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Complete List of Authors:	Bennett, Kyle; University of Edinburgh College of Medicine and Veterinary Medicine, Undergraduate - 5th Year Hare, Helen; Royal Edinburgh Hospital Department of Psychiatry Waller, Robert; Waitemata District Health Board Mental Health Unit, He Puna Waiora Adult Mental Health Inpatient Unit Alderson, Helen; Queen Margaret Hospital, Department of Psychiatry Lawrie, Stephen; Kennedy Tower, Psychiatry
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TITLE

The effect of prohibition and seizure on the prevalence of Novel Psychoactive Substance (NPS) use in psychiatric patients

CORRESPONDING AUTHOR

Dr Helen L Alderson: h.alderson@nhs.net, Department of Psychiatry, Queen Margaret Hospital, Whitefield Road, Dunfermline, KY12 0SU, UK. Telephone: 01383 627041

AUTHORS

Kyle Hemingway Bennett[1], Helen Mary Hare[2], Robert Marten Waller[3], Helen Louise Alderson[4], Stephen MacGregor Lawrie[5]

1. Undergraduate – 5th year, University of Edinburgh, Edinburgh, UK.
2. Royal Edinburgh Hospital, Morningside Terrace, Edinburgh, EH10 5HF, UK.
3. He Puna Waiora Adult Mental Health Inpatient Unit, Waitemata District Health Board, Private Bag 93503, Takapuna, Auckland 0622, New Zealand.
4. Department of Psychiatry, Queen Margaret Hospital, Whitefield Road, Dunfermline, KY12 0SU, UK.
5. Kennedy Tower, Royal Edinburgh Hospital, Morningside Park, Edinburgh, EH10 5HF, UK.

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ABSTRACT

Objectives: Assess the impact of selective prohibition and seizure of NPS supply on NPS use prevalence within psychiatric admissions and evaluate demographic characteristics of current NPS users.

Design: A 6-month retrospective review of discharge letters between 1st October 2015 – 31st March 2016.

Setting: General Psychiatry inpatients and Intensive Home Treatment Team community patients at a psychiatric hospital in a Scottish city.

Participants: All participants were between the ages 18-65. After application of exclusion criteria, 473 discharge letters of General Psychiatry patients were deemed suitable for analysis and 264 Intensive Home Treatment Team (IHTT) patient discharge letters were analysed.

Interventions: A nationwide Temporary Class Drug Order (TCDO) was placed on 10th April 2015 reclassifying methylphenidate-related compounds as Class B substances. On 15th October 2015, local Forfeiture Orders were granted to Trading Standards permitting the seizure of NPS supplies.

Primary and secondary outcome measures: The primary outcome measure was to determine the prevalence of NPS use in two cohorts. Secondly, demographic features of patients and details regarding their psychiatric presentation were analysed.

Results: The prevalence of NPS use in General Psychiatry and IHTT patients was 6.6% and 3.4%, respectively. Inpatients using NPS compared to non-users were more likely to be male (OR: 2.92, CI: 1.28-6.66, p=0.009), have a forensic history (OR: 5.03, CI: 2.39-10.59, p<0.001) and be detained under an Emergency Detention Certificate (OR: 3.50, CI: 1.56-7.82, p=0.004). NPS users were also more likely to be diagnosed under ICD-10 F10-19 (OR: 9.97, CI: 4.62-21.49, p<0.001).

Conclusions: Following interventions, the prevalence of NPS use in psychiatric inpatients has fallen. NPS continue to be used by a demographic previously described resulting in presentations consistent with a drug-induced psychosis and at times requiring detention under the Mental Health Act. Further research is required to evaluate the effectiveness of the recent prohibition of all NPS.

ARTICLE SUMMARY

Strengths and limitations of this study:

- Recent public health interventions concerning NPS have been evaluated, specifically their association with a reduction in the prevalence of NPS use in a psychiatric population.
- The strain placed on services by NPS use has been quantified by studying the duration of patients' admissions and the likelihood that they are detained under the Mental Health Act.
- As the NPS user sample was relatively small compared to previous work, figures pertaining to the demographic features of this group should be interpreted with caution.
- A number of the study outcomes were poorly recorded for in discharge letters, which may be accounted for by the variation in the quality of discharge letters.
- The study period encompasses a 6-month period following the issue of Forfeiture orders on 15th October 2015 therefore it is not possible to comment if the reduction of NPS use within this population is more attributable to a particular one of the two interventions.

INTRODUCTION

Background

In recent years, a new public health issue has arisen: Novel Psychoactive Substances (NPS), more commonly known as 'legal highs'. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) defines an NPS as a drug not controlled by UN drug conventions with potential to cause as much public health risk as classic illicit drugs.[1] Attempts have been made to classify NPS chemically,[2] of which synthetic cannabinoids (cannabis replacements) and synthetic cathinones (stimulants) account for the majority.[3] However, in 2014 alone over a hundred new NPS were introduced to the market, many of which are loosely termed 'research chemicals', signifying the challenges in studying and classifying such substances.[3]

Over the past decade, NPS have been assimilated into the repertoire of drugs available to habitual drug users.[4] Sophisticated marketing of NPS has rendered them as socially acceptable and safe,[5] despite their involvement in numerous drug-related deaths.[6] Until recently, NPS have escaped prohibitive legislation by including labels on packaging: 'not for human consumption' or 'for research only',[7] despite the contrary insinuations made elsewhere. Methylphenidate derivatives, such as ethylphenidate, have made a considerable impact across the UK. Ethylphenidate was first recognised in UK 'head-shops' (drug paraphernalia shops) in November 2011 via the UK Forensics Early Warning System[8] and was subsequently reported to the EMCDDA.[7] However, ethylphenidate had already been widely discussed on online user forums before this time.[9] Its effects bear similarity to that of cocaine and, to some extent, amphetamines, including euphoria, increased sociability,[10] tachycardia, hypertension, palpitations,[11] multi-sensory hallucinations,[12] and a considerable urge to reuse.[10, 13] NPS in general have been associated with various psychiatric symptoms, which often present as an acute transient psychotic episode[14] although the long term impact on mental health is unknown. Ethylphenidate has been implicated in numerous fatalities[6, 15] and was, in one study, discovered in the possession of two subjects following suicide, suggesting a possible association with psychiatric illness.[16] In Edinburgh, during 2014, ethylphenidate resulted in a significant burden for Police Scotland; the incidence of legal-high related casualties increased amidst reports of 'bizarre and violent behaviour'.[17] As well as admissions to acute mental health services, a cluster of soft tissue infections and necrotic ulcers resulted from parenteral ethylphenidate use.[12, 17]

On 10th April 2015 the UK Government responded by placing a Temporary Class Drug Order (TCDO) under the Misuse of Drugs Act 1971 on methylphenidate derivatives making supply and production, but not possession, punishable by imprisonment.[18-19] Police Scotland reported a reduction in parenteral infections, publicly discarded needles and emergency admissions since this time.[20] Forfeiture Orders were granted on 15th October 2015 from the Sheriff Court in Edinburgh to Trading Standards permitting seizure of all NPS from head-shops.[21] More recently, the Psychoactive Substances Act (2016) was imposed, which criminalises any NPS – a so-called blanket ban.[22] However, other substances classified under the Misuse of Drugs Act such as mephedrone have, since their selective banning, become integrated into the clubbing environment[23] and distributed under the guise of legal NPS,[24] raising questions as to how effective specific legislative bans are.

In recent years, the public health issue of NPS use has been widely researched, including a previous study at this centre. Work by Stanley *et al*. established that 22.2% of inpatients admitted to acute psychiatric wards at the Royal Edinburgh Hospital were using NPS, 59.3% of whom had psychiatric symptoms attributable to their drug use.[25] Since legislative changes have been implemented, no research has been conducted to analyse ongoing trends in NPS use.

Objectives

This study aimed to examine the possible impact of the recent public health interventions on NPS-related psychiatric admissions, building on the findings of a previous study by Stanley *et al*.[25] In addition to examining admissions to the acute psychiatric inpatient wards at the Royal Edinburgh Hospital, patients admitted to the Intensive Home Treatment Team (IHTT), a community-based psychiatric crisis team, covering the same catchment area as the Royal Edinburgh Hospital, were also included. The study aimed to evaluate how effective recent public health interventions have been in reducing NPS use, as reflected in NPS-related admissions to these two services. The primary hypothesis was that the interventions made on a national and local level would have reduced the prevalence of NPS use in patients admitted to these services.

METHODS

Study design and setting

This study was a retrospective review of discharge letters written for two cohorts of psychiatric patients - General Psychiatry inpatients and community based IHTT patients - at the Royal Edinburgh Hospital in Edinburgh, United Kingdom. Discharge letters were written by medical staff for inpatients; IHTT discharge letters were written by community psychiatric nurses and reviewed by medical staff.

Participants

Adult patients (18-65 years old) admitted to the Royal Edinburgh Hospital between 1st October 2015 and 31st March 2016 were identified from the TrakCare™ Electronic Patient Record (InterSystems) database.[26] Only patients admitted to General Psychiatry who had been subsequently discharged from hospital by 30th June 2016 were included in the study. Those admitted to specialist services or admitted as inpatient day-cases for electroconvulsive therapy (ECT) were excluded **(Figure 1)**. All adult patients admitted to IHTT were included.

Data collection

SAP BusinessObjects (SAP)[27] was used by KHB and RMW to extract details regarding patient admissions, including Principal Diagnosis and Code (consistent with International Statistical Classification of Diseases and Related Health Problems Version 10 (ICD-10)),[28] duration of admission, and legal status (Mental Health (Care and Treatment) (Scotland) Act 2003)[29] whilst in hospital, which was categorised as informal, Emergency Detention Certificate (EDC), Short Term Detention Certificate (STDC) or Compulsory Treatment Order (CTO). Patients were assigned subject numbers to ensure anonymity.

Additional study outcomes relating to patient demographics (age, gender, employment status and home circumstances); forensic history (any forensic history of note and custodial sentences); substance use (NPS use, contribution to psychiatric presentation, name of NPS, route of administration and other substance use); and any psychiatric symptoms recorded during admission were collected from patient discharge letters on eHealth systems by KHB. Some were extractable as free-text from TrakCare™ (Intersystems) using SAP Business Objects. Others were only available as PDF (Portable Document Format) files uploaded to the linked document storage system SCI-Store.[30] Both locations were searched.

When recorded, NPS brand names were cross-checked on an online database of NPS to reveal type and chemical details.[31] Where study outcomes were not recorded in discharge letters, these were

assumed to be negative and grouped with explicitly negative data. Patients referred to IHTT were identified using SAP Business Objects (SAP) and the above study outcomes were collected from IHTT discharge letters either within a free-text TrakCare™ extract or uploaded PDFs as above. Data collection was repeated for a sample of subjects by HMH for quality control purposes.

Statistical methods

Statistical analysis was carried out using SPSS V22.0.0.1 (IBM). Independent two-sample Student's t-tests were used to assess the differences in continuous dependent variables between NPS users and non-NPS users. Pearson χ^2 tests were used to compare differences and generate Odds Ratios (ORs) in subgroups for remaining categorical variables, using Fisher's exact test and Phi/Cramer's V symmetric measures for significance where appropriate. Two-tailed two-sample z-tests were performed for comparisons between the proportion of NPS users in this study and those in Stanley *et al*.[25]

RESULTS

A total of 473 General Psychiatry inpatient cases were included in the analysis after application of the exclusion criteria **(Figure 1)**. Of these, 31 patients were reported to be currently using NPS on admission. A two-tailed two-sample z-test between the proportion of NPS users in this population (6.6%, n=473) and of that in Stanley *et al.* (22.2%, n=488)[25] revealed a statistically significant difference (z=6.7, p<0.001). A total of 264 patients were discharged from IHTT, of which 9 cases (3.4%) were identified as NPS users at the time of admission. Across both cohorts, the prevalence of NPS use was 5.4%.

For General Psychiatry and IHTT NPS users, the types of NPS were recorded in 41.9% and 33.3% of cases, respectively. In cases where NPS types were identified, NPS use was recorded to contribute to the psychiatric presentation 77.4% and 22.2% of the time. Of those identified, stimulants (ethylphenidate, MPA, 3-FPM) and research chemicals (e.g. MDAI, MXP) comprise the largest proportion of reported NPS at 25.8% for General Psychiatry and 22.2% for IHTT NPS users. Data from the IHTT cohort were excluded from further analysis due to insufficient recording of outcome measures in discharge letters.

Figure 2 shows the percentage of admissions for NPS users and non-NPS users over the study period (October-March). The month of October accounted for the largest proportion of NPS user admissions in which 16.1% were admitted in the first fortnight and 19.4% in the remainder of the month (a total 35.5% across October). However, compared to non-NPS users these figures were not statistically significant.

The collective length of admission for all NPS users amounted to 4.41% of the total length of admission for all inpatients. Mean length of admission between NPS users and non-NPS users was not statistically significant.

NPS users were significantly more likely to be detained under the MHA than non-NPS users (OR: 3.37, CI: 1.57-7.21, p=0.002). When individual modes of detention were considered (EDC, STDC and CTO), there was a statistically significant difference between NPS users and non-NPS users only in detention under an EDC, where 32.3% of NPS users were detained under this order compared with 12.0% of non-NPS users (OR: 3.50, CI: 1.56-7.82, p=0.004).

The demographic features of NPS users compared to non-NPS users are shown in **Table 1**. Significant differences were observed between NPS users and non-NPS users for mean age (35.1 ± 9.8 (SD) years vs 40.0 ± 11.7 (SD) years, p=0.023). Furthermore, a bimodal distribution of age ranges emerged in NPS users where peaks were observed in the 18-25 and 41-45 age ranges. Age of NPS users was significantly more likely to be within the latter range compared to non-NPS users (OR: 2.87, CI: 1.29-6.37, p=0.007). NPS users were more likely to be male (OR: 2.92, CI: 1.28-6.66, p=0.009) and have a forensic history recorded in their discharge letter (OR: 5.03, CI: 2.39-10.59, p<0.001) compared to non-NPS users. However, no statistical differences between NPS users and non-NPS users were observed in the proportions of patients recorded to have served custodial sentences.

		NPS Users (n=31)	Per cent	Non-NPS Users (n=442)	Per cent
Mean age (SD)		35.1 (9.8)*		40 (11.7)*	
Gender	Male	23*	74.19%	218*	49.3%
	Female	8*	25.81%	221*	50.0%
	Transgender	0	0.00%	3	0.7%
Employment	Unemployed	12	38.71%	176	39.8%
	Student	1	3.23%	17	3.8%
	Employed	1	3.23%	51	11.5%
	Full-time	1	3.23%	44	10.0%
	Part-time	0	0.00%	7	1.6%
	Self-employed	0	0.00%	8	1.8%
	Retired	0	0.00%	1	0.2%
	Prison	0	0.00%	6	1.4%
	Not recorded	17	54.84%	183	41.4%
Home circumstances	Independent	12	38.71%	250	56.6%
	Fully independent	5	16.13%	165	37.3%
	Benefits	5	16.13%	71	16.1%
	Council tenancy	2	6.45%	14	3.2%
	Supported	6	19.35%	14	3.2%
	Homeless	2	6.45%	21	4.8%
	Prison	0	0.00%	1	0.2%
	Not recorded	11	35.48%	138	31.2%
Forensic History		17**	54.84%	86**	19.5%
Previous custodial sentence		4	12.90%	27	6.1%
Use of MHA	Any use of MHA	20	64.52%	155	35.1%
	EDC	10	32.26%	53	12.0%
	STDC	12	38.71%	133	30.1%
	CTO	1	3.23%	30	6.8%
ICD-10 Diagnosis Groupings	F00-09	0	0.00%	3	0.7%
	F10-19	17**	54.84%	48**	10.86%
	F20-29	11	35.48%	122	27.60%
	F30-39	1**	3.23%	144**	32.58%
	F40-49	1	3.23%	42	9.50%
	F50-59	0	0.00%	2	0.45%
	F60-69	1	3.23%	53	11.99%
	F70-79	0	0.00%	1	0.23%

	F80-89	0	0.00%	1	0.23%
	Not recorded	0	0.00%	16	3.62%
	Other	0	0.00%	11	2.49%
Substance use	cannabis	18**	58.10%	93**	21.00%
	alcohol	8	25.80%	120	27.10%
	non-substitute opiates	8*	25.80%	43*	9.70%
	substitute opiates	7	22.60%	46	10.40%
	other	7*	22.60%	17*	3.80%
	MDMA	4*	12.90%	16*	3.60%
	amphetamines	3	9.70%	25	5.70%
	cocaine	3	9.70%	39	8.80%
	benzodiazepines	3	9.70%	34	7.70%
Any substance use		26**	83.90%	217**	49.10%

*Table 1: Demographic features of NPS users and non-NPS users. *Denotes a statistically significant difference between NPS users and non-NPS users, p<0.05 and **p<0.001. SD, Standard Deviation; EDC, Emergency Detention Certificate; STDC, short term detention certificate; CTO, compulsory treatment order; ICD, International Statistical Classification of Diseases and Related Health Problems; F00-F09, Organic, including symptomatic, mental disorders; F10-19, Mental and behavioural disorders due to psychoactive substance use; F20-F29, Schizophrenia, schizotypal and delusional disorders; F30-39 Mood [affective] disorders; F40-F49, Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders; F50-F59, Behavioural syndromes associated with physiological disturbances and physical factors; F60-F69, Disorders of adult personality and behaviour; F70-F79, Mental retardation; F80-89, Disorders of psychological development; Other, Behavioural and emotional disorders with onset usually occurring in childhood and adolescence/Unspecified mental disorder; MDMA, 3,4-Methylenedioxymethamphetamine; NPS, novel psychoactive substances.*

NPS users were significantly more likely to use illicit substances other than NPS compared to non-NPS users (OR: 5.44, CI: 2.05-14.43, p<0.001). Compared to non-NPS users, NPS users were significantly more likely to use cannabis (OR: 4.56, CI: 2.17-9.58, p<0.001), non-substitute opiates (OR: 2.85, CI: 1.16-7.03, p=0.018), MDMA (OR: 3.94, CI: 1.23-12.61, p=0.013) and other uncategorised substances, which included hallucinogens and illegally acquired prescription drugs (OR: 5.88, CI: 1.97-17.58, p<0.001).

Figure 3 reveals that ICD-10 diagnosis groupings for NPS users compared to non-NPS users were more likely to be F10-19 (OR: 9.97, CI: 4.62-21.49, p<0.001) and less likely to be F30-39 (OR: 0.07, CI: 0.009-0.516, p<0.001). The most significant difference in diagnosis was for Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances disorder (ICD-10 F19), (OR: 28.66, CI: 11.85-69.30, p<0.001).

NPS users compared to non-NPS users were found to be significantly more likely to present with paranoia (OR: 2.34, CI: 1.08-5.08, p=0.036) and thought-disorder (3.44, CI: 1.50-7.90, p=0.002) and less likely to present with low mood (OR: 0.29, CI: 0.11-0.76, p=0.007) and suicidal thoughts (OR: 0.129, CI: 0.03-0.550, p=0.001).

DISCUSSION

Principal findings

The present study builds upon the findings made by Stanley *et al*.[25] by evaluating the impact of recent public health changes. As well as acute psychiatric inpatients, a second cohort was included, which comprised of patients admitted to IHTT – a population previously not considered. In contrast to the prevalence of 22.2% found by the previous work in psychiatric inpatients,[25] the present data revealed a prevalence of NPS use in this group of 6.6% following recent public health interventions – a 15.6% reduction. Additionally, the prevalence of NPS use reported in discharge letters from the IHTT cohort was found to be 3.4%. The present study found that of the NPS types recorded, 'research chemicals' have been commonly used by patients. The relative popularity of this diverse group of chemicals may suggest that other compounds have been recently adopted by NPS users as a substitute for ethylphenidate since the TCDO.

Strengths and weaknesses

Unfortunately, a large proportion of demographic outcome measures were not recorded in discharge letters and due to the relatively small sample size, it is not possible to comment on these. Generally, demographic characteristics were similar to those found in the previous study:[25] NPS users were more likely to be male, polysubstance misuse was more likely and mean age was similar (35.1 compared to 36.1 years old). The age distribution of NPS users was studied more thoroughly, however, and a bimodal distribution was observed with peaks in the 18-25 and 41-45 age groups, the latter of which was significant compared to non-NPS users. This is broadly in agreement with the findings of the Drugwise NPS: Come of Age report,[32] which suggested that NPS use is not confined to a single generation; it perhaps appeals to these discrete generations as a 'club drug'/'party pill'[4, 33] or as a drug substitute,[34] respectively. As in the previous work,[25] the present study suggested that NPS users were more likely to use cannabis concomitantly; however, rather than a higher prevalence of substitute opiates it was found that NPS users within this study were more likely to use non-substitute opiates and MDMA. It is possible that these drug choices relate again to the prominent age groups observed – MDMA users aged 18-25 have previously been shown to be more likely to use NPS;[35] and NPS have been implicated in opiates users, which may correspond to the 41-45 age group.[15-16] To assess differences in diagnoses between NPS users and non-NPS users this study adopted a standardised approach by recording ICD-10 codes. The most common principal diagnosis assigned to NPS users was F19.5 (Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances: psychotic disorder). Previous work also found that this was the most commonly recorded diagnosis.[25] On the basis of the present data, it is not possible to demonstrate a causal link between NPS and drug-induced psychosis. However, evidence from this study suggests that public health interventions may be effective in reducing the prevalence of NPS use in individuals vulnerable to their effects on mental state. In an effort to quantify the strain of these admissions on psychiatric services, length of stay and use of the Mental Health Act[29] were examined. Compared to Stanley *et al*.,[25] it was found that almost double the proportion of NPS users in this study were detained and significant differences were observed in the use of EDC between NPS users and non-NPS users. Initially this could, in combination with the above findings regarding diagnosis, suggest that more users than in the earlier study are presenting severely psychotic enough to warrant detention. However, this finding should be interpreted with caution as changes in the working patterns of medical staff locally has consequently resulted in more out-of-hours detentions placed by junior medical staff, who are only able to detain under an EDC. This change in practice may be acting as a confounding factor for an apparent increase in this type of detention for patients. Psychotic episodes in such patients have been documented previously as transient and acute;[36] no significant differences in average length of stay between NPS users and

non-NPS users were found. The total length of stay in this group accounts for 4% of length of stay across all patients, which is a smaller proportion than the proportion of NPS users within the General Psychiatry cohort (6.6%). Thus no disproportionate or considerable strain on services has been observed at present and due to lack of data from Stanley *et al*.[25] it is not possible to evaluate if there has been any significant change.

Limitations and future research

The study period covered 1st October 2015 – 31st March 2016, a 6-month period encompassing significant public health changes with regard to NPS. It is unfortunately not possible to say which of the two public health changes is associated with the reduction in prevalence of NPS use. However, these interventions together represent a ban and a seizure of supplies, and conclusions can be drawn about the collective impact of these changes. Whilst comparisons may be made with the previous study, it is important to bear in mind that Stanley *et al*.[25] examined admissions during the months of July and August and it is possible that seasonal differences may have some influence here.[37] One limitation is that the sample size of patients admitted to hospital/IHTT following NPS use is small and it most likely represents a small minority of the whole NPS using population. Recent data have estimated that 937,000 people aged 16-59 in England and Wales had used an NPS at least once and 279,000 in the past year.[38] With limited data on the prevalence and demographics of NPS use in the general population, it is only possible to apply conclusions drawn in this study to psychiatric inpatients. Due to the nature of the study design, it is also possible that NPS use prevalence was underestimated. Furthermore, reviewing discharge letters is vulnerable to two forms of bias: reporting bias, in which the quality of discharge letters is heterogeneous; and observer bias, which arises due to variation in summarising recorded clinical impressions. The study aimed to reduce observer bias by reporting only explicitly positive NPS use cases and coding all others as non-NPS cases. This relies on clinicians directly inquiring into NPS use. Some discharge letters stated that NPS use was unknown but clinically suspected, which is perhaps a consequence of clinicians not routinely asking about NPS use when interviewing patients. In cases where NPS users were identified by clinical inquiry, inadequate recording of NPS types across both cohorts highlights poor recognition of the contribution NPS may have to psychiatric illness, perhaps due to a lack of relevant training for healthcare practitioners.[39] The NEPTUNE project, a clinical guidance project, has made significant progress in resolving this gap by constructing an extensive document detailing the presentation and management of numerous NPS.[40] Assuming inquiry by clinicians, the recording of NPS use is still limited as this approach relies on self-reporting by patients. It is also possible that patients using other substances are unintentionally also ingesting NPS.[41] Approved clinical screening tests are not yet in place for identifying NPS, but some progress has been made in developing a method of tandem mass spectrometry for identifying the most common NPS in circulation.[42] Use of these biochemical techniques would allow for reliable measurements in future studies relating to NPS use. However, rapid changes in the chemical composition of NPS products may make such tests obsolete at an overwhelming rate. Whilst there are limitations associated with a retrospective review, it is useful for providing epidemiological findings and, as such, was deemed appropriate here for relatively simple data collection from an electronic patient database. Furthermore, this design provides a quantitative report on NPS users in contrast to the relative abundance of case reports in the literature, which do not allow for reliable systematic reviews to be conducted.[43] In order to address the methodological issue of poor recording of NPS use by clinicians, a long-term prospective cohort study could be carried out using standardised *pro formas* with well-defined reporting criteria available on wards. This type of study would be of particular benefit across the United Kingdom in the period following the Psychoactive Substances Act (2016).[22] More detailed analysis of NPS users will also identify whether these patients are previously known to suffer a psychiatric illness,

what services they subsequently use and if these patients successively develop chronic psychiatric illnesses.

Generalisability

Since the TCDO placed on ethylphenidate and forfeiture orders of NPS within Edinburgh, there has been a reduction in the prevalence of NPS use in psychiatric admissions locally. This study does not aim to suggest there is a causal link between NPS and psychiatric illness but other studies have provided evidence to support this link.[14] The current findings instead suggest that prohibitive legislation coupled with the intensive and organised seizure of NPSs may have contributed to the reduction of NPS-related admissions to acute psychiatric wards and to a local crisis team. The advent of the Psychoactive Substances Act (2016)[22] renders all NPS illegal and thus provides an opportunity to assess similar policy changes implemented on a national level. In response to the rise of NPS, New Zealand has adopted a regulatory licensing system whereby NPS can be approved for use if it is felt that there is a low-risk of associated harm.[44] Elsewhere however, countries have taken 'blanket ban' stances similar to the Psychoactive Substances Act (2016),[22] and these have failed to demonstrate reductions in NPS use and availability.[45] The present findings suggest that selective prohibition and general confiscation may be effective in reducing NPS-related admissions. Whilst these findings are from a population requiring psychiatric admission 6 months after public health measures were implemented, such results may be sustained and common to other clinical specialties. Future studies could be carried out to examine the impact of the Psychoactive Substances Act (2016)[22] on psychiatric and general hospital admissions.

FIGURE LEGENDS

Figure 1: Flowchart of inclusion/exclusion criteria and patient groups. Sub-groups of the lowest tier in the flowchart were analysed collectively as non-NPS users. REH, Royal Edinburgh Hospital; CAMHS, Child & Adolescent Mental Health Services; ECT, electroconvulsive therapy; NPS, novel psychoactive substance.

Figure 2: The percentage of NPS users and non-NPS users admitted in fortnightly intervals between October 2015 – March 2016. NPS, novel psychoactive substance.

Figure 3: The percentage of NPS users and non-NPS users assigned Principal Diagnoses in accordance with ICD-10 Groups. *Denotes a statistically significant difference between NPS users and non-NPS users ($\chi 2$), $p<0.001$. ICD, International Statistical Classification of Diseases and Related Health Problems; NPS, novel psychoactive substances.

ORIGINAL PROTOCOL

Supplementary file

FUNDING STATEMENT

This work was supported by the University of Edinburgh School of Medicine, which provided a basic salary for the primary author of this study.

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests with regards to this study.

AUTHOR'S CONTRIBUTIONS

The study design was adapted from that of Stanley *et al.* (2016) and the protocol was written by HLA. KHB collected and analysed the data. RMW supported the data collection process. HMH collected a sample of data as a means of quality control. HLA provided supervision on aspects of data collection. SML supervised all aspects of the project. All authors contributed to the review and editing of the final manuscript.

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DATA SHARING STATEMENT

We are awaiting the journal's instruction on data submission as per Dryad repository guidance on BMJ Open manuscript submissions (https://datadryad.org/pages/journalLookup). Thereafter the DOI for our dataset will be provided.

REFERENCES

1. European Monitoring Centre for Drugs and Drug Addiction. *Action on new drugs*. 2016. http://www.emcdda.europa.eu/activities/action-on-new-drugs (accessed 4 Dec. 2016).
2. Liechti M. Novel psychoactive substances (designer drugs): overview and pharmacology of modulators of monoamine signaling. *Swiss Med Wkly.* 2015;145:w14043.
3. European Monitoring Centre for Drugs and Drug Addiction. New psychoactive substances in Europe. An update from the EU Early Warning System. March 2015. http://www.emcdda.europa.eu/system/files/publications/65/TD0415135ENN.pdf (accessed 4 Dec. 2016).
4. Moore K, Dargan PI, Wood DM, *et al*. Do novel psychoactive substances displace established club drugs, supplement them or act as drugs of initiation? The relationship between mephedrone, ecstasy and cocaine. *Eur Addict Res*. 2013;19:276-82.
5. Corazza O, Valeriani G, Bersani FS, *et al*. "Spice,""Kryptonite,""Black Mamba": An Overview of Brand Names and Marketing Strategies of Novel Psychoactive Substances on the Web. *J Psychoactive Drugs*. 2014;46:287-94.
6. McAuley A, Hecht G, Barnsdale L, *et al*. Mortality related to novel psychoactive substances in Scotland, 2012: An exploratory study. *Int J Drug Policy*. 2015;26:461-7.
7. European Monitoring Centre for Drugs and Drug Addiction. *2016 EU Drug Markets Report – Chapter 7*: *New psychoactive substances — Understanding the market for new psychoactive substances in Europe*. 2016. http://www.emcdda.europa.eu/publications/eu-drug-markets/2016/online/new-psychoactive-substances/market (accessed 4 Dec. 2016).
8. Home Office. Annual Report on the Home Office Forensic Early Warning System (FEWS) A System to Identify New Psychoactive Substances in the UK. May 2012. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/225840/fews.pdf (accessed 4 Dec. 2016).
9. Bluelight.org. *Bluelight – Forum – Focus Forums, Other Drugs – Ethylphenidate*. 2010. http://www.bluelight.org/vb/threads/499397-Ethylphenidate (accessed 4 Dec. 2016).
10. Ho JH, Bailey GP, Archer JR, *et al*. Ethylphenidate: availability, patterns of use, and acute effects of this novel psychoactive substance. *Eur J Clin Pharmacol*. 2015;71:1185-96.
11. Bailey GP, Ho JH, Hudson S, *et al*. Nopaine no gain: Recreational ethylphenidate toxicity. *Clin Toxicol*. 2015;53:498-9.
12. Lafferty C, Smith L, Coull A, *et al*. The experience of an increase in the injection of ethylphenidate in Lothian April 2014-March 2015. *Scott Med J*. 2016: 0036933016649871.
13. Soussan C, Kjellgren A. "Chasing the High"–Experiences of Ethylphenidate as Described on International Internet Forums. *Subst Abuse*. 2015;9:9.
14. Schifano F, Orsolini L, Duccio Papanti G, *et al*. Novel psychoactive substances of interest for psychiatry. *World Psychiatry*. 2015;14:15-26.
15. Parks C, McKeown D, Torrance HJ. A review of ethylphenidate in deaths in east and west Scotland. *Forensic Sci Int*. 2015;257:203-8.
16. Maskell PD, Smith PR, Cole R, *et al*. Seven fatalities associated with ethylphenidate. *Forensic Sci Int*. 2016;265:70-4.
17. Advisory Council on the Misuse of Drugs. Methylphenidate-based NPS: A review of the evidence of use and harm. March 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/420983/TCDO_methylphenidate_NPS.pdf (accessed 4 Dec. 2016).
18. United Kingdom Parliament. *The Misuse of Drugs Act 1971 (Temporary Class Drug) Order 2015*. S.I. 2015/1027.

19. Home Office. *Circular 015/2015: temporary control of 5 methylphenidate-based NPS*. 2015. https://www.gov.uk/government/publications/circular-0152015-temporary-control-of-5-methylphenidate-based-nps/circular-0152015-temporary-control-of-5-methylphenidate-based-nps (accessed 4 Dec. 2016).
20. Iverson L, Advisory Council on the Misuse of Drugs. Re: TCDOs and ACMD position on methylphenidate-based NPS. February 2016. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/503873/TCDO_Letter_-_phenidates_and_12_month_29_Feb_2016.pdf (accessed 4 Dec. 2016)
21. Bury J, The City of Edinburgh Council Health, Social Care and Housing Committee. *Novel Psychoactive Substances – Trading Standards Enforcement Action.* 2015. www.edinburgh.gov.uk/download/meetings/id/48793/item_710_-_novel_psychoactive_subsdtances_–_trading_standards_enforcement_action (accessed 4 Dec. 2016)
22. United Kingdom Parliament. *Psychoactive Substances Act 2016*. c. 2.
23. Wood DM, Hunter L, Measham F, *et al*. Limited use of novel psychoactive substances in South London nightclubs. *QJM*. 2012:hcs107.
24. Brandt SD, Sumnall HR, Measham F, *et al*. Analyses of second-generation 'legal highs' in the UK: Initial findings. *Drug Test Anal*. 2010;2:377-82.
25. Stanley JL, Mogford DV, Lawrence RJ, Lawrie SM. Use of novel psychoactive substances by inpatients on general adult psychiatric wards. *BMJ Open*. 2016;6:e009430.
26. InterSystems. *TrakCare – Unified healthcare information system*. 2016. http://www.intersystems.com/our-products/trakcare/trakcare-overview-2/ (accessed 4 Dec. 2016).
27. SAP. *SAP BusinessObjects Business Intelligence*. 2016. http://go.sap.com/uk/product/analytics/bi-platform.html (accessed 4 Dec. 2016).
28. World Health Organization. International statistical classification of diseases and related health problems. World Health Organization; 2004.
29. Scottish Parliament. *Mental Health (Care and Treatment) (Scotland) Act 2003*. a.s.p. 13.
30. Scottish Care Information - Information Services of the NHS National Services Scotland. *SCI Store*. 2015. http://www.sci.scot.nhs.uk/products/store/store_main.htm (accessed 21 Dec. 2016).
31. Crew 2000. *Crew – Drugs Index*. 2016. http://m.crewknowledge.com/ListAllDrugs.php (accessed 4 Dec. 2016).
32. Shapiro H, DrugWise. NPS Come of Age: A UK Overview. May 2016. http://www.drugwise.org.uk/wp-content/uploads/NPSComeofAge.pdf (accessed 4 Dec. 2016)
33. Zamengo L, Frison G, Bettin C, *et al*. Understanding the risks associated with the use of new psychoactive substances (NPS): high variability of active ingredients concentration, mislabelled preparations, multiple psychoactive substances in single products. *Toxicol Lett*. 2014;229:220-8.
34. Kjellgren A, Andersson M. Aspects of Substance Displacement-From Illicit Drugs to Novel Psychoactive Substances. *J Addict Res Ther*. 2016;7.
35. Palamar JJ, Acosta P, Sherman S, *et al*. Self-reported use of novel psychoactive substances among attendees of electronic dance music venues. *Am J Drug Alcohol Abuse*. 2016:1-9.
36. Papanti D, Schifano F, Botteon G, *et al*. "Spiceophrenia": a systematic overview of "Spice"-related psychopathological issues and a case report. *Hum Psychopharm Clin*. 2013;28:379-89.

37. Home Office. *News story – Festivals warned over drug use*. 2011. https://www.gov.uk/government/news/festivals-warned-over-drug-use (accessed 4 Dec. 2016).
38. Lader D, Home Office. Drug Misuse: Findings from the 2014/15 Crime Survey for England and Wales. July 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/462885/drug-misuse-1415.pdf (accessed 4 Dec. 2016)
39. Public Health England. New psychoactive substances: toolkit for commissioners. November 2014. http://www.nta.nhs.uk/uploads/nps-a-toolkit-for-substance-misuse-commissioners.pdf (accessed 4 Dec. 2016).
40. Novel Psychoactive Treatment UK Network – NEPTUNE. Guidance on the Clinical Management of Acute and Chronic Harm of Club Drugs and Novel Psychoactive Substances. March 2015. http://neptune-clinical-guidance.co.uk/wp-content/uploads/2015/03/NEPTUNE-Guidance-March-2015.pdf (accessed 4 Dec. 2016).
41. Palamar JJ, Salomone A, Vincenti M, *et al*. Detection of "bath salts" and other novel psychoactive substances in hair samples of ecstasy/MDMA/"Molly" users. *Drug Alcohol Depend*. 2016;161:200-5.
42. Ford LT, Berg JD. ANNALS EXPRESS: Analysis of legal high materials by UPLC-MS/TOF as part of a toxicology vigilance system. What are the most popular novel psychoactive substances in the UK?. *Ann Clin Biochem*. 2016:0004563216651646.
43. Gray R, Bressington D, Hughes E, *et al*. A systematic review of the effects of novel psychoactive substances 'legal highs' on people with severe mental illness. *J Psychiatr Ment Health Nurs*. 2016.
44. Parliament NZ. *Psychoactive Substances Act 2013*. Public Act. 2013(53):17.
45. Stevens A, Fortson R, Measham F, *et al*. Legally flawed, scientifically problematic, potentially harmful: The UK Psychoactive Substance Bill. *Int J Drug Policy*. 2015;26:1167-70.

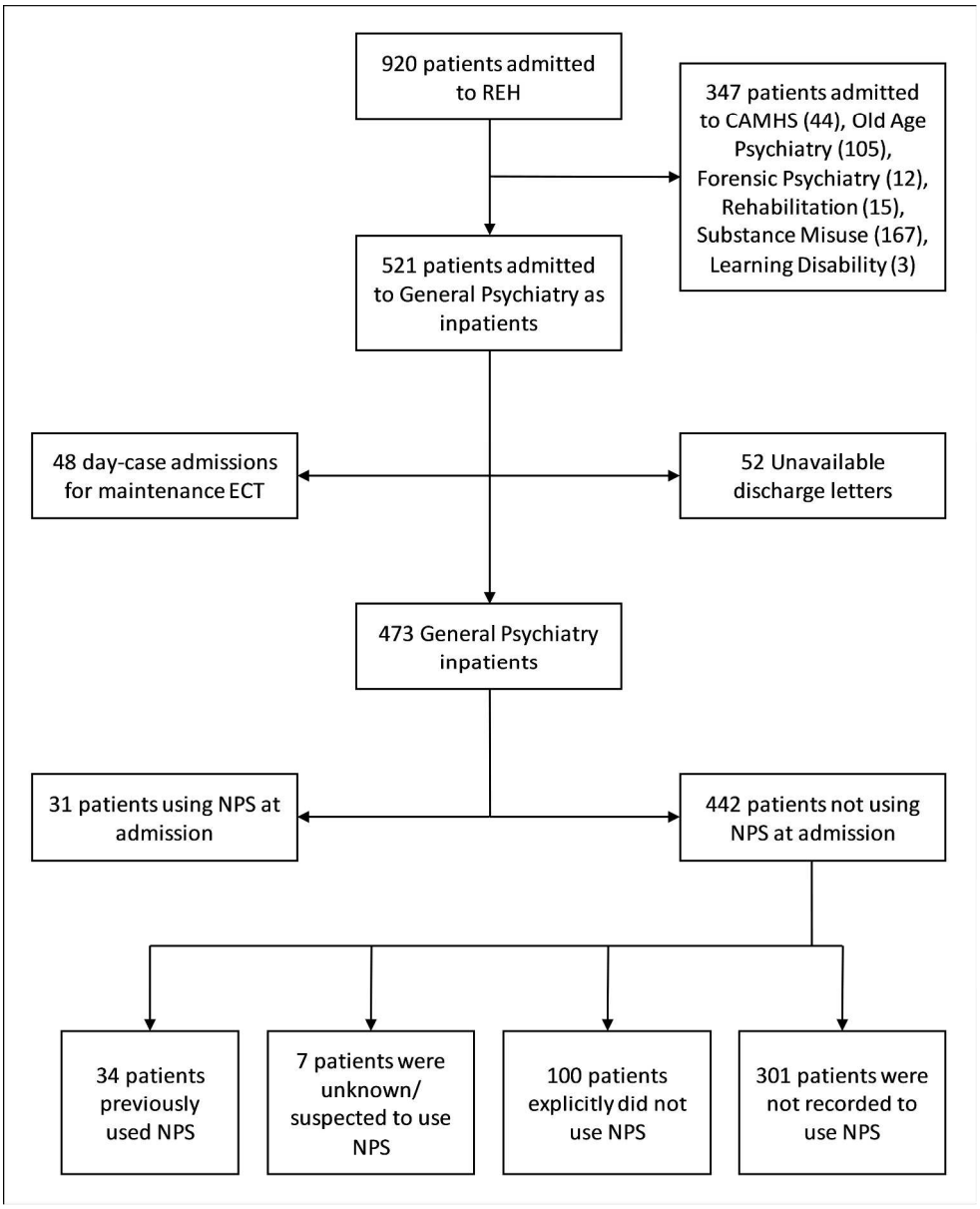

Figure 1: Flowchart of inclusion/exclusion criteria and patient groups. Sub-groups of the lowest tier in the flowchart were analysed collectively as non-NPS users. REH, Royal Edinburgh Hospital; CAMHS, Child & Adolescent Mental Health Services; ECT, electroconvulsive therapy; NPS, novel psychoactive substance.

147x181mm (600 x 600 DPI)

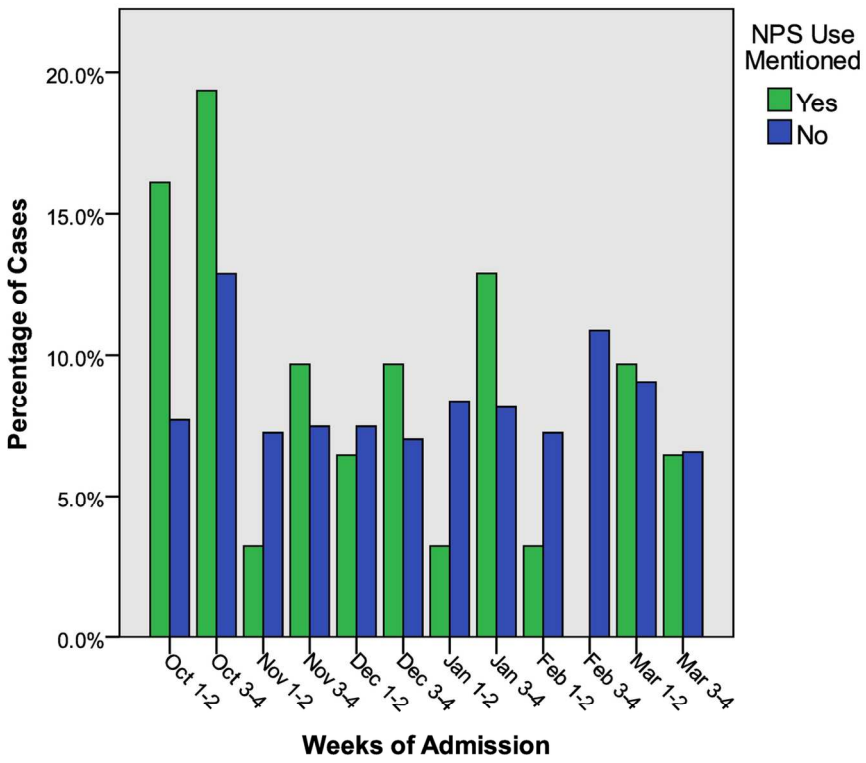

Figure 2: The percentage of NPS users and non-NPS users admitted in fortnightly intervals between October 2015 – March 2016. NPS, novel psychoactive substance.

131x105mm (300 x 300 DPI)

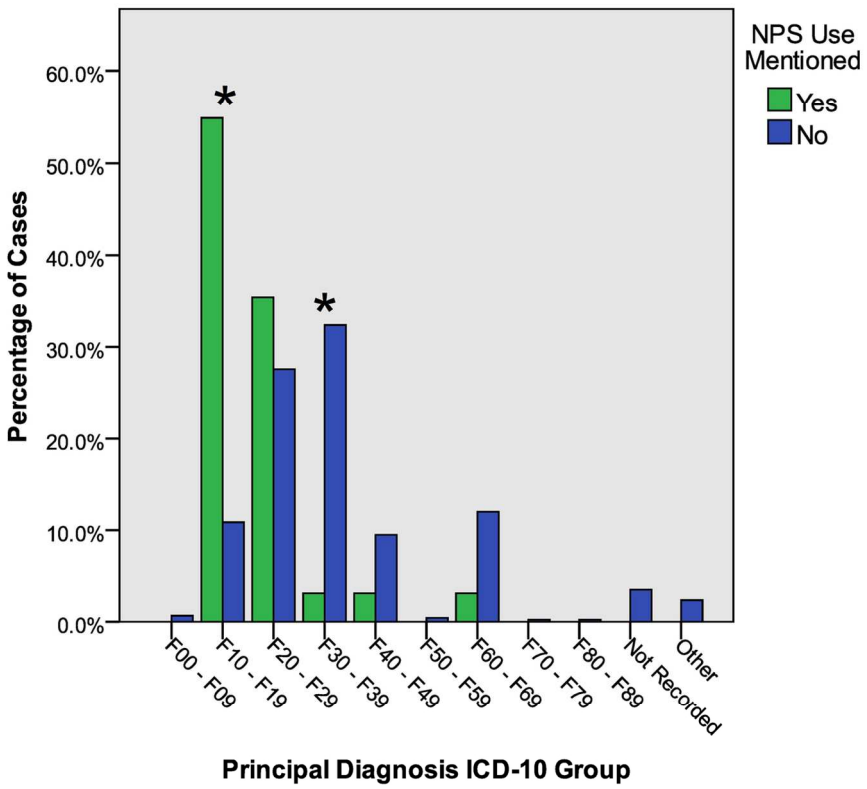

Figure 3: The percentage of NPS users and non-NPS users assigned Principal Diagnoses in accordance with ICD-10 Groups. *Denotes a statistically significant difference between NPS users and non-NPS users ($\chi 2$), $p<0.001$. ICD, International Statistical Classification of Diseases and Related Health Problems; NPS, novel psychoactive substances.

131x105mm (300 x 300 DPI)

NEW PSYCHOACTIVE SUBSTANCES STUDY PROTOCOL

Background

This study aims to examine the effect of two public health interventions on presentations to psychiatric services following use of new psychoactive substances. We will aim to quantify number of presentations, which drugs were used and whether there was psychiatric symptomatology, as well as looking at outcome of presentation (hospital admission, referral to other services).

REH Study

1. Identify individuals admitted to REH acute wards/taken on by IHTT for 6/12 prior to banning of ethylphenidate (10/04/15) and 6/12 after City Council forfeiture order (15/10/15) using Trak patient record database.
2. Using Trak, review discharge letters and extract information on: age, gender, drug used, method of administration, psychiatric diagnosis (if given), duration of admission, other substance use & symptomatology.
3. Data analysis:
    a. Make comparison of numbers of patients being admitted with psychiatric problems following NPS use compared to previous findings.
    b. Examine any changes in patterns of psychiatric presentation or admission to psychiatric hospital

Data Collection Sheet

Patient Demographics

Subject no:		Gender:	Male □ Female □ Transgender □
Age:			
Employment status:	Unemployed □ Full time □ Part time □ Self employed □ Student □	Home circumstances:	Independent □ Supported □ Homeless □ Not recorded □
Admission to:	REH □ IHTT □ A&E □ CAA6 □ Other □		

Primary diagnosis:			
Other diagnoses:			
Admission date:		Discharge date:	
Use of Mental Health Act:	Yes □ No □	Previous admissions/IHTT:	
Forensic History:	Yes □ No □ Not recorded □	Previous custodial sentence noted:	Yes □ No □ Not recorded □ Not applicable □

Substance Use

NPS Use:	Yes No Not recorded Previous	Contribution to psychiatric presentation?	Yes No Not recorded
Names of NPS(s):			
Route of administration:	IV Insufflation Oral Smoked Other…		
Other substance use:	Alcohol: current previous Cannabis: current previous Benzodiazepines: current previous Cocaine: current previous Amphetamines: current previous MDMA: current previous GBL/GHB - current previous Opiates (substitute):current previous Which…… Opiates (non substitute): current previous Other:……..		
Psychiatric symptoms:	Agitation □ Thought-disordered □ Paranoia □ Hallucinations □ Suicidal thoughts □ Disinhibition □ Delusions □ Disorientation □ Labile affect □ Low mood □ Lack of insight □ Anxiety □ Self-referential ideas □ Passivity phenomena □		

BMJ Open

Characteristics of Novel Psychoactive Substance (NPS) use in patients admitted to acute psychiatric services in South East Scotland: a retrospective cross-sectional analysis following public health interventions.

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TITLE

Characteristics of Novel Psychoactive Substance (NPS) use in patients admitted to acute psychiatric services in South East Scotland: a retrospective cross-sectional analysis following public health interventions.

CORRESPONDING AUTHOR

Dr Helen L Alderson: h.alderson@nhs.net, Department of Psychiatry, Queen Margaret Hospital, Whitefield Road, Dunfermline, KY12 0SU, UK. Telephone: 01383 627041

AUTHORS

Kyle Hemingway Bennett[1], Helen Mary Hare[2], Robert Marten Waller[3], Helen Louise Alderson[4], Stephen MacGregor Lawrie[5]

1. Undergraduate Medical Student [5th year], School of Medicine, University of Edinburgh, Chancellor's Building, 47 Little France Crescent, Edinburgh, EH16 4TJ, UK.
2. Royal Edinburgh Hospital, Morningside Terrace, Edinburgh, EH10 5HF, UK.
3. He Puna Waiora Adult Mental Health Inpatient Unit, Waitemata District Health Board, Private Bag 93503, Takapuna, Auckland 0622, New Zealand.
4. Department of Psychiatry, Queen Margaret Hospital, Whitefield Road, Dunfermline, KY12 0SU, UK.
5. Kennedy Tower, Royal Edinburgh Hospital, Morningside Park, Edinburgh, EH10 5HF, UK.

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ABSTRACT

Objectives: Assess the impact of selective prohibition and seizure of NPS supply on NPS use prevalence within psychiatric admissions and evaluate demographic characteristics of current NPS users.

Design: A 6-month retrospective cross-sectional analysis of discharge letters between 1st October 2015 – 31st March 2016.

Setting: General Psychiatry inpatients and Intensive Home Treatment Team community patients at a psychiatric hospital in a Scottish city.

Participants: All participants were between the ages 18-65. After application of exclusion criteria, 473 discharge letters of General Psychiatry patients were deemed suitable for analysis and 264 Intensive Home Treatment Team (IHTT) patient discharge letters were analysed.

Interventions: A nationwide Temporary Class Drug Order (TCDO) was placed on 10th April 2015 reclassifying methylphenidate-related compounds as Class B substances. On 15th October 2015, local Forfeiture Orders were granted to Trading Standards permitting the seizure of NPS supplies.

Primary and secondary outcome measures: The primary outcome measure was to determine the prevalence of NPS use in two cohorts. Secondly, demographic features of patients and details regarding their psychiatric presentation were analysed.

Results: The prevalence of NPS use in General Psychiatry and IHTT patients was 6.6% and 3.4%, respectively. Inpatients using NPS compared to non-users were more likely to be male (OR: 2.92, 95% CI: 1.28-6.66, p=0.009), have a forensic history (OR: 5.03, CI: 2.39-10.59, p<0.001) and be detained under an Emergency Detention Certificate (OR: 3.50, CI: 1.56-7.82, p=0.004). NPS users were also more likely to be diagnosed under ICD-10 F10-19 (OR: 9.97, CI: 4.62-21.49, p<0.001).

Conclusions: Compared to previous work, psychiatric inpatient NPS use has fallen. NPS continue to be used by a demographic previously described resulting in presentations consistent with a drug-induced psychosis and at times requiring detention under the Mental Health Act. Further research is required to evaluate the effectiveness of the recent prohibition of all NPS.

ARTICLE SUMMARY

Strengths and limitations of this study:

- Recent public health interventions concerning NPS have been evaluated, specifically their association with a reduction in the prevalence of NPS use in a psychiatric population.
- The strain placed on services by NPS use has been quantified by studying the duration of patients' admissions and the likelihood that they are detained under the Mental Health Act.
- As the NPS user sample was relatively small compared to previous work, figures pertaining to the demographic features of this group should be interpreted with caution.
- A number of the study outcomes were poorly recorded for in discharge letters, which may be accounted for by the variation in the quality of discharge letters.
- The study period encompasses a 6-month period following the issue of Forfeiture orders on 15th October 2015 therefore it is not possible to comment if the reduction of NPS use within this population is more attributable to a particular one of the two interventions.

INTRODUCTION

Background

In recent years, a new public health issue has arisen: Novel Psychoactive Substances (NPS), more commonly known as 'legal highs'. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) defines an NPS as a drug not controlled by UN drug conventions with potential to cause as much public health risk as classic illicit drugs.[1] Attempts have been made to classify NPS chemically,[2] of which synthetic cannabinoids (cannabis replacements) and synthetic cathinones (stimulants) account for the majority.[3] However, in 2014 alone over a hundred new NPS were introduced to the market, signifying the challenges in studying and classifying such substances.[3]

Over the past decade, NPS have been assimilated into the repertoire of drugs available to habitual drug users.[4] Sophisticated marketing of NPS has rendered them as socially acceptable and safe,[5] despite their involvement in numerous drug-related deaths.[6] Until recently, NPS have escaped prohibitive legislation by including labels on packaging: 'not for human consumption' or 'for research only',[7] despite the contrary insinuations made elsewhere.

In Edinburgh, during 2014, ethylphenidate, a methylphenidate derivative, resulted in a significant burden for Police Scotland; the incidence of legal-high related casualties increased amidst reports of 'bizarre and violent behaviour'.[8] As well as admissions to acute mental health services, a cluster of serious soft tissue infections and necrotic ulcers resulted from parenteral ethylphenidate use.[8,9] Ethylphenidate was first recognised in UK 'head-shops' (drug paraphernalia shops) in November 2011 via the UK Forensics Early Warning System[10] and was subsequently reported to the EMCDDA.[7] However, its use had already been widely discussed on online user forums before this time.[11] Its effects bear similarity to that of cocaine and, to some extent, amphetamines, including euphoria, increased sociability,[12] tachycardia, hypertension, palpitations,[13] multi-sensory hallucinations,[9] and a considerable urge to reuse.[12,14] NPS in general have been associated with various psychiatric symptoms, which often present as an acute transient psychotic episode[15] although the long term impact on mental health is unknown. Ethylphenidate has been implicated in numerous fatalities[6,16] and was, in one study, discovered in the possession of two subjects following suicide, suggesting a possible association with psychiatric illness.[17]

On 10th April 2015 the UK Government responded by placing a Temporary Class Drug Order (TCDO) under the Misuse of Drugs Act 1971 on methylphenidate derivatives making supply and production, but not possession, punishable by imprisonment.[18-19] Police Scotland reported a reduction in parenteral infections, publicly discarded needles and emergency admissions since this time.[20] Forfeiture Orders were granted on 15th October 2015 from the Sheriff Court in Edinburgh to Trading Standards permitting seizure of all NPS from head-shops.[21] More recently, the Psychoactive Substances Act (2016) was imposed, which criminalises any NPS – a so-called blanket ban.[22] However, other substances classified under the Misuse of Drugs Act such as mephedrone have, since their selective banning, become integrated into the clubbing environment[23] and distributed under the guise of legal NPS,[24] raising questions as to how effective specific legislative bans are.

In recent years, the public health issue of NPS use has been widely researched, including a previous study at this centre. Work by Stanley *et al*. established that 22.2% of inpatients admitted to acute psychiatric wards at the Royal Edinburgh Hospital were using NPS, 59.3% of whom had psychiatric symptoms attributable to their drug use.[25] Since legislative changes have been implemented, no research has been conducted to analyse ongoing trends in NPS use.

Objectives

This study aimed to examine the possible impact of the recent public health interventions on NPS-related psychiatric admissions, building on the findings of a previous study by Stanley *et al*.[25] In addition to examining admissions to the acute psychiatric inpatient wards at the Royal Edinburgh Hospital, patients admitted to the Intensive Home Treatment Team (IHTT), a community-based psychiatric crisis team, covering the same catchment area as the Royal Edinburgh Hospital, were also included. The study aimed to evaluate how effective recent public health interventions have been in reducing NPS use, as reflected in NPS-related admissions to these two services. The primary hypothesis was that the interventions made on a national and local level would have reduced the prevalence of NPS use in patients admitted to these services.

METHODS

Study design and setting

This study was a retrospective cross-sectional review of discharge letters written for two cohorts of psychiatric patients - General Psychiatry inpatients and community based IHTT patients - at the Royal Edinburgh Hospital in Edinburgh, United Kingdom. Discharge letters were written by medical staff for inpatients; IHTT discharge letters were written by community psychiatric nurses and reviewed by medical staff.

Participants

Adult patients (18-65 years old) admitted to the Royal Edinburgh Hospital between 1st October 2015 and 31st March 2016 were identified from the TrakCare™ Electronic Patient Record (InterSystems) database.[26] Only patients admitted to General Psychiatry who had been subsequently discharged from hospital by 30th June 2016 were included in the study. Those admitted to specialist services or admitted as inpatient day-cases for electroconvulsive therapy (ECT) were excluded **(Figure 1)**. All adult patients admitted to IHTT over the same period were included.

Data collection

SAP BusinessObjects (SAP)[27] was used by KHB and RMW to extract details regarding patient admissions, including Principal Diagnosis and Code (consistent with International Statistical Classification of Diseases and Related Health Problems Version 10 (ICD-10)),[28] duration of admission, and legal status (Mental Health (Care and Treatment) (Scotland) Act 2003)[29] whilst in hospital, which was categorised as informal, Emergency Detention Certificate (EDC), Short Term Detention Certificate (STDC) or Compulsory Treatment Order (CTO). Patients were assigned subject numbers to ensure anonymity.

Additional study outcomes relating to patient demographics (age, gender, employment status and home circumstances); forensic history (any forensic history of note and custodial sentences); substance use (NPS use, contribution to psychiatric presentation, name of NPS, route of administration and other substance use); and any psychiatric symptoms recorded during admission were collected from patient discharge letters on eHealth systems by KHB. Such data were collected during clerking of patients and routine consultations; thus, reporting of these outcomes were dependent on clinical inquiry and patient self-reporting. Some discharge letters were extractable as free-text from TrakCare™ (Intersystems) using SAP Business Objects. Others were only available as PDF (Portable Document Format) files uploaded to the linked document storage system SCI-Store.[30] Both locations were searched. All data were recorded in the data collection tool provided in the online supplementary file.

When recorded, NPS brand names were cross-checked on an online database of NPS to reveal the active ingredients reported to be present.[31] These chemicals were then classified in accordance with the Drugs Wheel to provide an NPS type;[32] supporting evidence was found elsewhere if these chemicals were not reported in the Drug Wheel.[33] Where study outcomes were not recorded in discharge letters, these were assumed to be negative and grouped with explicitly negative data. Patients referred to IHTT were identified using SAP Business Objects (SAP) and the above study outcomes were collected from IHTT discharge letters either within a free-text TrakCare™ extract or uploaded PDFs as above. Data collection was repeated for a sample of subjects by HMH for quality control purposes.

Statistical methods

Statistical analysis was carried out using SPSS V22.0.0.1 (IBM). Independent two-sample Student's t-tests were used to assess the differences in continuous dependent variables between NPS users and non-NPS users. Odds Ratios (ORs) were generated and Pearson χ^2 tests were used to compare differences between these groups for remaining categorical variables; Fisher's exact test and Phi/Cramer's V symmetric measures were performed where appropriate. Two-tailed two-sample z-tests were performed for comparisons between the proportion of NPS users in this study and those in Stanley *et al*. – a study conducted under the same methodology that reported the prevalence of NPS use in the General Psychiatry population between July-December 2014.[25]

Ethics and database protection

This study was assessed by the local clinical governance team who deemed that it did not require ethics committee approval. Data were collected into an Excel spreadsheet using a coded ID number which could not be used to retrospectively identify individual patients. This spreadsheet was password protected and stored on NHS servers only. The password was available only to the authors; each had access via their NHS user ID which allowed tracking of changes made.

RESULTS

A total of 473 General Psychiatry inpatient cases were included in the analysis after application of the exclusion criteria **(Figure 1)**. Of these, 31 patients were reported to be currently using NPS on admission. A two-tailed two-sample z-test between the proportion of NPS users in this population (6.6%, n=473) and of that in Stanley *et al.* (22.2%, n=488)[25] revealed a statistically significant difference ($z=6.7$, $p<0.001$). A total of 264 patients were discharged from IHTT, of which 9 cases (3.4%) were identified as NPS users at the time of admission. Across both cohorts, the prevalence of NPS use was 5.4%.

For General Psychiatry and IHTT NPS users, the types of NPS were recorded in 38.7% and 11.1% of cases, respectively. NPS use was recorded to contribute to the psychiatric presentation 77.4% and 22.2% of the time. Of all NPS products identified in the General Psychiatry cohort, including multiple NPS in individual patients, 24.2% contained stimulants (ethylphenidate, methiopropamine (MPA) and 3-fluorophenmetrazine (3-FPM)) and 18.2% were synthetic cannabinoids. Three of the recorded NPS products have been reported to include two active ingredients; 'Magic crystals' are reported to include 3-FPM and ethylphenidate whereas 'Pink panther' is reported to include MDAI, an empathogen, and MPA and 'K-Pax' is reported to include methoxphenidine, a dissociative, in addition to 3-FPM.[31, 34] The use of MPA could be identified in only one case of the IHTT cohort

(11.1%). Data from the IHTT cohort were excluded from further analysis due to insufficient recording of outcome measures in discharge letters.

Figure 2 shows the percentage of admissions for NPS users and non-NPS users over the study period (October-March). The month of October accounted for the largest proportion of NPS user admissions in which 16.1% were admitted in the first fortnight and 19.4% in the remainder of the month (a total 35.5% across October). However, compared to non-NPS users these figures were not statistically significant.

The collective length of admission for all NPS users amounted to 4.41% of the total length of admission for all inpatients. Mean length of admission between NPS users and non-NPS users was not statistically significant.

NPS users were significantly more likely to be detained under the MHA than non-NPS users (OR: 3.37, 95% CI: 1.57-7.21, p=0.002). When individual modes of detention were considered (EDC, STDC and CTO), there was a statistically significant difference between NPS users and non-NPS users only in detention under an EDC, where 32.3% of NPS users were detained under this order compared with 12.0% of non-NPS users (OR: 3.50, CI: 1.56-7.82, p=0.004).

The demographic features of NPS users compared to non-NPS users are shown in **Table 1**. Significant differences were observed between NPS users and non-NPS users for mean age (35.1 ± 9.8 (SD) years vs 40.0 ± 11.7 (SD) years, p=0.023). Furthermore, a bimodal distribution of age ranges emerged in NPS users where peaks were observed in the 18-25 and 41-45 age ranges. Age of NPS users was significantly more likely to be within the latter range compared to non-NPS users (OR: 2.87, 95% CI: 1.29-6.37, p=0.007). NPS users were more likely to be male (OR: 2.92, CI: 1.28-6.66, p=0.009) and have a forensic history recorded in their discharge letter (OR: 5.03, CI: 2.39-10.59, p<0.001) compared to non-NPS users. However, no statistical differences between NPS users and non-NPS users were observed in the proportions of patients recorded to have served custodial sentences.

		NPS Users (n=31)	Per cent	Non-NPS Users (n=442)	Per cent
Mean age (SD)		35.1 (9.8)*		40 (11.7)*	
Gender	Male	23*	74.19%	218*	49.3%
	Female	8*	25.81%	221*	50.0%
	Transgender	0	0.00%	3	0.7%
Employment	Unemployed	12	38.71%	176	39.8%
	Student	1	3.23%	17	3.8%
	Employed	1	3.23%	51	11.5%
	Full-time	1	3.23%	44	10.0%
	Part-time	0	0.00%	7	1.6%
	Self-employed	0	0.00%	8	1.8%
	Retired	0	0.00%	1	0.2%
	Prison	0	0.00%	6	1.4%
	Not recorded	17	54.84%	183	41.4%
Home circumstances	Independent	12	38.71%	250	56.6%
	Fully independent	5	16.13%	165	37.3%
	Benefits	5	16.13%	71	16.1%

	Council tenancy	2	6.45%	14	3.2%
	Supported	6	19.35%	14	3.2%
	Homeless	2	6.45%	21	4.8%
	Prison	0	0.00%	1	0.2%
	Not recorded	11	35.48%	138	31.2%
Forensic History		17**	54.84%	86**	19.5%
Previous custodial sentence		4	12.90%	27	6.1%
Use of MHA	Any use of MHA	20	64.52%	155	35.1%
	EDC	10	32.26%	53	12.0%
	STDC	12	38.71%	133	30.1%
	CTO	1	3.23%	30	6.8%
ICD-10 Diagnosis Groupings	F00-09	0	0.00%	3	0.7%
	F10-19	17**	54.84%	48**	10.86%
	F20-29	11	35.48%	122	27.60%
	F30-39	1**	3.23%	144**	32.58%
	F40-49	1	3.23%	42	9.50%
	F50-59	0	0.00%	2	0.45%
	F60-69	1	3.23%	53	11.99%
	F70-79	0	0.00%	1	0.23%
	F80-89	0	0.00%	1	0.23%
	Not recorded	0	0.00%	16	3.62%
	Other	0	0.00%	11	2.49%
Substance use	cannabis	18**	58.10%	93**	21.00%
	alcohol	8	25.80%	120	27.10%
	non-substitute opiates	8*	25.80%	43*	9.70%
	substitute opiates	7	22.60%	46	10.40%
	other	7*	22.60%	17*	3.80%
	MDMA	4*	12.90%	16*	3.60%
	amphetamines	3	9.70%	25	5.70%
	cocaine	3	9.70%	39	8.80%
	benzodiazepines	3	9.70%	34	7.70%
Any substance use		26**	83.90%	217**	49.10%

*Table 1: Demographic features of NPS users and non-NPS users. *Denotes a statistically significant difference between NPS users and non-NPS users, p<0.05 and **p<0.001. SD, Standard Deviation; EDC, Emergency Detention Certificate; STDC, short term detention certificate; CTO, compulsory treatment order; ICD, International Statistical Classification of Diseases and Related Health Problems; F00-F09, Organic, including symptomatic, mental disorders; F10-19, Mental and behavioural disorders due to psychoactive substance use; F20-F29, Schizophrenia, schizotypal and delusional disorders; F30-39 Mood [affective] disorders; F40-F49, Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders; F50-F59, Behavioural syndromes associated with physiological disturbances and physical factors; F60-F69, Disorders of adult personality and behaviour; F70-F79, Mental retardation; F80-89, Disorders of psychological development; Other, Behavioural and emotional disorders with onset usually occurring in childhood and adolescence/Unspecified mental disorder; MDMA, 3,4-Methylenedioxymethamphetamine; NPS, novel psychoactive substances.*

NPS users were significantly more likely to use illicit substances other than NPS compared to non-NPS users (OR: 5.44, 95% CI: 2.05-14.43, p<0.001). Compared to non-NPS users, NPS users were significantly more likely to use cannabis (OR: 4.56, CI: 2.17-9.58, p<0.001), non-substitute opiates (OR: 2.85, CI: 1.16-7.03, p=0.018), MDMA (OR: 3.94, CI: 1.23-12.61, p=0.013) and other uncategorised substances, which included hallucinogens and illegally acquired prescription drugs (OR: 5.88, CI: 1.97-17.58, p<0.001).

Figure 3 reveals that ICD-10 diagnosis groupings for NPS users compared to non-NPS users were more likely to be F10-19 (OR: 9.97, 95% CI: 4.62-21.49, p<0.001) and less likely to be F30-39 (OR: 0.07, CI: 0.009-0.516, p<0.001). The most significant difference in diagnosis was for Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances disorder (ICD-10 F19), (OR: 28.66, CI: 11.85-69.30, p<0.001).

NPS users compared to non-NPS users were found to be significantly more likely to present with paranoia (OR: 2.34, 95% CI: 1.08-5.08, p=0.036) and thought-disorder (3.44, CI: 1.50-7.90, p=0.002) and less likely to present with low mood (OR: 0.29, CI: 0.11-0.76, p=0.007) and suicidal thoughts (OR: 0.129, CI: 0.03-0.550, p=0.001).

DISCUSSION

Principal findings

The present study builds upon the findings made by Stanley *et al*.[25] by evaluating the impact of recent public health changes. As well as acute psychiatric inpatients, a second cohort was included, which comprised of patients admitted to IHTT – a population previously not considered. We hypothesised that since public health interventions, the prevalence of NPS use in psychiatric patients has fallen. In contrast to the prevalence of 22.2% found by the previous work in psychiatric inpatients,[25] the present data revealed a prevalence of NPS use in this group of 6.6% following recent public health interventions – a 15.6% reduction. Additionally, the prevalence of NPS use reported in discharge letters from the IHTT cohort was found to be 3.4%. The present study found that of the NPS types recorded, a considerable proportion (24.2%) were stimulants, several of which are reported to include more than one active ingredient. The relative popularity of this diverse group of chemicals may suggest that other compounds have been recently adopted by NPS users as a substitute for ethylphenidate since the TCDO.

Strengths and weaknesses

Unfortunately, a large proportion of demographic outcome measures (54.84% Employment and 35.48% Home circumstances) were not recorded in discharge letters and due to the relatively small sample size, it is not possible to comment on these. Generally, demographic characteristics were similar to those found in the previous study:[25] NPS users were more likely to be male, polysubstance misuse was more likely and mean age was similar (35.1 compared to 36.1 years old). The age distribution of NPS users was studied more thoroughly, however, and a bimodal distribution was observed with peaks in the 18-25 and 41-45 age groups, the latter of which was significant compared to non-NPS users. This is broadly in agreement with the findings of the Drugwise NPS: Come of Age report,[35] which suggested that NPS use is not confined to a single generation; NPS perhaps appeal to the 18-25 age group as have 'club drugs' like mephedrone[4] and 'party pills', such as those containing piperazine compounds.[36] Conversely, the 41-45 age group may utilise NPS as drug substitutes – so-called substance displacement, a phenomenon that has previously reported for synthetic cannabinoids.[37] As in the previous work,[25] the present study suggested that NPS users

were more likely to use cannabis concomitantly; however, rather than a higher prevalence of substitute opiates it was found that NPS users within this study were more likely to use non-substitute opiates and MDMA. It is possible that these drug choices relate again to the prominent age groups observed – MDMA users aged 18-25 have previously been shown to be more likely to use NPS, particularly synthetic cannabinoids, phenethylamines and synthetic cathinones;[38] and ethylphenidate has been implicated in opiates users, which may correspond to the 41-45 age group.[16-17] To assess differences in diagnoses between NPS users and non-NPS users this study adopted a standardised approach by recording ICD-10 codes. The most common principal diagnosis assigned to NPS users was F19.5 (Mental and behavioural disorders due to multiple drug use and use of other psychoactive substances: psychotic disorder). Previous work also found that this was the most commonly recorded diagnosis.[25] On the basis of the present data, it is not possible to demonstrate a causal link between NPS and drug-induced psychosis. However, evidence from this study suggests that public health interventions may be effective in reducing the prevalence of NPS use in individuals vulnerable to their effects on mental state. In an effort to quantify the strain of these admissions on psychiatric services, length of stay and use of the Mental Health Act[29] were examined. Compared to Stanley *et al*.,[25] it was found that almost double the proportion of NPS users in this study were detained and significant differences were observed in the use of EDC between NPS users and non-NPS users. Initially this could, in combination with the above findings regarding diagnosis, suggest that more users than in the earlier study are presenting severely psychotic enough to warrant detention. However, this finding should be interpreted with caution as changes in the working patterns of medical staff locally has consequently resulted in more out-of-hours detentions placed by junior medical staff, who are only able to detain under an EDC. This change in practice may be acting as a confounding factor for an apparent increase in this type of detention for patients. Psychotic episodes in patients using synthetic cannabinoids have been documented previously as transient and acute;[39] no significant differences in average length of stay between NPS users and non-NPS users were found. The total length of stay in this group accounts for 4% of length of stay across all patients, which is a smaller proportion than the proportion of NPS users within the General Psychiatry cohort (6.6%). Thus no disproportionate or considerable strain on services has been observed at present and due to lack of data from Stanley *et al*.[25] it is not possible to evaluate if there has been any significant change.

Limitations and future research

The study period covered 1st October 2015 – 31st March 2016, a 6-month period encompassing significant public health changes with regard to NPS. It is unfortunately not possible to say which of the two public health changes is associated with the reduction in prevalence of NPS use. However, these interventions together represent a ban and a seizure of supplies, and conclusions can be drawn about the collective impact of these changes. Whilst comparisons may be made with the previous study, it is important to bear in mind that Stanley *et al*.[25] examined admissions during the months of July and August and it is possible that seasonal differences may have some influence here.[40] One limitation is that the sample size of patients admitted to hospital/IHTT following NPS use is small and it most likely represents a small minority of the whole NPS using population. Recent data have estimated that 937,000 people aged 16-59 in England and Wales had used an NPS at least once and 279,000 in the past year.[41] With limited data on the prevalence and demographics of NPS use in the general population, it is only possible to apply conclusions drawn in this study to psychiatric inpatients. Due to the nature of the study design, it is also possible that NPS use prevalence was underestimated. Furthermore, reviewing discharge letters is vulnerable to two forms of bias: reporting bias, in which the quality of discharge letters is heterogeneous; and observer bias, which arises due to variation in summarising recorded clinical impressions. The study aimed to

reduce observer bias by reporting only explicitly positive NPS use cases and coding all others as non-NPS cases. This relies on clinicians directly inquiring into NPS use. Some discharge letters stated that NPS use was unknown but clinically suspected, which is perhaps a consequence of clinicians not routinely asking about NPS use when interviewing patients. In cases where NPS users were identified by clinical inquiry, inadequate recording of NPS types across both cohorts highlights poor recognition of the contribution NPS may have to psychiatric illness, perhaps due to a lack of relevant training for healthcare practitioners.[42] The NEPTUNE project, a clinical guidance project, has made significant progress in resolving this gap by constructing an extensive document detailing the presentation and management of numerous NPS.[43] Assuming inquiry by clinicians, the recording of NPS use is still limited as this approach relies on self-reporting by patients. It is also possible that patients using other substances are unintentionally also ingesting NPS as has been reported in an 18-25 year old population of club-goers who tested positive for a range of empathogen NPS despite denying any NPS use.[44] Ideally, laboratory analysis would have provided empirical evidence of NPS use and allowed for determination of the active ingredients ingested. Clinical screening for NPS is not routinely employed in clinical practice and limitations in immunoassays, particularly the variable cross-reactivity for different NPS lowers their sensitivity.[45] However, chromatographic methods offer an alternative approach; liquid chromatography-tandem mass spectrometry of the urine has shown promise in identifying a diverse range of NPS and has been successfully implemented in a clinical setting.[46] Use of such biochemical techniques would allow for reliable measurements in future studies relating to NPS use. Whilst there are limitations associated with a retrospective review, it is useful for providing epidemiological findings and, as such, was deemed appropriate here for relatively simple data collection from an electronic patient database. Furthermore, this design provides a quantitative report on NPS users in contrast to the relative abundance of case reports in the literature, which do not allow for reliable systematic reviews to be conducted.[47] In order to address the methodological issue of poor recording of NPS use by clinicians, a long-term prospective cohort study could be carried out using standardised *pro formas* with well-defined reporting criteria available on wards. This type of study would be of particular benefit across the United Kingdom in the period following the Psychoactive Substances Act (2016).[22] More detailed analysis of NPS users will also identify whether these patients are previously known to suffer a psychiatric illness, what services they subsequently use and if these patients successively develop chronic psychiatric illnesses.

Generalisability

Since the TCDO placed on ethylphenidate and forfeiture orders of NPS within Edinburgh, there has been a reduction in the prevalence of NPS use in psychiatric admissions locally. This study does not aim to suggest there is a causal link between NPS and psychiatric illness but other studies have provided evidence to support this link.[15] The current findings instead suggest that prohibitive legislation coupled with the intensive and organised seizure of NPSs may have contributed to the reduction of NPS-related admissions to acute psychiatric wards and to a local crisis team. The advent of the Psychoactive Substances Act (2016)[22] criminalises the supply of NPS and thus provides an opportunity to assess similar policy changes implemented on a national level. In response to the rise of NPS, New Zealand has adopted a regulatory licensing system whereby NPS can be approved for use if it is felt that there is a low-risk of associated harm.[48] Elsewhere however, countries have taken 'blanket ban' stances similar to the Psychoactive Substances Act (2016),[22] and these have failed to demonstrate reductions in NPS use and availability.[49] The present findings suggest that selective prohibition and general confiscation may be effective in reducing NPS-related admissions. Whilst these findings are from a population requiring psychiatric admission 6 months after public health measures were implemented, such results may be sustained and common to other clinical

specialties. Future studies could be carried out to examine the impact of the Psychoactive Substances Act (2016)[22] on psychiatric and general hospital admissions.

FIGURE LEGENDS

Figure 1: Flowchart of inclusion/exclusion criteria and patient groups. Sub-groups of the lowest tier in the flowchart were analysed collectively as non-NPS users. REH, Royal Edinburgh Hospital; CAMHS, Child & Adolescent Mental Health Services; ECT, electroconvulsive therapy; NPS, novel psychoactive substance.

Figure 2: The percentage of NPS users and non-NPS users admitted in fortnightly intervals between October 2015 – March 2016. NPS, novel psychoactive substance.

Figure 3: The percentage of NPS users and non-NPS users assigned Principal Diagnoses in accordance with ICD-10 Groups. *Denotes a statistically significant difference between NPS users and non-NPS users ($\chi 2$), $p<0.001$. ICD, International Statistical Classification of Diseases and Related Health Problems; NPS, novel psychoactive substances.

ORIGINAL PROTOCOL

Supplementary file

FUNDING STATEMENT

This work was supported by the University of Edinburgh School of Medicine, which provided a basic salary for the primary author of this study.

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests with regards to this study.

AUTHOR'S CONTRIBUTIONS

The study design was adapted from that of Stanley *et al.* (2016) and the protocol was written by HLA. KHB collected and analysed the data. RMW supported the data collection process. HMH collected a sample of data as a means of quality control. HLA provided supervision on aspects of data collection. SML supervised all aspects of the project. All authors contributed to the review and editing of the final manuscript.

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DATA SHARING STATEMENT

We are awaiting the journal's instruction on data submission as per Dryad repository guidance on BMJ Open manuscript submissions (https://datadryad.org/pages/journalLookup). Thereafter the DOI for our dataset will be provided.

REFERENCES

1. European Monitoring Centre for Drugs and Drug Addiction. *Action on new drugs*. 2016. http://www.emcdda.europa.eu/activities/action-on-new-drugs (accessed 4 Dec. 2016).
2. Liechti M. Novel psychoactive substances (designer drugs): overview and pharmacology of modulators of monoamine signaling. *Swiss Med Wkly.* 2015;145:w14043.
3. European Monitoring Centre for Drugs and Drug Addiction. New psychoactive substances in Europe. An update from the EU Early Warning System. March 2015. http://www.emcdda.europa.eu/system/files/publications/65/TD0415135ENN.pdf (accessed 4 Dec. 2016).
4. Moore K, Dargan PI, Wood DM, *et al*. Do novel psychoactive substances displace established club drugs, supplement them or act as drugs of initiation? The relationship between mephedrone, ecstasy and cocaine. *Eur Addict Res*. 2013;19:276-82.
5. Corazza O, Valeriani G, Bersani FS, *et al*. "Spice,""Kryptonite,""Black Mamba": An Overview of Brand Names and Marketing Strategies of Novel Psychoactive Substances on the Web. *J Psychoactive Drugs*. 2014;46:287-94.
6. McAuley A, Hecht G, Barnsdale L, *et al*. Mortality related to novel psychoactive substances in Scotland, 2012: An exploratory study. *Int J Drug Policy*. 2015;26:461-7.
7. European Monitoring Centre for Drugs and Drug Addiction. *2016 EU Drug Markets Report – Chapter 7*: *New psychoactive substances — Understanding the market for new psychoactive substances in Europe*. 2016. http://www.emcdda.europa.eu/publications/eu-drug-markets/2016/online/new-psychoactive-substances/market (accessed 4 Dec. 2016).
8. Advisory Council on the Misuse of Drugs. Methylphenidate-based NPS: A review of the evidence of use and harm. March 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/420983/TCDO_methylphenidate_NPS.pdf (accessed 4 Dec. 2016).
9. Lafferty C, Smith L, Coull A, *et al*. The experience of an increase in the injection of ethylphenidate in Lothian April 2014-March 2015. *Scott Med J*. 2016: 0036933016649871.
10. Home Office. Annual Report on the Home Office Forensic Early Warning System (FEWS) A System to Identify New Psychoactive Substances in the UK. May 2012. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/225840/fews.pdf (accessed 4 Dec. 2016).
11. Bluelight.org. *Bluelight – Forum – Focus Forums, Other Drugs – Ethylphenidate*. 2010. http://www.bluelight.org/vb/threads/499397-Ethylphenidate (accessed 4 Dec. 2016).
12. Ho JH, Bailey GP, Archer JR, *et al*. Ethylphenidate: availability, patterns of use, and acute effects of this novel psychoactive substance. *Eur J Clin Pharmacol*. 2015;71:1185-96.
13. Bailey GP, Ho JH, Hudson S, *et al*. Nopaine no gain: Recreational ethylphenidate toxicity. *Clin Toxicol*. 2015;53:498-9.
14. Soussan C, Kjellgren A. "Chasing the High"–Experiences of Ethylphenidate as Described on International Internet Forums. *Subst Abuse*. 2015;9:9.
15. Schifano F, Orsolini L, Duccio Papanti G, *et al*. Novel psychoactive substances of interest for psychiatry. *World Psychiatry*. 2015;14:15-26.
16. Parks C, McKeown D, Torrance HJ. A review of ethylphenidate in deaths in east and west Scotland. *Forensic Sci Int*. 2015;257:203-8.
17. Maskell PD, Smith PR, Cole R, *et al*. Seven fatalities associated with ethylphenidate. *Forensic Sci Int*. 2016;265:70-4.
18. United Kingdom Parliament. *The Misuse of Drugs Act 1971 (Temporary Class Drug) Order 2015*. S.I. 2015/1027.

19. Home Office. *Circular 015/2015: temporary control of 5 methylphenidate-based NPS*. 2015. https://www.gov.uk/government/publications/circular-0152015-temporary-control-of-5-methylphenidate-based-nps/circular-0152015-temporary-control-of-5-methylphenidate-based-nps (accessed 4 Dec. 2016).
20. Iverson L, Advisory Council on the Misuse of Drugs. Re: TCDOs and ACMD position on methylphenidate-based NPS. February 2016. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/503873/TCDO_Letter_-_phenidates_and_12_month_29_Feb_2016.pdf (accessed 4 Dec. 2016)
21. Bury J, The City of Edinburgh Council Health, Social Care and Housing Committee. *Novel Psychoactive Substances – Trading Standards Enforcement Action.* 2015. www.edinburgh.gov.uk/download/meetings/id/48793/item_710_-_novel_psychoactive_subsdtances_–_trading_standards_enforcement_action (accessed 4 Dec. 2016)
22. United Kingdom Parliament. *Psychoactive Substances Act 2016*. c. 2.
23. Wood DM, Hunter L, Measham F, *et al*. Limited use of novel psychoactive substances in South London nightclubs. *QJM*. 2012:hcs107.
24. Brandt SD, Sumnall HR, Measham F, *et al*. Analyses of second-generation 'legal highs' in the UK: Initial findings. *Drug Test Anal*. 2010;2:377-82.
25. Stanley JL, Mogford DV, Lawrence RJ, Lawrie SM. Use of novel psychoactive substances by inpatients on general adult psychiatric wards. *BMJ Open*. 2016;6:e009430.
26. InterSystems. *TrakCare – Unified healthcare information system*. 2016. http://www.intersystems.com/our-products/trakcare/trakcare-overview-2/ (accessed 4 Dec. 2016).
27. SAP. *SAP BusinessObjects Business Intelligence*. 2016. http://go.sap.com/uk/product/analytics/bi-platform.html (accessed 4 Dec. 2016).
28. World Health Organization. International statistical classification of diseases and related health problems. World Health Organization; 2004.
29. Scottish Parliament. *Mental Health (Care and Treatment) (Scotland) Act 2003*. a.s.p. 13.
30. Scottish Care Information - Information Services of the NHS National Services Scotland. *SCI Store*. 2015. http://www.sci.scot.nhs.uk/products/store/store_main.htm (accessed 21 Dec. 2016).
31. Crew 2000. *Crew – Drugs Index*. 2016. http://m.crewknowledge.com/ListAllDrugs.php (accessed 4 Dec. 2016).
32. Adley M, DrugWatch. The Drugs Wheel – A new model for substance awareness (UK version 2.0.4). April 2017. http://www.thedrugswheel.com/downloads/TheDrugsWheel_2_0_4.pdf (accessed 26 May 2017).
33. Helander A, Beck O, Bäckberg M. Intoxications by the dissociative new psychoactive substances diphenidine and methoxphenidine. *Clin Toxicol*. 2015;53:446-53.
34. Chemical Lab. *K-PAX | Chemical Lab.* 2015. http://chemicallab.co.uk/product/k-pax/ (accessed 26 May 2017).
35. Shapiro H, DrugWise. NPS Come of Age: A UK Overview. May 2016. http://www.drugwise.org.uk/wp-content/uploads/NPSComeofAge.pdf (accessed 4 Dec. 2016)
36. Zamengo L, Frison G, Bettin C, *et al*. Understanding the risks associated with the use of new psychoactive substances (NPS): high variability of active ingredients concentration, mislabelled preparations, multiple psychoactive substances in single products. *Toxicol Lett*. 2014;229:220-8.

37. Kjellgren A, Andersson M. Aspects of Substance Displacement-From Illicit Drugs to Novel Psychoactive Substances. *J Addict Res Ther*. 2016;7.
38. Palamar JJ, Acosta P, Sherman S, *et al*. Self-reported use of novel psychoactive substances among attendees of electronic dance music venues. *Am J Drug Alcohol Abuse*. 2016:1-9.
39. Papanti D, Schifano F, Botteon G, *et al*. "Spiceophrenia": a systematic overview of "Spice"-related psychopathological issues and a case report. *Hum Psychopharm Clin*. 2013;28:379-89.
40. Home Office. *News story – Festivals warned over drug use*. 2011. https://www.gov.uk/government/news/festivals-warned-over-drug-use (accessed 4 Dec. 2016).
41. Lader D, Home Office. Drug Misuse: Findings from the 2014/15 Crime Survey for England and Wales. July 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/462885/drug-misuse-1415.pdf (accessed 4 Dec. 2016)
42. Public Health England. New psychoactive substances: toolkit for commissioners. November 2014. http://www.nta.nhs.uk/uploads/nps-a-toolkit-for-substance-misuse-commissioners.pdf (accessed 4 Dec. 2016).
43. Novel Psychoactive Treatment UK Network – NEPTUNE. Guidance on the Clinical Management of Acute and Chronic Harm of Club Drugs and Novel Psychoactive Substances. March 2015. http://neptune-clinical-guidance.co.uk/wp-content/uploads/2015/03/NEPTUNE-Guidance-March-2015.pdf (accessed 4 Dec. 2016).
44. Palamar JJ, Salomone A, Vincenti M, *et al*. Detection of "bath salts" and other novel psychoactive substances in hair samples of ecstasy/MDMA/"Molly" users. *Drug Alcohol Depend*. 2016;161:200-5.
45. Favretto D, Pascali JP, Tagliaro F. New challenges and innovation in forensic toxicology: focus on the "New Psychoactive Substances". *J Chromatogr A*. 2013;1287:84-95.
46. Al-Saffar Y, Stephanson NN, Beck O. Multicomponent LC–MS/MS screening method for detection of new psychoactive drugs, legal highs, in urine—Experience from the Swedish population. *J Chromatogr B*. 2013;930:112-20.
47. Gray R, Bressington D, Hughes E, *et al*. A systematic review of the effects of novel psychoactive substances 'legal highs' on people with severe mental illness. *J Psychiatr Ment Health Nurs*. 2016.
48. Parliament NZ. *Psychoactive Substances Act 2013*. Public Act. 2013(53):17.
49. Stevens A, Fortson R, Measham F, *et al*. Legally flawed, scientifically problematic, potentially harmful: The UK Psychoactive Substance Bill. *Int J Drug Policy*. 2015;26:1167-70.

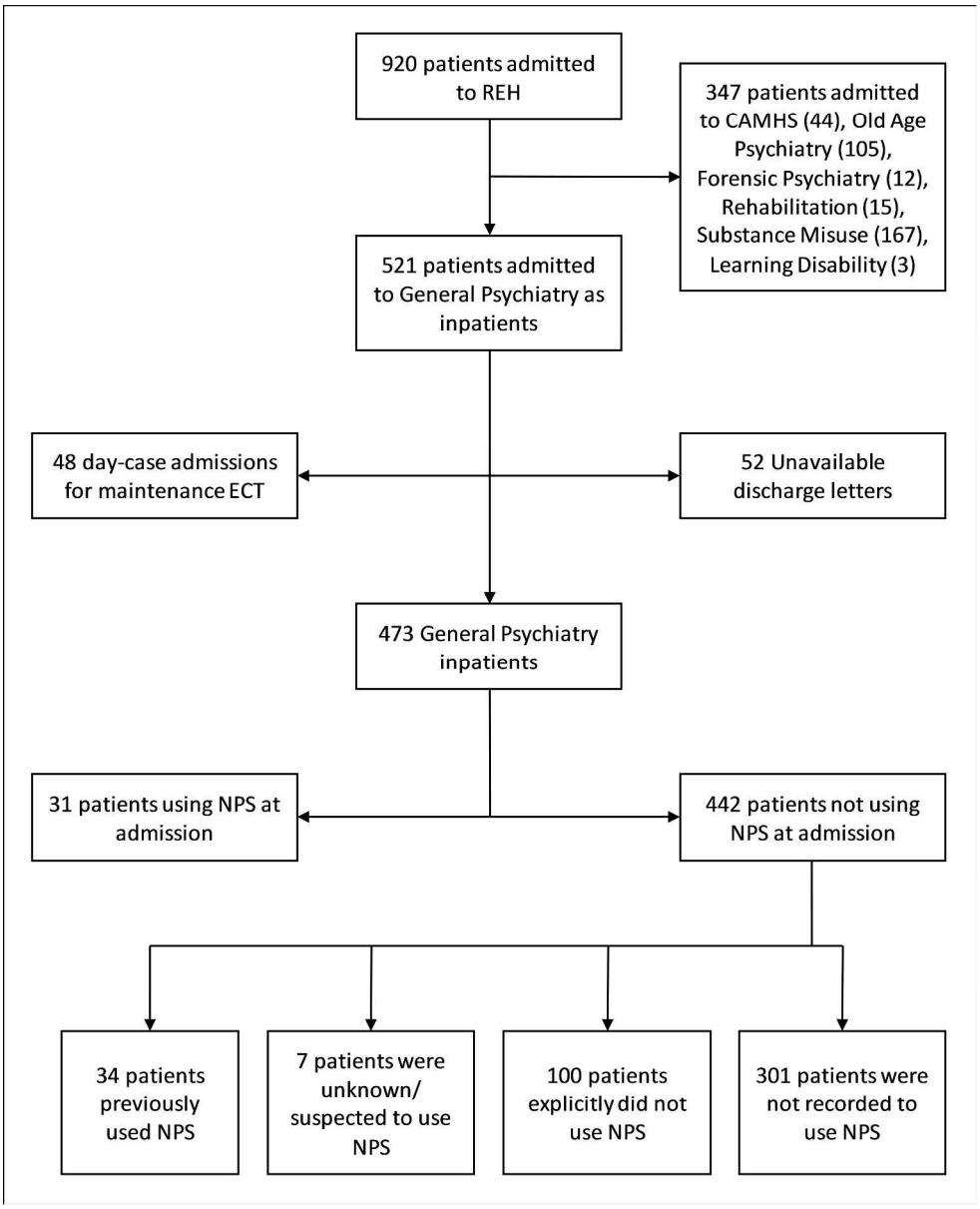

Figure 1: Flowchart of inclusion/exclusion criteria and patient groups. Sub-groups of the lowest tier in the flowchart were analysed collectively as non-NPS users. REH, Royal Edinburgh Hospital; CAMHS, Child & Adolescent Mental Health Services; ECT, electroconvulsive therapy; NPS, novel psychoactive substance.

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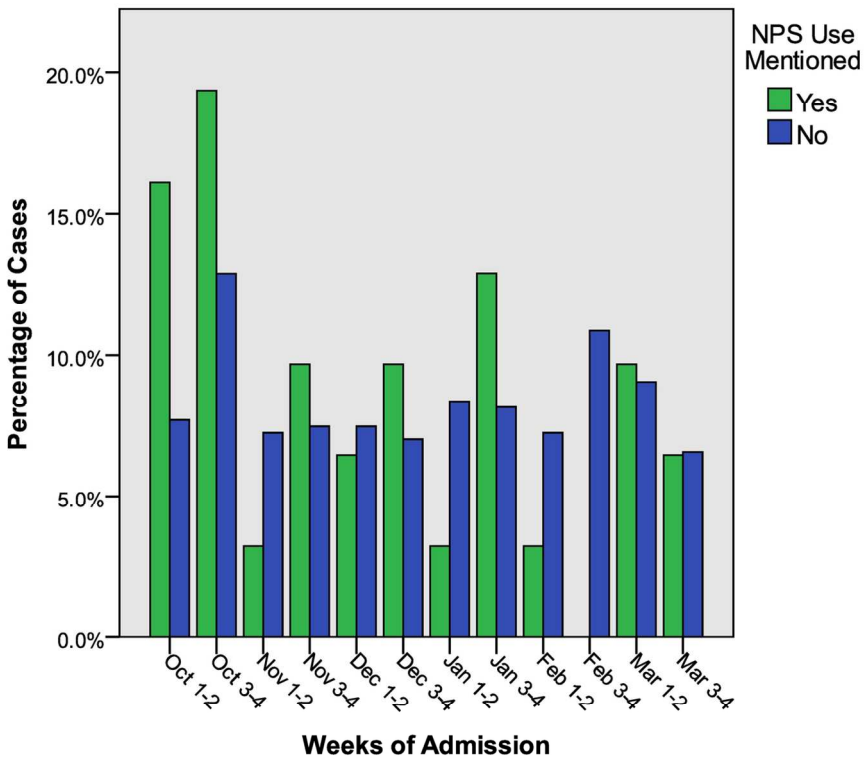

Figure 2: The percentage of NPS users and non-NPS users admitted in fortnightly intervals between October 2015 – March 2016. NPS, novel psychoactive substance.

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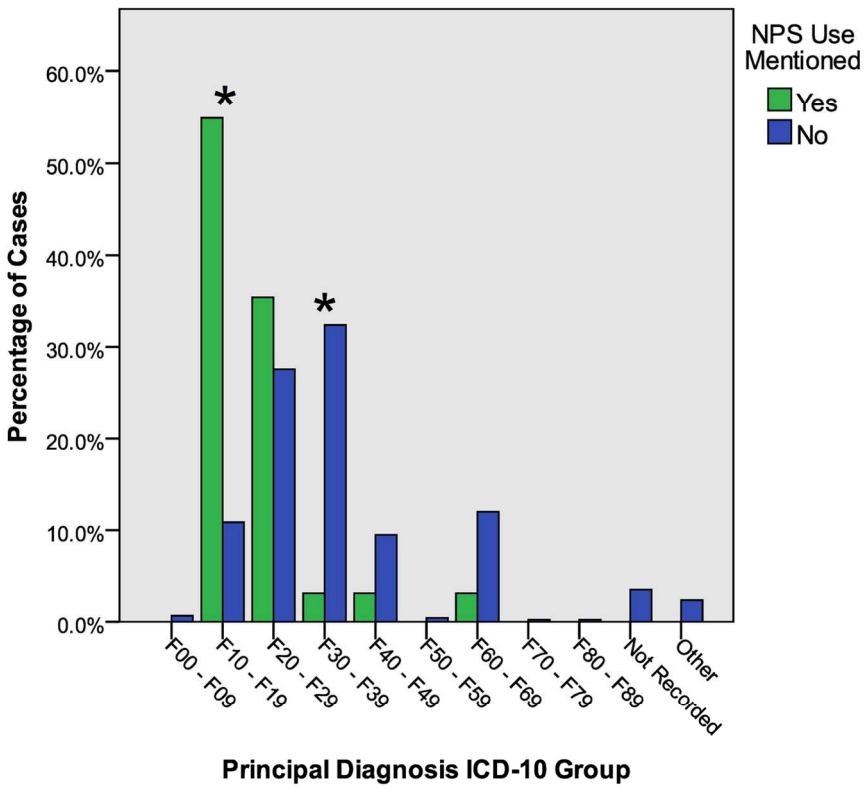

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NEW PSYCHOACTIVE SUBSTANCES STUDY PROTOCOL

Background

This study aims to examine the effect of two public health interventions on presentations to psychiatric services following use of new psychoactive substances. We will aim to quantify number of presentations, which drugs were used and whether there was psychiatric symptomatology, as well as looking at outcome of presentation (hospital admission, referral to other services).

REH Study

1. Identify individuals admitted to REH acute wards/taken on by IHTT for 6/12 prior to banning of ethylphenidate (10/04/15) and 6/12 after City Council forfeiture order (15/10/15) using Trak patient record database.
2. Using Trak, review discharge letters and extract information on: age, gender, drug used, method of administration, psychiatric diagnosis (if given), duration of admission, other substance use & symptomatology.
3. Data analysis:
    a. Make comparison of numbers of patients being admitted with psychiatric problems following NPS use compared to previous findings.
    b. Examine any changes in patterns of psychiatric presentation or admission to psychiatric hospital

Data Collection Sheet

Patient Demographics

Subject no:		Gender:	Male □ Female □ Transgender □
Age:			
Employment status:	Unemployed □ Full time □ Part time □ Self employed □ Student □	Home circumstances:	Independent □ Supported □ Homeless □ Not recorded □
Admission to:	REH □ IHTT □ A&E □ CAA6 □ Other □		

Primary diagnosis:			
Other diagnoses:			
Admission date:		Discharge date:	
Use of Mental Health Act:	Yes □ No □	Previous admissions/IHTT:	
Forensic History:	Yes □ No □ Not recorded □	Previous custodial sentence noted:	Yes □ No □ Not recorded □ Not applicable □

Substance Use

NPS Use:	Yes No Not recorded Previous	Contribution to psychiatric presentation?	Yes No Not recorded
Names of NPS(s):			
Route of administration:	IV Insufflation Oral Smoked Other…		
Other substance use:	Alcohol: current previous Cannabis: current previous Benzodiazepines: current previous Cocaine: current previous Amphetamines: current previous MDMA: current previous GBL/GHB - current previous Opiates (substitute):current previous Which…… Opiates (non substitute): current previous Other:……..		
Psychiatric symptoms:	Agitation □ Thought-disordered □ Paranoia □ Hallucinations □ Suicidal thoughts □ Disinhibition □ Delusions □ Disorientation □ Labile affect □ Low mood □ Lack of insight □ Anxiety □ Self-referential ideas □ Passivity phenomena □		

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **[In the title and under 'Design' of the abstract (page 2)]**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **[Within the 'Results' section of the abstract (page 2)]**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **[Under 'Background' within the Introduction (page 3)]**
Objectives	3	State specific objectives, including any prespecified hypotheses **[Within 'Objectives' under the Introduction (page 4)]**
Methods		
Study design	4	Present key elements of study design early in the paper **[Within 'Study design and setting' (page 4)]**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **[Within 'Participants' (page 4)]**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **[Within 'Participants' (page 4)]**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **[Outcomes are addressed under 'Data collection' (page 4), others are not applicable.]**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **[not applicable]**
Bias	9	Describe any efforts to address potential sources of bias **[Under 'Data collection' (page 5) and 'Limitations and future research' (page 9)]**
Study size	10	Explain how the study size was arrived at **[Under 'Participants' (page 4)]**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **[Detailed under 'Statistical methods' (page 5)]**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **[Under 'Statistical methods (page 5)]**
		(*b*) Describe any methods used to examine subgroups and interactions **[not applicable]**
		(*c*) Explain how missing data were addressed **[under 'Data collection' (page 5)]**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy **[not applicable]**
		(*e*) Describe any sensitivity analyses **[not applicable]**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **[Within the first paragraph of the Results (page 5) and in Figure 1]**
		(b) Give reasons for non-participation at each stage **[Under 'Participants' of the Methods (page 4) and the first two paragraphs of the Results (page 5-6]**
		(c) Consider use of a flow diagram **[see Figure 1]**

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **[Under the 6th paragraph of the Results and Table 1 (pagse 6-7)]**
		(b) Indicate number of participants with missing data for each variable of interest **[Recorded in Table 1 of the Results (pages 6-7)]**
Outcome data	15*	Report numbers of outcome events or summary measures **[The outcome event of this study is mention or no mention of NPS use, which is detailed throughout the Results (pages 5-8)]**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **[95% confidence intervals are stated throughout each paragraph of the Results (pages 5-8)]**
		(*b*) Report category boundaries when continuous variables were categorized **[not applicable]**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **[not applicable]**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **[not applicable]**
Discussion		
Key results	18	Summarise key results with reference to study objectives **[Under 'Principal findings' of the Discussion (page 8)**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **[Under 'Limitations and future research' of the Discussion (page 9)]**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **[Within the Discussion (pages 8-10)]**
Generalisability	21	Discuss the generalisability (external validity) of the study results **[Under 'Generalisability' of the Discussion (page 10)]**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **[Source of funding is stated on page 10 and the original study that the article is based on is referenced throughout (Stanley et al.)]**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.