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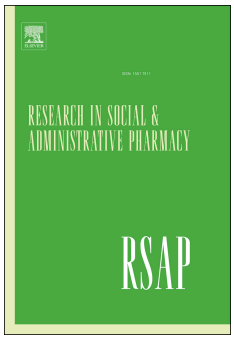

Randomized controlled trials covering pharmaceutical care and medicines management: A systematic literature review

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Randomized controlled trials covering pharmaceutical care and medicines management: A systematic literature review

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Conceived and designed the experiments: ZB. Performed the experiments: ZB, RK, LC.

Analyzed the data: ZB, RK, GM, SA, SA, LC. Contributed reagents/materials/analysis tools:,

LC. Wrote the paper: ZB, RK, LC.

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Randomized controlled trials of pharmaceutical care: A systematic review

Abstract

Objective

To review the effects of pharmaceutical care on hospitalizations, mortality and clinical outcomes in patients.

Methods

Systematic searches were conducted in MEDLINE, EMBASE and International Pharmaceutical Abstracts (IPA) databases to identify studies that were published between 2004 and January 2017. Studies included in this review were randomized controlled trials (RCTs) that spanned across both community and hospital settings. Using strict inclusion/exclusion criteria studies were included if they reported level 1 or 2 outcomes in the hierarchy of outcome measure i.e. clinical and surrogate outcomes (e.g. blood pressure (BP) control, blood glucose level, cholesterol BMI). Each study was assessed for quality using the Jadad scoring system.

Results

Fifty-four RCTs were included in the present review. Forty-six of these studies ranked high quality according to the Jadad scoring system. Studies were categorized into their general condition groups. Interventions in patients with diabetes, depression, respiratory disorders, cardiovascular disorders, epilepsy, osteoporosis, and interventions in older adults were identified. In the majority of studies pharmaceutical care was found to lead to significant improvements in clinical outcomes and/or hospitalizations when compared to the non-intervention group. Some conditions had a large number of RCTs, for example for cardiovascular conditions and in diabetes. Statistically significant improvements were seen in the majority of the studies included for both of these conditions, with studies indicating positive clinical outcomes and/or hospitalizations rates. Within the cardiovascular condition, a subset of studies, focusing on cardiac heart failure and coronary heart disease, had more mixed results. In other conditions the number of RCTs conducted was small and the evidence did not show improvements after pharmaceutical care, i.e. in depression, osteoporosis, and epilepsy. The majority of interventions were

face to face interactions with patients, whilst a smaller number were conducted via the telephone and one via a web-based system. Patient education was a key component of most interventions, either verbal and/or written. Longitudinal data, post intervention cessation, was not collected in the majority of cases.

Conclusions

RCTs conducted to evaluate pharmaceutical care appear to be effective in improving patient short-term outcomes for a number of conditions including diabetes and cardiovascular conditions, however, other conditions such as depression are less well researched. Future research should attempt to evaluate the conditions where there is a lack of data, whether the positive effects of pharmaceutical care persist in patient populations after the interventions cease and what the long-term clinical outcomes would be of continued pharmaceutical care.

Introduction

Worldwide, the demands on primary health care services are growing, mainly due to an ageing population (1). The consequence of this is an increased strain on the primary health care workforce (3-6) and as a result, primary health care systems have evolved to encompass new services. In some countries, this has led to extended roles for community pharmacists (7, 8). The pharmacy profession is evolving worldwide, moving from the traditional role of the technical dispenser to be more patient-focused (9). The concept of pharmaceutical care was first conceived by Hepler and Strand and is defined as the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life (10). According to the concept of pharmaceutical care, the patient care process is comprised of the establishment of a therapeutic relationship, assessment of medication related problems, development of a care plan, evaluation and continuous follow-up (11). Pharmacists are responsible for the quality and effectiveness of pharmaceutical care for the benefit of patients to improve their health care outcomes (12).

Since its conception, various terms have been used to describe pharmaceutical care including medication review, medication management, clinical pharmacy services and cognitive services and all of these are defined by similar practices (13). According to some authors, pharmaceutical care is closely related to medicines management but includes the patient's perspective and pharmacists societal perspective (14). Pharmacists counsel patients with a focus on educating health management or drug related-problems (identification, resolution or prevention), they develop a care-plan for the individual patient and follow-up the pharmacotherapy (15).

Studies investigating the effects of pharmaceutical care on short and long term patient outcomes have been increasing over the past two decades; however there are mixed reports of whether the pharmaceutical care interventions are effective or not, with the intervention not always showing significant differences (16-18). Systematic reviews often focus on specific conditions for example, reviews have been conducted in patients with hypertension (19, 20) and in chronic kidney disease (21) and others have looked at pharmaceutical care in specific settings for example, in community pharmacy (22).

A previous systematic review of studies published between 1990 and 2003 was published in 2005. This review evaluated the effectiveness of pharmaceutical care across all conditions and concluded that the pharmaceutical care is effective in improving surrogate outcomes but less conclusive in other outcomes (23). Evidence of the effect of pharmaceutical care is constantly growing and regular systematic evaluation is important and relevant to healthcare. This current study included randomized controlled trials (RCTs) published since 2004 across all conditions, to evaluate the evidence of whether pharmaceutical care is effective for patients. The objective of this systematic review was to examine the effects of pharmaceutical care using patient outcomes (i.e. clinical and surrogate outcomes) in both the hospital and community setting..

Methods

Search strategy

The PRISMA guidelines for conducting the systematic review were followed. A systematic search of the literature was conducted to identify RCTs published in English language between 2004 and January 2017 by using the electronic databases: Medline (Ovid SP), International Pharmaceutical Abstracts (IPA) and Embase. Our search included both mapped and unmapped terms, which are illustrated in figure 1. In addition, the following text words and MeSH/EMTREE terms were used to see if there were any additional relevant papers: The databases were searched for the following key terms in combination where appropriate: ("Pharmaceutical services"), ("Pharmaceutical care"), ("Medicine management"), ("Medicine therapy assessment"), ("Medicine therapy management"), ("Drug therapy management") ("Pharmacy services") ("Medication review"), ("Comprehensive medication review"), ("drug utilization management"), ("Drug therapy services"), ("Pharmacist intervention") and ("Patient centered care" and Medicines" or "Drug" or "Pharmac*"). We combined these keywords with the filter "Randomized controlled trial", if the filter was not available on that data base then a keyword was used and the study's methodology was evaluated to ensure only randomized controlled trials were included. See Figure 1 for Prisma flow diagram.

Inclusion/exclusion criteria

The inclusion and exclusion criteria are detailed in Table 1. Studies were included in this review if they referred to a pharmaceutical care intervention in adult patients and the intervention included the role/input of a pharmacist. All healthcare settings were included i.e. both hospital and community based interventions. Studies were excluded if they were not written in English, did not have a full text article available, or if they were reviews, commentaries or letters to the editor. Studies published before 2004 were also excluded. Our review's aim was to evaluate RCTs that assessed pharmaceutical care, so all studies were excluded if they were not RCTs, including cluster RCTs and any pilot data. RCTs were only included in this review if they measured patient outcomes that were either level 1 or 2 in the hierarchy of outcome measures (Table 2.)

Jadad scores of methodology quality

A quality assessment was completed for each randomized controlled trial using the Jadad checklist (24). A Jadad score of equal to or greater than 3 is indicative of a high-quality study (19). The assessment criteria for the Jadad scoring are detailed in Figure 2. The Jadad score has been used as a tool in previous literature evaluating RCTs (19, 25).

Table 1. Study inclusion and exclusion criteria

No	Category	Inclusion criteria
1	Language of publication	English
2	Year of publication	2004-January 2017
3	Publication type	Full text RCTs discussing effect of pharmacy (pharmacists) services on patients health care outcomes.
4	Outcomes measures	RCTs measuring patient's outcomes i.e. clinical and surrogate outcomes (e.g. blood pressure (BP) control, blood glucose level, cholesterol BMI). Outcome measures must fall in level one or two of the hierarchy of outcome measures, described in table 2.
5	Methodology	Studies included, must demonstrate pharmacist's induced interventions by patient's homes visits or in any of healthcare setting including primary, secondary or tertiary heath care settings or nursing home residents.
6	Pharmacists role	Pharmacist must play the significant or integral role, where multidisciplinary models were presented.
7	Patients	Adult patients only.
No		**Exclusion criteria**
1	Language of publication	Published in other than English
2	Year of publication	Published before 2004
3	Publication type	Abstracts, reports, commentaries, editorials, book chapters, reviews, secondary research (systematic reviews, meta-analysis)
4	Outcomes measures	RCTs with only patient's satisfaction as an outcome measure
5	Methodology	RCTs published as protocol of study
6	Methodology	Pilot studies were excluded
7	Methodology	Cluster RCTs

Results

Studies selection

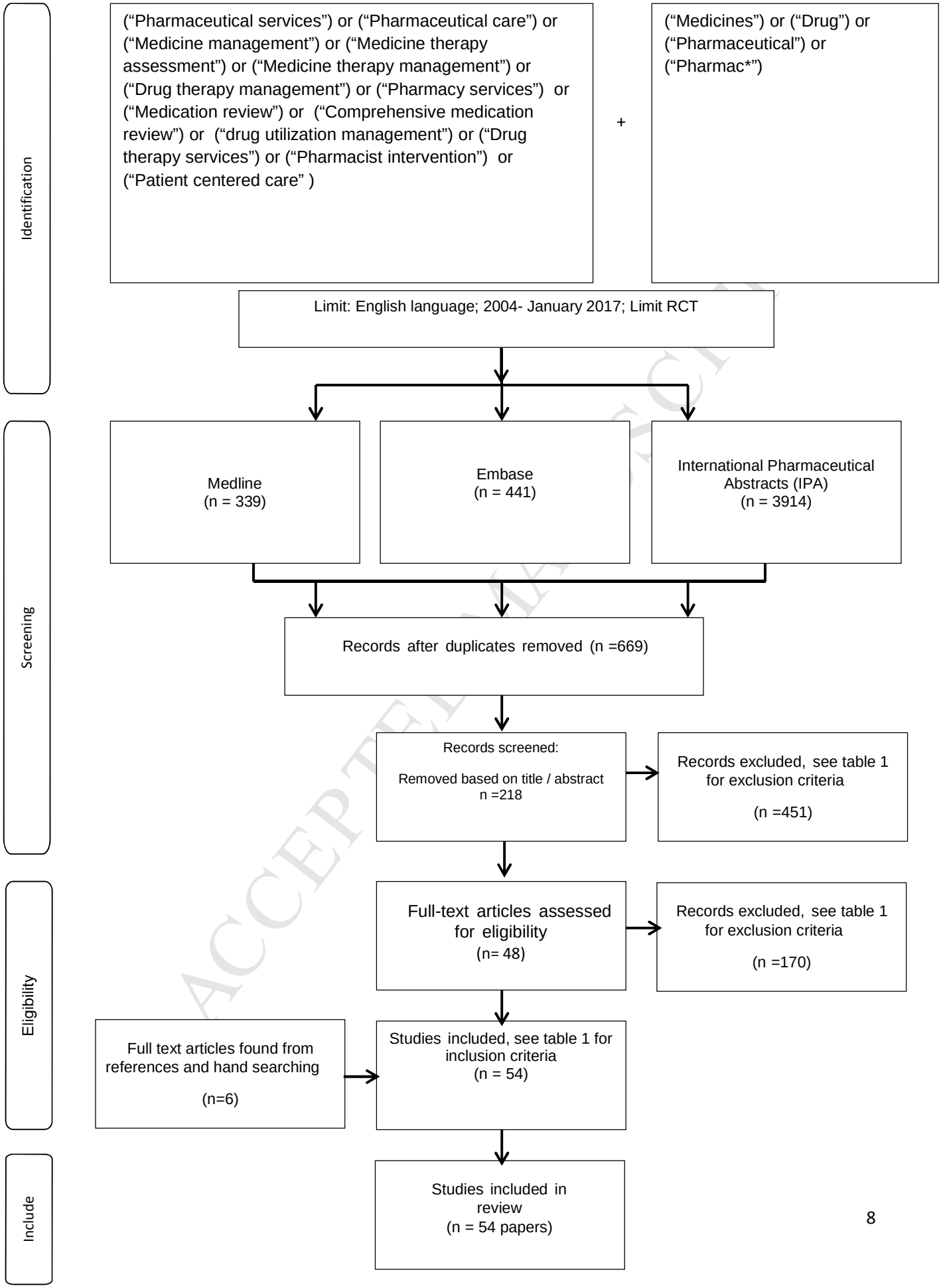
The literature search identified 669 titles/abstracts that contained the aforementioned key terms. The titles and abstracts of all selected articles were reviewed for relevance. The search results were further checked and reviewed by a second author. In case of any doubt regarding papers, the full text article was reviewed for relevance. Inclusion criteria were formulated in relation to the research aims.

A total of 218 studies were screened and assessed for eligibility. Of these 54 RCTs fulfilled the inclusion criteria. The flow diagram (Figure 1) details the process in which the studies were identified, screened and included in this review. The inclusion and exclusion criteria of study are summarized in Table 1.

Data extraction and analysis

Two researchers (LC, RK) independently extracted study characteristics, using an extraction table. One researcher (LC) compared all extracted data and discussed discrepancies with other researchers (ZB) when necessary. The data were then grouped based on the condition that they aligned with and a summary of the data extracted from the studies is presented in Tables 3-8. This includes the country of origin, patient group included, follow-up period, number of patients in each arm, setting, description of the intervention outcomes measured, level of hierarchy of outcome measured and a summary of results.

Figure 1: The process of identification, screening and inclusion of papers for this review.



126 **Table 2.** Hierarchy of outcome measures (Adapted from AHRQ, 2001)(26)

Level	Description
1	Clinical outcomes - morbidity, mortality, hospitalizations
2	Surrogate outcomes - observed errors, intermediate outcomes (eg, laboratory results) with well-established connections to the clinical outcomes of interest (usually adverse events).
3	Other measurable variables with an indirect or unestablished connection to the target safety outcome (e.g., pre-test/post-test after an educational intervention, operator self-reports in different experimental situations)
4	No outcomes relevant to decreasing medical errors and/or adverse events (e.g., study with patient satisfaction as only measured outcome; article describes an approach to detecting errors but reports no measured outcomes)

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128 **Figure 2.** Quality assessment of included randomized controlled trials through the Jadad checklist (24)

Assessment questions to ascertain Jadad score

1. Study randomized?
2. Randomization was described and appropriate?
3. Study double blind?
4. Double blinding was described and appropriate?
5. Withdrawals and dropouts were described?

Totals added to produce Jadad score (max 5)

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Studies Characteristics

The included studies (n=54) were performed over a number of countries including Australia (n=2), Belgium (n=2), Brazil (n=6), Canada (n=2), Chile (n=2), China (n=4), Colombia (n=1), Denmark (n=1), Hong Kong (n=2), Iraq (n=1), Jordan (n=5), Malaysia (n=2), Norway (n=1), Portugal (n=1), Spain (n=2), Sudan (n=1), Sweden (n=1), Taiwan (n=1) Tasmania (n=1), Thailand (n=1), the United Kingdom (UK) (n=4), United States of America (USA) (n=8) and United Arab Emirates (UAE) (n=3). All of the studies were conducted within the specified country, i.e. not over more than one country.

The targeted population included patients with specific condition(s) or those on a specific therapy. The RCTs can be further categorized into the following categories based on therapeutic condition; cardiovascular (CV) conditions (n=24), diabetes (n=15), depression (n=2), older adults (n=6), respiratory (n=3) conditions or other studies (those on multiple medicines, osteoporosis and epilepsy) (4).

The RCTs included in the review involved follow up period from 30 days to 36 months. The most common follow-up periods were as follows: 19 RCTs included interventions with a follow up period of 6 months, seventeen RCTs with 12 months, and six studies with 3 months follow-up. Follow-up was conducted in some studies by face-to-face meetings; others used web-based communications and telephone contact.

Jadad scores of methodology quality

Randomized controlled trials with a Jadad score equal to or greater than 3 are indicative of a high-quality study (19). In this review the Jadad scores were recorded in the data extraction tables. Forty-six of the studies in this review ranked 3 or above in the Jadad scale. One study ranked a 5 score. The main reason for loss of points on this score chart was nature of the study design i.e. not being double-blinded.

Interventions

The majority of the pharmaceutical care interventions assessed by RCTs in this review included educational interventions for patients. Educational interventions involved the verbal or written information to improve the knowledge and awareness of patients regarding their diseases. Behavioral interventions included changes in patient compliance by modifying their attitude to medication adherence to drug therapy.

Some RCTs used one of the above interventions as single and others applied in combination (multifaceted). The interventions were applied and their effects on patient's health care outcomes including clinical outcomes (morbidity, mortality, and hospitalizations) and surrogate clinical outcomes (laboratory results) were measured. Table 3-8 summarizes important characteristics of the studies included in the review.

Some studies used the Dader method of pharmaceutical care. This method includes "patient education about CV drugs, completion of a drug therapy profile and/ or drug history, assessment of drug compliance, patient counseling about lifestyle modifications, pharmacist-performed interventions not related to changes in drug therapy, and pharmacist-delivered treatment recommendations to physicians" (27).

In many RCTs in this review, follow-up took place on a frequent regular basis through the study, whereby a pharmacist contacted the patient either via home visits, appointments or via the telephone.

Outcomes

This review sought to identify RCTs that had evaluated pharmaceutical care interventions in patients across all conditions. The outcomes that we were interested in were those that are described in table 2, meeting criteria one or two, i.e. hospitalizations or unintended use of medical care, mortality and clinical outcomes that have been shown to be directly related to the progression/severity of the condition. In some instances these studies also reported other measures, which have been included in the table for completeness but are not discussed in the results section. Criteria that each study reported are recorded in the level of outcome measure in the tables 3-8.

176 **Table 3.** RCTs evaluating pharmaceutical care in cardiovascular disorders (n=24)

Reference and country	Jadad score	Sample size (completed follow up)	Study population	Follow up period	Setting for study recruitment	Study outline (Intervention provided)	Outcome Measure	Level of outcome measure (L)	Effect of intervention
AMARILES et al. 2012 (27) Spain	3	714 patients (Control=358, Intervention = 356)	Aged between 25-74 years Prescribed with at least one drug indicated for CVD or CV risk factors	8 months	Multicenter community pharmacies	Comparison between control and intervention group on the bases of Dader method for pharmaceutical care provided to intervention group only. Patients had at least 5 appointments with the pharmacist throughout the time frame.	BP,TC & BP/TC	L2	Statistical significant difference in all measures.
BELL et al. 2016 (28) USA	3	851 patients (Controls = 428; Intervention = 423)	Adults hospitalized with a diagnosis of acute coronary syndrome and/or acute decompensated heart failure	30 days	Vanderbilt University Hospital (VUH) and Brigham and Women's Hospital (BWH)	Reconciliation of preadmission medications and discharge medications with the patient and reported to the medical team. Provided tailored counselling to patient. At discharge, the pharmacist provided additional counselling, a written information chart and showed patient how to use pillbox. After hospital discharge, study coordinators contacted the patients for follow-up.	Time to first unplanned health care utilization.	L1	Statistically significant difference in unplanned health care utilization among patients with inadequate health literacy
Community Pharmacy Medicines Management Project Evaluation Team. 2007 (29) UK	2	1493 patients (Control= 513, Intervention = 980), 62 pharmacists & 164 general physicians.	Aged > 17 years, registered with general practices & with Coronary heart disease	12 months	9 study sites from primacy care organizations (community pharmacies with private consultation areas)	Consultation included: assessment of therapy and medicines. Compliance, lifestyle & social support	**Primary outcomes:** Proportion of pts receiving secondary prevention treatment for CHD, Health status (SF36, Euro QOL), health economic analysis. **Secondary outcomes:** 5-yr risk of CV death, patient satisfaction & compliance.	L2&3	No statistical significant difference. Statistical significant difference in NHS-related cost. No significant difference in 5-yr risk but significant difference in satisfaction
DE CASTRO et al. 2006 (30) Brazil	4	64 patients (Control=34, Intervention =30)	Aged ≥ 18 years , having uncontrolled hypertension, receiving treatment for hypertension	6 months	Hospital de Cliniicas de Porto Alegre	Pharmaceutical care provided by 9 trained pharmacists. Patients were also provided printed educational material. Control group patients were allocated to sham intervention. 5 meetings were conducted over the time period with a pharmacist. The intervention was compared	BP measured by ABP monitoring Medication adherence DRP identification	L2&3	Decrease in BP in intervention group. No significant difference in adherence 31 out of 37 DRP in intervention group were provided specific

						to sham condition.			intervention
FIRMINO et al. 2015 (31, 32) Brazil	3	36 patients (Controls = 15; Intervention = 21)	Patients with systemic hypertension who had uncontrolled blood pressure (BP) and/or presence of cardiovascular risk factors, or difficult control and adherence problems to the treatment	9 months	The pharmacy unit of Dr. Anastacio Magalhães Primary Health Care	Intervention group received orientation about taking medicines, actions aiming to prevent/solve medicine interactions and adverse effects and non-pharmacological interventions for 9 months	Glucose, total cholesterol and its fractions, triglyceride and BP measurements to calculate cardiovascular risk rate and Framingham score.	L2	Significant difference in cardiovascular risk rate and Framingham score.
GARCIA et al. 2015 (33) Norway	3	94 patients (Control = 46; intervention 48)	Only patients with established CHD were eligible for inclusion.	12 months	University Hospital of North Norway	Intervention group follow-up from the clinical pharmacist at three points of time; after discharge at the ward and at 3 months and 12 months at the hospital pharmacy .	Primary outcomes: adherence to clinical guideline recommendations concerning prescription, therapy goal achievement and lifestyle education. Secondary outcomes: changes in the biomedical risk factors cholesterol, BP and blood glucose.	L2&3	Overall adherence was significantly higher in the intervention group. No other significant differences.
GREEN et al. 2008 (34) USA	5	730 patients (Control = 247; Group 2 = 246; Group 3 = 237)	Patients with a hypertension diagnosis and taking antihypertensive medication.	12 months	10 medical centers	Two intervention groups. Group 2: Home BP monitoring and secure patient Web site training only, or group 3: home BP monitoring and secure patient Web site training plus pharmacist care management delivered through Web communications.	Percentage of patients with controlled and changes in systolic and diastolic BP	L2	Significant differences in the pharmacist group for all measures.
HAMMAD et al 2011 (35) Jordan	3	65 patients (Control = 22; Intervention 43)	Patients with metabolic syndrome as defined by the NCEP/ATP III criteria.	6 months	Outpatient clinics	Monthly meetings with the pharmacist. Pharmacists provided medication counselling, answered questions, offered instructions on self-monitoring BP and advised patients on healthy lifestyle choices. Educational materials were also distributed to patients in the intervention group, including brochures	Metabolic syndrome status, changes in mean values for each metabolic syndrome component (waist circumference, triglycerides, HDL-C, fasting blood glucose, and systolic and diastolic BP) and for body weight.	L2	Statistical significance in mean TG, SBP and DBP measures.
HOLLAND et al 2007 (36) UK	3	291 patients (Control = 143; Intervention	Patients with heart failure from three hospitals who had been	6 months	Outpatient (Discharged from hospital emergency).	Two home visits by a community pharmacist within two and eight weeks of discharge. Pharmacists reviewed drugs and	Primary outcome: total hospital readmissions at six months. Secondary outcomes:	L1&2	No significant difference in any measure

		= 148)	admitted to the emergency room (on discharge).			gave education on the condition, symptom self-management and lifestyle advice and advised use of symptom diary.	mortality and QOL		
LALONDE et al. 2008 (37) Canada	3	150 patients (Control = 122; Intervention = 128)	Patients prescribed warfarin that had no anticoagulation treatment in the past 24 months.	3 months	Community hospital	Follow up by pharmacist-managed anticoagulation services	INR control, incidence of complications, HRQOL, use of health care services, and direct incremental cost of PMAS	L1, 2 &3	No significant differences.
LEE et al 2006 (38) USA	3	159 patients (Control = 76; Intervention = 83)	Aged >75 who were taking 4 or more medications	6 months	Walter Reed Army Medical Center's Armed Forces Retirement Home	Patients in the intervention group met with pharmacists every 2 months, and were provided blister- packed medications and also continued medication education as needed.	Primary outcome: proportion of pills taken vs baseline; secondary end points: changes in BP and LDL-C	L2&3	Significant differences in adherence and systolic BP
LEE et al 2009 (39) Hong Kong	3	118 patients (Control = 60; Intervention = 58)	Patients taking one or more lipid-modifying agents for dyslipidemia; who had a baseline lipid profile not reaching targeted LDL-C goal	Unclear; within 16 weeks	Outpatient clinics	Patients in the intervention group were counselled and provided with written information. A phone follow-up was done every 4 weeks between the initial counselling and the next follow-up interview for each patient.	LDL-C, HDL-C, TC and TG	L2	Significant differences in the pharmacist group for all measures.
MA et al 2010 (40) USA	3	554 patients (Control = 261; Intervention = 293)	Known coronary heart disease	12 months	Cardiac catheterization laboratories at hospital.	Participants in the PI condition received 5 pharmacist-delivered telephone counselling calls post-hospital discharge. Also received an education packet, dietary goal booklet, medicine card and pillbox.	Percentage of patients with a serum LDL-C level <100 mg/dl	L2	No significant difference
MORGADO et al 2011 (41) Portugal	3	197 patients (Control = 99; Intervention = 98)	Hypertensive patients	9 months	Outpatient clinic in a teaching hospital	The pharmacist interventions, aimed to increase medication adherence and BP control, involved educational interventions and counselling tips directed to the patient and involved a quarterly follow up for 9 months	Systolic BP, diastolic BP and BP control, and adherence	L2	Significantly lower sBP, dBP, BP control and adherence
MURRAY et al 2007 (42) USA	3	270 patients (Control = 164; Intervention = 106)	Low-income patients with heart failure	9 months	University-affiliated, inner-city, ambulatory care practice.	When medications were dispensed, the pharmacist provided patient-centered verbal instructions and written materials about the medications written for those with low health literacy. Monthly calls to assess QOL and interviews at 3, 6, 9, and 12	Primary outcomes: adherence and exacerbations requiring emergency department care or hospital admission. Secondary outcomes: included health-related quality of life, patient	L1,2&3	Reductions seen but 3 months post intervention dissipated

						months.	satisfaction with pharmacy services, and total direct costs.		
PAULOS et al 2005 (43) Chile	1	42 patients (Control = 19; Intervention = 23)	Those who purchased their medication or requested blood cholesterol or triglyceride analysis	16 weeks	Outpatient pharmacy	Intervention included obtaining total blood cholesterol and triglyceride levels as well as patient education. Patients had five follow-up appointments	Total blood cholesterol level, triglyceride level, and body mass index (BMI) and adherence & QOL.	L2&3	Total cholesterol and TG significant improvements.
PETERSON et al 2004 (44) Tasmania	3	81 patients (Control = 42; Intervention = 39)	Patients with dyslipidaemia.	6 months	Royal Hobart Hospital	Intervention group were visited at home monthly by a pharmacist, who provided education, assessed patients for drug-related problems, and measured total blood cholesterol levels using point-of-care testing.	Blood cholesterol levels	L2	Significant improvements in the cholesterol levels in the intervention group
PLASTER et al. 2012 (45) Brazil	2	74 patients (Control=36, Intervention = 38)	At least 3 of conditions recommended by the NCEP-ATP III & BGMS for the diagnosis of metabolic syndrome.	6 months	Out patients of a primary health care unit (CHC)	Patients participated in PC program according to the Dader methodology	Mean Arterial Pressure (MAP), NOM, adherence level (Morisky test), CVD risk.	L2&3	Statistical significant improvements in CVD risk
QUDAH et al 2016 (46) Jordan	3	52 patients (Control = 25; Intervention = 27)	Hypertensive patients receiving hemodialysis	3 months	Outpatient hemodialysis units of Jordan University Hospital and Isra'a Hospital	Doctor-pharmacist collaboration in addition upon enrolment, educational materials were distributed and discussed with patients in the intervention arm. Monthly follow-up by pharmacist for DRP and education.	% of patients achieving BP below or equal 135/85 mmHg. Secondary measures that were assessed include absolute reduction in peridialysis BP, interdialytic weight gain, adherence to medications and dialysis sessions	L2&3	Statistical significance in the % of patients reaching BP target and weekly home systolic BP measurements
SADIK et al. 2005 (47) UAE	3	208 patients (Control= 104, Intervention = 104)	Diagnosed with heart failure & cognitive status	12 months	Al-Ain Hospital	Patients were education on HF, prescribed medications & management of HF symptoms, self- monitoring program. Printed booklet was also provided.	2-min walk test, forced vital capacity, SBP, DBP & pulse, QOL questionnaire (MLHFQ, SF36). Patient assessment questionnaires for medication knowledge & s elf- reported compliance	L1,2&3	Statistical significant difference
SOOKANEKNUN et al 2004 (48) Thailand	3	235 patients (Control = 117; Intervention = 118)	Hypertensive patients	6 months	Mahasarakham University pharmacy and 2 primary care units	The patients in the intervention group had monthly consultations The research pharmacist assessed the patient's understanding of medications, counselled on the use of their	BPs, tablet counts, lifestyle modifications	L2&3	Significant reductions in the systolic and diastolic BP and Patients whose BP stabilized and in adherence

						medications, assessed adherence and lifestyle habits, reviewed for adverse events due to drug-related problems, and discussed factors associated with uncontrolled BP and disease state control and made recommendations to the prescriber. Educational leaflets were also given			
VILLA et al 2009 (49) Chile	2	142 patients (Control = 57; Intervention = 85)	Diagnosed with dyslipidaemia	32 weeks	Primary Health Care centers	Intervention group patients received care twice a month by pharmacists and drug related problems were identified.	Knowledge about their illness and medications, adherence to drug therapy, and quality of life. In addition to HDL-c, LDL-c, TG and TC	L2&3	Significant improvements in all measures apart from HDL-c
WANG et al 2011 (50) China	3	59 patients (Control = 30; Intervention = 29)	Hypertensive patients	12 months	Outpatient receiving antihypertensive drugs	Intervention group received education and met with clinical pharmacists every 2 months. Any drug related problems identified were reported to the physician.	SBP and DBP plus adherence	L2&3	Significant differences in SBP and DBP
ZHAO et al. 2012 (51) China	3	Control=129 , Intervention =129	Aged b/w 21-85 years, diagnosed with hypertension,	6 months	Xijing Hospital	Recommendations to physicians and educational and counselling directly to patients. Follow-up at 6 months at clinic.	SBP, DBP, BP control and medication adherence	L2 &3	Significant difference

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179 **Table 4**. RCTs evaluating pharmaceutical care in diabetes mellitus (n=15)

Reference and country	Jadad score	Sample size	Study population	Follow up period	Setting for study recruitment	Study outline (Intervention provided)	Outcomes Measure	Level of outcome measure (L)	Effect of intervention
AL MAZROUI et al. 2009 (52) UAE	3	234 patients (control=117 , intervention = 117)	Diagnosed with type 2 diabetes mellitus, oral hypoglycemic therapy.	12 months	Zayed Military hospital	The intervention group received patient education about illness & medication, provided with leaflets, behavioural modifications from a pharmacist. The intervention group had 4 monthly appointments at hospital	BMI, fasting blood glucose level, HbA1c, BP, serum TC, LDL-C, HDL-C TG, HRQOL, 10-years risk assessment, disease knowledge & med. adherence	L2&3	Statistical significant difference in all measures.
CHEN et al. 2016 (53) Taiwan	3	100 (control = 50; intervention 50)	Diagnosed with type two diabetes with poor control	6 months	Nantou City hospital	Intervention group received pharmaceutical care including identification and resolution of drug-related problems and established a consultation procedure.	HbA1c Hospitalizations were also monitored	L1&2	Statistical significant difference in HbA1c. One person was hospitalized in the control group, none in the intervention group
CHUNG et al 2014 (54) Malaysia	1	241 (Control= 121, Intervention = 120)	Diagnosed with type 2 DM, taking at least one antidiabetic medication	12 months	Malaysian Teaching Hospital	Patient education on diabetes, hypertension, hyperlipidemia and medication adherence. Taught how to use a pill box, blood glucose meter and how to record readings. Received monthly calls from pharmacist. Data collected at baseline and at 4, 8 and 12 months.	Fasting blood glucose (FBG), HbA1c. Medication adherence.	L2&3	Statistical significant difference in HbA1c at month 4, 8 and 12 and on medication adherence.
CLIFFORD et al. 2005 (55) Australia	3	180 (control = 88; intervention 92)	Diagnosed with type two diabetes. Enrolled in the Fremantle Diabetes study	12 months	Community based patients	Counselling at 6 and 12 months in addition to 6 weekly telephone calls Diet, exercise and compliance was encouraged. Educational pamphlets were provided	BMI, systolic and diastolic BP, fasting plasma glucose, HbA1c, serum lipid parameters and urinary albumin-to-creatinine ratio and exercise	L2&3	Statistical significant difference in BMI, systolic and diastolic BP, fasting plasma glucose, and HbA1c
DOUCHETTE et al. 2009 (56) USA	2	66 (control = 35; intervention = 31)	Diagnosed with type two diabetes who had completed two education sessions previously.	12 months	Community based patients	Four visits by a trained pharmacist at community pharmacy to assess any issues patient had. Diabetes clinic at the start and end of study.	HbA1c, BP, LDL-cholesterol, diet self-care activities, diabetes self-care activities, exercise self-care activities	L2&3	Only self-care activities had a significant effect.
ELNOUR et al. 2008 (57) UAE	3	165 patients (control= 66, intervention = 99)	Diagnosed with gestational diabetes, within first 20 weeks of gestation, UAE national.	6 months	Al-Ain Hospital, UAE	Patients were educated on GDM & its management, insulin administration& storage, plasma glucose measurement. Provided with booklet.	HRQOL (SF36), diabetes knowledge, insulin & plasma glucose monitoring, HbA1c, BP. Maternal & neonatal complications.	L1&2	Significant differences in HRQOL scores, plasma glucose, insulin use, glucose monitoring & some maternal & neonatal

									complications.
JAMESON et al. 2010 (58) USA	3	103 (controls= 51; intervention = 52)	Diagnosed with type two diabetes.	12 months	Community based patients	Patient intervention included regular care plus medication management, patient education, and disease control. 6 office visits and 3 phone calls to patients	HbA1c	L2	Statistically significant difference overall
JARAB et al. 2012 (59) Jordan	3	156 (control = 77; intervention 79)	Diagnosed with type two diabetes.	6 months	Outpatient diabetes clinic	Patients received face-to-face education and necessary lifestyle changes, followed by 8 weekly telephone follow-up calls.	HbA1c, BP, lipid values, self-reported medication adherence, and self-care activities	L2&3	Statistically significant difference in all measures apart from BMI and HDL-cholesterol and adherence.
MAHWI et al. 2013 (60) Iraq	3	123 patients (control= 61, intervention =62)	Diagnosed with type 2 diabetes mellitus	3 months	Diabetic centre in Sulaimani	Intervention group received pharmaceutical care	HbA1c, fasting plasma glucose. Drug therapy problems & med. compliance	L2&3	Statistical significant difference in fasting plasma glucose and HbA1c.
MCLEAN et al 2008 (61) Canada	3	211 patients (Control = 109; Intervention = 102)	Patients with diabetes with BP >130/80mmHg on 2 screening visits separated by 2 weeks	24 weeks	Community pharmacy patients	The intervention was delivered by pharmacist-nurse teams at various pharmacy sites. Cardiovascular risk reduction counselling was provided The patient received a wallet card documenting their BP Intervention group patients were seen at 6-week intervals by the study nurse and pharmacist for counselling and measurement of BP.	Primary outcome: Change in SBP Secondary outcomes: BP targets <130/80mmHg, change in antihypertensive drug therapy, the proportion prescribed an angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist, and change in SBP in patients>160 mm Hg.	L2	Statistical significant difference in systolic BP and also proportion of patients who achieved the goal BP of less than or equal to 130/80 mm Hg
MOURAO et al. 2013 (62) Brazil	3	100 (control = 50; intervention 50)	Diagnosed with type two diabetes, using oral antidiabetic medications and presenting Hb A1c>7	6 months	Six primary health care units	Designed a care plan for each patient focusing on patient education/pharmacotherapy changes	HbA1c level, fasting blood glucose, TC*, LDLC, HDLC, DBP, SBP	L2	Statistical significant improvement in all biochemical data & SBP (except BMI & DBP)
OBRELI-NETO et al. 2011 (63) Brazil	3	194 Control=97 Intervention =97	Aged ≥60 years, Diagnosed with diabetes or hypertension.	36 months	Primary public health care unit (PHCU)	The interventions include assessment of non-adherence, discussions of the role of medication in their health, correct use of drugs and a visual aid. Group activities were carried out every 6 months. These discussed adherence, dangers of self-medication and correct storage of medicines.	SBP,DBP, LDL--cholesterol,HbA1c, fasting blood glucose, QALY	L2&3	Statistical Significant difference in surrogate outcomes Cost effective ICER*/QALY
ODEGARD et al 2005 (64) USA	3	77 (control – 34; intervention	Diagnosed with type two diabetes with HbA1c >9 and	12 months	University of Washington Neighbourhoo	Diabetes care plan followed by weekly visits or telephone calls, which was reduced to less	HbA1c, adherence	L2&3	No significant differences

		= 43)	taking >1 oral antidiabetic		d Clinics	frequent when needs were progressing.			
WISHAH et al. 2014 (65) Jordan	3	101 (control = 51; intervention 50)	Diagmosed with type two diabetes	6 months	Jordan University hospital outpatient clinic	Patient education about the condition and complications, lifestyle advice, medicines, adherence and written material. Follow-up phone calls to remind patients of adherence and of the appointments for follow-up visit.	HbA1c, fasting blood glucose, patient knowledge	L2&3	All measures show significant differences
XIN et al. 2015 (66) China	3	240 (control = 120; intervention 120)	Diagnosed with type two diabetes, newly prescribed insulin therapy	12 months	Tongde Hospital	Patients received individualized education, educative group activities, and telephone counselling. Group activities were carried out every 6 months. These discussed adherence, dangers of self-medication and correct storage of medicines.	HbA1c, hospitalization, measures of adherence	L1, 2 &3	Significant differences in HbA1c and hospitalizations

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181 **Table 5.** RCTs evaluating pharmaceutical care in depression (n=2)

Reference and country	Jadad score	Sample size	Study population	Follow up period	Setting for study recruitment	Study outline (Intervention provided)	Outcome Measure	Level of outcome measure (L)	Effect of intervention
MARQUES et al 2013 (67) Brazil	3	48 patients (Control= 22, Intervention= 26)	Patients with depression	3 months	Outpatient clinic	Pharmaceutical intervention according to the Dáder Method, receiving visits every 30 days, or more frequently if necessary. Oral and written information were given.	Beck Depression Inventory and Beck Anxiety Inventory	L2	Statistically significant difference in the Beck Depression Inventory score and Beck Anxiety Inventory score
RUBIO-VALERA et al 2013 (68) Spain	3	151 patients (Control= 87, Intervention= 64)	Patients with depression	6 months	4 Primary Care Health Centres	Adherence, satisfaction with service, HRQOL and clinical severity. Follow-up visits to monitor progress,	Outcome measurements included clinical severity of depression (PHQ-9), health-related quality of life (HRQOL) (Euroqol-5D) and satisfaction	L2&3	Statistically significant difference in HRQOL

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183 **Table 6.** RCTs evaluating pharmaceutical care in older adults (n=6)

Reference and country	Jadad score	Sample size	Study population	Follow up period	Setting for study recruitment	Study outline (Intervention provided)	Outcome Measure	Level of outcome measure (L)	Effect of intervention
CROTTY et al. 2004 (69) Australia	3	110 patients (Control= 54, Intervention= 56)	Hospital patients awaiting discharge to a long term care facility	8 weeks	Hospital patients awaiting discharge to a long term care facility	A medication review Within 10 to 14 days of the transfer. The transition pharmacist, patient, family physician, the community pharmacist, and a registered met between 14&28 days post transfer. Education concerning medication use and appropriateness was given.	Hospital usage, Medication Appropriateness Index, adverse drug events, falls, worsening mobility, worsening behaviors, increased confusion, and worsening pain.	L2 &3	Significant differences in hospital usage and worsening pain
HOLLAND et al. 2005 (70) UK	3	829 patients (Control= 414, Intervention= 415)	Home based medication review after discharge from acute or community hospitals	6 months	Home based medication review after discharge from acute or community hospitals in UK	Two home visits post discharge to educate patients and carers about their drugs, inform general practitioners of drug reactions or interactions.	Total emergency readmissions. Secondary outcomes included death and quality of life	L1, 2&3	Significant differences in hospital readmissions and QOL scores
LENAGHAN et al. 2007 (71) UK	3	105 patients (Control= 49, Intervention= 56)	> 80 years of age, living at home, taking four or more medicines, and had at least one additional medicines-related risk factor.	6 months	Home-based medication review	Two home visits for education of patient/carer about their medicines, pharmaceutical care issues were noted, assessed need for an adherence aid	Hospital admissions, QOL scores & number of medication prescribed	L1&3	Significant reduction in the mean number of medicines prescribed
LENANDER et al 2014 (72) Sweden	2	141 patients (Control= 66, Intervention= 75)	> 65 years with five or more different medications	12 months	GP practice	A medication review was performed open for patients questions Drugs and dosages were evaluated and patients were asked about concordance. Concluding pharmaceutical advice was given to patients and entered into the computerized patient record. Follow up at 12 months	Hospitalizations, self-rated health, drug related problems and number of drugs	L1&3	Significant differences in drug related problems, in the number of medications
OLESEN et al. 2014 (73) Denmark	**3**	517 patients (Control= 264, Intervention= 253)	Aged ≥ 65 years, with a least 5 current prescription drugs taken without assistance.	24 months	Patients were visited by pharmacists at their homes.	Medication review. Informed the patients about drugs, provided information leaflets & motivated adherence. Follow-up telephone call at 3, 6 and 9 months,	**Primary outcomes** Treatment adherence assessed by a pill-count. **Secondary outcomes** DRPs, hospitalization & mortality	L1&3	No significant difference.

SPINEWINE et al. 2007 (74) Belgium	3	172 patients (Control= 83, Intervention= 89)	Aged >70 with geriatric problems	12 months	Acute Geriatric Evaluation and Management unit	Pharmaceutical care was performed The appropriateness of treatment was analyzed, and a pharmaceutical care plan was prepared. At discharge, the pharmacist provided written and oral information on treatment changes to the patient or caregiver, as well as written information to the general practitioner.	Medication Appropriateness Index (MAI), Beers criteria, and Assessing Care of Vulnerable Elders (ACOVE) underuse criteria and mortality, readmission, and emergency visits.	L1&2	Significant differences in the MAI and in the ACOVE underuse criteria

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186 **Table 7.** RCTs evaluating pharmaceutical care in respiratory conditions (n=3)

Reference and country	Jadad score	Sample size	Study population	Follow up period (months)	Setting for study recruitment	Study outline (Intervention provided)	Outcome Measure	Level of outcome measure (L)	Effect of intervention
ABDELHAMID et al. 2008 (75) Sudan	3	78 Patients (Control=30, Intervention= 48)	Diagnosed with asthma	6 months	Shaab Teaching Hospital	Drug therapy for asthma was reviewed; patients were educated about the disease, non-drug therapy measures, pharmacotherapy, self-management & inhalation technique every two weeks.	Frequency of acute attacks, nocturnal symptoms, using short acting inhaled β2-agonist, days of sickness per week.	L1, 2 &3	Statistical significant difference in frequency of attacks, nocturnal symptoms and frequency of reliever use. Also significant difference in the days sick. Patient inhaler technique and knowledge also improved.
TOMMELEIN et al. 2014 (76) Belgium	3	692 patients (Control=346 , Intervention= 346)	Aged ≥ 50 years COPD patients, Prescribed with COPD medications	3 months	170 community pharmacies	Two session intervention one at the start and one at one month. Inhalation technique, med. adherence, hospitalization rate. Patients also given written information and demonstration units.	**Primary outcomes** Inhalation technique, med. adherence. **Secondary outcomes** Dyspnea, hospitalization rate, health status & smoking behavior.	L1&3	Statistical significant difference found in inhalation technique, adherence and hospitalization rates.
WEI et al. 2014 (77) China	3	87 patients (Control= 45, Intervention= 42)	Stable COPD patients with a t least 2 consecutive visits to this hospital for COPD treatment	12 months	Medical University affiliated Hospital	A comprehensive pharmaceutical care program composed of individualized patient education & a series of telephone counselling 5-6 sessions.	**Primary outcomes** Medication adherence by pill-count & questionnaire. **Secondary outcomes** Severe exacerbation rate & HRQOL.	L1&3	Statistical significance in adherence, hospital admissions and symptoms and impact.

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188 **Table 8.** RCTs other studies evaluating pharmaceutical care (n=4)

Reference and country	Jadad score	Sample size (completed follow up)	Study population	Follow up period (months)	Setting for study recruitment	Study outline (Intervention provided)	Outcome Measure	Level of outcome measure (L)	Effect of intervention
BASHETI et al. 2016 (78) Jordan	3	160 patients (Control=78, Intervention= 82)	>18 years, at least one long term condition and prescribed >3 medications	Average 3 months	Community pharmacy	Baseline MMR was conducted for all patients, recommendations regarding the identified TRPs were only submitted to the physicians of patients in the intervention group. Follow-up then occurred at the end of the study.	Resolution of treatment related problems. Prescriber acceptance of the advice; effect of the intervention on certain clinical outcomes: blood glucose levels, BP, and triglyceride levels.	L2 &3	Significant difference in the treatment related problems that were resolved, blood glucose, BP and TG levels
LAI et al. 2011 (79) Malaysia	3	177 patients (Control=89, Intervention= 88)	Aged≥ 45 years Postmenopausal women diagnosed with osteoporosis, prescribed with once weekly alendronate or risedronate.	12 months	University Malaya Medical Centre (UMMC)	Counselling on osteoporosis, risk factors, lifestyle modifications, and goals of therapy, side effects & the importance of adherence. Written information given. Monthly follow-up calls for the first 6 months, then 3 monthly thereafter.	Medication adherence, BTMs and persistence	L3	Significant higher adherence. No significant difference in persistence
LOSADA-CAMACHO et al. 2014 (80) Colombia	3	144 patients (Control=74, Intervention= 70)	Aged >18 years, diagnosed with epilepsy from over a year, receiving out-patient treatment with anti-consultants, experienced at least one seizure in last 3 years.	6 months	Fundacion Liga Central Contra La Epilepsia, sede Bogota.	Applied a pharmaceutical care program consisting of 5 parts. Medication review follow up according to Dader's method, Lecture in group education sessions, Treatment adherence, registration of seizures & possible triggers, TDM of anticonvulsants	**Primary outcomes:** HRQOL measured by QOLIE-31(Quality of Life in epilepsy Inventory-31). **Secondary outcomes:** Frequency of crises, adverse reactions, depression & adherence	L1&3	Statistical significant difference in HRQOL.
WU et al 2006 (81) Hong Kong	3	442 patients (Control=223, Intervention= 219)	> 5 medications and two appointments to the clinic	24 months	Specialist medical centre at hospital	Intervention group received a 10-15 minute telephone call from our pharmacist at the midpoint. The pharmacist asked about the patient's treatment regimens; provided education and reminded patients of their next clinic appointment; and reinforced the importance of compliance	The primary endpoint was death from any cause. Other endpoints included changes in the rate of admission to hospital.	L1	Statistically significant change in deaths

Impact of pharmaceutical care in disease management

Cardiovascular disorders (Table 3)

Twenty-four RCTs evaluated the impact of pharmaceutical care on the patients with cardiovascular diseases, of which 20 showed statistically significant clinical outcomes (27, 28, 30, 31, 34, 35, 38-51). Four studies showed no differences in the clinical outcome measures (29, 33, 36, 37) .

Table 3 illustrates the 24 RCTs that have been conducted on cardiovascular conditions. Included in this category are studies evaluating the effect of interventions on patients with cardiovascular diseases (e.g. heart failure (36, 42, 47) or coronary heart disease (28, 29, 33, 37, 40), in patients with high cardiovascular risk factors (27), hypertension (30, 31, 34, 38, 41, 46, 48, 50, 51) or dyslipidemia (39, 43, 44, 49) and in two studies patients with metabolic syndrome (35, 45). The four studies that did not show significant differences in hospitalizations or clinical outcomes were in cardiac heart failure patients (36) and three in those with coronary heart disease (29, 33, 37).

To note, two studies included patients that had been diagnosed with diabetes and cardiovascular conditions; these studies were included and discussed in the diabetes section.

Clinical outcomes measured included BP, cholesterol levels blood glucose and cardiovascular risk. Eleven studies found significant differences in diastolic and/or systolic BP readings after the intervention (27, 30, 34, 35, 38, 39, 41, 46, 48, 50, 51). One study specifically aimed to evaluate whether patients met a target BP (46). Two studies found no significant differences in BP; one study by Garcia and colleagues (33) and another by Sadiq et al (47).

Cholesterol readings were compared in twelve RCTs (27, 29, 31, 33, 35, 38-40, 43-45, 49); these measures included total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-c), and/or high density lipoprotein cholesterol (HDL-c) levels. Statistically significant differences were seen in TC (27, 39, 43, 44, 49), TG (35, 39, 43, 49), LDL-c (39, 40, 49) and HDL-c (39).

Blood glucose was measured in two of the studies, but neither reported significant differences (33, 35).

Cardiovascular risk was calculated and compared in two studies. One study showed a significant reduction in CV risk after the intervention (31), but the other study showed no differences (29).

Hospitalization rates were recorded Murray and colleagues, who found statistically significant differences after a pharmacist intervention in patients with low incomes and heart failure, however this difference dissipated after the intervention stopped (42) Furthermore, Holland et al. reported no significant differences in patients with cardiac heart failure after pharmacist intervention post-discharge from hospital. Unplanned health care utilization was found to be statistically significant in patients with low health literacy in the study by Bell et al. (28).

Another study in patients with cardiac heart failure used exercise tolerance (2-minute walk), and forced vital capacity in order to evaluate the intervention, in addition to the measures described above. Statistical significant differences were found in both measures (47).

Lalonde and colleagues' RCT included patients who had been prescribed warfarin. They evaluated whether there were changes in INR control, complications and use of health care services, and found no differences after intervention by a pharmacist anticoagulation service (37).

Diabetes mellitus (Table 4)

Fifteen of the RCTs assessed the effect of pharmaceutical care intervention on various outcomes of the patients diagnosed with diabetes mellitus (Table 4). The majority of these involved the patients with Type 2 diabetes mellitus (52-56, 58-60, 62, 64-66), one study included both Type 1 and Type 2 patients (61) and one study was unclear regarding the type of patient that was included. One RCT involved the gestational diabetes mellitus patients (57).

Ten studies found the significant reductions in HbA1c levels in the intervention group (52-55, 57, 59, 60, 62, 63, 65), a further three studies measured HbA1c and found no significant differences (56, 57, 64). Nine RCTs measured the fasting plasma glucose level and significant reduction was observed in the pharmaceutical care group (52, 53, 55, 57, 59, 60, 62, 63, 65), compared with only one that did not find differences in fasting plasma blood glucose (54). Statistical significant decrease was found in total

238 cholesterol, LDL-cholesterol and/or systolic BP (52, 55, 59, 61-63, 82-84) and an increase in HDL-
239 cholesterol (52, 62). One RCT also recorded improvements in some maternal and neonatal complications
240 (57).

241 Hospitalizations and unexpected medical usage was recorded by a number of studies, but only reached
242 statistical significance after a pharmaceutical care intervention in one study (66).

243 **Respiratory conditions** (Table 5)

244 Three studies evaluated the impact of pharmaceutical care and medicines management on the
245 respiratory disorders patients including asthma and chronic obstructive pulmonary diseases (COPD)
246 (Table 5). Two of these solely involved the COPD (76, 77) and one patients with asthma (75).

247 Statistical significant differences were found in symptoms of the conditions i.e. frequency of attacks,
248 nocturnal symptoms and frequency of reliever use in asthmatics (75) and exacerbations in COPD (77). In
249 addition hospitalization rates were also statistically significant after intervention with pharmaceutical care
250 (76, 77).

251 **Depression** (Table 6)

252 Two RCTs included in this review focused on pharmaceutical care interventions in depression. Clinical
253 outcomes measuring clinical severity in the intervention groups led to mixed results. One study found a
254 significant difference (67) in clinical measures whereas the other did not (68). The latter study did lead to
255 significant changes in HRQOL but not clinical severity.

Older adults (Table 7)

Six studies evaluated pharmaceutical care interventions in older adults, with mixed results (Table 6); four studies showed statistical significance in clinical outcomes or hospitalizations (69-71, 74), whereas two showed no difference (72, 73). Hospitalization rates were reported in all of the six RCTs, with two studies finding differences after intervention of pharmaceutical care (69, 70). One study reported significant differences in worsening of pain (69) and three studies reported improvements in appropriateness (74) or number (71, 72) of medicine prescribed.

Other studies included (Table 8)

Multiple medications

Two RCTs involved the implementation of interventions for patients who were on multiple medications; one study patients included in the RCT needed to be taking a minimum of three medicines (78) and the second study the patients needed to be taking five or more medications (81). The study by Basheti and colleagues (2016) was community pharmacy based using a medication management review and the primary outcome was resolution of drug related problems, acceptance of advice by prescribers plus clinical outcomes of blood glucose levels, BP and triglyceride levels. Significant differences were seen in drug related problems resolved and all clinical outcomes (78). The second study in this category was set in a specialist medical center and the primary endpoint was death of any cause and rate of hospitalizations. Differences were found in number of deaths (81).

Epilepsy

Losada- Camacho and colleagues (2014) evaluated the impact of pharmaceutical care program on women with epilepsy (80) (Table 8). The primary outcome was health related quality of life (HRQOL) measured by Quality of Life in Epilepsy Inventory-31 (QOLIE-31) and the secondary outcomes included the changes in frequency of seizures, depression measured by using the questionnaire of the Center for Epidemiologic Studies Depression Scale (CES-D), adverse drug reactions by Liverpool Adverse Event Profile (Liverpool AEP) and adherence by using Haynes-Sackett test and Moriski-Green test. Significant

differences were seen in QOLIE-31 scores. No significant differences were seen in the frequency of seizures.

Osteoporosis

A RCT assessed the effects of pharmaceutical care on adherence and persistence of bisphosphonate in postmenopausal osteoporotic women (79). Primary outcome measures were medication adherence, bone turnover markers (BTMs) and persistence (Table 8). Two BTMs serum C-terminal cross-linking telopeptide of type I collagen (CTX-I) and serum osteocalcin (OC) were assessed. No significant reduction was found in in CTX-1 and OC between the two groups (79).

Discussion

This systematic review aimed to evaluate the effectiveness of pharmaceutical care, based on RCTs that have been published between 2004 and January 2017. There have been a steady number of studies emerging over the past decade evaluating pharmaceutical care, leading to a high number of studies that were included in this review. Our findings suggest that pharmaceutical care, in the majority of cases, is effective in either decreasing hospitalizations or improving surrogate clinical outcomes particular to the presenting condition. The included studies are all RCTs, which are considered the gold standard of clinical effectiveness if the methodology is properly executed (19), however RCTs in pharmaceutical care are often challenging to conduct and this could be a reason for a bias toward studying certain conditions and not others – for example there are 24 studies for cardiovascular conditions versus 3 for respiratory conditions. The spectrum of papers include a wide a variety of interventions, outcome measures and follow-up frequency and schedules, often making it challenging for researchers and healthcare professionals to directly compare and evaluate why certain studies have not found significant results.

In addition to the current literature, our review has identified that there is strong evidence to support pharmaceutical care in long term conditions affecting patients with hypertension and dyslipidemia. Surrogate clinical outcomes of BP and cholesterol levels have shown to be systematically improved in the majority of studies; interestingly despite these two biomarkers being integral to the calculation of 5-year cardiovascular risk, only one study (out of two) showed significant improvements in 5-year cardiovascular risk. A systematic review published by Aguiar and colleagues (2012) focused on pharmaceutical care in hypertensive patients and found similar results to the present study (19). Systolic BP was the most positively impacted clinical outcome by the pharmaceutical intervention. The authors of the 2012 review described the need to improve research design, as there were limitations in hardiness (19). In 2011 Morgado and colleagues conducted a systematic review and meta-analysis of pharmacist interventions to enhance BP therapy; results of this review showed that pharmacist interventions can significantly improve medication adherence, systolic BP, diastolic BP, and BP control in patients with essential hypertension (20). However in this review, one important limitation noted by the authors were the databases available for the systematic review, potentially therefore missing potential eligible studies.

316 In this review, the outcomes in relation to CHF and CHD were mixed. In is not as clear whether
317 pharmacist intervention via pharmaceutical care is as effective; this may be due to fewer RCTs available
318 in these conditions. In 2008 Koshman et al. published a systematic review in patients with CHF, including
319 studies prior to 2007. Despite inclusion of 12 RCTs, outcomes were similar to our current review; mixed
320 results for HF hospitalizations (3 of 11 studies finding significant differences) and mortality rates showing
321 no significant differences. Overall, when the authors of this study pooled responses for outcomes,
322 benefits were seen in pharmacist intervention (85). Further studies need to be conducted to clarify the
323 effectiveness of pharmacists in these conditions.

324 Pharmacists play a significant role in the provision of a pharmaceutical care services in diabetes mellitus.
325 Our findings show strong evidence that pharmaceutical care interventions have significant positive effects
326 in the reduction of HbA1c level in patients with diabetes. This finding is similar to other studies that have
327 focused on diabetes, for example Fornos et al. (86) and Balaiah et al. (87), where glycemic control was
328 found to be significantly improved as a result of pharmaceutical care interventions; ultimately lowering of
329 HbA1c being a predictor of improved therapeutic outcomes of patients (88).

330 A previous Cochrane review did not show that pharmaceutical care is effective in older adults (89), this
331 current review reported mixed outcomes for hospitalizations and included measures of appropriateness of
332 medications and health related quality of life. Our study focused on surrogate clinical outcomes and
333 hospitalizations and included six RCTs, with an overall unclear conclusion regarding the benefit of
334 pharmaceutical care intervention in this population. Four studies showed improvements after
335 pharmaceutical care interventions, whilst two did not. This is also in line with a previous review by Holland
336 and colleagues who concluded that pharmaceutical care does not impact on hospitalizations and
337 mortality, however the authors do suggest that interventions could potentially improve knowledge
338 and adherence (90).

339 The three respiratory studies were included in this review, all showed significant changes after a
340 pharmaceutical care intervention. Health resource utilization (76, 77), symptoms (77) and inhalation
341 techniques (76) were found to be improved in COPD patients. Similar results were seen in asthmatic
342 patients, with improvements in symptoms, frequency of attached and reliever use (75).

No significant differences in hospitalizations or clinical surrogate outcomes were seen in patients with epilepsy, osteoporosis and depression. This could be due to the limited studies that have been conducted, and in the case of the study by Losada-Camacho et al. a relatively low number of patients returned their seizure diary (80).

Like previous literature, this study highlights the potential that pharmaceutical care has in a number of conditions, but goes further to identify some conditions that pharmaceutical care may not lead to changes in clinical outcomes. These non-significant results are challenging to interpret, they could be due to a myriad of factors including shorter follow up period insufficient for the examination of intervention effects and measurement of endpoints, the training of the pharmacists involved, the frequency of monitoring in the staff and the nature of those follow-up sessions.

This review also highlights the need for consistency across studies in the future in terms of the clinical outcomes measured. Despite grouping the studies in this review into condition groups, within each condition there was a wide range of outcomes reported. This makes it challenging to be able to conduct a meta-analysis. Only the cardiovascular and diabetes section had a sufficient number of studies to be able to further assess a subset of the condition, for example blood pressure. However, if a meta-analysis were to be conducted on such a specific subset, it may most appropriate to include all RCTs that have been conducted on the topic, with no date limitation. This is out of the scope of this potential review, but could be the topic of future research. If there could be a consensus of future research to all collect data on a specific outcome, a meta-analysis could be conducted to look at pharmaceutical care overall.

Currently there is a gap in current knowledge regarding the long term effects of pharmaceutical care interventions. Cooper and colleagues reported that patients show improvements in the first six months of interventions due to the psychological effects of being monitored, and this often drops off thereafter (91). The most frequently used follow up time in our review was six months, and one study did note that the beneficial effects seen dissipated when the intervention ceased (42). Future intervention studies with pharmaceutical care should bear this in mind. One of the studies in our review did have a sham intervention condition, and this study did find significant differences after pharmaceutical care (30).

Possibly future studies should aim to have a sham arm to the trial, therefore the pharmaceutical care aspect of the intervention can be differentiated in the methodology (19). In addition long term consequences of these interventions should be examined.

The present study has certain limitations. The study is limited to the English language literature and studies in other languages were not included. Only original research RCTs are included in the review; secondary studies were excluded. This study also included the specific outcomes of hospitalizations, mortality and surrogate clinical outcomes, therefore not incorporating HRQOL score, patient satisfaction or adherence scores, future studies could focus on these aspects to evaluate the full spectrum of pharmaceutical care effects on patients.

Conclusion

RCTs conducted to evaluate pharmaceutical care appear to be effective in improving patient short-term outcomes for a number of conditions including diabetes and cardiovascular conditions, however, other conditions such as depression are less well researched. Future research should attempt to evaluate whether these effects persist and the long-term clinical outcomes.

Authors Contributions

ZB conceived the study. RK and LC conducted the literature searches and extracted data with input from ZB. All authors were responsible for data interpretation. RK LC and ZB drafted the manuscript and all other authors revised and approved the manuscript.

Conflicts of interest

There were no conflicts of interest.

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