English papers, we screened 367 titles and abstracts and excluded 234 records. We assessed 133 articles for eligibility, excluding a total of 119 mostly because their focus was not on SMI (n=67) were reviews (n=8) or commentary articles (n=15). One paper was excluded as we were unable to retrieve a full text copy of the manuscript from the British Library. We included 12 full studies and 2 conference abstracts that met our inclusion criteria. Included studies were published between 2011 and 2015.

[Insert figure 1]

Study description

Thirteen of the 14 studies included in this review were non-comparative reports. Specifically, we identified 10 single case reports, 2 case-series and 1 study involving qualitative interviews with NPS

users about their experiences with the substances. One study (Lally et al, 2013), was an explorative questionnaire study comparing the prevalence of using ‘head shops’ to buy NPS by people with mental illness and people without. A total of 7 studies were conducted in Europe (3 in UK, 3 in Ireland, 1 in Slovenia), 3 in the USA, 1 in India and 2 studies were in other countries (unreported). Four studies were conducted in inpatient or acute psychiatric clinics (Anderson et al, 2015 and Smith et al, 2013 in the UK; Celofiga et al, 2014 in Slovenia and Tully et al, 2011 in Ireland), 2 in outpatient clinics (McClean et al, 2012 in the UK; Khanra et al, 2015 in India) , 6 in emergency departments within hospitals (Boucher et al, 2015 and Marques et al, 2013 in unreported countries; Falgiani et al, 2012; Imam et al, 2013; Thornton et al, 2012 in the USA and Fröhlich et al, 2011 in Ireland), 1 in a forensic rehabilitation centre, New Zealand (Every-Palmer, 2011) and 1 in Ireland in a day hospital (Lally et al, 2013).

Risk of bias and quality of the studies

The risk of bias and quality of the 12 case studies (including the conference abstract reports) were assessed using the Newcastle-Ottawa quality assessment scale for case control studies, due to a lack of appropriate assessment tools for non-comparative case reports. Since the studies did not involve control participants, we determined that three out of the eight questions in the tool were applicable for case reports. Case reports are subject of relatively high inherent risk of bias due to involving a small number of participants who are often selected conveniently, without an opportunity to compare the identified effects with a control group. The case reports included between one and four participants, making their samples unrepresentative of any given population. In addition to the high inherent risk of bias, all but two studies included in this review reported patient’s diagnosis but do not indicate how it was obtained. No study reported the number of other potential cases within their institution in any given time period. Patients’ exposure to NPS was in most cases determined by self-report, providing further opportunity for bias.

We also included one qualitative study (Every-Palmer, 2011) and one cross-sectional survey (Lally et al, 2013). Their risk of bias was assessed using the Critical Appraisal Skills Programme (CASP) tool for qualitative and cohort studies, respectively. Lally, et al (2013) was deemed to have a risk of sampling bias due to recruiting all presentations rather than only new cases within the eight local hospitals. The risk of recall bias was also present due to reliance on patients’ self-reports over the past 12 months. The authors identified—but did not measure and/or take account of—confounding factors such as alcohol use, employment and socioeconomic status, which again increased the study’s risk of bias. The qualitative study (Every-Palmer, 2011) also had a relatively high risk of bias. The authors provided scant details of the study. The study aims were not clearly stated, making it difficult to

determine how appropriate the research design was. Not enough detail was provided regarding the recruitment process, exploration of the relationship between the researcher and participants during data collection, and how the thematic analysis was undertaken.

Participants

Table 1 shows the key characteristics of the participants involved in the studies included in this review. The case studies involved a total of 19 participants, of whom 17 had prior SMI. This is because one of the case series described 2 participants with a history of SMI and two people without mental illness, we only included the two participants with SMI. Participants in the case studies had diagnoses of schizophrenia (n=10), bipolar disorder (n=4) and in one study the authors mentioned a patient had a psychiatric history without providing further details of their diagnosis (Thornton et al, 2012). The majority of the patients in the studies were male (n=14; 82%) and the mean age was 31 years (SD=7).

The qualitative study (Every-Palmer, 2011) included 21 participants. Of which, 15 were eligible for this review. All were male with mean age of 34 years (SD=8). The study using questionnaires (Lally et al, 2013) involved 608 participants, of whom 135 had psychotic disorders. Of the 135 patients, 23 (17%) had purchased NPS in specialised drug shops called ‘head shops’. Further demographic information about the sample in this survey was only provided for the whole group of 608 participants.

[Insert table 1]

Exposure: NPS used in the included studies

Table 2 shows that most of the case study participants had used substances described as “bath salts” without further specification (n=5), 4 had used same type of synthetic cannabinoid called (1-(5-fluoropentyl)-3-(1-naphthoyl) indole (AM-2201) and 6 had used other types of substances. The others included herbs *Datura stramonium*, *Salvia divinorum*, a substance called ‘el blanco’, an amphetamine type stimulant containing a mixture of Methylenedioxypropylamphetamine (MDPV) and flephedrone, and benzylpiperazine (BZP). All of the questionnaire study participants had used the same type of synthetic cannabinoid, called JWH-018 (n=15). Participants in the survey study (Lally et al, 2013) had used a number of different substances that included synthetic cannabinoids (e.g. ‘Spice’ and ‘Smoke XXX’), benzylpiperazine and piperazine derivatives mephedrone, methcathinone and methylone among others.

[Insert table 2]

1.6 Outcomes: Health and mental health effects of NPS

Table 3 summarises the mental and physical effects of NPS reported in the included studies. In all of the case studies, the authors reported that the NPS taken had a significant impact on the patients' mental state.

[Insert table 3]

Short term effects

Out of a total of 17 cases, 15 reported a range of psychotic symptoms after taking NPS. Two were reported as being unconscious as a result of NPS use on admission to hospital intensive care unit/emergency department (Boucher et al, 2015; Falgiani et al, 2012). The psychotic symptoms most commonly reported included delusions, hallucinations (including haptic, auditory, visual and tactile), severe thought disorder (including incoherent speech and tangential thought processes) and altered mental status (specific details not provided). Authors of a study involving 4 already hospitalised patients observed that all patients demonstrated new psychotic symptoms with no exacerbation of their previously known symptoms (Celofiga et al, 2014). In the qualitative study (Every-Palmer, 2011), all patients reported the onset of psychotic symptoms following the use of NPS. Psychotic symptoms were also identified by users as an effect of NPS in a survey study (Lally et al, 2013). Participants in the qualitative study appeared to perceive NPS as less harmful or 'natural' substances, which 'make you high' in a faster and safer way, compared to illicit drugs (Every-Palmer, 2011).

Patients' behaviour after the use of NPS was also severely affected. In 9 of the 17 cases, bizarre or chaotic behaviour was observed, which included repetitive movements, crawling on the floor or running naked in the streets. Five patients were described as agitated with three requiring chemical and/or physical restraint, and three patients displaying violent, aggressive or assaultive behaviour. In one case this led to the use of pepper spray by security personnel with a subsequent severe adverse reaction that resulted in the patient's death (Imam et al, 2013).

Effects on physical health

Of the 17 cases, 9 were reported to show considerable change in vital signs, most often elevated heart rate, blood pressure, increased temperature and profuse sweating, symptoms reported to be consistent with serotonin syndrome (Boucher et al, 2015). Serotonin syndrome is a potentially life-threatening condition involving sudden onset of mental and neurological symptoms caused by an overstimulation of serotonergic receptors in the brain (Birmes et al, 2003). In one person the vital signs returned to normal after one hour, while several patients improved after 6-12 hours, others after a considerably longer time (ranging between several days to several weeks). Three studies did not provide information about any physical effects of NPS and one patient had no significant physical symptoms due to the drug taken. In addition to directly affecting the vital signs as a result of neurological effects, NPS can also seriously disturb kidney and liver function. Six patients showed the signs of renal impairment based on increased levels of phosphokinase and/or creatinine (in one case creatinine was increased without renal impairment) and two patients subsequently experienced liver function damage requiring treatment in intensive care.

Long term effects

The duration of the effects caused by NPS varied considerably in the case studies. Six patients were reported as recovered within 2-12 hours of intoxication or admission. Two persons returned to their mental state baseline on day 3 and 4 (consequently). Three patients were still unwell or just improved after one month of intoxication. Four studies did not provide detail about the time needed to recover. No patients were reported to have long-term kidney or liver damage.

Out of the 17 cases, one death was reported. The authors (Imam et al, 2013) hypothesised that this could have been caused by a severe reaction (i.e. respiratory arrest) to the agent in pepper spray used to restrain the patient due to the aggressive and violent behaviour. The patient never regained consciousness and died several weeks after the incident.

How was NPS use confirmed?

The case studies generally provided little or no detail about how NPS use was objectively confirmed. In most cases NPS use was identified based on self-report (n=9), although two patients denied drug use at first and admitted taking drugs only after several weeks of treatment resistance (McClean et al, 2012) or after repeated hospitalisation (Anderson et al, 2010). Five patients were reported to have been seen taking drugs by clinical staff (Boucher et al, 2015 and Celofiga et al, 2014), in two cases

patients were found to be in possession of NPS (Imam et al, 2013 and Smith et al, 2013) and in one case the authors did not report any details about how drug use was determined (Imam et al, 2013).

Only 5 of the 12 authors reported having done any testing of the substances used. In seven cases a standard urine drug/toxicology screen was performed, usually negative for the NPS taken by the patient (Anderson et al, 2010; Boucher et al, 2015; Celofiga et al, 2014; Falgiani et al, 2012; Fröhlich et al, 2011; Marques et al, 2013; Thornton et al, 2012; Tully et al, 2011). In 3 cases the substance was sent to specialised laboratories for detailed testing (Boucher et al, 2015; Celofiga et al, 2014; Fröhlich et al, 2011). Authors of one study reported that poison control was contacted without providing any further details (Falgiani et al, 2012) and in four studies no substance testing was reported (Imam et al, 2013; Khanra et al, 2015; McClean et al, 2012; Smith et al, 2013).

Discussion

This review aimed to investigate evidence of the effects of NPS for people with serious mental illness. Through electronic databases search, of an initial 367 studies, we included 14 studies that met the inclusion criteria. Twelve of these were case studies focusing on reporting the acute effects of NPS.

Whilst the substances used by participants varied considerably, the majority experienced significant changes in vital signs and often significant and rapid alteration of mental status, involving psychotic symptoms and bizarre behaviour. A very common symptom across patients with all diagnoses and NPS was violent, assaultive or aggressive behaviour requiring restraint. The particular symptoms participants experienced were diverse, ranging from sedation and loss of consciousness, to bizarre repeated motions, to erratic running. The wide range of effects was most apparent in a study involving four hospitalised patients with schizophrenia who had smoked the same substance but exhibited very different symptoms (Celofiga et al, 2014). The authors mentioned that the four patients experiences of psychotic symptoms that were not typical of earlier presentations, which may suggest that these were “new symptoms” rather than an exacerbation of previous symptoms (Celofiga et al, 2014).

Overall, our findings of the NPS effects are consistent with the effects reported in the general population. This may be because we do not yet understand the interaction psychosis, brain dysfunction, prescribed medication and NPS. The changes in vital signs, mental status and behaviour were also observed in a Japanese retrospective survey of 518 patients (not specific MH

patients) brought to emergency department (Kamijo et al 2014) and in a New Zealand overdose database analysis (Theron et al, 2007). We did not identify any studies that described positive effects of NPS.

We suggest that NPS can have a relatively severe effect on people with psychotic disorders. Although, the limited available evidence suggests that the adverse physical health issues resulting from NPS use are likely to be similar in both the general population and the SMI population, the effects on mental health may differ. For example, one of the common effects of NPS in people with SMI was significant behaviour change. Agitation requiring restraint was reported in around a third of the case study patients, with one in five being aggressive or violent. For comparison, only 56 (11%) of 518 patients brought to emergency departments in Japan for NPS intoxication, demonstrated violent and aggressive behaviour to self or others and 24% were irritable or agitated (Kamijo et al, 2014). Most (96%) of the people in the Japanese study recovered completely and did not require any further treatment. Episodes of extreme agitation in the general population who have taken NPS may be likely to be solely attributed to the use of the drugs, whereas in people with SMI it is possible that levels of behavioural disturbance could be viewed by professionals as being part of the SMI diagnosis. In such circumstances it is possible that NPS-related aggression in people with SMI might negatively influence their future mental health treatment (i.e. in terms of types and doses of prescribed medications) or hinder their recovery (i.e. resulting from stigma associated with having a history of violent/dangerous behaviour).

It is very likely that the full extent of NPS use by people with SMI is under-recognised and may only be reported in the literature when this use results in extremely agitated behaviours and other serious health concerns. Due to this, it is also quite possible that there may be people with a SMI diagnosis who take NPS and do not come to the attention of health professionals because they may experience little harm. The beliefs of people with SMI that NPS are less harmful than illegal substances or are 'natural' (Every-Palmer, 2011) have also been reported in some studies conducted in the general population (Sheridan and Butler, 2010). These ideas may result in people with SMI believing it is unnecessary to mention that they have used them during mental health assessments. This issue, coupled with the fact that commonly used illicit drug- screening often fails to detect NPS use (Dresen et al., 2010), indicates that mental health and other health care professionals should routinely enquire about the use of NPS by people with SMI in order to obtain a comprehensive picture of factors affecting mental illness.

To date, this is the first systematic review of the evidence about the effects of novel psychoactive substances on the mental and physical health of people with severe mental illness. The studies included in this review provide some indication that for some people with serious mental illness, NPS can have potentially serious, effects on both physical and mental health.

1.7 Review limitations

This review had several limitations. Firstly, the papers included in this review were mostly case studies and a cohort and qualitative studies, which are inherently more likely to be of a lower quality and high risk of bias. Our findings, therefore, might not be applicable for the wider population of people with SMI and are not generalizable to the wider population. For practical reasons we excluded papers that were not written in English, and this may have resulted in us over-looking some relevant material. Reporting in the case studies was also frequently lacking details about patient clinical history and long-term follow up, which might not be crucial for the emergency purposes but are necessary for a better understanding of NPS effects on people with SMI. One study (Thornton et al, 2012) also lacked details about the patient's psychiatric history and provided no specific diagnosis. Similarly to several other reports, the patient's diagnosis was not independently verified, which seriously limits the generalisability of the review findings.

Another limitation is the small number of studies included in the review. Despite the reports of NPS use being relatively common among people with severe mental illness (Martinotti et al, 2014), we were only able to identify 14 studies focussing on this population. This observation suggests that the issue may be under-reported and/or under-researched and more evidence is needed to inform clinical decisions and policymaking. It might also indicate reporting bias, i.e. medical professionals selecting only severe and clinically interesting cases for publication, rather than reporting all cases of NPS intoxication. Due to the small number of studies and included patients, it is also difficult to directly compare the prevalence of the NPS effects in people with SMI and the effects within the general population published previously.

1.8 Clinical recommendations

Patients might not always perceive NPS use as “drug use” and may have a lack of knowledge and understanding of the likely effects and risks involved in their use. In order to make appropriate treatment choices, health professionals need to know what substance the patient had taken. To encourage truthful self-report, health professionals should have an understanding of how patients perceive NPS in terms of their origin, effects and risks.

No studies examined medical and nursing staff knowledge and perceptions of NPS. It is also unclear how the different NPS interact with other drugs and medicines used in practice, although some of the drug interactions could potentially have serious consequences. When coupled with patients' reluctance to disclose all substance use, health professionals should be particularly vigilant and actively enquire about illicit as well as NPS drug use by people with severe mental illness.

1.9 Research recommendations

Our review suggests that NPS may have serious and potentially lethal consequences for at least some people with severe mental illness. However, more research of higher quality is required to provide a better understanding of the short and long term effects of NPS. This in turn will aid in detection of use, management of intoxication as well as health education regarding effects and risks of such substances. The small number of publications about NPS use in the SMI population could potentially be related to the health professionals' lack of knowledge about NPS, but the understanding and attitude of health professionals about NPS is largely unknown. Future research should therefore provide more information about the ability of health professionals in emergency rooms and psychiatric departments, to recognise and address the NPS intoxication by people with SMI.

More observational and prevalence research is needed to provide a better evidence base about the effects of NPS on the vulnerable population of people with SMI. It would also be valuable to determine whether and to what extent, the effects of NPS differ between people with SMI and people without psychiatric illness. Future research could also focus on the entries into medical registers for reporting drug use, e.g. Toxbase (www.toxbase.org).

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Figure 1: Prisma flow diagram of studies in the review

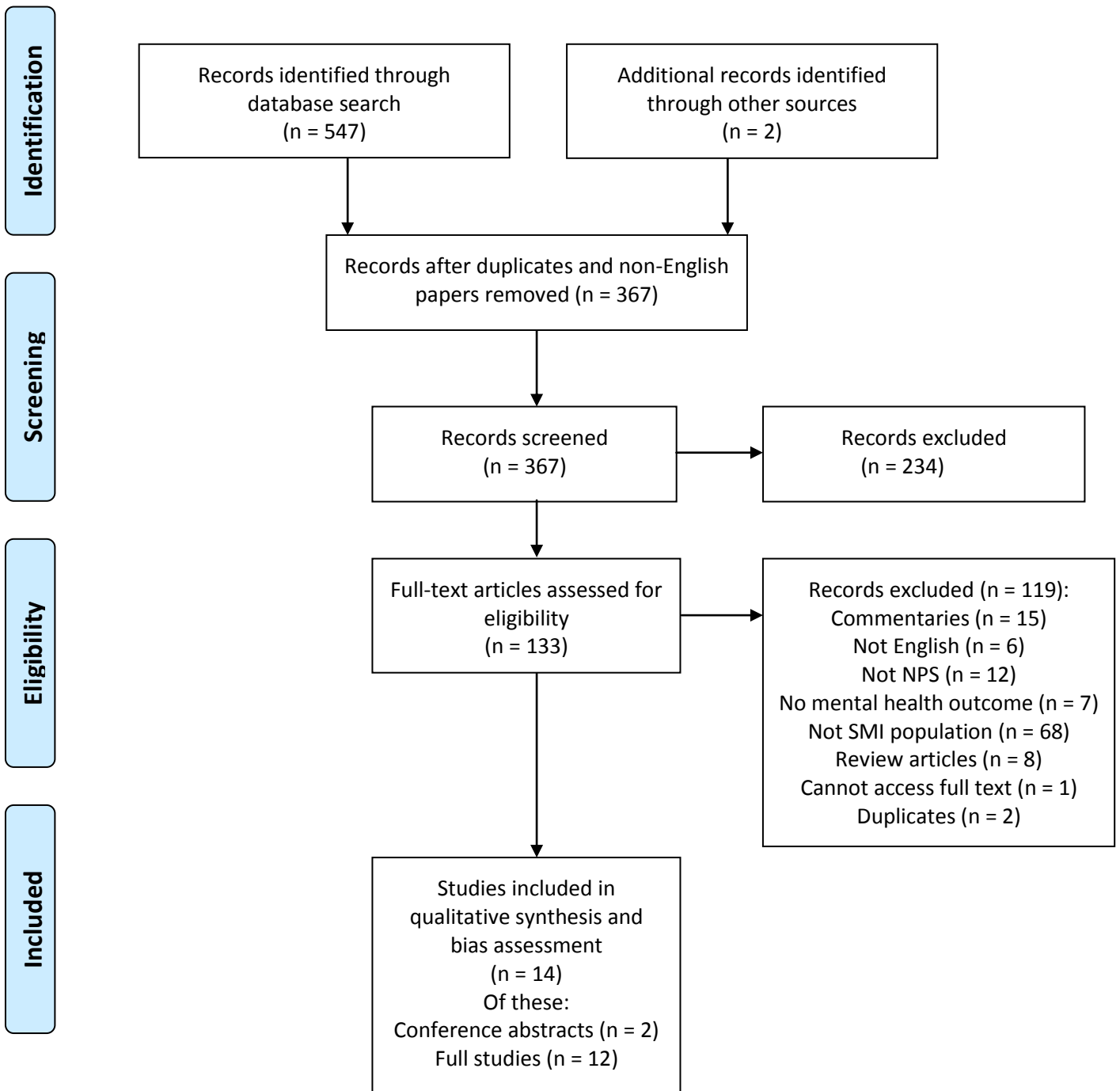


Table 1: Characteristics of participants

	Case studies	Questionnaire study	Qualitative study
Participants	N=19 (N=17 meeting our inclusion criteria)	N=608 (N=135 had psychotic disorders and met our inclusion criteria)	N=21 (N=15 eligible)
Age	Mean=31.3 (SD=7.3)	Mean=45 (SD=15)	Mean=34 (SD=7.9)
Gender	Male (N=14; 82%)	Female (N=322; 53%) Head shop drugs used by 6.5% of females and 19.9% of males.	Male (N=15; 100%)
Primary mental health diagnosis			All treated with antipsychotics
Schizophrenia	N=10		N=10
Bipolar disorder	N=6		N=1
other	Diagnosis not specified (N=1)	Psychotic disorders (N=23)	Schizoaffective disorders (N=4)
Substance taken			
Bath salts (not specified)	N=5		
Synthetic cathinone ‘NRG-3’	N=1		
Methylenedioxypropylamphetamine (MDPV) and flephedrone	N=1		
‘el blanco’ ¹	N=1		
synthetic cannabinoids	N=4 ²		N=15 ³
amphetamine type stimulant compounds ⁴	N=1		
Jimson Weed or „Datura stramonium“	N=1		
Benzylpiperazine (BZP)	N=1		
NBOMe ⁵	N=1		
Salvia divinorum	N=1		
Head shop customers		N=23 (17%)	

¹contains ethylphenidate and benzocaine²(1-(5-fluoropentyl)-3-(1-naphthoyl) indole (AM-2201)³synthetic cannabinoid JWH-018⁴Butylone - a phenethylamine derivative, and Methylenedioxypropylamphetamine - MDPV, a noradrenaline and dopamine reuptake inhibitor⁵NBOMe (25I-NBOMe, 25-CNOMe and 25H-NBOMe)

Table 2: Main characteristics of the included studies

n	Reference	Setting and design	NPS	Sample size	Patient characteristics
1	Anderson et al. (2015).	UK, inpatient psychiatric clinic, case study	'el blanco' containing ethylphenidate and benzocaine; patient drank it mixed with cola	N=1	Age in his 30s, male, paranoid schizophrenia
2	Boucher et al. (2015).	Intensive care unit, case study	NBOMe (25I-NBOMe, 25-CNBOme and 25H-NBOMe)	N=1	Aged 29, schizophrenia and addiction to cannabis (occasional) and LSD (weaned)
3	Celofiga et al. (2014).	Slovenia, intensive psychiatric unit, case study	synthetic cannabinoid (1-(5-fluoropentyl)-3-(1-naphthoyl) indole (AM-2201).	N=4	Aged between 21-35, all males, paranoid schizophrenia (n=2), undifferentiated schizophrenia (n=2)
4	Falgiani et al. (2012).	USA, ED hospital, case study	"Bath salts" (Methylenedioxypropylamphetamine – MDPV- a noradrenaline and dopamine reuptake inhibitor)	N=1	Age 29, female, bipolar disorder and polysubstance abuse
5	Fröhlich et al. (2011)	Ireland, ED hospital, case study	amphetamine type stimulant compounds (Butylone - a phenethylamine derivative, and MDVP)	N=1	Age 28, male, bipolar affective disorder
6	Imam et al. (2013).	USA, ED hospital, case series	"Bath salts" (MDVP)	N=3 (3 eligible out of 5)	Aged 28, 35 and 39, all male, bipolar disorder
7	Khanra et al. (2015).	India, outpatient psychiatric department, case study	Jimson Weed or „Datura stramonium“	N=1	Aged 32, male, paranoid schizophrenia with mental and behavioural disorders due to use of hallucinogens
8	Marques et al. (2013).	ED, hospital, case study	Salvia divinorum	N=1	Aged 24, female, bipolar I disorder
9	McClellan et al. (2012).	UK, outpatient service, case study	"Bath salts" (MDVP)	N=1	Aged 29, male, schizophrenia and past polysubstance use disorder
10	Smith et al (2013)	UK, inpatient psychiatric unit in hospital	Synthetic cathinone	N=1	Aged 45, male, paranoid schizophrenia

					and mood disorder
11	Thornton et al. (2012).	USA, ED hospital, case study	“Bath salts” (MDVP)	N=1	Aged 23, male, diagnosis unreported
12	Tully et al. (2011).	Ireland, acute psychiatric unit, case study	Benzylpiperazine (BZP)	N=1	Aged 48, male, schizophrenia
Cohort and qualitative studies					
1	Every-Palmer (2011).	New Zealand, forensic and rehabilitation service, interviews	synthetic cannabinoid JWH-018	N=15 (15 eligible out of 21)	Mean age 34 (SD=7.9), all males, all treated with antipsychotics. Schizophrenia (n=10), schizoaffective (n=4), bipolar with psychotic feat (n=1)
2	Lally et al. (2013).	Ireland, day hospitals, questionnaires	All types	N=608	Mean age 45 (SD=15), 322 (53%) female, 135 of all had psychotic disorders, 23 (17%) of them used head shop drugs. Head shop drugs used by 6.5% of females and 19.9% of males.

Abbreviations: ED (Emergency department in hospital)

Table 3: Health and mental health effects of NPS

n	Reference	NPS used	Patient characteristics	Mental health effects of NPS	Physical health effects of NPS	Intervention
Full research articles						
Case studies						
1	Anderson et al. (2015).	'el blanco' containing ethylphenidate and benzocaine; patient drank it mixed with cola	Age in his 30s, male, paranoid schizophrenia (N=1)	Unable to give any explanation about what had happened due to severe thought disorder; chaotic and bizarre behaviour pattern. On first occasion thought disorder lasted for 4 weeks and on the second occasion for 10 days.	Vital signs normal except for pulse 124 bpm, reduced to 85 bpm in 1 hour	Treatment with pipotiazine palmitate 50mg/4 weeks was changed to clozapine due to incomplete recovery and residual symptoms of mild thought disorder and poor insight. The patient then stabilised enough for a discussion and education about NPS and insight. He was discharged 6 months after admission, still stable at 3 months follow-up.
2	Boucher et al. (2015).	NBOMe (25I-NBOMe, 25-CNBOme and 25H-NBOMe)	Aged 29, schizophrenia and addiction to cannabis (occasional) and LSD (weaned) (N=1)	Patient instilled a drop of a pink liquid in the nose and became unconscious 1 hour later. One month later the patient still had persistent memory impairment and significant abnormalities in executive functions.	Patient suffered partial seizure with secondary extended generalisation, bilateral and reactive mydriasis, tachycardia (120 bpm), hypertension (225/70 mmHg), temperature	Invasive ventilation in the intensive care unit, no other intervention described

					39°C, profuse sweating (suggesting serotonin syndrome). Had increased creatine kinase without renal impairment. Encephalopathy 1 month later.	
3	Celofiga et al. (2014).	synthetic cannabinoid (1-(5-fluoropentyl)-3-(1-naphthoyl) indole (AM-2201).	Aged between 21-35, all males, paranoid schizophrenia (n=2), undifferentiated schizophrenia (n=2)	P1: elevated affect, prominent behavioural changes (crawling on knees repeating he is a cow), marked sedation, narrowed consciousness P2: severe agitation and anxiety, emergence of paranoid delusions, no altered consciousness P3: elevated affect (hypomanic), severe anxiety and agitation, behavioural changes (possible haptic hallucinations, whispering to himself that he was not free, that his wings were cut off) P4: agitation, severe formal thought symptoms, moderate anxiety, no changes in mood or consciousness, no positive symptoms	P1: no physical symptoms mentioned P2: chest pain, normal blood pressure, tachycardia (135 bpm), ECG normal P3: increased blood pressure (170/120 mm Hg), tachycardia (125 beats per minute) P4: tachycardia (140 beats per minute), normal blood pressure and ECG	P1: no additional psychopharmacotherapy given; signs of intoxication resolved in 6 hours P2: The dose of oral diazepam increased to 10 mg 3x a day. After 4 hours became less anxious, had paranoid ideas for 2-3 hours P3: lorazepam increased to 2.5 mg 3x a day, calmed down after 2 hours P4: intramuscular lorazepam 2 mg, less agitated after 2-3 hours
4	Falgiani et al. (2012).	Bath salts	Age 29, female, bipolar disorder and polysubstance abuse (N=1)	Altered mental state (non-responsive; no further details provided), patient was found curled up in a corner of a friend's home	Pulse 85, blood pressure 114/79, pupils sluggishly reactive	Initial stabilisation with normal saline and Narcan IV 0.4 mg (little response)
5	Fröhlich et al. (2011)	amphetamine type stimulant compounds	Age 28, male, bipolar affective disorder	Acute psychosis	Tonic-clonic seizure, increased heart rate (190 bpm), systolic	Intubation, cooling, mechanical ventilation, labetalol

		(Butylone - a phenethylamine derivative, and Methylenedioxypropylamphetamine - MDPV)	(N=1)		BP 230 mmHg, temperature 39.5° C, acute liver failure on day 2 post ingestion.	and phenytoin, hepatic failure treated conservatively
6	Imam et al. (2013).	Bath salts (ingested)	Aged 28, 35 and 39, all male, bipolar disorder (N=5; of them 3 eligible)	<p>P1: altered mental status and violent behaviour, running naked in the streets and through bushes, oriented to person, place and time, later got confused and agitated. Became unresponsive and did not regain consciousness</p> <p>P4: altered mental status due to bath salts overdose 8 hours before; agitated, making inappropriate comments and oriented to person and place only.</p> <p>P5: brought to the ED with a police escort due to delirious state. Agitated with violent behaviour, confused and disoriented, not answering questions directly.</p>	<p>P1: blood pressure 159/105 mm Hg, heart rate of 120 bpm, normal temperature</p> <p>P4: blood pressure 142/84 mm Hg, heart rate 108 bpm, normal temperature</p> <p>P5: blood pressure 133/94 mm Hg, heart rate 104 bpm, normal temperature</p>	<p>P1: pepper sprayed to manage aggressive behaviour, never gained consciousness and died after several weeks</p> <p>P4: Hydrated over 72 hours and further stay uneventful.</p> <p>P5: Given intravenous fluids for hydration and small amount of benzodiazepines for agitation. Full recovery on day 3 of admission</p>
7	Khanra et al. (2015).	Jimson Weed or „Datura stramonium“	Aged 32, male, paranoid schizophrenia with mental and behavioural disorders due to use of hallucinogens (N=1)	Based on self-report, patient was in a state of altered consciousness helping him forget his distress, and it helped him to get rid of the external control on him. NPS used to control his motor activity. He had preserved affect, delusions of control, persecution and reference. Derogatory 2nd person auditory hallucinations also present. Patient denied mental illness but admitted to regular NPS use.	None reported	Patient diagnosed with schizophrenia and mental and behavioural disorders due to use of hallucinogens based on ICD-10. Treated with haloperidol 20 mg/day

8	Marques et al. (2013).	Salvia divinorum	Aged 24, female, bipolar I disorder (N=1)	Psychotic symptoms: auditory hallucinations, persecutory and religious delusions, all in the absence of mood symptoms. Drug screen was negative but she reported snorting Salvia divinorum in the past month. Mild psychotic symptoms were already present 2 months before.	None reported	With antipsychotic treatment was discharged after 33 days and still stable on 2 months follow-up.
9	McClellan et al. (2012).	Bath salts	Aged 29, male, schizophrenia and past polysubstance use disorder (N=1)	Psychotic symptoms, tangential thought process, disorganised speech and behaviour. Auditory hallucinations and paranoid delusions. Erratic behaviours seemingly consistent with a relapse of methamphetamine use (denied by patient). Psychotic symptoms persisted for 4 weeks despite olanzapine treatment. Patient described the effects of bath salts as 'exactly the same as meth' but cheaper. The euphoria took effect immediately, lasting for 4-5 hours.	Decrease in appetite, no other physical symptoms reported	Olanzapine 20 mg/day increased to 40 mg/day, then intramuscular Risperdal Consta 50 mg every 2 weeks and oral risperidone 4 mg/day
10	Smith et al (2013)	Synthetic cathinone	Aged 45, male, paranoid schizophrenia and mood disorder	Increasing agitation (during a 6 month long hospitalisation), no further details provided	Sinus tachycardia, an apparent dislocation of a thumb and echymoses on both knees from a fall; hyperkalaemia 6.3 mol/L, hyponatraemia of 129 mmol/L, life-threatening acute kidney failure with creatine of 1032 µmol/L;	Intensive care unit, aggressive fluid regime and monitoring, treated under the Mental Capacity Act, antipsychotics stopped pending review of renal and hepatic function, which improved with treatment.
11	Thornton et	Bath salts	Aged 23, male,	Bizarre behaviour, suicidality,	blood pressure 133/68	Due to agitation he

	al. (2012).		diagnosis unreported (N=1)	hallucinations after insufflating a bath salt. Patient was agitated, had visual, tactile and auditory hallucinations. No evidence of trauma.	mmHg; heart rate 109 bpm; temperature 36.9°C, diaphoretic and tachycardic with mydriasis	was physically and chemically restrained. At awakening after 5 hours, he was no longer hallucinating or suicidal.
12	Tully et al. (2011).	Benzylpiperazine (BZP)	Aged 48, male, schizophrenia (N=1)	Taxi driver reported the patient nor responding to questions, murmuring to himself incoherently, engaged in repetitive movements. Staff in hospital described him as irritable, unable to concentrate on simple activities, incoherent when answering questions about his mental state or general topics.	No abnormal cardiovascular, respiratory or gastrointestinal findings; marked myoclonic jerking in all limbs	Treated with olanzapine and by the fourth day he returned to his baseline level of functioning.
Cohort and qualitative studies						
1	Every-Palmer (2011).	synthetic cannabinoid JWH-018	Total N=15 (15 eligible out of 21) Mean age 34 (SD=7.9), all males, all treated with antipsychotics. Schizophrenia (n=10), schizoaffective (n=4), bipolar with psychotic feat (n=1)	Anxiety and psychotic symptoms commonly reported; 69% of users experiencing symptoms consistent with psychotic relapse after smoking the drug. Nobody reported becoming physically unwell after using it. Three people reported developing tolerance but no one had withdrawal symptoms.		
2	Lally et al. (2013).	Any type of NPS participants self-reported to have used	Total N=608) Mean age 45 (SD=15), 322 (53%) female, 135 of all had psychotic disorders, 23 (17%) of them used head shop drugs. Head	Total of 41 (54%) of individuals reported deleterious effect of head shop products on mental health. Most commonly, people with psychosis had exacerbation or development of psychotic symptoms (65%). All in-patients with psychosis reported deleterious effects and		

			shop drugs used by 6.5% of females and 19.9% of males.	worsening of psychosis (67%) after ingesting head shop drugs.		
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