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Intervention effectiveness by pharmacists integrated within an interdisciplinary health team on chronic complex patients

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Background: Nowadays, it is difficult to establish a specific method of intervention by the pharmacist and its clinical repercussions. Our aim was to identify interventions by pharmacists integrated within an interdisciplinary team for chronic complex patients (CCPs) and determine which of them produce the best results. **Methods:** A systematic review (SR) was performed based on PICO(d) question (2008–18): (Population): CCPs; (Intervention): carried out by health system pharmacists in collaboration with an interdisciplinary team; (Comparator): any; (Outcome): clinical and health resources usage outcomes; (Design): meta-analysis, SR and randomized clinical trials. **Results:** Nine articles were included: one SR and eight randomized clinical trials. The interventions consisted mainly in putting in order the pharmacotherapy and the review of the medication adequacy, medication reconciliation in transition of care and educational intervention for health professionals. Only one showed significant improvements in mortality (27.9% vs. 38.5%; HR = 1.49; $P = 0.026$), two in health-related quality of life [according to EQ-5D (European Quality of Life—5 Dimensions) and EQ-VAS (European Quality of Life—Visual Analog Scale) tests] and four in other health-related results (subjective self-assessment scales, falls or episodes of delirium and negative health outcomes associated with medication). Significant differences between groups were found in hospital stay and frequency of visits to the emergency department. No better results were observed in hospitalization rate. Otherwise, one study measured cost utility and found a cost of €45 987 per quality-adjusted life year gained due to the intervention. **Conclusions:** It was not possible to determine with certainty which interventions produce the best results in CCPs. The clinical heterogeneity of the studies and the short follow-up of most studies probably contributed to this uncertainty.

Introduction

Most countries and large health maintenance organizations in the Western world are modifying their care systems for chronic patients. Among others, Kaiser Permanente, the US Veterans Health Administration and the British NHS are dedicating substantial and increasing efforts to implement comprehensive and multiprofessional care models. Sweden, the Netherlands and Denmark also have various integrated care projects.[1]

In all of these reforms, it is crucial to identify and develop specific models for chronic patients who can benefit most from specialized and comprehensive care and who consume a greater amount of resources.[2] Among chronic patients, those with high complexity exhibit the following characteristics: pluripathology, polypharmacy, advanced age, greater vulnerability to adverse events and greater consumption of healthcare resources.[3] Various concepts have been used in the literature to define these patients, including multipathological patients, patients with multimorbidity, polypathological patients and complex patients. In this study, we will refer to them as 'complex chronic patients (CCPs)'.

Caring for a CCP necessarily implies the modification and adaptation of the competences of many professionals, including both health and nonhealth professionals. The search for an integrated care model requires redefinition of the roles of traditional healthcare actors and defining new professional profiles by modifying or expanding their competences.[4]

In this context, the literature shows that pharmaceutical intervention can significantly resolve drug-related problems (DRPs) in chronic patients, contributing to the improvement of their pharmacotherapy. These interventions are usually aimed at pharmacotherapeutic optimization by reviewing the adequacy of the treatment, reconciling it and improving adherence, among other actions. However, evidence of the impact of pharmaceutical interventions on health outcomes, health-related quality of life (HRQOL) or the cost-effectiveness ratio is uncertain.[5] The best results usually are obtained when pharmacists are experts and work in the context of an interdisciplinary team.[5]

Although most plans and guidelines for CCP care agree that the necessary participation of all professionals and sometimes propose specific interventions, they rarely establish a specific method by which interventions should be carried out by the pharmacist, and if these interventions are described, their clinical repercussions are rarely evaluated (see Supplementary references A).

Therefore, the main objective of this systematic review (SR) is to identify interventions for CCPs, led by pharmacists as part or in collaboration with an interdisciplinary team, and determine which of them produce the best results with regard to health and resource utilization.

Methods

An SR was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The research question, formulated in PICO(d) format, is shown in table 1.

Literature search

A search was performed in the MEDLINE (through OvidSP), EMBASE, Nursing@Ovid, The Cochrane Library and the Center for Reviews and Dissemination databases through 11 October 2018. Search strategy is described in Supplementary appendix S1. The search was limited by language (English) and by date (2008–18). Furthermore, to identify additional studies, a cross-reference search of the included studies was performed.

Selection of studies and data extraction

Study selection was performed based on the criteria established in the PICO(d) question (see table 1), and one of the investigators (H.A.-G.) read the titles and abstracts of articles. Documents that met the inclusion criteria and those that did not provide sufficient information to determine their exclusion were selected. Finally, two investigators (H.A.-G. and B.S.-R.) read the complete texts of the articles selected for the review. Discrepancies were resolved through discussion and consensus.

Information extraction was performed by one of the investigators (H.A.-G.), and any discrepancies were resolved by discussion and consensus with a second investigator (B.S.-R.).

Quality assessment

The assessment of the methodological quality of the included studies was performed using the AMSTAR-2 scale (in the case of SR) and the Cochrane Collaboration's tool for assessing risk of bias [in the case of a randomized clinical trial (RCT)] (Supplementary references B).

Evaluation of the studies with the corresponding tools was conducted in pairs by two researchers (H.A.-G. and S.S.-F.), and any discrepancies were resolved by discussion and consensus.

Results

Search results

Through a systematic search, 1281 references were identified, of which 78 were initially included. Then, the full text of these studies was read and finally nine studies were only included in the final SR[6–14] (see figure 1). The excluded studies can be found in Supplementary appendix S2.

Subsequently, based on the cross-references, eight additional references were identified and analyzed, of which three were included in the study.[15–17] These studies were from the same authors as a previously included study[13] but provided additional results; therefore, they were considered a unique study.

A meta-analysis was not performed due to the clinical heterogeneity of the included studies. Clinical heterogeneity (also called clinical diversity) is the variability in the participants, interventions and outcomes studied, and is different from the methodological heterogeneity (variability in study design and risk of bias) and statistical heterogeneity (variability in the intervention effects being evaluated in the different studies) (Supplementary references B).

Description of the included studies

Nine studies were included, of which one was an SR[6] and eight were RCTs.[7–14] The included SR was published in 2016 and aimed to determine the effect of interventions to optimize the prescription of drugs in institutionalized patients >65 years old. With a total of 12 included studies and 10 953 patients recruited, the SR was considered to be of high quality. The interventions were composed, in most cases, of several actions. In 10 studies, a review of the medication was performed; four studies used a case management model with interdisciplinary teams; and in five studies, the health personnel involved was trained. In addition, other types of methods were used to a lesser extent, such as the coordination of transitional care, decision support technologies or the transfer of information among different professionals. The interventions performed by pharmacists did not show an important influence on the clinical results or the use of healthcare resources. None of the five studies that measured mortality showed differences between the control and intervention groups. For other variables, such as hospital admissions (six studies), HRQOL (one study) and adverse events related to treatment (one study), difference between the control and intervention groups was not demonstrated either. However, differences in pharmacological cost reduction in favor of the intervention group were found in three of five studies. Differences in variables regarding rational use of medication (RUM) were also detected, but this was not the subject of our study. The authors concluded that in most studies involving pharmacists, potential medication errors were detected and corrected, but this did not translate into improvements in clinical variables or in measured health frequencies, although it did produce improvements in the pharmacological cost.

Of the eight RCTs[7–14] included, one was a cluster randomized controlled trial.[10] The characteristics and results are shown in tables 2 and 3.

Interventions performed

The interventions conducted by the pharmacist in the eight included RCTs[7–14] consisted mainly in putting in order the pharmacotherapeutic history and the subsequent review of the medication adequacy using tools, such as STOPP-START[7] or similar criteria[14] and Beers criteria,[10] or through the experience of the research team.

In the two studies conducted in a hospital setting,[9,14] medications were reconciled in home–hospital transitions and vice versa. In one study, medication was reconciled in intrahospital transitions.[9]

In four studies, the pharmacist contacted the patient's doctor directly;[7,9,11,14] in two other studies,[10,12] the pharmacist contacted also with other health professionals involved in the patient's care; and in the last two studies,[8,13] the pharmacist was part of an interdisciplinary team led by the nursing staff.

In half of the studies, decision-making regarding the pharmacotherapeutic plan was performed in a consensual manner with the doctor or in an integrated manner within an interdisciplinary team.[7,8,10,13] In the remaining studies, the pharmacist, or the interdisciplinary medication review team, made recommendations to the doctor, but the physician exclusively decided whether the recommendations would be implemented.[9,11,12,14] In two studies, decision-making was shared between the professionals and the patient.[7,10]

In the study by Campins et al.,[7] the pharmacist obtained information about the pharmacotherapeutic treatment of the patient without personal contact. In the remaining studies, face-to-face or telephonic interviews were conducted.[8–14] In three of these studies, an educational intervention was conducted on different aspects related to the treatment (taking and storing of medications, side effects to monitor, healthy lifestyle habits, etc.).[8,11,12]

Finally, in the study by Lapane et al.,[10] an educational intervention was conducted for health professionals. In addition, a computerized risk warning system for DRPs was developed for use by dispensing pharmacies, and the clinical information was shared with the dispensing pharmacies and the prescribing physician.

Table 1 Clinical question PICO(d)

Population	Chronic complex patients defined as any of the following: • Multimorbidity as defined by NICE (two or more chronic diseases) • One or more chronic diseases and clinical or social frailty • Patients older than 65 and polymedicated (four or more regular medications) • Nursing home residents or geriatric ward inpatients provided that a majority of them with the above characteristics were confirmed, according to the basal demographic characteristics
Intervention	Interventions carried out by a health-system pharmacist as part or in collaboration with an interdisciplinary team
Comparator	Any
Outcomes	Clinical outcomes: • Mortality • HQROL • Any clinical outcome (arterial pressure decrease, glycated hemoglobin, etc.) only when it was the main outcome Healthcare resources utilization: • Hospital usage (hospitalization, readmission, visit to an emergency department or to the specialist, etc.) • Primary care usage (visit to GP, etc.) • Costs
Design	Meta-analysis, systematic review and primary studies (RCT or non-randomized intervention trial)

Note: GP, general practitioner; HQROL, health-related quality of life; NICE, National Institute for Health and Care Excellence (see Supplementary references A); RCT, randomized clinical trial.

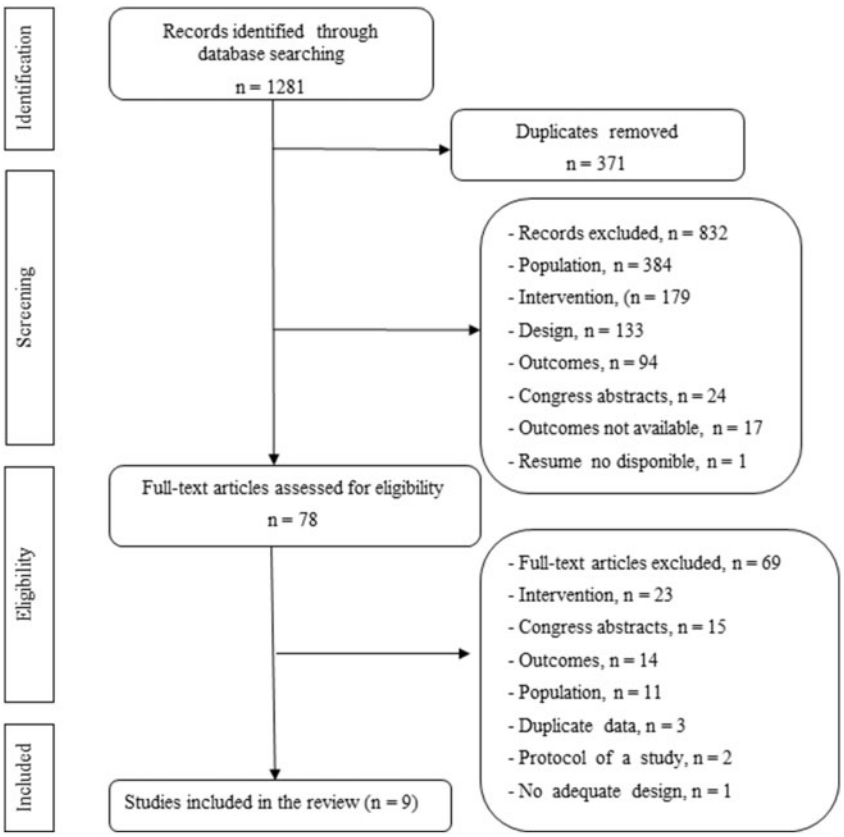

Figure 1 Flowchart of studies included in this systematic review

Clinical results

Only one of five studies showed significant improvements in mortality in the intervention group (in the 3-year analysis but not in the 2-year analysis, as initially projected).[13]

Regarding the other clinical variables, four studies measured HRQOL,[7,12–14] which was better in the intervention group in two of them [according to EQ-5D (European Quality of Life—5 Dimensions) test and EQ-VAS (European Quality of Life—Visual Analog Scale) test].[12,14] Other positive results, which were also significantly improved in the intervention group, were observed in different subjective self-assessment scales,[11,12] in falls or episodes of delirium[14] and in negative health outcomes associated with medication.[9]

Use of resources and health costs

Seven studies measured the number of hospital admissions and found no significant differences between groups.[7–9,11–14] Only one study showed better results regarding the hospital stay in the intervention group.[13] Regarding the frequency of visits to the emergency department, one study showed a decrease in visits that did not require hospital admission.[14] Finally, the two studies that measured the frequency of medical attention in primary care or specialized care settings did not find differences between the intervention and control groups.[7,8]

Costs were measured by different methods in various studies. Mazya et al.[13] measured cost-effectiveness and cost-utility and found

Table 2 Characteristics of primary studies included

Ref.	Design	Intervention	Comparator	Population (selection criteria)	Outcome measures
(7)	Randomized, open-label, multicenter, parallel-arm clinical trial with 1-year follow-up	Three consecutive phases: (1) A clinical pharmacist evaluated all drugs prescribed to each patient using the GP–GP algorithm and basing their decision about appropriateness on the STOPP/START criteria (2) The pharmacist discussed recommendations for each drug with the patient's physician in order to come up with a final set of recommendations (3) These recommendations were discussed with the patient, and a final decision was agreed by physicians and their patients in a face-to-face visit	Usual treatments and control procedures of their physicians	Community dwelling elderly people (non-institutionalized), receiving eight or more drugs	Clinical measures (3, 6 and 12 months): • Mortality rate • HQROL (EQ-5D test) • Adherence (Morisky–Green test) Healthcare resources utilization: • Hospitalization rate • Primary and specialist care and ED consultation rate for acute conditions • Complementary tests performed to patients Variables regarding RUM
(8)	Randomized, open-label, multicenter, clinical trial in a semirural family health network with 18-month follow-up (pharmacist intervention was carried out during 12 months) Subgroup analysis of frail patients	A nurse practitioner and a pharmacist reviewed the clinical charts of patients and performed initial home visits to complete their assessments and establish a care planning document for each patient. That contained the results of their assessments, medication information, health screening information and a breakdown of patient-care priorities based on five dimensions of care, including disease management, medical review, education and self-care, social support and community integration, and psychological issues. Care plans were reviewed with the patients' respective family physicians and were implemented and adapted throughout the study period. Care was provided by the nurse and the pharmacist almost exclusively in patients' homes and by telephone contact, with few clinical visits taking place at the practice	Usual care without the intervention of nurse practitioner and pharmacist	50 years and older with at least one chronic disease, who were considered frail by their general physician	Clinical measures: not reported Healthcare resources utilization: • Primary care visits • Hospitalization rate • ED visits • Days of surgery • Total costs: The cost of the intervention included costs incurred during the study period, which were measured in Canadian dollars and analyzed from the perspective of the provincial Ministry of Health Variables regarding RUM
(9)	Randomized, open-label, single-center, parallel-arm clinical trial with 6-month follow-up after discharge	Pharmaceutical care program from admission to ED until discharge, comprising the following steps: (1) Obtaining and recording the medication chart, by interviewing the patient or caregiver (2) Medication reconciliation in each of the care transitions (3) Medicine review and validation of physician prescriptions during the stay at the ED and during hospitalization (4) Patient follow-up. This consisted of evaluation of the effectiveness and safety of the treatment according to standard clinical practice and patients' objective data from clinical records (5) Provision of additional written information at discharge, with clear indications for drug therapy regimen	Usual pharmacist care (step 3 in intervention group)	Sixty-five years and older, length of stay in ED longer than 12 h, decompensation of HP and/or COPD and polypharmacy (four or more drugs) Institutionalized patients and those with severe cognitive deficits or mental illness documented in the medical record were excluded	Clinical measures: • Drug-related negative outcomes, defined as health problems that patients experience owing to drug use or non-use (poor control of glycaemia, blood pressure, anticoagulation, serum potassium or heart rate) • Mortality at 180 days Healthcare resources utilization: • Patients readmitted within 180 days to the same ED and/or to the hospital ward • Duration of the patient's hospital stay from ED admission to discharge

(continued)

Table 2 Continued

Ref.	Design	Intervention	Comparator	Population (selection criteria)	Outcome measures
		When potential DRPs were detected, the prescribing physician was informed by means of the electronic health record and the pharmacist proposed an alternative prescription that would be available for the health team in the electronic health record			
(10)	Cluster randomized, open-label, multicenter, controlled trial, with 2-year follow-up Both groups were compared with themselves before and after intervention	Two phases: (1) The research team conducted orientation sessions to the pharmacist staff; facilitated clinical training in the form of on-site workshops; provided a workshop with the goal of improving pharmacists' communication skills; supported the participation of several pharmacists in geriatric pharmacotherapy traineeships; developed an algorithm to flag residents at high risk for preventable ADE; worked with a commercial pharmacy software vendor to integrate the high-risk algorithm and a flag for residents using PIM into the real-time operations of the commercial pharmacy software; developed treatment algorithms for alternatives to PIM and delivered in-service training on how to use the materials; and designed, developed, trained and implemented a computer system to document pharmaceutical care plans and share information among consultant and dispensing pharmacists (2) Pharmacist carried out a prospective medication review based on Beers criteria 1997 with a direct communication with prescriber. Also they performed a patient assessment, working as part of an interdisciplinary team in the nursing homes discussed with dispensing pharmacists regarding the care of patients, and documented a formalized pharmacotherapy plan for residents at high risk for DRPs	Usual cares	Nursing home residents. Those with at least four of the following risk factor were given priority: use of antidepressant, antibiotic or anti-infective, antipsychotic, anticonvulsant medication, sedative/hypnotic, opioid, anticoagulant, muscle relaxant, three or more cardiovascular medications, or seven or more medications	Clinical measures: • Mortality • Number of hospitalizations • Number of hospitalization due to adverse events Variables regarding RUM
(11)	Randomized, open-label (evaluators were blinded), single-center, parallel-arm clinical trial with 1-year follow-up	The intervention involved a standardized semi-structured protocol that was open for patients' questions and remarks. Computerized patient records were checked for prescriptions, drug indications and plans for evaluation. Drugs and dosages were evaluated to correlate with renal function, good practice and the drug formulary A patient-centered technique was used, focusing on the patients' questionnaire answers to assess	Usual care by their GP	Sixty-five years and older, with five or more medications who were already scheduled for an appointment with a GP	Clinical measures: • Mortality • Self-rated health by answering a single question with the options 'very good', 'good', 'fair', 'bad' and 'very bad', rated from 1 to 5 Healthcare resources utilization: • Number of hospitalizations • Duration of the patient's hospital stay • Estimated cost of intervention

(continued)

Table 2 Continued

Ref.	Design	Intervention	Comparator	Population (selection criteria)	Outcome measures
		understanding of and concordance with drug treatment Pharmaceutical advice was given to patients and entered into the computerized patient record			Variables regarding RUM
(12)	Randomized, open-label, single-center, parallel-arm clinical trial with one-year follow-up (the recruitment period length was 4 months)	The pharmacist: • Carried out a medication review aimed to detect DRPs • Provided face-to-face and telephone counseling to patients on health education and medication adherence Cases with DRPs were presented at bi-weekly meetings of the MTM team if an appropriate intervention could not be determined by the clinical pharmacist alone or a complex patient needed team review. The MTM team included two geriatricians, one cardiologist, one nephrologist and one clinical pharmacist supervisor, in addition to the study's responsible clinical pharmacist. The team attempted to propose resolutions for any difficult issues which were raised by the clinical pharmacist during the 1-h case discussion meeting. After either the clinical pharmacist alone or the MTM team made a decision on the appropriate action to be taken, the clinical pharmacist would contact the patient's prescribing physician before the next appointment or contact patients directly through in person or telephone interactions. The prescribing physician was encouraged to follow the suggestions made by the clinical pharmacist or MTM team. However, the ultimate responsibility for the patients' prescription remained with the prescribing physician	Usual care without the participation of MTM team	Sixty-five and older who had three or more chronic diseases, more than six prescription items, and had made more than four outpatients visits or visited two or more different specialists during an assessment period from November 2007 to October 2008	Clinical measures: • Functional status (GDS index, Barthel index and IADL scale) • HQROL (EQ-5D and EQ-VAS test) Healthcare resources utilization: • Total medical cost of the entire 16-month implementation period consumed in the outpatient departments, emergency rooms and inpatient departments in hospital • Total costs compared within each group, using the 6-month period prior to study implementation as the control
(13) (15) (16) (17)	Randomized, open-label (evaluators were blinded), single-center, parallel-arm clinical trial with planned 2-year follow-up (the follow-up was extended to 3 years)	The intervention was carried out by an interdisciplinary team that includes nurses, physicians, a physiotherapist, an occupational therapist, pharmacists, a social worker and a dietician: (1) Initially, a nurse and a social worker went home to each participant and administered a survey of health, functional status and need for social care. The pharmacist collected information on compliance with the use of prescribed and non-prescription drugs by telephone. This information was conveyed to the physician, who consulted patients as part of the initial team evaluation (2) All information gathered was discussed at the following interdisciplinary team meeting; two	Usual medical and social care	Seventy-five years and older, who had been hospitalized three or more times in the previous year, and had three or more current medical diagnoses	Clinical measures: • Transition between frailty stages through identifying the presence of three or more of the following five characteristics: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed and low physical activity • Cognition (MMSE scale) • Symptoms (MSAS scale) • Depression (GDS scale) • HQROL (NPH and EQ-5D scales) • Personal and instrumental activities of daily living (Barthel index) • Self-reported number of falls the last 6 months • Feeling of security (A newly developed Questionnaire)

(continued)

Table 2 Continued

Ref.	Design	Intervention	Comparator	Population (selection criteria)	Outcome measures

		such meetings were held per week. Decisions regarding interventions were made at these meetings, often involving the need for additional assessments for example, by a physiotherapist, occupational therapist and/or dietician. When needed, participants were referred to specialized medical care.
		Personalized care and follow-up plans were created and revised when required, and all participants were offered annual medical evaluations
					Healthcare resources utilization:
					• Number of hospitalizations.
					• Cost per patient based on:
					  • Number and extent of contacts with the municipal services of care measured by working hours
					  • Number of visits to primary care facilities, day-care centers in-hospital stays, geriatric ambulatories and other specialist ambulatories
					  • Admissions to nursing care facilities

(14)	Non-randomized, open-label (geriatricians in the control group were not informed about the study), single-center, parallel-arm clinical trial with 3-month follow-up after discharge	Intervention consisted of trained clinical pharmacists performing medication reconciliation with a subsequent two-stage medication review. The reconciled drug information was registered in the electronic patient file (1) The RASP list was applied to by a trained clinical pharmacist. The RASP list consists of 76 items divided over 12 groups, of which approximately one-third was directly based on the STOPP criteria (2) The clinical pharmacist performed an additional comprehensive medication review covering mistreatment, overtreatment, as well as potential undertreatment In the intervention group, recommendations were actively reported to the treating physician on a daily basis. It was left to the discretion of the treating physician as to whether to follow the pharmaceutical recommendations Accepted recommendations were included in the discharge letter to the GP	Usual medical care. If PIM were observed, this was communicated to the treating physician	Patients admitted from home or from a nursing home. Patients were excluded if admitted for end-of-life care, if they did not take any drugs, or if they were not discharged back to their home or a nursing home	Clinical measures (during hospital stay and at 3 months after discharge) • Mortality • Prevalence of delirium (DOS scale), confirmed by geriatrician • Number of falls per patient • Patients with one or more falls • HQROL (EQ-5D test) Healthcare resources utilization (at 3 months after discharge): • Patients with one or more readmissions • Electively readmitted patients • Patients with one or more ED visits • Patients with one or more ED visits without readmission

Note: ADE, adverse drug effects; COPD, chronic obstructive pulmonary disease; DOS, Delirium Observation Scale; DRP, drug-related problems; ED, emergency department; EQ-5D, European Quality of Life—5 Dimensions; EQ-VAS, European Quality of Life—Visual Analog Scale; GDS, The Geriatric Depression Scale; GP, general practitioner; GP-GP, good palliative–geriatric practice; HP, heart failure; HQROL, health-related quality of life; IADL, instrumental activities of daily living; MPRs, medication-related problems; MTM, medication therapy management; MMSE, Mini Mental State Examination; MSAS, Memorial Symptom Assessment Scale; NPH, the Nottingham Health Profile; PIM, potentially inappropriate medications; RASP, rationalization of home medication by an Adjusted STOPP list in older Patients; RUM, rational use of medication.

Table 3 Basal characteristics and results of primary studies included

Ref.	Patient baseline characteristics (intervention group vs. control group)	Clinical results (intervention group vs. control group)	Healthcare resources utilization results (intervention group vs. control group)
(7) Intervention group ($n = 252$) vs. control group ($n = 251$)	Age (years) (mean): 79 vs. 78.8 Sex (women) (%): 60 vs. 57 Drugs (mean): 10.8 vs. 10.9 Comorbidities: Arthritis/rheumatism (%): 78 vs. 75 Heart disease/failure (%): 51 vs. 54 Peripheral vascular disease (%): 29 vs. 32 Cerebrovascular accident (%): 11 vs. 13 Parkinson disease (%): 2.8 vs. 2 Dementia (%): 8.7 vs. 5.2 Depression (%): 36 vs. 27 Cancer (%): 6 vs. 7.6 COPD/chronic bronchitis (%): 23 vs. 21 Asthma (%): 7 vs. 11 Diabetes (%): 41 vs. 40 Gastroduodenal ulcer (%): 8 vs. 6.8 Gastro-esophageal reflux (%): 19 vs. 16 Liver disease (%): 6.3 vs. 6 Chronic kidney failure (%): 12 vs. 18 Arterial hypertension (%): 81 vs. 83 Dyslipidemia (%): 69 vs. 68 Prostate syndrome (%): 56 vs. 52	Annual mortality (%): 2.8 vs. 2.4 ($P = 0.784$) Six-month HQROL (variation of EQ-5D test score): −2.09 vs 0.67 ($P = 0.324$) Six months' adherence (%): 76.4 vs. 64.1 ($P = 0.005$)	Annual primary care visits per patient (mean): 24 vs. 23 ($P = 0.670$) Annual hospital emergency visits per patient (mean): 0.9 vs. 1.1 ($P = 0.061$) Annual specialty care visits per patient (mean): 6.9 vs. 6.8 ($P = 0.302$) Annual complementary test per patient (mean): 2 vs. 2 ($P = 0.581$) Annual hospitalized patients (%): 23.3 vs. 25.2 ($P = 0.616$)
(8) Intervention group ($n = 74$) vs. control group ($n = 78$)	Age (years) (mean): 71.1 vs. 72.9 Sex (women) (%): 51 vs. 58 Self-reported health-status good or excellent (%): 68 vs. 60 Total no. of chronic conditions: 1.4 vs. 1.4 Polypharmacy (%)[a]: 62 vs. 62 Frequent visits to physician (%)[b]: 51 vs. 35 ($P < 0.005$) ED visits in previous year: 22 vs. 23		Appointments with physicians: 8.45 vs. 7.94 ($P =$ not reported) Hospital admissions: 0.53 *vs.* 0.58 ($P =$ not reported) ED visits: 0.86 vs. 0.79 ($P =$ not reported) Day surgeries: 0.42 vs. 0.32 ($P =$ not reported) Total costs ($): 9121 vs. 9222 ($P =$ not reported) Total costs including cost of intervention ($): 12 923 vs. 9222 ($P = 0.033$)
(9) Intervention group ($n = 59$) vs. control group ($n = 59$)	Age (years) (mean): 80 vs. 80 Sex (women) (%): 47.5 vs. 52.5 Patients admitted to hospital wards (%): 88.1 vs. 89.8 No. of medications taken regularly at home (mean): 10.5 vs. 10 No. of chronic health problems (mean): 5.5 vs. 5.3 Charlson index (mean): 6.8 vs. 6.7 Chronic diseases (%): Hypertension: 69.5 vs. 68.7 Diabetes: 44.1 vs. 44.1 Dyslipidemia: 44.1 vs. 25.4 ($P = 0.003$) Atrial fibrillation: 42.4 vs. 33.9 Chronic kidney failure: 23.7 vs. 25.4 Ischemic heart disease: 30.5 vs. 16.9	Drug-related negative outcomes (mean): 0.95 vs. 1.44 ($P = 0.01$). Drug-related negative outcomes (% patients with at least one): 62.7 vs. 79.7 ($P = 0.042$) Mortality at 6 months (%): 18.6 vs. 22 ($P = 0.647$)	Patients readmitted within 180 days after discharge (%): 54.2 vs. 37.3 ($P = 0.065$) Mean hospital stay (h): 194.7 vs. 242.5 ($P = 0.186$)

(continued)

Table 3 Continued

Ref.	Patient baseline characteristics (intervention group vs. control group)	Clinical results (intervention group vs. control group)	Healthcare resources utilization results (intervention group vs. control group)
(10) Intervention group ($n = 13$ nursing homes) vs. control group ($n = 12$ nursing homes) (number of patients included not available)	Age (%): < 65 years: 6.8 vs. 6.3 65–74 years: 16.6 vs. 15 75–84 years: 40.6 vs. 35.5 >84 years: 36 vs. 43.3 Sex (women) (%): 74.4 vs. 72.5 Physical functioning (%) Moderate impairment: 40.1 vs. 41.9 Severe impairment: 48.7 vs. 48.1 Cognitive function (%) Moderate impairment: 39.7 vs. 41 Severe impairment: 30.3 vs. 35.8 Number diagnoses (%): 4–5: 22.9 vs. 22.6 6: 15.3 vs. 15.4 Dementia (%): 21.7 vs. 19.6 Alzheimer's disease (%): 7 vs. 10.5 Diabetes (%): 31.5 vs. 26.1 Cerebrovascular accident (%): 28.7 vs. 23.2 Heart failure (%): 10.7 vs. 13.3 Coronary artery disease (%): 5.1 vs. 5 Arrhythmia (%): 8.5 vs. 11.7 Hypertension (%): 36.6 vs. 36.5 Other cardiovascular disease (%): 13.4 vs. 12.9 Cancer (%): 5.7 vs. 5.5	Mortality (mean): Pre-intervention: 12.1 vs. 17.13 Post-intervention: 14.4 vs. 17.08 Change pre–post intervention (%): 19 vs. -0.3 (P = not available)	Hospitalizations (mean): Pre-intervention: 45.4 vs. 35.8 Post-intervention: 49.8 vs. 44.1 Change pre–post intervention (%): 9.7 vs. 23.2 (P = not available) Number of hospitalizations due to adverse events (mean): Pre-intervention: 3 vs. 2.5 Post-intervention: 2.7 vs. 3.1 Change pre–post intervention (%): −10 vs. 24 (P = not available)
(11) Intervention group ($n = 107$) vs. control group ($n = 102$)	Age (years) (mean): 79 vs. 79.7 Sex (women) (%): 65.4 vs. 68.6 No. of medications taken regularly at home (mean): 8.5 vs. 7.4 ($P < 0.05$) Diagnoses per patient (mean): 5.1 vs. 4.5 ($P < 0.05$) Self-rated health score: 2.7 vs. 2.8 Hypertension (%): 67 vs. 61 Hyperlipidemia (%): 48 vs. 39 Ischemic heart disease (%): 40 vs. 40 Cardiac decompensation (%): 26 vs. 15 Atrial fibrillation (%): 20 vs. 16 Peripheral artery disease (%): 8 vs. 13 Cerebrovascular disease (%): 16 vs. 11 Cancer (%): 21 vs. 18 Pulmonary disease (%): 18 vs. 21 Polymyalgia rheumatica (%): 8 vs. 10 Diabetes (%): 28 vs. 26 Gastrointestinal disease (%): 18 vs. 19 Thyroid disease (%): 14 vs. 13 Anemia (%): 23 vs. 22 Osteoporosis (%): 14 vs. 15 Psychiatric disease (%): 12 vs. 23 Diseases of the urinary tract (%): 12 vs. 14 Chronic pain (%): 29 vs. 24	Self-rated health score change (mean): −0.02 vs. −0.27 (Dif: −0.25; $P = 0.047$)	Number of hospitalizations: 1.7 vs. 2.7 (mean); 1 vs. 2 (median) (P = n.s.) (not reported exact value of P) Mean hospital stay (days): 12 vs. 18 (median); 6 vs. 12.5 (mean) (P = n.s.) (not reported exact value of P) Cost of the intervention: €79 ($106)

(continued)

Table 3 Continued

Ref.	Patient baseline characteristics (intervention group vs. control group)	Clinical results (intervention group vs. control group)	Healthcare resources utilization results (intervention group vs. control group)
(12) Intervention group ($n = 87$) vs. control group ($n = 91$)	Aged (years) (mean): 77.9 vs. 78.4 Sex (women) (%): 41.4 vs. 35.2 Diabetes (%): 46 vs. 25 ($P = 0.004$) Hypertension (%): 29 vs. 23 Hyperlipidemia (%): 29 vs. 23 Cerebrovascular accident (%): 3.5 vs. 3.3 Ischemic heart disease (%): 24 vs. 32 Renal disease (%): 6.9 vs. 6.6 Hepatic disease (%): 0 vs. 1.1 Pulmonary disease (%): 13 vs. 10 Cancer (%): 4.6 vs. 7.7 GDS index score $\leq$ 5 (%): 79 vs. 76 Barthel index score: 93 vs. 93 IADL scale score: 19 vs. 18 EQ-5D test score: 0.833 vs. 0.819 EQ-VAS test score: 65 vs. 66	Mortality (%): 2 % vs. 8 % ($P = 0.06$) Changes from baseline in: GDS index score: −0.98 vs. −0.63 ($P = 0.0405$) Barthel index score: −4.09 vs. −1.94 ($P = 0.0391$) IADL scale score: −1.25 vs. −1.57 ($P = 0.0394$) EQ-5D test: 0.216 vs. −0.01 ($P = 0.0464$) EQ-VAS test: 2.10 vs. 4.98 ($P = 0.0455$)	Total outpatient department expenditure (€): 120 583 vs. 136 357 (Dif: −15 774) Total ED expenditure (€): 12 001 vs. 23 607 (Dif: −11 606) Total inpatient department expenditure (€): 90 195 vs. 137 171 (Dif: −46 976) Total expenditure (€): 222 781 vs. 297 130 (Dif: −74 349) Difference in total expenditure between groups (€): 854
(13) (15) (16) (17) Intervention group ($n = 208$) vs. control group ($n = 178$)	Age (years) (mean): 82.3 vs. 82.7 Sex (women) (%): 47 vs. 50 Hearing impairment with hearing aid (%): 75 vs. 59 Vision impairment with glasses (%): 49 vs. 56 MMSE score (mean): 26.2 vs. 26.6 Barthel Index score (mean): 89.6 vs. 92 EQ-5D test score: 0.62 vs. 0.63 Previous diagnoses: Infectious and parasitic diseases (%): 47 vs. 41 Neoplasms (%): 43 vs. 40 Blood diseases (%): 30 vs. 32 Endocrine, nutritional, and metabolic diseases (%): 49 vs. 50 Mental and behavioral disorders (%): 38 vs. 31 Diseases of the nervous system (%): 38 vs. 30 Diseases of the circulatory system (%): 95 vs. 97 Diseases of the respiratory system (%): 54 vs. 56 Diseases of the digestive system (%): 56 vs. 52 Diseases of the musculoskeletal system/connective tissue (%): 80 vs. 76	Results at 2-year follow up: Mortality (%): 18.8 vs. 27 (HR = 1.51; $P = 0.057$) EQ-5D test score: 0.60 vs. 0.62 ($P = 0.554$) Transition between frailty stages: the proportion of pre-frail participants were larger in the intervention group ($P = 0.004$) and the proportion of frail and deceased participants were smaller ($P = 0.002$) Results at 3-year follow up: Mortality (%): 27.9 vs. 38.5 (HR = 1.49; $P = 0.026$) NNT to avoid 1 death: 10 (CI 95% = 5–85)	Results at 2-year follow up: Number of hospitalizations (mean): 2.1 vs. 2.4 ($P = 0.212$) Mean hospital stay (days): 11.1 vs. 15.2 ($P = 0.035$) Nursing home admittance (%): 12.5 vs. 18.9 (HR = 1.63; $P = 0.065$) Total cost per patient (mean) (€): 33 371 vs. 30 490 ($P = 0.432$) Cost per life year gained (€): 23 400 Cost per QALY (€): 45 987 Results at 3-year follow up: Number of hospitalizations (mean): 2.8 vs. 3.4 ($P = 0.06$) Mean hospital stay (days): 18.4 vs. 21 ($P = 0.02$) Nursing home admittance (%): 14.4 vs. 18.4 ($P = 0.23$) Total cost per patient (mean) (€): 71 905 vs. 65 626 ($P = 0.43$)

(continued)

Table 3 Continued

Ref.	Patient baseline characteristics (intervention group vs. control group)	Clinical results (intervention group vs. control group)	Healthcare resources utilization results (intervention group vs. control group)
(14) Intervention group ($n = 91$) vs. control group ($n = 84$)	Age (years) (mean): 84.5 vs. 84.5 Sex (women) (%): 48 vs. 56 Age-adjusted Charlson comorbidity score (median): 7 vs. 6. EQ-5D test score in admission (mean): 0.33 vs. 0.31 Number of drugs (median): 9 vs. 10 Potentially inappropriate medication based in RASP list (median): 3 vs. 3	During hospital stay: Mortality (%): 2.2 vs. 1.2 ($P = 1.000$) Patients suffering from *de novo* delirium (%): 13.2 vs. 13.3 ($P = 1.000$) Number of falls per patient (median): 0 vs. 0 ($P = 0.742$) Patients with one or more falls (%): 4.5 vs. 7.5 ($P = 0.520$) After discharge: Mortality (%): 6.7 vs. 7.5 ($P = 1.000$) Number of falls per patient (median): 0 vs. 0 ($P = 0.954$) Patients with one or more falls (%): 29.3 vs. 28.2 ($P = 1.000$) EQ-5D test score change (mean): 0.358 vs. 0.294 ($P = 0.008$)	After discharge: Patients with one or more readmissions (%): 34.5 vs. 39.2 ($P = 0.629$) Electively readmitted patients (%): 5.7 vs. 8.9 ($P = 0.439$) Patients with one or more ED visits (%): 28.7 vs. 39.2 ($P = 0.189$) Patients with one or more ED visits without readmission (%): 1.1 vs. 8.7 ($P = 0.021$)

Notes: The study measured expenditures in Taiwan dollars. In our study, we show it in Euros. COPD, chronic obstructive pulmonary disease; ED, emergency department; EQ-5D, European Quality of Life—5 Dimensions; EQ-VAS, European Quality of Life—Visual Analog Scale; GDS, The Geriatric Depression Scale; HQROL, health-related quality of life; HR, hazard ratio; IADL, instrumental activities of daily living; MMSE, Mini Mental State Examination; NNT, number needed to treat; QALY, quality-adjusted life year.
a: Polypharmacy: four or more active medications.
b: Frequent visits to doctor: five or more visits in previous 6 months or 10 or more visits in previous year.

a cost of €23 400 per life year gained and €45 987 per quality-adjusted life year gained. However, they did not find differences in the average expenditure per patient although the expenditure was somewhat higher in the intervention group due to the costs associated with intervention care. In addition, two other studies measured different types of costs.[8,12] In one study, the care of patients in the intervention group during the study period cost ~$3000 more than that in the control group, mainly due to the cost of the intervention.[8] However, in another study, a savings of €854 per patient per year was documented in the intervention group although the cost of the intervention was not calculated.[12]

Assessment of the quality of the included studies

The assessment of the quality of the included studies is shown in Supplementary appendix S3.

The included SR is of very high quality, with low risk of bias in all the domains in which it was appropriate to evaluate (it was not evaluated in the meta-analyses domains).[6]

Primary studies were included and usually showed high or uncertain risk bias in several domains.[7–14] The study by Mazya et al.[13] had the fewest sources of bias.

Five studies had a low risk of bias in the domains of randomization and allocation concealment,[7–9,11,13] two studies were considered with an unclear risk,[10,12] because they had no data for assessment, and one study had a high risk because it did not use a correct randomization procedure.[14] Due to the nature of the studies, blinding of the patients and the participating staff was practically impossible. However, all studies were assigned a high risk of bias in this domain because it is likely that the results were influenced.

Regarding blinding of the evaluators, a low risk of bias was assigned to five of the included studies,[7–9,11,13] and a high risk was assigned to the other three studies because they did not perform blinding, and the variables evaluated were subjective.[10,12,14]

Four studies had a low risk of bias in the domain of selective reporting of results,[8,9,13,14] while in the other four studies,[7,10,11,13] an unclear risk of bias was assigned because the data were insufficient to determine the risk.

Finally, two of the studies were at high risk of bias in the domain of other biases because in both studies the doctors in the intervention group received recommendations by the pharmacist and could have been influenced because themselves provided cares to patients in control group.[7,8] Additionally, the study by Gray et al.[8] included a non-prespecified subgroup analysis.

Discussion

The included studies generally showed a modest effect of the interventions, for both the clinical variables and the health resources use related ones. Agreement was observed between the included SR and the primary studies.

The interventions carried out and the role played by pharmacists were variable between studies. We found studies with complex interventions integrated into a more ambitious care plan, with multiple professionals involved,[8,10,13] as well as simpler interventions with few professionals involved.[7,9] The role of pharmacist was very important in some studies,[7,9–12] and more secondary in others.[8,13] These results are in line with our previous thinking that the functions of pharmacists in the care of chronic patients are not established in a clear and generalized manner. This is partly due to the variability of health systems among countries and even among regions within the same country.[40] The definition of the role of each professional is, below our point of view, one of the cornerstones of the optimization of cares in these patients.

The studies included in the SR[6] showed improvements in surrogate RUM variables, correction of potential medication errors and pharmacological expenditure. However, improvements were not observed in mortality, HRQOL, adverse events and hospital admissions.

Regarding the individual studies, only one of the four studies that measured mortality[13] showed differences in favor of the intervention group. The longer follow-up time of this study probably influenced on this achievement. The chronic patients often show a slow deterioration of their health state; therefore, a longer follow-up time is usually required to observe the effect of an intervention.

Regarding the remaining clinical variables measured, including patient health status or other variables (HRQOL, falls, negative results associated with medication, etc.), only four of the studies analyzed showed significantly positive results in the intervention group.[9,11,12,14] Many of these variables were subjective and could be influenced by the open nature of most studies.

The results related to the use of health resources (hospital admissions, visits to the emergency room, medical visits) and costs did not show, in general, differences between the intervention and control groups although a tendency toward better results was observed in some studies.[10,11,13] The cost-effectiveness and cost-utility analyses performed by Mazya et al.[13] showed a good cost–benefit ratio in connection with the internationally accepted values.[18]

Some authors have performed reviews similar to ours, although with certain differences. Patterson et al.[19] examined interventions performed with or without pharmaceutical intervention in patients over 65 years of age with two or more chronic diseases and polypharmacy. In contrast, in the studies included in Holland et al.,[20] the interventions were conducted by pharmacists of the health system or community on patients over 60 years of age and with two or more chronic pathologies. Both reviews showed results similar to ours, with positive results in favor of the intervention group in some variables but not in others.

Unlike these studies, the reviews by Boult et al.[21] and Lee et al.[22] showed very positive results in favor of the intervention group. These results, however, may be partial artifacts due to the inclusion only of studies that reported some positive results[21] or because combined variables, which are less reliable than simple variables, were used.[22] The study by Boult et al.[21] analyzed models of care in elderly, chronic patients, including models with participation of a pharmacist, while the study by Lee et al.[22] focused on the effect of pharmaceutical interventions alone or within an interdisciplinary team on chronic or non-chronic patients over 65 years of age. Finally, Wallerstedt et al.[23] conducted an SR and meta-analysis on the influence of medication review, performed or not performed by pharmacists, in nursing home patients and did not find differences between the intervention and control groups in mortality and hospital admissions.

To the best of our knowledge, this is the first study aimed to synthesize clinical health results and the use of health resources achieved by interventions on CCPs conducted by the pharmacist of a health system in collaboration with other health professionals.

Evidence indicates that the actions carried out by an interdisciplinary team improve the health and economic results compared with the care provided by health professionals separately,[24] which is also more difficult to conduct and maintain over time.[25] This phenomenon is accentuated in chronic patients due to the complexity of the cases.[5,26] However, numerous examples exist in this field in which pharmacists perform interventions in isolation.[27–30] In contrast, numerous international health organizations and scientific societies have noted the need to form interdisciplinary teams including pharmacists to optimize the care of chronic patients.[31–35] Therefore, in the present study, it was decided to include only studies in which the pharmacist performed interventions while closely collaborating with the other professionals in charge of patient care. Although observational studies can provide more information about the effect of an intervention in real-life conditions than RCTs, this kind of studies has a higher risk of bias. Considering this, and the numerous factors that influence on the evolution of chronic patients, we decided only to include intervention trials to clarify more accurately the effect of the different interventions.

Another strength of the present study is that only studies that measured variables with a direct health impact were selected, i.e. studies measuring subrogate variables only were not included. This is because pharmaceutical intervention by an interdisciplinary team has been shown to achieve significant improvements in surrogate RUM variables, such as the reduction of potential DRPs, the improvement of adherence or the optimization of prescriptions,[5,36–38] but there is no solid evidence that it has a significant clinical and socioeconomic impact.[19,23] In addition, the use of surrogate variables usually results in greater effects than when final variables are used, which gives more value to our study.[39]

Limitations

One of the main limitations of this SR is the clinical heterogeneity of the included studies, which did not allow a synthesis and aggregation of the results in a meta-analysis. The main sources of heterogeneity include the population differences between studies and the different interventions used. To achieve significant representativeness, different populations were included in the present study, encompassing, within the definition of CCP, patients who are similar but who are not equal, such as patients with multimorbidity or fragile patients. As we stated before, the functions of pharmacists in the care of chronic patients are not established in a clear and generalized manner. This fact is partly due to the variability of health systems among countries and even among regions within the same country.[40] Thus, our study found complex interventions integrated into a more ambitious care plan, with multiple professionals involved,[8,10,13] as well as simpler interventions with few professionals involved.[7,9] Finally, the setting in which the study is performed, including a hospital[9,14] or primary care,[6–8,10–13] largely influences many of the aspects of the study and increases heterogeneity. The final limitations are due to the established time limit of 10 years, which may have reduced the number of studies, and the selection of studies in English, which may have also excluded some local experiences.

Conclusions

It was not possible to determine with certainty which interventions produce the best results and which do not provide relevant improvements. The clinical heterogeneity of the included studies, specially the population, the numerous factors that influence the clinical evolution of CCPs and the poor follow-up of most studies probably contributed to this uncertainty. A case management model in which health professionals create an interdisciplinary team, with periodic meetings in which each specific case is discussed, in the style of the study by Mazya et al.,[13] could be a good model to imitate because this obtained the best long-term results. Based on the uncertainty generated by the present study, well-designed RCTs with large populations of patients and with clearly defined and ambitious interventions, outcomes and follow-up times are needed to definitively determine the influence of interventions by interdisciplinary teams including a pharmacist on CCPs. Although with a higher risk of bias, observational or quasi-experimental studies can also contribute to know more about the effect of the interventions in the daily clinical practice.

Supplementary data

Supplementary data are available at *EURPUB* online.

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Conflicts of interest: None declared.

Key points

- Pharmaceutical intervention can significantly resolve drug-related problems in chronic patients as pharmacotherapeutic optimization by reviewing the adequacy of the treatment, reconciling it and improving adherence, among other actions.
- Evidences about results in health and resource utilization on specific interventions models for chronic patients with high complexity, led by pharmacists integrated within an interdisciplinary team.
- This review highlighted the need of defining the functions of pharmacists within interdisciplinary groups and also in the management of chronic patients.

References

1 Contel JC, Muntané B, Camp L. Care of the chronic patient in a complex situation: the challenge of building an integrated care scenario. *Aten Primaria* 2012;44:107–13.

2 McPhail SM. Multimorbidity in chronic disease: impact on health care resources and costs. *Risk Manag Healthc Policy* 2016;9:143–56.

3 Palmer K, Marengoni A, Forjaz MJ, et al.; Joint Action on Chronic Diseases and Promoting Healthy Ageing Across the Life Cycle (JA-CHRODIS). Multimorbidity care model: recommendations from the consensus meeting of the Joint Action on Chronic Diseases and Promoting Healthy Ageing across the Life Cycle (JA-CHRODIS). *Health Policy* 2018;122:4–11.

4 Fouche C, Kenealy T, Mace J, Shaw J. Practitioner perspectives from seven health professional groups on core competencies in the context of chronic care. *J Interprof Care* 2014;28:534–40.

5 Spinewine A, Fialová D, Byrne S. The role of the pharmacist in optimizing pharmacotherapy in older people. *Drugs Aging* 2012;29:495–510.

6 Alldred DP, Kennedy MC, Hughes C, et al. Interventions to optimise prescribing for older people in care homes. *Cochrane Database Syst Rev* 2016;2:CD009095.

7 Campins L, Serra-Prat M, Gózalo I, et al. (REMEI Group). Randomized controlled trial of an intervention to improve drug appropriateness in community-dwelling polymedicated elderly people. *Fam Pract* 2017;34:36–42.

8 Gray D, Armstrong CD, Dahrouge S, et al. Cost-effectiveness of Anticipatory and Preventive interdisciplinary Team Care for complex patients: evidence from a randomized controlled trial. *Can Fam Physician* 2010;56:e20–9.

9 Juanes A, Garin N, Mangues MA, et al. Impact of a pharmaceutical care programme for patients with chronic disease initiated at the emergency department on drug-related negative outcomes: a randomised controlled trial. *Eur J Hosp Pharm* 2018;25:274–80.

10 Lapane KL, Hughes CM, Christian JB, et al. Evaluation of the fleetwood model of long-term care pharmacy. *J Am Med Dir Assoc* 2011;12:355–63.

11 Lenander C, Elfsson B, Danielsson B, et al. Effects of a pharmacist-led structured medication review in primary care on drug-related problems and hospital admission rates: a randomized controlled trial. *Scand J Prim Health Care* 2014;32:180–6.

12 Lin HW, Lin CH, Chang CK, et al. Economic outcomes of pharmacist-physician medication therapy management for polypharmacy elderly: a prospective, randomized, controlled trial. *J Formos Med Assoc* 2018;117:235–43.

13 Marczya AL, Garvin P, Ekdahl AW. Outpatient comprehensive geriatric assessment: effects on frailty and mortality in old people with multimorbidity and high health care utilization. *Aging Clin Exp Res* 2019;31:519–25.

14 Van der Linden L, Decoutere L, Walgraeve K, et al. Combined use of the rationalization of home medication by an adjusted STOPP in older patients (RASP) list and a pharmacist-led medication review in very old inpatients: impact on quality of prescribing and clinical outcome. *Drugs Aging* 2017;34:123–33.

15 Ekdahl AW, Alwin J, Eckerblad J, et al. Long-term evaluation of the ambulatory geriatric assessment: a frailty intervention trial (AGe-FIT): clinical outcomes and total costs after 36 months. *J Am Med Dir Assoc* 2016;17:263–8.

16 Ekdahl AW, Wirehn AB, Alwin J, et al. Costs and effects of an ambulatory geriatric unit (the AGe-FIT study): a randomized controlled trial. *J Am Med Dir Assoc* 2015;16:497–503.

17 Lundqvist M, Alwin J, Henriksson M, et al. Cost-effectiveness of comprehensive geriatric assessment at an ambulatory geriatric unit based on the AGe-FIT trial. *BMC Geriatr* 2018;18:32.

18 Claxton K, Sculpher M, Carroll S. *Value-Based Pricing for Pharmaceuticals: Its Role, Specification and Prospects in a Newly Devolved NHS*. York, UK: Centre for Health Economics, University of York, 2011 (CHE Research paper 60).

19 Patterson SM, Cadogan CA, Kerse N, et al. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev* 2014;10: CD008165.

20 Holland R, Desborough J, Goodyer L, et al. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. *Br J Clin Pharmacol* 2008;65:303–16.

21 Boult C, Green AF, Boult LB, et al. Successful models of comprehensive care for older adults with chronic conditions: evidence for the Institute of Medicine's "retooling for an aging America" report. *J Am Geriatr Soc* 2009;57: 2328–37.

22 Lee JK, Slack MK, Martin J, et al. Geriatric patient care by U.S. pharmacists in healthcare teams: systematic review and meta-analyses. *J Am Geriatr Soc* 2013;61: 1119–27.

23 Wallerstedt SM, Kindblom JM, Nylén K, et al. Medication reviews for nursing home residents to reduce mortality and hospitalization: systematic review and meta-analysis. *Br J Clin Pharmacol* 2014;78:488–97.

24 Chisholm-Burns MA, Kim Lee J, Spivey CA, et al. US pharmacists' effect as team members on patient care: systematic review and meta-analyses. *Med Care* 2010;48: 923–33.

25 Smith SM, Wallace E, O'Dowd T, Fortin M. Interventions for improving outcomes in patients with multimorbidity in primary care and community settings. *Cochrane Database Syst Rev* 2016;3:CD006560.

26 Stokes J, Panagioti M, Alam R, et al. Effectiveness of case management for 'at risk' patients in primary care: a systematic review and meta-analysis. *PLoS One* 2015;10: e0132340.

27 Olesen C, Harbig P, Buus KM, et al. Impact of pharmaceutical care on adherence, hospitalisations and mortality in elderly patients. *Int J Clin Pharm* 2014; 36:163–71.

28 Jódar-Sánchez F, Martín JJ, López del Amo MP, et al. Cost-utility analysis of a pharmacotherapy follow-up for elderly nursing home residents in Spain. *J Am Geriatr Soc* 2014;62:1272–80.

29 Meid AD, Lampert A, Burnett A, et al. The impact of pharmaceutical care interventions for medication underuse in older people: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2015;80:768–76.

30 Geurts MM, Stewart RE, Brouwers JR, et al. Implications of a clinical medication review and a pharmaceutical care plan of polypharmacy patients with a cardiovascular disorder. *Int J Clin Pharm* 2016;38:808–15.

31 National Center for Chronic Disease Prevention and Health Promotion. A PROGRAM GUIDE FOR PUBLIC HEALTH: Partnering with Pharmacists in the Prevention and Control of Chronic Diseases. 2012.

32 The Academy of Medical Sciences. Multimorbidity: A Priority for Global Health Research. Available at: https://acmedsci.ac.uk/policy/policy-projects/multimorbidity (11 February 2019, date last accessed).

33 Royal Pharmaceutical Society. Medicines Optimisation: Helping Patients to Make the Most of Medicines. Good Practice Guidance for Healthcare Professionals in England. 2013.

34 European Association of Hospital Pharmacists. The EAHP Statement on an Ageing Society. 2016.

35 Sociedad Española de Farmacia Hospitalaria. Plan Estratégico de la Sociedad Española de Farmacia Hospitalaria sobre Atención Farmacéutica. 2012.

36 Chhabra PT, Rattinger GB, Dutcher SK, et al. Medication reconciliation during the transition to and from long-term care settings: a systematic review. *Res Social Adm Pharm* 2012;8:60–75.

37 Castelino RL, Bajorek BV, Chen TF. Targeting suboptimal prescribing in the elderly: a review of the impact of pharmacy services. *Ann Pharmacother* 2009;43:1096–106.

38 Verrue CLR, Petrovic M, Mehuys E, et al. Pharmacists' interventions for optimization of medication use in nursing homes: a systematic review. *Drugs Aging* 2009;26:37–49.

39 Ciani O, Buyse M, Garside R, et al. Comparison of treatment effect sizes associated with surrogate and final patient relevant outcomes in randomized controlled trials: meta-epidemiological study. *BMJ* 2013;346:f457.

40 Smith SM, O'Kelly S, O'Dowd T. GPs' and pharmacists' experiences of managing multimorbidity: a "Pandora's box". *Br J Gen Pract* 2010;60:e285–94.