

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	What is the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts? A systematic review of the international literature
AUTHORS	Assiri, Ghadah; Shebl, Nada; Mahmoud, Mansour; Aloudah, Nouf; Grant, Elizabeth; Aljadhey, Hisham; Sheikh, Aziz

VERSION 1 – REVIEW

REVIEWER	Dr Chi Huynh Pharmacy Department, School of Life and Health Sciences, Aston University, Aston Triangle, Birmingham, UK, B4 7ET
REVIEW RETURNED	30-Aug-2017

GENERAL COMMENTS	<p>This systematic review is unique to investigating the medication errors and error-related adverse drug events in primary, ambulatory and home settings. The authors and co-authors have been thorough and transparent regarding the hindsight of the omission to "dispensing errors".</p> <p>There are a few very minor issues that the authors may wish to consider when editing this for the final publication.</p> <p>Abstract Line 33 - "... self care safely" Safely is in italic font - is that deliberately highlighted?</p> <p>Line 45 - "... and polypharmacy with record of the currant....." - do you mean - current?</p> <p>Line 50 - see comment re: Line 33 - is safely deliberately spelt with italic font?</p> <p>Figure one - the excluded with reasons box n = 12935</p> <p>392 Illegal - Suggestion that the authors could possibly expand on this - e.g. Illegal/illicit drugs or medication?</p> <p>Figure 1 - Full text articles excluded, with reasons (n = 39)</p> <p>"1 Author did not replay" - do you mean Author did not reply when contacted for full text?</p> <p>Other than these very minor comments, the report content is thorough and systematic.</p>
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	<p>One final suggestion would be for the authors to consider including in the results an analysis of the results based on stratification of the settings if feasible with a comparison (settings - e.g. as listed per line 31-38 - e.g. primary health care, or general practice context, community setting, ambulatory care, community setting and home settings) and compare the epidemiology of the outcome measures of medication errors and error-related adverse drug events.</p>
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REVIEWER	Jorge Machado-Alba Universidad Tecnológica de Pereira
REVIEW RETURNED	09-Sep-2017

GENERAL COMMENTS	<p>Dear Editors</p> <p>Evaluation of manuscript: bmjopen 2017-019101</p> <p>* Originality - does the work add enough to what is already in the published literature? If so, what does it add? If not, please cite relevant references. A/ The research is original.</p> <p>* Importance of work to general readers - does this work matter to clinicians, patients, teachers, or policymakers? Is a general journal the right place for it? A/ The issue really is important for all actors in a system of health care.</p> <p>* Scientific reliability Research Question - clearly defined and appropriately answered? A/ Yes</p> <p>Overall design of study - adequate ? A/ Yes.</p> <p>Participants studied - adequately described and their conditions defined? A/ Yes.</p> <p>Methods - adequately described? Complies with relevant reporting standard - Eg CONSORT for randomised trials ? Ethical ? A/ the authors following appropriate criteria.</p> <p>Results - answer the research question? Credible? Well presented? Interpretation and conclusions - warranted by and sufficiently derived from/focused on the data? Message clear? A/ The results are well presented. But, the tables are too long.</p> <p>References - up to date and relevant? Any glaring omissions? A/ some references are misspelled, eg shortened name of the journal</p> <p>Abstract/summary/key messages/What this paper adds – reflect accurately what the paper says? A/ the abstract are too long.</p> <p>I consider that this is a good job that can be accepted for publication. It requires minimal adjustments from a proofreader to improve the writing of some sentences.</p>
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REVIEWER	Chenjuan Ma NYU, USA
REVIEW RETURNED	22-Oct-2017

GENERAL COMMENTS	This study of "Investigating the Epidemiology of Medication Errors
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	<p>and Error-Related Adverse Drug Events in Adults in Primary Care, Ambulatory Care and Home Settings: A systematic Review” is a very important research topic.</p> <p>Below are some comments from the reviewer:</p> <ol style="list-style-type: none"> 1. Page 4 lines 17-18, the data from 2001 is too old, suggest updating the estimate using more recent data. 2. Page 4 paragraph 2, the current the arguments can be stronger/more persuasive by providing some statistics related to the number of patients in community settings as well as expending literature of other countries. 3. Page 5 under “Data sources and search strategy”, the search terms are critical for a review paper; therefore, suggest the authors summarized the search terms in the main manuscript, in the text or a table, not only included it in the appendix. 4. Page 9 line 18, the use of “population-based...” is inappropriate as not all the studies the authors referred to as “population-based...” used national data, for example reference 23. Suggest remove the term “population-based” or replace with a more accurate term. 5. Page 11 line 53 and page 12 line 22, it is inappropriate to state the “in descending order of positive association” as findings were extracted from different studies and no meta-analysis was conducted. 6. Page 13 line 33, please clarify what does it mean “patient error”, error caused by patients or errors related to patient-factors? 7. The current discussion is limited. Suggest provide a more in depth discussion of the findings of this review. Also, the implication paragraph on page 16 is too broad and general, it should be more specific based on the findings.
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REVIEWER	Kristen Campbell University of Colorado Anschutz Medical Campus, USA
REVIEW RETURNED	03-Nov-2017

GENERAL COMMENTS	<ol style="list-style-type: none"> 1. What was your justification for including unpublished and research in progress pieces of work? Are these subject to a large amount of bias? 2. What was done with the level of bias information that you collected? If a study was deemed to have a high amount of bias, was it removed? If not, can you explain why it wasn't removed in the text? 3. Statistics: In the results, include confidence intervals around incidence rates/prevalence rates. 4. Presentation of Results: Reporting the range of 2-94% for the prevalence of medication errors and 2-58% for prevalence of DDIs is not very helpful. Including a plot that has the prevalence reported for each study and the overall average would be helpful to see how the distribution looks visually. 5. General: My main concern with this paper is whether there are any conclusions that could be used in practice. The ranges in prevalence/incidence rates are so wide that it's hard to draw anything useful from them. The main conclusion seems to be that there needs to be better rules around reporting medication errors, administration errors, and dispensing errors. The conclusions about risk factors for medication errors and ADEs are useful. But clinically, is this enough to justify publication of this piece?
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VERSION 1 – AUTHOR RESPONSE

We are grateful for the further editorial and expert peer-review feedback, which we have carefully considered and have in the light of this made a number of revisions to our manuscript. For your convenience, we have reproduced the feedback received verbatim (in emboldened italics) before detailing our responses. Our revisions to the manuscript are clearly highlighted in yellow.

Editorial Requirements:

- Please revise the title to indicate the research question, study design, and setting. This is the preferred format for the journal.

Response: We have revised the title to: 'What is the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts? A systematic review of the international literature'

Reviewer: 1

This systematic review is unique to investigating the medication errors and error-related adverse drug events in primary, ambulatory and home settings. The authors and co-authors have been thorough and transparent regarding the hindsight of the omission to "dispensing errors".

Response: Thank you.

There are a few very minor issues that the authors may wish to consider when editing this for the final publication.

Abstract

Line 33 - "... self care safely" Safely is in italic font - is that deliberately highlighted?

Response: This has now been corrected to non-italicised font.

Line 45 - "... and polypharmacy with record of the currant....." - do you mean - current?

Response: We have now corrected this typo.

Line 50 - see comment re: Line 33 - is safely deliberately spelt with italic font?

Response: This has now been corrected to non-italicised font.

392 Illegal - Suggestion that the authors could possibly expand on this - e.g. Illegal/illicit drugs or medication?

Response: This point has now been expanded on to make clear that we are referring to illegal/illicit drugs or medications.

"1 Author did not replay" - do you mean Author did not reply when contacted for full text?

Response: We have now corrected this typo.

Other than these very minor comments, the report content is thorough and systematic.

Response: Thank you

One final suggestion would be for the authors to consider including in the results an analysis of the results based on stratification of the settings if feasible with a comparison (settings - e.g. as listed per line 31-38 - e.g. primary health care, or general practice context, community setting, ambulatory care, community setting and home settings) and compare the epidemiology of the outcome measures of medication errors and error-related adverse drug events.

Response: We have now produced a chart of medication errors estimates stratified by the settings— see Figure 2.

Reviewer: 2

* Originality - does the work add enough to what is already in the published literature? If so, what does it add? If not, please cite relevant references.

The results are well presented. But, the tables are too long.

Response: This is inevitable given the number of studies identified and the need to provide detailed descriptions of the studies. The journal may wish to move some of these tables to an online supplement.

Some references are misspelled, eg shortened name of the journal Go back and see

Response: These have been corrected.

The abstract are too long.

Response: This has now been reduced to under 300 words.

I consider that this is a good job that can be accepted for publication. It requires minimal adjustments from a proofreader to improve the writing of some sentences.

Response: Thank you.

Reviewer: 3

This study of "Investigating the Epidemiology of Medication Errors and Error-Related Adverse Drug Events in Adults in Primary Care, Ambulatory Care and Home Settings: A systematic Review" is a very important research topic.

Response: Thank you.

1. Page 4 lines 17-18, the data from 2001 is too old, suggest updating the estimate using more recent data.

The cost of drug&related morbidity and mortality was estimated in 2001 to be \$177.4 billion annually in the United States of America (USA) alone.(5)

Response: We have updated the Introduction with more recent data.

2. Page 4 paragraph 2, the current the arguments can be stronger/more persuasive by providing some statistics related to the number of patients in community settings as well as expending literature of other countries.

Response: This argument has now been strengthened along the lines suggested with supporting references.

3. Page 5 under "Data sources and search strategy", the search terms are critical for a review paper; therefore, suggest the authors summarized the search terms in the main manuscript, in the text or a table, not only included it in the appendix.

Response: We have revised this section of the Methods accordingly.

4. Page 9 line 18, the use of "population-based..." is inappropriate as not all the studies the authors referred to as "population-based..." used national data, for example reference 23. Suggest remove the term "population-based" or replace with a more accurate term.

Response: Population-based has been changed to community setting.

5. Page 11 line 53 and page 12 line 22, it is inappropriate to state the “in descending order of positive association” as findings were extracted from different studies and no meta-analysis was conducted.
Response: The relevant text has now been accordingly revised.

6. Page 13 line 33, please clarify what does it mean “patient error”, error caused by patients or errors related to patient-factors?
Response: This has been clarified to error caused by patients.

7. The current discussion is limited. Suggest provide a more in depth discussion of the findings of this review. Also, the implication paragraph on page 16 is too broad and general, it should be more specific based on the findings.
Response: We have revised the Discussion to both situate this better in the context of the international literature and also to offer more specific suggestions on important next steps following on from this work.

Reviewer: 4

1. What was your justification for including unpublished and research in progress pieces of work? Are these subject to a large amount of bias?

Response: It is now standard practice in systematic reviews to look for and include published, unpublished and in progress work in order to provide a complete overview of the state of research in the area.

2. What was done with the level of bias information that you collected? If a study was deemed to have a high amount of bias, was it removed? If not, can you explain why it wasn't removed in the text?

Response: The general recommendation now is not to remove high risk of bias studies from systemic reviews. Rather, it is considered best to include these, but to focus on the studies judged to be at lower risk of bias, which is the approach we adopted.

3. Statistics: In the results, include confidence intervals around incidence rates/prevalence rates.

Response: We have provided these where they were included in the primary studies, but unfortunately in many cases these were not provided in the original reports.

4. Presentation of Results: Reporting the range of 2-94% for the prevalence of medication errors and 2-58% for prevalence of DDIs is not very helpful. Including a plot that has the prevalence reported for each study and the overall average would be helpful to see how the distribution looks visually.

Response: We have now included this plot – see Figure 2.

5. General: My main concern with this paper is whether there are any conclusions that could be used in practice. The ranges in prevalence/incidence rates are so wide that it's hard to draw anything useful from them. The main conclusion seems to be that there needs to be better rules around reporting medication errors, administration errors, and dispensing errors. The conclusions about risk factors for medication errors and ADEs are useful. But clinically, is this enough to justify publication of this piece?

Response: We believe that this study has helped to make clear the current state of evidence in relation to this important subject and provides a firm foundation on which investigators now need to build in order to provide more reliable estimates. The other 3 reviewers share this perspective on the importance of this piece.

The opportunity to respond to this feedback has helped us to strengthen the quality of our work, for which we are grateful. We believe that we have responded to all the points made and hope that these are to your satisfaction; we trust that the manuscript is now considered suitable for publication.

Yours sincerely,
Ghadah Assiri, on behalf of the research team.

VERSION 2 – REVIEW

REVIEWER	Kristen Campbell University of Colorado Anschutz Medical Campus
REVIEW RETURNED	18-Jan-2018

GENERAL COMMENTS	Thank you for addressing the comments, well done. This is a nice piece of work and ready for publication.
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REVIEWER	Jorge Machado-Alba Universidad Tecnologica de Pereira Colombia South America
REVIEW RETURNED	23-Jan-2018

GENERAL COMMENTS	the tables are too long. I think they can be adjusted.
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REVIEWER	Chi Huynh Aston Pharmacy School, School of Life and Health Sciences, Aston University, Aston Triangle, Birmingham, UK
REVIEW RETURNED	27-Jan-2018

GENERAL COMMENTS	<p>This review highlights an important issue regarding studies published looking at the prevalence of medication errors where there is differences in the definition of what constitutes to a "Medication error" and the need for a common or standardised set of outcome measures of medication errors.</p> <p>This report has identified a key finding that there is a lack of study data on the incidence of medication errors, and of those articles found that met the inclusion criteria - many were only estimates of the prevalence of errors.</p> <p>The only question I have are very minor. In the last sentence of the Introduction section, it is mentioned that "The cost of medication errors worldwide has been estimated as 4\$2 billion/year". The dollar sign seems of have been misplaced. Did you mean \$42 (US dollars)? I had a look at reference 5 and it says about \$500 is the estimated cost, of which 9% can be attributed to medication error. Should this then be \$45? It would be good to clarify also that it is US dollars.</p>
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VERSION 2 – AUTHOR RESPONSE

We are grateful for the further editorial and expert peer-review feedback, which we have carefully considered and have in the light of this made a number of revisions to our manuscript. For your convenience, we have reproduced the feedback received verbatim (in emboldened italics) before detailing our responses. Our revisions to the manuscript are clearly highlighted in yellow.

Reviewer: 4

Please leave your comments for the authors below

Thank you for addressing the comments, well done. This is a nice piece of work and ready for publication.

Response: Thank you

Reviewer: 2

Please leave your comments for the authors below

The tables are too long. I think they can be adjusted.

Response: This is inevitable given the number of studies identified and the need to provide detailed descriptions of the studies. The journal may wish to move some of these tables to an online supplement.

Reviewer: 1

Please leave your comments for the authors below

This review highlights an important issue regarding studies published looking at the prevalence of medication errors where there is differences in the definition of what constitutes to a "Medication error" and the need for a common or standardised set of outcome measures of medication errors.

This report has identified a key finding that there is a lack of study data on the incidence of medication errors, and of those articles found that met the inclusion criteria - many were only estimates of the prevalence of errors.

The only question I have are very minor.

In the last sentence of the Introduction section, it is mentioned that "The cost of medication errors worldwide has been estimated as 4\$2 billion/year". The dollar sign seems of have been misplaced. Did you mean \$42 (US dollars)? I had a look at reference 5 and it says about \$500 is the estimated cost, of which 9% can be attributed to medication error. Should this then be \$45? It would be good to clarify also that it is US dollars.

Response: for reference number 5 in page 110, it was mentioned that "a total of 0.7% of global total health expenditure (THE), or 42 bn USd worldwide, can be avoided if medication errors are prevented". This has been clarified to US\$ 42 billion.

Yours sincerely,

Ghadah Assiri, on behalf of the research team.