







STUDY PROTOCOL

REVISED Prescribing cascades in community-dwelling adults: protocol for a systematic review [version 2; peer review: 2 approved]

Ann Doherty ¹, Frank Moriarty ², Fiona Boland ^{1,3}, Barbara Clyne¹, Tom Fahey ¹, Seán Kennelly^{4,5}, Emma Wallace¹

¹Department of General Practice, RCSI University of Medicine and Health Sciences, Dublin 2, Ireland

²School of Pharmacy and Biomolecular Sciences, RCSI University of Medicine and Health Sciences, Dublin 2, Ireland

³Data Science Centre, RCSI University of Medicine and Health Sciences, Dublin 2, Ireland

⁴Department of Medical Gerontology, Trinity College Dublin, Dublin 2, Ireland

⁵Department of Age-related Healthcare, Tallaght University Hospital, Dublin 24, Ireland

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Abstract

Introduction: Internationally, health systems face the challenge of managing a growing ageing population living with multimorbidity and polypharmacy. Potentially inappropriate prescribing is common among patients with polypharmacy, increasing the risk for adverse drug reactions (ADRs). Several prescribing indicator sets exist to improve prescribing and reduce potentially inappropriate prescribing, but do not address prescribing cascades. Prescribing cascades occur when a medication is prescribed to treat an ADR to another prescribed medication, whether intentionally or unintentionally, and constitute an important area to consider when characterising problematic polypharmacy. This is a protocol for a systematic review examining prescribing cascades in community-dwelling adults.

Methods: The review will be reported adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. A systematic search of Medline (Ovid), EMBASE, PsycINFO, CINAHL and the Cochrane Library will be conducted from inception to March 2021, using a predetermined strategy. Grey literature will be searched using Open Grey, MedNar, Dart Europe, and the Turning Research Into Practice (TRIP) databases. No restrictions will be placed on language or publication year. Inclusion criteria are: population - community-dwelling adults (≥ 18 years); risk - prescription medication with the potential to cause side effects; outcomes - initiation of a new medicine to 'treat' or reduce the risk of experiencing an ADR. Prospective and retrospective cohort studies, case control and case series studies will be included. Two reviewers will independently screen titles and abstracts; studies meeting inclusion criteria will undergo independent full-text screening by two reviewers. A

Open Peer Review

Reviewer Status  

Invited Reviewers

1

2

version 2

(revision)

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report



version 1

13 Jul 2021



report



report

1. **Naghm J. Ailabouni** , University of South Australia, UniSA, Adelaide, Australia

2. **Rachel D. Savage**, Women's College Hospital, Toronto, Canada

Any reports and responses or comments on the article can be found at the end of the article.

narrative synthesis will be conducted. Study quality will be independently assessed using the relevant Joanna Briggs Institute Critical Appraisal Checklist.

Discussion: This systematic review will identify examples of prescribing cascades for community-dwelling adults and contribute to developing an evidence base regarding such cascades.

Registration: PROSPERO [[CRD42021243163](https://doi.org/10.1186/1745-6215-31-03), 31/03/2021].

Keywords

systematic review, protocol, prescribing cascades, adverse drug reactions, polypharmacy

Corresponding author: Ann Doherty (anndoherty@rcsi.ie)

Author roles: **Doherty A:** Methodology, Writing – Original Draft Preparation; **Moriarty F:** Funding Acquisition, Methodology, Writing – Review & Editing; **Boland F:** Writing – Review & Editing; **Clyne B:** Methodology, Writing – Review & Editing; **Fahey T:** Funding Acquisition, Methodology, Writing – Review & Editing; **Kennelly S:** Writing – Review & Editing; **Wallace E:** Conceptualization, Funding Acquisition, Methodology, Project Administration, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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REVISED Amendments from Version 1

Following peer review the authors have updated this manuscript to incorporate feedback and suggestions provided by the peer reviewers. Specifically, the following changes have been made:

- A definition for potentially inappropriate prescribing included in Introduction paragraph 1 (with citation).
- Revision of Introduction paragraph 2 (with citations).
- Additional citation for calcium channel blocker and loop diuretic prescribing cascade.
- Clarification for exclusion of inpatient samples.
- Exclusion of individuals in nursing homes and residential care in the community
- Rationale for exclusion of over the counter medications (with citations).
- Additional data extraction suggestions including time to prescribing of second subsequent medication; period of time the prescribing cascade has likely existed; details of prescriber who initiated the second prescription; intended duration of prescribing of second subsequent medication; plan to review second subsequent medication; variables considered to modify the association.
- Update to data synthesis strategy with stratification of results by prescribing cascade intent.
- Additional context in Discussion section for challenges faced by GPs when prescribing and deprescribing for multimorbid patients (with citation).
- Updated link to extended data (where extended data has been updated).
- Reference list updated with additional citations included.

Any further responses from the reviewers can be found at the end of the article

Abbreviations

ADR: adverse drug reaction; ATC: Anatomical Therapeutic Chemical; MeSH: Medical Subject Headings; NSAID: non-steroidal anti-inflammatory drug; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols; STOPP: Screening Tool for Potentially Inappropriate Prescriptions; TRIP: Turning Research Into Practice; WHO: World Health Organisation.

Introduction

Caring for older people with multiple chronic medical conditions, known as multimorbidity, is now the greatest challenge faced by health systems internationally. However, to date the vast majority of research and clinical guidelines have focused on single diseases, whereas in reality most patients have multimorbidity, necessitating multiple treatments¹. Treatment burden for older people has increased substantially. In Ireland, over 60% of those aged ≥ 65 years are taking five or more prescribed medications (known as polypharmacy) and 20% are taking 10 or more². Medications provide many therapeutic

benefits but these must be balanced against the potential for patient harm. Potentially inappropriate medications are those where the potential for harm outweighs the possible benefit for the patient³. Potentially inappropriate prescribing is common among older adults with polypharmacy and increases the risk for adverse drug reactions (ADRs)⁴.

However, the challenges posed by multimorbidity, polypharmacy and potentially inappropriate prescribing are not restricted to older adults alone and can affect people of any age¹. Multimorbidity has consistently been shown to be associated with increasing age^{5,6}. Nevertheless multimorbidity has also been shown to occur some 10–15 years earlier for those people living in socioeconomic deprivation than for those living in more affluent areas⁷. A higher prevalence of multimorbidity among younger adults is likely to increase the risk for inappropriate prescribing and ADRs among those under 65 years of age also.

While medication counts are the greatest predictor of medication-related harm, simple counts of medicines cannot account for clinical appropriateness^{8–11}. Several prescribing indicators sets have been developed to characterise overall prescribing quality, including explicit prescribing indicator sets such as the Screening Tool for Potentially Inappropriate Prescriptions (STOPP) and Beers criteria, as well as implicit measures such as the Medication Appropriateness Index^{12–14}.

However, much less is known about other causes of problematic polypharmacy such as prescribing cascades, which are not captured in existing explicit or implicit prescribing indicators. A prescribing cascade can occur when a prescribed medication causes an ADR^{15–17}. If the ADR is misinterpreted as a new medical condition and results in the subsequent prescription of another medication, an unintentional prescribing cascade occurs¹⁸. An example of an unintentional prescribing cascade is the prescribing of a loop diuretic to treat lower extremity oedema caused by calcium channel blockers^{19–21}. Intentional prescribing cascades occur when the ADR is recognised and attributed to the first medication and a subsequent medication is intentionally prescribed to combat this ADR or is prescribed at the same time as the first medication in order to prevent it¹⁸. An example of an intentional prescribing cascade is the prescribing of a proton pump inhibitor (PPI) to minimise the gastrointestinal effects of non-steroidal anti-inflammatory drugs (NSAIDs).

Prescribing cascades may occur at any age but may be more prevalent among older adults. ADRs can be difficult to recognize in older people as they often present with nonspecific symptoms, such as falls, fatigue or constipation, all of which have several potential causes²². Therefore, it can be difficult to recognize whether a new symptom is due to an ADR in an older person with multimorbidity or because of other underlying medical conditions. Failure to recognise an ADR may then result in a prescribing cascade, thus inadvertently continuing the patient's exposure to the culprit medication causing them harm, and additional potential risk from the newly prescribed medication¹⁵.

Prescribing cascades may also be further dichotomised as either appropriate (benefits outweigh risks) or problematic (risks outweigh benefits)¹⁸. Central to any assessment of the appropriateness of the cascade is the inclusion of the patient within the assessment, with particular consideration given to whether the initiation of the cascade aligns with the patient's goals and their awareness of the potential long-term risks of the cascade¹⁸.

Nevertheless, prescribing cascades are under-researched as highlighted by a previous scoping review where only 10 original investigations and seven case reports of prescribing cascades were identified²³. This scoping review adopted a broad perspective and sought to systematically describe the resources available to prevent, detect and reverse prescribing cascades. However, studies that did not report a strategy to prevent, identify or reverse a prescribing cascade were excluded from the review. In their review, Brath and colleagues argue that it is likely that some clinically relevant prescribing cascades have yet to be identified or characterised²³. The review authors found that the majority of included studies were published within the last two years of their search period (2015–2017), in spite of the phenomenon first being described more than 20 years ago. This current systematic review will build upon the work of this earlier scoping review and aims to identify and collate an exhaustive list of published prescribing cascades specifically in community-dwelling adults. Specifically, this study seeks to answer the following question: Which medications result in prescribing cascades experienced by community-dwelling adults?

Methods

The systematic review protocol has been prepared in line with Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P) guidance²⁴ and has been registered in PROSPERO [CRD42021243163]. In the event that protocol amendments are necessitated, a description of the change required and the rationale for change will be provided in conjunction with an amendment date. The PRISMA-P checklist is available as extended data²⁵. The systematic review will be reported as per the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines²⁶.

Eligibility criteria

Participants/population. Inclusion criteria: Community-dwelling adults (≥ 18 years).

Exclusion criteria: Those under 18 years, those living in nursing homes and residential care in the community, or where study samples are drawn from hospital inpatients or those attending hospital Emergency Departments (EDs).

Risk. The risk of interest will be the prescription of any medication which has the potential to cause a side effect that results in the prescription of further medication. Details of the initial medication prescribed, including the therapeutic indication and, where available, the side effect resulting from the initial medication, will be recorded. Whilst over the counter (OTC) medications constitute an important aspect of the prescribing cascade phenomenon, it is unlikely that details of OTC

medication use will feature in many studies that are likely to be included in the review. For example, prescription sequence symmetry analysis is predominantly conducted on administrative claims data comprised of prescribing dispensing datasets. Data on OTC medication use is often absent from electronic patient records^{27,28}. Medications will be categorised according to the World Health Organisation (WHO) Anatomical Therapeutic Chemical (ATC) classification system. In cases where ATC codes are not reported within the study text, ATC codes will be assigned at the appropriate level e.g. 5th level where the chemical substance name is reported or 4th level where the chemical subgroup is reported etc.

Outcome. Prescribing cascade defined as the initiation of a new medicine to 'treat' an adverse reaction to another medication (unintentional cascade) or to reduce the risk of experiencing an adverse reaction to a medication (intentional cascade).

Types of studies. Prospective and retrospective studies, case control and case series studies will be included. Case reports will be excluded.

Studies identified during full text screening which report on a prescribing cascade will be included irrespective of whether the primary aim of the study was to identify or evaluate a prescribing cascade or not.

Setting. Primary care and community settings including ambulatory care settings.

Search strategy

The following databases will be searched: Medline (Ovid), EMBASE, PsycINFO, CINAHL and the Cochrane Library from inception to March 2021. There is no medical subject heading (MeSH) for prescribing cascades. Databases will be searched using combinations of keywords to capture concepts related to incremental, sequential or cascading prescribing. MeSH terms that relate to ADRs will also be included within the search strategy to capture potential prescribing cascades that have yet to be identified and characterised.

Grey literature will be searched using Open Grey, MedNar, Dart Europe, and the Turning Research Into Practice (TRIP) databases. The search will be supplemented by forward and backward citation searching of retrieved articles. No restrictions will be placed on language or year of publication. The search strategy for MEDLINE (Ovid) is available as extended data and will be adapted for the different databases²⁵. The search strategies will be developed in consultation with a librarian experienced in systematic review searching.

Data management

Search results will be exported to [Endnote X9](#) reference management system. Following this, [Covidence](#) will be used to screen abstracts according to inclusion and exclusion criteria and manage selected articles. Data extraction will be conducted in Microsoft Excel using a standardised proforma (available as extended data)²⁵.

Study selection

Titles and abstracts will be independently screened by two reviewers (AD and EW) to identify studies that potentially meet inclusion criteria and to remove ineligible and duplicate titles. Studies that do not meet inclusion criteria will be excluded. Where it is unclear whether a study meets the inclusion criteria it will be selected for full text review. Disagreements will be managed by consensus or via a third reviewer where necessary. Additional data will be sought from authors where necessary. A PRISMA flow diagram will be used to indicate the flow of information through the different phases of the systematic review.

Data extraction

Data will be extracted by two independent reviewers (AD and EW) using a standardised data proforma²⁵ on;

- Author and year
- Study setting
- Study population
- Type of study
- Outcome (prescribing cascade)
 - How outcome was measured e.g. patient self-report, routine data etc.
 - Details of the initial medication(s) prescribed (medication class or individual medication including ATC code) and how recorded (e.g. dispensed medication, prescribed medication etc.)
 - Details of the medical condition(s) for which the initial medication(s) was prescribed, or a priori cohort selection, where appropriate
 - Type of adverse reaction(s), where reported (e.g. symptoms or diagnoses resulting in prescription of subsequent medication)
 - Details of new medication(s) prescribed (medication class or individual medication including ATC code)
 - Time to prescribing of the second subsequent medication
 - Period of time the prescribing cascade has likely existed
 - Details of the prescriber who initiated the second prescription (e.g. GP, specialist, other healthcare professional etc.), where available
 - Intended duration of prescribing of the second subsequent medication
 - Plan to review the second subsequent medication (e.g. deprescribing etc.), where applicable
 - Where relevant, frequencies/percentages of participants prescribed new medications
- Contextual and systems-based factors which may influence prescribing (where available) e.g. demographics, polypharmacy, inappropriate prescribing, recent hospitalisation etc.
- Type of statistical analysis, where applicable (e.g. prescription sequence symmetry analysis, survival analysis etc.)
- Confounders accounted for in the analysis (e.g. age, gender, deprivation, other medications, comorbidity, frailty etc.)
- Quantitative measure of association between initial medication prescription and ADR occurrence and new medication prescription, where reported, such as the adjusted sequence ratio (ASR) for prescription sequence symmetry analysis^{20,29}
- Variables considered to modify the association/effect e.g. sex, gender etc.

Quality assessment

Studies that meet inclusion criteria will be included, irrespective of quality. Methodological quality assessment of included studies will be independently performed by two reviewers using the relevant Joanna Briggs Institute Critical Appraisal Checklist, dependent on study type³⁰.

Strategy for data synthesis

We will narratively summarise the following for each prescribing cascade under the following headings;

- Initial medication(s) prescribed to patient (medication class or individual medication including ATC code)
- Subsequent adverse reaction(s) (symptom(s) or new diagnoses)
- New medication(s) prescribed (medication class or individual medication including ATC code)
- Intentional and unintentional cascades (stratification by intent)
- Study population demographics
- Methodological approach to analysis (if appropriate)
- Clinical importance of prescribing cascade (potential risk to patient)
- Hypothesis generation data (case series)

Study status

The search strategy for this study was developed in February 2021 with searches conducted in March 2021. Title and abstract screening commenced in April 2021, with full text screening expected to be completed by July 2021.

Discussion

Prescribing cascades are a contributor to problematic polypharmacy but are not captured within the numerous prescribing indicator sets aimed at reducing the use of inappropriate medications. Known prescribing cascades include those resulting from commonly used medications such as anti-hypertensives, NSAIDs and cholinesterase inhibitors^{19,20,31,32}. Calcium channel blockers, particularly dihydropyridine calcium channel blockers, have been shown to result in a prescribing cascade whereby the resultant lower extremity oedema is treated with loop diuretics^{19,20}. A dry cough is a common side effect of ACE inhibitors and has been shown to result in the

prescription of a cough suppressant and antibiotics³¹. Cholinesterase inhibitors prescribed for older adults with dementia may precipitate urinary incontinence which may be interpreted by the clinician as part of the natural progression of dementia, resulting in the inappropriate prescribing of anticholinergic medications³². In some instances, this prescribing cascade may be considered appropriate if the individual experiences a noticeable benefit in cognitive and functional status from the cholinesterase inhibitor¹⁸. Prescribing cascades may also occur intentionally, for example the prescribing of a PPI to minimise the gastrointestinal effects of NSAIDs.

Multimorbidity and resultant polypharmacy increases the risk of experiencing medication-induced injury. Prescribers, particularly GPs who are responsible for providing ongoing care, face many challenges when prescribing for older adults with multimorbidity. Single disease guidelines often fail to account for how to optimise prescribing for older adults living with multimorbidity. When faced with a hypothetical patient case study GP opinions and awareness on deprescribing of preventative and symptomatic medications was found to vary greatly³³. The influence of other prescriber's opinions was a particular barrier that was identified to deprescribing³³. Identifying medications that result in prescribing cascades will support clinicians to optimise their prescribing to benefit patient care. This systematic review will collate all available information pertaining to prescribing cascades that commonly occur in community dwelling adults and will thus contribute to developing an evidence base for this topic. In addition, an evaluation of the relative likelihood of various prescribing cascades, and their clinical importance, may help to prioritise cascades for attention or intervention. The identification of the ADRs most often implicated in prescribing cascades may guide prescribers to intervene to avert unintentional prescribing cascades in the future. Examining the study designs and analyses used to identify prescribing cascades may have implications for the design of future studies which seek to identify new prescribing cascades. It is intended that this systematic review

will form part of a project which will provide GPs with a tool that they can use to support their prescribing decisions during multimorbidity consultations.

Data availability

Underlying data

No underlying data are associated with this article.

Extended data

Open Science Framework: Prescribing cascades in community-dwelling people: protocol for a systematic review. Extended Data. <https://doi.org/10.17605/OSF.IO/JCZ3925>.

This project contains the following extended data:

- Data extraction proforma.xlsx (Excel proforma document with all headings under which study characteristics will be extracted)
- Medline (Ovid) Search Strategy.pdf (The combination of keywords and MeSH terms that will be used to search Medline and which will be adapted to other databases)

Reporting guidelines

Open Science Framework: PRISMA-P checklist for "Prescribing cascades in community-dwelling people: protocol for a systematic review". <https://doi.org/10.17605/OSF.IO/JCZ3925>.

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public Domain Dedication).

Acknowledgments

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Open Peer Review

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Reviewer Report 20 October 2021

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Naghm J. Ailabouni 

Clinical and Health Sciences, Quality Use of Medicines and Pharmacy Research Centre (QUMPRC), University of South Australia, UniSA, Adelaide, SA, Australia

Thank you for addressing my previous comments. I am satisfied with the changes the authors have made.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Geriatric pharmacy; deprescribing; multimorbidity

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 17 August 2021

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Rachel D. Savage

Women's College Research Institute, Women's College Hospital, Toronto, ON, Canada

This is a well-written systematic review protocol on a worthwhile topic – prescribing cascades. Results have clear implications (i.e., the potential to support deprescribing efforts) that can be

used to reduce medication harms and improve patient safety.

Abstract:

1. In describing your population (“community-dwelling adults (≥ 18 years), including those in residential or nursing homes”), I was surprised that you included individuals residing in residential or nursing homes in your definition of community-dwelling. These populations are typically classified as distinct in scientific literature. Could authors please provide a justification for classifying as such?
2. If the volume of evidence supports it, stratifying results by setting (community vs. nursing home) would be helpful to guide preventive efforts given that contextual factors that contribute to prescribing cascades differ in these settings.

Introduction:

1. “In absolute terms multimorbidity is more prevalent in those aged 65 years or younger”. I agree with reviewer 1 that the statements about multimorbidity in <65 years are misleading given the use of the terms absolute and prevalent/prevalence. Do you mean to say that multimorbidity affects more younger adults because the population size is larger, is the prevalence of multimorbidity higher in younger adults, or both? The prevalence of multimorbidity increases with age; as a result, this statement is inconsistent with established evidence.
2. In your example of an example of an unintentional prescribing cascade (i.e., CCB -> edema -> loop diuretic), I recommend also citing our study: Savage RD *et al.* Evaluation of a Common Prescribing Cascade of Calcium Channel Blockers and Diuretics in Older Adults With Hypertension. *JAMA Intern Med.* 2020 May 1;180(5):643-651¹.

Methods:

1. Eligibility Criteria - What is the rationale for exclusion of those attending hospital Emergency Departments (EDs)? Adults using these services are often considered community-dwelling, and most prescribed medicines would be filled in community pharmacies. Also are EDs not considered ambulatory care settings (see Setting)?
2. Risk – I agree that it would be useful to capture data on the therapeutic indication and the side effect; however, these details are often not available in health administrative data, and so would likely only be available in case studies. While therapeutic indication will not necessarily be available, studies using health administrative data may have selected certain patient cohorts (i.e., those with hypertension, etc) to study a particular cascade – this information would be relevant to capture.
3. Data extraction – This is a comprehensive list but suggest adding – i) time to prescribing of drug B (i.e., time from initiation of drug A to initiation of drug B) – if recorded, this information is helpful to identify a relevant time window that providers can think about/be aware of when the side effect is likely to occur, and ii) variables considered to modify the association/effect, specifically sex and gender. This information again would be helpful in considering whether there are cascades which affect women vs. men, which can help inform targeted interventions.

Discussion:

1. I wonder about the inclusion of intentional prescribing cascades if the intent is to “support clinicians to optimize their prescribing to benefit patient care”? If cascades are started

intentionally, clinicians have likely already carefully considered that benefits outweigh harms. If you wish to have an exhaustive list, I understand the desire to include both intentional and unintentional; however, I agree with reviewer 1 that stratifying results based on intent is helpful, since those that are unintentional are more amenable to deprescribing and improving patient safety.

References

1. Savage R, Visentin J, Bronskill S, Wang X, et al.: Evaluation of a Common Prescribing Cascade of Calcium Channel Blockers and Diuretics in Older Adults With Hypertension. *JAMA Internal Medicine*. 2020; **180** (5). [Publisher Full Text](#)

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Health services research in older adults, including studying prescribing cascades

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 07 Sep 2021

Ann Doherty, RCSI University of Medicine and Health Sciences, Dublin 2, Ireland

Dear Dr Savage,

Thank you for reviewing our submission and for your thoughtful feedback. Below you will find our responses to the specific comments in turn. Text labelled 'Reviewer' are the comments of the reviewer. Text labelled 'Authors' are the responses of the authors.

Reviewer 2: In describing your population (“community-dwelling adults (≥ 18 years), including those in residential or nursing homes”), I was surprised that you included individuals residing in residential or nursing homes in your definition of community-dwelling. These populations are typically classified as distinct in scientific literature. Could authors please provide a justification for classifying as such?

Authors: We accept that those in residential or long-term care are typically classified as a distinct population within the literature. We have updated the inclusion and exclusion criteria of the manuscript to exclude those individuals residing in residential care or nursing homes.

Reviewer 2: If the volume of evidence supports it, stratifying results by setting (community vs. nursing home) would be helpful to guide preventive efforts given that contextual factors that contribute to prescribing cascades differ in these settings.

Authors: We agree with the reviewer that stratification of results by setting would be helpful. However, as we are now excluding individuals in residential care and nursing homes this will not be possible.

Reviewer 2: "In absolute terms multimorbidity is more prevalent in those aged 65 years or younger". I agree with reviewer 1 that the statements about multimorbidity in <65 years are misleading given the use of the terms absolute and prevalent/prevalence. Do you mean to say that multimorbidity affects more younger adults because the population size is larger, is the prevalence of multimorbidity higher in younger adults, or both? The prevalence of multimorbidity increases with age; as a result, this statement is inconsistent with established evidence.

Authors: We understand that our attempt to be concise has raised some queries regarding this section of the text. It was our intention to state that whilst multimorbidity is predominantly associated with older adults, there are often a large number of younger adults living with multimorbidity and who are thus consequently also at risk for polypharmacy and inappropriate prescribing. We have updated this section of text to state the predominant association between multimorbidity as outlined in the response to Reviewer 1 (Dr Ailabouni).

Reviewer 2: In your example of an example of an unintentional prescribing cascade (i.e., CCB -> edema -> loop diuretic), I recommend also citing our study: Savage RD *et al.* Evaluation of a Common Prescribing Cascade of Calcium Channel Blockers and Diuretics in Older Adults With Hypertension. *JAMA Intern Med.* 2020 May 1;180(5):643-651¹.

Authors: We have updated the Introduction section to include the recommended citation, which appears as citation number 20 in the revised manuscript.

Reviewer 2: Eligibility Criteria - What is the rationale for exclusion of those attending hospital Emergency Departments (EDs)? Adults using these services are often considered community-dwelling, and most prescribed medicines would be filled in community pharmacies. Also are EDs not considered ambulatory care settings (see Setting)?

Authors: Our rationale for excluding those attending hospital EDs is that it can be challenging to determine whether subsequent hospital admission occurs at an individual level. As we are excluding hospital based studies we feel that it is also appropriate to exclude studies based in EDs. We do accept the reviewer point that adults using these

services are often considered community-dwelling and will obtain medication in community pharmacies. However, it is difficult to determine whether episodic ED visits lead to prolonged changes in the individuals prescribed medication. Furthermore, we do not consider EDs as ambulatory care settings. We view ambulatory care as clinical care provided on an outpatient basis outside the hospital setting and that does not result in a hospital admission e.g. primary care centres, outpatient clinics, day treatment clinics e.g. dialysis. *Reference:* Medicare Payment Advisory Committee. (2021). Ambulatory Care Settings. Retrieved from <http://www.medpac.gov/research-areas/ambulatory-care-settings>.

Reviewer 2: Risk – I agree that it would be useful to capture data on the therapeutic indication and the side effect; however, these details are often not available in health administrative data, and so would likely only be available in case studies. While therapeutic indication will not necessarily be available, studies using health administrative data may have selected certain patient cohorts (i.e., those with hypertension, etc) to study a particular cascade – this information would be relevant to capture.

Authors: We agree that for many studies it is unlikely that information will be provided on the therapeutic indication and side effect experienced. The examination of specific patient cohorts may well be explicitly stated within administrative studies and as such we have updated our data extraction proforma to include details of any *a priori* cohort selection techniques applied (see also Page 7 of manuscript).

Reviewer 2: Data extraction – This is a comprehensive list but suggest adding – i) time to prescribing of drug B (i.e., time from initiation of drug A to initiation of drug B) – if recorded, this information is helpful to identify a relevant time window that providers can think about/be aware of when the side effect is likely to occur, and ii) variables considered to modify the association/effect, specifically sex and gender. This information again would be helpful in considering whether there are cascades which affect women vs. men, which can help inform targeted interventions.

Authors: We agree that where available the timing to initiation of Drug B is valuable information and have updated the data extraction proforma to capture this information, where available. Furthermore, details of variables that modify the association, particularly sex and gender will now be extracted (Page 7). This is particularly relevant when one considers the associations between female sex, inappropriate prescribing and ADRs. Several studies have found an association between female sex and the likelihood for inappropriate prescribing (see Hill-Taylor *et al.*, 2013 for a review; Ukhanova *et al.*, 2021). An examination of global pharmacovigilance data found that women report more ADRs than men (Watson, Caster, Rochon, den Ruijter, 2019). Biological sex differences including differing muscle mass, body fat, volumes of distribution and metabolic enzymes have the potential to result in altered pharmacokinetic responses to medication. Social and cultural gender differences may also influence health behaviour via differences in help seeking and adherence to behavioural actions. An international research consortium is currently embarking on a project to sex and gender differences in prescribing cascades (iKASCADE project; Sternberg *et al.*, 2021) and so the extraction of data on sex and gender is highly relevant and pertinent. *References:*

Hill-Taylor B, Sketris I, Hayden J, Byrne S, O'Sullivan D, Christie R. Application of the

STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. *J Clin Pharm Ther.* 2013;38(5):360-372. doi:[10.1111/jcpt.12059](https://doi.org/10.1111/jcpt.12059)

Ukhanova M, Markwardt S, Furuno JP, Davis L, Noble BN, Quiñones AR. Are there sex differences in potentially inappropriate prescribing in adults with multimorbidity?. *J Am Geriatr Soc.* 2021;69(8):2163-2175. doi:[10.1111/jgs.17194](https://doi.org/10.1111/jgs.17194)

Watson S, Caster O, Rochon PA, den Ruijter H. Reported adverse drug reactions in women and men: Aggregated evidence from globally collected individual case reports during half a century. *EClinicalMedicine.* 2019;17:100188. Published 2019 Oct 25. doi:[10.1016/j.eclinm.2019.10.001](https://doi.org/10.1016/j.eclinm.2019.10.001)

Sternberg SA, Petrovic M, Onder G, *et al.* Identifying key prescribing cascades in older people (iKASCADE): a transnational initiative on drug safety through a sex and gender lens—rationale and design. *Eur Geriatr Med.* 2021;12(3):475-483. doi:[10.1007/s41999-021-00480-w](https://doi.org/10.1007/s41999-021-00480-w)

Reviewer 2: I wonder about the inclusion of intentional prescribing cascades if the intent is to “support clinicians to optimize their prescribing to benefit patient care”? If cascades are started intentionally, clinicians have likely already carefully considered that benefits outweigh harms. If you wish to have an exhaustive list, I understand the desire to include both intentional and unintentional; however, I agree with reviewer 1 that stratifying results based on intent is helpful, since those that are unintentional are more amenable to deprescribing and improving patient safety.

Authors: We agree that intentional cascades should follow careful consideration by the prescriber on the potential harms and benefits. McCarthy, Visentin and Rochon (2019) note that appropriate prescribing cascades are always intentional. Nevertheless, even those prescribing cascades which are appropriate at the time of initiation have the potential to become problematic or inappropriate over time. The failure to reassess the cascade within an appropriate time frame may result in the continuation of a once appropriate intentional cascade which has subsequently become a problematic one. In order to expand on these nuances we feel it is important to collate all clinically relevant prescribing cascades. We agree that stratifying the results by intent will help to demarcate those cascades where deprescribing initiatives can be targeted from those intentional cascades which require a reassessment in the future so as to ensure their appropriateness.

References: McCarthy LM, Visentin JD, Rochon PA. Assessing the Scope and Appropriateness of Prescribing Cascades. *J Am Geriatr Soc.* 2019;67(5):1023-1026. doi:[10.1111/jgs.15800](https://doi.org/10.1111/jgs.15800)

Competing Interests: No competing interests were disclosed.

Reviewer Report 09 August 2021

<https://doi.org/10.21956/hrbopenres.14533.r29875>

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Nagham J. Ailabouni 

Clinical and Health Sciences, Quality Use of Medicines and Pharmacy Research Centre (QUMPRC), University of South Australia, UniSA, Adelaide, SA, Australia

Thank you for the opportunity to read your work. This is interesting and worthwhile research regarding a topic that is underreported. The protocol is written well and is comprehensive. The planned systematic review addresses a pertinent gap and will hopefully give researchers and clinicians who care for people living with multimorbidity a greater appreciation for the negative health impacts of prescribing cascades. I hope you find my minor comments and suggestions useful and beneficial.

Method:

- Consider changing the inclusion criteria from “prescribed medication with potential to cause a side effect” to “any medication”. This is because even medications that are taken OTC can constitute as an important contributor to prescribing cascades. If the authors believe that details of OTC medications taken will not be captured in studies that are likely to be included in the systematic review, please mention this as a rationale for only considering prescribed medication(s).

Introduction:

- Whilst readers in this field might be well versed with what potentially inappropriate prescribing (PIP) is, it might be useful to clarify the definition of PIP in the first paragraph. So, for example, when “Medications provide many therapeutic benefits but these must be balanced against the potential for patient harm.” is mentioned, perhaps add that potentially inappropriate medications are those with greater potential harm than possible benefit.

Introduction, paragraph 2, line 3:

- “multimorbidity is prevalent in those aged 65 years or older? (not younger).” The reference cited here is a cross-sectional study that found that multimorbidity in absolute terms is more prevalent in younger than 65 years. However, I still believe the first sentence should be that generally speaking multimorbidity worldwide increases with increasing age and is more prevalent as aging occurs. Then if the authors wish to include this specific point, they could specifically mention that this particular study found this finding (i.e. multimorbidity is higher in those younger than 65 years particularly if they have a lower socioeconomic status or deprivation score).

Data extraction:

- Another confounder to potentially look out for, is frailty. Additionally, if frailty is not reported or taken into account in included studies, this would be an interesting finding to be discussed as frailty is often a confounder that is unmeasured and unaccounted for and frailty could be associated with the occurrence of prescribing cascades.
- Where “adjusted sequence ratio (ASR) for prescription” and “sequence symmetry analysis” are mentioned, I recommend adding some example references that used these methods.

Strategy for data synthesis:

- Good list of items to be extracted. Also, it might be interested the consider narratively describing the following:

1) The period of time the prescribing cascade has likely existed. In other words, how long has the second subsequent medication been prescribed or taken by the individual?

2) The prescriber who initiated the prescription of the second medication (if this information is available). This is because there may be differences in rates of new medications prescribed by specialists vs GPs vs other healthcare professionals.

3) Authors might have already considered this but grouping the identified prescribing cascades as either "intentional" or "unintentional" could be interesting to readers.

4) Details for how long the second medication is intended to be prescribed for. So, in other words, when the second medication used to treat the ADR was prescribed, did the prescriber or the individual's clinical notes mention the likely duration this medication is ought to be prescribed and if there is a plan to eventually review and consider stopping or reducing (i.e. deprescribing) this medication?

Discussion:

- The authors have done a good job summarising issues of prescribing in the introduction of the protocol. It may also be helpful to also briefly highlight that prescribers, specifically GPs, often face challenges prescribing for people living with multimorbidity (recommend citing this article of mine or a similar article: Ailabouni *et al.* (2016)¹). This will further support what the authors plan to do with the findings of this systematic review outlined in the discussion such as for example developing a decision tool to support GPs/prescribers making prescribing decisions for people with multimorbidity.

References

1. Ailabouni NJ, Nishtala PS, Mangin D, Tordoff JM: General practitioners' insight into deprescribing for the multimorbid older individual: a qualitative study. *Int J Clin Pract.* 2016; **70** (3): 261-76
[PubMed Abstract](#) | [Publisher Full Text](#)

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Geriatric pharmacy; deprescribing; multimorbidity

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 07 Sep 2021

Ann Doherty, RCSI University of Medicine and Health Sciences, Dublin 2, Ireland

Dear Dr Ailabouni,

Thank you for reviewing our submission and for your thoughtful feedback. Below you will find our responses to the specific comments in turn. Text labelled 'Reviewer' are the comments of the reviewer. Text labelled 'Authors' are the responses of the authors.

Reviewer: Consider changing the inclusion criteria from “prescribed medication with potential to cause a side effect” to “any medication”. This is because even medications that are taken OTC can constitute as an important contributor to prescribing cascades. If the authors believe that details of OTC medications taken will not be captured in studies that are likely to be included in the systematic review, please mention this as a rationale for only considering prescribed medication(s).

Authors: Indeed, we agree that over the counter (OTC) medications constitute an important aspect of the prescribing cascade phenomenon. We opted to consider only prescribed medication(s) as we believe that a large proportion of studies likely to be included in the review will comprise of prescription sequence symmetry analysis of administrative claims data, comprised of prescription dispensing datasets. Such datasets are not likely to provide information on OTC medication use. A Dutch study comparing patient self-report medication use with data contained in the pharmacy electronic patient record found that data on non-prescription medication use was absent for 44% of study participants (Floor-Schreudering *et al.*, 2013). Similarly, pharmacist medication reconciliation and concurrent electronic medication review in a primary care clinic found a high proportion of patients (74%) had at least one discrepancy between self-reported medication use and the electronic record, with the use of OTC medication the most common type of discrepancy (Stewart & Lynch, 2012). The manuscript has been updated (Page 5- Eligibility criteria section) to explicitly mention the rationale for examining prescribed medication only.

References: Floor-Schreudering A, Heringa M, Buurma H, Bouvy ML, De Smet PA. Missed drug therapy alerts as a consequence of incomplete electronic patient records in Dutch community pharmacies. *Ann Pharmacother.* 2013;47(10):1272-1279. doi:

[10.1177/1060028013501992](https://doi.org/10.1177/1060028013501992)

Stewart AL, Lynch KJ. Identifying discrepancies in electronic medical records through pharmacist medication reconciliation. *J Am Pharm Assoc (2003).* 2012;52(1):59-66. doi:

[10.1331/JAPhA.2012.10123](https://doi.org/10.1331/JAPhA.2012.10123)

Reviewer: Whilst readers in this field might be well versed with what potentially inappropriate prescribing (PIP) is, it might be useful to clarify the definition of PIP in the first paragraph. So, for example, when “Medications provide many therapeutic benefits but these must be balanced against the potential for patient harm.” is mentioned, perhaps add that potentially inappropriate medications are those with greater potential harm than possible benefit.

Authors: We have included a sentence (Page 4, paragraph 1) as follows: “Potentially inappropriate medications are those where the potential for harm outweighs the possible

benefit for the patient”.

Reference: Beers MH, Ouslander JG, Rollinger I, Reuben DB, Brooks J, Beck JC. Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine. *Arch Intern Med*. 1991;151(9):1825-1832. PMID: [1888249](https://pubmed.ncbi.nlm.nih.gov/1888249/)

Reviewer: Introduction, paragraph 2, line 3:

“multimorbidity is prevalent in those aged 65 years or older? (not younger).” The reference cited here is a cross-sectional study that found that multimorbidity in absolute terms is more prevalent in younger than 65 years. However, I still believe the first sentence should be that generally speaking multimorbidity worldwide increases with increasing age and is more prevalent as aging occurs. Then if the authors wish to include this specific point, they could specifically mention that this particular study found this finding (i.e. multimorbidity is higher in those younger than 65 years particularly if they have a lower socioeconomic status or deprivation score).

Authors: We agree that this section of text requires clarification. It was our intention to state that whilst the prevalence of multimorbidity increases with increasing age, it is important not to disregard the impact of multimorbidity in younger age groups (younger than 65 years) particularly for those who experience deprivation. Hence why we are examining prescribing cascades in all adults and not those aged 65 years and older. This section of text has been updated to state the predominant association between multimorbidity and increasing age (with appropriate citations). We also note that multimorbidity can also present at an earlier age for those living in socioeconomic deprivation.

References: Salisbury C, Johnson L, Purdy S, Valderas JM, Montgomery AA. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract*. 2011;61(582):e12-e21. doi:[10.3399/bjgp11X548929](https://doi.org/10.3399/bjgp11X548929)

Raffaele Palladino, John Tayu Lee, Mark Ashworth, Maria Triassi, Christopher Millett, Associations between multimorbidity, healthcare utilisation and health status: evidence from 16 European countries, *Age and Ageing*, Volume 45, Issue 3, May 2016, Pages 431–435, <https://doi.org/10.1093/ageing/afw044>

Reviewer: Data extraction:

Another confounder to potentially look out for, is frailty. Additionally, if frailty is not reported or taken into account in included studies, this would be an interesting finding to be discussed as frailty is often a confounder that is unmeasured and unaccounted for and frailty could be associated with the occurrence of prescribing cascades.

Author response: We agree and thank the reviewer for this suggestions. We have updated our data extraction form to consider whether frailty is reported or not within the study under the heading “Confounders accounted for in the analysis”. The “Data Extraction” section (Page 7) of the manuscript has also been updated to reflect this.

Reviewer 1: Where "adjusted sequence ratio (ASR) for prescription" and "sequence symmetry analysis" are mentioned, I recommend adding some example references that used these methods.

Authors: We agree that some example references will aid the reader to understand these methods and have thus included two examples that have used this methodology (Data extraction section, Page 7).

Reviewer: Strategy for data synthesis:

Good list of items to be extracted. Also, it might be interesting to consider narratively describing the following:

- 1) The period of time the prescribing cascade has likely existed. In other words, how long has the second subsequent medication been prescribed or taken by the individual?
- 2) The prescriber who initiated the prescription of the second medication (if this information is available). This is because there may be differences in rates of new medications prescribed by specialists vs GPs vs other healthcare professionals.
- 3) Authors might have already considered this but grouping the identified prescribing cascades as either “intentional” or “unintentional” could be interesting to readers.
- 4) Details for how long the second medication is intended to be prescribed for. So, in other words, when the second medication used to treat the ADR was prescribed, did the prescriber or the individual's clinical notes mention the likely duration this medication is ought to be prescribed and if there is a plan to eventually review and consider stopping or reducing (i.e. deprescribing) this medication?

Author response: We agree that the inclusion of these additional aspects will strengthen the data synthesis. As such as we have updated the data extraction proforma and Data Extraction section (Page 7) to include: period of time the cascade has likely existed; prescriber who initiated the second medication; duration the second medication was intended to be prescribed for; and plan to review this second medication, where available. We also agree that stratifying the identified cascades by intentionality will be helpful to readers and so we have updated the data synthesis section (Page 8) to explicitly state this.

Reviewer: Discussion: The authors have done a good job summarising issues of prescribing in the introduction of the protocol. It may also be helpful to also briefly highlight that prescribers, specifically GPs, often face challenges prescribing for people living with multimorbidity (recommend citing this article of mine or a similar article: Ailabouni *et al.* (2016)1). This will further support what the authors plan to do with the findings of this systematic review outlined in the discussion such as for example developing a decision tool to support GPs/prescribers making prescribing decisions for people with multimorbidity.

Authors: We agree that the inclusion of further detail on the challenges faced by prescribers when prescribing for those with multimorbidity and have included a brief section on this and included the suggestion citation to provide context for this (Discussion section, paragraph 2).

Competing Interests: No competing interests were disclosed.