PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Drugs causing adverse events in patients aged 45 or older, a randomized survey of Australian general practice patients
AUTHORS	Miller, Graeme; Valenti, Lisa; Britt, Helena; Bayram, Clare

VERSION 1 - REVIEW

REVIEWER	Whitstock, Margeret Deakin University Australia
REVIEW RETURNED	28-Aug-2013

GENERAL COMMENTS	The listing of ADEs associated with commonly prescribed drugs at recommended therapeutic dosage levels (and the manifestations associated with them) is most useful, and may help doctors and patients to better weigh up the symptoms of a morbidity vs. the likely side-effects of a drug prescribed to address those symptoms. Patients recalling an ADE may not note a co-medication or comorbidity if they judge it to be irrelevant. It would be useful if earlier work on multimorbidity (e.g the 2008 paper contributed to by Britt and Miller) were able to be addressed in a future study, as an ADE associated with a given drug may only occur in the presence of another morbidity or medication.

REVIEWER	Louis MERLE, MD Professor of Clinical Pharmacology I do not have any conflict of interest
REVIEW RETURNED	01-Sep-2013

GENERAL COMMENTS	This is an interesting study on the adverse effects caused by drugs within the field of the daily activity of general practitioners (GPs) in Australia. The method used in order to select the GPs as well as the patients who participated is logical and well described. The results are a good reflect of the iatrogenesis identified in patients aged 45 years and over who visit a GP. This study shows that commonly used drugs, given in normal doses, and according to good indications, are fairly harmful even in case of correct monitoring; the only way to mitigate this toxic potential is to limit as far as possible the number of the different drugs given to a patient. The text is easy to read and gives an interesting insight into an often underestimated problem. However, some points are to be raised: - The study addresses the adverse drug events that occurred within the sixth months preceding the interview; this obviously induces a recall bias. The severe adverse events which occurred a long time before the interview will be recalled whereas milder ones will be

	forgotten. On the contrary, the adverse events which happened a shorter time before the interview will be recalled whether they are serious or not. This bias, its weight in the study, should be more precisely evaluated. - The authors studied patients within a wide age range. It would have been interesting to divide the sample into four groups, for instance: middle aged (45 – 65 years), young olds (65 – 75), olds (75 – 85) and old-olds patients (> 85 years). The drugs given to these categories of patients are different, especially when comparing the middle aged and the old-old patients; so these age categories should be identified. - There is a contradiction between the text in page 7, lines 15 to 20 and figure 1. Contrary to what is written, figure 1 clearly shows that the rate of adverse drug events increases with age. This is another reason for selecting various age groups - In order to record the origin of an adverse drug event, nine options were available. One of them was “a recognised side effect”. This could have two meanings: i) the adverse event is first recognised by the patient and spontaneously reported to the GP who assesses the signal and considers that this event is definitely or not an adverse drug effect, ii) the GP identifies an event still prevalent on the day of the visit and considers after assessment that it is an adverse drug effect, whatever the opinion of the patient. In the first case, events which occurred several months before the visit and then spontaneously healed are not included. In other words, what degree of assessment is needed to identify an adverse drug event. - In page 11, lines 39 to 51, an important piece of information is given. However, who judges the appropriateness of the dosage and of the indication? The GP. Who prescribed the drug? The same GP who becomes both judge and judged. The authors could comment on this point. A misspelling in table 2: in the lipid modifying agents row, in the last box on the right, "feeling" should replace "felling"

REVIEWER	Amaia Calderón Larrañaga PhD Aragon Health Sciences Institute (IACS), Spain I declare that I have no competing interests.
REVIEW RETURNED	02-Sep-2013

GENERAL COMMENTS	The present study tackles an important issue as is the epidemiology of adverse drug events among patients attending primary care in Australia. Pharmacoepidemiological studies such as the present one are essential to decrease the negative results caused by drug therapy in those contexts where the number of individuals with polypharmacy is very high and still expected to raise. Please find below some minor comments/suggestions that could help improve the manuscript. RESULTS The last paragraph of the Results section compares the rates of ADEs with prescribing rates for each of the drugs in Table 2, based on the non-overlapping of CIs. It would be helpful if the authors clarified the pertinence of such a comparison in the Methods section. How can judgements be made based on the CIs of two different variables?

	In the before-mentioned paragraph, it is mentioned that H2RAs show a lower ADE rate than their relative prescribing rate. If the paragraph is eventually incorporated, H2RAs should be included in Table 2. DISCUSSION The authors conclude that "the large majority of ADEs occurring in primary medical care in Australia fall into the WHO category of adverse drug reactions (ADRs), occurring in patients on appropriate dosages of medication, prescribed for appropriate indications". However, it could be argued that ADRs are the type of ADEs that can most easily be identified by practitioners. The evidence suggests ADEs related to drug indication and/or effectiveness (beyond drug safety problems) represent a big share of the submerged part of the iceberg. Improving GPs' access to rigorous and understandable information on ADEs, implementing computer system alerts and/or promoting GP-pharmacist collaborations in the primary care setting are some of the measures that have been shown to prevent and reduce avoidable ADEs. Some reflection in this regard would be appreciated. Further comparison with other studies carried out in similar primary care contexts is missing, especially regarding the main drug groups implicated as causes of ADEs, as well as the prevalence of ADEs.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Dr. Margaret T. Whitstock
Independent Researcher (formerly Research Fellow at Deakin University) Australia

Whilst the Introduction makes clear references to the occurrence of ADEs in elderly patients (generally considered to be over age 65, when contributing factors include decreasing physiological resilience, effects of cumulative morbidities and the effects of the increasing numbers of medications taken simultaneously to manage these morbidities), the study itself focuses on the older patient, which is defined as commencing at age 45 years (with the first age bracket examined being a twenty-year span of 45-64 years).

Subdividing the 45-64 age bracket into 45-54 and 55-64 ten-year age groups would allow a better understanding of the relationship of age to ADE burden, and would allow better comparison with the 10-year age bracket used for patients aged 65-74. It may be that data for age bracket 45-64 might not support the conclusion as presented.

Response: We reanalysed the 45-64 age group into 45-54 and 55-64 groups and there was no statistically significant difference in age specific rate of ADEs between the two groups.(see response to reviewer 2)

The term "cause" is used differently in different sections (see Abstract – Results & Conclusion, Data Collected, Classification of Data, and Cause of Adverse Drug Events). Use of the term needs clarification.

Response: use of the word 'cause' has been restricted to the relationship of drugs to ADEs and 'cause 'when used to designate type of ADE has been replaced by 'type'

This study presents updated data to those recorded in a 2006 publication by Miller, Britt and Valenti "Adverse drug events in general practice patients in Australia" (MJA, 184(7):321-324). The Discussion section uses text that is very similar to that in the Discussion section of the 2006 paper, and the text includes references that were referred to in the 2006 paper. Later references could be useful.

Response: additional references added and discussed in Discussion

The listing of ADEs associated with commonly prescribed drugs at recommended therapeutic dosage levels (and the manifestations associated with them) is most useful, and may help doctors and patients to better weigh up the symptoms of a morbidity vs. the likely side-effects of a drug prescribed to address those symptoms.

Patients recalling an ADE may not note a co-medication or comorbidity if they judge it to be irrelevant. It would be useful if earlier work on multimorbidity (e.g the 2008 paper contributed to by Britt and Miller) were able to be addressed in a future study, as an ADE associated with a given drug may only occur in the presence of another morbidity or medication.

Response: Thank you for your thoughtful suggestion. We intend to publish a paper on the relationship of multimorbidity, poly-pharmacy and ADEs

Reviewer: Louis MERLE, MD
Professor of Clinical Pharmacology
Hôpital Dupuytren

I do not have any conflict of interest

This is an interesting study on the adverse effects caused by drugs within the field of the daily activity of general practitioners (GPs) in Australia. The method used in order to select the GPs as well as the patients who participated is logical and well described. The results are a good reflect of the iatrogenesis identified in patients aged 45 years and over who visit a GP. This study shows that commonly used drugs, given in normal doses, and according to good indications, are fairly harmful even in case of correct monitoring; the only way to mitigate this toxic potential is to limit as far as possible the number of the different drugs given to a patient.
The text is easy to read and gives an interesting insight into an often underestimated problem.
However, some points are to be raised:
- The study addresses the adverse drug events that occurred within the sixth months preceding the interview; this obviously induces a recall bias. The severe adverse events which occurred a long time before the interview will be recalled whereas milder ones will be forgotten. On the contrary, the adverse events which happened a shorter time before the interview will be recalled whether they are serious or not. This bias, its weight in the study, should be more precisely evaluated.

Response: The recall bias is discussed in the section on limitations of the study. It is not possible to evaluate the extent of the bias in a study of this nature.

- The authors studied patients within a wide age range. It would have been interesting to divide the sample into four groups, for instance: middle aged (45 – 65 years), young olds (65 – 75), olds (75 – 85) and old-olds patients (> 85 years). The drugs given to these categories of patients are different, especially when comparing the middle aged and the old-old patients; so these age categories should be identified.
- There is a contradiction between the text in page 7, lines 15 to 20 and figure 1. Contrary to what is written, figure 1 clearly shows that the rate of adverse drug events increases with age. This is another reason for selecting various age groups

Response: The overlapping confidence intervals mean that there is no statistically significant difference in the rate of ADEs in patients of age 45 and over even though there appears to be a trend for frequency to increase with age when 45 and over. While it looks like ADEs increase with age, if there is no statistically significant difference , there is no difference.
We reanalysed the frequency of ADE data with the patients separated into age groups 45-54, 55-64,65-74,75-84 and 85+. There was no significant difference in the age specific rate of ADEs between any of those age groups.(45-54 10.3 (95% CI: 8.6-11.9), 55-64 10.6 (95% CI: 9.1-12.2) 65-74 13.0 (95% CI: 11.2-14.7), 75-84 13.4 (95% CI: 11.5-15.4), 85+ 10.0 (95% CI: 7.3-12.7)). The overlapping CIs indicate that there is no statistical difference in the age specific rate of ADEs between these age groups in this study. Other studies such as those by Gandhi and Calderon show no correlation between ADEs and increasing age as an independent variable.

- In order to record the origin of an adverse drug event, nine options were available. One of them was “a recognised side effect”. This could have two meanings: i) the adverse event is first recognised by the patient and spontaneously reported to the GP who assesses the signal and considers that this event is definitely or not an adverse drug effect, ii) the GP identifies an event still prevalent on the day of the visit and considers after assessment that it is an adverse drug effect, whatever the opinion of the patient. In the first case, events which occurred several months before the visit and then spontaneously healed are not included. In other words, what degree of assessment is needed to identify an adverse drug event.

Response: as described in the method, GPs asked the patient if they had experienced reactions, related to the drugs prescribed, in the previous six months. This was assessed by the GP to reach a conclusion as to the certainty of the relationship to the drug and the nature of the reaction. The term “recognised side effect” means a side effect known to occur with that drug.

- In page 11, lines 39 to 51, an important piece of information is given. However, who judges the appropriateness of the dosage and of the indication? The GP. Who prescribed the drug? The same GP who becomes both judge and judged. The authors could comment on this point.

Response: Comments added to text

A misspelling in table 2: in the lipid modifying agents row, in the last box on the right, "feeling" should replace "felling"

Response:Corrected

Reviewer: Amaia Calderón Larrañaga PhD
Aragon Health Sciences Institute (IACS), Spain

I declare that I have no competing interests.

The present study tackles an important issue as is the epidemiology of adverse drug events among patients attending primary care in Australia. Pharmacoepidemiological studies such as the present one are essential to decrease the negative results caused by drug therapy in those contexts where the number of individuals with polypharmacy is very high and still expected to raise.

Please find below some minor comments/suggestions that could help improve the manuscript.

RESULTS

The last paragraph of the Results section compares the rates of ADEs with prescribing rates for each of the drugs in Table 2, based on the non-overlapping of CIs. It would be helpful if the authors clarified the pertinence of such a comparison in the Methods section. How can judgements be made based on the CIs of two different variables?

Response: paragraph added to method to explain the approach taken to comparison of prescribing and ADE rates

In the before-mentioned paragraph, it is mentioned that H2RAs show a lower ADE rate than their relative prescribing rate. If the paragraph is eventually incorporated, H2RAs should be included in Table 2.

Response: reworded in paper: Acid suppressant medications (including H2RAs and PPIs) as a group had a lower ADE rate in comparison to their prescribing rate

DISCUSSION

The authors conclude that “the large majority of ADEs occurring in primary medical care in Australia fall into the WHO category of adverse drug reactions (ADRs), occurring in patients on appropriate dosages of medication, prescribed for appropriate indications”. However, it could be argued that ADRs are the type of ADEs that can most easily be identified by practitioners. The evidence suggests ADEs related to drug indication and/or effectiveness (beyond drug safety problems) represent a big share of the submerged part of the iceberg. Improving GPs’ access to rigorous and understandable information on ADEs, implementing computer system alerts and/or promoting GP-pharmacist collaborations in the primary care setting are some of the measures that have been shown to prevent and reduce avoidable ADEs. Some reflection in this regard would be appreciated.

Response: brief comment on the use of ADE data in decision support added to end of discussion.

Further comparison with other studies carried out in similar primary care contexts is missing, especially regarding the main drug groups implicated as causes of ADEs, as well as the prevalence of ADEs

Response: Comparison with some more recent relevant papers is now included in the paper