STUDY PROTOCOL

The effectiveness of integrating clinical pharmacists within general practice to optimise prescribing and health outcomes in primary care patients with polypharmacy: A protocol for a systematic review [version 1; peer review: 1 approved with reservations]

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Abstract

Introduction: Coordinating prescribing for patients with polypharmacy is a challenge for general practitioners. Pharmacists may improve management and outcomes for patients with polypharmacy. This systematic review aims to examine the clinical and cost-effectiveness of pharmacist interventions to optimise prescribing and improve health outcomes in patients with polypharmacy in primary care settings.

Methods: The review will be reported using the PRISMA guidelines. A comprehensive search of 10 databases from inception to present, with no language restrictions will be conducted. Studies will be included where they evaluate the clinical or cost-effectiveness of a clinical pharmacist in primary care on potentially inappropriate prescriptions using validated indicators and number of medicines. Secondary outcomes will include health related quality of life measures, health service utilisation, clinical outcomes and data relating to cost effectiveness. Randomised controlled trials, non-randomised controlled trials, controlled before-after, interrupted-time-series and health economic studies will be eligible for inclusion.

Titles, abstracts and full texts will be screened for inclusion by two reviewers. Data will be extracted using a standard form. Risk of bias in all included studies will be assessed using the Effective Practice and Organisation of Care (EPOC) criteria. Economic studies will be assessed using the Consensus Health Economic Criteria (CHEC) list as per the Cochrane Handbook for critical appraisal of methodological quality. A narrative synthesis will be performed, and the certainty of evidence will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. Where data support quantitative synthesis, a meta-analysis will be performed.
Discussion: This systematic review will give an overview of the effectiveness of pharmacist interventions to improve prescribing and health outcomes in a vulnerable patient group. This will provide evidence to policy makers on strategies involving clinical pharmacists integrated within general practice, to address issues which arise in polypharmacy and multimorbidity.

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Keywords
Systematic review, Polypharmacy, Multimorbidity, Pharmaceutical Services, Pharmacist, Primary Care

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Introduction

Patients with multimorbidity and polypharmacy have complex health needs. Polypharmacy has commonly been defined as being on five or more medications, however recent studies have highlighted the rising prevalence of more significant polypharmacy defined as being on 10 or more medications. Complex polypharmacy increases the risk of potentially inappropriate prescribing (PIP) and treatment burden in this patient cohort. PIP is described as potential sub-optimal prescribing and is typically identified using screening tools such as the Screening Tool of Older People’s Prescriptions (STOPP)-Screening Tool to Alert to Right Treatment (START) criteria, Beers criteria or prescribing appropriateness indices.

Polypharmacy is also associated with adverse drug events, which may create significant cost to both the healthcare system/health service and patients. An Irish study conducted in 2010 found that an estimated 36% of adult patients over the age of 70 had at least one PIP event. This resulted in an additional €45 million in healthcare expenditures.

Integration of clinical pharmacists within general practices may be an effective way to address PIP, and implement deprescribing through medication reviews and address challenges with general practice workload. Evidence suggests that clinical pharmacists improve the quality and safety of prescribing, and that non-dispensing pharmacists integrated into the primary care setting add value to patient-centred clinical pharmacy services. Heterogeneity of outcomes reported in systematic reviews tend to make meta-analysis challenging and thus it is unclear whether such interventions can result in clinically significant improvements in patient outcomes. There is evidence to suggest that clinical pharmacist review of medications and pharmacist-physician collaboration results in cost avoidance in the hospital setting, and that such interventions are cost-effective. However, there is limited evidence to date surrounding the cost-effectiveness of clinical pharmacists integrated within general practice to optimise medications and health outcomes in primary care. Previous systematic reviews cite heterogeneity in terms of role, and duration and frequency of intervention as a limitation. They also focussed on interventions where the clinical pharmacist and general practitioner (GP) were geographically co-located. This systematic review will differ in that it focuses on patients with multimorbidity and polypharmacy, without a focus on specific conditions. It will include studies that involve remote clinical pharmacist and GP integration, provided there is on-going collaboration and clear evidence of working together to improve patient outcomes.

The overall aim of this systematic review is to examine the effectiveness of interventions involving the integration of clinical pharmacists within general practice, to improve prescribing practices and health outcomes in primary care settings. We will also examine the cost-effectiveness of such interventions.

Review questions

What is the effectiveness of interventions integrating clinical pharmacists within general practice on medicines optimisation and health outcomes in adult patients with polypharmacy in comparison to usual care?

Is integrating clinical pharmacists within general practice, to improve medicines optimisation and health outcomes in adult patients with polypharmacy, cost-effective?

Methods

The systematic review will be conducted in line with the PRISMA guidelines. The protocol will be reported in line with the PRISMA-P guidelines.

Eligibility criteria

Participants/population. Patient participants must be adult patients aged 18 years and over in the primary care setting with polypharmacy as defined by study author. Patients will not be considered eligible if they are under the age of 18 or resident in a nursing home. Studies must have a majority of patients (≥80%) identified as having polypharmacy (using any definition). The generally accepted definition is five or more routine medicines.

Clinical pharmacists participating in the intervention must be involved in medicines optimisation roles and integrated physically or remotely as per the definition below, within the primary care setting. The definition of primary care for this review will be; a system which is “integrated, easy to access, health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained and continuous relationship with patients, and practicing in the context of family and community.” Integration will be defined as per the framework adapted from Walshe and Smith. The framework consists of six pillars; organisational, informational, clinical, functional, financial and normative dimensions.

Intervention/exposure. To be eligible for inclusion, studies must involve a clinical pharmacist optimising medication for patients in a primary care setting through a variety of services. Interventions can be targeted at patient or prescriber behaviours. The relationship between pharmacist and GP can be conducted in a co-located setting or remotely where the pharmacist is not in the same geographical location as the GP. The relationship must be continued for the duration of the intervention. This relationship will be defined as a collaborative relationship where “health care professionals assume complementary roles and cooperatively working together, sharing responsibility for problem-solving and making decisions to formulate and carry out plans for patient care.” Contact can be face to face, virtual, by telephone or via an online forum once the contact is in real-time.

‘Once-off’ interventions where the clinical pharmacist does not maintain a relationship with the GP will be excluded. Such interventions will demonstrate a single instance of unidirectional communication of a medication review issue to the GP (e.g. sending a fax or email) with no collaborative follow-up. We will exclude studies with interventions only targeting a single condition unless the intervention addresses all medicines for the patients, not only those medications which are condition specific.
Comparator/control. Usual care in primary care setting.

Types of studies. We will include randomised controlled trials (RCTs), non-randomised controlled trials (nRCTs), controlled before-after (CBA), and interrupted-time-series (ITS) studies using Cochrane Effective Practice and Organisation of Care (EPOC) study design criteria\(^{16}\). Health economic studies including comparative resource use studies and economic evaluations (cost-effectiveness analysis, cost-utility analysis, cost-minimisation analysis and cost-benefit analysis) will also be included.

Setting. Only studies in a primary care setting will be included. Clinical pharmacist interventions in a secondary or tertiary care setting will be excluded.

Outcomes

Main outcomes. Potentially inappropriate or high risk prescriptions (using validated indicators which may include explicit criteria such as STOPP/START\(^2\), Beers criteria\(^1\), or implicit criteria such as the Medicines Appropriateness Index\(^{17}\) and Prescribing Appropriateness Index\(^{18}\)).

Number of medicines.

Additional outcomes.

- Patient reported outcomes measures (PROMs): For example, Health Related Quality of Life measured using standardised questionnaires such as EQ-5D, SF-12, SF-36.
- Adverse events or harms, for example measured using the adverse drug withdrawal reaction scale\(^{19}\).
- Health service utilisation (including GP visits, emergency department (ED) visits, outpatient clinic attendances, inpatient admissions, other healthcare professional appointments).
- Clinical outcomes (physical and mental health outcomes).
- Economic evaluations;
  - Direct costs
  - Incremental cost-effectiveness ratio (ICER)
  - Cost per unit of effect
  - Quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs)
  - Cost differences (in measured in cost-benefit / cost-minimisation analysis)
  - Other economic measures where data available.

Data extraction

Two reviewers (AC and OJ) will use a standardised, pre-piloted form (see extended data\(^ {20}\) to perform data extraction of the following information: name of first author, year of publication, country of publication, study setting; study population and participant demographics, intervention details and design, control setting details, recruitment and study completion rates, outcomes and times of measurement.

Economic evaluation data will be extracted as per the Health Information and Quality Authority (HIQA) guidelines for interpretation of economic evaluations in Ireland;
- Study question, population, intervention, comparator and setting
- Modelling methods
- Sources and quality of clinical data
- Cost data
- Resource usage
- Study outcomes
- Methods for dealing with uncertainty.

Where disagreement arises between reviewers, a third reviewer will be consulted (SS or FM).
Quality assessment
Studies will be included if they meet all inclusion criteria irrespective of quality. The risk of bias in all included effectiveness studies will be assessed using standard EPOC criteria (EPOC 2015) including the following domains: allocation (sequence generation and concealment); baseline characteristics; incomplete outcome data; contamination; blinding; selective outcome reporting; and other potential sources of bias. Publication bias will be assessed using a funnel plot if ten or more studies are identified.

The economic evaluation studies will be assessed for methodological quality using the CHEC list as per the Cochrane Handbook for critical appraisal of methodological quality.

Assessing the quality of the body of evidence. The certainty of evidence for each outcome will be assessed, where appropriate, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria and GRADEPro software.

Strategy for data synthesis
A narrative synthesis is anticipated for effectiveness studies. Similarly, for the economic evaluations a narrative synthesis is anticipated and results displayed in tables.

A statistician will advise if there are sufficient data to support meta-analysis. RevMan 5.3 or Stata version 15 software will be used. A random effects model will be employed to account for between-study heterogeneity. As per the Cochrane Handbook the chi-square test will assess heterogeneity between individual studies. An I² statistic will assess the impact of heterogeneity on meta-analysis where I² value greater than 75% indicates significant heterogeneity.

Analysis of subgroups
Subgroup analysis will be performed if adequate studies exist for interventions and outcomes. Subgroup analysis will be based on age of patients (cut point of 65 years), degree of polypharmacy (<10 vs 10 or more) and location of intervention (co-located vs remote location). The effect of each individual study on the overall estimates of effect size and determinants will be assessed using sensitivity analyses.

Dissemination of information
The review will be published in a relevant peer reviewed journal, reported using the PRISMA guidelines. The review will also be presented at a relevant conference and disseminated to policy-makers, patients, and the public.

Study status
Database searches have been completed and title and abstract screening is currently underway.

Discussion
This systematic review will give an overview of the effectiveness of interventions involving clinical pharmacist integration within general practice, to improve prescribing and health outcomes in patients with polypharmacy and multimorbidity.

We will focus on interventions where the clinical pharmacist and GP work collaboratively to improve patient outcomes, whether co-located or remotely. It is intended that this will address patient populations that live in geographically isolated regions in tandem with patients who live in more geographically connected settings.

This systematic review can contribute to the evidence base for managing multimorbidity. Good quality evidence is required to develop guidelines directed at such complex patients and interventions have been focused on the patients who use clinical services most in recent years. This review focuses on patients with polypharmacy, a factor in treatment burden for patients with multimorbidity. By addressing this issue in the primary care setting this may improve patient outcomes.

This will provide evidence to policy makers on strategies involving pharmacists integrating within general practice settings to address issues which arise in patients with polypharmacy in a primary care setting.

Data availability
Underlying data
No data are associated with this article

Extended data
Open Science Framework: The effectiveness of integrating clinical pharmacists within general practice to optimise prescribing and health outcomes in primary care patients with polypharmacy: A protocol for a systematic review. https://doi.org/10.17605/OSF.IO/38CU5

This project contains the following extended data:

- Data extraction template.xlsx (Excel file containing the data extraction sheet for the study)
- PubMed Search Strategy.docx (Word document containing the PubMed search strategy)

Reporting guidelines
PRISMA-P checklist for “The effectiveness of integrating clinical pharmacists within general practice to optimise prescribing and health outcomes in primary care patients with polypharmacy: A protocol for a systematic review” https://doi.org/10.17605/OSF.IO/38CU5

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

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Naghm J. Ailabouni
School of Pharmacy, Department of Pharmacy, University of Washington, Seattle, WA, USA

Thank you for the opportunity to review this work. This is an area that requires more attention and the results of this systematic review may have positive consequences that promote increased utilisation of pharmacists in primary care settings to review and optimise medication regimens whilst reducing inappropriate medication use. I look forward to reading the findings of this systematic review.

Major Comments

Methods:

- **Main outcomes:** Will all of the listed different medication appropriateness criteria (explicit: STOPP/START, Beer’s criteria and implicit: MAI etc.) be used to assess the medication changes of each pharmacist intervention study included in this systematic review? Can the authors please comment on what will determine the use of explicit vs implicit or the use of both explicit and implicit criteria to assess the outcomes of the included studies?

- **Additional Outcomes:** More clarity is needed regarding physical and mental clinical outcomes that will be used as secondary outcome measures. Please list a few specific measures as examples. What are some key clinical outcomes that would be important to consider? (e.g. Falls? Mortality? Blood Pressure? etc.)

- Since the “number of medicines” is mentioned as a major outcome of this systematic review and the introduction discusses deprescribing, is the intention to focus on the reduction of the number of medicines through pharmacist medication/deprescribing medication reviews and reduction of prescribing of high-risk medications that are inappropriately prescribed, or will potential prescription omissions as defined by the START criteria also be applied? It seems the authors intend on the later since medicines optimisation is mentioned under the heading of ‘Review questions’ and in the title of the study. Perhaps defining the concept of optimising medicines as reducing potentially inappropriate prescribing/sub-optimal prescribing via reducing potentially inappropriate medications (PIMs) as defined by Beer’s and STOPP and potential prescription omissions (PPOs) defined by START in the introduction might provide a clearer preface for the
main goal of the systematic review.

- Analysis of subgroups: Inappropriate polypharmacy and inappropriate prescribing is a common problem in older adults. Can the authors please comment on why the cut off chosen here is patients aged 65 years old? For example, is there enough evidence for cost-effectiveness of pharmacist interventions for this age population? Also, if studies that are purely older adult focused (i.e. 65 years and older) are meant to be excluded and are outside the scope of this intended systematic review, please list this explicitly under eligibility/exclusion criteria.

Minor Comments:

Abstract:
- Methods: Can the authors please clarify what is meant by ‘validated indicators’? Is STOPP/START, Beer's criteria etc. what is meant? If so, please use screening tools or criteria to assess medication appropriateness instead. Please change in the remainder of the protocol for consistency.

Introduction:
- Lines 2-3: “Polypharmacy has commonly been defined as being on five or more medications, however recent studies have highlighted the rising prevalence of more significant polypharmacy defined as being on 10 or more medications”. Whilst I agree with the content of this statement, I would recommend to:
  1. Refer to more significant polypharmacy (i.e. being prescribed or taking 10 or more medications) as hyperpolypharmacy or excessive polypharmacy as described in the literature.
  2. Please clarify that polypharmacy overall regardless of which type is on the rise in different age populations.
- Line 3: The referenced article does not mention the term ‘complex polypharmacy’, but rather the complex treatment burden associated with treating comorbidities. Please rephrase to ‘polypharmacy’ to remain consistent with the rest of the introduction.
- I would suggest combining the second paragraph beginning with “Polypharmacy is also associated with adverse drug events…” with the earlier paragraph and consolidate main concepts related to the negative consequences of polypharmacy and how polypharmacy is associated with an increased likelihood of experiencing inappropriate polypharmacy.
- Line 11: Please define deprescribing.
- Line 21: Could the authors please clarify what is meant by this systematic review will not focus on specific conditions? If previous systematic reviews focused on specific conditions (e.g. Hypertension, Diabetes etc.) could this be added to the previous sentence (line 20) that listed what other systematic reviews focused on with an appropriate reference.

Methods:
- Eligibility criteria (line 2-3): Recommend editing “Patients will not be considered eligible if they are under the age of 18 or resident in a nursing home.” to “Patients will be excluded if they are younger than 18 years old.” Will pharmacist interventions in hospital settings be excluded as well? If so, please list as an exclusion criterion. Suggestion to move text currently under the Setting heading, “Clinical pharmacist interventions in a secondary or tertiary care setting will be excluded” to this section.

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?**
Partly

**Are the datasets clearly presented in a useable and accessible format?**
Not applicable

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Deprescribing, Pharmacist interventions, Translational Research, Geriatric Pharmacy.

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.