PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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.
AUTHORS	Bennett, Kyle; Hare, Helen; Waller, Robert; Alderson, Helen; Lawrie, Stephen

VERSION 1 – REVIEW

REVIEWER	Chris Wilkins Massey University, New Zealand None
REVIEW RETURNED	07-Feb-2017

GENERAL COMMENTS	This is potentially an interesting paper and approach, but has some significant problems with the methodology. In terms of changes in prevalence, the comparison is made with Stanley et al., but there is no information on whether the Stanley methodology is the same as the present study, were there any ways it was different, if so then the comparison is not valid? It was unclear who the non-NPS users were, if they were all inpatient who had not used NPS then is is no surprise they were different from the NPS users as you are essentially comparing a drug using group with the general population. How was NPS use identified (self-report, forsenic, drug test). Finally, "a large proportion of demographic outcome measures were not recrorded in discharger letters" what percentage? this is a big limitation given you are comparing demographic characteristics.

REVIEWER	Hazel Torrance Department of Forensic Medicine and Science, University of Glasgow, Scotland, UK
REVIEW RETURNED	24-Apr-2017

GENERAL COMMENTS	Abstract: The objective is to assess the impact of different legislation on the prevalence, yet in the results you only state the prevalence for, what looks like, the whole time period and don't compare time periods to assess the impact of different legislative measures. However in the conclusions the first statement states the inpatient numbers have fallen. I think it needs some further information to clarify how you come to this conclusion, ie. by comparing to a previous study.

	Page 3 line 13: This last sentence seems to confuse why NPS are labelled "research chemicals". It might be just the grammar giving an unintended meaning. Page 3 line 19: Most NPS in drug related deaths are new benzodiazpines e.g. phenazepam, etizolam, which have not been mentioned in this paper. Page 4 line 57: It should be mentioned that whilst this may be a way to identify the most probably active ingredients involved looking up brand names for active ingredients found in a particular instance is not always reliable. Drug brands and their ingredients change over time, and this information should be used with caution. The only reliable way is to analytically test the drugs associated with each individual case. Page 5 line 34: There should be more clear definitions between the terms you are using, "research chemicals" is not appropriate, MDAI and methoxphenidine could be described as hallucinogenic or dissociative. Page 8 line 14: did the patients use the term "research chemicals"? If so then it is OK to include this. Page 8 line 15: where is the evidence that other compounds have been substituted for ethylphenidate? There is potentially more evidence they have gone back to heroin use. Page 8 Strengths and weaknesses: There seems to be a skew towards defining NPS in this paper to "club drugs" and stimulants, and forgetting Synthetic Cannabinoids Receptor Agonists and new benzodiazepines which account for a large percentage of use. In addition when comparing your results to other literature you need to be clear about what they consider to be "NPS". Page 9 Limitations and future research: Ref 42 not relevant as it refers to testing bulk drug and not a clinical test for testing blood/urine of which there are several published methods out there. The sentences around this should be rewritten as there are analytical tests which can cope with changing trends in chemical composition of NPS. Page 10 line 9: Presumably the TCDO on ethylphenidate and related substances has not made an impact on other NPS which maybe needs clarified. Page 10 line 15: I'd be careful about saying the PSA "renders all NPS illegal" it's a bit of a sweeping statement which doesn't clarify the different situations when they are not illegal, e.g. possession, definition of psychoactvitity etc.

REVIEWER	Nadra UCSF, California, USA
REVIEW RETURNED	16-May-2017

GENERAL COMMENTS	I have three major comments: -It is stated that a "Person chi-sq were used to compare differences and generate Odds Ratios (ORs)" - the Pearson chi-sq cannot generate ORs. Perhaps ORs were computed using the table generated? And the p's reflect that? -Why not do logistic regression analyses and control for possible covariates? -The title of the study is misleading. This is more a study on users and non-users of NPS and does not really address the prohibition and seizure

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Chris Wilkins
Institution and Country: Massey University, New Zealand
Please state any competing interests: None declared

Please leave your comments for the authors below

Comment: This is potentially an interesting paper and approach, but has some significant problems with the methodology. In terms of changes in prevalence, the comparison is made with Stanley et al., but there is no information on whether the Stanley methodology is the same as the present study, were there any ways it was different, if so then the comparison is not valid? It was unclear who the non-NPS users were, if they were all inpatient who had not used NPS then is is no surprise they were different from the NPS users as you are essentially comparing a drug using group with the general population. How was NPS use identified (self-report, forsenic, drug test). Finally, "a large proportion of demographic outcome measures were not recrorded in discharger letters" what percentage? this is a big limitation given you are comparing demographic characteristics.

Response: We thank Dr Wilkins for highlighting that the methodology of Stanley et al. could be further clarified. Changes have since been made to address this point (page 5, lines 19-20).
The non-NPS users were indeed all inpatients who were not using NPS. Whilst the NPS using population is indeed likely to be different from the remaining population in a psychiatric hospital, they are at least similar in terms of having been admitted to hospital and are arguably more similar than either group are to the general population. Furthermore, the main aim of comparing these two groups was to facilitate comparison with Stanley et al., to determine if there was any shift in usage since public health interventions.
In the Discussion, reference has been made to clinical inquiry as the approach for recording NPS use; however, we agree that this could have been better reported in the methodology. We have taken steps to make this clearer in the Methods (page 4, lines 42-44).
Table 1 presents the percentages for where demographic outcomes were poorly recorded. We have since included these figures in the Discussion under Strengths and weaknesses (page 8, line 36-37).]

Reviewer: 2
Reviewer Name: Hazel Torrance
Institution and Country: Department of Forensic Medicine and Science, University of Glasgow, Scotland, UK
Please state any competing interests: None declared

Please leave your comments for the authors below

Abstract:
The objective is to assess the impact of different legislation on the prevalence, yet in the results you only state the prevalence for, what looks like, the whole time period and don't compare time periods to assess the impact of different legislative measures. However in the conclusions the first statement states the inpatient numbers have fallen. I think it needs some further information to clarify how you come to this conclusion, ie. by comparing to a previous study.

Response: Thank you for your review, Dr Torrance. The objective of the study is not to assess different public health interventions on the prevalence of NPS use. Due to the study design, this is not possible. As mentioned in the 'Strengths and limitations of this study:', the 6-month period of the study started 6 months after the TCDO on methylphenidate derivatives and included the preceding 2 weeks of the issue of Forfeiture Orders. Therefore, we cannot compare time periods to assess the impact of each intervention. However, by comparison with Stanley et al., we can conclude that the prevalence of NPS use in this 6-month period is considerably less than that found in the aforementioned study. We do agree that our method of comparison could be made clearer in the Abstract and have changed this accordingly (page 2, line 23).

Page 3 line 13: This last sentence seems to confuse why NPS are labelled "research chemicals". It might be just the grammar giving an unintended meaning.

Response: We agree that this is potentially misleading and we have revised this sentence (page 3, line 9.)

Page 3 line 19: Most NPS in drug related deaths are new benzodiazpines e.g. phenazepam, etizolam, which have not been mentioned in this paper.

Response: We understand that this is true. However, the objective of this study was to address the impact of two public health interventions, one of which was a nationwide classification of methylphenidate derivatives. Also, considering the local public health impact of this particular group of NPS, our focus was directed on this one group. We have since amended the text to contextualise the relevance of ethylphenidate in Edinburgh. page 3, lines 17-20.

Page 4 line 57: It should be mentioned that whilst this may be a way to identify the most probably active ingredients involved looking up brand names for active ingredients found in a particular instance is not always reliable. Drug brands and their ingredients change over time, and this information should be used with caution. The only reliable way is to analytically test the drugs associated with each individual case.

Response: We agree that this is not the most accurate method of identifying active ingredients in NPS. Unfortunately, laboratory analysis of NPS is not readily available at our centre, which is why this less reliable approach was adopted. However, we respect that this is an important limitation of the study and have since raised this in the Discussion under 'Limitations and future research' (page 10, lines 13-19).

Page 5 line 34: There should be more clear definitions between the terms you are using, "research chemicals" is not appropriate, MDAI and methoxphenidine could be described as hallucinogenic or dissociative.

Response: We appreciate that ‘research chemicals’ is perhaps too vague a term for the purposes of this paper. Instead we have now classified NPS in accordance with the Drug Wheel and found supporting evidence for a classification where the NPS is not documented in the Drug Wheel (page 5, lines 2-5, 45-46).

Comment: Page 8 line 14: did the patients use the term "research chemicals"? If so then it is OK to include this.

Response: This has been altered in line with the above comment (page 8, lines 30-31).]

Comment: Page 8 line 15: where is the evidence that other compounds have been substituted for ethylphenidate? There is potentially more evidence they have gone back to heroin use.

Response: We agree that this statement is not fully supported by our reported results. In response to your previous comment, we have changed our definition of NPS classifications, and have reported the diversity of NPS types found in the Results section (page 5, line 38-page 6, line 1). We cannot conclude that ethylphenidate has been substituted or that its use has fallen, especially with no previous data – Stanley et al. made the broad binary distinction of stimulants and synthetic cannabinoids. Instead, based on the diversity of stimulants found, we made the suggestion that there were more options available in the market from users to choose from. With regards to heroin use, we do not have evidence to support that assertion.]

Comment: Page 8 Strengths and weaknesses: There seems to be a skew towards defining NPS in this paper to "club drugs" and stimulants, and forgetting Synthetic Cannabinoids Receptor Agonists and new benzodiazepines which account for a large percentage of use. In addition when comparing your results to other literature you need to be clear about what they consider to be "NPS".

Response: We acknowledge that SCRAs and new benzodiazepines account for a large percentage of NPS use. This statement was not intended to refer to stimulants only as ‘drug substitute’ could encompass SCRAs and benzodiazepines. These NPS could equally be used as club drugs. We instead speculate that NPS are utilised by different age groups for different reasons. The text has been amended to reflect this (page 8, lines 34-38). We also take on board your comments regarding NPS definitions throughout the literature and have implemented the following changes (page 8, lines 44-48; page 9, lines 5-6, line 24; page 10, lines 11-13.).]

Comment: Page 9 Limitations and future research: Ref 42 not relevant as it refers to testing bulk drug and not a clinical test for testing blood/urine of which there are several published methods out there. The sentences around this should be rewritten as there are analytical tests which can cope with changing trends in chemical composition of NPS.

Response: Thank you for directing us to this evolving area of analytical chemistry. We have amended the text in line with your recommendations (page 10, line 13-19).

Comment: Page 10 line 9: Presumably the TCDO on ethylphenidate and related substances has not made an impact on other NPS which maybe needs clarified.

Response: Again, as comments previously raised, due to the study design it is not possible to make this conclusion.

Omment: Page 10 line 15: I'd be careful about saying the PSA "renders all NPS illegal" it's a bit of a sweeping statement which doesn't clarify the different situations when they are not illegal, e.g. possession, definition of psychoactvitity etc.

Response: We agree. We have revised this phrase (page 10, line 40).

Reviewer: 3
Reviewer Name: Nadra
Institution and Country: UCSF, California, USA
Please state any competing interests: None declared'

Please leave your comments for the authors below

I have three major comments:

1. It is stated that a "Person chi-sq were used to compare differences and generate Odds Ratios (ORs)" the Pearson chi-sq cannot generate ORs. Perhaps ORs were computed using the table generated? And the p's reflect that?

Response: Yes, this is correct. We have rewritten this statement to reflect this process (page 5, line 15-17).

2. Why not do logistic regression analyses and control for possible covariates?

Response: We did not feel a logistic regression analysis would be appropriate in addressing the aims of this study. We sought to find the prevalence of NPS use in the psychiatric inpatient population and report the demographic of these users; a logistic regression may identify predictors of NPS use but this does not coincide with our aims. Furthermore, it is likely there would be multicollinearity between the predictor variables (i.e. substance use), thereby precluding its suitability.]

3. The title of the study is misleading. This is more a study on users and non-users of NPS and does not really address the prohibition and seizure

Response: We report that the prevalence of NPS use is lower than the 22.2% figure previously reported at our centre in Stanley et al. However, we acknowledge that this title may not reflect the primary findings of this study. As such, we have revised the title accordingly.

VERSION 2 – REVIEW

REVIEWER	Hazel Torrance University of Glasgow, UK
REVIEW RETURNED	17-Jul-2017

GENERAL COMMENTS	Previous comments have been addressed.

REVIEWER	Nadra Lisha UCSF, USA
REVIEW RETURNED	28-Jun-2017

GENERAL COMMENTS	While this paper has potential, the authors did not adequately address the comments from the reviewers. I am not satisfied with the explanation on why logistic regression was not used. In addition, the others do write more than once that they are not assessing whether the changes caused the lower percentages based on the Stanley et al, paper, they mostly discuss this and the whole discussion is based on this finding. For me, there is just not enough there for this to be portrayed as the main outcome of this paper. The findings regarding NPS and non-NPS users are barely discussed in the discussion but might help make the paper more useful had they been.

REVIEWER	Mark Bahr Bond University Australia
REVIEW RETURNED	11-Sep-2017

GENERAL COMMENTS	I have mixed feelings as to the suitability for publication. The issue is interesting but the writing is less than clear in places. Framing statements regarding the seizure of NPS supplies at the start of the data collection period suggest to me that changes in usage patterns are probably attributable to that event rather than anything more meaningful. The role of discharge letters is unclear as is the inclusion of IHTT in the sample. I don't see the rationale for including the group and hetereogeneity of the resultant sample raises questions as to the representativeness or otherwise of the obtained sample. I suspect that there may be an audience for the paper based on interest in the material and propose acceptance on that basis.

REVIEWER	Hui Nian Vanderbilt University Department of Biostatistics None
REVIEW RETURNED	20-Sep-2017

GENERAL COMMENTS	The manuscript is clearly written. Data are properly analyzed and results are appropriately interpreted. No further comments.