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Intervention effectivenessby pharmacistsintegrated within an interdisciplinary health teams on chronic complex patients.

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ABSTRACT

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 (2008-2018): (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 (RCTs).

Results: Nine article were included, one SR and eight RCTs. 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 and EQ-VAS test), 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€ perquality-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.

Key words: Multiple Chronic Conditions, Multimorbidity, Clinical Pharmacist, Interdisciplinary Health Team, Systematic Review

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, polypatholgical 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 non-health professionals. The search for an integrated care model requires redefinition of the roles of traditional health care 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 October 11, 2018. Search strategy is described in Appendix 1. The search was limited by language (English) and by date (2008-2018). 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 (HAG) 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 (HAG and BSR) 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 (HAG), and any discrepancies were resolved by discussion and consensus with a second investigator (BSR).

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 (HAG and SSF), 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 Appendix 2.

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 themethodological 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 a 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 ten 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 included, seven were RCTs[7-9,11-14], and one was a cluster randomized controlled trial[10]. The characteristics and results are shown in Table 2and 3.

Interventions performed

The interventions conducted by the pharmacist in the eight included RCTs[7-14]consisted mainly inputting 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[8,13], 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. (2017)[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. (2011)[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.

Clinical results

Only one of five studies showed significant improvements in mortality in the intervention group (in the three-year analysis but not in the two-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 test and EQ-VAS 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. Marcya et al. (2019)[13]measured cost-effectiveness and cost-utility and found 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 approximately $ 3,000 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 Appendix 3.

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 Marcya et al.(2019)[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 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. (2018)[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 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…), 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 utility cost analysis performed by Marcya et al. (2019)[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. (2014)[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. (2008)[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 Boultet al. (2009)[21]and Lee et al. (2013)[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 Boultet al.(2009)[21]analyzed models of care in elderly, chronic patients, including models with participation of a pharmacist, while the study by Lee et al. (2013)[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.(2014)[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 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 to 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 have a higher risk of bias. Considering this, and the numerous factors that influence on the evolution of chronic patients, we decided only 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 multimorbidityor 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 Marcya et al. (2019)[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.

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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 specific interventions models for chronic patients with high complexity, led by pharmacists integrated within an interdisciplinary team, and about which of them produce the best results with regard to health and resource utilization in this special population
- 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 ManagHealthc Policy*. 2016; 5;9:143-56.
3. Palmer K, Marengoni A, Forjaz MJ, Jureviciene E, Laatikainen T, Mammarella F, Muth C, Navickas R, Prados-Torres A, Rijken M, Rothe U, Souchet L, Valderas J, Vontetsianos T, Zaletel J, Onder G, 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(1):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 InterprofCare*. 2014; 28(6): 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, Chen TF, Miller P. 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, López D, Palomera E, Agustí C, Cabré M; (REMEI Group). Randomized controlled trial of an intervention to improve drug appropriateness in community-dwelling polymedicated elderly people. *FamPract*. 2017; 34:36-42.
8. Gray D, Armstrong CD, Dahrouge S, Hogg W, Zhang W. 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, Herrera S, Puig M, FausMJ, Baena MI. 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; 25:274–280.

10. Lapane KL, Hughes CM, Christian JB, Daiello LA, Cameron KA, Feinberg J. 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, Midlöv P, Hasselström J. 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, Chou CY, Yu IW, Lin CC, Li TC, Li CI, Hsieh YW. Economic outcomes of pharmacist-physician medication therapy management for polypharmacy elderly: A prospective, randomized, controlled trial. *J Formos Med Assoc.* 2018; 117: 235-243.
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 ClinExp Res*. 2019; 31(4): 519-525.
14. Van der Linden L, Decoutere L, Walgraeve K, Milisen K, Flamaing J, Spriet I, Tournoy J. 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(2):123-133.
15. Ekdahl AW, Alwin J, Eckerblad J, Husberg M, Jaarsma T, Mazya AL, Milberg A, Krevers B, Unosson M, Wiklund R, Carlsson P. 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, Jaarsma T, Unosson M, Husberg M, Eckerblad J, Milberg A, Krevers B, Carlsson P. 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, Husberg M, CarlssonP, Ekdahl AW. 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. Cardwell CR, Bradley MC, Ryan C, Hughes C. 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, Hall S, Wright D, Loke YK. Does pharmacist-led medication review help to reduce hospital admissions and deaths in older people? A systematic review and meta-analysis. *Br J ClinPharmacol.* 2008; 65:303-16.
21. Boult C, Green AF, Boult LB, Pacala JT, Snyder C, Leff B. Successful models ofcomprehensive 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, Ehrman C, Chisholm-Burns M. 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, Samuelsson O, Strandell A. Medication reviews for nursing home residents to reduce mortality and hospitalization: systematic review and meta-analysis. *Br J ClinPharmacol.* 2014; 78: 488-97.
24. Chisholm-Burns MA, Kim Lee J, Spivey CA, Slack M, Herrier RN, Hall-Lipsy E, Graff Zivin J, Abraham I, Palmer J, Martin JR, Kramer SS, Wunz T. US pharmacists' effect as

team members on patient care: systematic review and meta-analyses. *Med Care*. 2010; 48:923–933.

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, Checkland K, Cheraghi-Sohi S, Bower P. 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, Barat I, Damsgaard EM. 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, García L, Araújo-Santos JM, Epstein D. 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, Seidling HM, Haefeli WE. The impact of pharmaceutical care interventions for medication underuse in older people: a systematic review and meta-analysis. *Br J ClinPharmacol.* 2015; 80: 768-76.
30. Geurts MM, Stewart RE, Brouwers JR, de Graeff PA, de Gier JJ. 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. Morrison CM, Glover D, Gilchrist SM, Casey MO, Lanza A, Lane RI, Patanian M. (2012). Partnering with Pharmacists in the Prevention and Control of Chronic Diseases. Available at https://www.cdc.gov/dhdsp/programs/spha/docs/pharmacist_guide.pdf. Accessed February 2, 2019.
32. The Academy of Medical Sciences. Multimorbidity: a priority for global health research.Available at https://acmedsci.ac.uk/policy/policy-projects/multimorbidity. Accessed Febraury, 11, 2019.

33. Picton C, Wright H (2013). Medicines Optimisation: Helping patients to make the most of medicines. Good practice guidance for healthcare professionals in England. Available at https://www.nhs.uk/about-the-nhs-website/professionals/healthandcare professionals/your-pages/documents/rps-medicines-optimisation.pdf. Accessed February 11, 2019.
34. European Association of Hospital Pharmacists. The EAHP statement on an Ageing Society. Available at http://statements.eahp.eu/sites/default/files/resources/EHAP%20 Policy%20Statement%20on%20Ageing%20Society.pdf. Accessed Febraury, 11, 2019.
35. Sociedad Española de Farmacia hospitalaria. Plan Estratégico de la SEFH sobre Atención Farmacéutica al Paciente Crónico. Available at https://www.sefh.es/sefhpdfs/plan_estrategico_sefh_af_paciente_cronico2012.pdf. AccessedMay 11, 2019.
36. Chhabra PT, Rattinger GB, Dutcher SK, Dutcher SK, Hare ME, Parsons KL, Zuckerman IH. 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; 43:1096–1106.
38. Verrue CL, Petrovic M, Mehuys E, Remon JP, Vander Stichele R. 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, Pavey T, Stein K, Sterne JA, Taylor RS. 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: 285–94.

Table 1
Clinical question PICO(d)

Population	Chronic complex patients defined as any of the following: • Multimorbidity as defined by NICE[11] (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)

GP: general practitioner; HQROL: Health Related Quality of Life; NICE: National Institute for Health and Care Excellence; RCT: Randomized clinical trial.

Table 2
Characteristics of primary studies included.

Ref	Design	Intervention	Comparator	Population (selection criteria)	Outcome measures
(17)	Randomized, open-label, multicentre, 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 (3,6,12 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
(18)	Randomized, open-label, multicentre, clinical trial in a semirural family health network with 18-months 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.

(19)	Randomized, open-label, single centre, 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. 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	Usual pharmacist care (step 3 in intervention group)	65 years and older, length of stay in ED longer than 12 hours, 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
(20)	Cluster randomized, open-label, multicentre, 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	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	Clinical measures: • Mortality • Number of hospitalizations • Number of hospitalization due to adverse events Variables regarding RUM.

		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.		or more cardiovascular medications, or seven or more medications	
(21)	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 understanding of and concordance with drug treatment. Pharmaceutical advice was given to patients and entered into the computerized patient record.	Usual care by their GP	65 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 one to five Healthcare resources utilization: • Number of hospitalizations • Duration of the patient's hospital stay • Estimated cost of intervention Variables regarding RUM

(22)	Randomized, open-label, single center, parallel-arm clinical trial with one-year follow-up. (the recruitment period length was four 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 one-hour 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	65 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
(23) (25) (26) (27)	Randomized, open-label (evaluators were blinded), single centre, parallel-arm clinical trial with planned 2-year follow-up.	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	Usual medical and social care	75 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, low physical activity

	(The follow-up was extended to 3 years)	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 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.			• 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) Healthcare resources utilization: • Number of hospitalizations. • Cost per patient based on: o Number and extent of contacts with the municipal services of care measured by working hours. o Number of visits to primary care facilities, day-care centers in-hospital stays, geriatric ambulatories and other specialist ambulatories. o Admissions to nursing care facilities.

(24)	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 three 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

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 analogue 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

Study	Patient baseline characteristics (Intervention group *vs.* Control group)	Clinical results (intervention group *vs.* control group)	Healthcare resources utilization results (intervention group vs. control group)
(17) 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-oesophageal reflux (%): 19 *vs.* 16 Liver disease (%): 6,3 *vs.* 6 Chronic kidney failure (%): 12, *vs.* 18 Arterial hypertension (%): 81 *vs.* 83 Dyslipidaemia (%): 69 *vs.* 68 Prostate syndrome (%): 56 *vs.* 52	Annual mortality (%): 2.8 *vs.* 2.4 (p = 0.784) Six months 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)
(18) 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 (%)*: 62 *vs.* 62		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)

	Frequent visits to physician (%)†: 51 *vs.* 35 (p < 0.005) ED visits in previous year: 22 *vs.* 23 **Polypharmacy: four or more active medications.* *† Frequent visits to doctor: five or more visits in previous 6 mo or 10 or more visits in previous year*		Total costs ($): 9,121 *vs*. 9,222 (p=not reported) Total costs including cost of intervention ($): 12,923 *vs.* 9,222 (p=0.033)
(19) 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: p=not *vs.* 68.7 Diabetes: 44.1 *vs.* 44.1 Dyslipidaemia: 44.1 *vs.* 25.4 (p=0.003) Atrial fibrillation: 42.4 *vs*. 33.9 Chronic kidney failure: 23.7 *vs.* 25.4 Ischaemic 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 (hours): 194.7 *vs*. 242.5 (p=0.186)
(20) 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	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)

	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		
(21) 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 Hyperlipidaemia (%): 48 *vs.* 39 Ischaemic 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 Anaemia (%): 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 $)

(22) 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 Hyperlipidaemia (%): 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 ≤ 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: -0.89 *vs.* -0.63 (p=0,333)* 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)§ **GDS score5 infers no depression tendency.* *†Total score of Barthel index is 100 and a higher score represents better daily function.* *‡Total score of IADL is 24 and a higher score represents better instrumental daily activity.* *§Using per-protocol analysis, EQ index (0 to 1) and EQ-5D VAS (0 to 100): a higher score represents better health status.*	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 *The study meassured expenditures in Taiwan dollars. In our study we show it in Euros.*
(23) (25) (26) (27) 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 behavioural 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	Results at 2-years-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-years-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-years-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-years-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)

	Diseases of the musculoskeletal system/connective tissue (%): 80 *vs.* 76		Total cost per patient (mean) (€): 71,905 *vs.* 65,626 (p=0.43)
(24) 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)
COPD: Chronic obstructive pulmonary disease. ED: Emergency department. EQ-5D: European Quality of Life-5 Dimensions; EQ-VAS: European Quality of Life-visual analogue 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			

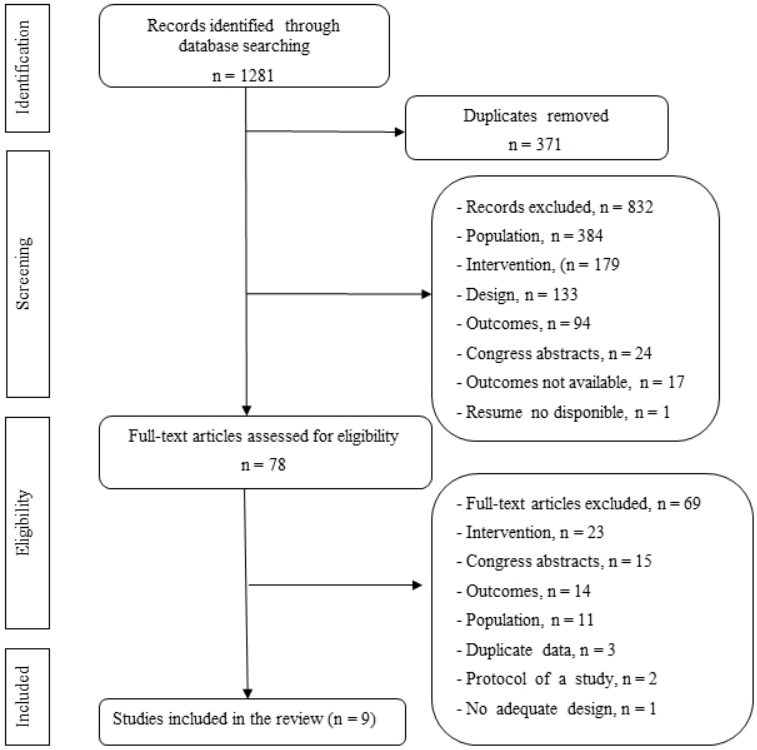

Figure 1. Flowchart of studies included in this systematic review

60x81mm (300 x 300 DPI)

Appendix 1. Search strategies.

Medline

1. pharmacist*.mp.
2. pharmacists/ or pharmacist.ti,ab.
3. (pharmac* adj2 (care* or intervention* or service* or clinical)).ti,ab.
4. (interdisciplinary adj (team or approach or care or healthcare)).ti,ab.
5. (geriatrics or institutionalized or nursing home).ti,ab.
6. (polypatology or polypharm* or multimorbidity or pluripathology or frail*).ti,ab.
7. (chronic* adj (disease* or condition* or patient or complex*)).ti,ab.
8. ((complex or vulnerable or frail) adj patient*).ti,ab.
9. 5 or 6 or 7 or 8
10. 1 or 2 or 3 or 4
11. 9 and 10
12. limit 11 to (english language and yr="2008 -Current")
13. limit 12 to "all child (0 to 18 years)"
14. 12 not 13
15. limit 14 to clinical trial, all
16. limit 14 to comparative study
17. limit 14 to meta analysis
18. limit 14 to systematic reviews
19. 15 or 16 or 17 or 18

Embase

#1 polypathology:ab,ti OR polypharm*:ab,ti OR multimorbidity:ab,ti OR pluripathology:ab,ti OR frail*:ab,ti
#2 (chronic* NEAR/1 (disease* OR condition* OR patient OR complex*)):ab,ti
#3 ((complex OR vulnerable OR frail) NEAR/1 patient*):ab,ti
#4 (geriatrics:ab,ti OR institutionalized:ab,ti OR nursing home:ab,ti
#5 pharmacists:ab,ti OR pharmacist:ab,ti
#6 (pharmac* NEAR/2 (care* OR intervention* OR service* OR clinical)):ab,ti
#7 (interdisciplinary NEAR/1 (team OR approach OR care OR healthcare)):ab,ti
#8

#1 OR #2 OR #3 OR #4
#9 **#5 OR #6 OR #7**
#10 **#8 AND #9**
#11 **#8 AND #9 AND [english]/lim AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [2008-2018]/py**
#12 **#8 AND #9 AND [english]/lim AND ([adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [2008-2018]/py AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)**
#13 **#11 AND ('controlled clinical trial'/de OR 'prospective study'/de OR 'randomized controlled trial'/de)**
#14 **#12 OR #13**

NursingOvid

1. pharmacist*.mp. or Exp Pharmacists/
2. (interdisciplinary adj (team or approach or care or healthcare)).ti,ab.
3. (pharmac* adj2 (care* or intervention* or service* or clinical)).ti,ab.
4. Exp Pharmacists/ or Exp Multidisciplinary Care Team/
5. (geriatrics or institutionalized or nursing home).ti,ab.
6. (polypatology or polypharm* or multimorbidity or pluripathology or frail*).ti,ab.
7. (chronic* adj (disease* or condition* or patient or complex*)).ti,ab.
8. ((complex or vulnerable or frail) adj patient*).ti,ab.
9. 1 or 2 or 3 or 4
10. 5 or 6 or 7 or 8
11. 9 and 10
12. limit 11 to (english language and yr="2008 -Current")
13. limit 12 to "all child (0 to 18 years)"
14. 12 not 13
15. limit 14 to clinical trial, all
16. limit 14 to comparative study
17. limit 14 to meta analysis
18. limit 14 to systematic reviews
19. 15 or 16 or 17 or 18

Cochrane Library

#1 polypathology or polypharm* or multimorbidity or pluripathology or frail*:ti,ab,kw
#2 chronic* near/1 (disease* or condition* or patient or complex*):ti,ab,kw
#3 geriatrics or institutionalized or nursing home:ti,ab,kw
#4 (complex or vulnerable or frail) near/1 patient*:ti,ab,kw
#5 pharmac* near/2 (care* or intervention* or service* or clinical):ti,ab,kw
#6 Pharmacists or pharmacist:ti,ab,kw
#7 interdisciplinary near/1 (team or approach or care or healthcare):ti,ab,kw
#8 #1 OR #2 OR #3 OR #4
#9 #5 OR #6 OR #7
#10 #8 AND #9
#11 #10 with Publication Year from 2008 to 2017
#12 "systematic review":ti,ab,kw (Word variations have been searched)
#13 "meta analysis":ti,ab,kw (Word variations have been searched)
#14 "randomized clinical trial":ti,ab,kw (Word variations have been searched)
#15 "clinical trial":ti,ab,kw (Word variations have been searched)
#16 "comparative study":ti,ab,kw (Word variations have been searched)
#17 #12 or #13 or #14 or #15 or #16
#18 #10 and #17
#19 #18 with Publication Year from 2008 to 2017

Centre for Reviews and Dissemination

1. (polypatology or polypharm* or multimorbidity or pluripathology or frail*) pharmacist*.mp.
2. (geriatrics or institutionalized or nursing home)
3. (chronic* near1 (disease* or condition* or patient or complex*)).
4. ((complex or vulnerable or frail) near1 patient*)
5. (pharmac* near2 (care* or intervention* or service* or clinical))
6. (Pharmacist or pharmacists)
7. (interdisciplinary near1 (team or approach or care or healthcare))
8. #1 OR #2 OR #3 OR #4
9. #5 OR #6 OR #7
10. #8 AND #9
11. (#10) FROM 2008 TO 2017

Appendix 2. Full text articles excluded and causes of exclusion.

Full text articles excluded and causes.	
Reference	**Cause of exclusion**
Adams J, Adinaro D, Baumlin K, Aldeen A, Christensen M, Courtney DM, et al. Gedi wise: Geriatric emergency department innovations in care through workforce, informatics, and structural enhancements. Ann Emerg Med. 2013;62(4):S54–5.	Congress abstract
Altavela JL, Jones MK, Ritter M. A prospective trial of a clinical pharmacy intervention in a primary care practice in a capitated payment system. J Manag Care Pharm. 2008 Nov-Dec;14(9):831-43.	Population
Balsom C,Kelly D, Legge K, King R, Vaters M, Pittman N, Stennett D. Impact of a pharmacist-administered deprescribing intervention on nursing home residents: A randomized controlled trial. Can Pharm J. 2018;151(5):S20.	Congress abstract
Beer C, Loh P, Peng YG, Potter K, Millar A. A pilot randomized controlled trial of deprescribing. Therapeutic Advances in Drug Safety. 2011;2(2):37-43. doi:10.1177/2042098611400332.	Outcomes
Boult C, Green AF, Boult LB, Pacala JT, Snyder C, Leff B. Successful models ofcomprehensive 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 Dec;57(12):2328-37. doi: 10.1111/j.1532- 415.2009.02571.x.	Intervention not carried out by a pharmacists or without collaboration
Burkhardt C, Melton B, Mason R, Kalender-Rich J, Hayley D. Interprofessional geriatric chronic care management outcomes. J Am Geriatr Soc. 2017;65:S101.	Congress abstract
Choudhry NK, Isaac T, Lauffenburger JC, Gopalakrishnan C, Patel L, Lee M et al. Results of the study of a tele-pharmacy intervention for chronic diseases to improve treatment adherence (STIC2IT). Circulation. 2017;136:e460.	Congress abstract
Connolly MJ, Boyd M, Broad JB, Kerse N, Lumley T, Whitehead N, Foster S. The Aged Residential Care Healthcare Utilization Study (ARCHUS): an interdisciplinary, cluster randomized controlled trial designed to reduce acute avoidable hospitalizations from long-term care facilities. J Am Med Dir Assoc. 2015 Jan;16(1):49-55. doi: 10.1016/j.jamda.2014.07.008.	Population
Cooper JA, Cadogan CA, Patterson SM, Kerse N, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy in older people: a Cochrane systematic review. BMJ Open. 2015 Dec 9;5(12):e009235. doi: 10.1136/bmjopen-2015-009235. Review.	Duplicate data
Damery S, Flanagan S, Combes G. Does integrated care reduce hospital activity for patients with chronic diseases? An umbrella review of systematic reviews. BMJ Open. 2016 Nov 21;6(11):e011952. doi: 10.1136/bmjopen-2016-011952.	Intervention not carried out by a pharmacists or without collaboration
Darbon F, Pettersen-Coulombe F, Barbier A, Bussière JF. Impact of pharmaceutical care in elderly patients: A review of the literature. Eur J Hosp Pharm. 2017;24:A23–4. A	Congress abstract
Davies SL, Goodman C, Bunn F, Victor C, Dickinson A, Iliffe S, et al. A systematic review of integrated working between care homes and health care services. BMC Health Serv Res. 2011 Nov 24;11:320. doi: 10.1186/1472-6963-11-320. Review.	Intervention not carried out by a pharmacists or without collaboration
Dennis SM, Zwar N, Griffiths R, Roland M, Hasan I, Powell Davies G, Harris M. Chronic disease management in primary care: from evidence to policy. Med J Aust. 2008 Apr 21;188(8 Suppl):S53-6.	Intervention not carried out by a pharmacists or without collaboration
Elliott LS, Henderson JC, Neradilek MB, Moyer NA, Ashcraft KC, Thirumaran RK. Clinical impact of pharmacogenetic profiling with a clinical decision support tool in polypharmacy home health patients: A prospective pilot randomized controlled trial. PLoS One. 2017 Feb 2;12(2):e0170905. Doi: 10.1371/journal.pone.0170905.	Population
Fletcher M, Rottman-Sagebiel RA, Cupples N, Wang C, MacCarthy D, Conde A et al. Potentially inappropriate medication use in older veterans enrolled in a hospital to home transitional care program. J Am Geriatr Soc. 2017;65:S135–6.	Congress abstract
Forsetlund L, Eike MC, Gjerberg E, Vist GE. Effect of interventions to reduce potentially inappropriate use of drugs in nursing homes: a systematic review of randomised controlled trials. BMC Geriatr. 2011 Apr 17;11:16. doi: 10.1186/1471-2318-11-16.	Outcomes
Foster SJ, Boyd M, Broad JB, Whitehead N, Kerse N, Lumley T, et al. Aged Residential Care Health Utilisation Study (ARCHUS): a randomised controlled trial to reduce acute hospitalisations from residential aged care. BMC Geriatr. 2012;12:54. doi: 10.1186/1471-2318-12-54	Population
Frankenthal D, Lerman Y, Kalendaryev E, Lerman Y. Intervention with the screening tool of older persons potentially inappropriate prescriptions/screening tool to alert doctors to right reatment criteria in elderly residents of a chronic geriatric facility: a randomized clinical trial. J Am Geriatr Soc. 2014 Sep;62(9):1658-65. doi: 10.1111/jgs.12993.	Population
Geurts M, Stewart R, Brouwers J, de Graeff P, de Gier J. Patient beliefs about medicines and quality of life after a clinical medication review and follow-up by a pharmaceutical care plan: A study in elderly polypharmacy patients with a cardiovascular disorder. J Pharm Heal Serv Res. 2015;6(4):171–6. doi: 10.1111/jphs.12104	Intervention not carried out by a pharmacists or without collaboration
Geurts MM, Stewart RE, Brouwers JR, de Graeff PA, de Gier JJ. Implications of a clinical medication review and a pharmaceutical care plan of polypharmacy patients with a cardiovascular disorder. Int J Clin Pharm. 2016 Aug;38(4):808-15. doi: 10.1007/s11096-016-0281-x.	Outcomes

Gines A, Sanchez Navarro I, Santolaya Perrin R, Galan N, Sierra J, Moreno MT, et al. Innappropriate prescribing in elderly patients attending the emergency room. Eur J Hosp Pharm. 2016;23:A56.	Congress abstract
Gorgas Torner MQ, Pàez Vives F, Camós Ramió J, de Puig Cabrera E, Jolonch Santasusagna P, Homs Peipoch E, et al. [Integrated pharmaceutical care programme in patients with chronic diseases]. Farm Hosp. 2012 Jul-Aug;36(4):229-39.	Population
Graabaek T, Hedegaard U, Christensen MB, Clemmensen MH, Knudsen T, Aagaard L. Effect of a medicines management model on medication-related readmissions in older patients admitted to a medical acute admission unit-A randomized controlled trial. J Eval Clin Pract. 2018 Aug 7.	Population
Hasan SS, Thiruchelvam K, Kow CS, Ghori MU, Babar ZU. Economic evaluation ofv pharmacist-led medication reviews in residential aged care facilities. Expert Rev Pharmacoecon Outcomes Res. 2017 Oct;17(5):431-439. doi: 10.1080/14737167.2017.1370376.	Population
Hisashige A. The effectiveness and efficiency of disease management programs for patients with chronic diseases. Glob J Health Sci. 2012 Nov 26;5(2):27-48. doi: 10.5539/gjhs.v5n2p27. P	Intervention not carried out by a pharmacists or without collaboration
Hogg W, Lemelin J, Dahrouge S, Liddy C, Armstrong CD, Legault F,et al. Randomized controlled trial of anticipatory and preventive interdisciplinary team care: for complex patients in a community-based primary care setting. Can Fam Physician. 2009 Dec;55(12):e76-85.	Population
Jódar-Sánchez F, Martín JJ, López del Amo MP, García L, Araújo-Santos JM, Epstein D. Cost-utility analysis of a pharmacotherapy follow-up for elderly nursing home residents in Spain. J Am Geriatr Soc. 2014 Jul;62(7):1272-80. doi: 10.1111/jgs.12890.	Intervention not carried out by a pharmacists or without collaboration
Kaur S, Mitchell G, Vitetta L, Roberts MS. Interventions that can reduce inappropriate prescribing in the elderly: a systematic review. Drugs Aging. 2009;26(12):1013-28. doi: 10.2165/11318890-000000000-00000.	Outcomes
Komagamine J, Sugawara K, Kaminaga M, Tatsumi S. Study protocol for a single-centre, prospective, non-blinded, randomised, 12-month, parallel-group superiority study to compare the efficacy of pharmacist intervention versus usual care for elderly patients hospitalised in orthopaedic wards. BMJ Open. 2018 Jul 30;8(7):e021924. doi: 10.1136/bmjopen-2018-021924.	Study protocol
LaMantia MA, Scheunemann LP, Viera AJ, Busby-Whitehead J, Hanson LC. Interventions to improve transitional care between nursing homes and hospitals: a systematic review. J Am Geriatr Soc. 2010 Apr;58(4):777-82. doi: 10.1111/j.1532-5415.2010.02776.x.	Intervention not carried out by a pharmacists or without collaboration
Lee JK, Slack MK, Martin J, Ehrman C, Chisholm-Burns M. Geriatric patient care by U.S. pharmacists in healthcare teams: systematic review and meta-analyses. J Am Geriatr Soc. 2013 Jul;61(7):1119-27.	Population
Leikola S, Tuomainen L, Peura S, Laurikainen A, Lyles A, Savela E, Airaksinen M. Comprehensive medication review: development of a collaborative procedure. Int J Clin Pharm. 2012 Aug;34(4):510-4. doi: 10.1007/s11096-012-9662-y.	Outcomes
Loganathan M, Singh S, Franklin BD, Bottle A, Majeed A. Interventions to optimise prescribing in care homes: systematic review. Age Ageing. 2011 Mar;40(2):150-62. doi: 10.1093/ageing/afq161.	Outcomes
MacNeil Vroomen JL, Boorsma M, Bosmans JE, Frijters DH, Nijpels G, van Hout HP. Is it time for a change? A cost-effectiveness analysis comparing an interdisciplinary integrated care model for residential homes to usual care. PLoS One. 2012;7(5):e37444. Doi: 10.1371/journal.pone.0037444.	Intervention not carried out by a pharmacists or without collaboration
Malet-Larrea A, Goyenechea E, Gastelurrutia MA, Calvo B, García-Cárdenas V, Cabases JM, et al. Cost analysis and cost-benefit analysis of a medication review with follow-up service in aged polypharmacy patients. Eur J Health Econ. 2017 Dec;18(9):1069-1078. doi: 10.1007/s10198-016-0853-7.	Intervention not carried out by a pharmacists or without collaboration
Martin P, Tamblyn R, Ahmed S, Tannenbaum C. An educational intervention to reduce acute health care consumption in elderly patients with inappropriate drugs - A cluster randomised trial in primary care. Pharmacoepidemiol Drug Saf. 2016;25:378–9.	Congress abstract
Mazya AL, Garvin P, Unosson M,Ekdahl AW. Outpatient comprehensive geriatric assessment: Effects on frailty. Eur Geriatr Med. 2016;7:S16.	Congress abstract
Michalek C, Wehling M, Schlitzer J, Frohnhofen H. Effects of "Fit fOR The Aged" (FORTA) on pharmacotherapy and clinical endpoints--a pilot randomized controlled study. Eur J Clin Pharmacol. 2014 Oct;70(10):1261-7. doi: 10.1007/s00228-014-1731-9.	Intervention not carried out by a pharmacists or without collaboration
Milos V, Rekman E, Bondesson Å, Eriksson T, Jakobsson U, Westerlund T, et al. Improving the quality of pharmacotherapy in elderly primary care patients through medication reviews: a randomised controlled study. Drugs Aging. 2013 Apr;30(4):235-46. doi: 10.1007/s40266-013-0057-0.	Outcomes
Moczygemba LR, Barner JC, Gabrillo ER. Outcomes of a Medicare Part D telephone medication therapy management program. J Am Pharm Assoc (2003). 2012;52(6):e144-52. doi: 10.1331/JAPhA.2012.11258.	Outcomes
Musameh K, Drumm B, Hickey P, O'Sullivan F, O'Malley G, Casey M. A prospective study of standard medical care vs comprehensive geriatric assessment in the care of the frail elderly. Age Ageing. 2017;46:iii13.	Congress abstract
Nazir A, Unroe K, Tegeler M, Khan B, Azar J, Boustani M. Systematic review of interdisciplinary interventions in nursing homes. J Am Med Dir Assoc. 2013 Jul;14(7):471-8. doi: 10.1016/j.jamda.2013.02.005.	Intervention not carried out by a pharmacists or without collaboration
Olsson IN, Runnamo R, Engfeldt P. Drug treatment in the elderly: an intervention in primary care to enhance prescription quality and quality of life. Scand J Prim Health Care. 2012 Mar;30(1):3-9. doi: 10.3109/02813432.2011.629149.	Intervention not carried out by a pharmacists or without collaboration

Pande S, Hiller JE, Nkansah N, Bero L. The effect of pharmacist-provided non-dispensing services on patient outcomes, health service utilisation and costs in low- and middle-income countries. Cochrane Database Syst Rev. 2013 Feb 28;(2):CD010398. doi: 10.1002/14651858.CD010398.	Population
Parekh N, Ali K, Stevenson JM, Davies JG, Schiff R, Van der Cammen T,Harchowal J, et al; PRIME study group. Incidence and cost of medication harm in older adults following hospital discharge: a multicentre prospective study in the UK. Br J Clin Pharmacol. 2018 Aug;84(8):1789-1797. doi: 10.1111/bcp.13613.	Desing
Patterson SM, Cadogan CA, Kerse N, Cardwell CR, Bradley MC, Ryan C, et al. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database of Systematic Reviews 2014, Issue 10. Art. No.: CD008165. DOI: 10.1002/14651858.CD008165.pub3.	Outcomes
Patterson SM, Hughes C, Kerse N, Cardwell CR, Bradley MC. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst Rev. 2012 May 16;(5):CD008165. doi: 10.1002/14651858.CD008165.pub2. Review.	Duplicate data
Patterson SM, Hughes CM, Cardwell C, Lapane KL, Murray AM, Crealey GE. A cluster randomized controlled trial of an adapted U.S. model of pharmaceutical care for nursing home residents in Northern Ireland (Fleetwood Northern Ireland study): a cost-effectiveness analysis. J Am Geriatr Soc. 2011 Apr;59(4):586-93. doi: 10.1111/j.1532-5415.2011.03354.x.	Intervention not carried out by a pharmacists or without collaboration
Patterson SM, Hughes CM, Crealey G, Cardwell C, Lapane KL. An evaluation of an adapted U.S. model of pharmaceutical care to improve psychoactive prescribing for nursing home residents in northern ireland (fleetwood northern ireland study). J Am Geriatr Soc. 2010 Jan;58(1):44-53. doi: 10.1111/j.1532-5415.2009.02617.x.	Intervention not carried out by a pharmacists or without collaboration
Rantz MJ, Zwygart-Stauffacher M, Flesner M, Hicks L, Mehr D, Russell T, et al. The influence of teams to sustain quality improvement in nursing homes that "need improvement". J Am Med Dir Assoc. 2013;14(1):48–52.	Intervention not carried out by a pharmacists or without collaboration
Rodríguez-Perez A, González-Bueno J, Alfaro-Lara ER, Toscano-Guzmán MD, Sierra-Torres MI, Villalba-Moreno AM. Deprescribing strategies in elderly patients or patients with several chronic conditions. Eur J Hosp Pharm. 2014;21:A103–4.	Congress abstract
Rosen SL, McGalliard B, Shane R, Luong D, Tantipinichwong N, Amer K. Safe medication transitions in frailty patients. J Am Geriatr Soc. 2017;65:S43.	Congress abstract
Ruikes FG, Zuidema SU, Akkermans RP, Assendelft WJ, Schers HJ, Koopmans RT. Multicomponent Program to Reduce Functional Decline in Frail Elderly People: A Cluster Controlled Trial. J Am Board Fam Med. 2016 Mar-Apr;29(2):209-17. doi: 10.3122/jabfm.2016.02.150214.	Intervention not carried out by a pharmacists or without collaboration
Ruikes FGH, van Gaal BGI, Oudshoorn L, Zuidema SU, Akkermans RP, Assendelft WJJ, et al. The association between implementation and outcome of a complex care program for frail elderly people. Fam Pract. 2018 Jan 16;35(1):47-52.	Intervention not carried out by a pharmacists or without collaboration
Shim YW, Chua SS, Wong HC, Alwi S. Collaborative intervention between pharmacists and physicians on elderly patients: a randomized controlled trial. Ther Clin Risk Manag. 2018;14:1115-1125. doi:10.2147/TCRM.S146218	Outcomes
Shyh G, Crossman D, Bruneus M, Kochhar S. Impact of pharmacist-led medication reconciliation and discharge counseling on 30-day all-cause hospital readmissions in high-risk patients: A single center study. Pharmacotherapy. 2016;36(12):e209.	Congress abstract
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 Mar 14;3:CD006560. doi: 10.1002/14651858.CD006560.pub3. Review.	Duplicate data
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 Mar 14;3:CD006560. doi: 10.1002/14651858.CD006560.pub3.	Intervention not carried out by a pharmacists or without collaboration
Spoorenberg SLW, Wynia K, Uittenbroek RJ, Kremer HPH, Reijneveld SA. Effects of a population-based, person-centred and integrated care service on health, wellbeing and self-management of community-living older adults: A randomised controlled trial on Embrace. PLoS One. 2018 Jan 9;13(1):e0190751. doi: 10.1371/journal.pone.0190751.	Intervention not carried out by a pharmacists or without collaboration
Tan EC, Stewart K, Elliott RA, George J. Pharmacist services provided in general practice clinics: a systematic review and meta-analysis. Res Social Adm Pharm. 2014 Jul-Aug;10(4):608-22. doi: 10.1016/j.sapharm.2013.08.006.	Population
Thillainadesan J, Gnjidic D, Green S, Hilmer SN. Impact of Deprescribing Interventions in Older Hospitalised Patients on Prescribing and Clinical Outcomes: A Systematic Review of Randomised Trials. Drugs Aging. 2018 Apr;35(4):303-319. doi: 10.1007/s40266-018-0536-4.	Population
Thiruchelvam K, Hasan SS, Wong PS, Kairuz T. Residential Aged Care Medication Review to Improve the Quality of Medication Use: A Systematic Review. J Am Med Dir Assoc. 2017 Jan;18(1):87.e1-87.e14. doi: 10.1016/j.jamda.2016.10.004.	Population
Thomas R, Huntley AL, Mann M, Huws D, Elwyn G, Paranjothy S, Purdy S. Pharmacist-led interventions to reduce unplanned admissions for older people: a systematic review and meta-analysis of randomised controlled trials. Age Ageing. 2014 Mar;43(2):174-87.	Population
Tjia J, Velten SJ, Parsons C, Valluri S, Briesacher BA. Studies to reduce unnecessary medication use in frail older adults: a systematic review. Drugs Aging. 2013 May;30(5):285-307. doi: 10.1007/s40266-013-0064-1.	Outcomes

Tong EY, Roman C, Mitra B, Yip G, Gibbs H, Newnham H, et al. Partnered pharmacist charting on admission in the General Medical and Emergency Short-stay Unit - a cluster-randomised controlled trial in patients with complex medication regimens. J Clin Pharm her. 2016 Aug;41(4):414-8. doi: 10.1111/jcpt.12405.	Population
Touchette DR, Masica AL, Dolor RJ, Schumock GT, Choi YK, Kim Y, Smith SR. Safety-focused medication therapy management: a randomized controlled trial. J Am Pharm Assoc (2003). 2012 Sep-Oct;52(5):603-12.	Outcomes
van Leeuwen KM, Bosmans JE, Jansen AP, Hoogendijk EO, Muntinga ME, van Hout HP, et al. Cost-Effectiveness of a Chronic Care Model for Frail Older Adults in Primary Care: Economic Evaluation Alongside a Stepped-Wedge Cluster-Randomized Trial. J Am Geriatr Soc. 2015 Dec;63(12):2494-2504. doi: 10.1111/jgs.13834.	Intervention not carried out by a pharmacists or without collaboration
Vázquez Vela V, Jimenez Pichardo L, Martin Fernandez N, Piedrabuena Molina J, Cachero Alba B, Arcas de Los Reyes L, et al. Optimisation of pharmacotherapy in institutionalised patients in a socio-health centre. Eur J Hosp Pharm. 2018;25:A157–8.	Congress abstract
Verdoorn S, Kwint HF, Bouvy ML. Feasibilty of goal attainment scales during medication review: An interim analysis of the DREAMeR study. Int J Clin Pharm. 2017;39(1):243.	Congress abstract
Verrue CL, Petrovic M, Mehuys E, Remon JP, Vander Stichele R. Pharmacists' interventions for optimization of medication use in nursing homes : a systematic review. Drugs Aging. 2009;26(1):37-49. doi: 10.2165/0002512-200926010-00003.	Outcomes
Wallerstedt SM, Kindblom JM, Nylén K, Samuelsson O, Strandell A. Medication reviews for nursing home residents to reduce mortality and hospitalization: systematic review and meta-analysis. Br J Clin Pharmacol. 2014 Sep;78(3):488-97. doi: 10.1111/bcp.12351.	Intervention not carried out by a pharmacists or without collaboration
Williams A, Manias E, Walker R. Interventions to improve medication adherence in people with multiple chronic conditions: a systematic review. J Adv Nurs. 2008;63(2):132–43.	Outcomes
Wouters H, Quik EH, Boersma F, Nygard P, Bosman J, Böttgeret WM, et al. Discontinuing Inappropriate Medication in Nursing Home Residents (DIM-NHR Study): protocol of a cluster randomised controlled trial BMJ Open 2014;4:e006082. doi: 10.1136/bmjopen-2014-006082	Study protocol
Zulman DM, Pal Chee C, Ezeji-Okoye SC, Shaw JG, Holmes TH, Kahn JS, Asch SM. Effect of an Intensive Outpatient Program to Augment Primary Care for High-Need Veterans Affairs Patients: A Randomized Clinical Trial. JAMA Intern Med. 2017 Feb 1;177(2):166-175. doi: 10.1001/jamainternmed.2016.8021.	Intervention not carried out by a pharmacists or without collaboration

Appendix 3. Quality assessment of included studies.

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or nonrandomised studies of healthcare interventions, or both	
Questions	**(16)**
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes
5. Did the review authors perform study selection in duplicate?	Yes
6. Did the review authors perform data extraction in duplicate	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8. Did the review authors describe the included studies in adequate detail?	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	Yes
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	No meta-analysis conducted
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No meta-analysis conducted
13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	No meta-analysis conducted
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.									
Dominios		**17)**	**(18)**	**19)**	**(20)**	**(21)**	**(22)**	**(23)**	**(24)**
Selection bias	Random sequence generation	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	High risk
	Allocation concealment	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk	High risk
Performance bias	Blinding of participants and personnel	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk
Detection bias	Blinding of outcome assessmen	Low risk	Low risk	Low risk	High risk	Low risk	Unclear risk	Low risk	High risk
Attrition bias	Incomplete outcome data	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
Reporting bias	Selective reporting	Uncl ear risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk
Other bias	Anything else, ideally prespecified	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Supplementary references A

1. Morrison CM, Glover D, Gilchrist SM, Casey MO, Lanza A, Lane RI, Patanian M. Partnering with Pharmacists in the Prevention and Control of Chronic Diseases. 2012. Available at https://www.cdc.gov/dhdsp/programs/spha/docs/pharmacist_ guide.pdf. Accessed February 2, 2019.
2. American Pharmacists Association (APhA). Medication Therapy Management in Pharmacy Practice: Core Elements of an MTM Service Model Version 2.0 Available at https://www.pharmacist.com/sites/default/files/files/core_elements_of_an_mtm_practice .pdf. Accessed February 2, 2019.
3. Giberson S, Yoder S, Lee MP. Improving Patient and Health System Outcomes through Advanced Pharmacy Practice. A Report to the U.S. Surgeon General. Office of the Chief Pharmacist. U.S. Public Health Service; 2011.
4. National Institute for Health and Care Excellence (NICE). Multimorbidity: clinical assessment and management. Available at https://www.nice.org.uk/guidance/ng56. Accessed February 2, 2019.
5. Scottish Government Polypharmacy Model of Care Group. Polypharmacy Guidance, Realistic Prescribing. 3rd Edition, 2018. Scottish Government.

Supplementary references B

6. Shea, B.J., Reeve, B.C., Wells, G., Thuku, M., Hamel, C., Moran, J., Moher, D., Tugwell, P., Welch, V., Kristjansson, E., & Henry, D.A.. (2017). AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ, 358, j4008.
7. Centro Cochrane Iberoamericano (trad). Manual Cochrane de Revisiones Sistemáticas de Intervenciones, versión 5.1.0. Retrieved May 7, 2018 from http://www.cochrane.es/?q=es/node/269.