PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Adverse drug reactions, multimorbidity and polypharmacy: A prospective analysis of one month of medical admissions
AUTHORS	Osanlou, Rostam; Walker, Lauren; Hughes, Dyfrig; Burnside, Girvan; Pirmohamed, Munir

VERSION 1 – REVIEW

REVIEWER	Menditto, Enrica Faculty of Pharmacy, University of Naples Federico
REVIEW RETURNED	22-Sep-2021

GENERAL COMMENTS	Dear Authors, this is an interesting and innovative study asessing and quantifying avoidable ADRs due to inappropriate prescribing in a real-world context. These findings will give an important contribute to the actual scientific research in order to reduce the burden of ADRs on patients and healthcare systems. In my opinion, this study was well conducted with a very clear and well described methodology that allows its reproducibility. In addition, the discussions and conclusions are perfectly relevant to the results obtained and well argued. I have only a Minor remarks to improve the paper: • Abstract: The cost analysis carried out is certainly an added value of the paper. Thus emphasise this aspect in the abstract will have a greater appeal with the audience. • Introduction - Lines 33-35: After these lines, the authors could improve the intro section by exploding this aspect of the burden of ADRs on healthcare systems. It would be interesting to add some studies from recent literature about avoidable costs related to the ADRs quantifying it. • Tables: For a better reading of the data, it is recommended to format the tables and insert the appropriate notes below them (e.g. specifying 'CLD' and 'CKD' below Tab4, as done for Tab3).

REVIEWER	Nwadiugwu, Martin University of Stirling, Health
REVIEW RETURNED	08-Oct-2021

GENERAL COMMENTS	Page 4. "Polypharmacy is the concurrent use of multiple medications by an individual. Numerical definitions vary but it is most commonly defined as taking 5 or more regular medications." Comment: There is currently no consensus on what the numerical definitions are for polypharmacy. It may be worth looking at this article: https://www.hindawi.com/journals/jar/2020/6759521/

	"There were 1,187 admissions with 218 patients with an ADR (18.4%). As some of those had multiple ADRs 235 were identified in total." Comment: What were baseline statistics of the data? Did you consider how race, ethnicity and other variables impacted the findings? Page 8 - "64 (29.4%) of ADRs were possibly or probably cause by a drug-drug interaction as per DIPS(17)." Comment: How did you reach this conclusion? It is important to limit all assumptions. Page 9 How were the commonly implicated medicines found? General comments: It is vital to reduce assumptions in the communication and only state the facts. Allow the data/evidence to drive the discussions.

REVIEWER	Zazzara, Maria Fondazione Policlinico Gemelli IRCCS
REVIEW RETURNED	22-Oct-2021

GENERAL COMMENTS	Thank you for your work! The authors have performed a prospective observational study to ascertain the burden of adverse drug reactions on hospital admissions. The topic is of great interest and importance. ADRs are a significant healthcare issue and there is an urge to take actions in order to reduce them and reduce costs as well. For example, I found it very concerning that diuretics were the medications most associated to ADRs, yet in line with clinical experiences. The study is clear and technically sound and I found the reading quite pleasant. I have a couple of recommendations: 1. I find slightly confusing the way results for Table 3 and Table 2 are reported in the text. My understanding is that table 3 shows different characteristics of patients according to presence of ADRs or absence of ADRs while Table 4 shows results from the logistic regression of the associations between each of the variables and the probability expressed in terms of OR of experiencing ADRs as cause of admission ect. I would suggests splitting the two results in two separate parts in the text especially (as the tables are very clear) and possibly provide pvalues for table 3 using a T-test or a Wilcoxon test depending on your sample (I guess the latter). I would add those pvalues to the text not only in the “Characteristics of adverse drug reactions” section but also later on. For example, in the discussion on page 10 line 58: “….than those without (10.5 v 7.8), which is an established risk factor for ADRs” and similarly on page 11 line 14: “…non ADR group (6.1 vs 5.2), which is a known risk factor…”. I find this also especially important for table 3 were percentages of liver and renal impairment are presented and that, to a very superficial eye, might seem less frequent in those with ADR than NON-ADR, where of course sample size is different and the ORs in table 4 speak for themselves.

	2. The sentence at page 9 line 48 seems incomplete (?). Please try to empathize a bit the role of deprescribing: it's a crucial tool to reduce ADRs and perhaps it is worth a bit more insight in your discussion. 3. In the comparison to the Pirmohamed study you have outlined that in 2004 two of the main causative medicines were NSAIDs (11.8%) and the antiplatelets (23.8%) where in your study these medicines were implicated in 0.85% and 7.4% of the ADRs respectively. Your suggestion is that “This is likely due to changes in prescribing practice including co-administration of proton pump inhibitors (PPI).” As much as I agree with this I find this results fascinating! Could this also be related to increased awareness of NSAIDs adverse effects especially amongst older adults and with the change in indications for prescribing antiplatelets? I would expand on this! 4. “In recent years, concerns of an opiate crisis due to excessive community prescription has occurred in the USA (25).” I think this sentence is redundant for the discussion: readers of this work will be both aware of the American events and possible ADRs opioids related. Furthermore, it does not seem to add any specific information in relation to the Pirmohamed study. 5. Thank you for having address in the limitations that some ADRs may have occurred regardless of prescription, like for steroid inhalers and pneumonia in COPD patients. Still it underlines that both scenario are possible. I have another suggestion for your limitations. As per your methods, assessment of ADRs was a thorough and fairly complex process justified by research purpose and performed for a limited duration. I find it quite hard that such a thorough assessment could be easily carried out in daily clinical practise. I would suggest to evaluate the possibility of adding this to your limitations. I have two last suggestions: I would suggest spelling “billions” instead of bn. Please specify what HRG stands for.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Enrica Menditto, Faculty of Pharmacy, University of Naples Federico

Comments to the Author:

Dear Authors, this is an interesting and innovative study assessing and quantifying avoidable ADRs due to inappropriate prescribing in a real-world context. These findings will give an important contribute to the actual scientific research in order to reduce the burden of ADRs on patients and healthcare systems.

In my opinion, this study was well conducted with a very clear and well described methodology that allows its reproducibility. In addition, the discussions and conclusions are perfectly relevant to the results obtained and well argued. I have only a Minor remarks to improve the paper:

- Abstract: The cost analysis carried out is certainly an added value of the paper. Thus emphasise this aspect in the abstract will have a greater appeal with the audience.

Thank you to the reviewers for raising this important point. We have edited so that cost is included in the objectives, results and conclusion of the abstract.

- Introduction - Lines 33-35: After these lines, the authors could improve the intro section by exploding this aspect of the burden of ADRs on healthcare systems. It would be interesting to add some studies from recent literature about avoidable costs related to the ADRs quantifying it.

We have expanded the introduction to include an important 2016 BPS estimation of costs of inappropriate and inefficient medicines in the NHS.

- Tables: For a better reading of the data, it is recommended to format the tables and insert the appropriate notes below them (e.g. specifying 'CLD' and 'CKD' below Tab4, as done for Tab3).

Amended – thank you

Reviewer: 2

Dr. Martin Nwadiugwu, University of Stirling

Comments to the Author:

Page 4.

"Polypharmacy is the concurrent use of multiple medications by an individual. Numerical definitions vary but it is most commonly defined as taking 5 or more regular medications."

Comment: There is currently no consensus on what the numerical definitions are for polypharmacy. It may be worth looking at this article: https://www.hindawi.com/journals/jar/2020/6759521/

Thank you for highlighting this important point. We have used a numerical definition in order to standardise our assessment. In the recent over prescribing review, the issue of numerical uncertainty of poly pharmacy was highlighted and the use of 5 was deemed to be the most common numerical definition. We agree with the reviewer that it is nuanced and hence have described both appropriate and inappropriate poly pharmacy in the introduction.

"There were 1,187 admissions with 218 patients with an ADR (18.4%). As some of those had multiple ADRs 235 were identified in total."

Comment: What were baseline statistics of the data? Did you consider how race, ethnicity and other variables impacted the findings?

In retrospect we agree this would be relevant and important however due to the nature of data collection we cannot retrospectively capture this. In future analyses we will prioritise such information. Estimates of ethnicity in Liverpool is 91% white and this is therefore important to note. We have therefore added this to the 'Strengths and weakness'' section of the paper.

Page 8 - "64 (29.4%) of ADRs were possibly or probably cause by a drug-drug interaction as per DIPS(17)."

Comment: How did you reach this conclusion? It is important to limit all assumptions.

We used the drug interaction probability scale (DIPS) which is a validated probability scale similar to the Narajo ADR probability scale and is used to determine probability of causal relationship.

Page 9

How were the commonly implicated medicines found?

In person case note review for each patient was undertaken to identify accurate drug lists and all investigations by two doctors specialising in general internal medicine and clinical pharmacology (one registrar, one consultant). Arbitration was undertaken by in person discussion including a third consultant. This was a clinical consensus definition as outlined in the methods.

General comments: It is vital to reduce assumptions in the communication and only state the facts. Allow the data/evidence to drive the discussions.

Many thanks for raising this important point. Assessment of causality is a difficult clinical skill and where possible we erred on the side of caution when making clinical judgements. For example admissions relating to electrolyte disturbance could be caused by PPI or myriad of other medical problems and therefore required review of entire history and inpatient admission. We did this to try and minimise any missed classification. To reduce potential assumptions, we used multiple assessment tools as outlined in the methods section.

Reviewer: 3

Dr. Maria Zazzara, Fondazione Policlinico Gemelli IRCCS

Comments to the Author:

Thank you for your work!

The authors have performed a prospective observational study to ascertain the burden of adverse drug reactions on hospital admissions.

The topic is of great interest and importance. ADRs are a significant healthcare issue and there is an urge to take actions in order to reduce them and reduce costs as well. For example, I found it very concerning that diuretics were the medications most associated to ADRs, yet in line with clinical experiences.

The study is clear and technically sound and I found the reading quite pleasant.

I have a couple of recommendations:

1. I find slightly confusing the way results for Table 3 and Table 2 are reported in the text.

My understanding is that table 3 shows different characteristics of patients according to presence of ADRs or absence of ADRs while Table 4 shows results from the logistic regression of the associations between each of the variables and the probability expressed in terms of OR of experiencing ADRs as cause of admission ect.

I would suggests splitting the two results in two separate parts in the text especially (as the tables are very clear) and possibly provide pvalues for table 3 using a T-test or a Wilcoxon test depending on

your sample (I guess the latter). I would add those pvalues to the text not only in the “Characteristics of adverse drug reactions” section but also later on.

For example, in the discussion on page 10 line 58: “….than those without (10.5 v 7.8), which is an established risk factor for ADRs” and similarly on page 11 line 14: “…non ADR group (6.1 vs 5.2), which is a known risk factor…”.

I find this also especially important for table 3 were percentages of liver and renal impairment are presented and that, to a very superficial eye, might seem less frequent in those with ADR than NON-ADR, where of course sample size is different and the ORs in table 4 speak for themselves.

Thank you for these multiple important points. We have expanded the patient characteristics description particularly with regard to renal and liver impairment. We have also added the p values to the text for the calculations that you suggest so this is more clear to any reader without having to refer to the tables.

With regards to table 3 we agree and have amended this to include the percentages only where relevant (such for liver & renal impairment) to avoid the potential confusion you have outlined.

2. The sentence at page 9 line 48 seems incomplete (?). Please try to empathize a bit the role of deprescribing: it's a crucial tool to reduce ADRs and perhaps it is worth a bit more insight in your discussion.

Thank you. We had not intended for this to be omitted. For this reason we have added further detail on the importance of de prescribing into the discussion.

3. In the comparison to the Pirmohamed study you have outlined that in 2004 two of the main causative medicines were NSAIDs (11.8%) and the antiplatelets (23.8%) where in your study these medicines were implicated in 0.85% and 7.4% of the ADRs respectively. Your suggestion is that “This is likely due to changes in prescribing practice including co-administration of proton pump inhibitors (PPI).” As much as I agree with this I find this results fascinating! Could this also be related to increased awareness of NSAIDs adverse effects especially amongst older adults and with the change in indications for prescribing antiplatelets? I would expand on this!

Thank you for mentioning this. We have expanded this paragraph to highlight how increased pharmacovigilance may have contributed to a reduction in ADRs from NSAIDs and antiplatelets. Furthermore on how the indications for such medicines have changed since 2004, in particular as you mention with regards to aspirin in AF.

4. “In recent years, concerns of an opiate crisis due to excessive community prescription has occurred in the USA (25).” I think this sentence is redundant for the discussion: readers of this work will be both aware of the American events and possible ADRs opioids related. Furthermore, it does not seem to add any specific information in relation to the Pirmohamed study.

Thank you for your comment. As Liverpool is a deprived area where issues such as chronic pain and multimorbidity often lead to issues of persistent opiate usage we feel it is important to emphasise that admissions due to ADRs from these medications has not increased. This is relevant as it is a significant burden on local services.

5. Thank you for having address in the limitations that some ADRs may have occurred regardless of prescription, like for steroid inhalers and pneumonia in COPD patients. Still it underlines that both scenario are possible. I have another suggestion for your limitations. As per your methods, assessment of ADRs was a thorough and fairly complex process justified by research purpose and performed for a limited duration. I find it quite hard that such a thorough assessment could be easily carried out in daily clinical practise. I would suggest to evaluate the possibility of adding this to your limitations.

This is an important point and the time taken to undertake these assessments and the potential utilisation of technology as a time saving approach has been emphasised in the strengths and weakness' section.

I have two last suggestions:

I would suggest spelling "billions" instead of bn.

Please specify what HRG stands for.

We have amended both as per your suggestion. Thank you

VERSION 2 – REVIEW

REVIEWER	Nwadiugwu, Martin University of Stirling, Health
REVIEW RETURNED	29-Jan-2022

GENERAL COMMENTS	Thank you for your important study aimed at finding the impact of ADRs on multimorbidity, polypharmacy, hospital admissions, and the economic impact on NHS. The finding will be important for improving medical prescription and healthcare practices and lowering healthcare cost. However, I have a few comments below. Introduction "Polypharmacy is the concurrent use of multiple medications by an individual. Numerical definitions vary but it is most commonly defined as taking 5 or more regular medications" Comment: It is important to state the lack of consensus on what number constitutes polypharmacy. See this article https://www.hindawi.com/journals/jar/2020/6759521/ What is "Appropriate polypharmacy"? It would be ideal to briefly explain the purpose of using each of these tools: Liverpool causality assessment tool, LAAT and other tools for the readership that may not be familiar with the aim and distinction of using each of them. Is it possible to include the length of stay of all patients in the baseline statistics? Discussion Was EHRs used by MPs for data collection? Multimorbidity and polypharmacy It would be nice to discuss the findings on ADR with respect to the type of ADR for more clarity. A reader may find it hard to decipher what type of ADR was implicated as you compare the numbers for ADR vs non-ADR. Since it makes sense that co-morbidity is often directly related with polypharmacy in people with LTCs, more coherent explanation is needed on why it does not influence the number of medications a patient is taking in this study.

REVIEWER	Zazzara, Maria Fondazione Policlinico Gemelli IRCCS
REVIEW RETURNED	14-Feb-2022

GENERAL COMMENTS	Thank you for addressing all comments. The manuscript has improved. Also, thank you for clarifying comments on opioids!

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Dr. Martin Nwadiugwu, University of Stirling
Comments to the Author:
Thank you for your important study aimed at finding the impact of ADRs on multimorbidity, polypharmacy, hospital admissions, and the economic impact on NHS. The finding will be important for improving medical prescription and healthcare practices and lowering healthcare cost. However, I have a few comments below.

Introduction
"Polypharmacy is the concurrent use of multiple medications by an individual. Numerical definitions vary but it is most commonly defined as taking 5 or more regular medications"

Comment: It is important to state the lack of consensus on what number constitutes polypharmacy. See this article https://www.hindawi.com/journals/jar/2020/6759521/

Thank you for your comments. We have altered the introduction to highlight this lack of consensus. Thank you for sharing this article which highlights issues of polypharmacy particularly in older persons. This has been discussed and added to the discussion section also where stratification for ADR risk and avoidance is discussed.

What is "Appropriate polypharmacy"?
Thank you. We have added further information to the introduction to clarify this.

It would be ideal to briefly explain the purpose of using each of these tools: Liverpool causality assessment tool, LAAT and other tools for the readership that may not be familiar with the aim and distinction of using each of them.
Thank you for your comment. We agree this would benefit the reader and have provided a short explanation of each tool used with appropriate referencing.
Is it possible to include the length of stay of all patients in the baseline statistics?
Unfortunately, the length of stay was only captured for those with an ADR. Therefore, we included it in the descriptive results but did not add it to Table 3 – baseline characteristics.
Discussion
Was EHRs used by MPs for data collection?
No this was not available in 2004. Thank you for highlighting this as it may have contributed to increased ADR identification. We have included this in the discussion section under ‘comparison with Pirmohamed 2004’
Multimorbidity and polypharmacy
It would be nice to discuss the findings on ADR with respect to the type of ADR for more clarity. A reader may find it hard to decipher what type of ADR was implicated as you compare the numbers for ADR vs non-ADR.

Thank you for your comments. Type of reaction as per Rawlins and Thompson definition was in the result section and not in the discussion. Importantly as the majority of ADRs were Type A reaction they were pharmacologically predicable and therefore potentially more likely avoidable. We have added this to the discission.
Since it makes sense that co-morbidity is often directly related with polypharmacy in people with LTCs, more coherent explanation is needed on why it does not influence the number of medications a patient is taking in this study.
On page 8, we already state that “Patients with ADRs were older than those without (mean age 73.2 (14.5) vs 66.7 (19.2), OR 1.02 (1.01, 1.03)) and were taking more medicines (mean 10.5 (4.6) vs 7.8 (5.1), OR 1.11 (1.07, 1.14)), with polypharmacy present in 91%, compared to 73% in the non-ADR group. They had more comorbidities (mean 6.1 (3.0) vs 5.2 (3.3), OR 1.08 (1.04, 1.13)), although this variable was not included in the multivariable model (possibly due to its correlation with number of medicines). Because of the correlation between number of medicines and number of co-morbidities, as would be expected, we did not include the latter in the logistic regression analysis. We have clarified this in the discussion.

Reviewer: 3
Dr. Maria Zazzara, Fondazione Policlinico Gemelli IRCCS
Comments to the Author:
Thank you for addressing all comments. The manuscript has improved.
Also, thank you for clarifying comments on opioids!

VERSION 3 – REVIEW

REVIEWER	Nwadiugwu, Martin University of Stirling, Health
REVIEW RETURNED	24-May-2022

GENERAL COMMENTS	Thank you for revising the work. Review for little typos in the final version of the manuscript such as "This is a validated a tool to support the assessment of the avoidability of ADRs based on available patient information." I am guessing you meant "This is a validated tool to support the assessment of the avoidability of ADRs based on available patient information."

REVIEWER	Zazzara, Maria Fondazione Policlinico Gemelli IRCCS
REVIEW RETURNED	30-May-2022

GENERAL COMMENTS	No further comments.