PEER REVIEW HISTORY

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This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Trends in self-poisoning and psychotropic drug use in people aged 5-19 years: a population based retrospective cohort study in Australia
AUTHORS	Cairns, Rose; Karanges, Emily; Wong, Anselm; Brown, Jared A; Robinson, Jeff; Pearson, Sallie-Anne; Dawson, Andrew; Buckley, Nicholas

VERSION 1 – REVIEW

REVIEWER	Helinä Hakko Oulu University Hospital, Department of Psychiatry
REVIEW RETURNED	03-Sep-2018

GENERAL COMMENTS	BMJ Open Trends in self-poisoning and psychotropic drug use in people aged 5-19 years_ a population based retrospective cohort study in Australia. INTRODUCTION The introduction section is concise and covers the articles relevant to the research topic. The aims of the study are clearly stated. MATERIAL AND METHODS Study subjects were Australians aged 5-19 years; "child" 5-14 years, "adolescent" 15-19 years. PIC data: The NSWPIC and VPIC databases were searched from 2006-2016 for calls categorized as intentional poisonings (PIC data). In addition, Psychotropic dispensing data from July 2012 to June 2016 were used for in-depth analysis (PBS data). If multiple calls about the same exposure were received, the subsequent calls were excluded. * The data sources are sufficient for the purpose of this study. RESULTS In general, a lot of results (3 tables, 3 figures, 3 supplementary figures, 1 supplementary table) are presented either in the manuscript or as supplementary material. Some results are worth of reporting only in the text. * Some results are worth of reporting by gender, like in Figure 1, since the prevalence of psychiatric disorders and, consequently, use of psychotropic medication is known to differ by gender. This gender-difference is particularly seen in young patient populations. Intentional poisonings: * 11 -year period of 2006-2016, 8053 poisonings in children,

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	25448 poisonings among adolescents * First, Figure 1 is a bit misleading due to different scaling of y-axis in sub-figures A and B. The figures A and B should be combined to one figure, and should be easy to be done, since the amount of poisonings in children and adolescents differs clearly in their magnitude. If Figure 1 presents the number of different persons with self-poisoning in each year, state that clearly in y-axis title and Figure 1 legend. * Check carefully throughout the manuscript, that the results are clearly presented whether those relate to different individuals with self-poisoning or whether those are relating to number of self-poisoning calls (an individual may have occurred several poisonings during a year). * Table 1 lacks of information that the numbers reported in the table means “number of individuals”, so add this clarification to the title of the table. * How many individuals were included only to age group 5-14 yrs, only to age group 15-19 yrs and to the both age groups? Do the results, throughout of the manuscript, differ if a person belonged to either age-group or to both age-groups? Psychotropic dispending: * Table 2 and Table 3 include enormous amount of results (number), which may cause difficulties for readers to find the most essential ones. Consider removing from tables the rows without any observations and non-significant findings or report only three most commonly used SSRIs. DISCUSSION * As noted earlier, it is not clear for reader whether the authors discuss about the number of different individuals or number of poisoning incidents. * The methodological discussion about the data sources used in the study is relevant. * Generally, the comparison the results to those of previous studies is appropriate, but needs for greater focus to age-groups 5-14 and 15-19 years, separately. Check also the abstract.

REVIEWER	A Erlangsen Danish Research Institute for Suicide Prevention, Denmark
REVIEW RETURNED	27-Sep-2018

GENERAL COMMENTS	The authors should be congratulated on this very interesting study. The study examines trends in calls to major poison hotlines in Australia as well as prescription sales. A strength of the study is the completeness in the data sources and the age-specific, drug-specific dispersion rates. A weakness is the fact that calls to poison lines is a proxy for self-poisoning and it might represent a conservative estimate. The increasing rates of self-poisoning among young Australians has been noted using data from emergency departments in NSW and Victoria, hence the novel part of this study is to assess the same hypothesis in a different data source – and to measure trends in prescription data. The study surely presents original findings meriting a publication. There are some minor issues which would benefit from being addressed, as listed below. ABSTRACT Setting: some of this information relates to outcomes and would be better to list under ‘Main Outcome Measures’. METHODS

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	Pg 4, line 3-14, This text segment seems to discuss the strengths and weaknesses of different data sources and would fit better in a dedicated paragraph in the Discussion. Also, the authors might consider whether some of the other information listed in the 'Design' section would fit better characterized as 'Measures' and 'Outcomes'. Pg. 5 top: the text would benefit from a slight edit to improve text flow. This will help future readers. Pg. 5 Pharmaceutical Benefits Scheme: it seems that the 10% sample is not a random sample – at least prior to 2012. How was the sample composed during the follow-up? If it was not a random sample, it would be relevant to discuss potential selection bias in the Limitations. Were these nationwide data? Were data available by gender? (given that you find an increase in self-poisoning among young girls, a gender-break down could provide relevant information). Pg. 6. Please describe with more detail which population estimates were obtained from the ABS, i.e. was it for all of Australia – or just NSW and Victoria? RESULTS It would be beneficial to present test statistics (or CI-95%) for the observed trends in self-poisonings. Table 1. were there any trends in drug types as noted in the calls to poison centers? The time trends in PBS are explored extensively. Yet, it would be relevant to know what drugs were accountable for the observed increase in girls as this would give indications for what futures interventions might address. DISCUSSION It would be essential to know if there were any changes in the referral practice/usage of poison hotlines with respect to self-poisonings over the follow-up period, e.g. campaigns at participating hospital wards to inform of the service or other initiatives which could explain a surge in calls. The fact that poison hotlines experienced a decline in other types of calls is a strength of the validity as mentioned by the authors. Pg. 8, line 25-34: Could this be rephrased in to a strength rather than a summary? Also, calls to poison hotlines is likely represents a minimum figure (a conservative estimate) of the actual incidences of self-poisoning. This ought to be clearly pointed out in this section. As it appears now, this information is mixed with information regard type of drug. Pg. 10, line 14+: As mentioned in the result section, paracetamol is reported as the most frequently used drug in self-poisoning. It would, thus, be good to assess this finding in the Discussion, particularly, considering the existing evidence base for means restriction from the UK.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Helinä Hakko
Institution and Country: Oulu University Hospital, Department of Psychiatry Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
BMJ Open
Trends in self-poisoning and psychotropic drug use in people aged 5-19 years_ a population based retrospective cohort study in Australia.

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INTRODUCTION
The introduction section is concise and covers the articles relevant to the research topic. The aims of the study are clearly stated.

Response: We thank the reviewer for their time taken to review our manuscript and for this comment

MATERIAL AND METHODS
Study subjects were Australians aged 5-19 years; “child” 5-14 years, “adolescent” 15-19 years.
PIC data: The NSWPIC and VPIC databases were searched from 2006-2016 for calls categorized as intentional poisonings (PIC data). In addition, Psychotropic dispensing data from July 2012 to June 2016 were used for in-depth analysis (PBS data). If multiple calls about the same exposure were received, the subsequent calls were excluded.
* The data sources are sufficient for the purpose of this study.

Response: we thank the reviewer for their comment

RESULTS
In general, a lot of results (3 tables, 3 figures, 3 supplementary figures, 1 supplementary table) are presented either in the manuscript or as supplementary material. Some results are worth of reporting only in the text.

Response: Supplementary Figure 1 has been removed (as has the reference to it in Results 3.1), this result has been described in text only.

We believe Supplementary table 1 is important to show how we constructed our birth cohorts. We believe the other supplementary figures will be of interest to some readers as they show longer term trends in psychotropic dispensings. However, we are happy to take editorial guidance on this matter.

We believe Table 1 provides useful information with detail about agents taken in overdose. This is one of the strengths of PIC data and thus we believe it belongs in the paper (and would be difficult to describe in text).

The other 2 tables have been edited to increase clarity. We agree that they do present a lot of data, and we have highlighted the most interesting findings in the text. We have left these in the paper however Tables 2 and 3 could be moved to supplementary if desired.

Figure 1 has been condensed as per Reviewer 1 Comment below. Figure 2 shows the cohort effect and graphical representation is the standard way to display cohort data (per Gunnell et al., Br J Psychiatry. 2003;182:164–70.) Figure 3 shows SSRI dispensing trends by gender, age and drug, and we think this visual representation is complementary to Table 2.

* Some results are worth of reporting by gender, like in Figure 1, since the prevalence of psychiatric disorders and, consequently, use of psychotropic medication is known to differ by gender. This gender-difference is particularly seen in young patient populations.

Response: Thank you for your comment. As per the comment by Reviewer 2, psychotropic medication dispensing by gender has been added to the manuscript.

Intentional poisonings:
* 11 -year period of 2006-2016, 8053 poisonings in children, 25448 poisonings among adolescents
* First, Figure 1 is a bit misleading due to different scaling of y-axis in sub-figures A and B. The figures A and B should be combined to one figure, and should be easy to be done, since the amount of poisonings in children and adolescents differs clearly in their magnitude. If Figure 1 presents the

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number of different persons with self-poisoning in each year, state that clearly in y-axis title and Figure 1 legend.

Response: Thank you for this suggestion. A and B have now been combined into the one figure. The results text has been updated accordingly. The y-axis title has been changed to "number of self-poisoning events".

* Check carefully throughout the manuscript, that the results are clearly presented whether those relate to different individuals with self-poisoning or whether those are relating to number of selfpoisoning calls (an individual may have occurred several poisonings during a year).

Response: We believe that the text added to the methods (below) make it clear that these are self-poisoning events.

* Table 1 lacks of information that the numbers reported in the table means "number of individuals", so add this clarification to the title of the table.

Response: Table 1 title now reads: "The most common substances ingested in child and adolescent self-poisoning events to NSWPIC and VPIC, 2006-2016 (n = 33,501)"

For clarification, the following text has been added:
Methods: 2.2.1 "Note that this data relates to self-poisoning events, one individual may have repeated self-poisonings, and thus may be included several times in this dataset."

* How many individuals were included only to age group 5-14 yrs, only to age group 15-19 yrs and to the both age groups? Do the results, throughout of the manuscript, differ if a person belonged to either age-group or to both age-groups?

Response: Age is assigned at the time of the call, individuals are either categorised as 5-14 years or 15-19 years. As this data relates to self-poisoning events rather than individuals, if a person has repeated self-poisonings e.g. one at 13 years old in 2007, and another at 15 years old in 2009, and PIC is called about these, this person will be included twice, in the 5-14 bracket as a 2007 exposure and in 2009 in the 15-19 bracket.

For clarification, the following section (methods 2.2.1) has been amended to read (underlined text added):
"The NSWPIC and VPIC databases were searched from 2006 – 2016 for calls where the exposure type was "intentional" (this includes deliberate self-poisoning, recreational use and intentional misuse), where the patient's age category <u>at the time of poisoning</u> was coded as "Child" or "Adolescent"."

Psychotropic dispensing:

* Table 2 and Table 3 include enormous amount of results (number), which may cause difficulties for readers to find the most essential ones. Consider removing from tables the rows without any observations and non-significant findings or report only three most commonly used SSRIs.

Response: We have made changes to Table 2 and 3 which we believe will enhance clarity. This includes merging of rate of increase and confidence interval columns, bolding significant % changes, and shading of rows for drug classes and sub-classes to sub-divide the table. We tried removing rows with no observations or non-significant findings however we believe it is clearer to show the same list of drugs/classes for each age group. Although these tables are still data-dense, we believe the data will be of interest for some readers looking to understand trends in more detail. However, we will happily take editorial guidance on this. As discussed above, these two tables could be moved to supplementary material.

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DISCUSSION

* As noted earlier, it is not clear for reader whether the authors discuss about the number of different individuals or number of poisoning incidents.

  Response: we hope that the clarification in the methods as described above will be sufficient to ensure the reader knows that "self-poisonings" refers to "self poisoning events" not individuals. We could change all instances of "self poisonings" to "self poisoning events" if required, and will take editorial guidance on this.

* The methodological discussion about the data sources used in the study is relevant.

  Response: we thank the reviewer for this comment

* Generally, the comparison the results to those of previous studies is appropriate, but needs for greater focus to age-groups 5-14 and 15-19 years, separately. Check also the abstract.

  Response: we agree with the reviewer that a focus on the age groups we reported on would be ideal. Unfortunately many papers use different age cut offs (in particular, many do not report on the 5-9 years age group). We believe we discuss the most relevant evidence in the field and that even if the age brackets do not completely align with ours, useful comparisons can be made.

  The following has been added to Discussion 4.2:
  "Self-harm was not in the top 25 causes of death in children aged 5-9 years"

  For the comparison with previous studies on dispensing patterns, the Karanges et al Paper did not report on psychotropic dispensing in the younger 5-9 years age group and we were unable to find other recent Australian data on this age group.

  We have incorporated some other international studies which report on children 0-18 and 017 years. The following has been added to Discussion 4.2:
  "In Canada, antipsychotic use in children 18 and under increased 4-fold, 1998-2008, with the largest increases in those aged 7-18 years [26]. In Denmark, psychotropic use in children 017 years increased nine fold 1996-2010 (two fold increase when adjusting for increasing patient numbers) [27]. Use of antidepressants in children has remained stable in the USA however is increasing in the UK [11]. A review of international trends in psychotropic medication use in children and adolescents found a general trend in many countries of increasing prescription rates [28]."

  We are unsure what the reviewer means by "check also the abstract" since we did not report on previous studies in the abstract.

Reviewer: 2

Reviewer Name: Annette Erlangsen
Institution and Country: Danish Research Institute for Suicide Prevention, Denmark
Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below
The authors should be congratulated on this very interesting study. The study examines trends in calls to major poison hotlines in Australia as well as prescription sales. A strength of the study is the completeness in the data sources and the age-specific, drug-specific dispersion rates. A weakness is the fact that calls to poison lines is a proxy for self-poisoning and it might represent a conservative estimate. The increasing rates of self-poisoning among young Australians has been noted using data from emergency departments in NSW and Victoria, hence the novel part of this study is to assess the same hypothesis in a different data source – and to measure trends in prescription data. The study

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surely presents original findings meriting a publication. There are some minor issues which would benefit from being addressed, as listed below.

> Response: we thank the reviewer for the time taken to review our manuscript and for their constructive feedback.

ABSTRACT
Setting: some of this information relates to outcomes and would be better to list under 'Main Outcome Measures'.

> Response: Thank you, the abstract has been amended accordingly.
>
> Setting now reads:
>
> "Setting: Calls taken by the New South Wales and Victorian Poisons Information Centres (2006–2016, accounting for 70% of Australian poisoning calls); medicine dispensings in the 10% sample of Australian Pharmaceutical Benefits Scheme data (July 2012–June 2016).
>
> Main outcome measures now reads:
>
> Main outcome measures: yearly trends in intentional poisoning exposure calls, substances taken in intentional poisonings, prevalence of psychotropic use (dispensing of antidepressants, antipsychotics, benzodiazepines and medicines for attention deficit hyperactivity disorder (ADHD))

METHODS
Pg 4, line 3-14, This text segment seems to discuss the strengths and weaknesses of different data sources and would fit better in a dedicated paragraph in the Discussion.

Also, the authors might consider whether some of the other information listed in the 'Design' section would fit better characterized as 'Measures' and 'Outcomes'.

> Response: these lines have been removed from the methods and incorporated into the discussion section.
>
> Text removed from methods:
> "As discussed above, there have been recent reports of increases in adolescent self-harm presentations to emergency departments in New South Wales (NSW) and Victoria (Australia's to most populous states). Hospital presentation data has limited sensitivity, and many self-poisonings may be coded as the presenting symptom [18]. Even when selfpoisonings are identified, the agents involved cannot be well classified with clinical coding systems (such as ICD-10 and SNOMED-CT), and are often coded under broad pharmacological groups."
>
> "Substances are coded in real-time by specialists in poisons information (pharmacists and pharmacologists with postgraduate toxicology training) to a high standard. Coding of exposure intent has been stable with time, with categorisation of exposure intent (accidental, intentional) collected reliably since the early 1980s. Each call is reviewed within 12 hours by a colleague to further enhance accuracy."
>
> We believe the above restructure of the "Design" section improves flow, and would prefer to not make new "measures" and "outcomes" subsection in the Methods which already contains many subdivisions.

Pg. 5 top: the text would benefit from a slight edit to improve text flow. This will help future readers.

> Response:
> Text amended, Design 2.1:

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"We used data from the New South Wales PIC (NSWPIC) and Victorian PIC (VPIC), which together take approximately 70% of the nation's 200,000 yearly poisoning calls."

Text removed, methods 2.2.1:
"The NSWPIC is Australia's largest poisons centre, taking approximately 50% of the nation's 200,000 poisoning calls annually [20]. VPIC takes approximately 40,000 calls annually. "

This paragraph now reads:
"The NSWPIC and VPIC databases were searched from 2006 – 2016 for calls where the exposure type was "intentional" (this includes deliberate self-poisoning, recreational use and intentional misuse). Calls were included if the patient's age category at the time of poisoning was coded as "Child" or "Adolescent". Exact age was recorded in over 97% of cases (other calls were coded as either child or adolescent without a precise age specified)."

Pg. 5 Pharmaceutical Benefits Scheme: it seems that the 10% sample is not a random sample – at least prior to 2012. How was the sample composed during the follow-up? If it was not a random sample, it would be relevant to discuss potential selection bias in the Limitations. Were these nationwide data? Were data available by gender? (given that you find an increase in self-poisoning among young girls, a gender-break down could provide relevant information).

Response: It is indeed a random sample. The PBS 10% sample contains dispensing data for a random 10% sample of Australians (selected based on the last digit of their Medicare number). The change in 2012 related to dataset capture of cheaper medicines. In Australia, the patient pays a patient contribution or "co-payment" (currently $39.50AUD for general beneficiaries, $6.40 for concessional beneficiaries). If a medicine costs more than this, the government pays the remainder. Prior to 2012, the dataset only captured dispensings where the government paid a contribution, i.e. medicines where the cost was above the "copayment" cost. Thus, some cheaper medicines were not captured in the dataset. This is why we used data from July 2012 onwards for our detailed analysis.

The following text (Methods 2.2.2) has been amended to make clarify that it was the dispensings that were not captured, rather than the beneficiaries:
"For cheaper medicines, some beneficiaries pay the full cost of the medicine (defined as "under co-payment"), and these dispensings were not captured prior to 2012 [19]."

We believe it is out of the scope of our paper to go into further detail about the medicines subsidy framework in Australia. We mentioned this data capture change to explain to the readers why we didn't go back farther than 2012 in our detailed analysis. We have referenced a methods paper (Mellish et al., 2015) which goes into more detail which the reader can access if desired.

We are not sure what the reviewer means regarding "How was the sample composed during the follow-up?" – this is a retrospective analysis of administrative data and no follow up was conducted.

Yes, these data were nationwide,
Text amended: Design 2.1;
"This nationwide data source has been described in detail previously"

Thank you for your suggestion to display data by gender. We re-ran the data extraction and now include gender information in Tables 2 and 3 and Figure 3.

The results text has been amended accordingly:
"Males received ~60% of antidepressants in the 5-14 year age group. Conversely, in those aged 15-19, females received 65% of antidepressant dispensings (Table 2, Figure 3). Fluoxetine was the most dispensed SSRI across both genders and age groups (increasing 54% and 44% in those aged 5-14 and 15-19, respectively)…

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Males received ~80% of antipsychotics in the 5-14 year age group, decreasing to ~60% in the 15-19 year age group (Table 3)….
In people aged 5-19 years, 80% of ADHD medication dispensing was to males….
Females were dispensed ~60% of benzodiazepines"

Added to discussion:
"Young females were over-represented in self-poisoning events, and the rate of increase was higher in females"

"Interestingly, males received the majority of antidepressant dispensings in the 5-14 year age group, and yet females in this age group were more likely to self-poison, providing some information to support point (iii) above, at least in younger children."

Pg. 6. Please describe with more detail which population estimates were obtained from the ABS, i.e. was it for all of Australia – or just NSW and Victoria?

Response: Text amended, Data analysis 2.3:
"We reported prevalence as the number of users per 10,000 population, using population estimates obtained from the Australian Bureau of Statistics (using national population figures, as the PBS 10% sample is a nationwide database)."

RESULTS
It would be beneficial to present test statistics (or CI-95%) for the observed trends in self-poisonings.

Response: Thank you for this suggestion. The following was added to Results 3.1:
"Self-poisonings in those aged 5-19 years increased by 8.39% per year (95%CI 6.08-10.74%, P
< 0.0001), with an overall increase of 98%, 2006-2016 (Figure 1). Self-poisonings in children increased by 9.00% per year (95% CI 6.26% - 11.81%, P<0.0001), overall 107%, 2006-2016. Adolescent self-poisonings increased by 8.21% per year, (95% CI 5.96%-10.5%, P<0.0001), or 96% over the study period…
Self-poisoning in females increased by 108% in total, 9.21% per year, (95% CI, 6.63% - 11.86%, P<0.0001), while in males increased by 72% in total, 6.03% per year (95% CI, 3.96% -
8.14% P<0.0001)."

Test statistics were also added to the abstract:
"…with an increase of 8.39% per year (95%CI 6.08-10.74%, P < 0.0001)"

Accordingly, the following was added to Methods 2.3:
"We analysed time trends in poisonings using negative binomial regression with a log link function."

Table 1. were there any trends in drug types as noted in the calls to poison centers? The time trends in PBS are explored extensively. Yet, it would be relevant to know what drugs were accountable for the observed increase in girls as this would give indications for what futures interventions might address.

Response: We have seen large increases in intentional poisonings with psychotropics and non-narcotic analgesics (paracetamol, NSAIDs). To demonstrate this we propose the inclusion of supplementary figure 2 (see updated supplementary material file).

The following was added to the results text:
"Time trends in exposures to agents broken down by broad substance classes (Supplementary Figure 2) show large increases in poisonings with psychotropics and nonnarcotic analgesics."

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The following has been added to Methods 2.2.1 (to explain broad agent categories):
"Substances were divided into broad categories: non-narcotic analgesics (paracetamol, aspirin, non-steroidal anti-inflammatory drugs), psychotropics (antidepressants, antipsychotics, anxiolytics/sedatives, psychostimulants), opioids (non-illicit), other prescription pharmaceuticals, other over-the-counter pharmaceuticals, gases (e.g. carbon monoxide), and other non-pharmaceutical substances (including household products, chemicals, pesticides, plants)."

DISCUSSION
It would be essential to know if there were any changes in the referral practice/usage of poison hotlines with respect to self-poisonings over the follow-up period, e.g. campaigns at participating hospital wards to inform of the service or other initiatives which could explain a surge in calls. The fact that poison hotlines experienced a decline in other types of calls is a strength of the validity as mentioned by the authors.

Response: There have been no such campaigns/initiatives that could explain the surge in calls.

The following has been added to the discussion section:
"In addition, the increases observed in this study are on the background of decreasing overall calls to PICs [22]. There have been no changes in referral practices/PIC utilisation that could explain a surge in calls."

Pg. 8, line 25-34: Could this be rephrased in to a strength rather than a summary?

Response: This has been rephrased as follows:
"Another strength of this study is it's capture of over a decade's worth of data from two of Australia's poisons centres, amounting to ~70% of the nation's poisoning calls. This includes almost complete capture of poisons calls for the South East of Australia, plus some calls from the rest of the nation (due to the after-hours call handling structure shared by Australian PICs). NSWPIC and VPIC receive calls from members of the public and healthcare professionals across Australia and thus may provide better estimates of trends than studies conducted out of single hospitals."

Also, calls to poison hotlines is likely represents a minimum figure (a conservative estimate) of the actual incidences of self-poisoning. This ought to be clearly pointed out in this section. As it appears now, this information is mixed with information regard type of drug.

Response: The discussion strengths and limitations section has been restructured to separate out coding of agents and case capture. The following has been added to make this important point clear:
"Thus, this represents a conservative estimate of actual incidences of self-poisoning."

Pg. 10, line 14+: As mentioned in the result section, paracetamol is reported as the most frequently used drug in self-poisoning. It would, thus, be good to assess this finding in the Discussion, particularly, considering the existing evidence base for means restriction from the UK.

Response: The following has been added to the discussion:
"Importantly, we observed high rates of poisonings with readily available over-the-counter medicines, with paracetamol and ibuprofen being the top two substances used in selfpoisonings in this age group. When compared to adults (aged 20 and over), children and adolescents are more likely to use over-the-counter medicines in intentional poisonings [29]. Paracetamol poisoning is the leading cause of acute liver failure in Western countries [30]. In Australia, paracetamol can be purchased in 100 x 500mg (50g) and 96 x 665mg (modified

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release, ~64g) packs in pharmacies, and 20x 500mg packs (10g) outside of pharmacies. Previous studies have demonstrated that paracetamol overdoses are often impulsive and involve the use of paracetamol present in the home [31]. In 1998 the UK restricted paracetamol pack sizes in response to increasing overdoses, liver transplants and deaths. Sales were restricted to 16g within pharmacies or 8g outside of pharmacies. This legislation appears effective, with a subsequent reduction in large overdoses, liver unit admissions and deaths in England and Wales [32–34]. Although we did not assess outcomes of the paracetamol poisonings in our sample, similar means restriction in Australia could be implemented to reduce harm from paracetamol overdose."

VERSION 2 – REVIEW

REVIEWER	Helinä Hakko Oulu University Hospital, Department of Psychiatry
REVIEW RETURNED	18-Nov-2018

GENERAL COMMENTS	The manuscript is corrected and modified following the major suggestions made by the reviewers. I believe that the revised manuscript fulfills the publishing criteria.

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