



Pharmacist-led Chronic Disease Management: A Systematic Review of Effectiveness and Harms Compared to Usual Care

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for four ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from VHA Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

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Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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EVIDENCE REPORT

INTRODUCTION

Increased involvement of clinical pharmacists in patient care may offer increased access to primary care services and improved health care for patients.^{1,2} Recently introduced bills H.R. 592 and S. 314, the Pharmacy and Medically Underserved Areas Enhancement Act, are aimed to improve patient access to health care through pharmacists' patient care services. The bills would help officially establish pharmacists as health care providers and enable coverage of pharmacists' services through Medicare Part B in medically underserved communities.

Furthermore, pharmacist involvement in patient care may help to reduce inappropriate medication use, specifically in the elderly. A study in 2007 revealed that more than 85% of Veterans over the age of 65 who received care in VA outpatient facilities were given a potentially inappropriate medication.³ Inappropriate prescriptions cost the United States billions of dollars in healthcare expenditures annually and can result in increased morbidity, adverse drug events, hospitalization, and mortality.^{4,5} A study in Canada saw the proportion of patients receiving an inappropriate medication drop significantly after medication review and optimization by a team that included a pharmacist.⁶

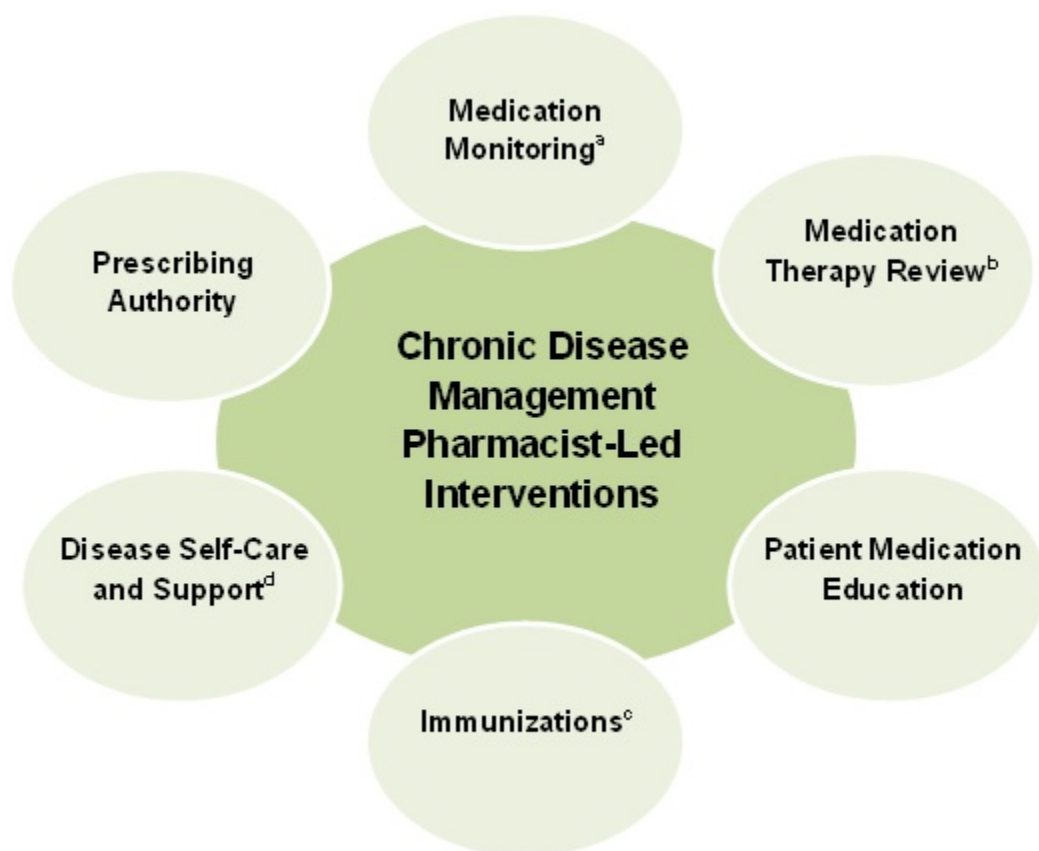
Hepler and Strand defined pharmaceutical care as pharmacist collaboration with health team members to optimize therapeutic outcomes by identifying, solving, and preventing actual and potential drug therapy problems.⁷ Since 1995, the Department of Veterans Affairs has allowed Clinical Pharmacy Specialists (CPS) an expanded scope of practice with independent prescribing privileges.⁸ In this capacity, CPS have been detailed to perform "pharmaceutical care" or comprehensive medication management along with disease state management services in addition to less complex services such as patient medication counseling or responding to drug information questions. In the VA primary care setting, CPS are likely to be responsible for therapeutic outcomes for a multitude of conditions for any patient referred to CPS or proactively identified by CPS as a high-risk patient.

A 2014 systematic review of outpatient medication therapy management (MTM) interventions addressed 5 areas: 1) intervention components and features, 2) effectiveness in comparison to usual care, 3) factors under which outpatient-based MTM is effective and optimally delivered, 4) types of patients likely to benefit, and 5) types of patients at risk of harms from such programs.⁹ The review did not address MTM services provided by pharmacists shortly after hospital discharge, independent disease management services, or single episode contact. Interventions needed, at minimum, 3 elements to satisfy the inclusion criteria for the systematic review: comprehensive medication review, patient-directed education and counseling, and coordination of care, including prescriber-directed interventions. The MTM intervention criteria for the review were broader than the Medicare Part D MTM-defined interventions. Outpatient settings included long-term care settings, pharmacy call centers, and retail pharmacies. The review included interventions conducted in non-U.S. countries but published in English. Evidence was insufficient for many patient-centered outcomes of interest; however, MTM interventions improved medication appropriateness, adherence, and percentage of patients achieving a threshold adherence level while medication dosing was reduced. For some patient conditions,

MTM interventions were associated with lowered odds of hospitalization and lower hospitalization costs. There was no observed benefit of MTM for patient satisfaction.

The purpose of this review is to identify the effectiveness and harms of pharmacist-led chronic disease management for community-dwelling adults with chronic diseases. Chronic disease management is a type of care that can be provided by pharmacists and aims to control symptoms and slow or stop disease progression. Chronic disease management is a multi-component intervention. We categorized intervention components as medication monitoring, medication therapy review, patient medication education, immunizations, disease self-care and support, and/or prescribing authority as detailed in Figure 1.

Figure 1. Components of Pharmacist-Led Chronic Disease Management



^a Medication Monitoring: follow-up after prescription for medication effectiveness and safety, drug-related problems

^b Medication Therapy Review: includes medication reconciliation

^c Immunizations: pharmacist provides immunization; immunization was not an outcome of interest

^d Disease Self-care and Support: facilitate access to other health care professionals; education about disease, lifestyle changes; aspirin therapy; tobacco cessation

SCOPE OF REVIEW

This review focused on chronic disease management for outpatients in health care facilities excluding retail pharmacies. We emphasized patient- or health system-centered outcomes but also addressed intermediate measures including achievement of recommended therapeutic goals. Due to differences in pharmacy practices in other countries, this review was limited to U.S. studies.

We address the following key question developed with input from the topic nominator and a technical expert panel (TEP). The scope of the review is also depicted in an analytic framework (Figure 2).

Key Question: What are the effectiveness and harms of pharmacist-led chronic disease management compared to usual care?

Population: Adults (age 18 or older)

Interventions: Chronic disease management; pharmacist takes responsibility for some component of the management or prevention of one or more chronic diseases (*eg*, chronic obstructive pulmonary disease [COPD], congestive heart failure [CHF], diabetes, hypertension, cancer, chronic kidney disease [CKD], pain, depression) (*ie*, pharmacist-led care)

Comparator: Usual care without the services provided by the pharmacists to the intervention group

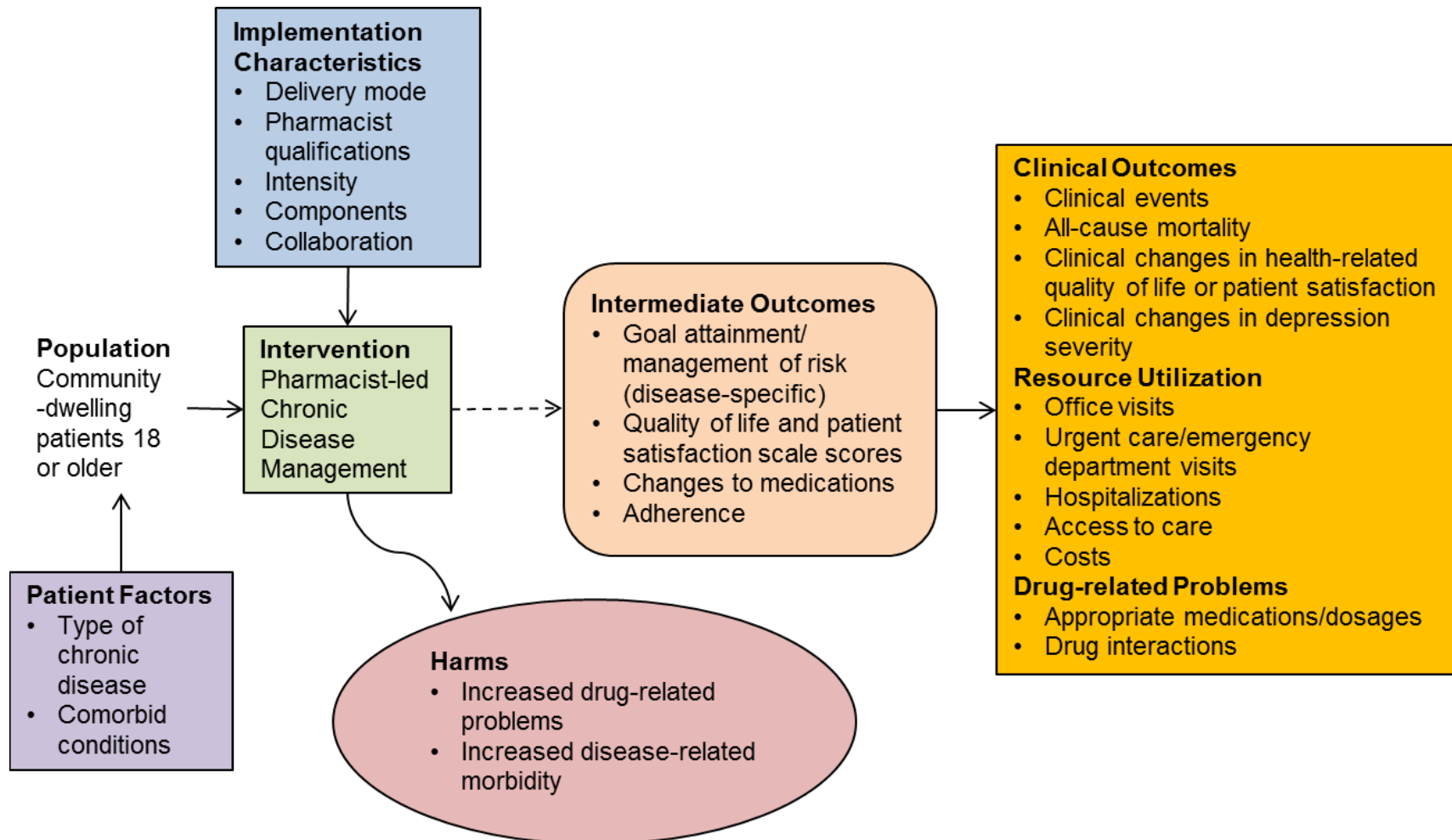
Outcomes:

- *Clinical Outcomes (including intermediate clinical measures):* disease specific clinical events (*ie*, severe hypoglycemia or hypotension requiring additional interventions), depression, mortality, health related quality of life, patient satisfaction, disease specific intermediate goal attainment such as glycated hemoglobin [HbA1c], blood pressure, and lipid levels
- *Resource Use:* office visits, urgent care or emergency room visits, hospitalizations, access to care, and costs
- *Medications:* appropriate medications and dosages, drug interactions, (non)adherence, other

Timing: No minimum follow-up required

Setting: Interventions that take place within the United States and are provided to outpatients by pharmacists based in healthcare facilities

Figure 2. Analytic Framework



METHODS

TOPIC DEVELOPMENT

This topic was nominated by Heather Ourth, PharmD, VACO Pharmacy Benefits Management Program Manager, on behalf of the National Clinical Pharmacy Research Group, chartered by the VACO Clinical Pharmacy Practice Office of VACO Pharmacy Benefits Management (PBM). The evidence review examines the effectiveness (both clinical and economic) of pharmacist-led chronic disease management compared to usual care.

SEARCH STRATEGY

We searched MEDLINE (Ovid), CINAHL, the Cochrane Library, and the International Pharmaceutical Abstracts (IPA) database for articles published from 1995 through June 2015. Our search was designed to identify studies that included control groups and was limited to studies enrolling adults and published in the English language. The search included the MeSH terms pharmacists, disease management, patient care, case management, patient education as topic, medication therapy management, drug interactions, drug therapy, drug monitoring, medication reconciliation, and patient care management. The full search strategies are presented in Appendix A. We obtained additional articles by hand-searching the reference lists of systematic reviews and other reports and from peer reviewer suggested references.

STUDY SELECTION

Abstracts from MEDLINE (n=504) were independently reviewed in duplicate by investigators and research associates. Abstracts from the CINAHL database (n=5 unique to CINAHL), IPA (n=588), and Cochrane (n=245) were reviewed by a co-investigator or research associate. We included studies of any design (including quality improvement projects) reporting on the effectiveness or harms of pharmacist-led care in outpatient adults with, or at risk for developing, a chronic disease. We excluded the following:

- Studies that did not include outpatient adults with or at risk for a chronic disease,
- Studies that did not test an intervention that was pharmacist-led, where the pharmacist was responsible for a component of patient care and, if part of a collaborative care team, the contribution of the pharmacist could be distinguished from other team members
- Studies that did not involve interventions intended to manage or prevent one or more chronic disease(s),
- Studies without a comparator,
- Studies that did not take place in a healthcare facility in the US (*eg*, studies set in retail pharmacies), and
- Studies of anticoagulation clinics because pharmacist management is considered standard care.

Full-text reports of studies identified as potentially eligible were obtained for further review using the inclusion and exclusion criteria described above. Each article was independently reviewed by 2 investigators or research associates. Reasons for excluding a study at full text review were noted.

DATA ABSTRACTION

Study characteristics (target population, inclusion/exclusion criteria, goal of intervention, primary outcome, duration/follow-up of study, type of pharmacist, study setting, intervention and comparator descriptions, and collaboration) as well as study-reported primary and secondary outcomes (drug-related problems, mortality, quality of life, access, patient satisfaction, healthcare utilization, cost, and goal attainment) were extracted onto evidence tables by one investigator or research associate and verified by another.

RISK OF BIAS ASSESSMENT

We assessed the risk of bias based on the following criteria: sequence generation, allocation concealment, risk of bias from confounding (for non-randomized studies), blinding, incomplete outcome reporting, and selective outcome reporting – a modification of the Cochrane approach to determining risk of bias. (Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Intervention Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.) Individual studies were rated as low, medium, or high risk of bias. Low risk of bias RCTs had adequate allocation concealment, blinding, and outcome reporting. Low risk of bias non-randomized studies also had low risk of bias from confounding.

DATA SYNTHESIS

We organized evidence tables by disease state of the study population. We described and qualitatively compared the characteristics and findings of included studies. If pooling was feasible, data were analyzed in RevMan 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark). Random effects models (DerSimonian-Laird) were used to calculate pooled risk ratios (RR) with 95% confidence intervals (CI) for categorical outcomes. However, pooled analyses were not possible for many outcomes due to heterogeneity of interventions and outcome reporting across studies. Therefore, most findings are summarized in narrative form.

RATING THE BODY OF EVIDENCE

We rated the overall strength of the body of evidence for clinical events, patient satisfaction, target goal attainment, urgent care/emergency department visits and hospitalizations, and medication adherence using the method reported by Owens et al.¹⁰

PEER REVIEW

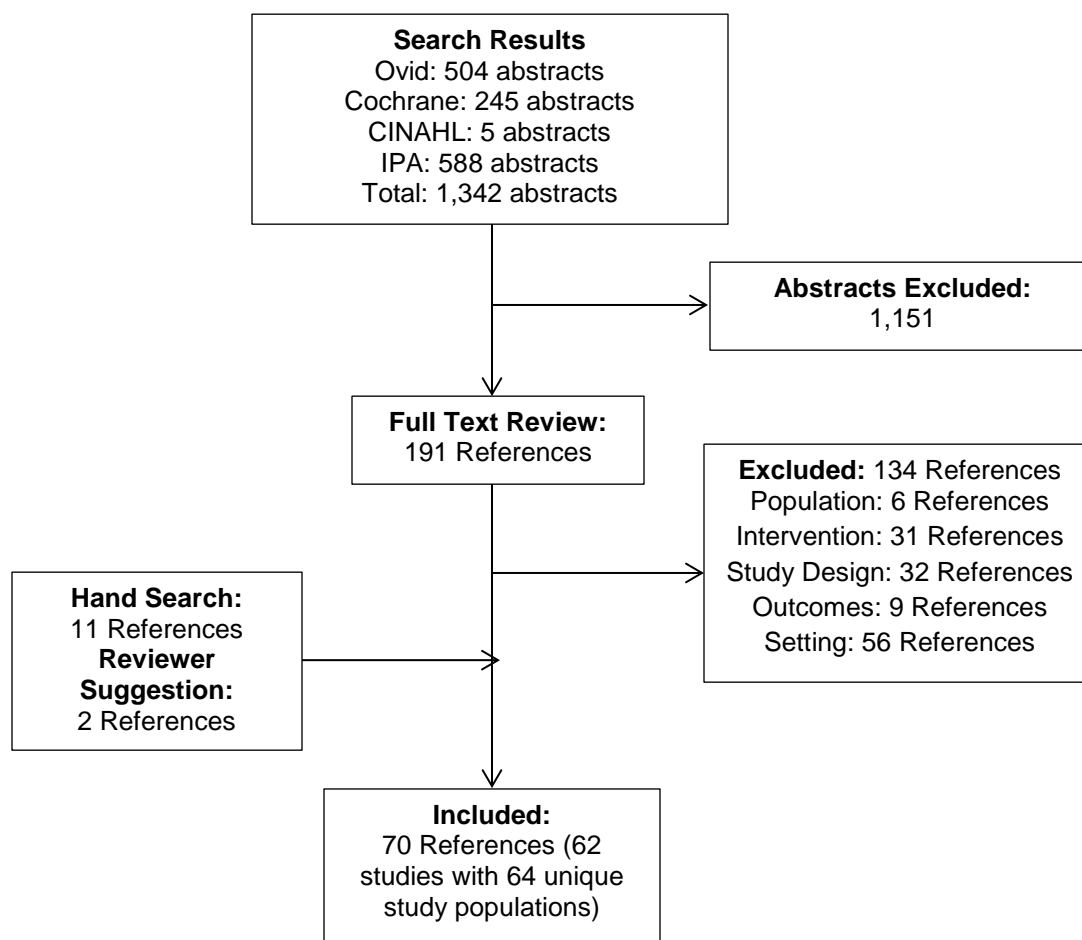
A draft version of this report was reviewed by content experts as well as clinical leadership. Reviewer's comments and our responses are presented in Appendix B and the report has been modified as needed.

RESULTS

LITERATURE FLOW

We reviewed 1,342 abstracts, 504 from MEDLINE, 588 from IPA, and the remaining from Cochrane and CINAHL. We excluded 1,151 abstracts and reviewed the full text of 191 references. During full-text review we excluded 134 articles leaving 57 eligible for inclusion. Hand-searching pertinent trials and systematic reviews identified an additional 11 references. Two additional references were suggested by a peer reviewer. Figure 3 details the process.

Figure 3. Literature Flow Chart



OVERVIEW OF INCLUDED STUDIES

We included 70 papers representing 62 studies with 64 unique study populations (k) in cardiovascular diseases (k=6), chronic kidney disease (k=4), chronic obstructive pulmonary disease (k=1), depression (k=4), diabetes mellitus (k=24), dyslipidemia (k=7), hypertension (k=15), and polypharmacy/high risk (k=3). Characteristics of the included studies are summarized in Table 1.

Table 1. Summary of Included Studies

| Characteristic | (Risk of) Cardio-vascular Disease | Chronic Kidney Disease | Chronic Obstructive Pulmonary Disease | Depression | Diabetes Mellitus | Dyslipidemia | Hypertension | Polypharmacy/ High Risk | Total |
|-------------------------------|-----------------------------------|------------------------|---------------------------------------|------------|-------------------|--------------|--------------|-------------------------|-----------------|
| Total | | | | | | | | | |
| Studies | 6 | 4 | 1 | 4 | 24 | 7 | 15 | 3 | 64 ^a |
| Total Patients | 3,403 | 2,920 | 98 | 926 | 17,716 | 1,834 | 6,278 | 1,282 | 34,457 |
| Design | | | | | | | | | |
| RCT | 4 | 2 | 1 | 3 | 12 | 2 | 13 | 3 | 40 |
| Other | 2 | 2 | 0 | 1 | 12 | 5 | 2 | 0 | 24 |
| Setting | | | | | | | | | |
| VA | 1 | 2 | 1 | 0 | 4 | 4 | 4 | 1 | 17 |
| Non-VA | 5 | 2 | 0 | 4 | 20 | 3 | 11 | 2 | 47 |
| Intervention | | | | | | | | | |
| Medication Monitoring | 6 | 4 | 1 | 3 | 22 | 6 | 14 | 2 | 58 |
| Medication Therapy Review | 2 | 2 | 0 | 3 | 13 | 3 | 10 | 2 | 35 |
| Patient Medication Education | 2 | 0 | 0 | 3 | 9 | 3 | 4 | 2 | 23 |
| Prescribing Authority | 3 | 2 | 0 | 3 | 12 | 5 | 7 | 1 | 33 |
| Disease Self-Care and Support | 4 | 2 | 1 | 4 | 22 | 3 | 14 | 2 | 52 |
| Immunizations | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 2 |
| Delivery Mode | | | | | | | | | |
| Remote | 1 | 0 | 0 | 1 | 2 | 2 | 1 | 0 | 7 |
| In-Person | 4 | 3 | 0 | 0 | 14 | 4 | 8 | 2 | 35 |
| Mixed | 1 | 1 | 1 | 3 | 8 | 1 | 6 | 1 | 22 |
| Intervention Frequency | | | | | | | | | |
| One-time | 2 | 0 | 0 | 0 | 4 | 1 | 0 | 0 | 7 |
| Multiple | 4 | 4 | 1 | 4 | 20 | 6 | 15 | 3 | 57 |
| Risk of Bias | | | | | | | | | |
| Low | 1 | 1 | 0 | 1 | 5 | 0 | 2 | 1 | 11 |
| Medium | 3 | 3 | 1 | 2 | 15 | 3 | 12 | 2 | 41 |
| High | 2 | 0 | 0 | 1 | 4 | 4 | 1 | 0 | 12 |

RCT = randomized controlled trial; VA = Veterans Affairs

^a 2 studies reported separate results for 2 different disease conditions

Table 2 depicts all outcomes of interest reported in the studies (with study-defined primary outcomes in parentheses). Goal attainment (*ie*, reaching target goals for HbA1c, blood pressure, and/or cholesterol levels) was the primary outcome for 25 of the 64 unique population studies. Few studies identified other clinical, resource use, or medication outcomes as their primary outcome.



Table 2. Number of Studies Reporting Each Outcome (and Study-defined Primary Outcome)^a

| Condition (number of included studies) | Clinical | | | | | | Resource Use | | | | | Medication | | | | | |
|--|-----------------|--------------|---------------------|--------------------------------|----------------------|-----------------|---------------|-----------------------------------|------------------|-----------------------------|---------------|------------------------------------|-----------------|-------------------|-----------------|--|----------|
| | Clinical Events | Depression | All-Cause Mortality | Health-Related Quality of Life | Patient Satisfaction | Goal Attainment | Office Visits | Urgent Care/Emergency Room Visits | Hospitalizations | Access to Care ^b | Costs | Inappropriate Dosage/ Prescription | Ineffectiveness | Drug Interactions | (Non)-adherence | Number/Dose of Appropriate Medications | Other |
| Cardiovascular Diseases (k=6) | 2 | | 2 (1) | 1 | 1 | 3 (2) | 2 | 3 (1) | 5 (1) | | 2 | 1 | | | 3 (1) | 3 | |
| Chronic Kidney Disease (k=4) | 2 | | 2 | 1 | 1 | 3 (1) | | | 1 | | 3 | 1 | | | 1 | 4 | |
| Chronic Obstructive Pulmonary Disease (k=1) | | | | 1 | 1 | | 1 (1) | 1 (1) | 1 (1) | | | 1 | | 1 | | 1 | |
| Depression (k=4) | | 2 (2) | | 3 | 4 (1) | | 3 (1) | 2 | | 2 | 1 | | | | 3 (2) | 3 (1) | |
| Diabetes (k=24) | 4 | | 3 | 3 | 3 | 16 (10) | 6 | 8 (1) | 8 (1) | 1 | 3 | 1 | | | 4 | 15 | 4 |
| Dyslipidemia (k=7) | | | | | | 7 (3) | 4 | 1 | | | 2 | | | | 1 | 6 | |
| Hypertension (k=15) | 6 | | 1 | 7 (2) | 7 (1) | 13 (8) | 9 | 3 | 4 | 1 | 4 (1) | 2 | | 1 | 11 (1) | 13 | |
| Polypharmacy/ High-risk (k=3) | 1 | | | 2 (2) | 2 (1) | 2 (1) | 1 | 1 (1) | 2 (1) | | 2 | 1 (1) | 1 | 1 | 2 (2) | 3 | |
| TOTAL (64 unique study populations)^c | 15 | 2 (2) | 8 (1) | 18 (4) | 19 (3) | 44 (25) | 26 (2) | 19 (4) | 21 (4) | 4 | 17 (1) | 7 (1) | 1 | 3 | 25 (6) | 48 (1) | 4 |

^a some studies didn't have one of our outcomes as their primary outcome and some had more than one primary outcome; table entries are number of studies reporting that outcome as their primary outcome

^b access to care assessed as patient satisfaction (reaching someone in an emergency, availability of advice) or patient perceptions (communication with the care team and problems getting care)

^c 2 studies reported separate results for 2 different disease conditions



KEY QUESTION: WHAT ARE THE EFFECTIVENESS AND HARMS OF PHARMACIST-LED CHRONIC DISEASE MANAGEMENT COMPARED TO USUAL CARE?

Cardiovascular Disease (4 RCTs, 2 Cohort Studies)

Key Findings

- Pharmacist-led care
 - resulted in mortality and rates of disease-specific clinical events that were similar to usual care; only one study reported a clinical event as a primary outcome,
 - was associated with mixed results for maintenance or attainment of HbA1c and blood pressure goals compared to usual care,
 - resulted in hospitalization rates that were similar to usual care; there were mixed results for office visits, urgent care visits, and costs; only one study reported resource use as a primary outcome, and
 - was associated with mixed results for medication use and adherence as compared to usual care.
- No studies reported on access to care, or drug interactions or other drug-related problems.

Characteristics of Studies (Appendix C, Table 1)

We identified 2 studies of pharmaceutical care for patients with cardiovascular disease or risk factors for cardiovascular disease,^{11,12} 2 studies of care for patients with coronary artery disease,^{13,14} and 2 studies of patients with congestive heart failure.^{15,16} A total of 3,403 patients were enrolled; study sample sizes ranged from 117 to 2,170. Overall, we rated one study as low risk of bias, 3 as medium risk of bias, and 2 as high risk of bias.

The studies of patients with cardiovascular disease or risk factors included a 12-month RCT conducted in a cardiovascular risk reduction clinic (CRRC) at a VA Medical Center¹¹ and a retrospective cohort study from a university-affiliated cardiology group.¹² In the VA study, patients had achieved HbA1c, blood pressure, and LDL goals and were randomized upon discharge from the CRRC to either group medical visits facilitated by a clinical pharmacist, individual sessions with a clinical pharmacist, or standard primary care.¹¹ Both clinical pharmacist interventions were multifaceted. In the cohort study, the goal was to optimize blood pressure medication management and patients participated in either a multifaceted program based on a collaborative care model or usual care.¹² The patients were followed until they maintained therapy goals for several months.

One study of patients with coronary artery disease was a 2-year RCT with a multifaceted pharmacist intervention delivered via telephone compared to usual care.¹⁴ The goal was to maintain lipid control. The second study was a retrospective cohort study from an outpatient pharmacy clinical service and focused on improving medication adherence.¹³ Patients identified as non-adherent and not at clinical goals for HbA1c and LDL-C had either a pharmacist consult at the time of prescription pick-up or usual care. Follow-up was one year.

The studies of patients with CHF, both RCTs, involved multifaceted interventions – education, medication recommendations, and telephone follow-up in one¹⁵ and protocol-driven education and medication monitoring in the other.¹⁶ Both studies focused on optimizing heart failure

therapy. In one study, median follow-up was 6 months.¹⁵ The other study included a 9-month intervention period and a 3-month post-intervention assessment.

Clinical Outcomes (Appendix C, Table 3)

Two studies (n=602) reported all-cause mortality, finding intervention and control groups to be similar.^{14,15} However, in one of these studies, the primary outcome was a combination of all-cause mortality and non-fatal heart failure events.¹⁵ There was a significant difference between groups for the composite outcome favoring the intervention group (OR 0.22 [95% CI 0.06, 0.63]).

Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 3)

One of the CHF studies reported similar improvement in health-related quality of life from baseline for the intervention and control groups.¹⁶ Satisfaction with pharmacy services improved significantly from baseline for the intervention group relative to the control group.¹⁶

Goal Attainment (Appendix C, Table 5)

The VA-based cardiovascular disease/risk factors RCT reported maintenance of HbA1c, blood pressure, and LDL goals.¹¹ Failure rates for HbA1c and blood pressure per quarter were significantly lower for intervention patients in either the individual or group pharmacist interventions relative to control. Adherence to LDL guidelines was lowest in the individual pharmacist intervention patients. In the cohort study of high cardiac-risk patients, blood pressure goals were achieved in a significantly higher percentage of patients in the intervention group.¹² In the study of patients with coronary artery disease, the study groups were similar in the percentages of patients maintaining LDL goals (either less than 100 mg/dL or less than 70 mg/dL) or blood pressure less than 130/80 mmHg.¹⁴ Significantly more patients in the control group achieved the blood pressure goal of less than 140/90 mmHg. Neither of the CHF studies reported a goal attainment outcome. Goal attainment findings are summarized in Table 3.

Medications (Appendix C, Table 2)

Few studies reported on drug-related problems. A study of patients with coronary artery disease reported persistence with lipid-lowering therapy, finding the intervention and control groups to be similar.¹⁴ Figure 4 is a forest plot of adherence outcomes from the RCTs. Another study, focused on adherence, reported a significantly lower medication possession ratio (MPR) at one year in the intervention group compared to control (0.70 vs 0.74) but the percentage of patients defined as adherent at one year was similar in the 2 groups (37% vs 38%).¹³

One of the CHF studies reported the fraction of target ACE inhibitor dose taken.¹⁵ Patients in the intervention group were taking a significantly higher fraction of the target dose than were patients in the control group. The other CHF study reported the incidence of adverse events or medication errors to be similar for the intervention and control groups but higher refill adherence in the intervention group.¹⁶

Table 3. Goal Attainment - Cardiovascular Diseases^a (6 studies)

| Author, year | Attained Goals for HbA1c Levels | Attained Goals for Blood Pressure | Attained Goals for Lipid Levels |
|-----------------------------|---------------------------------|-----------------------------------|---------------------------------|
| Spence, 2014 ¹³ | | | |
| Taveira, 2014 ¹¹ | ↑ | ↑ | ↔ |
| Irons, 2012 ¹² | | ↑ | |
| Olson, 2009 ¹⁴ | | ↕ ^b | ↔ |
| Murray, 2007 ¹⁶ | | | |
| Gattis, 1999 ¹⁵ | | | |

↑ = significantly higher proportion of intervention group reached goal compared to control group (P<.05)

↔ = results not significant

↕ = mixed results

Bold indicates a study-defined primary outcome

^a Cardiovascular disease or risk factors for cardiovascular disease, coronary artery disease, and congestive heart failure

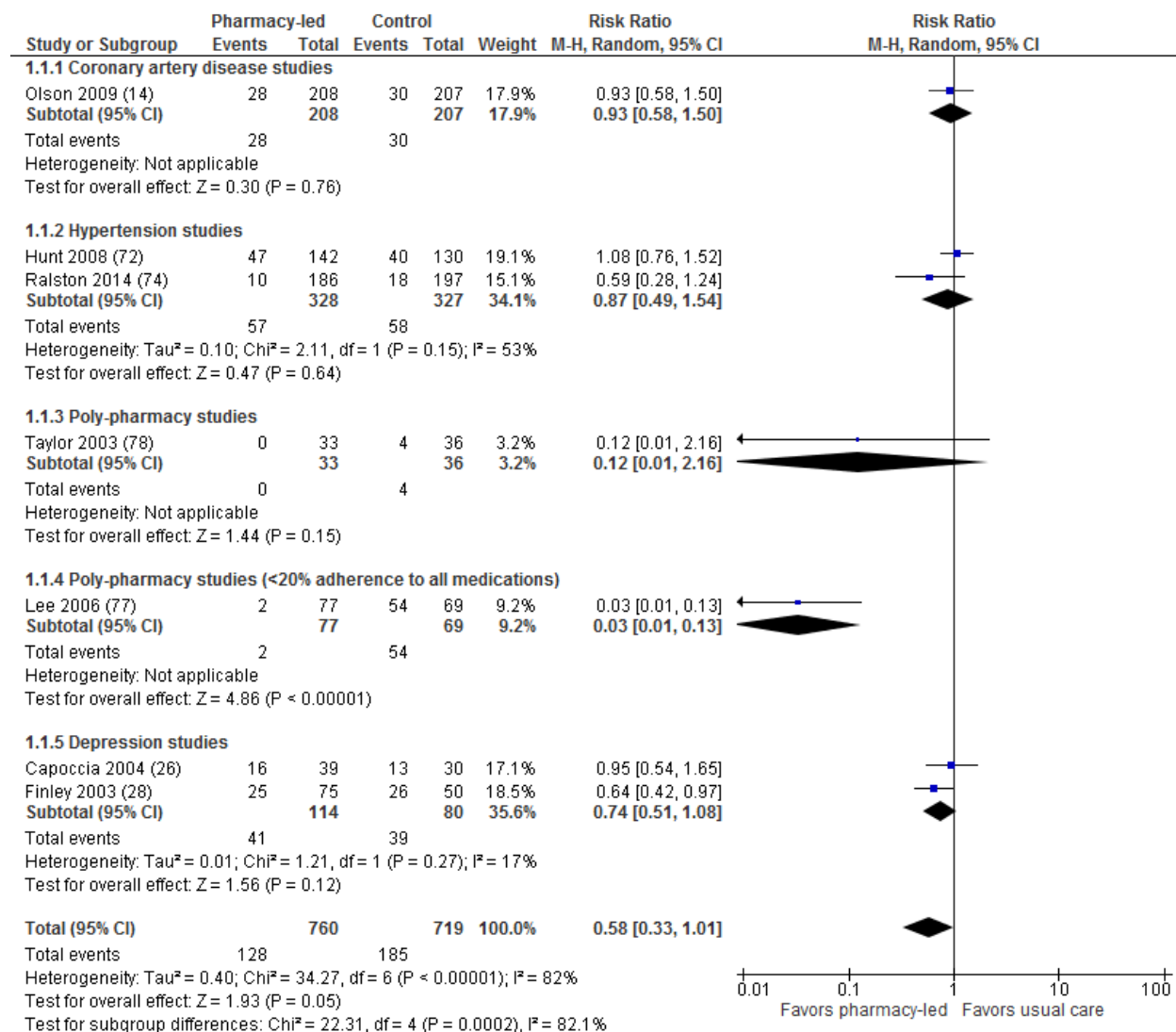
^b Goal of BP <140/90 mmHg reached by a significantly higher proportion of control group; proportion of patients in each group reaching goal of <130/80 mmHg was similar

The RCT enrolling patients with cardiovascular disease or risk factors assigned to individual or group pharmacist interventions reported no change in medications from baseline for patients in the individual intervention group but significantly increased use of blood pressure and anti-hyperglycemic medications in the group intervention patients. A significant decrease in cholesterol and anti-hyperglycemic medications from baseline was noted for the control group.¹¹ The cohort study of patients with cardiovascular disease or risk factors reported a significant difference in the number of antihypertensive medications with greater use in the intervention group.¹² One RCT of patients with CHF reported a similar percentage of patients receiving an ACE inhibitor at follow-up for the intervention and control groups. More patients in the intervention group were receiving an ACE alternative.¹⁵

Resource Use (Appendix C, Tables 3 and 4)

Each of the studies reported a measure of resource use. Results were mixed for office visits with no differences between intervention and control groups in primary care visits in the VA RCT,¹¹ while more clinic visits or blood pressure assessments outside of scheduled appointments were noted for the intervention group in a retrospective cohort study.¹² Two studies (one RCT from the VA and one cohort study) reported no differences between groups in urgent care/emergency department visits,^{11,13} while a study of patients with CHF reported fewer all-cause emergency department visits in the intervention group but similar numbers of emergency department visits for heart failure between study groups.¹⁶ Hospitalizations (reported in 4 studies) were similar between study groups^{11,13,14,16} but one heart failure study reported a lower readmission rate in the intervention group.¹⁵ Two studies reported costs outcomes. The one-time pharmacist consult to improve adherence resulted in cost savings such that approximately \$5.79 was saved for every dollar spent on the intervention program.¹³ This result was based on data from implementing the intervention for patients with diabetes and patients with coronary artery disease. A study of patients with CHF reported lower outpatient and inpatient costs in the intervention group; the statistical significance was not reported.¹⁶ No studies reported on access to care.

Figure 4. Non-adherence to Prescribed Medications, Proportion of Patients (RCTs Only)



Chronic Kidney Disease (2 RCTs, 2 Cohort Studies)

Key Findings

- Pharmacist-led care
 - improved kidney disease-related quality of life at one year but not 2 years among patients at a university-affiliated dialysis center but resulted in similar quality of life for Veterans with CKD in primary care.
 - lowered medication use in the intervention group in the dialysis study,
 - increased use of anti-hypertensive medications in the VA study with intervention and control groups similar on blood pressure goal attainment,
 - resulted in similar all-cause mortality between groups in both studies, and
 - to manage anemia due to CKD was associated with a lower weekly dose of EPO (k=1), more medication adjustments if hemoglobin levels were low (but not high) (k=1), cost savings (k=2 s), and better attainment of target hemoglobin (k=2) and iron



- saturation values (k=1) versus usual care; intervention and control sites reported similar rates of adverse events (k=1).
- No studies reported on office or emergency department visits, access to care, or drug interactions or other drug-related problems.

Characteristics of Studies (Appendix C, Table 6)

Four studies (reported in 6 papers) enrolled patients with CKD.^{17-19,20,21,22} One was a medium risk of bias RCT conducted at a university-affiliated dialysis clinic and focused on drug-related problems, drug use and costs, and hospitalizations.¹⁸ Another was a high risk of bias retrospective cohort conducted at a nephrology clinic and addressing use of epoetin alfa (EPO).¹⁹ A more recent low risk of bias RCT, based in VA community-based outpatient clinics (CBOCs) focused on care for patients with CKD, especially blood pressure control.²⁰ The last was a medium risk of bias cohort study done at VA Medical Centers.^{21,22} The goal was improved quality of erythropoiesis-stimulating agent (ESA) prescribing for non-dialysis dependent CKD patients.

The interventions varied. In a dialysis clinic-based RCT, pharmacists conducted one-on-one in-depth drug therapy review meetings with patients every 8 weeks.¹⁸ Pharmacists also provided health care provider and patient education. The comparator was usual care which included drug therapy reviews by dialysis nursing staff. The study enrolled 57 intervention group and 47 control group patients. However, 53% of the intervention group and 45% of the control group did not complete the 2-year study due to death, transplant, or transfer to another dialysis facility.¹⁸ In the RCT based in VA CBOCs, the goal was increased pharmacist interaction with patients (primarily telephone-based) and communication of recommendations to primary care physicians.²⁰ The one-year study enrolled 2,199 patients; 870 had blood pressure values greater than 130/80 mmHg at baseline. Among the cohort studies, one (n=141) involved a protocol-driven program to manage anemia of CKD.¹⁹ Maximum follow-up was one year. Patients in the intervention group also received intravenous sucrose while the control group received only EPO. The other compared clinics (10 clinics, n=314) where pharmacists managed dosing and monitored ESA therapy to clinics (6 clinics, n=167) where physicians managed care.^{21,22} Follow-up was 6 months.

Clinical Outcomes (Appendix C, Table 8)

Both RCTs reported clinical outcomes. In the larger study (n=2,199), at one year follow-up, all-cause mortality was 4.7% in the intervention group and 6.6% in the control group (P=.06).²⁰ In the second study (n=104), all-cause mortality was 26% at 2 years in both the intervention and control groups.¹⁸ The cohort study comparing pharmacist-managed ESA clinics to usual care clinics reported that adverse event rates (thromboembolic events, heart failure, uncontrolled hypertension) were similar between the clinic types.²¹

Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 8)

The study of drug-related problems found a significant difference in health-related quality of life between groups at one year (with higher quality of life in the intervention group) but no difference was observed at 2 years.¹⁷ The study of care for CKD found the intervention and control groups had similar results for measures of quality of life.²⁰ This study also reported that 92% of the intervention patients surveyed responded that the pharmacists provided useful information and they would recommend the program to others.²⁰

Goal Attainment (Appendix C, Table 10)

The EPO study reported a significantly higher percentage of measured hemoglobin and iron saturation values within target ranges in the intervention groups (Table 4).¹⁹ Similarly the study of ESA prescribing found a higher proportion of patients with hemoglobin values within range in the pharmacist-managed group.²¹ The RCT of CKD care reported the groups were similar in blood pressure goal attainment.²⁰

Table 4. Goal Attainment - Chronic Kidney Disease (4 studies)

| Author, year | Attained Goals for Iron Saturation | Attained Goals for Hemoglobin | Attained Goals for Blood Pressure |
|------------------------------|------------------------------------|-------------------------------|-----------------------------------|
| Pai, 2009 ¹⁸ | | | |
| Bucaloiu, 2007 ¹⁹ | ↑ | ↑ | |
| Aspinall 2012 ²¹ | | ↑ | |
| Cooney 2015 ²⁰ | | | ↔ |

↑ = significantly higher proportion of intervention group reached goal compared to control group (P<.05)

↔ = results not significant

Medications (Appendix C, Table 7)

The RCT focused on drug-related problems reported results only for the intervention group.¹⁸ Of 530 identified drug-related problems, 14% were related to sub-therapeutic dosage, 25% for untreated indications, and 5% for overdose. The RCT of CKD care found patients in the intervention group were prescribed significantly more classes of anti-hypertensive drugs than the control group. The intervention and control groups were similar in medication adherence.²⁰ The ESA prescribing study found significantly more adjustments to medications if hemoglobin levels were low in the intervention clinics; the frequency of medication adjustments if hemoglobin levels were high was similar in the intervention and usual care clinics.²¹

Resource Use (Appendix C, Tables 8 and 9)

The RCT focused on drug-related problems reported significantly fewer all-cause hospitalizations, lower number of medications, and lower mean drug costs (significantly lower at one of the drug reviews) in the intervention group.¹⁸ The EPO study reported a significantly lower weekly dose of EPO in the intervention group with estimated annual cost savings per patient of \$3,860.¹⁹ The study of pharmacist-managed ESA clinics modeled costs over 5 years and found lower costs (drug, laboratory test, clinic visit, and hospitalization costs were included) in the pharmacist-managed clinics.²² No study reported access to care.

Chronic Obstructive Pulmonary Disease (1 RCT)*Key Findings*

- Multifaceted pharmacist-led care from 8 VA Medical Centers
 - resulted in health-related quality of life, number of new medications, number of emergency department visits, and a rate of hospitalization that were similar to usual care,
 - decreased office visits, and
 - resulted in mixed findings for patient satisfaction (*ie*, significant differences on some subscales).

- Effects on drug-related problems were reported only for the intervention group.
- All-cause mortality, disease-specific clinical events, access to care, and costs were not reported.

Characteristics of Studies (Appendix C, Table 11)

One medium risk of bias RCT (reported in 2 papers), conducted at 8 VA Medical Centers, enrolled 98 patients with COPD.^{23,24} The intervention consisted of regularly scheduled therapeutic and educational interventions with pharmacists responsible for implementing the care plan, educating and counseling patients, and performing patient assessments. The comparator was usual care. Outcomes were assessed at 6 months follow-up.

Clinical Outcomes (Appendix C, Table 13)

No clinical outcomes were reported.

Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 13)

A global symptom assessment and quality of life were similar for intervention and control groups although bodily pain was significantly worsened from baseline to 6 months in the control group.^{23,24} On a 10-item Pharmaceutical Care Questionnaire, intervention group patients had more favorable responses than control group patients for all items; the difference was significant for 7 of the 10 items.

Goal Attainment (Appendix C, Table 10)

No goal attainment outcomes were reported.

Medications (Appendix C, Table 12)

The study reported drug-related problems for the intervention group only.

Resource Use (Appendix C, Tables 13 and 14)

There were significantly fewer office visits in the intervention group but similar incidence compared to usual care control for emergency department visits, hospitalizations, or new medications.^{23,24} Access to care was not reported.

Depression (3 RCTs, 1 non-RCT)

Key Findings

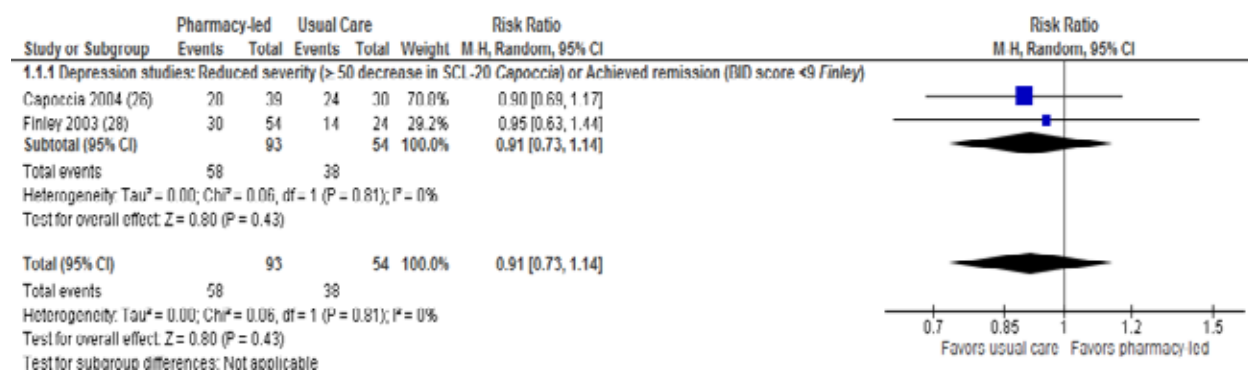
- Pharmacist-led care
 - was similar to usual care for depressive symptoms and health-related quality of life,
 - was similar to usual care for medication adherence (2 RCTs reporting); self-reported use of antidepressant medications and changes in antidepressant medications were more frequent in the pharmacist-led care groups,
 - resulted in numbers/rates of primary care or urgent care visits that were similar to usual care, and
 - increased patient satisfaction with availability of advice.
- All-cause mortality, hospitalizations, costs, inappropriate prescriptions, drug interactions, and other drug-related problems and harms were not reported.

Characteristics of Studies (Appendix C, Table 16)

Three RCTs of pharmacists' interventions in primary care clinics (reported in 4 articles) were reviewed.²⁵⁻²⁸ In addition, we included a non-randomized comparison group pilot study.²⁹ A total of 926 patients were enrolled with samples sizes ranging from 74^{26,27} to 507.²⁵ None of the studies was conducted at VA facilities. All of the studies tested multifaceted interventions provided in multiple contacts over 6 to 12 months by experienced Doctors of Pharmacy (PharmD). The pharmacists' interventions included medication histories and reviews, patient education and frequent monitoring (primarily by telephone), dose titration, and changes in antidepressant medications. The interventions were compared to usual care. In one study, usual care included access to services of the same clinic pharmacists.^{26,27} The targeted patient population was newly diagnosed or treated episodes of depression. Patients with complicating mental co-morbidities were excluded from all studies. The primary patient outcome in 2 of the RCTs was one or more measure of symptoms of depression.²⁵⁻²⁷ The third RCT focused on the intermediate outcome of antidepressant adherence, but included a measure of symptoms of depression.²⁸ The non-randomized study focused on medication adherence, patient satisfaction, and resource utilization.²⁹ We rated one study as low risk of bias, 2 as medium risk of bias, and one as high risk of bias.

Clinical Outcomes (Appendix C, Table 18)

Two RCTs looked at reduction in severity of depression as a clinical outcome – a reduction of at least 50% in a symptom score.^{26,28} The pharmacist-led intervention and usual care control groups were similar (Figure 5). The pooled risk ratio for at least 50% reduction in a symptom score in the intervention group compared to usual care was 0.91 (95% CI 0.73, 1.14). One of the studies also reported the percent achieving remission (a Brief Inventory for Depressive Symptoms score of less than 9); the study groups were similar.²⁸

Figure 5. Clinical Outcomes for Depression Trials*Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 18)*

All 3 RCTs reported health-related quality of life measures, finding groups to be similar.²⁵⁻²⁸ Each of the studies reported on patient satisfaction. One reported that intervention and control groups expressed similar satisfaction with depression care and overall health care.²⁶ Two reported mixed results for a single question about patient satisfaction with treatment of depression, finding either higher satisfaction in the intervention group²⁸ or similar satisfaction in

the 2 groups.²⁹ The fourth study reported that patients expressed high satisfaction with the pharmacist intervention but results for the intervention and control groups were not reported separately.²⁵

Goal Attainment (Appendix C, Table 20)

No goal attainment outcomes were reported.

Medications (Appendix C, Table 17)

Two RCTs reported medication adherence (Figure 4). One observed similar adherence between pharmacist-led care and usual care.²⁶ The second, which specified adherence as the primary study endpoint, reported significantly greater adherence in the intervention group.²⁸ However, the medication possession ratio was similar in the 2 groups (0.83 vs 0.77, P=.26).²⁸ The largest RCT reported a significant 12% higher percentage of intervention group patients on antidepressants at 3 and 6 months.²⁵ Two studies (one RCT and the non-randomized trial) reported more changes in antidepressants in the intervention groups.^{28,29} The non-randomized study reported a significantly higher medication possession ratio at 6 months and significantly higher use of antidepressants at 3 months in the intervention group.²⁹

Resource Use (Appendix C, Tables 18 and 19)

Two RCTs reported the intervention and control groups were similar in primary care provider visits^{26,28} although the non-randomized study reported a significantly greater decrease in primary care provider visits in the pharmacist-led care group.²⁹ In 2 RCTs reporting, there were no differences in urgent care visits.^{26,28} No study reported hospitalizations. Both the RCT and the non-randomized pilot study from the same research group reported greater availability of advice in the intervention groups.^{28,29} One study reported drug costs were similar between groups.²⁶

Diabetes Mellitus (12 RCTs, 2 CCTs, 10 Cohort Studies)

Key Findings

- Pharmacist-led care
 - resulted in all-cause mortality, disease-specific clinical events, and health-related quality of life that was similar to usual care, although few studies reported these outcomes,
 - improved rates of goal attainment for HbA1c, blood pressure, and lipids; the 3 studies in VA settings reported increased attainment of HbA1c and blood pressure goals in patients receiving pharmacist-led care,
 - resulted in significantly higher numbers and/or doses of medications, and
 - resulted in resource use (office visits, urgent care or emergency department visits, and hospitalizations) that was similar to usual care.
- One study reported access to care favoring the intervention group; no studies reported drug interactions or other drug-related problems.

Characteristics of Studies (Appendix C, Table 21)

We included 24 trials (12 RCTs or cluster RCTs, 2 CCTs, 10 cohort studies) in 25 papers of pharmacist-led care interventions for patients with diabetes mellitus. Four were conducted at VA facilities.^{30-32,33,34} A total of 17,716 patients were enrolled. All studies used multifaceted

interventions. In one study the intervention consisted of a single session,¹³ one study did not specify the frequency of the intervention,³⁵ and the remaining studies were conducted over one to 24 months. The pharmacist had some level of collaboration with other healthcare professionals in 19 studies, typically the patient's primary care provider (16 studies). The comparator groups received usual care generally delivered by their primary care provider. In all studies, the primary outcomes included physiological markers (blood pressure, HbA1c, or cholesterol) – either achieving control, change in level, or rate of testing. Fifteen studies were rated medium risk of bias; of the remaining 9 studies, 5 were rated low risk of bias and 4 as high risk of bias.

Clinical Outcomes (Appendix C, Table 23)

Four studies reported on clinical events.³⁶⁻³⁹ One study reported the pharmacist-led intervention and usual care groups were similar for rates of hypoglycemic or hypotensive episodes.³⁹ Another study reported an increase in hypoglycemic events in the intervention group compared to the usual care group but significance could not be determined.³⁷ One study reported one severe hypoglycemic event in the intervention groups but events were not documented in the control group.³⁶ Another study reported no adverse events caused by the study protocol.³⁸

Three studies assessed mortality with 2 reporting the study groups were similar in all-cause mortality^{32,39} and one reporting no diabetes-related deaths.³⁰

Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 23)

No significant findings were reported for health-related quality of life.^{32,37,40} Three studies reported patient satisfaction with care with 2 of the 3 reporting a significantly higher level of satisfaction in the intervention groups.^{39,40}

Goal Attainment (Appendix C, Table 25)

Most of the included studies measured attainment of goals for HbA1c, blood pressure, and lipid levels (Table 5, Figure 6). Fifteen studies reported attainment of HbA1c goals, typically an HbA1c less than 7%. Twelve studies found improved goal attainment in the intervention groups compared to the usual care groups although the difference was significant in just 8 of the studies.^{30-32,36,41-44} Three found lower goal attainment in intervention groups compared to controls with significant differences in 2 of the studies.^{45,46} All 3 VA studies reporting on HbA1c goal attainment showed that pharmacist-led care significantly improved goal attainment.³⁰⁻³² Pooled results from the RCTs (Figure 6) showed significantly greater HbA1c goal attainment in the intervention groups (RR 1.83 [95% CI 1.44, 2.33]).

Twelve studies reported on attainment of blood pressure control, typically defined as blood pressure less than 130/80 mmHg. Of these, 10 showed increased attainment of blood pressure goals in the intervention groups compared to controls with 6 finding significant differences.^{31,32,40,42-44} Two studies found study groups were similar.^{41,45} All 3 VA studies reporting this outcome saw increased goal attainment in patients in the intervention group compared to patients in the control group with significant results in 2 studies.^{31,32}

Lipid goal attainment (LDL-C <100mg/dL) was measured in 11 studies. Pharmacist-led care increased goal attainment compared to usual care with significant findings in 6 studies.^{42,43,45-48} The 3 VA studies found the study groups were similar.³⁰⁻³²

Medications (Appendix C, Table 22)

Thirteen studies reported number and/or dose of medications. In 9 studies, patients in intervention groups had significantly higher medication use than patients in control groups.^{30-32,38-40,45,48,49} Two studies reported medication use was similar between groups^{41,46} and significance was not reported for 2 studies.^{36,47} All 3 of the studies at VA facilities reported a significant increase in medication use and/or dose in patients receiving pharmacist-led care.³⁰⁻³² Five studies reported on use of medications for diabetes (*eg*, insulin). All 5 found significantly more medication use in patients being cared for by pharmacists.^{30-32,36,49} Two reported on hypertension medications and found significantly higher medication use and/or dose in intervention group patients as compared to controls.^{30,32} Four studies reported on lipid medications with 3 finding significantly higher use in the intervention group^{31,32,48} and one reporting no difference.³⁰

Table 5. Goal Attainment - Diabetes Mellitus (24 studies)

| Author, year | Attained goals for HbA1c levels | Attained goals for blood pressure | Attained goals for lipid levels |
|-------------------------------------|---------------------------------|-----------------------------------|---------------------------------|
| McAdam-Marx 2015 ⁵³ | | | |
| Skinner 2015 ³⁵ | | | |
| Chung, 2014 ⁵⁰ | | | |
| Spence, 2014 ¹³ | | | |
| Brummel, 2013 ⁴⁶ | ↓ ^a | ↔ | ↑ ⁺ |
| Ip, 2013 ⁴³ | ↑ | ↑ | ↑ |
| Jacobs, 2012 ³⁸ | ↔ | ↔ | ↔ |
| Salvo, 2012 ⁴⁹ | ↔ | | |
| Cohen, 2011 ³² | ↑ | ↑ | ↔ |
| Padiyara, 2011 ⁴⁵ | ↓ | ↔ | ↑ |
| Pape, 2011 ⁴⁸ | ↔ | ↔ | ↑ |
| Taveira, 2011 ³⁰ | ↑ | ↔ | ↔ |
| Heisler, 2010/2012 ^{33,34} | | | |
| Jameson, 2010 ³⁶ | ↑ | | |
| Johnson, 2010 ⁴² | ↑ | ↑ | ↑ |
| Taveira, 2010 ³¹ | ↑ | ↑ | ↔ |
| Fox, 2009 ⁴⁷ | | | ↑ |
| Scott, 2006 ⁴⁰ | ↔ | ↑ ^b | |
| Odegard, 2005 ⁵¹ | ↔ | | |
| Rothman, 2005 ³⁹ | | | |
| Shane-McWhorter, 2005 ⁴¹ | ↑ | ↔ | ↔ |
| Stroup, 2003 ⁵² | | | |
| Kelly, 2000 ⁴⁴ | ↑ | ↑ ^b | |
| Jaber, 1996 ³⁷ | | | |

↑ = significantly higher proportion of intervention group reached goal compared to control group (P<.05)

↓ = significantly higher proportion of control group reached goal compared to intervention group (P<.05)

↔ = results not significant

⁺ = significant change from baseline

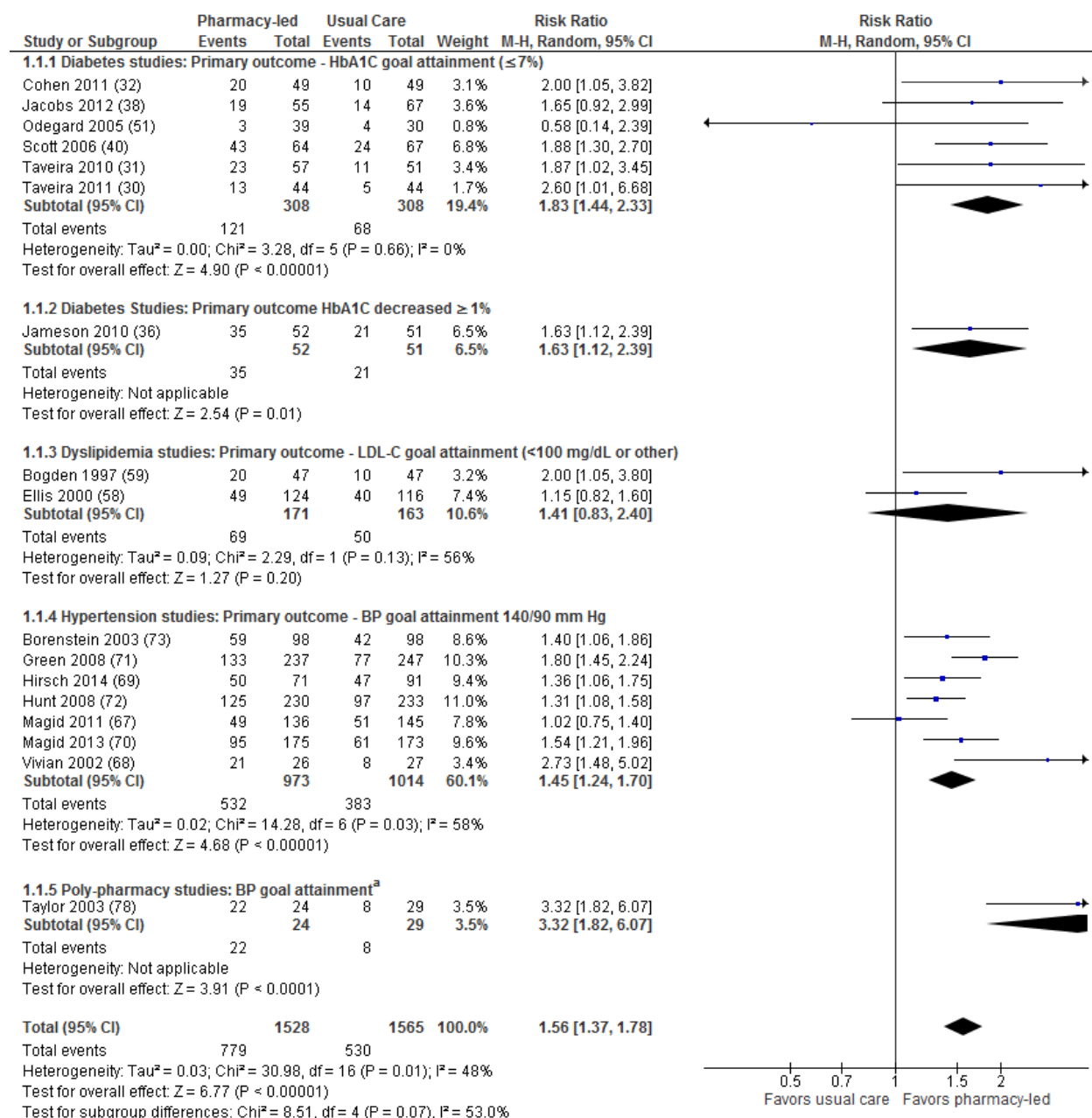
Bold indicates a study-defined primary outcome

^a HbA1c goal attainment was significantly improved from baseline to end of study and end of follow-up by intervention but at the end of follow-up the proportion of patients at goal HbA1c was significantly lower in the intervention group.

^b Significantly more people in the intervention group met the goal for systolic blood pressure but groups were similar for diastolic blood pressure.

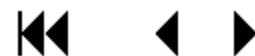
No studies reported on ineffectiveness or drug interactions. Only one study reported on medication inappropriateness finding mean medication appropriateness index scores were similar to usual care after 6 or 12 months of pharmacist-led care.⁵¹ Four studies measured non-adherence^{13,32,35,51} finding that patients receiving pharmacist-led care had higher adherence to their prescribed regimens; the difference was significant in 2 of the studies.^{13,35} Out of 6 studies that measured aspirin use, 2 found significantly higher use in patients receiving care from pharmacists,^{39,45} 2 found groups to be comparable,^{31,46} and 2 did not report significance.^{40,41} Two studies looked at the total number of medications that patients were prescribed and found groups were similar.^{38,47}

Figure 6. Goal Attainment for Diabetes, Dyslipidemia, Hypertension, and Polypharmacy Studies Based on Primary Outcome (RCTs Only)



Resource Use (Appendix C, Tables 23 and 24)

Six studies measured office visits,^{30,32,34,39,51,53} including 3 studies in VA settings.^{30,32,34} Office visits were similar between intervention and control groups in 3 studies while one found increased outpatient utilization in the intervention group.⁵³ Seven studies looked at hospitalizations with similar results for intervention and control groups.^{13,30,34,37,39,50,52,53} Two studies reported decreased urgent care or emergency room visits in intervention group patients compared to control group patients^{13,52} while 6 other studies found study groups were similar.^{30,34,39,40,50,53} One study found that patients under a pharmacist’s care were significantly more satisfied with their ability to reach somebody in an emergency.⁴⁸ Three studies reported cost outcomes with one finding a lower increase in total patient charges (inpatient and outpatient)



over the study period for the intervention group⁵³ and 2 not reporting the significance of their findings.^{13,47}

Dyslipidemia (2 RCTs, 2 CCTs, 3 Cohort Studies)

Key Findings

- Pharmacist-led care
 - improved goal attainment (typically LDL < 100 mg/dL) compared to usual care although pooled results from 2 RCTs showed groups were similar,
 - was associated with increased medication use; one study reported adherence in the intervention group but not the usual care group, and
 - led to mixed results for office visits and similar results for urgent care or emergency department visits and costs as usual care.
- No studies reported other clinical outcomes (*ie*, mortality, disease-specific clinical events, health-related quality of life, and patient satisfaction), hospitalizations, access to care, inappropriate prescriptions, or drug interactions or other drug-related problems.

Characteristics of Studies (Appendix C, Table 26)

We included 7 studies (total n=1,834) of pharmaceutical care for dyslipidemia.⁵⁴⁻⁶⁰ There was one RCT,⁵⁹ 2 controlled clinical trials,^{57,60} one prospective cohort study,⁵⁵ and 2 retrospective cohort studies.^{54,56} The remaining study was a sub-study of an RCT.⁵⁸ Follow-up ranged from 4 weeks to 46 months. Four studies were conducted at VA clinics.^{54,56,58,60} All studies enrolled patients from primary care (*ie*, family medicine, general medicine) clinics. In one study, although the intervention group consisted of family medicine center patients, the control group was from family medicine, cardiology, and endocrinology clinics.⁵⁵ We rated 3 studies as medium risk of bias and 4 as high risk of bias.

Intervention components included medication evaluation,^{54,56,58,59} medication prescription and adjustment,^{54,56-58} therapeutic conversion,⁵⁵ ordering and reviewing of laboratory results,^{54,57,59} patient education,^{55,57,60} follow-up contacts,^{54,56,60} physician collaboration,^{55,57,59,60} identification and prevention of drug-related problems,⁵⁸ and referral to other resources (*ie*, smoking cessation).⁵⁷ The comparator was usual care in all studies.

Clinical Outcomes (Appendix C, Table 28)

None of the studies reported all-cause mortality or clinical events.

Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 28)

None of the studies reported health-related quality of life or patient satisfaction outcomes.

Goal Attainment (Appendix C, Table 30)

Each of the studies reported a goal attainment outcome (Table 6, Figure 6). Significantly more patients in the intervention groups achieved LDL goals in 5 studies.^{54,56,57,59,60} Another study reported a significant increase in goal attainment from before to after therapeutic conversion in the intervention group and a significant decrease during that time period in the control group.⁵⁵ The last study reported significant improvements in goal attainment for both the intervention and control groups but groups were similar at the end of the study.⁵⁸ Pooled results from the 2 RCTs

(Figure 6)^{58,59} showed the effect of pharmacist-led care on goal attainment was similar to usual care (RR 1.41 [95% CI 0.83, 2.40]).

Table 6. Goal Attainment - Dyslipidemia (7 studies)

| Author, year | Attained Goals for Lipid Levels |
|-------------------------------|---------------------------------|
| Smith, 2013 ⁵⁴ | ↑ |
| Miller, 2008 ⁵⁵ | ↑ ⁺ |
| Mazzolini, 2005 ⁵⁶ | ↑ |
| Straka, 2005 ⁵⁷ | ↑ |
| Ellis, 2000 ⁵⁸ | ↔ |
| Bogden, 1997 ⁵⁹ | ↑ |
| Konzem, 1997 ⁶⁰ | ↑ |

↑ = significantly higher proportion of intervention group reached goal compared to control group (P<.05)

↔ = results not significant

⁺ = significant change from baseline

Bold indicates a study-defined primary outcome

Medications (Appendix C, Table 27)

Number and/or dose of medications was significantly higher in the pharmacist-led care groups compared to control groups in 3 of 5 studies reporting this outcome.^{56,57,60} Significance was not reported in 2 other studies^{55,59} One study reported significantly more medication interventions per patient in the intervention group.⁵⁴ The study of therapeutic conversion reported more patients in the intervention group received an equivalent dose post-conversion while more patients in the control group received a lower dose.⁵⁵ One study reported compliance for the intervention group but not the control group.⁶⁰

Resource Use (Appendix C, Tables 28 and 29)

Three studies reported office visits with 2 finding intervention and control groups were similar^{54,56} and one finding more office visits in the intervention group.⁵⁹ One study reported that the frequencies of emergency department visits were similar between groups.⁵⁹ None of the studies reported hospitalizations. Two studies reported costs finding similar changes from the baseline period between intervention and control groups for hospitalization, clinic visit, and drug costs⁵⁸ or medication costs.⁵⁹

Hypertension (13 RCTs, 1 CCT, 1 Case-Control Study)

Key Findings

- Pharmacist-led care
 - resulted in similar health-related quality of life as usual care; patient satisfaction results were mixed and few studies reported other clinical outcomes,
 - increased medication use but adherence was similar to usual care,
 - led to mixed results for resource use outcomes including office visits and costs; few studies reported urgent care or emergency room visits, and
 - resulted in patient perceptions similar to usual care for “had problems getting needed care.”

- No studies reported drug interactions or other drug-related problems; one study reported inappropriate medications for the intervention group but not the control group.

Characteristics of Studies (Appendix C, Table 31)

We identified 13 randomized controlled trials (RCTs) reported in 15 papers that evaluated the effect of pharmacist-led care for the management of uncontrolled hypertension (HTN). Four trials were cluster-randomized (*ie*, trials that randomized clinics and not patients).⁶¹⁻⁶⁴ We also included one controlled clinical trial⁶⁵ and one case-control study.⁶⁶ The studies enrolled a total of 6,278 patients. Four studies included patients from Veterans Affairs Medical Centers.^{23,24,66-68}

In 5 studies, pharmacists had the ability to initiate and change medical therapy for HTN management although some physician oversight may have been involved.^{62,66-70} In 6 studies, pharmacists provided guidance and made recommendations to the patient's physician or worked directly with the physician (team-based or co-management care) on how to best implement the medical therapy for HTN management.^{61,63,64,71-73} Usual care was typically continued care with the patient's primary care physician although in one study, some control group patients were provided with home blood pressure monitors.^{71,74} Study periods ranged from 6 to 24 months. One study also included a 6-month follow-up period after the 12-month intervention to observe the maintenance of any affects following the discontinuation of the intervention.⁶² Overall risk of bias was medium; 2 studies were rated low risk of bias.^{66,71,74}

Clinical Outcomes (Appendix C, Table 33)

Overall, the included trials were short-term, underpowered, or not designed to evaluate the impact of a pharmacist component of patient care on all-cause mortality or other clinical events. One trial reported deaths during the study period – one in the pharmacist component arm due to cardiac arrest and none in the usual care arm.⁷¹ Other trials reported clinical events in the intervention and control groups were similar,^{62,64,71} or the significance of the findings was not provided.^{69,75}

Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 33)

Patient satisfaction with care was evaluated in 8 trials. Two studies reported a clinical patient satisfaction outcome. One study reported a significantly higher percentage of patients reporting high satisfaction with their hypertension care in the pharmacist component group compared with the usual care group (58% vs 42%, $P < .001$).⁷⁰ The other reported the percentage of patients very satisfied with pharmacy services to be similar between groups (88% vs 68%, $P = .098$).⁶⁸ The other studies reported scale score changes with mixed results.^{23,24,62,69,71,72,74} Health-related quality of life was evaluated in 7 trials.^{23,24,62,65,68,71,72,75} Patient health-related quality of life did not differ between the pharmacist component and usual care groups.

Goal Attainment (Appendix C, Table 35)

Nearly all trials reported the proportion of patients who attained controlled BP, typically defined as a systolic BP < 140 mm Hg and diastolic BP < 90 mm Hg (Table 7, Figure 6). Ten studies reported greater goal attainment in the intervention group compared to the usual care group^{62-64,66,68-73} while 3 reported the groups to be similar.^{61,65,67} Pooled data from 7 RCTs showed the proportion of patients who attained controlled BP was significantly greater in the pharmacist-led care group (54%) compared with the usual care group (38%) (RR 1.45 [95% CI 1.24 1.70])

(Figure 6). There was a moderate level of heterogeneity ($I^2 = 58\%$) Similar to the findings for all patients, greater attainment in controlled blood pressure was also observed in the pharmacist intervention group for the subgroup of patients with diabetes with or without chronic kidney disease.^{63,64,70}

Table 7. Goal Attainment - Hypertension (15 studies)

| Author, year | Attained Goals for Blood Pressure |
|---|-----------------------------------|
| Carter 2015 ⁶¹ | ↔ |
| Zillich 2015 ⁶⁶ | ↑ |
| Hirsch, 2014 ⁶⁹ | ↑ |
| Magid, 2013 ⁷⁰ | ↑ |
| Margolis, 2013 ⁶² | ↑ |
| Magid, 2011 ⁶⁷ | ↔ |
| Carter, 2009 ⁶³ | ↑ |
| Carter, 2008 ⁶⁴ | ↑ |
| Green, 2008, Ralston 2014 ^{71,74} | ↑ |
| Hunt, 2008 ⁷² | ↑ |
| Borenstein, 2003 ⁷³ | ↑ |
| Vivian, 2002 ⁶⁸ | ↑ |
| Okamoto, 2001 ⁷⁵ | |
| Solomon 1998, Gourley, 1998 ^{23,24} | |
| Erickson, 1997 ⁶⁵ | ↔ |

↑ = significantly higher proportion of intervention group reached goal compared to control group (P<.05)

↔ = results not significant

Bold indicates a study-defined primary outcome

Medications (Appendix C, Table 32)

No trial reported inappropriate dosage/prescription or omission, ineffectiveness, or drug interactions for both the pharmacist-led care group and the usual care group. One study reported drug-related problems including need for additional therapy, need for dose increase, and adverse drug reaction data for intervention group.⁶⁹ Poor or less than perfect adherence to the prescribed regimen, determined from the inverse of typically self-reported good adherence, was not significantly different between study groups in 6 trials.^{62-64,67,68,71,72,74} One trial reported better compliance in the intervention group^{23,24} and 2 trials only reported results for the intervention group.^{69,70} Pooled data from 2 RCTs (Figure 4) showed no difference in adherence (RR 0.87 [95% CI 0.49, 1.54]). The case-control study reported that medication possession ratios and the percentage of patients with possession ratios of at least 80% for all blood pressure medications were similar between the intervention and control groups.⁶⁶

Significant increases in medication use associated with a pharmacist component in patient care were reported in 9 trials.^{61-64,67,70-73} Compared with usual care patients, pharmacist component patients were prescribed more antihypertensive medications during the intervention intervals. Four trials reported similar medication use between intervention and control groups.^{65,66,68,75}

Resource Use (Appendix C, Tables 33 and 34)

Health care utilization results were mixed. Three trials reported patients in the pharmacist-led care groups had significantly fewer primary care visits compared with usual care patients.^{69,72,73} However, in one trial, with the addition of pharmacy visits, total visits were comparable with or greater than those in the usual care group.⁷² Four trials reported the number of primary care visits to be similar between study groups^{65,68,70,71} and one reported a significantly greater number of clinic visits in the pharmacist-led care group.⁷⁵ Pharmacist-led care and usual care were similar in the number of urgent care or emergency room visits and hospitalizations although few studies reported these outcomes.

Four trials provided estimates of costs associated with pharmacist-led care. One study estimated that direct program costs would total about \$1,350 per patient but did not provide costs for usual care.⁶² In a publication⁷⁶ based on data from a cluster randomized trial,⁶⁴ the adjusted total costs per patient were \$775 in the pharmacist-led care group compared to \$446 in the control group (difference \$329, $P < .001$). However, a cost-benefit analysis was not done to determine if the financial savings related to potentially reduced morbidity and mortality achieved from lower blood pressure outweighed the costs of the pharmacist component. Another study reported that the average provider visit costs per patient were lower in the pharmacist component group compared to usual care (\$160 and \$195, respectively; $P = .04$).⁷³ These costs were based on average number of visits to the primary care physician during the study which were lower in the pharmacist-led care group (3.4 compared with 6.6 for usual care patients; $P < .01$) and lower provider visit costs for pharmacists (\$20 for a 30-minute appointment) than physicians (\$35 for a 15-minute appointment). Average monthly drug costs were similar at the end of the study period. The fourth study reported drug costs per patient and total costs per patient did not differ between study groups.⁷⁵ Clinical visit costs (based on the salary of the provider – pharmacist or physician) were significantly higher in the pharmacist-led care group.

Polypharmacy/High Risk for Drug-related Problems (3 RCTs)

Key Findings

- Pharmacist-led care
 - resulted in health-related quality of life; patient satisfaction, and rates/numbers of disease-specific clinical events that were similar to usual care; goal attainment was improved,
 - resulted in similar medication use as usual care; results were mixed for medication adherence; significance of other medication findings could not be determined, and
 - increased the number of office visits compared to usual care but decreased use of urgent care facilities; results were mixed for hospitalizations and costs.
- No studies reported all-cause mortality or access to care.

Characteristics of Studies (Appendix C, Table 36)

We identified 3 RCTs (in 4 papers) of clinical pharmacist interventions in primary care clinics for patients judged to be at high risk for drug-related problems.⁷⁷⁻⁸⁰ The studies enrolled a total of 1,282 patients (range 69 to 1054). One study was rated low risk of bias and 2 were rated medium risk of bias. Two studies targeted ambulatory adults with multiple risk factors for drug-related problems⁷⁸⁻⁸⁰ and one study targeted ambulatory adults aged 65 years or older with polypharmacy (4 or more medications).⁷⁷ Patients were considered at high risk due to use of

multiple medications, multiple changes in medications in the past year, multiple concurrent diseases, a history of non-compliance, and/or use of medications requiring therapeutic monitoring. One study was conducted at VA primary care clinics.^{79,80} Patients were excluded from the trials if they had cognitive impairment, lived in nursing homes, had life expectancy less than 12 months, or had other problems with verbal or written communication. All 3 studies tested multifaceted interventions delivered by a clinical pharmacist over 6- to 12-month periods. The comparator groups received routine care by physicians and nurses in clinic without contact with a clinical pharmacist. In one of the studies, the RCT phase followed a 6-month cohort phase in which all patients received the intervention. Patients were then randomized to continue the intervention or return to usual care follow-up.⁷⁷

Clinical Outcomes (Appendix C, Table 38)

No study reported all-cause mortality. In one study, the percentage of patients with at least one “medication misadventure” was similar between the study groups (2.8% intervention vs 3.0% control, $P=.73$).⁷⁸ Another study noted less decline in the “change in health” component in the intervention group patients but the difference between intervention and usual care groups was not clinically meaningful (defined as a 5-point difference).⁸⁰

Quality of Life and Patient Satisfaction Scale Scores (Appendix C, Table 38)

Two studies, including the VA-based study, found health-related quality of life (assessed with the SF-36) to be similar between intervention and usual care groups.^{78,80} The VA study reported no differences in patient satisfaction at baseline or over the course of the study.⁸⁰ Another study reported significantly higher pharmacy-related satisfaction in the usual care group although the reporting is unclear.⁷⁸

Goal Attainment (Appendix C, Table 40)

One study found statistically significant improvements in goal attainment for hypertension, diabetes mellitus, and dyslipidemia but similar anticoagulation goal attainment between groups (Table 8, Figure 6).⁷⁸ The trial comparing on-going pharmacist intervention to usual care found a higher percentage of patients with medication adherence at greater than 80% at the end of the randomized trial phase in the intervention group.⁷⁷ The VA study did not report goal attainment.

Table 8. Goal Attainment - Polypharmacy/High Risk (3 studies)

| Author, year | Attained Goal for Medication Adherence | Attained Goal for Hypertension | Attained Goal for Diabetes | Attained Goal for Dyslipidemia | Attained Goal for Anticoagulation |
|---------------------------------------|--|--------------------------------|----------------------------|--------------------------------|-----------------------------------|
| Lee, 2006 ⁷⁷ | ↑ | | | | |
| Taylor 2003 ⁷⁸ | | ↑ | ↑ | ↑ | ↔ |
| Malone 2000 and 2001 ^{79,80} | | | | | |

↑ = significantly higher proportion of intervention group reached goal compared to control group ($P<.05$)

↔ = results not significant

Bold indicates a study-defined primary outcome

Medications (Appendix C, Table 37)

In one study, pharmacist-led interventions were associated with fewer inappropriate dosage prescriptions (13% vs 64%), fewer inappropriate indication prescriptions (16% vs 48%), fewer ineffective prescriptions (14% vs 45%), and fewer drug-drug (6% vs 23%) and drug-disease (9% vs 20%) interactions at 12 months compared to the usual care group.⁷⁸ The statistical significance of the findings was not reported. Study groups were similar for compliance (100% intervention, 89% usual care) (Figure 4). The study of improvement maintenance reported significantly greater medication adherence in the group that continued the intervention compared to the group that received usual care (Figure 4).⁷⁷ The VA study reported groups were similar for the increase in drug fills over the course of the study.^{79,80} Another study reported mean number of anti-hypertensive medications was similar⁷⁷ while the third study reported a significantly lower number of prescribed medications in the intervention group.⁷⁸

Resource Use (Appendix C, Tables 38 and 39)

A significant increase in office visits but not hospitalizations was reported in the VA pharmacist-led care group compared to VA usual care.^{79,80} Another study reported a significant decrease in urgent care visits and hospitalizations during the study period in the intervention group compared to the usual care group.⁷⁸ Cost outcomes included a similar mean cost for the pharmacist intervention (including clinic visits, drug costs, laboratory costs, and hospitalizations) compared to usual care in the VA study^{79,80} and a determination that a lower percentage of patients in the intervention group had the least expensive drug option following the intervention compared to the usual care group.⁷⁸ No study reported on access to care.

Intervention Frequency, Delivery Mode, and Number of Components

To examine the effects of intervention frequency, delivery mode, and number of components, we compared the results from one-session interventions, the remotely delivered (no in-person contact) interventions, and the interventions with one or 2 components to the overall data set.

Frequency (one-time compared to pooled total)

Four studies used one-time interventions and 3 of these defined a pooled outcome, goal attainment or non-adherence, as their primary outcome. In general, the results of studies without follow-up visits agreed with the trends seen in the pooled analysis. The 2 studies reporting LDL goal attainment both found better goal attainment in the group receiving pharmacist-led care^{48,55} and one of them reported a significant between group difference.⁴⁸ Pooled data for dyslipidemia resulted in a non-significant improvement in goal attainment (RR 1.41 [95% CI 0.83, 2.40]). The other outcome was only reported by one study. Murray 2007 found that a one-time pharmacist intervention significantly decreased medication non-adherence.¹⁶ The pooled data followed this trend but did not reach significance (RR 0.72 [95% CI 0.51, 1.08]). Results of the one-time studies did not always have as strong of an effect as seen in the pooled data. However, having only a one-time intervention did not change the direction of effect on goal attainment or non-adherence.

Delivery Mode (remotely delivered compared to pooled data)

Seven studies used a remote intervention, with no in-person contact between pharmacist and patient; 6 of them had goal attainment as their primary outcome. Overall, the results of these

studies were not different than the pooled data. Five of the studies looked at attaining LDL control. The pooled data showed that pharmacist-led care tended to increase attainment of LDL control, although the effect was not significant. Four studies of remote interventions^{47,48,55,57} also found greater LDL goal attainment in the intervention groups and 3 of them had a significant result.^{47,48,57} The fifth found the groups were similar.¹⁴ A remote intervention seemed to have the same effect as the pooled data, if not more of an impact. Only one study using a remote intervention reported goal attainment for hypertension as its primary outcome.⁷¹ This study had results consistent with the pooled data; the group receiving pharmacist-led care had a larger proportion of patients with blood pressure control.⁷¹ This data suggest that the effect of a pharmacist-led care may be weakened without in-person contact but that pharmacist involvement is still beneficial.

Number of Components (one or 2 component interventions compared to pooled data)

Thirteen studies used interventions with just one or 2 of our 6 defined components. Of these, 4 specified goal attainment or non-adherence as a primary outcome. Three reported goal attainment including one in dyslipidemia, and one in hypertension. Goal attainment for blood pressure was shown in pooled data to be significantly improved by pharmacist-led care (RR 1.38 [95% CI 1.18, 1.62]). The study reporting on blood pressure goal attainment had the same result, significantly better blood pressure control in the intervention group as compared to the control.⁶³ The pooled data showed a non-significant improvement in lipid goal attainment with pharmacist-led care and the study reporting on dyslipidemia also did not report a significant difference, although the trend was in the same direction.⁵⁵ For non-adherence the pooled data showed that pharmacist care led to less non-adherence but the difference was not significant (RR 0.72 [95% CI 0.49, 1.06]). Lee 2006, however, found the proportion of patients' adherent was significantly greater in the intervention group.⁷⁷ Having fewer components did not decrease the effect of the pharmacists' interventions on goal attainment or non-adherence.

Quality of Evidence

Strength of evidence for key outcomes is summarized in Table 9.

Table 9. Strength of Evidence^a

| Outcome | Strength of Evidence | Direction | Number of RCTs (N) | Summary |
|---|----------------------|--|--|---|
| Disease-specific clinical events^b | Low | Similar | 12 (3,355) | Most trials found similar outcomes between pharmacist-led care and usual care. Outcomes were sporadically and inconsistently reported and there were few events. Overall risk of bias was moderate. |
| Patient satisfaction | Insufficient | Mixed | 16 (12,793) | Results were inconsistent for measures of patient satisfaction between pharmacist-led care and usual care. There was variation in how patient satisfaction was reported (scale score or proportions), some measures may not be validated, and some trials used a single item from a multi-item scale. Overall risk of bias was moderate. Given these limitations, conclusions regarding the strength of evidence for patient satisfaction cannot be determined. |
| Urgent care/ER and hospitalizations | Moderate | Similar | Urgent care/ER 16 (7,166) Hospitalizations 12 (7,455) | Incidence or rates of urgent care/ER visits or hospitalizations were similar between pharmacist-led care and usual care. Overall risk of bias was moderate. |
| Non-adherence to medications | Low | Similar | 17 (5,933) | In most trials medication non-adherence was similar between pharmacist-led care and usual care. Overall risk of bias was moderate. Pooled results from 7 (n=1479) demonstrated a substantial relative reduction but findings were imprecise, not significant, and had substantial heterogeneity (RR 0.58 [95% CI 0.33, 1.01]; $I^2 = 82\%$). |
| Goal attainment | Moderate | Improved in pharmacist-led care groups | 19 (5,816) | Pharmacist-led care improved the proportion of patients achieving guideline recommended laboratory or physiologic treatment goals versus usual care, 51% vs 34% (RR 1.56 [95% CI 1.37, 1.78]; $I^2 = 48\%$). Results were precise and fairly consistent. Cluster RCTs, CCTs, and cohort studies not included in the pooled analysis generally reported improved goal attainment in the pharmacist-led care group. Overall risk of bias was moderate. |

^a Strength of evidence determined for specific outcomes across all chronic disease conditions

^b *ie*, severe hypoglycemia or hypotension requiring additional interventions

SUMMARY AND DISCUSSION

SUMMARY OF FINDINGS AND STRENGTH OF EVIDENCE

We identified 70 papers (published from 1995 to 2015) representing 62 studies of 64 unique study populations (including 40 RCTs) and enrolling 34,457 patients. Fifty-two of the unique populations studied (81%) were adults with cardiovascular disease, diabetes, dyslipidemia, or hypertension; other conditions included depression, chronic kidney disease, chronic obstructive pulmonary disease, and polypharmacy. Seventeen studies were conducted, at least in part, at VA Medical Centers. Most pharmacist-led interventions were multifaceted, conducted in person, and included multiple contacts between pharmacists and patients. Most studies were not primarily designed to evaluate the effect of pharmacist-led care on clinical or resource use outcomes. Intermediate measures were the most frequently reported outcome with the most common (k=45) being target goal attainment for HbA1c, blood pressure, and cholesterol levels. We included a wide range of studies (randomized controlled trials, controlled trials, interrupted time series, and cohort studies) in order to evaluate a diverse body of literature related to system-level quality improvement projects and pharmacist-led care.

We rated strength of evidence for disease-specific clinical events (low strength of evidence that pharmacist-led care and usual care were similar), patient satisfaction (insufficient evidence), urgent care/emergency department visits and hospitalizations (moderate strength of evidence that pharmacist-led care and usual care were similar), non-adherence to medications (low strength of evidence that pharmacist-led care and usual care were similar), and goal attainment (moderate strength of evidence that pharmacist-led care increased the proportion of patients achieving glycemic, blood pressure, and cholesterol goals compared to usual care). While we did not formally assess strength of evidence on other outcomes we did find that pharmacist-led care was also similar to usual care for depression, health-related quality of life, all-cause mortality, and cost outcomes. However, due to differences in costs reported across studies (program costs, medication costs, visit costs), it is difficult to reach a conclusion about costs. Very few studies reported drug-related problems (inappropriate medication or dosage, drug interactions). Patients in the pharmacist-led care groups generally received a greater number or dose of medications though it was difficult to evaluate whether increased number or dose of medications was an indicator of better care quality.

We identified one additional study that attempted to address the gap in reporting of adverse events.⁸¹ In a post-hoc analysis, the authors achieved a larger sample size by pooling data from 2 similarly conducted RCTs comparing pharmacist-led interventions to usual care for patients with heart failure¹⁶ and hypertension. Adverse drug events and medication errors were secondary outcomes in the original trials. There were 75 events in the intervention groups and 135 events in the control groups. The risk ratio for all events (adverse drug events, preventable adverse drug events, potential adverse drug events, and medication errors) was 0.66 (95% CI 0.50, 0.88) favoring the intervention groups over the control groups. Risk ratios for the individual event categories were similar although not significant for preventable or potential adverse drug events.

Our results concur with findings from other recent systematic reviews. Viswanathan et al, in a review for the Agency for Healthcare Research and Quality (AHRQ), focused on MTM and required interventions to include at least 3 elements: comprehensive medication review, patient-directed education and counseling, and coordination of care.⁹ They found low strength of

evidence for a benefit of MTM for health plan expenditures (based on 3 RCTs) although the evidence from non-randomized trials and cohort studies was rated as insufficient strength. There was also a benefit of MTM for hospitalization risk for diabetes (based on one cohort study) but not CHF or COPD (insufficient evidence). There were mixed results for number of hospitalizations with 3 RCTs finding no benefit and one cohort finding a benefit of MTM. Only 5 studies were included in both the AHRQ review and our review. However, both reviews found limited reporting of outcomes such as clinical events, mortality, adverse drug events, and drug-related problems. The authors of the AHRQ review also commented on difficulty interpreting findings as higher values for some outcomes (*eg*, office visits, medication use) may indicate better care for some patients and poorer care for others and many sources of variability are not accounted for in the data analyses.

Another review focused exclusively on blood pressure control in patients with or without diabetes.⁸² Included studies were RCTs with interventions delivered by a pharmacist alone or in collaboration with other healthcare professionals. In pooled analyses, pharmacist interventions were associated with reductions in systolic and diastolic blood pressure although heterogeneity was high ($I^2=67\%$ for the systolic blood pressure analysis, $I^2=83\%$ for the diastolic blood pressure analysis). Subgroup analyses by the type of pharmacist intervention showed greater changes in systolic and diastolic blood pressure with pharmacist-led care compared to collaborative care. No other outcomes were reported.

A 2010 review included studies of interventions, conducted in the US, where the pharmacist was involved in direct patient care (with a “discernable contribution”).⁸³ Outcomes of interest were categorized as therapeutic (*eg*, blood pressure, hospitalizations, mortality, appropriate medication use, eye exams), safety (*eg*, adverse drug events, medication errors), or humanistic (*eg*, patient adherence, patient knowledge, quality of life). The authors reported the percentage of studies reporting an outcome with favorable, non-favorable, mixed, no effect, and unclear findings then performed meta-analyses with data from RCTs if more than 4 RCTs reported the outcome. The therapeutic outcomes eligible for meta-analysis were HbA1c, LDL, and blood pressure. Pooled standard mean difference data favored the pharmacist involvement. Data on adverse drug events (safety outcome) were pooled with an odds ratio favoring the pharmacist involvement (OR 0.53 [95% CI 0.33, 0.83]). Standard mean difference data could also be pooled for 6 humanistic outcomes. Significant differences favoring pharmacist involvement were noted for medication adherence, patient knowledge, and quality of life (general health). Non-significant findings were reported for patient satisfaction and 2 quality of life dimensions – physical functioning and mental health.

APPLICABILITY

The chronic disease conditions addressed in the included studies (cardiovascular disease, chronic kidney disease, COPD, depression, diabetes mellitus, and hypertension) are common among Veterans. Seventeen studies were conducted in VA facilities. The model of pharmacist-led care reported in these studies varied but likely is similar to ongoing programs in VA.

LIMITATIONS AND RESEARCH GAPS/FUTURE RESEARCH

Many of the outcomes reported in this review were not the study-defined primary endpoints and therefore not supported by rigorous research methods or statistical inferences. Among studies included in our review, sample sizes were too small and follow-up periods too short to detect

differences in mortality. There was limited reporting of other clinical events, health-related quality of life, and patient satisfaction. When assessed, authors used varied methods for determining health-related quality of life and patient satisfaction. Scale scores were often not validated, of unknown clinical importance, or included selected findings from subscales. Interventions varied in composition, delivery mode, and intensity as did the usual care comparator, making it difficult to draw conclusions about important intervention characteristics.

One hypothetical benefit of pharmacist-led care for chronic diseases is increased access to care for patients. None of the included studies reported typical measures of access and only 4 studies (2 in patients with depression and one each in patients with hypertension or diabetes) reported patient satisfaction or patient perception measures related to access (*eg*, satisfaction with ability to reach someone in an emergency or satisfaction with availability of advice). Intervention-based increases in the number of scheduled visits or telephone calls may not represent improved access. Further research is needed with conventional measures of access.

A consistent definition of an office visits outcome is needed to distinguish regularly scheduled office visits, study-related office visits, and unplanned office visits. In many cases it was unclear whether the visit was with a pharmacist or primary care provider. Also, a consistently reported cost outcome that includes all of the important economic factors involved in pharmacist-led care would facilitate comparisons across studies and provide more accurate cost-effectiveness estimates.

There was limited reporting of important drug-related problems, in particular drug interactions and inappropriate medications and/or dosages. Some studies did report on adherence with mixed, inconclusive results. Despite existing definitions of polypharmacy, an isolated measure of the number of medications is not an indicator of quality of care as there are situations where adding medications and/or increasing dosages may be helpful. Similarly, de-prescribing medications that emerging evidence suggests are not beneficial and may provide harm may also be helpful. Further research is needed to define and describe these interventions and their association with patient outcomes and value

Finally, the demonstrated improvement in laboratory and physiologic goal attainment due to pharmacist-led care is potentially encouraging. Intervention group pharmacists successfully achieved the intended study objectives. The target goals were based, in part, on recommendations from selected existing clinical practice guidelines and performance measures. The results indicate that future pharmacist-led programs are likely to achieve intended goals. However, there is conflicting evidence that target goals for glycemic, blood pressure, or cholesterol control have long-term beneficial effects on patient outcomes including clinical events, satisfaction, access, hospitalizations, and costs. Therefore, future research needs to carefully assess whether the magnitude of effect on selected intermediate laboratory and physiologic goals translate to improved patient outcomes including clinical events, satisfaction, access, hospitalizations, and costs. Few studies reported differences in potential harms. Thus the available evidence does not answer the question about whether the benefits of pharmacy-led interventions justify potential harms and costs. Ideally, future studies will be designed to fully and accurately address final patient outcomes and cost effectiveness.

CONCLUSIONS

Evidence is limited on the effectiveness and harms of pharmacist-led chronic disease management compared to usual care for clinical outcomes (*ie*, clinical events, all-cause mortality, patient satisfaction, quality of life, and resource utilization). Moderate-strength evidence indicates that pharmacist-led chronic disease management increases goal attainment for HbA1c, blood pressure, and cholesterol levels. Moderate- or low-strength evidence also indicates that pharmacist-led chronic disease management and usual care were similar for urgent care visits or hospitalizations, clinical events, and adherence to medications. Evidence was insufficient for patient satisfaction. There was little reporting of access to care and drug-related problems. These results suggest that future programs are likely to achieve intended laboratory and physiologic goals. However, to accurately assess health care value, future research studies and implementation projects that utilize intermediate laboratory and physiologic goals as measures of effectiveness need to be certain that these goals are clearly linked to improved patient outcomes including clinical events, satisfaction, access, hospitalizations, costs, medication adherence, and drug-related problems without undue harms and costs.

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