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Prescribing for older people with reduced kidney function in primary care – a systematic scoping literature review

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ADMINISTRATIVE INFORMATION

Support - N/A.

Review Stage at time of this submission - Formal screening of search results against eligibility criteria.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 September 2023 and was last updated on 15 September 2023.

INTRODUCTION

Review question / Objective Review area 1. **R**To what extent are older people (≥ 65 years) on drugs and doses not recommended at their level of kidney function in primary care?

Review area 2. What are the risks to the older person in primary care of not following the recommendations for prescribing in reduced kidney function?

Review area 3. Why do prescribers not apply prescribing recommendations in reduced kidney function in primary care?

Review area 4. Have interventions been evaluated to help prescribers in primary care to apply recommendations for use of drugs in reduced kidney function?

Background The majority of medicines are eliminated from the human body through the kidney (1). Whilst the kidney's primary excretion target is hydrophilic drugs, hepatic metabolism often transforms lipophilic medicines into more

hydrophilic molecules to facilitate excretion by the kidneys (2). Although some medications can be actively excreted or metabolised by the kidney, the majority of kidney medication elimination occurs through direct renal filtration. In such cases of medication filtration and elimination, there is a predictable relationship between the glomerular filtration rate (GFR) and medication elimination. It is common therefore for patients with a reduced GFR to be at risk of medication accumulation, which may require such patients to undergo dose adjustment or even cessation of treatment depending on the severity of their reduced kidney function (3).

It has been well established that as part of the process of normal aging there is a variable decline in GFR from the age of 30. This occurs on average at a rate of around 1mL/min/1.73m²/year and is thought to decrease at an accelerated rate after the age of 65 (4). Caution is also advised when prescribing for older people due to complex and unpredictable changes on pharmacodynamics that occur with aging, such as albumin changes

impacting protein-bound drugs, altered medication distribution occurring due to muscle wasting and changes to fat tissue, altered receptor stimulation, decreased homeostatic apparatus, and altered medication efficacy related directly to kidney function (2,5). Despite this, with increasing age it becomes increasingly likely that a person will take regular medication. The 2016 Health Survey for England showed that over 90% of those aged over 75 were taking at least one medication regularly compared to only 19% of those aged 16-24 (6).

Rationale Measuring GFR directly is impractical in the clinical context, so multiple formulae exist to calculate an approximation of the GFR (7). The term estimated GFR (eGFR) is often reserved in practice to signify either the 'Modification of Diet in Renal Disease' (MDRD) equation or the more recent CKD Epidemiology Collaboration (CKD-EPI) equation. These formulae were designed to aid the classification of kidney disease and assessment of risk to the kidney, rather than for use in medication dose decision-making (8). Another formula that estimates kidney function is the Cockcroft-Gault creatinine clearance (CrCl-CG) equation, which is used most commonly in pharmacokinetic studies for medication manufacturing and licencing decisions (9). These equations are known to produce different results with increasing age, with some studies suggesting that CrCl-CG underestimates kidney function by 10% across all older ages, whilst eGFR formulae overestimates kidney function by 29% up to 69% (10). The British National Formulary updated its guidance in 2017, stating that CrCl-CG should be used to estimate kidney function when making drug dosing decisions when dealing with toxic drugs, specific named drugs, and in elderly patients aged over 75 or those at extremes of muscle mass (11). Most primary care workplaces in England receive laboratory results that give an eGFR rather than CrCl-CG, most likely relating to its role in classifying CKD and Acute Kidney Injury, as well as the requirement of CrCl-CG to incorporate patient characteristics that are unknown to the laboratory, such as weight and height (12). Wood et al., 2018 showed that with increasing age, patients in primary care in the north of England have higher odds of having a kidney function estimates that were too low for the medication dose they were prescribed (12). This research also highlighted that for 22% of older people, prescribing decisions would have been different depending on which equation (MDRD Vs CrCl-CG) had been used. Given the importance of prescribing for older people and the evidence that there is a safety concern within primary care current practice in England, this scoping review has been designed to

explore what the size and nature of the evidence base is for prescribing for older people (≥ 65 years) with reduced kidney function in primary care, whether there are gaps in the literature, and what future primary research is needed.

METHODS

Strategy of data synthesis The framework proposed by Arksey and O'Malley (2005), incorporating the Levac et al (2009) recommendations, will be used to conduct and structure this scoping review to provide a rigorous, robust, and reproducible method (13,14). Once initial search plans and criteria had been drafted, advice was sought from the University of Leeds Health Library Services to ensure the search terms and strategies were comprehensive enough to find the relevant literature. This strategy consisted of a 5-step process:

Stage 1 – identify the key areas for review and the research question for each:

Arksey and O'Malley recommend maintaining a wide approach to ensure breadth of coverage, and that parameters can be set once the scope of the field has been assessed (13). The findings from an unpublished prior case-note review by the authors were interrogated using a mind map approach to identify the key areas for review and for each research question. This led to the identification of the following review areas:

1. To what extent are older people (≥ 65 years) on medicines and doses not recommended at their level of kidney function in primary care?
2. What are the risks to the older person in primary care of not following the recommendations for prescribing in reduced kidney function?
3. Why do prescribers not apply prescribing recommendations in reduced kidney function in primary care?
4. Have interventions been evaluated to help prescribers in primary care to apply recommendations for use of drugs in reduced kidney function?

The development of the research questions was an iterative process and only fully defined through the initial literature search.

Stage 2 – identify relevant studies for each key area for review:

The literature for key areas 1, 2, 3, and 4 were identified by database literature searches, searched with an intent to be as comprehensive as possible. For each key area, the review was based on stages defined by Hagell and Bourke Dowling (15).

The database searches were first run on October 2015, covering all past dates of release. They were

then re-run in January 2023 to cover the time-period of October 2015 and December 2022.

Research reviews:

The Cochrane Library database of systematic reviews will be searched to identify any reviews relating to prescribing for older people with reduced kidney function in the 4 key areas. The Database of Abstracts of Reviews of Effects (DARE) will also be checked for existing or ongoing reviews. Research reviews will be searched for in Medline and then highlighted from each database searched.

Database search:

The search for each key area aimed to comprehensively identify relevant studies and will be run on each of the following databases: 'Medline', 'Embase', 'PsychINFO' (for the psychological perspective on healthcare), 'CINAHL' (for a nursing perspective), and 'Web of Science'.

The search terms for each key area were set up using the following categories where appropriate (See appendix 1 for full details of the subject headings, key words, search terms, and synonyms under each category, along with specific differences for each review area search):

- Prescribers (which includes physician as well as the misspelling 'phycisian' as the library expert advised it can find more studies being a term that is frequently misspelled). Non-medical prescribers were included by the use of the term 'prescriber'.

- Prescribing.
- Primary Care.
- Renal impairment.
- Elderly.
- Adverse drug reactions (ADRs).
- Decision support tools.
- Prescriber Behaviour.
- Kidney function Equations/diagnostic tests.
- Additions – English language/reviews/qualitative.

Within each category the synonyms will be searched using 'OR'. The relevant categories will then be used in the searches for each key review area using 'AND'.

Reference organisation:

EndNote X5© will be used to organise and manage the references found for each key area and background to the research.

Terms and electronic databases included in the review.

Eligibility criteria The framework proposed by Arksey and O'Malley (2005), incorporating the Levac et al (2009) recommendations, will be used to conduct and structure this scoping review to provide a rigorous, robust, and reproducible method (13,14). Once initial search plans and criteria had been drafted, advice was sought from

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Reference organisation:

EndNote X5© will be used to organise and manage the references found for each key area and background to the research.

Terms and electronic databases included in the review.

Source of evidence screening and selection

Stage 3 – study selection for each key area for review:

By aiming to keep the search sensitive and comprehensive, specificity can be reduced so that many irrelevant studies are picked up. To eliminate irrelevant studies, inclusion and exclusion criteria were developed and listed under each key area section.

Pre-2015 review:

The resultant list of articles found for each search were initially reviewed by title and abstract. The selected articles were exported to EndNote X5© and then the abstracts reviewed having removed any duplicates. Full text copies were obtained for the studies identified to be included for review. The entire pre-2015 scoping review went through a peer review process during a PHD viva undertaken by Dr Wood.

Post-2015 review:

The resultant list of articles found for each search will be initially reviewed by title and abstract. The selected articles will be exported to EndNote X5©

and then the abstracts reviewed having removed any duplicates. Ten percent of all results will be double screened by a second reviewer. Any disagreements that could not be settled through discussion will be settled by a third reviewer with a final vote.

Full text copies will be obtained for the studies identified by the above process. A final screening process will be undertaken to select papers relevant to the scoping review. Ten percent of all full text copies will be double screened by a second reviewer. Any disagreements that could not be settled through discussion will be settled by a third reviewer with a final vote.

The scoping review protocol should describe the process of source selection for all stages of selection and the procedures used for solving disagreements between reviewers.

Data management Stage 4 – chart the data:

The significance of the included studies will then be considered, and the quality assessed. A data charting form was developed based on the criteria used by Arksey and O'Malley (2005) to collect:

- Author(s), year of publication, study location.
- Intervention type and comparator (if any); duration of intervention.
- Study populations.
- Aims of study.
- Methodology.
- Outcome measures.
- Important results.

The form also listed the 'Critical Appraisals Skills Programme' (CASP) screening questions to aid appraisal. All studies identified for review will be charted. This stage allows further scrutiny as to whether the study fitted the search criteria, or whether the search criteria needed amendment.

The level of evidence for the review area question will also be assessed and the selected literature appraised. The 'Oxford Centre for Evidence-Based Medicine' (OCEBM) Levels of Evidence applicable to the research question will be used to develop a hierarchy of evidence table, adapted for each key review area. Each study will then be assessed for level of evidence and methodological quality using the relevant checklists (CASP, CEEM or the 'Consolidated criteria for REporting Qualitative research' (COREQ)), which will be added to the charting process, and allows ordering of the included studies.

For the pre-2015 charting process, entire pre-2015 scoping review went through a peer review process during a PhD viva undertaken by Dr Wood. For the post-2015 charting process, Ten percent of all data extraction underwent double completion by a second reviewer. Any disagreements that

could not be settled through discussion will be settled by a third reviewer with a final vote.

Reporting results / Analysis of the evidence

Stage 5 – collate, summarise, and report the results: The final literature to be included in each key search area will be assessed and the findings scrutinised. The studies will be categorised and evaluated for common themes and findings to collate and summarise the results of the review.

Presentation of the results

The following chart headings will be used for each review area:

Review area 1:

Principal author

Hierarchy of evidence (based on OCEBM)

Year

Country

Study type

Prospective, cross-sectional, or retrospective

Setting

Participant numbers

Participant type

Outcomes

Methodological concerns from checklist

Review area 2:

Principal author

Hierarchy of evidence (based on OCEBM)

Year

Country

Study type

Setting

Participant numbers

Participant type

Outcomes

Methodological concerns from checklist

Review area 3:

Principal author

Hierarchy of evidence (based on OCEBM)

Year

Country

Study type

Setting

Focus

Participant numbers

Participant type

Outcomes

Methodological concerns from checklist.

Language restriction Only sources written in the English language will be included.

Country(ies) involved This systematic scoping review is being carried out from England; however, it will include reviews published from any country.

Keywords Elderly; Renal impairment; Cockcroft Gault; eGFR; prescribing; safety; Adverse Drug Reaction.

Dissemination plans Early results have been disseminated through a PhD viva. Full results will be disseminated through local presentations, national conferences, and through publication through a respected international scientific journal.

Contributions of each author

Author 1 - Owen Thomas - Final protocol construction; Post-2015 data collection / 1st reviewer; Manuscript construction.

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Author 2 - Sarah Alderson - Study design advisor; Post-2015 data collection final reviewer; Manuscript construction.

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Author 3 - Su Wood - Pre-2015 data collection and review; Post-2015 data collection second reviewer; Manuscript construction.

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References:

1. Brenner G, Stevens C. Chapter 2 - Pharmacokinetics. In: Brenner and Stevens' Pharmacology [Internet]. 5th ed. Elsevier; 2017 [cited 2023 Jun 27]. Available from: <https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780323391665000025>
2. Ponticelli C, Sala G, Glassock RJ. Drug management in the elderly adult with chronic kidney disease: a review for the primary care physician. *Mayo Clin Proc.* 2015 May;90(5):633–45.
3. Craig Brater D. Measurement of renal function during drug development. *Br J Clin Pharmacol.* 2002 Jul;54(1):87–95.
4. Glassock RJ, Winearls C. Ageing and the Glomerular Filtration Rate: Truths and Consequences. *Trans Am Clin Climatol Assoc.* 2009;120:419–28.
5. Ashley C, Dunleavy A. *The Renal Drug Handbook: The Ultimate Prescribing Guide for Renal Practitioners, 5th Edition.* CRC Press; 2018. 1109 p.
6. Moody A, Mindell J, Faulding S. Health Survey for England 2016 - Prescribed medicines [Internet]. Health and Social Care Information Centre; 2017 [cited 2023 Jun 27]. Available from: <http://healthsurvey.hscic.gov.uk/support-guidance/public-health/health-survey-for-england-2016/prescribed-medicines.aspx>
7. Boron WF, Boulpaep EL. Chapter 34 - Glomerular Filtration and Renal Blood Flow. In: *Medical Physiology E-Book.* Elsevier Health Sciences; 2016.
8. Levey AS, Stevens LA, Schmid CH, Zhang Y

-
- (Lucy), Castro AF, Feldman HI, et al. A New Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med.* 2009 May 5;150(9):604–12.
9. Helou R. Should we continue to use the Cockcroft-Gault formula? *Nephron Clin Pract.* 2010;116(3):c172-185; discussion c186.
10. Roberts GW, Ibsen PM, Schiøler CT. Modified diet in renal disease method overestimates renal function in selected elderly patients. *Age Ageing.* 2009 Nov;38(6):698–703.
11. Joint Formulary Committee. Prescribing in renal impairment. In: *British National Formulary (online)* [Internet]. London: BMJ and Pharmaceutical Press; [cited 2023 Jun 27]. Available from: <https://bnf.nice.org.uk/medicines-guidance/prescribing-in-renal-impairment/>
12. Wood S, Petty D, Glidewell L, Raynor DT. Application of prescribing recommendations in older people with reduced kidney function: a cross-sectional study in general practice. *Br J Gen Pract.* 2018 May 1;68(670):e378–87.
13. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol.* 2005 Feb 1;8(1):19–32.
14. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implement Sci.* 2010 Sep 20;5(1):69.
15. Hagell A, Bourke Dowling S. Scoping review of literature on the health and care of mentally disordered offenders [Internet]. York: University of York; 1999 Oct [cited 2023 Jun 27]. Available from: <http://www.york.ac.uk/inst/crd/crdreports.htm>