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A systematic review of general practice-based pharmacists' services to optimise medicines management in older people with multimorbidity and polypharmacy

Running/short title: Practice-based pharmacists' services in optimising medicines management

Article category: Systematic review

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Key Messages

- Optimising medicines in older people is a major challenge in primary care.
- The role of practice-based pharmacists (PBPs) in this area was evaluated.
- PBPs' interventions had mixed effects on medicines optimisation for older people.
- PBPs' interventions improved outcomes such as prescription appropriateness.
- There had been little or no effect on outcomes e.g. adherence or quality of life.
- Further high-quality research is needed.

Abstract

Background: Few studies have evaluated roles of general practice-based pharmacists (PBPs), particularly in optimising medicines management for older people with **both** multimorbidity and polypharmacy.

Objective: To explore the types and effectiveness of services provided by PBPs, either alone or in collaboration with other primary healthcare professionals, that sought to optimise medicines management for older people with multimorbidity and polypharmacy.

Methods: Eight electronic databases and three trial registries were searched for studies published in English until April 2020. Inclusion criteria were randomised controlled trials, non-randomised controlled trials, and controlled before-and-after studies of services delivered by PBPs in primary care/general practice, for patients aged ≥ 65 years with **both** multimorbidity and polypharmacy that focused on a number of outcomes. The Cochrane risk of bias tool for randomised trials (RoB 1) and the Risk of Bias in Non-randomised Studies-of Interventions (ROBINS-I) assessment tool were used for quality assessment. A narrative synthesis was conducted due to study heterogeneity.

Results: Seven studies met inclusion criteria. All included studies employed PBP-led medication review accompanied by recommendations agreed and implemented by general practitioners. Other patient-level and practice-level interventions were described in one study. The limited available evidence suggested that PBPs, in collaboration with other practice team members, had mixed effects on outcomes focused on optimising medicines management for older people. Most included studies were of poor quality and data to estimate risk of bias were often missing.

Conclusion: Future high-quality studies are needed to test the effects of PBP interventions on a well-defined range of medicines management-related outcomes.

Key Words: Multimorbidity, older people, polypharmacy, practice-based pharmacists, primary health care, systematic review.

Lay summary

Optimising medicines use for older people (aged ≥ 65 years) with multimorbidity (the presence of two or more long-term conditions) and polypharmacy (the concomitant use of four or more medicines) is urgent due to an ageing population which commonly has complex medications regimens. It is anticipated that pharmacists who have been integrated into general practices [also called practice-based pharmacists (PBPs)] will positively impact on patient outcomes through various roles and activities. As the role of PBPs is relatively new, little is known about the exact nature of their role and how these pharmacists will optimise medicines management for older people in a patient-centred manner. The aim of this research was to provide a detailed understanding of how PBPs may enhance optimisation of medication management in older people and to study the effects of PBPs' interventions on outcomes focused on optimising medicines management for older people with multimorbidity and polypharmacy such as quality of life. The seven included studies indicated that PBP-led interventions such as medication reviews improved a number of outcomes but had either a limited effect or no effect on other outcomes. Further high-quality research is needed in this area.

Background

The use of medicines in older people is considered a major healthcare intervention (1). Approximately 67% of older people are reported to have two or more chronic conditions (multimorbidity), resulting in complex medication regimens (2,3) and polypharmacy (the concomitant use of four or more medicines) (4,5).

Medicines management covers the continuum of how medicines are selected, procured, delivered, prescribed, administered and reviewed to achieve intended outcomes for patients (6). To optimise medicines management, patient-centred care should be achieved through successful healthcare professional co-operation and active engagement of the patient in decision-making about their medicines (6,7). Pharmacists play a key role in improving medication use and management in older people and reducing related risks (8). A systematic review found that pharmacists' interventions can improve patients' outcomes through simplifying the drug regimen, increasing adherence, and preventing adverse drug reactions (ADRs) (9).

High demand for primary care services has emerged from the growing complexity of caring for older people, alongside difficulties in recruiting and retaining staff within the primary care workforce, particularly general practitioners (GPs) and practice nurses, placing general practice under strain (10). To alleviate some of these pressures, pharmacists have been integrated into general practices [also called general practice-based pharmacists (PBPs)] (11).

It is anticipated that PBPs may have a positive impact on patient outcomes through delivery of a range of activities (12). Activities may include medication review (13–15), and conducting medicines reconciliation after hospitalisation (14); these activities are within the usual scope of pharmacist practice (16). However, providing education and drug information (13–15), chronic disease management (e.g. formulating care plans) (16), and performing repeat and independent prescribing are activities undertaken by PBPs (16).

Some of these activities may require extra study and/or qualifications such as independent prescribing (17), and may also be dependent on the underpinning pharmacy degree which will differ from country to country. To become an independent prescriber in the United Kingdom (UK), registered pharmacists, in addition to their primary pharmacy degree must have at least two years of experience in a UK hospital, community or primary care setting (17). In addition to the UK, independent prescribing by pharmacists may be practised in New Zealand, Canada and the United States, but is not currently within the scope of pharmacist practice in other countries such as Australia (16).

Multiple studies have proposed that more research is required to evaluate the impact of PBPs' services on health- and patient-related outcomes (13,18–20). In addition, previous systematic reviews included studies in which community pharmacists provided non-dispensing services for patients in general practice rather than focusing only on those who were integrated in primary care practices as PBPs (12,19,21). Moreover, those reviews did not focus specifically on optimising medication management for older people (12,21,22). Furthermore, previous reviews that have addressed the effect of pharmacist-led interventions on older people did not focus specifically on those experiencing both polypharmacy and multimorbidity in primary care/general practice (8,9,23–25), with some reviews focused on investigating a specific intervention (26,27), or the effect on a specific outcome (28–30). Therefore, the aim of this review was to understand how PBPs contribute to care of older people by assessing the types and effectiveness of services provided by PBPs, either alone or in collaboration with other healthcare professionals, seeking to optimise medicines management for older people with both polypharmacy and multimorbidity.

Methods

This systematic review was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (31) (Supplementary Material 1). The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42019122186) (32).

Search strategy

A systematic search was conducted across eight electronic databases [Ovid Medline, Embase, Scopus, Web of Science, International Pharmaceutical Abstracts, Cumulative Index to Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials, Cochrane Library] to identify eligible studies published in English from date of inception to April 2020. Three trial registries [Research Registry, International Clinical Trials Registry Platform, ClinicalTrials.gov] were also searched to identify any ongoing or completed clinical trials. Search terms were developed and refined with the assistance of a subject librarian (see Supplementary Material 2 for search strategy). The reference lists of included articles were searched to identify relevant studies.

Study selection

Types of studies

Randomised controlled trials (RCTs) including cluster trials, non-randomised controlled trials and controlled before-and-after (CBA) studies were eligible for inclusion in this review.

Types of participants

All patients aged 65 years or over with **both** multimorbidity **(the presence of two or more long-term conditions)** and polypharmacy **(the concomitant use of four or more medicines)** who presented in primary

care/general practice and who received services delivered by PBPs were considered. To be considered eligible, studies had to include older people with both multimorbidity and polypharmacy. We accepted studies where the mean age of participants in each study arm was ≥ 65 years. There were no restrictions on classes of medicines or types of diseases. Residents of care homes were excluded as residents of such facilities do not usually present in person in general practices.

Types of services

Studies were eligible for inclusion if they involved a service from PBPs, either alone or in collaboration with other healthcare professionals, which affected the outcomes of optimising medicines management for older patients. In addition, studies which analysed the effects of one or more PBPs' services on outcomes were included. The service must have been implemented in primary care/general practice. Primary care settings were defined as either the home of an older person or a GP practice where a PBP provided the service. Care home, ambulatory care and transition care settings were excluded. A comparator/control group was identified as a group of older patients (aged ≥ 65 years) receiving usual care (the care as usually received by patients in everyday practice) or no service (no intervention provided for patients).

Types of outcomes

Included studies needed to report at least one outcome resulting from optimising medicines management in older people by PBPs. Outcomes were categorised as either primary (medicine-related problems, prescription appropriateness, adherence to medicine) or secondary (number of medicines, medicine safety, patient satisfaction, quality of life, shared decision-making between patients and healthcare professionals (e.g. GP, PBP), admissions and readmissions to hospital related to medicines usage). However, we also present other reported outcomes across the included studies to provide an overview of all outcomes resulting from optimising medicines management by PBPs.

Screening process

After removing duplicates, two reviewers (CH and AHI) independently screened titles and abstracts of retrieved articles to identify potential studies. Full-texts of potential studies were also read independently by two reviewers (CH and AHI) to assess if they met inclusion criteria. After that, both reviewers discussed their results to resolve any discrepancies and a third reviewer (HB) was consulted if consensus could not be reached.

Data extraction and synthesis

Two review authors (AHI, and either HB or CH) independently performed data extraction using the Cochrane data collection form as a template (33). Discrepancies between authors were resolved through discussion. Corresponding authors were contacted if key data were missing. The heterogeneity of reported outcomes across the included studies meant that meta-analysis was not possible. Therefore, it was decided to conduct a descriptive narrative synthesis using the extracted data.

Quality assessment

Two review authors (AHI, and either HB or CH) independently assessed risk of bias in each included RCT using the Cochrane Collaboration Risk of Bias assessment tool (RoB 1) (34). The Risk of Bias in Non-randomised Studies-of Interventions (ROBINS-I) assessment tool (35) was used to assess risk of bias in the CBA study. Disagreements were resolved by consensus, and another review author was consulted to resolve disagreements if necessary.

Results

Study selection

A total of 8,107 articles were retrieved until January 2019. The search was updated in April 2020 and an additional 832 articles were retrieved. Full-texts of 318 articles were assessed for eligibility, and seven articles (six RCTs and one CBA study) were deemed eligible for inclusion (Figure 1) (see Supplementary Material 3 for a list of excluded studies reviewed and reasons for exclusion).

Study characteristics

The studies were heterogeneous in terms of intervention duration, patient characteristics, number of settings, data analysis, measured outcomes, and follow-up periods (Table 1). The studies, published between 2001 and 2019, were conducted in five countries: three in the UK (36–38) and one each in Canada (39), Sweden (40), Spain (41), and the Netherlands (42). Length of follow-up periods in the studies ranged from 3 months to 6.2 years. Moreover, the total number of medications taken by patients in intervention groups (range 4-11.1), as well as the number of chronic conditions of intervention groups (range 2-5.3), differed among the studies (Table 1). The median sample size was 503 (range 141-11,928).

Characteristics of interventions

PBPs delivered the interventions either alone (n=5) or in collaboration with other practice team members (e.g. nurse practitioners) (n=2). All studies considered medication review for evaluating and optimising patients' medication regimens. After the medication reviews, different recommendations (e.g. starting, discontinuing, or changing medications) were suggested to patients' GPs, which were either accepted or rejected, and agreed recommendations were then finalised, discussed with patients and implemented. Only the CBA study (42) reported that the PBP offered both patient-level (medication reconciliations; individual consultations for patients with specific drug therapy problems) and practice-level (organisation

of quality improvement projects to recognise and treat patients at risk of medication errors; education of GPs involved and staff members) interventions.

The interventions differed in terms of the specific aims, degree of patient involvement, level of patient contact, level of discussion between PBPs and other practice team members, and patient data sources (Table 1). In the study by Krska et al. (36), the PBP developed a pharmaceutical care plan documenting all pharmaceutical care issues (PCIs; e.g. ADRs) for patients using information from practice computer records and prescriptions, as well as interviews with patients in their own homes. Hogg et al. (39) evaluated if collaborative care provided by the multidisciplinary team involving nurse practitioners, a PBP and a GP improved quality of care for older patients. Lowrie et al. (37) evaluated if a PBP-delivered intervention would reduce hospital admission for deteriorating heart failure or death by optimising medical treatments according to guidelines in left ventricular systolic dysfunction patients. Lenander et al. (40) assessed whether the PBP could decrease the number of drugs and the number of drug-related problems (DRPs). PBPs performed the medication review by checking patient records and all patients were sent a questionnaire to ask about their medications. Campins et al. (41) evaluated the effectiveness and safety of PBPs carrying out assessments to all medications prescribed to each patient in electronic primary care clinical histories using the Good Palliative-Geriatric Practice (GP-GP) algorithm and the Screening Tool of Older Person's Prescriptions (STOPP)/Screening Tool to Alert doctors to Right Treatment (START). Salisbury et al. (38) evaluated if a comprehensive 3D review provided by a nurse, a PBP, and a physician would improve health-related quality of life for older patients with multimorbidity. Sloeserwij et al. (42) assessed the effect of PBPs on medication-related hospitalisations in older people using ≥ 5 chronic medications.

Effect of interventions on outcomes

In total, 41 outcomes were reported across the seven studies (Table 1). The number of reported outcomes in each study ranged from three to eight. Protocols or clinical trials registry reports were identified for five studies (37–39,41,42).

Medicines-related problems

Krska et al. (36) reported the number and percentage of PCIs that had been resolved. At baseline, there was an imbalance as the number of PCIs in the control group was significantly greater than in the intervention group. At the 3-month follow-up period, there was a significant difference in the number or percentage of all types of PCIs that were resolved in the intervention group vs. control group.

Lenander et al. (40) found no significant difference between two groups in the change in the number of DRPs during the 12-month follow-up period. Significant changes were seen in the before-and-after comparison in the intervention group, but not in the control group.

Prescription appropriateness

Campins et al. (41) found a significant increase in medicine discontinuations, dose adjustments and substitutions in the intervention group than in the control group at follow-up periods (3, 6 and 12 months).

Lowrie et al. (37) optimised medications (ACE inhibitors, ARBs, or β -blockers) of patients with heart failure. There was a significant difference between two groups (intervention vs. usual care) in the changes in these medications (e.g. starting the medications or dose increases) between baseline and end of the first year of follow-up.

Adherence to medicine

Campins et al. (41) used the Morisky-Green test to evaluate treatment adherence at baseline, 3 months and 6 months. At baseline, no significant difference between two groups in treatment adherence was found, while at 6 months, adherence was higher in the intervention group. No data were reported at 3 months.

Salisbury et al. (38) assessed medication adherence using the eight-item Morisky Medication Adherence Score. No significant difference between two groups in medication adherence was found at 9 and 15 months.

Number of medicines

Lenander et al. (40) reported that at baseline, the intervention group used a greater number of medicines than the control group, while after 12 months, there was a mean reduction in the number of medicines per patient in the intervention group but not in the control group.

Campins et al. (41) did not report if there was a significant difference between two groups in the number of restarted drugs after discontinuation at 3, 6 and 12 months. However, they noted that after the intervention, the number of medicines prescribed to patients in the intervention group was reduced significantly compared with the control group.

Salisbury et al. (38) found no evidence that the intervention reduced the number of medicines prescribed at 15 months.

Quality of life

Four studies reported no significant difference between two groups in quality of life at baseline or at follow-up periods (31,33,34,36).

Admissions and readmissions to hospital related to medicines usage

All RCTs found no significant difference in hospital admissions between two groups during follow-up periods, irrespective of cause. Only the CBA study found lower rates of medication-related hospitalisations in the intervention group vs. usual care group, however, no difference was found in the intervention group vs. usual care plus (care provided by GPs and community pharmacists who had trained in performing medication reviews) group (42).

Quality assessment

The risk-of-bias summary across the studies is shown in Figures 2, 3, and 4. For RCTs, five of the studies were judged to be at high risk of bias (36,38–41), while the sixth study was judged as being of unclear risk of bias (37). Two domains were at high risk of bias in at least two studies: 'blinding of participants and personnel' and 'other bias' domains. Two studies (36,39) were judged as high risk in the 'other bias' domain due to baseline imbalance and contamination of the control arm by GPs seeing patients in both the control and intervention groups. 'Blinding of outcome assessment' was clearly described in three studies (38–40), whilst the remaining studies either inadequately reported blinding or used the PBP to also collect outcome data. Several unclear risks were detected in the domains and it was the highest-rated risk in two domains: 'incomplete outcome data' and 'other bias' (Figure 2).

The CBA study was found to be at moderate risk of bias (42). Six domains were judged to be at low or moderate risk of bias except the domain of 'bias due to missing data' as the information on this domain had not been clearly provided (Figure 4).

Discussion

This systematic review demonstrated a paucity of evidence with seven studies investigating PBPs' services to optimise medication management for older people with multimorbidity and polypharmacy. PBP

interventions involved medication reviews followed by various recommendations agreed by GPs and implemented in all included studies. Pharmacist-led medication reviews were also the most commonly identified interventions in previous studies in the literature (19,43–45). There was only one study in which more than one intervention, in addition to medication review, was offered by PBPs (42).

Polypharmacy is known to be associated with a higher probability of inappropriate prescribing among older people (46). Approximately 6–7% of hospital admissions of the older people are attributable to DRPs and up to 60% of such admissions could be prevented if medicines were appropriate (47). In two of the included studies (36,40), PBPs' interventions clearly identified and resolved various types of DRPs, especially those related to dosage, prescription problems, patients' information needs and monitoring to prevent adverse drug reactions. Reduction in DRPs for older people following a pharmacist intervention has been observed in various settings such as in care homes (48), domiciliary settings (49) and acute care for elders units (50).

This review also showed that PBP-led medication reviews could enhance the quality of prescribing and medication appropriateness for older people. Making decisions to prescribe appropriate medicines among older people is difficult. These difficulties arise from factors such as age-related changes, several co-morbidities and the number of medicines being prescribed (51). In addition, there is little clinical evidence available about risks and benefits of drugs in older patients (51). A retrospective cohort study revealed that medication review for older patients with polypharmacy provided by a pharmacist in primary care in collaboration with GPs, led to a reduced number of medications and potentially inappropriate medications per patient, and improved adherence to guidelines (52). It is possible that the ability of the pharmacists to prescribe could improve medication appropriateness in older people which may improve clinical outcomes. The first RCT of pharmacist prescribing in the UK identified that pharmacist prescribing may improve chronic pain for patients through medication review (53). However, in the current systematic review, no PBPs were reported to be independent prescribers.

Polypharmacy is a risk factor for non-adherence among older people which has been linked to higher rates of hospitalisations, increased healthcare costs and medicine wastage (54). Medication review could improve patients' understanding of their drug regimen and perhaps increase adherence. Although improved adherence to medicines in older people is important to achieve optimal clinical patient outcomes (55), only two trials in this review (38,41) investigated treatment adherence as a secondary outcome. A recent Cochrane review recommended that future studies should seek to achieve well-designed, feasible and long-term effect interventions intended to enhance patient adherence (56).

Polypharmacy is associated with adverse events which may include ADRs, morbidity and mortality (57).

All RCTs found no significant effect of medication review on hospital admissions, emergency department (ED) visits and mortality. Most of the trials reported these as secondary outcomes and were not powered to detect any difference. The translation of optimising medication management into a reduction in these outcomes may require a more prolonged intervention over time, longer follow-up period and a larger sample size. Furthermore, these results suggest that, despite there being no significant effect on these outcomes, the interventions were safe.

All included trials (31,33,34,36) which measured quality of life as an outcome found no significant effect of PBPs' interventions on quality of life as many of these studies did not have a sufficient sample size to detect significant changes. A systematic review found that the evidence of impact of pharmacist-led medication review on improving quality of life for older people across all care settings is uncertain (26).

This may be due to the heterogeneous nature of the patients in the existing trials and variations in the delivery of care in addition to small sample sizes (26).

The quality of evidence from the included trials was quite poor and critical data for risk of bias assessment were often missing. Reporting of adequate random sequence generation, allocation sequence concealment, and blinding of outcome assessors incompletely or unclearly produced larger estimations

of intervention effects (58,59). Low quality evidence was observed in other systematic reviews that investigated the impact of pharmacist interventions in primary care (19,22,60). Clay et al. indicated that the quality of published studies demonstrating the impact of pharmacist patient care intervention is poor and they have developed a checklist to enhance the quality of reporting of pharmacist patient care intervention studies (61). Baseline imbalance in some studies potentially weakened the final results and perhaps lowered the overall quality of evidence (62). Moreover, contamination of the control group may have decreased the estimate of an intervention's effect and rejection of an effective intervention as ineffective (63). To avoid 'contamination' between intervention and control groups, cluster trials are often used (63).

Heterogeneity of studies arose from different outcomes reported across the small number of included studies which impeded meta-analysis. This issue has been highlighted in the literature, with the development of Core Outcome Sets (COSs) increasingly encouraged. A COS is defined as a specific set of outcomes that should be measured and reported as a minimum in a particular clinical area (64). This approach can decrease both the heterogeneity of studies and outcome-reporting bias (64).

Strengths and limitations

This review explored all PBP interventions to optimise medication management and investigated a wide range of pre-specified outcomes, rather than focusing on specific interventions or outcomes. The searches across a wide range of electronic databases and trial registries, along with hand-searching of reference lists, facilitated identification and possible inclusion of a wide range of potential studies. Moreover, abstract screening and data extraction were completed through compliance with best practice. Nevertheless, the review has several limitations. The inclusion of studies only published in English could lead to exclusion of eligible studies in other languages. The paucity of studies and the inability to conduct a meta-analysis weakened the quality of the evidence and it was difficult to draw firm conclusions. Risk of

bias assessment can be subjective. However, two reviewers independently evaluated the studies, and a third author resolved any discrepancies. Additionally, we did not contact authors to resolve unclear information when judging risk of bias.

Future research and application to practice

This is the first systematic review to describe how PBPs contribute to optimising medicines management of older people with both multimorbidity and polypharmacy. Future high-quality, well-designed studies are needed to test the effects of PBP interventions provided with multidisciplinary teams on a well-defined range of management-related outcomes. In addition, there is a need to conduct sufficiently powered trials with adequate follow-up and blinding of outcome assessment. This review supports the need for a COS for trials studying the effect of PBPs on medicines management. Indeed, testing and comparing the effect of multiple PBPs' interventions using robust study designs are warranted as no study compared different PBPs' interventions.

Conclusion

This systematic review assessed the effect of PBPs' interventions on optimising medication management for older people. The review adds to the evidence base regarding the involvement of pharmacists in primary healthcare teams for older people and highlights the impact of integrating pharmacists within primary care/general practice on optimising medicines management for older people. We found that PBPs' interventions had improved a number of outcomes (e.g. reduced the number of medicines-related problems and improved appropriateness of prescribing). However, there was limited effect on the number of medicines prescribed, adherence to medicines, or no effect on other outcomes such as quality of life. These interventions likely caused no harm and seemed to be safe for older people. However, robust conclusions about the effect of PBPs' interventions on optimising medication management for older people could not be drawn due to poor quality of the limited evidence. This highlights the need for future

high-quality well-designed research to investigate the effect of PBPs on optimising medication management for older people.

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Conflicts of interest: none.

Data availability statement

Data derived from a source in the public domain. All data were obtained from published papers.

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Table 1. Characteristics of included studies on the effect of practice-based pharmacists' services on optimising medicines management in older people with multimorbidity and polypharmacy (published between 2001 and 2019)

Author, country	Study type	Study settings	Sample size of analysed patients	Intervention provider	Description of intervention	Follow-up period	Measured outcomes
Krska et al. (36), UK	RCT	6 General medical practices	332	Clinically-trained pharmacists	Intervention group: PBPs reviewed the drug therapy of patients, and care plan was then developed and implemented by PBPs with assistance from practice staff Control group: were similarly interviewed, and PCIs identified, although no care plan was developed and continued to receive usual care	3 months	Presence of PCIs (number of PCIs and % of PCIs resolved: at baseline: significantly more PCIs were in the control group than in the intervention group (1380 v. 1206; $P < 0.05$). At 3 months: significant percentage (number) of remaining PCIs had been totally resolved in intervention group vs. control group (70% (587) vs. 14% (136); $P < 0.0001$)
							Medication costs (at baseline and 3 months): no significant differences in the average monthly costs of prescribed medication per patient between groups, either at initial interview (39.29 ± 29.07 vs 42.80 ± 33.50 , P NR) or after intervention (38.83 ± 29.60 vs 42.61 ± 31.84 , P NR)
							Health-related quality of life (at baseline and 3 months): no significant differences in any of the scores between two groups at baseline and 3 months (figures NR)
							Use of health and social services (at baseline and 3 months): no difference in hospital clinic attendance, use of social services, and contacts with district nurses and health visitors between two groups before and after the pharmacist review (figures NR). Slight increase in contacts with both practice nurses (from 15 to 28) and GPs (from eight to 22) in the intervention group, which was not seen in the control group (P NR)
							Use of health and social services (elective and emergency admissions) at baseline: more elective (13) and emergency admissions (23) in intervention group than the control group (five elective and 11 emergency admissions) (P NR). At 3 months: numbers of elective admissions were similar in both groups (six intervention, five control). Emergency admissions was decreased by 74% in the intervention group compared with 27% in the control group, the numbers were too small for statistics to be meaningful (six emergency admissions vs. eight emergency admissions: P NR)
							Use of health and social services (number of the patients who received help in collecting or taking medicines) at baseline and 3 months: no changes in the number of patients who received help in collecting or taking medicines in either group after the intervention (35 vs. 37, P NR)

Table 1. Continued

Author, country	Study type	Study settings	Sample size of analysed patients	Intervention provider	Description of intervention	Follow-up period	Measured outcomes
Hogg et al. (39), Canada	RCT	One Family health network (family practice)	240	Anticipatory and Preventive Team Care (composed of patients' physicians, 1 of 3 NPs, and a pharmacist)	Intervention group: PBP and NPs: conducted chart reviews and home visits for each patient at the start of the study. The PBP then performed a medication review, to identify the drug-related problems and necessary actions to address these issues. NP developed care plan in collaboration with the patient and in discussion with the PBP and the patient's GP Control group: usual care	12 to 18 months (mean of 14.9 months in each arm)	Quality of care for chronic disease management in 4 conditions (i.e., diabetes, coronary artery disease, congestive heart failure and chronic obstructive pulmonary disease): significant increase in the quality of care for chronic disease management in intervention group compared with control group (absolute difference of 9.1%, 95% CI 3.7% to 14.4%; $P<0.001$)
							Quality of preventive care: significant improvement in preventive care by 16.5% ($P<0.001$) in intervention group compared with control group. An 18.1% (95% CI 10.8% to 25.5%) absolute difference in prevention was observed between two groups
							Intermediate clinical outcomes: no significant difference in intermediate clinical outcome measures between two groups ($P\geq 0.071$)
							Quality of life: -no significant differences in scores of Short-Form 36 between two groups [Physical component, score out of 100 (D1 2.7 vs. D2 1.1, D1-D2 1.6; 95% CI -0.8 to 4.1; $P=0.18$), Mental component, score out of 100 (D1 -1.2 vs. D2 -0.1, D1-D2 -1.1; 95% CI -3.7 to 1.6; $P=0.44$)] -no significant differences in scores of health-related quality-of-life scales between two groups (Self-assessed poor or fair health, % (D1 3.6 VS. D2 3.5, D1-D2 0.1; 95% CI -12.8 to 13.1; $P=0.98$), No. of unhealthy days in last 30 days (D1 -1.0 VS. D2 0.4, D1-D2 -1.4; 95% CI -4.5 to 1.8; $P=0.39$))
							Functional status: no significant difference in score of Instrumental activities of daily living, score out of 31, between two groups (D1 0.3 vs.D2 0.6, D1-D2 -0.3; 95% CI -1.1 to 0.5; $P=0.50$)
							Service usage (emergency use): no significant difference in emergency use between two groups [any emergency department visit,% of patients (D1 38 vs.D2 42, D1-D2 -4; 95% CI -16.4 to 8.4; $P=0.46$), average no. of ED visits (D1 0.63 vs.D2 0.73, D1-D2 -0.10; 95% CI -0.38 to 0.18; $P=0.48$)]
							Service usage (hospitalization): no significant difference in hospital admission between two groups [any hospital admission, % of patients (D1 26 vs.D2 26, D1-D2 0; 95% CI -11.1 to 11.1; $P=0.97$), average no. of hospital admissions (D1 0.40 vs.D2 0.46, D1-D2 -0.06; 95% CI -0.31 to 0.2; $P=0.67$)]
							Caregiver burden score out of 88: no significant difference in the score between groups (D1 1.7 vs. D2 -3.3,D1-D2 5.0; 95% CI 1.4 to 8.6; $P=0.007$)

Table 1. Continued

Author, country	Study type	Study settings	Sample size of analysed patients	Intervention provider	Description of intervention	Follow-up period	Measured outcomes
Lowrie et al. (37), UK	Cluster RCT	Intervention in 87 general practices and usual care in another 87 general practices	2164	Non-specialist primary care-based pharmacists	Intervention group: were offered a 30-min appointment with a PBP. If there was agreement between the PBP and the patient during the consultation and later with the GP, medications were started, discontinued, or changed Control group: usual care	Median : 4.7 years (range 6 days to 6.2 years)	Death from any cause or hospital admission for heart failure: no significant difference in patients with event between two groups (35.8% vs. 35.4%, adjusted HR 0.97, 95% CI 0.83 to 1.14; adjusted P=0.72)
							Death from any cause or admission for cardiovascular cause: no significant difference in patients with event between two groups (45% vs. 44%, adjusted HR 0.97, 95% CI 0.83 to 1.12; adjusted P=0.70)
							Death from any cause or admission for any reason: no significant difference in patients with event between two groups (70% vs. 70%, adjusted HR 0.96, 95% CI 0.86 to 1.07; adjusted P=0.41)
							Number of patients admitted to hospital for heart failure, cardiovascular causes, and any reason: no significant difference in patients with event between two groups (for heart failure: 107 vs. 114, adjusted HR 0.88, 95% CI 0.67 to 1.16; adjusted P=0.36, for cardiovascular causes: 292 vs. 280, adjusted HR 0.98, 95% CI 0.81 to 1.19; adjusted P=0.83, for any cause: 711 vs. 695, adjusted HR 0.97, 95% CI 0.87 to 1.09; adjusted P=0.61)
							Total numbers of hospital admissions (including second and subsequent hospital admissions) for heart failure, cardiovascular causes, and any reason: no significant difference in total number of hospital admissions between two groups (for heart failure: 149 vs. 194 (P=0.08), for cardiovascular causes: 474 vs. 517 (P=0.19), for any reason: 2205 vs. 2191 (P=0.84)
							Death from any cause: no significant difference in patients with event between two groups (337 (31%) vs. 331 (31%), adjusted HR 0.96, 95% CI 0.80 to 1.16; adjusted P=0.68)
							Healthcare utilization (e.g. the number of primary care contacts and hospital emergency room visits): no significant difference in any aspect of healthcare utilization at 1 and 2 years of follow up, all figures reported in supplementary material online and all P values >0.05
							Prescribing of medications: Treatment was started, or the dose increased in patients not receiving one or other of ACE inhibitor or ARB or receiving less than the recommended dose (33.1% vs. 18.5%; OR 2.26; 95% CI 1.64 to 3.10; P<0.001) - Treatment was started, or the dose increased in patients not receiving a β -blocker (17.9% vs. 11.1%; OR 1.76; 95% CI 1.31 to 2.35; P<0.001)

Table 1. Continued

Author, country	Study type	Study settings	Sample size of analysed patients	Intervention provider	Description of intervention	Follow-up period	Measured outcomes
Lenander et al. (40), Sweden	RCT	One primary care centre	141	Certified geriatric pharmacist	Intervention group: the PBP reviewed all medications regarding recommendations and giving pharmaceutical advice to patients Control group: usual care	12 months	Number of drugs: significant difference in the change in the number of drugs between two groups $P<0.046$ (at baseline: 8.6; 95% CI 7.8 to 9.3; vs. 7.4; 95% CI 6.9 to 8.0, at 12 month follow up: 7.9; 95% CI 0.10 to 0.75 vs. 7.5; 95% CI -0.02 to 0.57)
							Drug-related problems: - no significant difference in the change in the number of drug-related problems $P=0.72$ (at baseline: 1.73; 95% CI 1.42 to 2.05 vs. 1.37; 95% CI 1.07 to 1.69, at 12 month follow up: 1.31; 95% CI 1.02 to 1.59 vs. 1.11; 95% CI 0.84 to 1.37) -a significant decrease in the number of drug-related problems before-and-after the intervention in the intervention group only (from 1.73; 95% CI 1.42 to 2.05 at baseline to 1.31; 95% CI 1.02 to 1.59 at 12-month follow-up, $P=0.02$)
							Utilization of medical care: no significant difference between the two groups during 12 month follow-up regarding the mean number of primary care visits (1.6; 95% CI 0.8 to 1.3 vs. 1.4; 95% CI 0.7 to 1.4, P NR), mean length of hospitalization (days) (12 vs. 18, P NR), and mean number of admissions to hospital (1.7 vs. 2.7, P NR)
							Self-rated health: significant difference in change in self-rated health between the two groups (0.02; 95% CI -0.15 to 0.19 vs. 0.27; 95% CI 0.06 to 0.48, $P=0.047$) at 12-month follow-up
							Estimated cost of the intervention: the cost of implementing this intervention in everyday practice was estimated at €79 (\$106) per patient, based on the estimated total cost of one clinically trained, experienced pharmacist

Table 1. Continued

Author, country	Study type	Study settings	Sample size of analysed patients	Intervention provider	Description of intervention	Follow-up period	Measured outcomes
Campins et al. (41), Spain	RCT	7 primary healthcare centres	503	A trained and experienced clinical pharmacist	Intervention group: PBP reviewed of all medication according to the GP-GP algorithm and the STOPP/START criteria and then discussed recommendations for each drug with the GPs. A final decision was agreed by GPs and their patients in a face-to-face visit Control group: usual care	At 3, 6, 12 months	Number of medications prescribed at 3, 6 and 12 months: number of drugs discontinued, dose adjusted or substituted per patient at 3, 6, 12 months or the percentage of patients with at least one medication discontinued, dose adjusted or substituted were significantly higher in the intervention group than in the control group at 3, 6 and 12 months ($P<0.001$)
							Number of restarted drugs at 3, 6 and 12 months: the number of intervention group-restarted drugs at 3, 6 and 12 months were 12.0%, 15.9% and 17.3%, respectively. Control group-restarted drugs were 5.7% and 11.3% at 6 and 12 months, respectively; restarts at 3 months could not be calculated as there were no baseline discontinuations (P NR)
							New prescriptions: no differences were observed at 3, 6 and 12 months between the control group (120, 78 and 208 prescriptions, respectively) and intervention groups (135, 62 and 209 prescriptions, respectively) (P NR)
							Treatment adherence at baseline, 3-month and 6-month: - at baseline: no significant differences were observed between two groups in initial treatment adherence (61.8% in the intervention group vs. 60.2% in the control group; $P=0.713$); - at 3 months: figures NR - at 6 months: adherence was higher in the intervention group (76.4% versus 64.1%; $P=0.005$)
							Number of primary care visits per patient: Significant differences were observed between two groups in the mean number of primary care visits at 3 months (7.32 ± 5.48 vs. 6.02 ± 4.69 , $P=0.001$) and 6 months (12.92 ± 9.59 vs. 11.4 ± 8.01 , $P=0.048$) but not at 12 months (24.0 ± 16.8 vs. 23.0 ± 14.1 , $P=0.670$)
							Number of hospital emergency visits per patient: no significant differences were observed between two groups in mean number of emergency department visits during the entire follow-up period [at 3 months (0.27 ± 0.94 vs. 0.22 ± 0.53 , $P=0.726$), at 6 months (0.47 ± 1.02 vs. 0.43 ± 0.81 , $P=0.985$), at 12 months (0.9 ± 1.5 vs. 1.1 ± 1.5 , $P=0.061$)]
							Number of specialty care visits per patient: no significant differences were observed between two groups in number of specialty care visits per patient during the entire follow-up period [at 3 months (1.50 ± 2.12 vs. 1.61 ± 2.41 , $P=0.986$), at 6 months (2.89 ± 3.46 vs. 2.81 ± 3.61 , $P=0.253$), at 12 months (6.9 ± 7.3 vs. 6.8 ± 7.6 , $P=0.302$)]

						<p>Number of complementary tests (image testing, i.e. x-rays, scans, ultrasounds, and blood tests) per patient: no significant differences were observed between two groups in mean number of additional tests during the entire follow-up period [at 3 months (0.53 ± 0.94 vs. 0.49 ± 0.89, $P=0.604$), at 6 months (1.02 ± 1.56 vs. 0.91 ± 1.59, $P=0.227$), at 12 months (2.0 ± 2.6 vs. 2.0 ± 2.9, $P=0.581$)]</p> <p>Number and percentage of hospitalized patients: no differences were found between two groups in number of hospitalized patients (%) during the entire follow-up period [at 3 months (17 (7.0%) vs. 20 (8.0%), $P=0.672$), at 6 months (33 (13.5%) vs. 29 (11.6%), $P=0.530$), at 12 months (57 (23.3%) vs. 63 (25.2%), $P=0.616$)]</p> <p>Number and percentage of death: no differences were found between two groups in number of death (%) during the entire follow-up period [at 3 months (2 (0.8%) vs. 1 (0.4%), $P=1.000$), at 6 months (5 (2.0%) vs. 1 (0.4%), $P=0.216$), at 12 months (7 (2.8%) vs. 6 (2.4%), $P=0.784$)]</p> <p>Self-reported quality of life at baseline, 3-month and 6-month: no difference in self-reported quality of life between two groups (at 3 months: figure NR, at 6 months: a change from the baseline score (on a scale of 0–100) of -2.09 points vs. 0.67 points, $P=0.324$)</p> <p>Drug appropriateness for intervention group only: the clinical pharmacist made at least 1 recommendation for 95.6% of the patients (n = 241) with a mean change of 2.07 (1.64) drugs per patient</p>
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Table 1. Continued

Author, country	Study type	Study settings	Sample size of analysed patients	Intervention provider	Description of intervention	Follow-up period	Measured outcomes
Salisbury et al. (38), UK	Cluster RCT	Intervention in 16 general practices and usual care in another 17 general practices	1546	Each 6-monthly 3D review consisted of a review by a nurse, a physician, and a pharmacist. A two half-days of training were received by healthcare professionals involved in the study	Intervention group: comprehensive multidisciplinary 3D review (nurse review e.g. identified the health problems most important to the patient, pharmacist review i.e. reviewed medication and made recommendations about simplifying drug regimen, physician review i.e. considered the nurse and pharmacist reviews and agreed health plans with the patient Control group: usual care	At 9, 15 months	Health-related quality of life: no significant difference in mean EQ-5D-5L score between two groups (at 9 months (adjusted mean difference 0.01, 95% CI -0.01 to 0.03; $P=0.53$), at 15 months (adjusted mean difference 0.00, 95% CI -0.02 to 0.02; $P=0.93$))
							Illness burden: no significant difference between two groups in measuring of illness burden [self-rated health of good or better: at 9 months (adjusted mean difference 0.95, 95% CI 0.76 to 1.19; $P=0.66$), at 15 months (adjusted mean difference 0.84, 95% CI 0.67 to 1.05; $P=0.13$), Bayliss measure of illness burden: at 9 months (adjusted mean difference 0.30, 95% CI -0.65 to 1.26; $P=0.54$), at 15 months (adjusted mean difference -0.64, 95% CI -1.54 to 0.27; $P=0.17$), HADS anxiety score: at 9 months (adjusted mean difference -0.18, 95% CI -0.50 to 0.14; $P=0.26$), at 15 months (adjusted mean difference -0.24, 95% CI -0.57 to 0.08; $P=0.15$), HADS depression score: at 9 months (adjusted mean difference 0.07, 95% CI -0.22 to 0.36; $P=0.65$), at 15 months (adjusted mean difference -0.01, 95% CI -0.33 to 0.30; $P=0.94$)]
							Treatment burden: no significant difference between two groups in measuring of treatment burden (Multimorbidity Treatment Burden Questionnaire score: at 9 months (adjusted mean difference -1.09, 95% CI -2.29 to 0.12; $P=0.08$), at 15 months (adjusted mean difference -0.46, 95% CI -1.78 to 0.86; $P=0.49$), eight-item Morisky Medication Adherence Score: at 9 months (adjusted mean difference -0.03, 95% CI -0.14 to 0.08; $P=0.55$), at 15 months (adjusted mean difference 0.06, 95% CI -0.05 to 0.17; $P=0.27$), number of different drugs prescribed in past 3 months: at 9 months (figures NR), at 15 months (adjusted mean difference 1.02, 95% CI 0.97 to 1.06; $P=0.46$))
							Patient-centred care: significant improvements in measures of patient-centred care in intervention group vs. usual care group (PACIC score: at 9 months (adjusted mean difference 0.28, 95% CI 0.18 to 0.38; $P<0.0001$), at 15 months (adjusted mean difference 0.29, 95% CI 0.16 to 0.41; $P<0.0001$), CARE doctor score: at 9 months (adjusted mean difference 1.44, 95% CI 0.47 to 2.41; $P=0.0035$), at 15 months (adjusted mean difference 1.20, 95% CI 0.28 to 2.13; $P=0.0109$), CARE nurse score: at 9 months (data not collected), at 15 months (adjusted mean difference 1.11, 95% CI 0.03 to 2.19; $P=0.044$), Patients reporting they almost always discuss the problems most important to them in managing their own health: at 9 months (adjusted mean difference 1.60, 95% CI 1.27 to 2.01; $P=0.0001$), at 15 months (adjusted mean difference 1.85, 95%

						<p>CI 1.44 to 2.38; $P < 0.0001$), Patients reporting that support and care is almost always joined-up: at 9 months (adjusted mean difference 1.34, 95% CI 1.03 to 1.74; $P = 0.0305$), at 15 months (adjusted mean difference 1.48, 95% CI 1.18 to 1.85; $P = 0.0006$), Patients reporting being very satisfied with care: at 9 months (adjusted mean difference 0.07, 95% CI -0.22 to 0.36; $P = 0.65$), at 15 months (adjusted mean difference -0.01, 95% CI -0.33 to 0.30; $P = 0.94$), Patients reporting being very satisfied with care: at 9 months (adjusted mean difference 1.62, 95% CI 1.30 to 2.03; $P < 0.0001$), at 15 months (adjusted mean difference 1.57, 95% CI 1.19 to 2.08; $P = 0.0014$), Patients reporting having a written care plan, health plan, or treatment plan: at 9 months (figures NR), at 15 months (adjusted mean difference 1.97, 95% CI 1.32 to 2.95; $P = 0.0010$)</p> <p>Process of care outcomes: -significant difference between two groups in the Continuity of Care index, Visit Entropy, number of primary care physician consultations, and number of nurse consultations at 15 months (Continuity of Care index: adjusted mean difference 0.08, 95% CI 0.02 to 0.13; $P = 0.0045$, Visit Entropy: adjusted mean difference -8.76, 95% CI -18.07 to 0.55; $P = 0.07$, number of primary care physician consultations: adjusted mean difference 1.13, 95% CI 1.02 to 1.25; $P = 0.0209$, number of nurse consultations: adjusted mean difference 1.37, 95% CI 1.17 to 1.61; $P = 0.0001$)</p> <p>-No significant difference between two groups in number of QOF indicators met (quality of disease management), the number of indicators of high-risk prescribing, and number of hospital admissions or outpatient attendances at 15 months (number of QOF indicators met: adjusted mean difference 0.41, 95% CI -3.05 to 3.87; $P = 0.82$, number of indicators of high-risk prescribing: adjusted mean difference 1.04, 95% CI 0.87 to 1.25; $P = 0.68$, number of hospital admissions: adjusted mean difference 1.04, 95% CI 0.84 to 1.30; $P = 0.71$, number of hospital outpatient attendances: adjusted mean difference 1.02, 95% CI 0.92 to 1.14; $P = 0.72$)</p> <p>Completion of the 3D reviews for intervention group only: 75% of patients received at least one 3D review over 15 months, and 49% had two complete 3D reviews. No evidence that patients who attended two 3D reviews were more likely to have an improvement in quality of life</p>
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Table 1. Continued

Author, country	Study type	Study settings	Sample size of analysed patients	Intervention provider	Description of intervention	Follow-up period	Measured outcomes
Sloeserwij et al. (42), Netherlands	CBA	Intervention in 9 general practices, usual care in another 10 general practices, and usual care plus in another 6 general practices	11,928	Specially trained non-dispensing pharmacists integrated in general practices	<p>Intervention group: PBP provided medication therapy management services both at patient level (e.g. clinical medication review and medication reconciliations) and practice level (e.g. quality improvement projects)</p> <p>Control group: usual care provided by general practitioners and community pharmacists, or usual care plus provided by general practitioners and community pharmacists who had trained in performing medication reviews</p>	12 months	Medication-related hospitalisations:- lower rate of medication-related hospitalisations in intervention group vs. usual care group (adjusted rate ratio 0.68, 95% CI 0.57 to 0.82)
							-No difference in rate of medication-related hospitalisations in intervention group vs. usual care plus group (adjusted rate ratio 1.05, 95% CI 0.73 to 1.52)
							Drug burden index: no differences between the intervention group and both usual care groups on treatment effect on lowering drug burden index in high-risk patients (adjusted treatment effects in intervention group vs usual care group -0.02, 95% CI -0.07 to 0.02; $P=0.291$), (adjusted treatment effects in intervention group vs usual care plus group -0.01, 95% CI -0.06 to 0.04; $P=0.609$)
							Costs (direct primary and secondary healthcare costs and total medication costs): no differences in costs in intervention group vs. usual care group (ratio of primary care costs 1.08, 95% CI 0.99 to 1.17; $P=0.073$, ratio of secondary care costs 0.92, 95% CI 0.65 to 1.29; $P=0.622$, ratio of medication costs 1.04, 95% CI 0.98 to 1.10; $P=0.172$)

ACEI: angiotensin-converting enzyme, *ARB*: angiotensin receptor blocker, *CARE*: Consultation and Relational Empathy, *CBA*: *controlled before-and-after*, *CI*: confidence interval, *D1*: difference between data available for individual patients at baseline and at the end of the study for intervention group, *D2*: difference between data available for individual patients at baseline and at the end of the study for control group, *GP-GP*: *Good Palliative-Geriatric Practice*, *HADS*: *Hospital Anxiety Depression Scale*, *HR*: hazard ratio, *NR*: not reported, *NPs*: nurse practitioners, *OR*: odds ratio, *PACIC*: Patient Assessment of Care for Chronic Conditions, *PCIs*: pharmaceutical care plan, *QOF*: Quality and Outcomes Framework, *RCT*: randomised controlled trial, *SD*: standard deviation, *STOPP/START*: Screening Tool of Older Person's Prescriptions-Screening Tool to Alert Doctors to the Right Treatment criteria

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