PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Trends in Attention Deficit and Hyperactivity Disorder (ADHD) medications among children and young adults in Ireland: a repeated cross-sectional study from 2005-2015
AUTHORS	Mac Avin, MaryJo; Teeling, Mary; Bennett, Kathleen

VERSION 1 – REVIEW

REVIEWER	Tamsin Newlove-Delgado University of Exeter Medical School, UK
REVIEW RETURNED	11-Dec-2019

GENERAL COMMENTS	Thank you for inviting me to review this manuscript. Overall this is a clearly written paper which answers a defined question and adds to the body of knowledge about prescribing patterns in ADHD. I have a number of comments and suggestions to make: Introduction: The authors may wish to review the references used for the prevalence estimates e.g. one of these is from a 2007 paper whilst another quotes a systematic review of interventions. There are more recent prevalence papers available, for example Polanczyk 2014. Whilst the introduction includes a summary of the literature on prescribing, it could be strengthened with discussion of the clinical relevance of the question and why it is important to update the prescribing estimates for Ireland. Methods: Further information on the GMS scheme and the socio-economic profile of those entitled to these services would be useful here; can this be placed in a more international context? Is it also possible to expand on where the 'eligibility' figures come from which form the denominator for calculations, and whether this source is complete. It would also be useful to know whether there were any limits placed on the length of prescriptions included, and to include some consideration of this in the discussion (e.g. month-long prescriptions could represent 'trials' of medication). Findings: For Figure 4, it would be helpful to see absolute numbers, as well as percentages and confidence intervals - for these small numbers a table might be preferable. Trends in concomitant medications would be especially interesting to see by age group, as comorbidities such as anxiety and depression would be expected to be more common in the older age groups. Discussion: I would suggest that the discussion could be edited to make it more concise, and allow room for some more in-depth consideration of limitations and implications. In particular, the 2nd, 3rd and 4th paragraphs discuss some explanations for the rising trend in prescribing, but these explanations are scattered throughout these

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	paragraphs and contain some repetition. Relating to these discussions of trends, whilst I agree it is valuable to consider explanations including over-diagnosis and over-prescription, I would be cautious about over-emphasising these, both in the discussion and the conclusion. In my view it would be important to underline that this study design does not allow any exploration of whether or not these prescriptions were appropriate. Whilst I am not familiar with the Irish literature, I am also not aware of evidence for over-diagnosis or over-prescription of ADHD medication in a UK population context (e.g. the latest English population child mental health survey found that just under half of children meeting diagnostic criteria for ADHD were prescribed medication). It would also be helpful to place these prescribing rates in the context of overall population prevalence of ADHD in Ireland, if possible – i.e. are these incidence rates higher than expected given the expected prevalence of ADHD in this group? Further discussion of the meaning and implications of the findings regarding concomitant medication would be valuable – especially in light of any differences by age group, and in the context of the prevalence of comorbidities in ADHD. With respect to the limitations, I would be interested in the authors' views on how the use of this particular sample population could have affected their findings as opposed to using a database with a more representative socio-economic profile. Finally, as in my comments about the introduction above, I would be interested to see further discussion of what the relevance and implications of these findings are for those planning and delivering services and clinicians; and some reflections on future research.

REVIEWER	Melissa Danielson National Center on Birth Defects and Developmental Disabilities, CDC, United States
REVIEW RETURNED	18-Dec-2019

GENERAL COMMENTS	Thank you for the opportunity to review "Trends in Attention Deficit and Hyperactivity Disorder (ADHD) medications among children and young adults in Ireland: a repeated cross-section study from 2005-2015". This manuscript is well-written and would provide an important contribution to the body of literature estimating the prevalence of ADHD in different countries, however, I think there are a few sections of the manuscript that could be strengthened prior to publication. Introduction - Page 3, rows 30-31: Citation #5 does not seem to match up with the prevalence estimates presented in this paragraph, as this reference is a systematic review of ADHD treatment in adolescents. Additionally, another reference that might be informative to this portion of the introduction by Polanczyk et. al that provides a meta-analysis of mental disorders among children and adolescents, and provides pooled estimates for ADHD (Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry. 2015;56(3):345-65). Methods - Page 5, rows 27-29: The authors appropriate indicate in the introduction that pharmacological management of ADHD is recommended for children aged 6 and older in clinical guidelines, yet the statistical analyses group children aged 5 years along with children aged 6-11 years. It might be worth considering adjusting the age groups to match clinical guidance (0-5 years, 6-11 years, etc.).

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	- Page 5, rows 45-50: It would be helpful for the authors to provide additional detail about their statistical methods about the negative binomial regression model, particularly if they are truly measuring incidence of prescription medication (i.e. only new prescriptions of ADHD medications), or is prevalence being modeled instead of incidence. Results - It would be helpful to have a denominator of the number of children and young adults in the study population (or even a range across years). - There is inconsistency in the number of significant figures reported throughout the results section (e.g. some IRRs and associated confidence intervals have 2 digits, some have 3.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Introduction:
The authors may wish to review the references used for the prevalence estimates e.g. one of these is from a 2007 paper whilst another quotes a systematic review of interventions. There are more recent prevalence papers available, for example Polanczyk 2014. Whilst the introduction includes a summary of the literature on prescribing, it could be strengthened with discussion of the clinical relevance of the question and why it is important to update the prescribing estimates for Ireland.

Response: Thank you for this suggestion. The references relating to the prevalence have been updated in the introduction and we include reference to the paucity of studies on the prevalence of ADHD in Ireland and that the prescribing data is being use as a surrogate in the first paragraph of the introduction.

Methods:
Further information on the GMS scheme and the socio-economic profile of those entitled to these services would be useful here; can this be placed in a more international context? Is it also possible to expand on where the 'eligibility' figures come from which form the denominator for calculations, and whether this source is complete. It would also be useful to know whether there were any limits placed on the length of prescriptions included, and to include some consideration of this in the discussion (e.g. month-long prescriptions could represent 'trials' of medication).

Response: Thank you. We have included more information on the GMS scheme and socio-economic profile of those entitled in the methods.
The eligibility figures come from the Health Service Executive Annual reports which provide the eligible population by age and gender as of December of each year. This source is complete for all the years included in the study. (see https://www.sspcrs.ie/portal/annual-reporting/report/annual).
The maximum length of any prescription is for one month, although shorter durations are possible, and repeat prescriptions of up to 3 months before contacting the GP. This has been included in the methods section.

Findings:
For Figure 4, it would be helpful to see absolute numbers, as well as percentages and confidence intervals - for these small numbers a table might be preferable. Trends in concomitant medications would be especially interesting to see by age group, as comorbidities such as anxiety and depression would be expected to be more common in the older age groups.

Response: We have replaced Figure 4 with a table (Table 1)
which provides numbers, percentages and 95% CIs as suggested by the reviewer. In addition, the table on concomitant therapy has been split by those under 16 years and those 16-24 years; however, due to space we suggest this might be supplementary tables (Supplementary appendix 1) to the main table in the manuscript.

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Discussion:
I would suggest that the discussion could be edited to make it more concise, and allow room for some more in-depth consideration of limitations and implications. In particular, the 2nd, 3rd and 4th paragraphs discuss some explanations for the rising trend in prescribing, but these explanations are scattered throughout these paragraphs and contain some repetition.

Response: Thank you. The discussion has been updated based on this comment, particularly reducing any repetition and further explanation of the rising trends in prescribing.

Relating to these discussions of trends, whilst I agree it is valuable to consider explanations including over-diagnosis and over-prescription, I would be cautious about over-emphasising these, both in the discussion and the conclusion. In my view it would be important to underline that this study design does not allow any exploration of whether or not these prescriptions were appropriate. Whilst I am not familiar with the Irish literature, I am also not aware of evidence for over-diagnosis or over-prescription of ADHD medication in a UK population context (e.g. the latest English population child mental health survey found that just under half of children meeting diagnostic criteria for ADHD were prescribed medication).
Response: Thank you. We have modified the discussion and conclusions as suggested to be more cautious over the interpretation of the findings and limitations of the study design and data available.

It would also be helpful to place these prescribing rates in the context of overall population prevalence of ADHD in Ireland, if possible – i.e. are these incidence rates higher than expected given the expected prevalence of ADHD in this group?
Response: Thank you. We have included a reference to another study on the prevalence of ADHD in those aged 12-15 years in Ireland in the introduction. However, there is a lack of information on prevalence of ADHD in Ireland at present. We have clarified in the manuscript that the rates presented are prevalence and not incidence rates.

Further discussion of the meaning and implications of the findings regarding concomitant medication would be valuable – especially in light of any differences by age group, and in the context of the prevalence of comorbidities in ADHD.

Response: Thank you. We found greater use of concomitant therapy overall in the older age groups (16-24 years) and particularly greater concomitant antidepressants over time. Discussion of these findings is now included in the amended manuscript.

With respect to the limitations, I would be interested in the authors' views on how the use of this particular sample population could have affected their findings as opposed to using a database with a more representative socio-economic profile.
Response: The study population includes a more socio-economically disadvantaged population which is likely to have over-estimated the prevalence of ADHD prescribing in this group. Others (https://www.ncbi.nlm.nih.gov/pubmed/28801917) have shown that the more deprived the background the higher the risk of ADHD, in those aged 6-14 years.

Finally, as in my comments about the introduction above, I would be interested to see further discussion of what the relevance and implications of these findings are for those planning and delivering services and clinicians; and some reflections on future research.

Response: Thank you. Since the study was undertaken there has been the development of a National Clinical Programme for adult ADHD. There has been concern regarding the resources for child and adult psychiatry in Ireland in general and a sentence has been included in the discussion to the effect that the findings from the study support additional resources for this sector.

Reviewer: 2

Introduction

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- Page 3, rows 30-31: Citation #5 does not seem to match up with the prevalence estimates presented in this paragraph, as this reference is a systematic review of ADHD treatment in adolescents. Additionally, another reference that might be informative to this portion of the introduction by Polanczyk et. al that provides a meta-analysis of mental disorders among children and adolescents, and provides pooled estimates for ADHD
(Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry. 2015;56(3):345-65).
Response: Thank you for this. We have included this reference in the introduction and added additional references for the prevalence.

Methods
- Page 5, rows 27-29: The authors appropriate indicate in the introduction that pharmacological management of ADHD is recommended for children aged 6 and older in clinical guidelines, yet the statistical analyses group children aged 5 years along with children aged 6-11 years. It might be worth considering adjusting the age groups to match clinical guidance (0-5 years, 6-11 years, etc.).
Response: Unfortunately, due to the information provided by the HSE-Primary Care Reimbursement Services (PCRS) used in the study we were only able to group data by the age groups available from the PCRS which includes: 0-4 years, 5-11, 12-15 and 16-24 years.

- Page 5, rows 45-50: It would be helpful for the authors to provide additional detail about their statistical methods about the negative binomial regression model, particularly if they are truly measuring incidence of prescription medication (i.e. only new prescriptions of ADHD medications), or is prevalence being modeled instead of incidence.
Response: We measured prevalence of ADHD medicines and not incidence in this study. Additional text has been included in the methods to clarify this further as follows: 'The negative binomial regression can be used to analyse the prevalence (risk) ratios with 95% confidence intervals.'

Results
- It would be helpful to have a denominator of the number of children and young adults in the study population (or even a range across years).
Response: This is now included in the new Table 1 replacing the previous Figure 4.

- There is inconsistency in the number of significant figures reported throughout the results section (e.g. some IRRs and associated confidence intervals have 2 digits, some have 3.
Response: We have amended the manuscript so that only 2 decimal places are presented throughout for consistency.

VERSION 2 – REVIEW

REVIEWER	Tamsin Newlove-Delgado University of Exeter, UK
REVIEW RETURNED	09-Feb-2020

GENERAL COMMENTS	Thank you for addressing the original comments on this manuscript so thoroughly. I enjoyed reading this revised version, and have only a few further minor suggestions. On page 4, for the reference about ADHD persisting into adulthood I would suggest referring back to the original Faraone and Biederman 2006 meta-analysis rather than using the review article cited. On page 12, the discussion of the findings on concomitant medications appears to be confined to the whole age range. As there is now a breakdown by age in the appendix, it would be interesting to see some discussion of patterns by age – this would also be relevant in comparing the findings of this study with other studies On page 13, in the discussion of the relationships of socio-economic

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	status and ADHD it may be helpful to note that there is a systematic review and meta-analysis published on this topic that could be drawn on; Russell, A.E., Ford, T., Williams, R. et al. The Association Between Socioeconomic Disadvantage and Attention Deficit/Hyperactivity Disorder (ADHD): A Systematic Review. Child Psychiatry Hum Dev 47, 440–458 (2016). https://doi.org/10.1007/s10578-015-0578-3 Finally, on page 14, it would be useful to hear the authors' views on how 'linkage between prescribing data and clinical particulars' would be useful in future studies and which specific questions these linkages might answer.

REVIEWER	Melissa Danielson Centers for Disease Control and Prevention, United States
REVIEW RETURNED	04-Feb-2020

GENERAL COMMENTS	Generally, the authors have responded to the comments provided in the initial round of peer review, though I would like to offer a few additional points of feedback: Abstract - In the primary and secondary outcomes section, I think the parentheses around anxiolytics and hypnotics/sedatives can be removed (comment applies elsewhere in the manuscript) Methods - In the introduction, guanfacine as listed as being a medication authorized for ADHD in Ireland, but it's not included in the analysis, despite the statement that "all authorized medications used to treat ADHD during the study period…" are included. It would be to note why guanfacine was not included in the analysis. Results - Table 1: In the response to reviewers, the authors indicate that the denominator has been added to Table 1; it looks like the number of children and young adults with ADHD medication prescriptions was only added to the Supplemental Tables 1A and 1B. It would be helpful to add the corresponding column to Table 1 as well.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2
Generally, the authors have responded to the comments provided in the initial round of peer review, though I would like to offer a few additional points of feedback:

Abstract
- In the primary and secondary outcomes section, I think the parentheses around anxiolytics and hypnotics/sedatives can be removed (comment applies elsewhere in the manuscript)

Thank you – we have removed any parentheses as suggested throughout the manuscript.

Methods
- In the introduction, guanfacine as listed as being a medication authorized for ADHD in Ireland, but it's not included in the analysis, despite the statement that "all authorized medications used to treat ADHD during the study period…" are included. It would be to note why guanfacine was not included in

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the analysis.

Thank you. We did not include guanfacine in the analysis as, although authorised for use in ADHD in Ireland, it only received it's authorisation in September 2015 in Ireland, and marketed from 2016 onwards, which was outside the scope of this study.

Results
- Table 1: In the response to reviewers, the authors indicate that the denominator has been added to Table 1; it looks like the number of children and young adults with ADHD medication prescriptions was only added to the Supplemental Tables 1A and 1B. It would be helpful to add the corresponding column to Table 1 as well.
We have included the total number on any ADHD drugs in Table 1 as the denominator.

Reviewer: 1

Thank you for addressing the original comments on this manuscript so thoroughly. I enjoyed reading this revised version, and have only a few further minor suggestions.

On page 4, for the reference about ADHD persisting into adulthood I would suggest referring back to the original Faraone and Biederman 2006 meta-analysis rather than using the review article cited.
Thank you – we have replaced the reference back to the original reference by Faraone and Biederman 2006 as suggested (reference 3 in the list).

On page 12, the discussion of the findings on concomitant medications appears to be confined to the whole age range. As there is now a breakdown by age in the appendix, it would be interesting to see some discussion of patterns by age – this would also be relevant in comparing the findings of this study with other studies
We have included a sentence in the discussion on the concomitant medications by the specific age groups (<16 years and 16-24 years) as suggested.

On page 13, in the discussion of the relationships of socio-economic status and ADHD it may be helpful to note that there is a systematic review and meta-analysis published on this topic that could be drawn on; Russell, A.E., Ford, T., Williams, R. et al. The Association Between Socioeconomic Disadvantage and Attention Deficit/Hyperactivity Disorder (ADHD): A Systematic Review. Child Psychiatry Hum Dev 47, 440–458 (2016).
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Thank you for the reference. We now include this in the discussion on the relationships between SES and ADHD (reference 40).

Finally, on page 14, it would be useful to hear the authors' views on how 'linkage between prescribing data and clinical particulars' would be useful in future studies and which specific questions these linkages might answer.

Thank you. We have included additional text to expand on the usefulness of linkage as follows:
'…if linkage between prescribing data and clinical data, such as diagnosis and outcomes data, were possible. This would enable research questions on the appropriateness of ADHD and concomitant medicines and the likely impact these have on short, medium and long term outcomes.

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