PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Chronic condition comorbidity and multi-drug therapy in general practice populations: a cross-sectional linkage study
AUTHORS	Roberts, Tope; Green, Daniel; Kadam, Umesh

VERSION 1 - REVIEW

REVIEWER	Colin McCowan Robertson Centre for Biostatistics, University of Glasgow, UK
REVIEW RETURNED	06-May-2014

GENERAL COMMENTS	Abstract It would make the rest of the abstract clearer if the authors identified how they got form the 6 chronic condition groups to co-morbidity +-. Introduction Pg 4 line 6 “and is an important”. Pg4 Line 16 “drugs interventions” Pg5 Lines 3-11 I did not like the terms “multiple drug prescribing” or “multi-drug prescribing” but thought authors had decided against using polypharmacy. However the explanation for why they chose to do this is not very clear and makes decision to use these terms more confusing. The justification for the terms needs to be better with more clarity. Pg5 Lines 32-35 The last sentence of the Intro is difficult to understand. “We investigated the number of prescribed drugs for patients with one of the index chronic conditions and compared this to others with the same condition but also co-morbid disease. We also investigated whether optimal prescribing for the index chronic condition is affected by presence of a co-morbid disease.” The authors could add something around “optimal prescribing” to the intro as readers may be unfamiliar with this concept. Methods Pg6 Line 32 This is a poor description of how they identified patients with co-morbid conditions which is made redundant by a later section so remove Pg 7 Lines 3-17. This paragraph is useful but I think might be better placed in the discussion as it is a rationale for what the authors did rather than a description of the methods. Pg 7 The “Prescribed drug measure” used is very crude and it might be better to have subdivided the BNF chapters into more defined classes. I’m happy with grouping similar drugs into classes to give a measure of drug burden but think using chapters does not break down into enough detail. By using more defined classes the

	individual effect of each condition on the patient is better defined i.e. someone on 3 different cardio drug classes is likely to have a more severe condition (or conditions) than someone on a single drug. Pg8 Lines 9-11. Amitryptilline is very commonly used for pain in the population under study. Classifications here would see it classed as an anti-depressant although it is unlikely to be prescribed at sufficient dose to have anti-depressive effect. This is likely to be sufficient to skew analysis of depression. It should be excluded from this definition. I did not see anything relating to approvals that had been sought to perform this piece of research. Results Pg 9 Lines 9-14. Authors should report actual number of individuals with each of the conditions and prevalence as a percentage. Basing prevalence on a fictional 10k population would be better for comparisons in the discussion, here they should report what they actually found. Pg9 Lines 17-28. Authors need to justify these statements by showing proportions and results of the tests performed which showed significant results. Pg9 Lines 45-53 Is it of any real interest to know that people with a co-morbid condition are more likely to get drugs to treat that condition than patients with the index condition alone? Discussion The authors do not comment on limitations based on the measure they have decided to use or on the fact that these patients are likely to have been given drugs for other conditions and will also have had other conditions aside from the ones within the study. There is no comment on the fact that a substantial number of patients with a single condition and no co-morbid disease still receive a high number of treatments for co-morbid disease. I would expect some comment with regards to data quality as if someone was prescribed a respiratory drug I would be surprised if it was for something other than a respiratory condition. If this was an acute episode rather than chronic this would work within this study but it needs to be discussed. Overall, I think the use of BNF chapters as a measure for drug count is too crude for this analysis. It reduces the majority of the analysis to whether patients with a co-morbid condition get some form of medication for it compared to those with only the index condition. A more detailed investigation of the BNF classes at a greater level of detail would have given more information and been of greater interest. The authors could then have examined whether the presence of a co-morbid condition meant that you were given more or less treatment for the index condition. The analysis of optimal prescribing is of greater interest but is again hampered by the crude reporting of drug use and the fact amitriptylline will be included as an anti-depressant which may affect the results shown for depression. The design and rational for this work was good but I think the use of BNF chapters is too crude to give any sort of meaningful message. Greater granularity of detail on the prescribing could potentially have given much more interesting results.

REVIEWER	Parker Magin University of Newcastle Australia
REVIEW RETURNED	09-May-2014

GENERAL COMMENTS	This is a rather dense, but interesting, paper on an important topic. The influence of co-morbidity on prescribing is of everyday clinical importance. The findings relating to number of drug categories associated with 'stand-alone' compared to co-morbid conditions are useful in illustrating the relationship between co-morbidity and increased drug use from the interesting perspective of number of classes of drugs rather than number of drugs. As the authors say, this provides a different way of approaching the issue of polypharmacy and provides a measure not influenced by multiple drugs used for the same condition. It does however introduce other issues. The question posed by 'stand-alone ' conditions in some subjects being associated with prescription of drugs from four or five BNF categories (Table3) is, 'for what are these drugs being used?'. A patient with 'stand-alone' diabetes could be using (as well as endocrine system drugs), for example, lipid regulating drugs from the CVS chapter related purely to CVS risk associated with diabetes, and analgesics (or tricyclic antidepressants) from the CNS drugs category for diabetes-related pain. But it's likely that some drugs from multiple BNF chapters in patients with 'stand alone' index conditions are being used for conditions not captured by the study methodology of nominating six index conditions, or that there is under-reporting of some of the index conditions by the GPs' records. The authors might address how this may influence interpretation of the findings. The exploration of the association of vascular co-morbidity with prescribing related to guideline recommendations in the three other index conditions is an intriguing approach. But the Methods doesn't make clear exactly how this is being done (pg 7 line 56 to pg 8 line 11). It reads as though prescription of all drugs from the relevant BNF sections may qualify as 'optimal' treatment, but clinically this doesn't seem likely. Does it mean any drug from the BNF sections? The text needs to be clear on this point. I'm also not sure about the use of the word 'optimal' here. Perhaps the authors could find an alternative word. Apart from ongoing prescribing of hypnotics and anxiolytics for depression and opiates for OA not really being 'optimal', the real issue is whether prescribing as per single-disease guidelines is desirable ('optimal') in multimorbidity. This is the really interesting finding of this study – co-morbidity seems to be associated with less (single-disease) guideline compliance by GPs (Table 5). Whether this is due to some kind of therapeutic inertia or is due to GPs' reasoned consideration of drug-drug and drug-disease interactions and the overall well-being of the patient is the important question raised by the findings. The statistical methods/tests used should be stated. The abstract is not particularly easy to understand. It may be that it is struggling to convey the study methodology and findings within a word-limit. The authors might consider if they could improve the clarity of the abstract. Thus this study represents an interesting approach to an important topic. The results should prompt further exploration of the issue.

REVIEWER	Andrea Corsonello, MD Italian National Research Center on Aging (INRCA), Italy
REVIEW RETURNED	11-May-2014

GENERAL COMMENTS	This is a very interesting paper investigating the impact of comorbidity on multi-drug therapy inthe context of a cross-sectional linkage study of general practice populations. Overall, the manuscript is well written, and results well described and discussed. 1. Abstract: The last sentence of conclusions is out of the scope of this study. The lack of data about outcomes of care of selected chronic conditions is rather a limitation. 2. Introduction: In the first paragraph of the introduction the Authors correctly report a definition of comorbidity. However, the concept of comorbidity can not be considered universal. Several studies report about multimorbidity, especially when dealing with populations in which the identification of an index disease is very difficult or impossible, such as older ones. I think that the concept of multimorbidity should find at least a small place in the introduction. 3. Methods, page 8: Are the Authors sure that mucolytics should be considered as recommended drugs in COPD? 4. Discussion: In my opinion, the main problem is that findings from this study arise from a population where the conceptual framework of "comorbidity" can be applied only to a limited extent. Indeed, about one third of study population is aged 70 or more, and multimorbidity is more frequently observed than comorbidity among older people. So, while I can understand that the dataset did not allow to consider multimorbidity in this study, what I would suggest is to recognize this important limitation .

VERSION 1 – AUTHOR RESPONSE

Reviewer: Dr Colin McCowan
1. Abstract – identification of 6 chronic condition groups to co-morbidity +-.
Response: We have revised the abstract, particularly the participant section (Page 2, line 8 in tracked changes copy), so that is much clearer.

2. Introduction - Pg 4 line 6 “and is an important”.
Response: Typo amended

3. Pg4 Line 16 “drugs interventions”
Response: Typo amended

4. Pg5 Lines 3-11 - justification for the “multi-drug prescribing” terms needs to be better.
Response: We agree that the justification for’ multi-drug’ instead of polypharmacy needs to be better. We have edited, added sentences, and emphasised the specific reference (no. 17) which argues for this change (page 5 lines 6 to 10).

5. Pg5 Lines 32-35 The last sentence of the Intro is difficult to understand.
Response: We have edited the whole of the last paragraph in the introduction to improve clarity on the

purpose of the study (from page 5 line 30 to page 6 lines 1 to 5).

6. Add something around “optimal prescribing” to the intro
Response: Reviewer 3 recommends that the word ‘optimal’ is changed, so we have changed it to the “key group of drugs prescribed for COPD….” (page 6 lines 2 to 5) and throughout the manuscript and the tables.

7. Pg6 Line 32 made redundant by a later section so remove
Response: The study group section has been removed.

8. Pg7 Lines 3-17. This paragraph might be better placed in the discussion
Response: The paragraph has been moved to page 13 from line 19 in the discussion.

9. Pg7 “Prescribed drug measure” used is very crude and it might be better to have subdivided.
Response: This is a very good point. In our linked work using this same dataset, we had used the specific drug groups as a more detailed measure of counts (up to 17) and one could even measure drug counts at the specific drug category level. There is a trade-off on whether a measure is too broad not to have any meaning and too specific so that one is unable to understand because of the complexity that it generates. Our view and remit in this paper is that we wanted to understand the likelihood of understanding what the simpler broad and different system counts (up to 5) were for key and common chronic conditions.
In addition to deciding whether the approach is sufficiently empirical, reviewers 1 and 2 have identified the key methodological challenges in this emerging field. We would propose that our current approach is reasonable with caveats, as it sign-posts significant and important evidence gaps, but requires further methodological developments in terms of precision.

10. Pg8 Lines 9-11. Amitryptiline is very commonly used for pain but classed as an anti-depressant

Response: We agree that there will be individual drugs that may be for indications other than the defined chronic conditions. However the approach taken was outlined for reasons given in point 9 above.

11. Approvals for research
Response: Apologies for our oversight and a sentence has been added to page 6 line 20.

12. Pg9 Lines 9-14 - report actual number of individuals with each condition and % prevalence
Response: The paragraph on page 10 beginning line 13 has been amended to report actual numbers and the 2-year period prevalence.

13. Pg9 Lines 17-28 show proportions and significance tests
Response: The descriptive analyses for socio-demographic characteristics and the main drug prescribing have been analysed using chi-square tests. Sentences added page 9 and line 21 and page 10 paragraph beginning line 20.

14. Pg9 Lines 45-53 Obvious that co-morbid conditions are more likely to get drugs than index condition alone?
Response: We would refer to the starting statements made by Reviewer 2 below which captures the rationale.
“The influence of co-morbidity on prescribing is of everyday clinical importance…”, and linking the chronic condition status to the drug prescribed is what has been addressed in our paper.
“The findings relating to number of drug categories associated with ‘stand-alone’ compared to co-morbid conditions are useful in illustrating the relationship between co-morbidity and increased drug

use from the interesting perspective of number of classes of drugs rather than number of drugs. As the authors say, this provides a different way of approaching the issue and provides a measure not influenced by multiple drugs used for the same condition."

15. Patients are likely to have been given drugs for other conditions and will also have had other conditions aside from the ones within the study
Response: We agree that this can be an issue and have included this as a limitation with sentences added page 14 (from line 11).

16. Comment on the substantial number of patients with a single condition receive a high number of treatments for co-morbid disease
Response: We have addressed this specific point in the discussion page 14 from line 14.

17. Comment on data quality
Response: Reference 32 is on the local general practice network from which the databases were derived.

18. Use of BNF chapters and analysis of optimal prescribing is crude

Response: This issue has been addressed in point 9 above.

Reviewer: Dr. Parker Magin

1. Question posed by 'stand-alone' conditions is 'for what are these drugs being used?' The authors might address how this may influence interpretation of the findings.
Response: Thank you for this excellent question and we agree that it requires explanation of why it was chosen and how it might influence interpretation. We have addressed this specific point in the discussion page 14 from line 11 as follows:
"The construction of our study defined index or 'alone' groups (without the other 5 conditions) provided the relative multi-drug level estimates to when the index condition was comorbid with one of the other 5 conditions. So the multi-drug levels in the 'alone' group provide an estimate of main drug system prescribing without the associated condition (i.e. for other indications) compared to levels when there is a clear comorbidity record. However, this is time-defined by a 2-year time window, so some mis-classification may be possible and further research could explore how broad system drug definitions capture the underlying and specific common diagnostic categories."

2. Exploration of the association of vascular co-morbidity with prescribing related to guideline recommendations in the three other index conditions requires clarity in the methods section (pg 7 line 56 to pg 8 line 11).
Response: We have changed the sub-title to this paragraph and improved the explanation for our approach to defining vascular comorbidity and non-vascular condition drug prescribing (page 8 from line 27).

3. 'optimal' treatment - does it mean any drug from the BNF sections and an alternative word for 'optimal'.
Response: Yes, we identified a group of specific drugs categories as the key ones for COPD, OA and depression, which means that any drug within the specific group is included. This does carry the assumption that the diagnostic category and drug category are clearly linked.
We thought long about the use of the word 'optimal' and agree that in this context we need to change, and we have now called it key drug treatments. Our initial premise was that absence or presence of a drug category would be a sufficient start for defining 'optimal' but in the current study approach we have revised as advised.

4. Implications of findings for non-vascular conditions
Response: Whilst this was a generic comment, we have included the reviewer's statement "Whether this is due to some kind of therapeutic inertia or is due to GPs' reasoned consideration of drug-drug and drug-disease interactions and the overall well-being of the patient is the important question raised by the findings" as this was a much better articulation of the findings (page 13 line 14).

5. The statistical methods/tests used should be stated.
Response: These have been added to the analysis section on page 9.

6. Improve the clarity of the abstract.
Response: We have edited the abstract as advised by reviewer 1 and 2.

Reviewer: Dr. Andrea Corsonello

1. Abstract: The last sentence of conclusions is out of the scope of this study.
Response: We have edited the abstract as advised by reviewer 1 and 2, and also changed the last sentence as reference to future research.

2. Introduction: The concept of multimorbidity should find at least a small place in the introduction.

Response: We agree that multimorbidity and comorbidity concepts are clearly linked and added the reference by van den Akker M et al page 4 and line 1.

3. Methods, page 8: Mucolytics should be considered as recommended drugs in COPD?

Response: There is evidence that Mucolytics are beneficial to patients with COPD and they have been included in UK guidelines (http://www.bmj.com/content/322/7297/1271). However, in our analysis in general practice populations, these were not observed and it is possible that they are used more in hospital-based patients.

4. Discussion: Multimorbidity is more frequently observed than comorbidity among older people, and is a limitation.
Response: As the reviewer states in his point 2 that multimorbidity and comorbidity are important inter-linked concepts. However, this different question that he poses, we have addressed on page 14 line 21 as a future research question.
All authors have seen and approve of changes and we hope these changes meet with your approval. Thank you.

VERSION 2 – REVIEW

REVIEWER	Colin McCowan Robertson Centre for Biostatistics Institute of Health and Wellbeing College of Medical, Veterinary and Life Sciences University of Glasgow
REVIEW RETURNED	10-Jun-2014

GENERAL COMMENTS	Page 5 line 52. Remove "of". Page 7 l 6-7. I did not understand what the authors meant with this sentence around capturing morbidity outside the study conditions. Do they mean to say that patients identified as "alone" may also

	have other conditions outside the ones within the study? P9 line 25 "top 20% deprivation" is ambiguous - is this the most deprived or most affluent quintile? P9 L55 Should "multi-group" read "multi-drug"? P11 l8 "or the non-vascular" should be "or non-vascular" P11 l52 replace "has" with "have" P11 L54 I found the use of "outcome of analgesia" confusing and would prefer the authors to state what this means in relation to outcomes they actually used. Is it drugs from BNF Chapter 4, which is a different thing. I remain unconvinced that the use of BNF chapters is not too broad and think there would be a better paper using finer detail of drug classes examined. However the authors have stated their reasoning for using the broader definitions.

REVIEWER	Parker Magin University of Newcastle Australia
REVIEW RETURNED	10-Jun-2014

GENERAL COMMENTS	The issues in my original review have been adequately addressed by the authors. I note, though, that the term 'optimal' still appears in the Abstract "Objectives' though it's been changed elsewhere in the text.

REVIEWER	Andrea Corsonello Italian National Research Center on Aging (INRCA)Italy
REVIEW RETURNED	06-Jun-2014

- The reviewer completed the checklist but made no further comments.

VERSION 2 – AUTHOR RESPONSE

Reviewer: Dr. Andrea Corsonello: No further comments.
Response – Thank you.

Reviewer: Dr. Parker Magin
Response – ‘optimal’ edited to ‘key drug’ in abstract tracked change copy page 2 line 7

Reviewer: Dr. Colin McCowan
1. Page 5 line 52. Remove "of".
Response – deleted tracked change copy page 5 line 52

2. Page 7 l 6-7. I did not understand what the authors meant with this sentence around capturing morbidity outside the study conditions.
Response – edited to “The index ‘alone’ group would also enable the capture of the other morbidity that was outside of the study selected conditions ones within the study” page 7 line 8

3. P9 line 25 "top 20% deprivation" is ambiguous - is this the most deprived or most affluent quintile?
Response – edited to “top 20% most deprivation deprived status” page 7 line 8

4. P9 L55 Should "multi-group" read "multi-drug"?
Response – edited page 9 line 26

5. P11 l8 "or the non-vascular" should be "or non-vascular"
Response – edited page 11 line 7

6. P11 l52 replace "has" with "have"
Response – edited page 11 line 52

7. P11 L54 I found the use of "outcome of analgesia" confusing
Response – edited to “study definition of analgesia” page 11 line 53