PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Associations between polypharmacy and treatment intensity for hypertension and diabetes: a cross-sectional study of nursing home patients in British Columbia, Canada
AUTHORS	McCracken, Rita; McCormack, James; McGregor, Magaret; Wong, Sabrina; Garrison, Scott

VERSION 1 - REVIEW

REVIEWER	Dr. Michael Dörks Department of Health Services Research Carl von Ossietzky University Oldenburg/Germany
REVIEW RETURNED	17-May-2017

GENERAL COMMENTS	The manuscript is well written and deals with the very important topic of polypharmacy and overtreatment. It focusses on hypertension and diabetes medication. The subject is of interest, since the understanding of reasons for overtreatment could help to improve patient safety. However, I have some suggestions, which might be useful for the authors to improve their manusript. Although there is a reference, the authors might consider to explain a bit more detailed why furosemide is a marker for congestive heart failure. Is this due to the indication? In Europe, this drug is licensed for various indications. With respect to the definition of polypharmacy, the authors wrote „items requiring a physicians order, regardless of route and including vitamins and supplements.“ Is it possible that the authors quantify the amount of such vitamins and supplements? This could be interesting, since a lot of other studies considering polypharmacy were restricted to prescription drugs only. As the authors wrote, the gathering of only one measurement of A1c is a considerable limitation. With respect to the underlying data, is it possible to show which blood glucose lowering drugs like for example glyburide or metformin were specifically responsible for A1c <=7.5% and overtreatment/polypharmacy? In the discussion section, the authors may consider to mention that a more „aggressive“ drug regime might also be due to concomitant drug prescriptions with blood glucose raising effects.

REVIEWER	Marco Proietti - Department of Internal Medicine and Medical Specialties, Sapienza-University of Rome, Rome, Italy - Department of Neuroscience, IRCCS – Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy - Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom

	Small fee from Boheringer Ingelheim for consulting activity
REVIEW RETURNED	30-May-2017

GENERAL COMMENTS	The paper presented is quite interesting. Despite that there are some issues that need to be addressed. First of all, the threshold used for polypharmacy is not adequate. Despite the authors reported a couple of references stating 9 drugs as a threshold, several papers about polypharmacy in various clinical setting, established 5 drugs as a threshold for polypharmacy. I would like to suggest to the authors to add an analysis using 5 drugs as a threshold and then consider 9 drugs as a further threshold as "severe polypharmacy". Second, the authors stated some assumptions to justify the collected sample size, but they don't provide any source for these data. Please amend. In the first paragraph of Results, the authors stated some analyses, despite not showing those results. Maybe they would like to add those data as supplementary materials. One of the main limitation of the study is the low number of subjects enrolled. Despite stating this clearly in the Limitations section, they do not state this issue in the Abstract. Indeed, the authors should mitigate the Conclusions section in the abstract.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

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1) Although there is a reference, the authors might consider to explain a bit more detailed why furosemide is a marker for congestive heart failure. Is this due to the indication? In Europe, this drug is licensed for various indications.

Response:
The patient-chart documentation of congestive heart failure was often erratic and appeared to be incomplete/inaccurate.
However, given the possible confounding of CHF as a cause of lower blood pressure (independent to or intentionally related to specific pharmacotherapy choices) The authors felt that being able to have some other indicator of CHF would be more useful. One of our authors (JM) was an author on the paper cited as rationale for choice of furosemide (Lancet 1998; 352: 943–48) and suggested doing the same for this paper.
As per your suggestion, I have done some review to ensure that this assumption is reasonable (i.e. furosemide is a fair estimate for presence of a diagnosis of CHF) and have found the following that supports this decision.
While treatment of hypertension was an original indication for furosemide when released in 1962, a 2005 study comparing hypertension prescribing in Canada, France, Germany, UK, US and the Nordic countries did not include loop diuretics as a drug class even considered for treatment of hypertension. BMC Health Serv Res. 2005 Mar 11;5(1):21

Also, the American College of Cardiology Foundation/American Heart Association Task Force has considered furosemide a first line treatment for symptomatic heart failure since at least 2013

Circulation. 2013 Oct 15;128(16):e240-327

We acknowledge this indicator could lead to including some people who received the drug for a different indications and having a more accurate method to identify CHF patients would have been ideal (e.g. ejection fraction measure or even a billing code denoting CHF) but impractical. Given that, and the very limited use we see of furosemide clinically for hypertension we feel this is a reasonable surrogate.

2) With respect to the definition of polypharmacy, the authors wrote „items requiring a physicians order, regardless of route and including vitamins and supplements.“ Is it possible that the authors quantify the amount of such vitamins and supplements? This could be interesting, since a lot of other studies considering polypharmacy were restricted to prescription drugs only.

Response: I have added a table as supplementary material which includes details about prescribing, including supplements. (Supp Table 1 Found after References in new version of manuscript)

3) As the authors wrote, the gathering of only one measurement of A1c is a considerable limitation. With respect to the underlying data, is it possible to show which blood glucose lowering drugs like for example glyburide or metformin were specifically responsible for A1c <=7.5% and overtreatment/polypharmacy?

Response: An additional Supplementary table (Supp Tables 3 and 4) has been added for both hypertension and diabetes, comparing those over treated to those not and showing frequency of the drugs prescribed. This was not included originally, given the small sample size, but as you note, the data may be interesting to other people doing this kind of study on a larger scale.

4) In the discussion section, the authors may consider to mention that a more „aggressive“ drug regime might also be due to concomitant drug prescriptions with blood glucose raising effects.

Response: Thank you for this suggestion. The study team reviewed it while we agree that some drugs, e.g. statins and thiazides are known to cause increase in serum glucose, and in doing so, they might initiate a prescribing cascade that would add another drug on to dealing with the “high” sugar, we observed the opposite. Despite the tendency of other medications to raise glucose, we are still finding that lower sugars are associated with greater use of non-glucose lowering medication.

Reviewer: 2

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1) First of all, the threshold used for polypharmacy is not adequate. Despite the authors reported a couple of references stating 9 drugs as a threshold, several papers about polypharmacy in various clinical setting, established 5 drugs as a threshold for polypharmacy. I would like to suggest to the authors to add an analysis using 5 drugs as a threshold and then consider 9 drugs as a further threshold as "severe polypharmacy".

Response: Thank you for this comment. The definition of what constitutes polypharmacy is indeed arbitrary. We have found that accurate descriptions of what is counted and how are actually quite sparse and processes used, as well as “cut points” seem to be incredibly varied. For this sample, only 12.6% were prescribed <=4 medications, as they were counted in this study. Upon review of the data and the other studies done in Canada, the study team decided that Bronskill’s (PMID: 21839687) (and many others PMID: 25869992) use of 9 would be best suited to our intention to present information about treatment intensity of hypertension and diabetes.

To help illuminate this rationale, we have made the following change in the manuscript:

“The number of medications at which polypharmacy is “diagnosed” varies widely in the published literature. For this study, 9 or more medications was chosen as the definition as one of the most robust studies done in Canada[13] did the same and our results will likely be most comparable to data also collected in this country. In Jokanovic et al’s systematic review of prevalence, 24 studies used 9 medications or greater as the cut off, versus 11 studies using 5 medications .”

2) Second, the authors stated some assumptions to justify the collected sample size, but they don't provide any source for these data. Please amend.

Response: As per both yours and the editor’s comment (see above for exact wording and reference details), I have made a change and provided a reference in the manuscript.

3) In the first paragraph of Results, the authors stated some analyses, despite not showing those results. Maybe they would like to add those data as supplementary materials.

Response: Included as Supp Table 2, after the References.

4) One of the main limitation of the study is the low number of subjects enrolled. Despite stating this clearly in the Limitations section, they do not state this issue in the Abstract. Indeed, the authors should mitigate the Conclusions section in the abstract.

Response:
Change made to both abstract and conclusion.

ABSTRACT CONCLUSON
Over treated diabetes and hypertension may be quite prevalent in nursing home patients and the presence of polypharmacy is associated with more aggressive disease treatment. This study was limited by its small sample size and cross sectional design, further study of interventions designed to reduce over treatment of hypertension and diabetes is needed to fully understand the potential links between polypharmacy and potential of harms of disease-specific over treatment.

CONCLUSION:
Additional research that provides concrete quantifications of benefits and harms for ranges of treatment intensity with a larger sample and more accurate measures of surrogates are needed.

VERSION 2 – REVIEW

REVIEWER	Michael Dörks Carl von Ossietzky University Oldenburg Germany
REVIEW RETURNED	26-Jun-2017

GENERAL COMMENTS	Thank you very much. I have no more comments.

REVIEWER	Marco Proietti Research Fellow IRCCS – Istituto di Ricerche Farmacologiche Mario Negri Milan, Italy Small fee from Boheringer Ingelheim

REVIEW RETURNED	15-Jun-2017

GENERAL COMMENTS	The authors properly replied to all my queries. Manuscript is surely improved.