PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Unintended discontinuation of medication following hospitalisation: a retrospective cohort study
AUTHORS	Redmond, Patrick; McDowell, Ronald; Grimes, Tamasine C.; Boland, Fiona; McDonnell, Ronan; Hughes, Carmel; Fahey, Tom

VERSION 1 - REVIEW

REVIEWER	Tao He San Francisco State University USA
REVIEW RETURNED	01-Jul-2018

GENERAL COMMENTS	Very interesting study. But the methods part could be more clearly written with more details. For example, page 10, lines 22-25, the author didn't mention the specific "multilevel multivariable model" were fitted. The statements were too general.

REVIEWER	Professor Derek Bell Imperial College London, UK
REVIEW RETURNED	20-Jul-2018

GENERAL COMMENTS	Polypharmacy is a major problem in this group of patients leading to harm. Medicine reconciliation is a recommended approach which includes discontinuation of medication. These concepts should be explored in the introduction and discussion. The authors assume that discontinuation of these drugs is unlikely and unintended but do not explain how this was ascertained although it is implied in the title The drug classes used are in fact broad for example antithrombotics - this group of drugs is also associated with measurable harm which varies considerably between say aspirin and warfarin. If the authors reviewed reasons (i.e. a form of medicine reconciliation then their approach may be valid but this must be stated) The time frame for enrolment could be expressed more clearly in a diagram between the two groups. The objectives of the study and conclusions should be much clearer.

REVIEWER	Martin Beyer, MSocSc Goethe Univ. Frankfurt Institute of General Practice D-60590 Frankfurt Germany
REVIEW RETURNED	06-Aug-2018

| GENERAL COMMENTS | I congratulate the authors for their submission - it is clearly conceived and written.

I have no major concerns.

In many health systems, hospital stays are a major source of disruptions in pharmacotherapy, mainly enforced by communication barriers. The authors could (or should) admit, that their setting was very favourable: EHRs in the primary care setting and electronical access to hospital discharge reports. That is not very common in European (or overseas) health systems. However, in their setting, they find points to improve (lack of hospital discharge medication plans, and a documented medication reconcilliation at discharge). So the discontinuation rates reported are seemingly low. (A minor remark: of course, GP prescription notices may very markedly from that, what patients are really fillig in). So their data are very optimistic. The authors shed some light by comparing private patients.

In my own country, Germany, the things are much more complcated: involving a lack of common electronic communication. A detail would be interesting: do the hospital physicians and the GPs use the same formularies? In Germany, in hospitals are special 'house lists', differing from the formulary (or plural: depending on the insurance fund). Therefore, all patients are switched from an 'ambulatory list' of agents to the 'hospital list' and re-stored after discharge: a major source of disruptions. (See the papers of Wolfgang Himmel et. al.)

The paper should be accepted. |

VERSION 1 – AUTHOR RESPONSE

Reviewers

Reviewer: 1

"Very interesting study. But the methods part could be more clearly written with more details. For example, page 10, lines 22-25, the author didn't mention the specific "multilevel multivariable model" were fitted. The statements were too general."

Response 3

Additional detail has now been provided on the analytical model employed. (Page 10)

Reviewer: 2

"Polypharmacy is a major problem in this group of patients leading to harm. Medicine reconciliation is a recommended approach which includes discontinuation of medication. These concepts should be explored in the introduction and discussion. "

Response 4

Additional background, rationale and discussion points (including reference to medication reconciliation) are now provided in the introduction and discussion. (Page 5 & 18)

"The authors assume that discontinuation of these drugs is unlikely and unintended but do not explain how this was ascertained although it is implied in the title."

Response 5

The reviewer is correct. The narrow range of medications studied, along with the strong evidence base for their continued usage, are detailed in the manuscript as the basis for the assumption that they are likely to be unintended. Nevertheless, the limitations section acknowledges that without individual chart review, this is only an assumption. (Page 18)

"The drug classes used are in fact broad for example antithrombotics - this group of drugs is also associated with measurable harm which varies considerably between say aspirin and warfarin. If the authors reviewed reasons (i.e. a form of medicine reconciliation, then their approach may be valid, but this must be stated)"

Response 6

Thank you. In the updated limitations section of the manuscript, we have acknowledged the broad categorisation of medications (especially antithrombotics) and the loss of nuances between different classes. Unfortunately, the second sentence of this critique is unclear. We have performed some speculative examination of the differences between different hospitals (and possibly their individual reconciliation efforts). This may be subject to additional risk of bias and is beyond the original tight scope of the study and therefore was deemed not appropriate to present here. (Page 18)

"The time frame for enrolment could be expressed more clearly in a diagram between the two groups.

The objectives of the study and conclusions should be much clearer."

Response 7

The required timeframe for enrolment was the same for the two groups (see Figure 2). Additional background, rationale and discussion points (including reference to medication reconciliation) are now provided in the introduction and discussion. (Page 5 & 18)

Reviewer: 3

"In many health systems, hospital stays are a major source of disruptions in pharmacotherapy, mainly enforced by communication barriers. The authors could (or should) admit, that their setting was very favourable: EHRs in the primary care setting and electronic access to hospital discharge reports. That is not very common in European (or overseas) health systems. However, in their setting, they find points to improve (lack of hospital discharge medication plans, and a documented medication reconciliation at discharge). So, the discontinuation rates reported are seemingly low. (A minor

remark: of course, GP prescription notices may very markedly from that, what patients are really filling in). So, their data are very optimistic. The authors shed some light by comparing private patients."

Response 8

The external validity of this study's findings are open to discussion (in particular given the varied availability of primary care EHRs) and is now acknowledged in the limitations section. In addition, it is underlined that this study examines GP prescribing data and not pharmacy dispensing data ("What patients are really filling in"). Nevertheless, we believe these findings are important as this pharmacoepidemiology data is rarely discussed and is an essential component of GP clinical decision-making when prescribing. (Page 18)

"In my own country, Germany, the things are much more complicated: involving a lack of common electronic communication. A detail would be interesting: do the hospital physicians and the GPs use the same formularies? In Germany, in hospitals are special 'house lists', differing from the formulary (or plural: depending on the insurance fund). Therefore, all patients are switched from an 'ambulatory list' of agents to the 'hospital list' and re-stored after discharge: a major source of disruptions. (See the papers of Wolfgang Himmel et. al.)"

Response 9

Hospital formularies are also a feature of the health system examined here. However, the study's methodology accounted for this by allowing for changes within Anatomic Therapeutic Chemical (ATC) classification groups within patients. (e.g. patient switched from one brand of proton pump inhibitor to another). (Page 9)

VERSION 2 – REVIEW

REVIEWER	Derek Bell Imperial College London, UK
REVIEW RETURNED	30-Oct-2018

GENERAL COMMENTS	The authors have largely re-ordered text and have addressed some of the limitations. They could have minimised the limitations by undertaking sub-analysis = for example lumping antithrombotics which carry different risks and benefits could have been re analysed. My main concern is how will this alter practice and improve patient care the main message appears to be difference between private and public prescribing? This remains an important topic but is a descriptive study and not sure messages are broad enough or transferable for a BMJ open audience

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer 2-

We have conducted a sub-group analysis as requested by Reviewer 2. The attached spreadsheet show that antiplatelets are independently associated with increased discontinuation after hospitalization (adjusted odds ratio 1.30, 95 % CI 1.12, 1.52), whilst for Warfarin and New Oral Anticoagulants, no association between hospitalization and discontinuation was observed (adjusted odds ratio 0.97, 95% CI 0.68, 1.39).

We have added the following to the Results section (Univariable and Multivariable sub-heading):

In a sub-group analysis of the Antithrombotics (B01) drug category, we found that Aspirin is independently associated with increased discontinuation after hospitalization (adjusted odds ratio 1.30, 95 % CI 1.12, 1.52), whilst for Warfarin and New Oral Anticoagulants (NOACs) , no association between hospitalization and discontinuation was observed (adjusted odds ratio 0.97, 95% CI 0.68, 1.39). For both Aspirin and NOACs older age and private patients were independently associated with discontinuation.

We have added the following to the discussion section:

Differential discontinuation within the Antithrombotic (B01) class of drugs was observed in a sub-group analysis, with Aspirin discontinuation associated with hospitalization, whilst for NOACs hospitalization was not associated with discontinuation. These findings need to be treated with caution, as they were not pre-specified and the magnitude of association with Aspirin is relatively modest."

We hope these changes satisfactorily address the reviewers' concerns. Thank you again for your further consideration of this manuscript and we look forward to hearing from you in due course.